Review

Nonbiomimetic total synthesis of indole alkaloids using alkyne-based strategies

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Biomimetic natural product synthesis is generally straightforward and efficient because of its established feasibility in nature, utility in comprehensive synthesis, and cost advantage of naturally derived starting materials. On the other hand, nonbiomimetic strategies can be an important option in natural product synthesis since (1) nonbiomimetic synthesis offers more flexibility and can demonstrate the originality of chemists, and (2) the structures of derivatives accessible by nonbiomimetic synthesis can be considerably different from those that are synthesised in nature. This review summarises nonbiomimetic total syntheses of indole alkaloids using alkyne chemistry for construction the core structures, including ergot alkaloids, monoterpene indole alkaloids (mainly corynanthe, aspidosperma, strychnos, and akuammiline), and pyrroloindole and related alkaloids. To clarify the differences between alkyne-based strategies and biosynthesis, alkynes in nature and the biosyntheses of indole alkaloids are also outline.

1. Introduction

1.1 Biomimetic and nonbiomimetic syntheses

In nature, series of compounds are synthesised from a common intermediate that is accessible from natural sources. Evolutionary selection can be considered as compound screening in nature, and the organisms which efficiently produce compounds beneficial for their survival remain.[1] Through these processes, the structures, chemical properties and biosyntheses of natural compounds are optimised and refined. Among biosynthesised compounds, those attractive to humans have been isolated as “natural products” through fractionation, biological evaluation, and sometimes derivatisation.

When we chemists carry out natural product synthesis, the use of a biomimetic/bioinspired approach is reasonable.[2] The feasibility of the core synthetic strategy is established in nature, and the comprehensive synthesis of a series of natural products can be realised by employing naturally occurring branch-point compounds as key synthetic intermediates.[3] Importantly, natural product structures are limited to those suitable for biomimetic synthesis and naturally occurring reactions. Biomimetic synthesis has a cost advantage because naturally derived starting materials are inexpensive and readily available in many cases. Thus, there is no doubt that the biomimetic approach is rational for synthesising desired natural products efficiently, quickly and in large quantities. Biomimetic synthesis is also useful for production of natural product derivatives. Although structures of such derivatives are sometimes similar to those synthesized in nature, structural novelty can be increased by using synthons and reagents unavailable in nature.

Nonbiomimetic synthesis employs a completely different approach. Among the nonbiomimetic synthetic strategies, “anti-biomimetic synthesis”[4] can be defined as the opposite of biosynthesis and does not use bond formations that occur in nature. What is the significance of nonbiomimetic natural product synthesis? There are at least two possible answers: (1) Nonbiomimetic synthetic strategies are not restricted and can demonstrate the originality of chemists. Even when difficulties hamper unexplored synthetic routes, these may provide new research project in organic chemistry. (2) The structures of derivatives accessible through nonbiomimetic synthesis can be considerably different from those synthesised in nature,[5a] including the compounds that organisms have ceased to synthesise. Although natural products possess structures that have been optimised through compound screening in nature, there may be another possibility for further refining through nonbiomimetic approaches, resulting in new pseudo-natural products[5b,c] or supernatural products.[5d,e] Thus, nonbiomimetic synthesis can be an important option in natural product synthesis comparable to biomimetic one (Table 1).

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Table 1 Biomimetic and nonbiomimetic syntheses

	Biomimetic synthesis	Nonbiomimetic synthesis
Strategy feasibility	Often guaranteed	Not guaranteed
Comprehensive synthesis	Often convenient	Case dependent
Starting material	Generally inexpensive	Case dependent
Strategy freedom	Lower	Higher
Structures of accessible derivatives	Sometimes similar to those synthesised in nature	Not related to those synthesised in nature

How can we design nonbiomimetic synthetic strategies? Retrosynthetic analysis based on the cleavage of key bonds that are not formed in biosynthesis is a primary design method. A good option is to design synthetic strategies that employ bio-orthogonal reactions.[6] Alkynes are one of the most ideal functional groups for nonbiomimetic total synthesis, as alkynes are widely used as synthons in bio-orthogonal reactions.[6a] In this regard, many alkyne-based total syntheses can be classified as nonbiomimetic syntheses.

1.2 Alkynes in nature

To describe the natural occurrence of alkynes, this section introduces the structures and biosyntheses of alkyne-containing natural products. Although alkynes are a biologically rare functional group,[7] they form a class of natural products including acetylenic fatty acids (*e.g*. stearolic acid, crepenynic acid and dihydromatricaria acid), acetylenic amino acids (*e.g*. ethynylglycine,[8] propargylglycine[9] and β-ethynylserine[10]), meroterpenoids (*e.g*. biscognienyne B[11]), enediynes (*e.g*. calicheamicin[12]), bacterial polyynes (*e.g*. Sch 31828[13] and cepacins[14]) and acetylenic polyketides (*e.g*. jamaicamides[15]) (Fig. 1). Acetylenic fatty acids can be incorporated in lipopeptides such as kurahyne.[16]

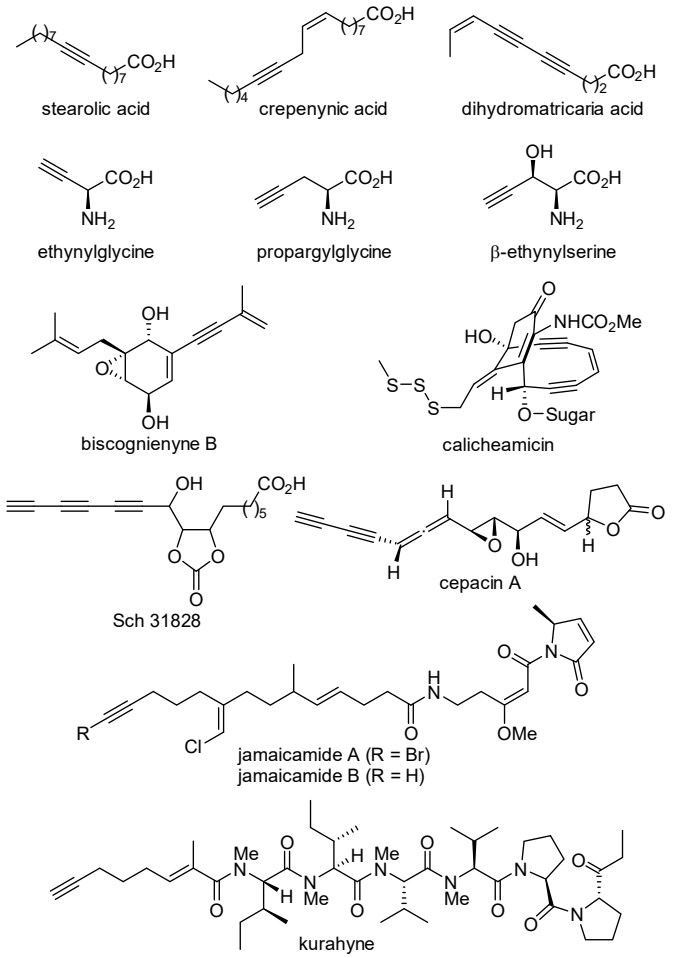
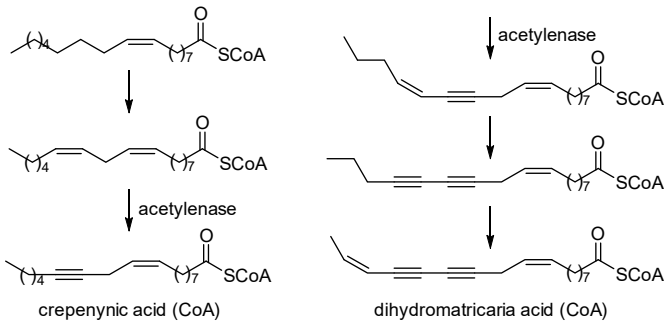


Fig. 1 Alkyne-containing natural products.

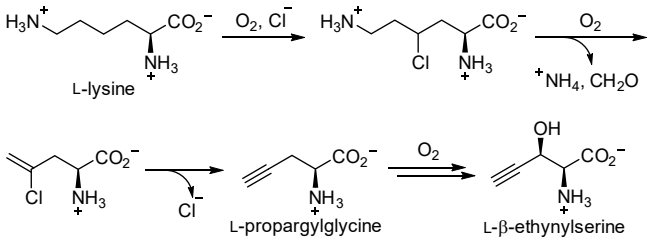
These acetylenic natural products are of particular interest owing to their important biological activities such as antitumor, antibacterial, antimicrobial, antifungal and immunosuppressive properties. For example, it has been proposed that ethynylglycine exhibits antibacterial activity by binding to bacterial alanine racemase.[8] Ethynylserine and cepacins A and B also possess antibacterial activity.[10b,14] Enediynes are widely known as naturally occurring anticancer agents that cleaves double-stranded DNA. Jamaicamides and kurahyne also exhibit antitumor activity against human cancer cells.[15,16] Thus, acetylenic natural products are not only important for organism survival but also for humans as a drug resource.[17]

Recently, considerable progress has been made in clarifying the biosynthesis of alkynes. The typical biosynthesis of acetylenic natural products utilises increasing unsaturation from alkenes or haloalkenes.[18] For example, Hamburg reported that the biosynthetic pathway of acetylenic fatty acids in soldier beetles is based on acetylenase, which catalyses formation of the alkyne moiety in crepenynic acid and dihydromatricaria acid via dehydrogenation of the corresponding alkenes (Scheme 1).[19] This type of desaturase is employed in the synthesis of acetylenic polyketides.[20]



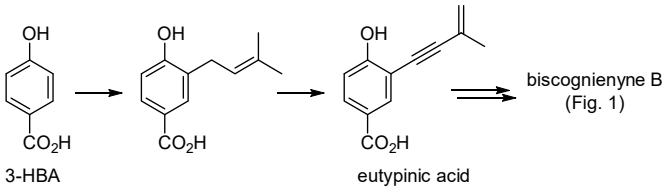
Scheme 1 Proposed biosynthetic pathway of acetylenic fatty acids.

The biosynthetic pathway of acetylenic amino acids in the bacterium *Streptomyces cattleya* is shown in Scheme 2.[21] Oxidative chlorination and carbon–carbon bond cleavage of L-lysine produces chloroalkene, which then forms propargylglycine by dehydrochlorination through the formation of an allene intermediate and isomerisation to the corresponding alkyne.



Scheme 2 Biosynthesis of alkyne-containing amino acids.

Quite recently, Gao reported the biosynthesis of biscognienyne B, which proceeds through P450-dependent oxidation (Scheme 3).[22] Thus, prenylation of 3-hydroxybenzoic acid (3-HBA) followed by alkyne formation produces eutypinic acid, the precursor of biscognienyne B. The alkyne formation step is proposed to proceed through 1,3-diene or allene.

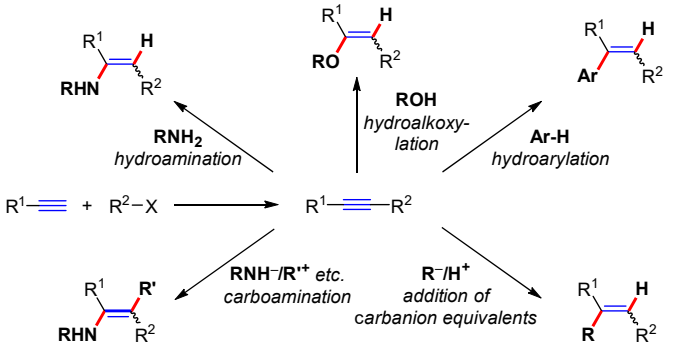


Scheme 3 Biosynthesis of biscognienyne B.

Although alkynes are synthesised and used in nature, their reactions are not often used in nature. Thus, taking advantage of alkyne reactivity leads to the nonbiomimetic total synthesis of natural products.

1.3 Alkynes for nonbiomimetic total synthesis

The transformations of alkynes that are useful for constructing natural product core structures are summarised in Scheme 4.[23] The hydroamination of alkynes promoted by base or transition metal catalysts provides facile access to indole and other heterocycles.[24] Similarly, the addition of alcohols and related oxygen nucleophiles to alkynes (hydroalkoxylation/hydration) is an important approach to achieve various oxacycles.[25] The hydroarylation of alkynes can be used to construct styrene-type structures, including heteroaryl-containing structures.[26] The addition of carbanion equivalents, such as silyl enol ether, easily forms carbon–carbon bonds by reacting with activated alkynes. When using an appropriate pair of carbon and nitrogen active species, both the carbon and nitrogen substituents can be introduced in a single step (carboamination). Other transformations such as alkyne metathesis, migration/isomerisation to allene, and cycloaddition reactions are also important for nonbiomimetic total synthesis. Most of these transformations are catalysed by a transition metal complex that is not found in nature. Furthermore, considering that widely used alkyne preparation methods such as Sonogashira coupling, Glaser-type coupling and acetylide addition are not used in alkyne biosynthesis, employing alkyne reactivity as the key reaction makes the total synthesis nonbiomimetic.



Scheme 4 Representative reactions of alkynes useful for nonbiomimetic synthesis.

This review article summarises the nonbiomimetic total syntheses of indole alkaloids using alkyne-based strategies. We specifically focused on the total syntheses in which alkyne reactions are used to construct the core structures of natural products.

2. Ergot alkaloids

Ergot alkaloids are among the most important indole alkaloids in human history and have diverse structures and biological activities.[27] Currently, over 10 natural ergot alkaloids and their derivatives, including pergolide and bromocriptine, are clinically used for the treatment of Parkinson's disease, migraines, hyperprolactinemia and other conditions. Many ergot alkaloids contain the common 3,4-fused tetracyclic indole core (ergoline skeleton, Fig. 2). Other types of ergot alkaloids are also found, such as clavicipitic acid (**4**) and aurantioclavine (**5**), which bears a tetrahydroazepine-fused indole structure.

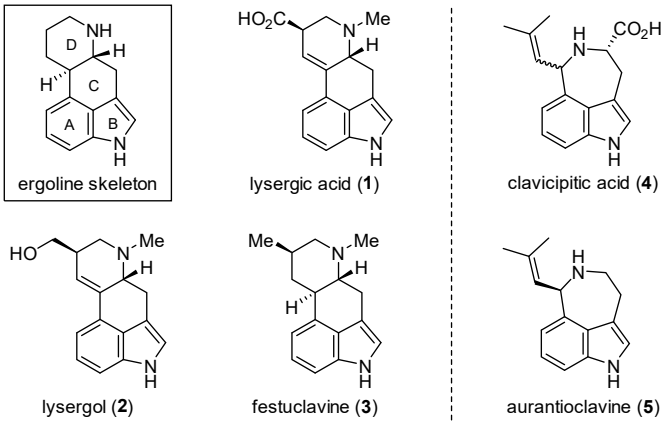
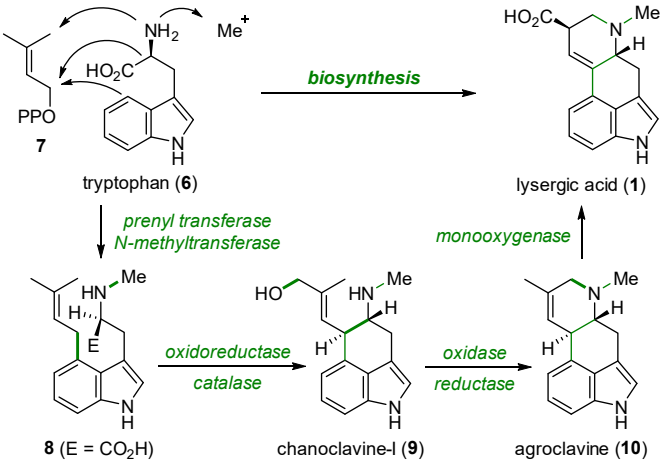


Fig. 2 Structures of ergot alkaloids.

2.1 Biosynthesis

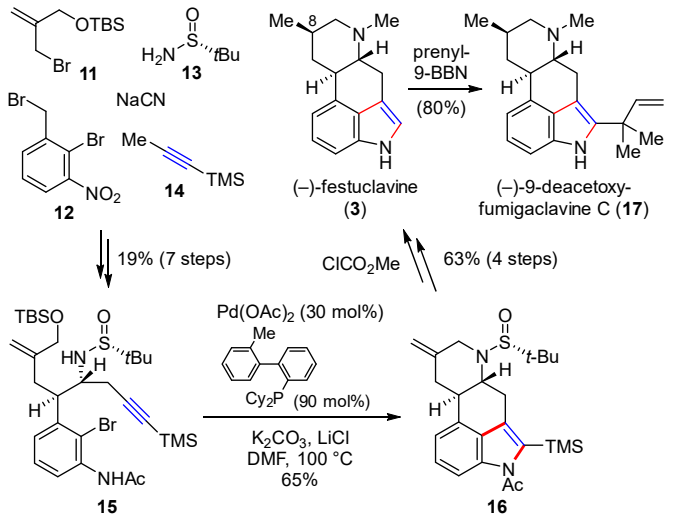
Ergot alkaloids are biosynthesised from tryptophan (**6**) and dimethylallyl pyrophosphate (DMAPP) in a stepwise manner (Scheme 5).[28] Prenylation of tryptophan (**6**) at the indole 4 position with DMAPP (**7**), followed by methylation with a SAM-dependent methyltransferase produces 4-(dimethylallyl)-L-abrine (**8**). Oxidative ring closure of **8** accompanying decarboxylation forms the C-ring of ergot alkaloids to afford chanoclavine-I (**9**). Oxidation of **9** to an aldehyde followed by reductive amination via isomerisation into *cis*-enal affords agroclavine (**10**), which is then converted to lysergic acid (**1**) by allylic oxidation and alkene migration.



Scheme 5 Biosynthetic pathway of lysergic acid. Throughout the manuscript, green bonds show those formed in a biosynthetic pathway.

2.2 Alkyne-based synthesis of ergot alkaloids

Alkyne-based reactions provide a powerful nonbiomimetic approach for construction of the ergoline skeleton. Typically, intramolecular Larock indole annulation[29] in which carboamination of an alkyne proceeds with 2-haloanilines in the presence of a palladium catalyst directly affords 3,4-fused indole skeletons.

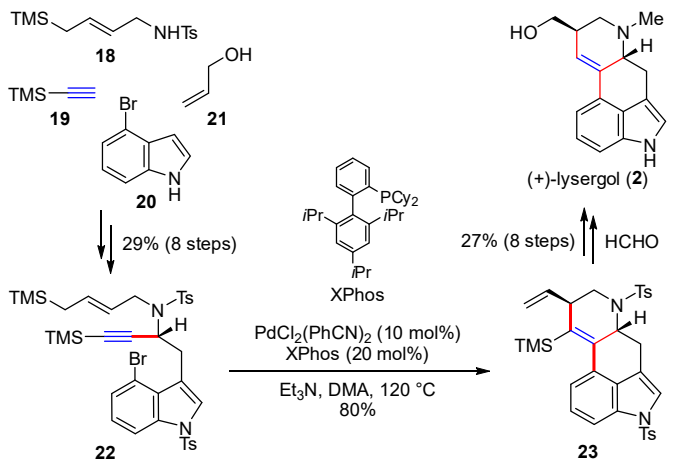


Scheme 6 Total syntheses of festuclavine and related alkaloids by Jia. Throughout the manuscript, red bonds show those formed during the alkyne-based reactions.

Jia reported the total synthesis of festuclavine (**3**) and related ergot alkaloids based on Larock indole annulation (Scheme 6).[30] The cyclisation precursor **15** was prepared in seven steps from dibromide **12** through cyanation with NaCN, coupling with allylic bromide **11** and sulfinamide **13**, followed by propargylation with an allenylzinc reagent derived from alkyne **14**. Intramolecular Larock indole annulation of **15** accompanying Tsuji–Trost allylation directly provided the tetracyclic indole **16** bearing the ergoline skeleton with requisite functionalities. Modification of the nitrogen functional groups and hydrogenation of the exo-olefin moiety using Pd/C gave (–)-festuclavine (**3**) and its stereoisomer at the 8-position in a ratio of 8:1. They showed that festuclavine is an important synthetic intermediate for other ergot alkaloids, including (–)-9-deacetoxyfumigaclavine C (**17**). Jia and others also reported that the clavicipitic acid-type scaffold can be readily constructed using Larock indole annulation.[31]

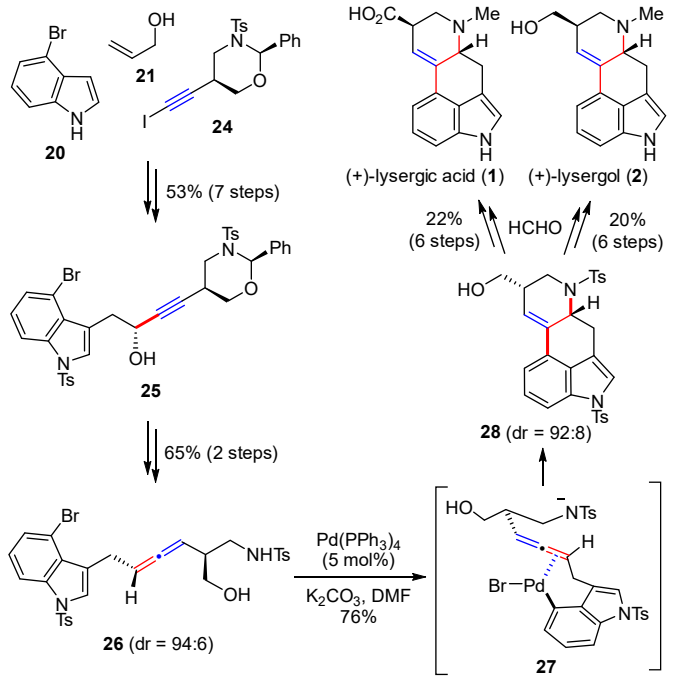
Palladium-catalysed cascade cyclisation of alkynes is also useful for introducing two carbon units to alkynes. In 2017, Werz reported the total synthesis of lysergol using a β-silyl-directed Heck reaction via formal anti-carbopalladation (Scheme 7).[32] The allylsilane substrate **22** for the cascade reaction was synthesised in eight steps from 4-bromoindole (**20**) via palladium-catalysed allylation with alcohol **21**, oxidative cleavage of the terminal alkene, alkynylation with TMS-acetylide, and introduction of the allylsilane moiety with tosylamide **18** under Mitsunobu conditions. The palladium-catalysed reaction of **22** using $PdCl_2(PhCN)_2$ (10 mol%) and XPhos gave tetracyclic indole **23** in a completely stereoselective manner. The reaction proceeded via carbopalladation onto the alkyne and a β-silyl-directed Heck reaction. Notably, the two carbon units were introduced to the alkyne in an anti-selective manner, presumably via syn-carbopalladation followed by isomerisation. The important factors for the formal anti-carbopalladation are the absence of β-hydrogen atoms at the alkyne terminus, the use of monodentate phosphine ligands for

palladium, and the use of polar aprotic solvents. The total synthesis of (+)-lysergol (**2**) based on a stepwise reductive Heck reaction and alkene metathesis was previously reported by Martin *et al*.[33]

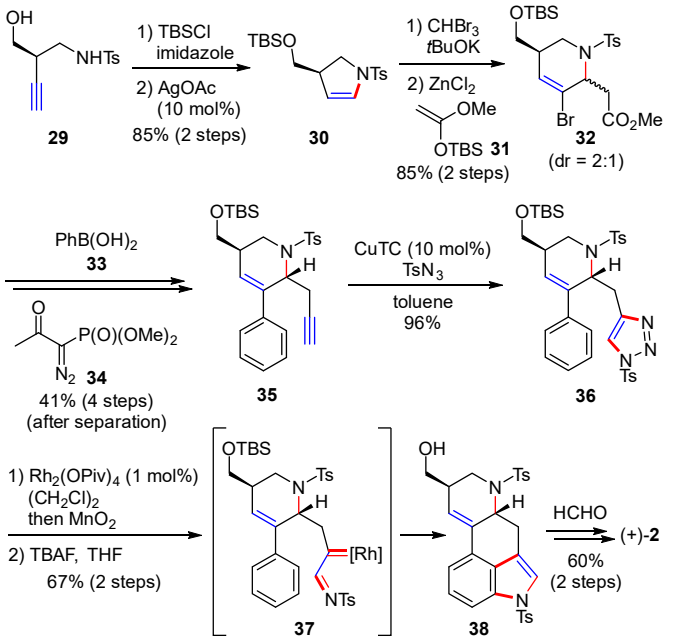


Scheme 7 Total synthesis of lysergol by Werz.

The palladium-catalysed cascade reaction after transformation to allene is also useful for ergot alkaloid synthesis, as reported by Inuki, Ohno *et al*. in 2011.[34] Propargylic alcohol **25** was prepared via the allylation of **20**, oxidative cleavage, and Nozaki–Hiyama–Kishi coupling with iodide **24** (Scheme 8). The reductive allene formation reaction of **25** under the Myers conditions[35] gave allene-type cyclisation precursor **26** bearing a tosylamide moiety. Cascade cyclisation of **26** with $Pd(PPh_3)_4$ and K_2CO_3 in DMF furnished the tetracyclic indole **28** in a 92:8 diastereomeric ratio, presumably via the anti-aminopalladation pathway, as shown with **27**. The tetracyclic indole **28** has proven to be a good precursor of (+)-lysergic acid (**1**), (+)-lysergol (**2**) and (+)-isolysergol.



Scheme 8 Total synthesis of lysergic acid and lysergol by Inuki and Ohno.



Scheme 9 Total synthesis of lysergol by Luo.

The final example in this section is Luo's total synthesis of (+)-lysergol (**2**) using alkyne hydroamination and [3 + 2] annulation of alkyne-derived triazole (Scheme 9).[36] Silylation and silver(I)-catalysed hydroamination of alkyne **29** gave dihydropyrrole derivative **30**. Elaborations including the cyclopropanation of **30** with dibromocarbene, a nucleophilic ring-opening reaction with ketene silyl acetal **31**, Suzuki coupling with $PhB(OH)_2$ (**33**) and Seyferth–Gilbert homologation using Ohira–Bestmann reagent **34** gave the key alkyne intermediate **35**. Transformation to *N*-tosyl-1,2,3-triazole **36** using a copper-catalysed [3 + 2] cycloaddition followed by rhodium-catalysed [3 + 2] annulation afforded the lysergol-type tetracyclic indole **38** after desilylation. The reaction can be rationalised by the formation of rhodium carbenoid species formed by the elimination of nitrogen from **36**. The tetracyclic indole **38** was readily converted to (+)-lysergol (**2**) by detosylation and methylation.

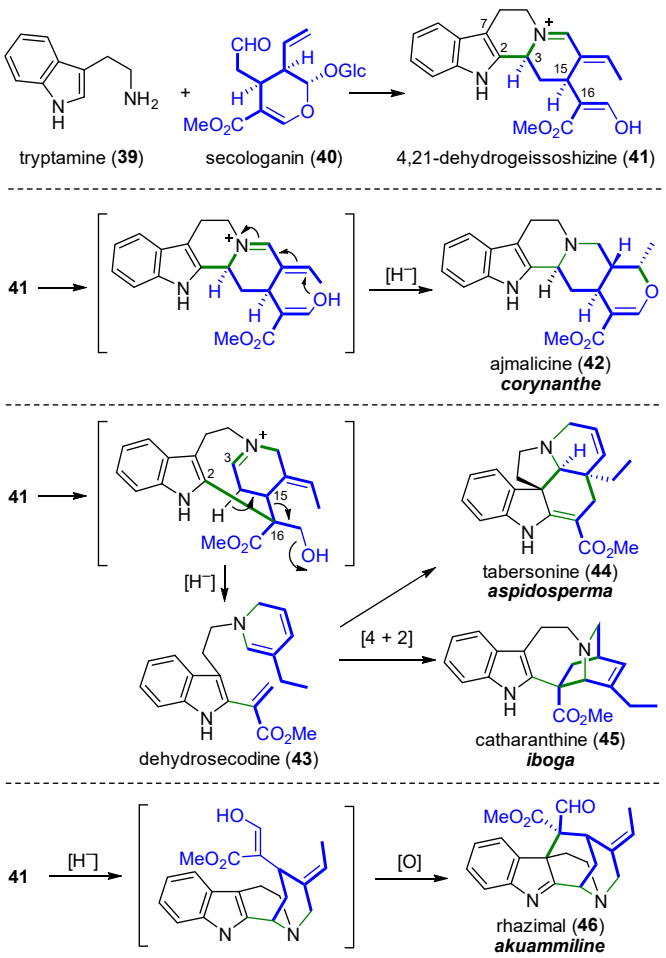
The described alkyne-based synthetic strategies provide practical nonbiomimetic access to ergot alkaloids. In particular, the transition metal-catalysed cascade cyclisation of alkynes or alkyne-derived allenes is useful for late-stage construction of the ergoline skeleton, which can potentially lead to the identification of non-natural ergot alkaloid derivatives useful for medicinal study. It should be clearly noted that asymmetric syntheses of ergot alkaloids not dependent on alkyne chemistry have been reported by some other research groups including Szántay,[27c] Fukuyama/Yokoshima,[27d-f] and Bisai.[27g-i]

3. Monoterpene indole alkaloids

Monoterpene indole alkaloids constitute an important class of natural products.[37] Numerous monoterpene indole alkaloids with diverse structures have been isolated from medicinal plants. These compounds are an important source of natural product drug discovery because of their relevant biological activities including anticancer, antimalarial and anti-arrhythmic properties. Thus, further structural modifications of monoterpene indole alkaloids is an important area of organic and medicinal chemistry.

3.1 Biosynthesis

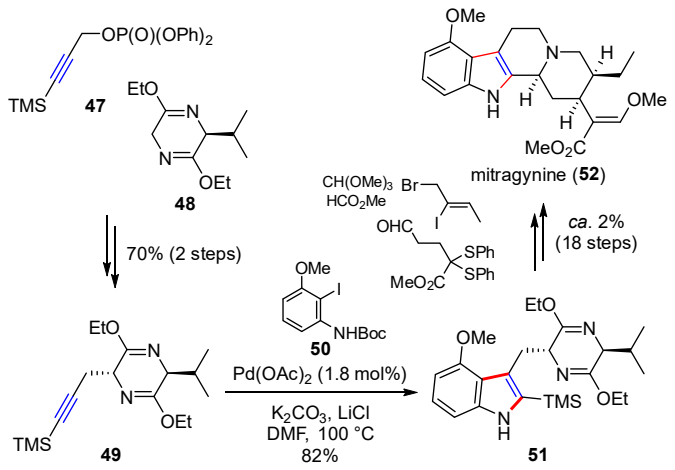
Monoterpene indole alkaloids are biosynthesised as shown in Scheme 10.[38] The Pictet–Spengler reaction of tryptamine (**39**) and secologanin (**40**), a monoterpene glycoside produced in the mevalonate pathway, affords 4,21-dehydrogeissoshizine (**41**), the common biosynthetic intermediate of monoterpene indole alkaloids. The corynanthe-type alkaloids, such as ajmalicine (**42**), are produced through functional group modifications such as oxa-Michael-type cyclisation. Other types of indole alkaloids bearing a geometric arrangement of the terpenoid-derived unit can be constructed from **41**. Thus, dehydrosecodine (**43**) is biosynthesised through formal cleavage of the C2-C3 and C15-C16 bonds and formation of the C2-C16 bond. The compound **43** is the important substrate for [4 + 2] cycloaddition reactions for the biosynthesis of aspidosperma and iboga alkaloids: cycloaddition of dehydrosecodine (**43**) employing the 1,2-dihydropyridine moiety as a dienophile produces aspidosperma alkaloids, including tabersonine (**44**), whereas cycloaddition using the 1,2-dihydropyridine moiety in **43** as the diene produces iboga alkaloids, including catharanthine (**45**). In addition to these major groups, the biosynthetic pathway forming akuammiline alkaloids is also shown in Scheme 10. After reduction of the iminium moiety of **41**, oxidative carbon–carbon bond formation between C7 and C16 leads to the production of akuammiline alkaloids, such as rhazimal (**46**). Overall, the biosynthesis of monoterpene indole alkaloids is highly dependent on the imine/enamine chemistry and cycloaddition.



Scheme 10 Biosynthesis of monoterpene indole alkaloids.

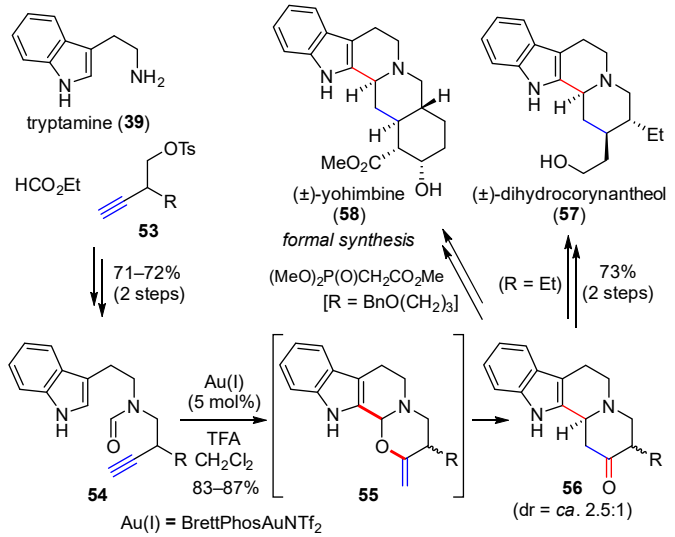
3.2 Alkyne-based synthesis of corynanthe alkaloids

Larock indole synthesis is also a powerful tool for the total synthesis of corynanthe alkaloids. Cook prepared methoxy-substituted tryptophan analogue **51** using the Larock's strategy employing iodoaniline derivative **50** and alkyne **49**, which was prepared by α-propargylation of cyclic dipeptide **48** with **47** (Scheme 11).[39] The TMS-substituted alkyne **49** is the key to achieving high regioselectivity in the intermolecular indole formation. The subsequent Pictet–Spengler reaction to construct the tetrahydro-β-carboline skeleton led to the asymmetric total synthesis of mitragynine (**52**) and related corynanthe alkaloids. Although the latter part of this synthesis can be considered a biomimetic synthetic route, this synthesis is a good example of preparing an unnatural amino acid synthon based on a nonbiomimetic strategy.



Scheme 11 Asymmetric total synthesis of mitragynine by Cook.

Zhang reported a gold-catalysed cascade process involving Ferrier rearrangement for construction of the tetracyclic core of corynanthe alkaloids (Scheme 12).[40] The cyclisation precursor **54** was easily prepared from tryptamine (**39**), homopropargyl tosylate **53** and ethyl formate in two steps. The gold-catalysed reaction of **54** in the presence of TFA afforded the desired indolo[2,3-*a*]quinolizine **56** as a mixture of diastereomers (ca. 2.5:1) via nucleophilic attack of the carbonyl oxygen on the activated alkyne, nucleophilic addition of indole, and Ferrier rearrangement of the resulting *N*,*O*-acetal **55**. This tetracyclic indole is a good precursor of corynanthe alkaloids, such as dihydrocorynantheol (**57**) and yohimbine (**58**).



Scheme 12 Total and formal synthesis of dihydrocorynantheol and yohimbine by Zhang.

3.3 Alkyne-based synthesis of aspidosperma and strychnos alkaloids (biomimetic strategy)

The aspidosperma alkaloids are one of the largest groups of monoterpene indole alkaloids, with over 250 members. Vinblastine and vincristine are important examples of aspidosperma alkaloid-derived anticancer agents (Fig. 3). Strychnos alkaloids, represented by strychnine, also constitute a major class of indole alkaloids. Aspidosperma and strychnos alkaloids are an attractive target of synthetic chemists because of their challenging structures and important bioactivities.[41] These alkaloids share the tetracyclic indoline core structure, which makes them accessible owing to their highly related synthetic strategy. Many total syntheses of these alkaloids have been reported since the first total synthesis of (±)-aspidospermine and (±)-quebrachamine by Stork *et al*. in 1963.[42] Notably, the biosyntheses of aspidosperma and strychnos alkaloids are sufficiently straightforward that the total synthesis becomes biomimetic, even when using alkyne-based strategies as shown below.

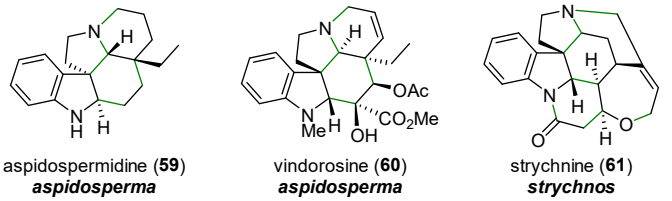
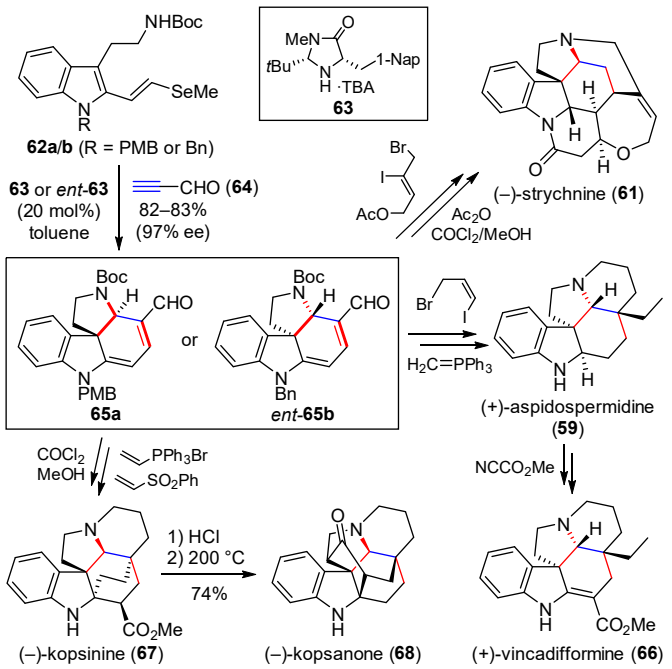


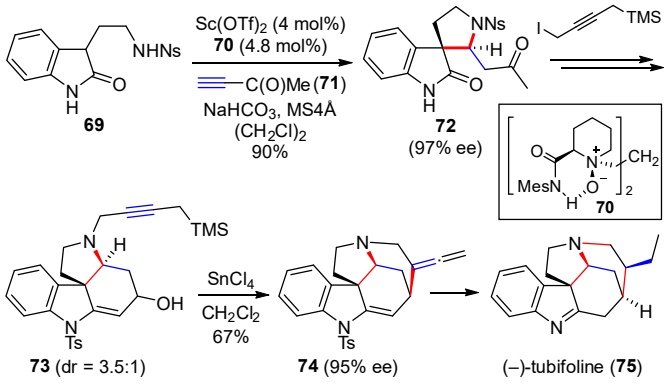
Fig. 3 Structures of aspidosperma and strychnos alkaloids.

In 2011, MacMillan reported the short-step collective synthesis of strychnos, aspidosperma and kopsia alkaloids based on organocatalytic cascade reactions using propynal as the reaction partner (Scheme 13).[43a] The asymmetric cascade reaction of tryptamine-derived vinyl selenide **62a** (R = PMB) with propynal (**64**) using **63** as an organocatalyst produced tetracyclic indoline **65a** in 97% ee, a precursor for (–)-strychnine (**61**) and akuammicine. This reaction proceeds through an asymmetric [4 + 2] cycloaddition and aza-Michael addition, both catalysed by the chiral organocatalyst **63**. Similarly, the pseudo-enantiomeric tetracyclic indoline **65b**, obtained by the reaction of *ent*-**62b** (R = Bn) with propynal (**64**) in the presence of the organocatalyst *ent*-**63**, was efficiently converted to (+)-aspidospermidine (**59**). A related strategy was also applied to the total syntheses of (–)-minovincine,[43b] (+)-minfiensine[43c] and an akuammiline alkaloid (–)-vincorine.[43d]



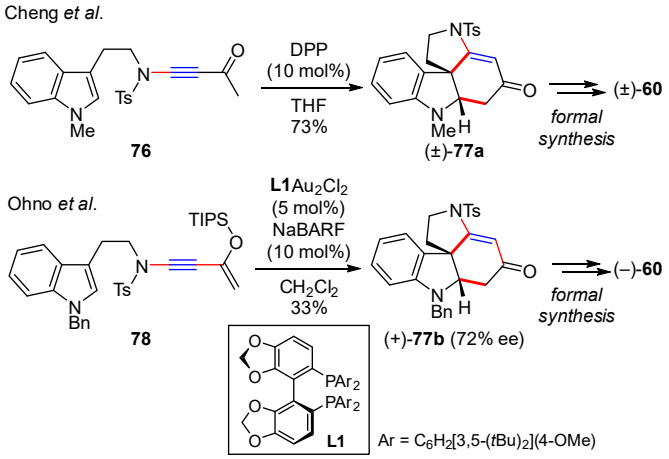
Scheme 13 Collective synthesis of indole alkaloids by MacMillan.

Xie reported the total synthesis of strychnos alkaloids using two alkyne-based reactions (Scheme 14).[44] The first was a double Michael addition of tryptamine-derived oxindole **69** to 3-butyn-2-one (**71**) to construct the spirocyclic structure. The second was a Lewis acid-mediated S_N1-type cyclisation using an alkyne as the nucleophile to afford pentacyclic product **74**, a precursor of tubifoline (**75**). By comparing the green bonds in the biosynthesis (Scheme 10 and Fig. 3) and the red bonds in the chemical synthesis formed during the alkyne-based reactions (Schemes 13 and 14), it is clear that the strategies for the core structure construction are highly related to each other.



Scheme 14 Total synthesis of tubifoline by Xie.

Syntheses of the precursor of vindorosine (**60**) based on alkyne chemistry have been independently reported by Cheng[45a] and Ohno[45b] (Scheme 15). The diphenyl phosphate (DPP)-catalysed cyclisation of ynamide **76** gave tetracyclic indoline (±)-**77** through the nucleophilic attack of indole on the activated alkyne, followed by the second carbon–carbon bond formation. Use of the chiral gold catalyst **L1**Au_2Cl_2 and the silyl enol ether **78** enabled the asymmetric version of this reaction to produce the same tetracyclic product **77** in 72% ee. This type of ring construction is also highly related to the biosynthesis of aspidosperma alkaloids (Scheme 10).



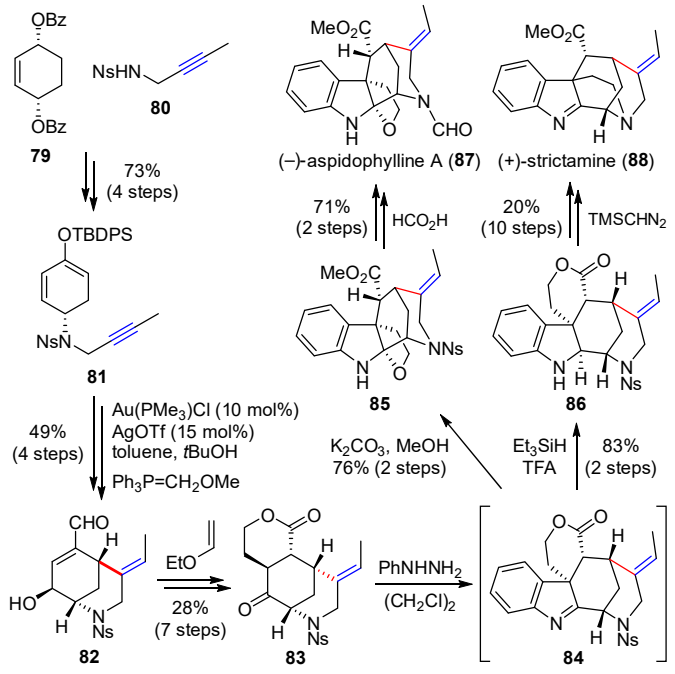
Scheme 15 Synthesis of the vindorosine precursor by Cheng and Ohno.

As another important example, the bioinspired total synthesis of strychnine using a radical cascade reaction of alkynes has been reported by Qin and co-workers.[46] The total syntheses shown in this section indicate that the alkyne-based total synthesis of strychnos and aspidosperma alkaloids is strongly related to the biosynthesis. This can be attributed to the biosynthesis being so reasonable to produce these alkaloids. In other words, when the structure of natural products is highly suitable for biosynthesis, the rational chemical synthesis will inevitably be similar to the biosynthesis, even if a strategy based on alkynes is employed.

3.4 Alkyne-based synthesis of akuammiline alkaloids

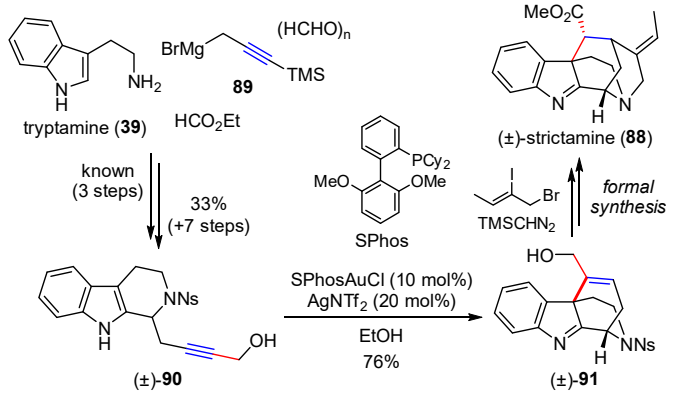
Akuammiline alkaloids have a specific cage-like structure and a broad range of biological activities. An alkyne-based core strategy is useful for the nonbiomimetic total synthesis of these alkaloids. In 2016, Garg reported the total synthesis of several akuammiline alkaloids based on the efficient construction of the [3.3.1]-azabicyclic core (Scheme 16).[47] The cyclisation precursor **81** was prepared in four steps through the palladium-catalysed desymmetrisation of dibenzoate **79** with nosylamide **80** using a Trost ligand. Gold(I)-catalysed carbocyclisation of **81** efficiently produced the corresponding bicyclic adduct in a regioselective manner (6-*exo*/7-*endo* = 10:1), which was converted to **82** (96% ee) by desilylation, epoxidation and Wittig reaction. The subsequent seven-step conversion, including introduction of the C2 unit via NIS-mediated mixed acetal formation and radical cyclisation, gave the key intermediate **83**. The Fischer indolisation with phenylhydrazine and TFA produced **84**, which was subjected to the next step in the same pot. The cleavage of lactone **84** with K_2CO_3/MeOH gave **85** via cyclic *N*,*O*-acetal formation, leading to the first enantioselective total synthesis of (–)-aspidophylline A. On the other hand, reductive treatment of **84** with triethylsilane gave indoline **86** with complete control of the stereoselectivity. The first total synthesis of (+)-

strictamine (**88**) was achieved through careful conversion of the lactone moiety in **86** to suppress epimerisation. Notably, until this report, no synthesis had been reported in the 50 years since strictamine was isolated in 1966 despite considerable synthetic efforts by many chemists.



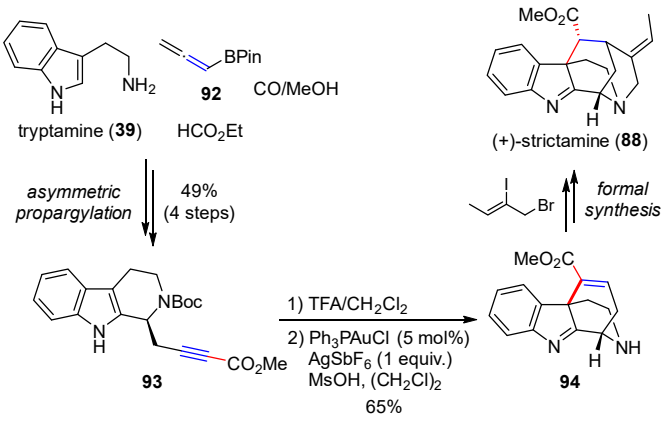
Scheme 16 Total synthesis of aspidophylline A and strictamine by Garg.

In 2016, Ohno reported the formal synthesis of racemic strictamine (**88**) via the gold-catalysed hydroarylation of tetrahydro-β-carboline derivative **90** (Scheme 17).[48] The hydroarylation toward the propargyl alcohol moiety proceeded effectively in protic solvent to afford tetracyclic indoline **91**. Construction of the methyl ester moiety followed by introduction of an iodobutenyl unit gave the Zhu's precursor[49] of strictamine.



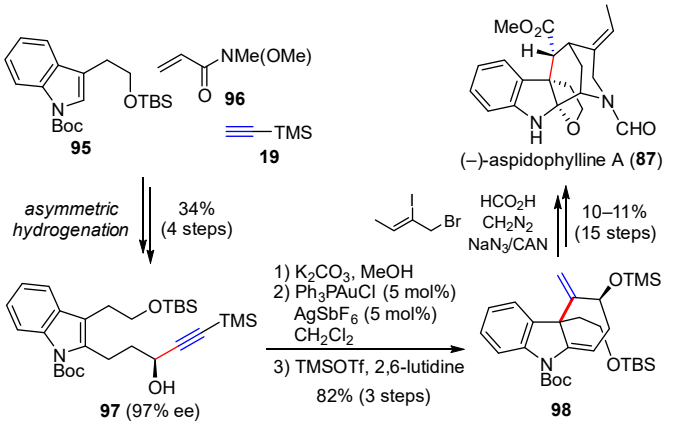
Scheme 17 Formal synthesis of (±)-strictamine by Ohno.

A highly related enantioselective formal synthesis of strictamine was reported in 2017 by Snyder (Scheme 18).[50] Asymmetric propargylation of the tryptamine-derived dihydro-β-carboline using allenylboronic acid pinacol ester (**92**) in the presence of CuCl and (*R*)-DTBM-SEGPHOS and the construction of methyl ester produced **93**. After conversion to ammonium salt with TFA, the gold(I)-catalysed 6-*endo-dig* cyclisation afforded **94** in 65% yield. Introduction of an iodobutenyl group accomplished a seven-step formal asymmetric synthesis of (+)-strictamine (**88**) from tryptamine (**39**).



Scheme 18 Asymmetric formal synthesis of strictamine by Snyder.

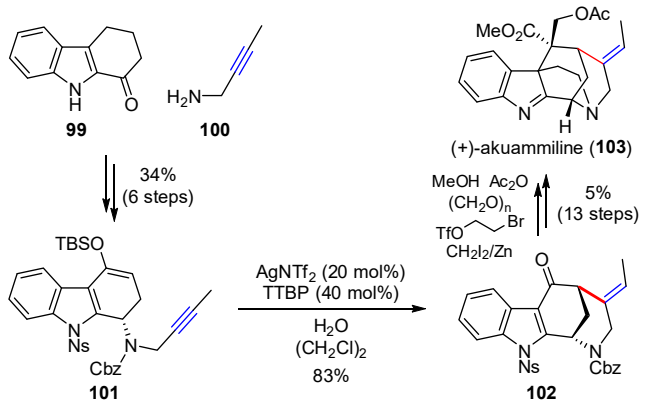
The gold-catalysed *exo*-cyclisation of linear-type substrates is also useful for akuammiline alkaloid synthesis. Zhai achieved the enantioselective total synthesis of (–)-aspidophylline A (**87**) using a gold(I)-catalysed 6-*exo-dig* cyclisation of propargyl alcohol **97** (Scheme 19).[51] The cyclisation precursor **97** was prepared via asymmetric hydride transfer hydrogenation of the acetylenic ketone derived from protected tryptophol **95**, amide **96** and TMS-acetylene (**19**).



Scheme 19 Total synthesis of aspidophylline A by Zhai.

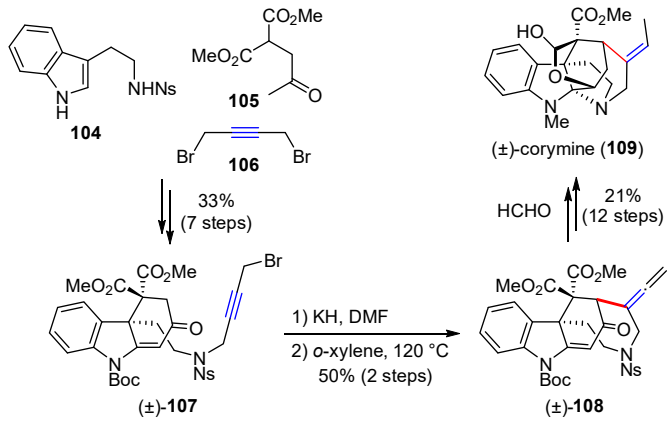
Li recently reported the efficient construction of the bicyclic structure of akuammiline alkaloids via the silver(I)-catalysed cyclisation of silyl enol ether **101** bearing a propargylamine moiety (Scheme 20).[52] This cyclisation precursor was readily prepared from ketone **99** in six steps through imine formation with **100**, Noyori asymmetric hydrogenation (95% ee) and benzylic oxidation. The silver-catalysed carbocyclisation of **101** using TTBP (2,4,6-tri-*tert*-butylpyrimidine) as the ligand proceeded in a highly 6-*exo-dig* manner (ca. 90:10) to produce the azabicyclo[3.3.1]nonane derivative **102**. Notably, the same

group reported the total synthesis of some akuammiline alkaloids via a similar gold(I)-catalysed cyclisation in 2016.[53] They employed the silver-catalysed reaction for the synthesis of akuammiline (**103**) owing to scale and cost advantages. Further elaboration of **102** including introduction of the C2 unit for the final ring closure and a hydroxymethyl group using paraformaldehyde completed the total synthesis of (+)-akuammiline (**103**) and other related alkaloids.



Scheme 20 Total synthesis of akuammiline by Li.

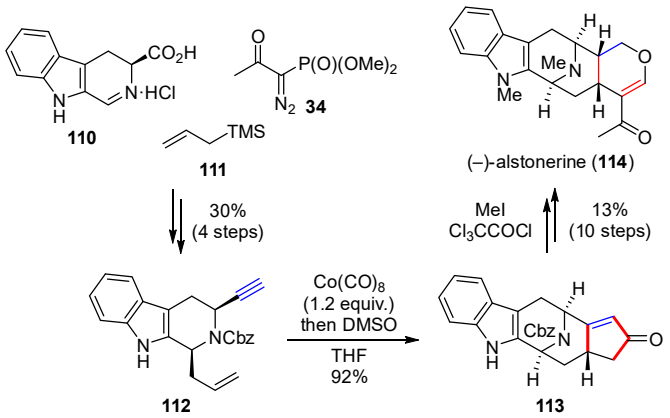
The final example of akuammiline alkaloid synthesis is the total synthesis of (±)-corymine (**109**) reported by the group of Sun and Li (Scheme 21).[54] Corymine is structurally different from representative akuammiline alkaloids in that it has an azepine-fused iminoethanocarbazole skeleton with an extra six-membered hemiacetal ring. The authors prepared racemic propargyl bromide **107** from protected tryptamine **104**, malonate derivative **105** and dibromo-2-butyne **106**. Treatment of **107** with KH for enol ether formation afforded the corresponding macrocyclic alkyne, which was heated in *o*-xylene at 120 °C for 4 h to promote propargyl Claisen rearrangement, giving rise to the vinylidene-azocane **108**. This compound was converted to (±)-corymine (**109**) via Pd/C-catalysed hydrogenation of the allene moiety, formal 1,2-oxo-migration, reductive methylation using formaldehyde, and hemiacetal formation. These syntheses clearly demonstrate the utility of alkyne cyclisation reactions for the total synthesis of akuammiline alkaloids.



Scheme 21 Total synthesis of corymine by Sun and Li.

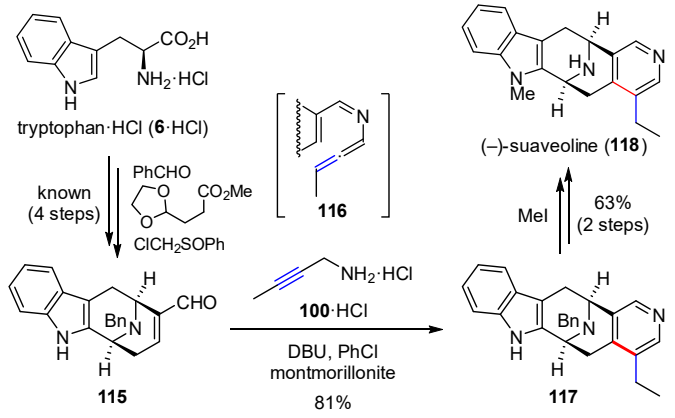
3.4 Alkyne-based synthesis of other monoterpene indole alkaloids

Syntheses of other types of monoterpene indole alkaloids are summarised in this section. The first one is Martin's total synthesis of (–)-alstonerine (**114**), a member of the sarpagine alkaloids (Scheme 22).[55] These alkaloids have a characteristic indole-fused azabicyclo[3.3.1]nonane skeleton related to akuammiline alkaloids. Martin and co-workers prepared tryptophan-derived enyne **112**[55b] and subjected it to a Pauson-Khand reaction, resulting in formation of the desired pentacyclic cyclopentenone **113** in good yield. A further ten-step conversion including oxidative cleavage of the enone-derived silyl enol ether, acylation and methylation afforded alstonerine (**114**).



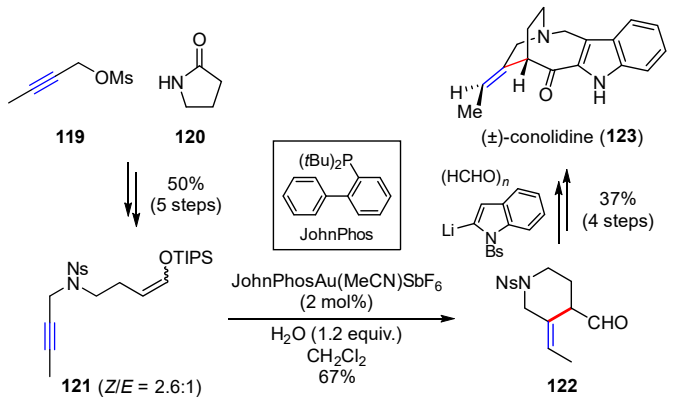
Scheme 22 Total synthesis of alstonerine by Martin.

Suaveoline alkaloids have a sarpagine-type core structure with a fused pyridine skeleton. Li reported the short-step, concise access to (–)-suaveoline (**118**) and its related alkaloids through 6π-electrocyclisation (Scheme 23).[56] Treatment of the known tetracyclic aldehyde **115**, prepared from tryptophan (**6**) in four steps,[57] with amine **100** in the presence of montmorillonite-K10 (the dehydrating agent) and DBU gave the desired tetracyclic pyridine **117** in 81% yield. The reaction is believed to proceed through condensation, alkyne isomerisation to allene, and 6π-electrocyclisation of the resulting azatriene **116**. Methylation of the indole nitrogen atom and benzyl deprotection provided (–)-suaveoline (**118**).



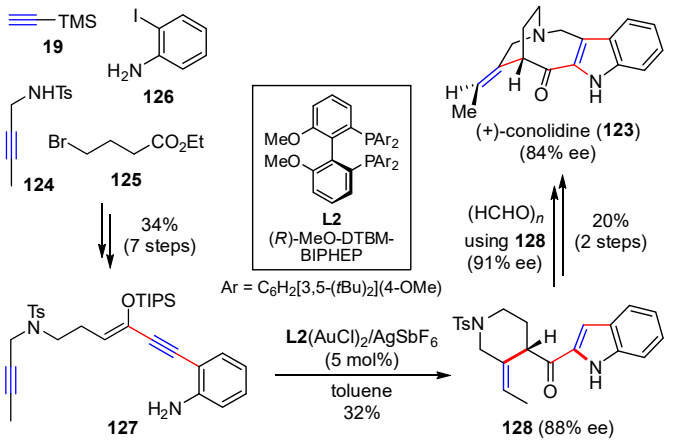
Scheme 23 Total synthesis of suaveoline by Li.

Conolidine is known as a C-5-nor stemmadenine-type indole alkaloid and possesses non-opioid analgesic activity.[58] In 2016, Takayama reported the total synthesis of (±)-conolidine based on a gold(I)-catalysed carbocyclisation (Scheme 24).[59] Silyl enol ether **121** (*Z*/*E* = 2.6:1) was prepared from 2-pyrrolidinone **120** in five steps via a $NaBH_4$-mediated ring-opening reaction and alkylation with **119**. The expected 6-*exo*-*dig* cyclisation of **121** was efficiently promoted by JohnPhosAu(MeCN)SbF_6 (2 mol%), which suppressed side product formation. The total synthesis of (±)-conolidine **123** was then achieved via the addition of lithiated indole to the aldehyde **122** and final ring closure through a Mannich-type reaction with paraformaldehyde.



Scheme 24 Total synthesis of (±)-conolidine by Takayama.

In the same year, Ohno reported the enantioselective total synthesis of conolidine using a highly related gold(I)-catalysed cascade cyclisation (Scheme 25).[60] The silyl enol ether **127** bearing an alkynylaniline moiety was prepared through the successive coupling of tosylamide **124** with **125**, **19**, and **126**. The cascade 5-*endo*-*dig* indole formation and 6-*exo*-*dig* carbocyclisation of **127** efficiently proceeded in an enantioselective manner by using a chiral gold complex **L2**$(AuCl)_2$/$AgSbF_6$ to produce bicyclic ketone **128** in 88% ee. Detosylation and cyclisation with paraformaldehyde gave (+)-conolidine. In 2019, Qi described a six-step total synthesis of conolidine using a gold-catalysed 6-*endo*-*dig* carbocyclisation of silyl enol ether bearing an indolyl group related to **127**.[61]



Scheme 25 Total synthesis of (+)-conolidine by Ohno.

The described alkyne-based strategies enable the nonbiomimetic total synthesis of monoterpene indole alkaloids including aspidosperma and corynanthe alkaloids. Many of the total syntheses of monoterpene indole alkaloids use carbon–carbon bond formation at the indole 2 and/or 3 positions, similar to biosynthesis. In particular, for the synthesis of strychnos and aspidosperma alkaloids, the alkyne-based strategies are similar to biosynthesis owing to their structural features for which the biosynthetic approach is suitable.

4. Pyrroloindole and related alkaloids

Pyrroloindole (or pyrroloindoline) alkaloids constitute an important class of indole alkaloids with a broad array of biological activities.[62] These alkaloids have a common hexahydro[2,3-*b*]pyrroloindole core structure with several substitution and oligomerisation patterns. As shown in Fig. 4, esermethole (**129**) has a monomeric tryptophan derivative with a bridgehead methyl group. Dimerisation at the indole 3 position of each tryptophan produces pyrroloindole alkaloids bearing vicinal quaternary stereogenic carbon centres at C3a and C3a', such as chimonanthine (**130**). Dimerisation/oligomerisation at the nitrogen atom of one of the tryptophan derivatives gives oligomeric pyrroloindole alkaloids with a C3a-N1' linkage, such as psychotriasine (**131**), psychotrimine (**132**) and pestalazine B (**133**). Pestalazine A (**134**) has a C3a-C8' bond derived from arylative oligomerisation of the tryptophan derivative.

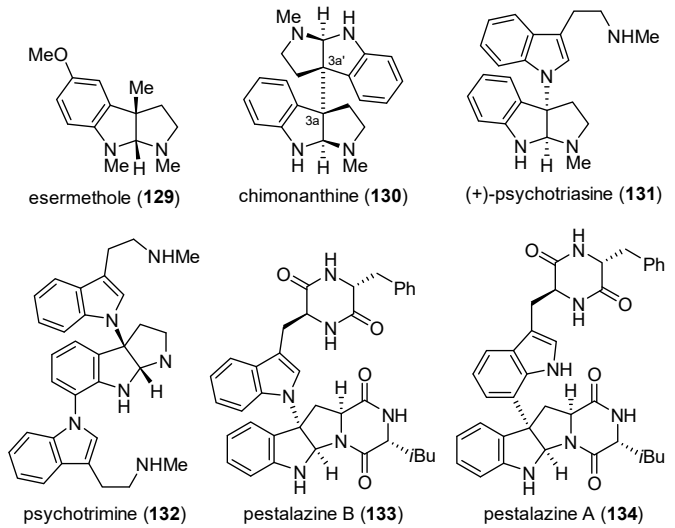
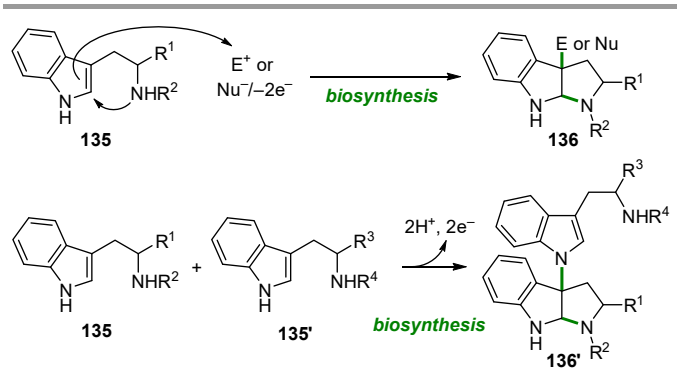


Fig. 4 Structures of pyrroloindole alkaloids.

4.1 Biosynthesis

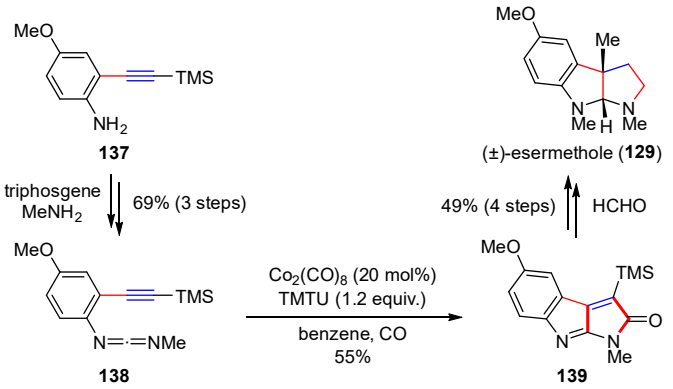
Pyrroloindole alkaloids **136** are biosynthesised through electrophilic functionalisation (E^+) or oxidative coupling with a nucleophile (Nu^-/–$2e^-$) at the indole 3 position of tryptophan derivative **135** (Scheme 26).[63] Polymeric pyrroloindole **136'** would also be produced through the oxidative coupling of two tryptophan derivatives **135** and **135'**. If aiming for the total synthesis of polymeric pyrroloindole alkaloids following the biosynthetic route, then controlling dimerisation would be key to an efficient total synthesis. Furthermore, the structural diversity of synthetic products relies on the availability of the tryptophan/tryptamine derivatives.



Scheme 26 Biosynthesis of pyrroloindole alkaloids

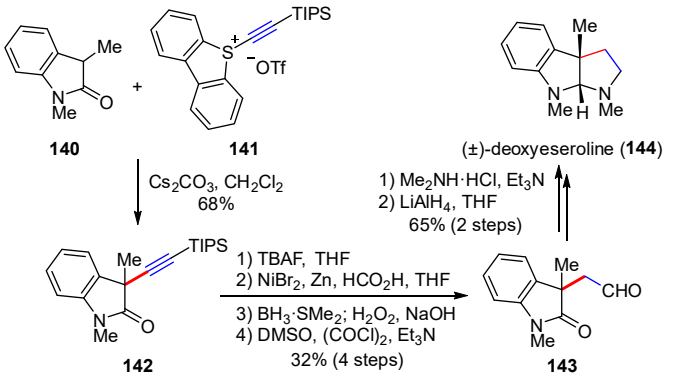
4.2 Alkyne-based synthesis of monomeric pyrroloindole alkaloids

Mukai reported the aza-Pauson–Khand reaction of alkynylcarbodiimide for the construction of the pyrroloindole scaffold (Scheme 27).[64] The cyclisation precursor **138** was prepared from alkynylaniline **137** in three steps. The $Co_2(CO)_8$-catalysed aza-Pauson–Khand reaction of **138** efficiently produced **139** in 55% yield, which was converted to (±)-esermethole (**129**) via reductive homologation with formalin and reduction.



Scheme 27 Total synthesis of esermethole by Mukai.

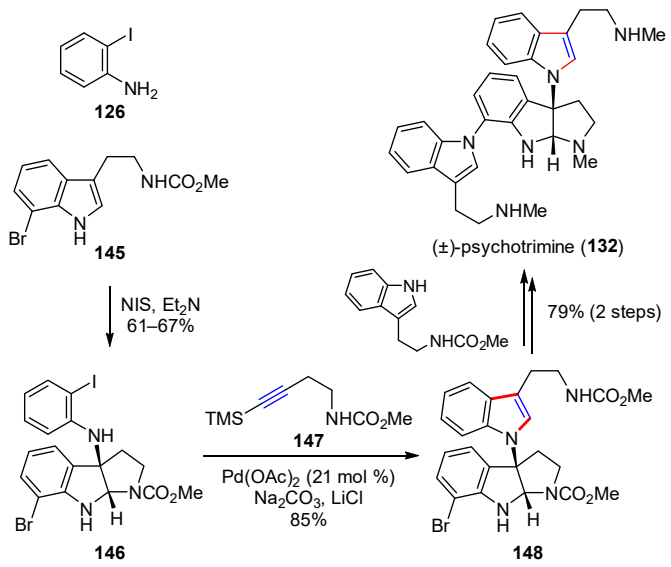
In 2020, Bisai reported total synthesis of (±)-deoxyeseroline (**144**) based on alkynylation of oxindole **140** with dibenzothiophenium salt **141** (Scheme 28).[65] The resulting alkynylated product **142** was efficiently converted to (±)-deoxyeseroline (**144**) through hydrogenation of the alkyne, hydroboration–oxidation, and introduction of the methylamine moiety. This synthesis features introduction of the C2 unit for construction of the pyrrole fusion by using the alkynylating reagent as a cation equivalent.



Scheme 28 Total synthesis of deoxyeseroline by Bisai.

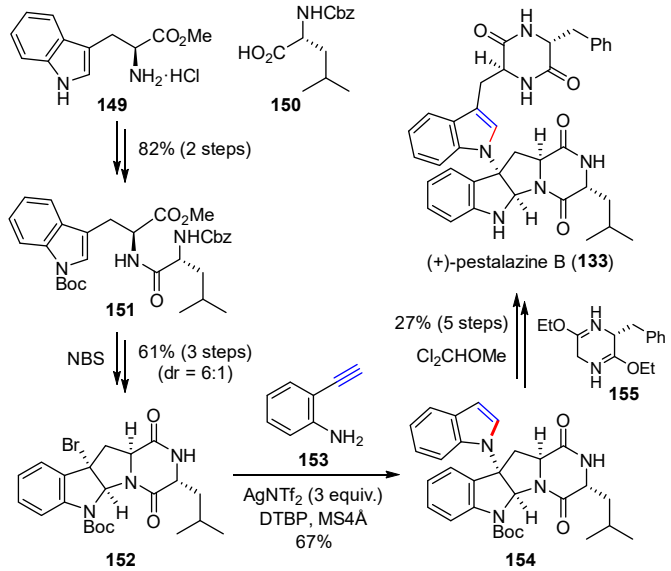
4.3 Alkyne-based synthesis of oligomeric pyrroloindole alkaloids

To synthesise oligomeric pyrroloindole alkaloids including dimeric ones, the nonbiomimetic approach is useful for controlling the oligomerisation of tryptophan units. Baran and Newhouse designed a strategy based on the oxidative coupling of iodoaniline **126** and tryptophan derivative **145**, followed by Larock indole synthesis (Scheme 29).[66] The coupling reaction was efficiently promoted by NIS to produce the desired product **146**, presumably through iodination of aniline **126**, C-3 amination of **145** and cyclisation. Larock indole formation of **146** with protected alkyne **147** afforded the bis-indole product **148**, which was converted to (±)-psychotrimine (**132**) through the Buchwald–Goldberg–Ullmann reaction to introduce the third indole moiety. This is a diversity-oriented strategy that can introduce three different indole groups.



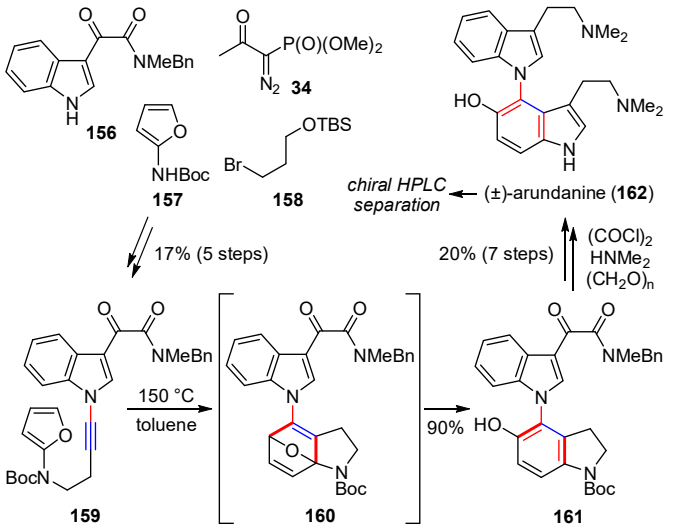
Scheme 29 Total synthesis of psychotrimine by Baran.

Recently, Tokuyama reported the total synthesis of (+)-pestalazine B (**133**) based on a related C3 amination–indole formation strategy (Scheme 30).[67] The precursor bromide **152** for the amination was prepared via condensation of the protected amino acids **149** and **150**, followed by lactam formation and NBS-mediated cyclisation. The $AgNTf_2$-mediated amination/cyclisation sequence using ethynylaniline **153** in the presence of 2,6-di-*tert*-butylpyridine (DTBP) and MS4A afforded the target coupling product **154** in 67% yield. The authors succeeded in the total synthesis of (+)-pestalazine B (**133**) through formylation using dichloromethyl methyl ether and condensation with an anionic reagent derived from imidate **155**. The nonbiomimetic synthetic strategies reported by Baran and Tokuyama have an advantage over the biosynthetic route in that each unit can be freely diversified by using different coupling partners.



Scheme 30 Total synthesis of pestalazine B by Tokuyama.

The final example in this section is the total synthesis of arundanine (**162**), a related bis-indole alkaloid not forming the pyrroloindole scaffold, reported by Beaudry in 2014 (Scheme 31).[68] The cyclisation precursor **159** was prepared through the coupling of aminofuran **157** with bromide **158**, alkyne construction using Ohira–Bestmann reagent **34**, and oxidative coupling with indole **156**. Intramolecular Diels–Alder reaction of **159** efficiently proceeded to afford indoline **161** via aromatisation of the cycloadduct **160**. Further elaborations of **161** including introduction of the aminoethyl unit using oxalyl chloride/dimethylamine and reductive methylation produced (±)-arundanine (**162**) in seven steps. It is noteworthy that they succeeded in resolution of (±)-arundanine (**162**) by chiral HPLC and determined the absolute stereochemistry (conformational chirality). This is a striking example of nonbiomimetic indole alkaloid synthesis that chemically constructs the benzene ring of an indole moiety.

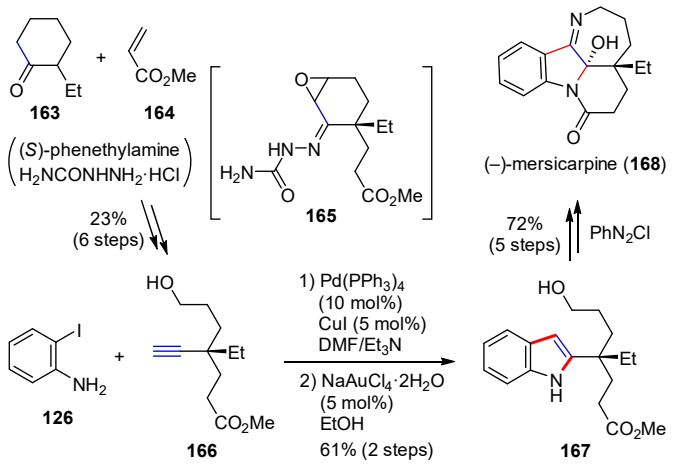


Scheme 31 Total synthesis of arundanine by Beaudry.

5. Other indole alkaloids

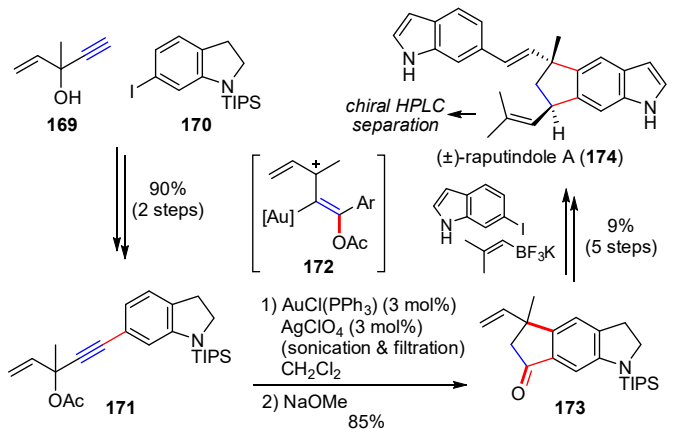
This section introduces the nonbiomimetic total syntheses of miscellaneous indole alkaloids.

Yokoshima and Fukuyama reported the total synthesis of (–)-mersicarpine (**168**) using the gold(III)-catalysed hydroamination of alkynes to produce indole derivative **167** (Scheme 32).[69] This synthesis also featured the construction of the alkyne moiety in **166** using the Eschenmoser–Tanabe fragmentation[70] of epoxy-semicarbazone **165**, prepared through the asymmetric Michael addition of **163**. The nitrogen functionality required for the total synthesis of mersicarpine was efficiently introduced to the indole 3 position of **167** by using PhN_2Cl as the nitrogen source. Lactam formation, *O*-mesylation and seven-membered ring formation via a one-pot reduction–cyclisation–oxidation sequence provided (–)-mersicarpine (**168**) in an excellent overall yield.



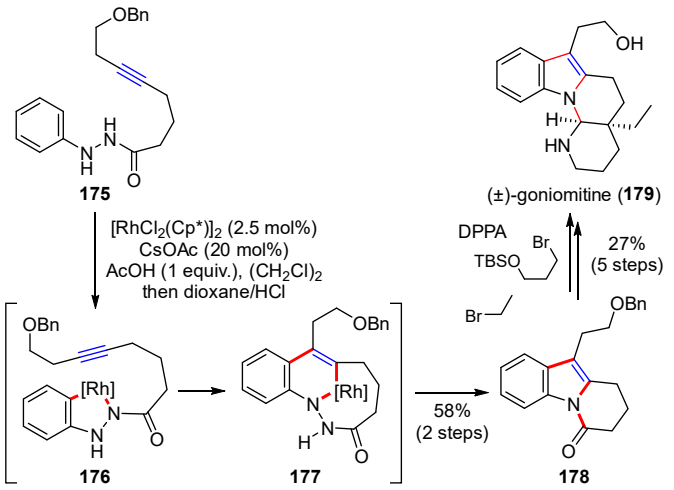
Scheme 32 Total synthesis of mersicarpine by Yokoshima/Fukuyama.

Lindel reported the total synthesis of raputindole A (**174**) using the gold(I)-catalysed hydroarylation of alkyne-derived reactive species (Scheme 33).[71a] After the gold catalyst was activated by sonication and filtration to remove silver salts, propargyl acetate **171** was successively treated with this activated catalyst and NaOMe to produce the tricyclic ketone **173**. This reaction is assumed to proceed through migration of an acetoxy group, followed by intramolecular arylation of the resulting cationic intermediate **172**. Introduction of an isobutenyl group and carbon chain elongation by the Mizoroki-Heck reaction afforded (±)-raputindole A (**174**) and its epimer. Employing an indoline derivative as a cyclisation precursor is a convenient method to protect a highly reactive indole in nonbiomimetic total synthesis. Quite recently, enantioselective total synthesis of a related natural product, dihydroraputindole D, using desymmetrisation of a diol derivative was also reported by the same group.[71b]



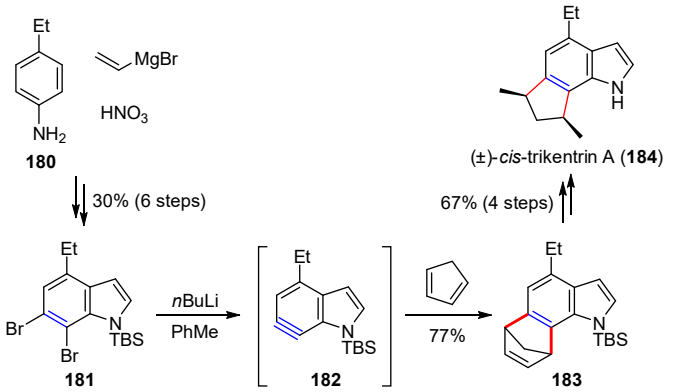
Scheme 33 Total synthesis of raputindole A by Lindel.

Zhou and Li reported the total synthesis of goniomitine (**179**) using a redox-neutral annulation of an alkyne (Scheme 34).[72] Treatment of hydrazine **175** tethered to an internal alkyne with a rhodium(III) catalyst in the presence of CsOAc and AcOH gave pyrido[1,2-*a*]indole **178** via lactam formation promoted by HCl. This key reaction can be considered as a transition-metal-catalysed redox-neutral annulation via C-H activation and is related to the Fischer indole synthesis. The pyrido[1,2-*a*]indole **178** was easily converted to (±)-goniomitine (**179**) in five steps, including a sequential α-alkylation, DPPA-mediated azidation, and *N*,*N*-acetal formation.



Scheme 34 Total synthesis of goniomitine by Zhou and Li.

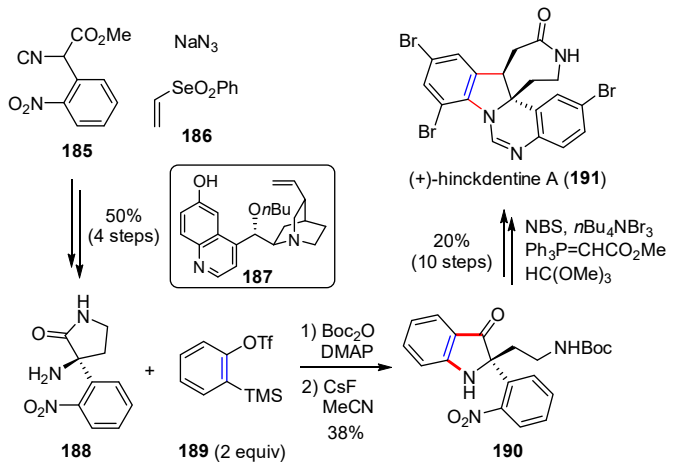
An aryne-based approach is extremely useful for the total synthesis of natural products having a polycyclic aromatic ring system,[73] including carbazole alkaloids[74] and peptide-indole hybrid alkaloids[75] (not included in this review). However, the aryne-based total synthesis of typical indole alkaloids has received limited investigation. Two examples of aryne-based total synthesis of indole-type alkaloids are introduced in this section. The first example is the total synthesis of *cis*-trikentrin A (**184**), reported by Buszek in 2009 (Scheme 35).[76] The authors successfully constructed the *cis*-dimethylcyclopentene unit via the cycloaddition of indolyne **182** (formed through the halogen-lithium exchange of dibromide **181** followed by elimination) with cyclopentadiene. Oxidative cleavage of the alkene in **183** and reduction then afforded (±)-*cis*-trikentrin A (**184**).



Scheme 35 Total synthesis of *cis*-trikentrin A by Buszek.

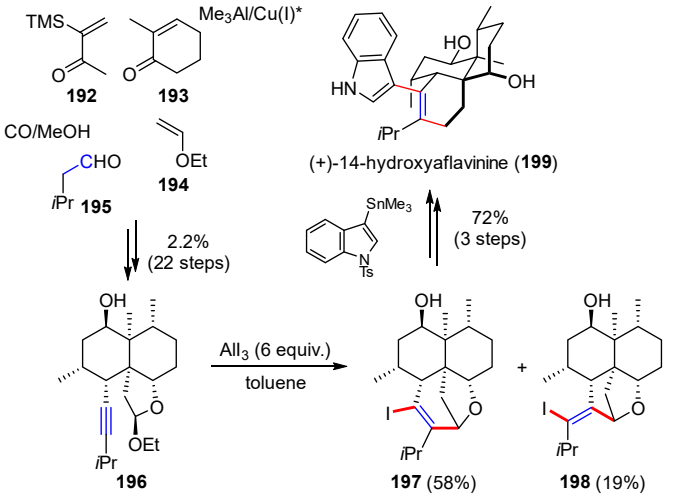
The second example of an aryne-based strategy is Zhu's total synthesis of hinckdentine A (**191**) based on the carboamination of benzyne (Scheme 36).[77] 3-Aminopyrrolidin-2-one **188** was prepared in four steps from α-isocyanoacetate

185, including the asymmetric Michael addition to vinyl selenone **186** using a quinidine-derived bifunctional catalyst **187**. The reaction of **188** with benzyne derived from triflate **189** furnished indolin-3-one **190** in moderate yield. A further ten-step conversion, including amidine formation, seven-membered ring lactam formation and bromination, accomplished the asymmetric total synthesis of (+)-hinckdentine A (**191**). Other arynes such as indolyne are also useful for the total synthesis of marine alkaloids.[78]



Scheme 36 Total synthesis of hinckdentine A by Zhu.

The final example is Li's total synthesis of 14-hydroxyaflavinine (**199**) based on Prins cyclisation of an alkyne (Scheme 37).[79] The substrate **196** was prepared from **193** in 22 steps through asymmetric 1,4-addition using Me_3Al, followed by annulation with Ganem reagent **192**, oxidation and acetal formation with **194**, and alkyne construction using isovaleraldehyde **195**. The Prins-type cyclisation of **196** was successfully promoted by AlI_3 in toluene to give the desired tetracyclic product **197** (58%) and its regioisomer **198** (19%) in good combined yield. A further three-step sequence, including a cross-coupling reaction with an indolyl stannane and reductive C-O bond cleavage, gave (+)-14-hydroxyaflavinine (**199**). This is a striking example of a nonbiomimetic total synthesis where an alkyne undergoes carbocyclisation to construct a vinyl iodide moiety, which is useful for further elaborations.



Scheme 37 Total synthesis of 14-hydroxyaflavinine by Li.

Conclusions

The use of alkyne-based reactions to construct natural product core structures is a synthetic strategy that is far different from biosynthesis because alkyne chemistry is not often found in nature. Alkyne reactions such as hydroamination, hydroarylation, the addition of carbanion equivalents, carboamination and cycloaddition provide powerful nonbiomimetic approaches to construct the core structures of ergot alkaloids, monoterpene indole alkaloids and pyrroloindole alkaloids. Notably, the most total syntheses of aspidosperma and strychnos alkaloids are similar to the biosynthesis even using alkyne-based strategy, because the structure of these natural products is highly suitable for biosynthesis.

The structures and biosyntheses of natural products are the result of evolutionary selection, which can be thought of as compound screening in nature. However, we believe that nonbiomimetic natural product synthesis offers an important option to produce new, useful pseudo/supernatural products that are not naturally accessible, leading to the acceleration of natural product-based drug discovery in combination with biology-oriented synthesis (BIOS).[80]

Conflicts of interest

There are no conflicts to declare.

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