Total Synthesis of *Aspidosperma* and *Strychnos* Alkaloids through Indole Dearomatization

Jordy M. Saya, Eelco Ruijter,* and Romano V. A. Orru*[a]


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Abstract: Monoterpenoid indole alkaloids are the major class of tryptamine-derived alkaloids found in nature. Together with their structural complexity, this has attracted great interest from synthetic organic chemists. In this Review, the syntheses of Aspidosperma and Strychnos alkaloids through dearomatization of indoles are discussed.

1. Introduction

Tryptamine (1) is a frequently appearing building block in nature’s repertoire. It is biosynthetically derived from decarboxylation of the essential amino acid tryptophan. With this fairly simple component, evolutionary process afforded a rich palette of complex alkaloids in which the tryptamine backbone is sometimes difficult to identify. Monoterpenoid indole alkaloids represent the largest class of tryptamine-derived alkaloids, with over 3000 examples reported in the literature.[1] Next to tryptamine, the residual carbon backbone of these natural products is supplied by secologanin (2). This monoterpenoid is part of the secoiridoids class, which show interesting bioactivity (e.g., anticancer, antimicrobial, and anti-inflammatory) and are known pheromones.[2]

In monoterpenoid indole alkaloid biosynthesis, the first step involves an enzyme-catalyzed Pictet–Spengler reaction to connect both fragments (Scheme 1). The resulting strictosidine (3) is a common intermediate in the biosynthesis of all monoterpenoid indole alkaloids, which we categorized into four classes based on structural differences. The first class are the Corynanthe type alkaloids (e.g., 19E-geissoschizine, 4) resulting from deglucosylation and subsequent condensation between the aldehyde and amine. The Strychnos type alkaloids (e.g., akuammicine, 8) are the second class and have been appealing targets for synthetic chemists ever since Woodward’s pioneering total synthesis of strychnine.[3] In the biosynthesis, after a few transformations of cathenamine (4) the indole C3 position is selectively oxidized, facilitating a cascade of chemical transformations consisting of a Mannich reaction, indole rearomatization and a Pictet–Spengler-type cyclization. The resulting Strychnos core structure then undergoes a series of redox reactions, rearrangements and fragmentations to end at achiral triene 11. This is the common precursor of the third and fourth classes, the Aspidosperma (e.g., tabersonine, 12) and Iboga type (e.g., catharantine, 13) alkaloids. Both classes are proposed to be formed through a biocatalytic Diels–Alder-type cyclization through different pairings of the two dienes.[4]

A wide range of synthetic procedures have been reported over roughly the 70 years that have passed since Woodward et al. initiated the field of complex natural product synthesis—and in particular monoterpenoid indole alkaloid synthesis. Even so, these complex tryptamine-derived natural products are still vividly present in the minds of organic chemists as demonstrated by the frequently appearance of new synthetic strategies in the literature. In this review, we present a comprehensive overview of all total syntheses of Aspidosperma and Strychnos alkaloids that follow a dearomatization strategy over the last 65 years.

The similar pentacyclic carbon skeleton (14) of Aspidosperma and Strychnos alkaloids often makes them accessible through similar strategies.[5] Based on the type of chemical transformations and retrosynthetic disconnections, the literature exam-
ples are organized into four main categories (Scheme 2): 1) dearmative ring contractions of β-carbolines, 2) electrophilic aromatic additions, 3) cycloadditions, and 4) C-ring formation. We primarily discuss the dearmative strategies used and will not focus on an in-depth discussion of the entire synthetic route.

2. Dearmative Ring Contractions of β-Carbolines

As mentioned above, the common biosynthetic intermediate for most monoterpenoid indole alkaloids is the β-carboline strictosidine (3). Many organic chemists have been inspired to mimic nature’s strategy to convert the β-carboline structure to the spiroindoline backbone of Aspidosperma and Strychnos alkaloids (Scheme 3). Harley-Mason and co-workers have been the first to achieve this biomimetic synthetic transformation.[9] By treatment of β-carboline 20 with BF₃·OEt₂ at 100–110 °C, the indole C2 position attacks the activated double bond, after which it rearranges to the pentacyclic framework 21. The slightly modified β-carboline 22 was converted through a similar reaction pathway to the Aspidosperma-type alkaloid 25.[7] Then, lithium aluminium hydride reduction gave (±)-aspidospermidine (26) in three steps from tryptamine in 20–25% overall yield.

To translate Harley-Mason’s approach into an asymmetric process, Fuji et al. started from enantoienriched 27 (85% ee).[9] The Pictet–Spengler reaction in this case gave β-carboline 22 as a mixture of two diastereomers that could be separated by column chromatography to afford optically pure β-carboline 22. In their hands, the BF₃·OEt₂ induced dearmatization reported by Harley-Mason proceeded in low yields. Switching to triflic acid gave the pentacyle 25 in 60% yield, representing the first asymmetric synthesis of the pentacyclic backbone of Aspidosperma-type alkaloids. Other groups have reported alternative routes towards similar scaffolds.[9]

In a similar cascade cyclization, Takano et al. have employed diazo compounds 27 to obtain ketones 28a and 28b, albeit in only modest yield.[10] Furthermore, Langlois et al. have employed sulfoxides 30 in efficient Pummerer-type cyclizations to afford the pentacyclic 31a and 31b, which acted as intermediates in the total syntheses of (±)-vindorosine (32) and (±)-vin-doline (33), respectively.[11]

In a complementary bioinspired route, Kuehne et al. have applied the indole C3 chlorination of β-carboline 34 with tert-butyl hypochlorite (Scheme 4).[12] They cleverly used existing knowledge of the biosynthesis (i.e., an intramolecular Mannich reaction) by treating 3-chloroindolinene 35 with thallium diethyl malonate in benzene heated to reflux to form spiroindoline 37 in 47% yield. Massiot et al. have extended this procedure to the use of tethered malonate 38, resulting in the formation of tetracycle 42.[13] After chlorination the 1:1 mixture of diastereomers could be separated. Interestingly, only the cis diastereoisomer of 39 underwent the desired rearrangement. It is likely that the chloride needs to be trans with respect to the migrating moiety, as the 1,2-syn migration occurs through an S₉₂-type mechanism. After the rearrangement, a Krapcho de-carboryation mediated by the liberated NaCl occurs under the...
reaction conditions to afford tetracycle 43. Martin et al. later have translated this strategy into a remarkable biomimetic synthesis of (±)-akuammicine starting from 43. Also in this procedure, only one diastereoisomer of the 3-chloroindolenine intermediate was susceptible to spirocyclization.

3. Electrophilic Aromatic Additions

3.1. Pictet–Spengler-type cyclizations with C2 substituents

In the early days of natural product synthesis, Woodward et al. have been the first to tackle a complex indole monoterpenoid alkaloid, that is, strychnine (48). The structure of strychnine had been elucidated after more than 100 years of extensive spectroscopic and synthetic studies following the first isolation in 1818. It is amazing to see how the total synthesis of strychnine was completed in 1954 with such limited resources, which certainly contributed to Woodward winning the Nobel Prize in Chemistry in 1965. One of the first steps in the strategy was indole dearomatization by Pictet–Spengler reaction of tryptamine 45 and ethyl glyoxalate (Scheme 5). To facilitate the Pictet–Spengler cyclization, the imine was activated by tosyl chloride making it sufficiently electrophilic for nucleophilic attack of the indole C3 position. After constructing the core spiroindoline ring system (47), Woodward et al. completed the synthesis of (±)-strychnine in a total of 28 steps with 0.00006% overall yield.

Important biosynthetic insights of Wenkert, who was interested in uncovering the relationship of structurally related indole alkaloids, were corroborated by his group in the total synthesis of (±)-strychnine by Woodward et al. through a dearomative Pictet–Spengler reaction.
synthesis of the pentacyclic core of Aspidosperma and Strychnos alkaloids (Scheme 6).\textsuperscript{16} Wenkert’s strategy took advantage of tetrahydropyridines 49 as substrates for key Pictet–Spengler type spirocyclizations. The dearomative cyclization of 49a in hydrobromic acid was successful, but required reduction of the resulting imine to obtain spiroindoline 51a as a stable product in fairly low yield (14%). Using the ester analogue 49b the spirocyclization afforded enamine 51b as a stable product, but cyclization to form the desired pentacyclic core proved elusive. It took almost half a century to elaborate this rather elegant strategy to a pentacyclic product, when Pandey et al. completed the cascade cyclization to directly obtain (±)-vincadifformine (55) as a single optical isomer.\textsuperscript{17} By mixing optically pure tetrahydropyridine 53 (> 99% ee) and indole 52 in DMF at 135–140 °C, the resulting iminium ion (similar to 50) 54a undergoes a similar Pictet–Spengler reaction followed by a second cyclization. By performing the reaction at lower temperature (90 °C), diastereoisomers 54a and 54b can be observed, however, it remains unclear whether only 54a or both isomers are converted to the natural product (55). Similarly, Takano et al. have demonstrated that intramolecular condensation of tricycle 58 gives tetracyclic ketones 29.\textsuperscript{18} In a mixture of acetic acid and acetic anhydride (2:3) tryptamines 56 undergo acyl iminium ion formation and subsequent Pictet–Spengler cyclization to give 58, after which an intramolecular Claisen condensation affords ketones 29a–c in 45–52% yield. In Wenkert’s approach, plausibly the D-ring prevents effective Claisen condensation as a result of poor orbital overlap between the enamine and the ester moieties.

Rather than condensation of aldehydes and tryptamines to generate the iminium ion, Schumann and Schmid have used platinum(IV) oxide catalyzed oxidation of 59 to obtain a mixture of (±)-tubifoline (61) and (±)-condyfoline (62, Scheme 7).\textsuperscript{18} The regioselectivity is directed by steric repulsion of the ethyl substituent with the oxidant, favoring 60a over 60b. Alternatively, Kutney et al. have found that dihydrocleavamine (64) could be oxidized with mercuric acetate in acetic acid.\textsuperscript{19} Subsequent reduction of spirowindoline 65 afforded pseudoaspidospermidine (66) in 30% yield over two steps. The authors have used the same strategy for the synthesis of a series of Aspidosperma type alkaloids.\textsuperscript{20} Moreover, Magnus et al. have applied this oxidation/Pictet–Spengler cyclization approach in the second total synthesis of (±)-strychnine, almost 40 years after Woodward’s synthesis.\textsuperscript{21} As in the oxidation of 59, a mixture of isomeric oxidation products formed

\begin{equation}
\text{Scheme 6. Pictet–Spengler approaches of preformed imines/enamines (Wenkert, Pandey and Takano et al.).}
\end{equation}
upon treatment of 71 with mercuric acetate in acetic acid, however, the undesired minor isomer formed in undefined small amounts.

Instead of using a carbon substituent at the indole C2 position, Ban et al. have chosen to use 2-hydroxytryptamine (Scheme 8).[22] Considering the alkaline reaction conditions, these Pictet–Spengler reactions are complementary to the conventional quite acidic conditions. Although 75 is obtained as a diastereomeric mixture, both isomers react in the ensuing condensation to afford the tetracyclic indoline 29c. The authors demonstrated the synthetic utility of this strategy by synthesizing a large series of Aspidosperma-type alkaloids.[23] Later, Okada et al. have shown that this strategy can be used in an asymmetric approach.[24]

Ban et al. have also developed a reduction strategy to the Aspidosperma alkaloid core (Scheme 9).[25] Tetracyclic lactam 84 was first selectively reduced to hemiaminal 85. Next, treatment with hydrochloric acid removed the THP group and triggered the dearomatization step in a transannular Pictet–Spengler reaction towards 1,2-dehydroaspidospermidine (86) in 48% yield over two steps.

Not long after Magnus' total synthesis, Kuehne et al. have presented their Pictet–Spengler approach towards strychnine (Scheme 10).[26] Tryptamine derivative 89a and aldehyde 90 were activated by BF₃·OEt₂ as the Lewis acid catalyst in toluene heated to reflux. After a first Pictet–Spengler reaction, the resulting enamine undergoes a [3,3]-sigmatropic rearrangement to rearomatized 92. This tricyclic ring system can now undergo a transannular Pictet–Spengler reaction to afford tetracycle 94a in 51% yield after acetal deprotection. Kuehne et al. used their approach for an asymmetric synthesis of (-)-strychnine by starting from tryptophan derived 89b.[27] The chiral pool derived stereogenic center completely controls this diastereoselective cascade process. The ester could afterwards be removed by conversion to the nitrile, followed by α-aminonitrile reduction.

In an alternative approach, Bonjoch et al. have envisioned a double ring closure of tricyclic 96a through a transannular
Pictet–Spengler reaction to obtain deethylbophyllidine (97; Scheme 11). In a direct approach, the tricyclic 95 should undergo a series of chemical transformations, including deprotection, conversion of the nitrile to the methyl ester, and a Pictet–Spengler reaction. The double cyclization was successful, however, in the process the nitrile was partially converted to the imidate affording a mixture of the natural product 97 and its imidate analogue 98 (1:1) in 60% overall yield. In a subsequent less convergent approach, 99 was treated with a large excess of trifluoroacetic acid (TFA) in toluene under reflux conditions to afford known intermediate 100 in 90% yield. Surprisingly, introduction of the carbamate did not hamper nucleophilic attack of the indole C3 position. Fukuyama et al. have used a similar concept in their asymmetric total synthesis strategies. By incorporating an element of chirality in enantioenriched 101 and 104, the Pictet–Spengler cyclization can proceed with complete diastereoselectivity. The authors applied this strategy in the total synthesis of (−)-aspidophytine (103) and (−)-strychnine.

3.2. Pictet–Spengler-type cyclizations followed by trapping of the iminium intermediate

It is important to note that Pictet–Spengler reactions of C2-substituted indoles cannot be concluded with the conventional rearomatization step. Contrarily, in Pictet–Spengler reactions of indoles lacking the C2-substituent it is difficult to maintain the deaminated indolene structure. Van Tamelen et al. have been able to interrupt the Pictet–Spengler reaction by trapping the generated iminium ion by intramolecular nucleophilic addition (Scheme 12). Treatment of dialdehyde 106 with sodium acetate in acetic acid triggers a cascade towards pentacyclic core 109, starting with a condensation reaction between one aldehyde and the amide. Then, the resulting acyliminium intermediate undergoes a Pictet–Spengler reaction and a final Mannich-type cyclization. Although the authors did not complete the total synthesis of a Strychnos type alkaloid in this or later studies, this strategy represents an inspiring concept for other syntheses.

In 1971, Büchi et al. have reported an elegant Pictet–Spengler/Mannich cascade approach (which may also be considered as a formal [4+2] cycloaddition). Initial attempts with the enamine derived from a condensation reaction of N1-methyl tryptamine and 3-oxobutanal were unsuccessful. However, reaction of the acetylated analogue 110a in BF₃·OEt₂ at 90°C afforded tetracyclic indoline 111a (38%) and β-carboline 112a (20%; Scheme 13). Electron-withdrawing substituents on the indole core favored the formation of tetracyclic indoline 111, whereas electron-donating substituents favored β-carboline formation (112). The authors applied 111a (also referred to in the literature as Büchi’s ketone) in the synthesis of (−)-vindorosine and (±)-vindoline. Winkler et al. developed an asymmetric approach to ketone 111a through an intramolecular photocycloaddition reaction of 113 by using optically pure tryptophan as the source of chirality. Unlike the Lewis acid-catalyzed process, an initial [2+2]-photocycloaddition is followed by a retro-Mannich fragmentation. As a result of the bulky OBO orthoester (OBO = 4-methyl-2,6,7-trioxa-bicyclo[2.2.2]octan-1-yl), photocyclization product 115 is formed as a single diastereomer in 91% yield. To subsequently access...
Büchi’s ketone (±)-111a, the authors performed a Mannich cyclization, followed by fragmentation of the OBO ester.

In continuation of his earlier Pictet–Spengler approach with tetrahydropyridines 49, Wenkert has developed a similar strategy based on this Pictet–Spengler/Mannich sequence resulting in pentacycle 117 (Scheme 14).[35] In this study, tetrahydropyridines 116 were rapidly converted by using BF₃·OEt₂ or polyphosphoric acid at 100 °C to obtain diastereomeric mixtures of 117. Although they are not formed selectively, 117a-1c have been employed in the synthesis of several indoline alkaloids.

An elegant approach using an aza-Sakurai reaction to install the spiroindoline structure has been reported by the group of Corey (Scheme 15).[36] The required rather complex dialdehyde 122 was obtained optically enriched (97% ee) and reacted with tryptamine derivative 121. In the presence of triflic anhydride in acetonitrile the double condensation delivers dihydropyridinium 123. This intermediate undergoes a Pictet–Spengler/aza-Sakurai cascade to form iminium ion 126, which was reduced in situ by addition of NaBH₄CN. The product 127, containing essentially the entire framework of (±)-aspidophytine, was isolated as a single diastereoisomer in 66% yield. Later, this Pictet–Spengler/aza-Sakurai cascade has been employed by Blakey and co-workers in the synthesis of tetracyclic indolines 129.[37] Interestingly, the structure contained a trans-ring junction, rarely seen in indole alkaloids, and was applied in the total synthesis of (±)-malagashanine (Blakey et al.).
The age of this method is the poor diastereoselectivity. Even in the intramolecular strategy, the reaction was only moderately diastereoselective (about 3:2) in favor of the desired diastereisomer. Similarly, Tang and co-workers have developed an intramolecular annulation of malonate-derived donor-acceptor cyclobutanes (135). The authors achieved mild activation by CuII catalysis in good diastereoselectivity. Advantageously, indoline 136, which was their building block for the total synthesis of (±)-akammicine, was formed as a single diastereoisomer in 50% yield. Prior to their endeavor in the donor–acceptor cyclobutane strategy, Tang and co-workers have described a formal [2+2+2]-cycloaddition approach towards tetracyclic indolines 140. Starting from tosyl enamines 137, an intermolecular conjugate addition to methylene malonate 138 occurs. This generates iminium ion 139, which undergoes a double cyclization to give tetracyclic 140 (i.e., the ring system contained a trans-ring junction like 129). The authors explored a broad range of core substituents on the indole ring, generally obtaining the indoline products with high diastereoselectivity. This method was applied in the total synthesis of (±)-11-de-methoxy-16-epi-myrtoidine (141).

3.3. Interrupted Bischler–Napieralski-type reaction

Considering that the Bischler–Napieralski reaction is mechanistically analogous to the Pictet–Spengler reaction, it is not surprising that this reaction also found application in the synthesis of monoterpene indole alkaloids. Jackson et al. were the first to study the feasibility of such a strategy (Scheme 17). Initially, they established an interrupted Bischler–Napieralski reaction for the conversion of melatonin \[142\]; trifluoroacetic anhydride (TFAA), benzene, 5 °C to spiroindoline 143 in 70% yield. A few years later, this method has been used in the synthesis of pentacyclic skeleton 145, which was achieved in 51% yield from lactam 144. Remarkably, only pentacyclic 145 was isolated even though 10 equivalents of trifluoroacetic anhydride were used. Although Jackson et al. constructed basically the entire carbon skeleton of the Aspidosperma alkaloids, no application in monoterpene indole alkaloid total synthesis was reported.

Magnus et al. have recognized the potential of this Bischler–Napieralski strategy and applied it in the total synthesis of...
Kopsia alkaloids. In their approach, starting from 11-membered ring system 146, activation of the carbamate triggers an interrupted Bischler-Napieralski cyclization. After this a vinylous enamine adduct to the resulting imidate gave pentacyclic dienes 149. After the conversion to iminium ions 149 was complete, a Streeker reaction by in situ treatment with trimethylsilyl cyanide (TMSCN) results in the formation of amino-nitriles 150. This manipulation was necessary because the hemiaminal proved unstable (i.e., hydrolysis of 149) under the subsequent Diels–Alder reaction conditions. The nitrile function in 150 was readily removed by AgBF₄-mediated retro-Strecker reaction to set the stage for the final reaction sequence towards the Kopsia alkaloids 151–153.

Under similar Bischler–Napieralski conditions, Movassaghi and co-workers have reported a double cyclization strategy using lactam 154 (Scheme 18). Enantioenriched starting material was obtained in 94%ee, through a chiral auxiliary-based approach. Treatment of lactam 154 with triflic anhydride and 3-cyanopyridine in acetonitrile under reflux temperature, afforded bisiminium ion 157 as a single diastereoisomer. Although the authors did not further comment on this diastereoselectivity, it may either arise from the instability of the other diastereoisomer or by epimerization to the more stable diastereoisomer via a reamination/deamination mechanism. Bisiminium ion 157 could either be completely reduced to aspidospermidine-type product 159 (50 %) or hydrolyzed to 9-membered lactam 158 (57 %). Alternatively, the lactam 158 could be more efficiently converted to 159 in 95% yield. Then 158 and aspidospermidine-type framework 159 were dimerized through the above method to obtain (+)-dideepoxytabernaemobine (161).

Later, this concept has been exploited for the asymmetric synthesis of a range of Aspidosperma-type natural products (Scheme 19). For this, either chiral pool starting material, biocatalytic kinetic resolution or enantioselective ring-closing metathesis (RCM) mediated desymmetrization was employed to access enantioenriched lactam 162 as starting material.

A related approach relies on isocyanides derived from tryptamines, which have recently been reported to efficiently provide spiroindoline products. Ji et al. were the first to recognize the potential of these tryptamine-derived isocyanides 173 in 1,4-addition/spirocyclization cascade reactions (Scheme 20). After in situ condensation of aldehydes with malonitrile, a nucleophilic addition of isocyanide generates nitrilium ion 174. Like the interrupted Bischler–Napieralski reaction of 144, this intermediate is trapped by a Mannich-type cyclization to afford tetracycles 176. In addition to Michael acceptors, other electrophiles proved suitable in similar cascade processes. We have reported N-iodosuccinimide (NIS) as a compatible electrophile in iodospirocyclization reactions. The resulting products, especially regarding the imidoyli odide moiety, are remarkably flexible and can undergo a range of post cyclization modifications. For example, treatment of isocyanide 177 with NIS efficiently gave spiroindolenine 178, which could be reduced in situ towards indoline 179 with complete diastereoselectivity. This spirocyclic product was used in a formal total synthesis of (+)-aspidofractinine (80).

![Scheme 18. Interrupted Bischler–Napieralski cyclizations in the synthesis of (+)-dideepoxytabernaemobine (Movassaghi et al.).](image)

![Scheme 19. Continuations of the Interrupted Bischler–Napieralski cyclizations of Movassaghi et al. in the synthesis of Aspidosperma-type alkaloids. DABCO = 1,4-diazobicyclo[2.2.2]octane.](image)
4. Cycloadditions

4.1. Normal electron-demand Diels–Alder reactions

The Aspidosperma-type alkaloids biosynthetically originate from an enzyme-catalyzed [4+2]-cycloaddition of stemmadenine acetate (9). This has been first established by Scott and co-workers in 1968 in several studies on stemmadenine and analogues. After serious criticism by Smith and Poisson on the reproducibility of these results, Scott et al. have countered by a series of communications which clarified the controversy on the experimental data (Scheme 21).

Upon platinum-catalyzed oxidation of 180 to 19,20-dihydroprekammicine acetate (181), followed by methanolysis (4 h, room temperature), a 9:1 diastereomeric mixture of 185a and 185b was obtained in 3.5% yield. They believed that this reaction proceeds via rearomatization of the indole, followed by a retro-Mannich reaction to form iminium 183. After 1,4-addition of methanol, the enamine undergoes a formal [4+2]-cycloaddition resulting in a diastereomeric mixture of pseudotabersonine analogues. Through the same mechanism, thermolysis of 183 on silica at 150 °C for 20 minutes afforded (±)-pseudotabersonine (187) in 5% yield. Thermolysis studies of 189 gave in a similar way both (±)-tabersonine (0.2% yield) and its reduced analogue (±)-vincadifformine (0.2% yield), presumably via the corresponding trienes 11 and 190. Conclusive evidence for a biosynthetic Diels–Alder pathway and the existence of achiral trienes was obtained when stemmadenine acetate 9 was hydroxylated [Pt, H₂ (1 bar) in EtOH] to reduced product 191 in 75% yield. Despite the low yields, the efforts of Scott et al. were extremely valuable in understanding the biosynthesis of Aspidosperma alkaloids, and additionally have laid the foundation for multiple synthetic strategies later on.

Scheme 20. Tryptamine-derived isocyanides in dearomatization strategies towards spiroindolines (Ji and Orru/Ruijter et al.).

Scheme 21. Biomimetic studies by Scott et al. in finding proof of the biosynthetic [4+2]-cycloaddition (Diels–Alder reaction) towards Aspidosperma alkaloids.

Already a few years later, based on the biosynthesis proposed by Scott et al., the group of Kuehne has cleverly devised a plan based on in situ generation of triene 190 (Scheme 22). From condensation of azepine 192 with bromoaldehyde 193, spiroenammonium salt 194 was found to be converted to vincadifformine (55) in 70% yield. The authors postulated that E1cB elimination of ammonium salt 194 leads to triene 190, which immediately undergoes an intramolecular Diels–Alder reaction. Impressive follow-up work has resulted in a better understanding of the reactivity of the spiroenammonium salts and their fragmentations to Diels–Alder reaction substrates, which provided several synthetic strategies to construct a diverse set of Aspidosperma and Strychnos alkaloids.

Based on the above, the authors also developed an enantioselective pathway using ferrocenylalkyl chiral auxiliaries. This typically resulted in a 5:1 mixture of diastereoisomers, which could be separated by silica gel chromatography. A more selective approach based on chiral sulfonamide 208 has been successfully applied by Fukuyama and co-workers in...
the asymmetric total synthesis of (−)-vindoline and (+)-vinblas- 
tine (Scheme 23).35 After the inspiring work by the group of 
Kuehne, other syntheses have been developed that convert tri- 
ynes similar to 190.35c Even quite recently, this biomimetic 
strategy has been again exploited by Oguri and co-workers (in 
2014)35d and Dixon and co-workers (in 2016).35e Although 
most indole deoxygenation strategies towards the Aspido- 
sperma or Strychnos alkaloids are in general not enantioselec-
tive, MacMillan and co-workers have been the first to develop 
an catalytic asymmetric deoxygenation approach (Scheme 24).35f 
As one of the pioneers of asymmetric organo-
catalysis, they used this expertise in the asymmetric total syn-
thesis of six indole alkaloids, hence developing arguably the 
most elegant approach towards the Aspidosperma and Sty-
chnos backbone in both efficiency and selectivity. Their synthetic 
plan was based on the cleverly designed 2-vinyltryptamine 
213 as a diene in Diels–Alder reactions. When treated with pro-
pynal in the presence of imidazolidinone catalyst 217, a 
domino process provides tetracyclic indoles 216 which serve as 
common intermediates in several natural product syntheses 
as depicted in Scheme 24. In the formal [4+2]-cycloaddition, 
the chiral information of the organocatalyst is transferred to 
the spiroindoline center. This is followed by diastereoselective 
conjugate addition and β-elimination of methyl selenol. In a 
later communication, MacMillan and co-workers have extended 
their methodology to the total synthesis of (−)-minovincine 
(204) by simply exchanging propynal for 3-butyn-2-one.35g 
The selectivity was slightly lower (i.e., 91% ee compared to 
97% ee) and required small changes in the reaction conditions. 
Other groups recognized that the formal [4+2]-cycloaddition 
can alternatively be considered as a conjugate addition/Mann-
ich cyclization process. As a result, several catalytic asymmetric 
conjugate additions of C2-substituted tryptamines to prop-
argyl aldehydes and ketones have been developed.35h 

As an alternative to the biomimetic Diels–Alder approach, 
Kraus et al. have developed an intramolecular [4+2]-cycloaddi-
tion (Scheme 25).35i Diels–Alder substrate 223 was obtained ef-

ciently from 3-acetylindole, by first tethering the dienophile 
followed by conversion of ketone 222 to silyl enol ether 223. 
Due to the relatively electron-rich dienophile in the normal 
electron-demand Diels–Alder cyclization, heating to 275 °C for 
48 hours was required to achieve full conversion. Although 
these harsh conditions could potentially initiate several side re-
actions, the product 224 was isolated in a moderate 50% 
yield. This tetracycle was applied in their model synthesis of 
hexacyclic indoline 225, which contains nearly the full back-
bone of strychnine. Recently, based on the strategy of Kraus 
et al., Nishida and co-workers have developed an intermolecu-
lar enantioselective Diels–Alder approach catalyzed by a chiral 
holmium complex.35j By employing electron-deficient acryloyl 
oxazolidinones 227 as the dienophile, a reduced HOMO–LUMO 
gap allowed for much milder reaction conditions (i.e., −20 to 
0 °C in < 2 hours). Tricyclic indolines 228 were obtained in

Scheme 22. Biomimetic approaches of Kuehne et al. through [4+2]-cycload-
dition towards Aspidosperma and Strychnos alkaloids.

Scheme 23. An asymmetric alternative by Fukuyama and co-workers based 
on the biosynthetic [4+2]-cycloaddition to Aspidosperma alkaloids.
good yields (86–99 %) and with high ee (up to 94 %). This catalytic enantioselective approach was applied in the total synthesis of \((-\text{minovincine})\).

4.2. Indole as the dienophile/dipolarophile

The 4+2 connectivity described in the previous section has resulted in the synthesis of several monoterpene indole alkaloids. An interesting alternative to these approaches has been provided by Padwa et al., who introduced a 1,3-dipolar cycloaddition to promote indole dearomatization (Scheme 26).

Based on earlier findings in generating mesoionic oxazolium ylides in situ under Rh\(^{1+}\) catalysis, they designed 230 as a suitable substrate for intramolecular 1,3-dipolar cycloaddition to give pentacyclic indoline 232. Initially, the rhodium catalyst is converted to the rhodium carbenoid which is subsequently trapped by the imide carbonyl to form oxazolium ylide 231. This 1,3-dipolar intermediate is sufficiently reactive under the reaction conditions (50 °C in benzene) to give full conversion in 3 hours, affording the product as a single diastereoisomer in 90% yield.
Using this method, the authors synthesized (±)-aspidophytine as well as several natural product analogues. Notably, the quite obvious possibility of using an enantioenriched starting material in the cyclization cascade to achieve an asymmetric approach has not been reported thus far.

In continuation of this Rh(I)-catalyzed 1,3-dipolar cycloaddition, Padwa et al. have moved to 2-aminofuran 233 in the synthesis of tetracyclic backbone 236. This involves the de aromatization of two aromatic ring systems under elevated temperatures (i.e., 200 °C in toluene, sealed tube) in an inverse electron-demand Diels–Alder reaction. In contrast to most indole de aromatization strategies, an electron-withdrawing group on the indole N1 position was required to promote the reaction. After the cycloaddition, the C–O bond of the N,O-acetal fragments to form indoline 236. This methodology was applied in the synthesis of (±)-strychnine, in which O-methylbenzyl substituted 233 was utilized in the presence of MgI₂. The authors did not include any additional details on how they developed this catalyst and furthermore do not comment on the necessity of MgI₂ or any alternative catalyst in other communications.

In 2001, just before Padwa et al. demonstrated the cycloaddition of 2-aminofuran tethered indoles, Bodwell and Li had already demonstrated an inverse electron-demand Diels–Alder approach. By tethering pyridazines to indoles (237), they ingeniously made use of the electron deficiency of pyridazines (Scheme 27). Following the cycloaddition, release of N₂ generates pentacycle 239. With 237a (X = CH₃), the authors found that both reaction rate and yield (2 days, 90%) improved using N,N-diethylaniline instead of mesitylene as the reaction solvent. Electron-deficient substrate 237b (X = NCO₂Me) reacted significantly faster and complete conversion to 239b in quantitative yield was achieved within 1 hour. The authors recognized the similarities of this compound with pentacycle 240, which is an intermediate in the total synthesis of (±)-strychnine as described by Rawal.

Shortly after Bodwell’s strategy, Boger and co-workers have entered the field of monoterpene indole synthesis with a highly efficient cycloaddition cascade approach. Inspired by the 1,3-dipolar cycloaddition strategy of Padwa, and perhaps also of the work of Bodwell et al., Boger has introduced a very elegant tandem [4+2]/[3+2] cycloaddition reaction using tethered 1,3,4-oxadiazoles (Scheme 28). Upon heating in either 1,2-dichlorobenzene or 1,3,5-trisopropylbenzene, oxadiazole 241 first undergoes an inverse electron-demand Diels–Alder reaction, which sets the stage for the [3+2] cycloaddition. In four straightforward steps and a wide variety of products could be synthesized efficiently generating the core backbone of the Aspidosperma alkaloids (244). Notably, the reaction always proceeds with complete diastereocontrol with respect to the relative stereochemistry that is generally found in this class of natural products. Boger and co-workers have exploited this concise cycloaddition cascade in the synthesis of a remarkable repertoire of monoterpene indole alkaloids.

An alternative cycloaddition approach has been found by the group of Vanderwal, who has made efficient use of Zincke aldehydes 248 (Scheme 29). Heating to 80 °C in the presence of a base, results in a formal Diels–Alder reaction towards tetracyclic spiroindoline 249. Switching to acidic conditions mainly lead to decomposition of the starting material. In several cases, pentacycle 239a (X = CH₃) and pentacycle 239b (X = NCO₂Me) were obtained.
reports, Vanderwal has described the synthetic versatility of the tetracyclic building block towards several Strychnos alkaloids. It is worth noting that this methodology forms the basis of the shortest total synthesis of (-)-strychnine (only six steps) so far. Unfortunately, no attempts to an asymmetric cycloaddition have been described.

4.3. Other cycloaddition strategies

As an alternative to the [4+2] cycloaddition approach constructing the E-ring, Volhardt and co-workers have developed a cobalt-mediated [2+2+2] cycloaddition (Scheme 30). By using N1 tethered alkynes in combination with external alkynes or C3 tethered alkyne, a [2+2+2] cycloaddition is initiated by CpCo(C2H4)2. This method was applied to the total synthesis of (-)-strychnine. Starting from 257, de aromatization through [2+2+2] cycloaddition gave indoline 258 as a single diastereomer of its CoCp complex in 46% yield.

Scheme 29. Employment of Zincke aldehydes in Diels–Alder reactions towards tetracyclic indolines (Vanderwal et al.).

Scheme 30. Other approaches based on CoI-mediated cycloadditions (Volhardt et al.) and SmI2-mediated cascade cyclizations (Reissig et al.). HMPA = hexamethylphosphoramide.

Reissig and co-workers have obtained a similar synthetic intermediate through a SmI2-mediated cascade cyclization from N1 tethered ketoester 259. SmI2 mediates a reductive coupling initiated by formation of a ketyl radical which then adds intramolecularly to the indole C2 position. The resulting radical at C3 is subsequently reduced by another equivalent of SmI2 after which the carbanion can condense onto the ester to form the corresponding ketone 262. The reaction is very fast and the product is obtained in 70–75% yield as a single diastereomer. The authors also applied this strategy in the formal total synthesis of (-)-strychnine.

5. Dearomative Assembly of the C-Ring

A retrosynthetic disconnection of the C-ring of the pentacyclic core of Aspidosperma and Strychnos alkaloids at first sight seems trivial. Nevertheless, this transformation should be deemed difficult, given the poor yields in separate communications of Potier and co-workers and Ziegler et al., based on a seemingly straightforward dearomative S-N2 cyclization (Scheme 31).

Magnus et al. have identified this problem and used a 1,2-addition of the indole C3 position on the in situ generated sulfonium ion 269 (Scheme 32). Treatment of sulfoxide 267 with trifluoroacetic anhydride triggers a Pummerer reaction. Subsequent dilution and heating in chlorobenzene then leads to the spirocyclization. A final desulfurization with Raney nickel concludes formation of pentacycle 271 in 64% yield from sulfoxide 267. This strategy has been incorporated in syntheses of several Aspidosperma alkaloids. Similarly, Bosch and co-workers found that thioacetal 275 efficiently undergoes ring closure by treatment with dimethyl(methylthio)sulfonium fluoroborate (DMTSF), which was exploited in several Strychnos alkaloid syntheses.

Although the work from Magnus et al. and Bosch and co-workers was innovative, constructing the C-ring via an S-N2 cyclization strategy would be more concise. Natsume et al. have shown that this is possible through a two-step sequence from primary alcohol 277, albeit with moderate efficiency because they obtained 280 in only 26% yield (Scheme 33). After
slightly modifying the reaction conditions, Rawal and co-workers have improved this transformation and the analogous pentacycle 282 was obtained in 78% yield. This two-step sequence is the most frequently found approach in the literature to construct the C-ring. Martin et al. cleverly employed this principle by using alcohol 283 under basic conditions, allowing a sulfenylation transfer activating both the indole C3 position and the resulting sulfonate to promote an S$_{N}$2 cyclization (Scheme 34). Alternatively to 2-hydroxyethyl substituents, Heathcock et al. showed that α-chloroamide 287 could be used under Finkelstein conditions to construct the C-ring. However, this requires reduction of the amide to reach the pentacyclic core of the Aspidosperma alkaloids. Alternative routes involving carbene chemistry and radical chemistry were developed by others.

Natsume et al. have dealt with the low yield in the conversion of 277 to 280 by introducing less rigid tricyclic 290 to a cascade double cyclization (Scheme 35). In the presence of potassium bis(trimethylsilyl)amide (KHMDS) at $-70^\circ$C, a deaeromative S$_{N}$2 cyclization occurs, which is followed by trapping of the iminium ion in a Mannich cyclization to give pentacycle 293. Similarly, the group of Andrade has developed another double cyclization strategy. Inspired by Heathcock’s C-ring cyclization strategy, a one-pot, two-step cyclization starting from indole 294 was achieved efficiently. Under Finkelstein conditions the C-ring is first constructed to give tricycle 295. Upon subsequent in situ treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), an aza-Baylis–Hillman cyclization
furnished pentacycle 296 in 70% yield (13:1 d.r.; d.r. = diastereomeric ration). The authors have developed several total syntheses of both Aspidosperma and Strychnos alkaloids based on this approach. Recently, Zhang and co-workers have achieved a true cascade cyclization under the Finkelstein conditions starting from tricycle 305, as this reaction provides the C- and E-ring in a single step.\(^{[6]}\)

### 6. Summary and Outlook

Total synthesis strategies towards Aspidosperma and Strychnos alkaloids have appeared frequently in the literature over the past six decades, ever since Woodward’s pioneering synthesis of strychnine. Deearomatization strategies of indoles allow for facile access to large parts of the required carbon skeleton, as illustrated by the wide variety of approaches described in this review. In the early days, total synthesis of these indole monoterpoid alkaloids was essential to unravel biosynthetic pathways and provide ultimate proof of the structural composition of these alkaloids. Over time, the general interest has shifted, focusing more on efficiency rather than just “getting there”. Nowadays, these structurally complex backbones also serve as attractive targets to showcase newly developed synthetic methodologies. In terms of stereochemistry, great accomplishments have been made. Diastereomeric control can usually be attributed to the rigidity of the pentacyclic backbone of these natural products, which is simply less stable in the unnatural relative configuration. As a result, most asymmetric dearomatization strategies make use of enantiomerically enriched starting materials to diastereoselectively obtain the spiroindoline core. Although great accomplishments have been made in asymmetric catalysis in general, an application to this field is still in its infancy. The MacMillan group has pioneered with their inspiring organocatalytic asymmetric Diels–Alder approach. In continuation, more catalytic asymmetric dearomatization strategies will undoubtedly follow. The overview that is presented here serves to highlight the current state of the art in dearomatic strategies towards Aspidosperma and Strychnos alkaloid synthesis.

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### Conflict of interest

The authors declare no conflict of interest.

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