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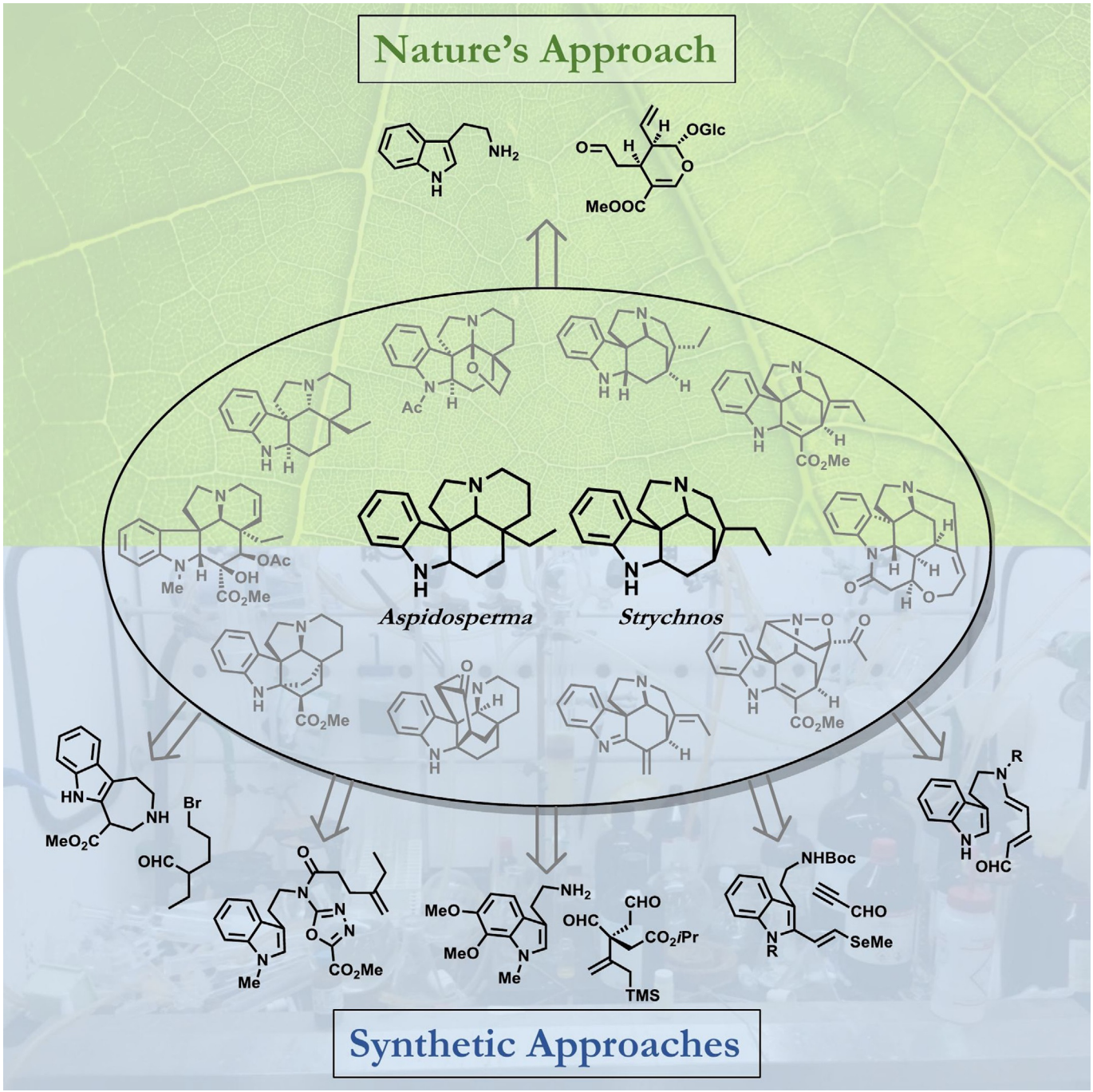
Total Synthesis of *Aspidosperma* and *Strychnos* Alkaloids through Indole Dearomatization

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

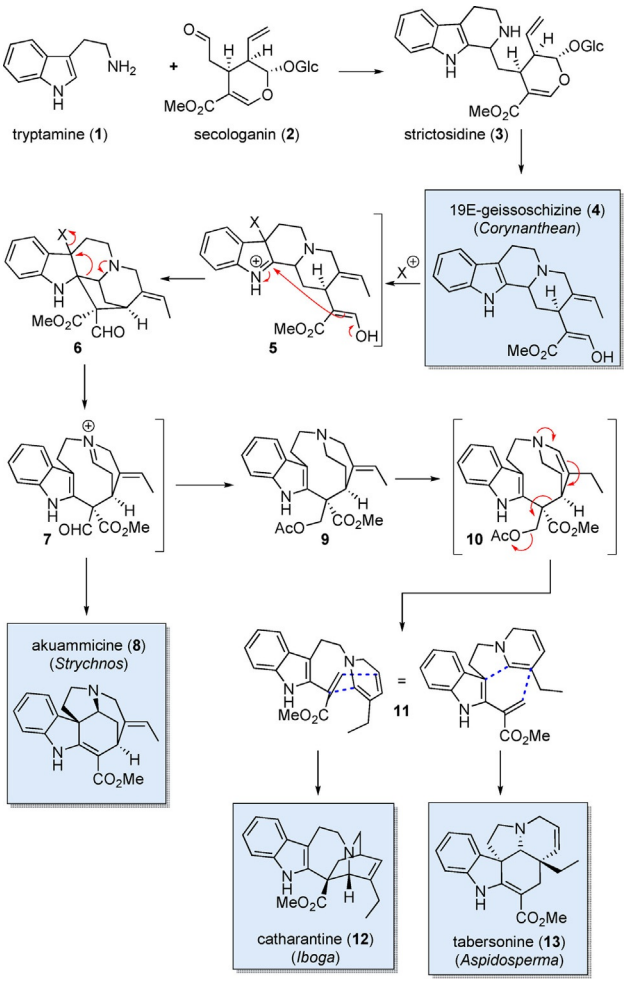


Abstract: Monoterpenoid indole alkaloids are the major class of tryptamine-derived alkaloids found in nature. Together with their structural complexity, this has attracted great interest from synthetic organic chemists. In this Review, the syntheses of *Aspidosperma* and *Strychnos* alkaloids through 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, evolutive 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., 19*E*-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]



Scheme 1. Biosynthetic pathway of the monoterpenoid indole alkaloids from tryptamine and secologanin.

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-

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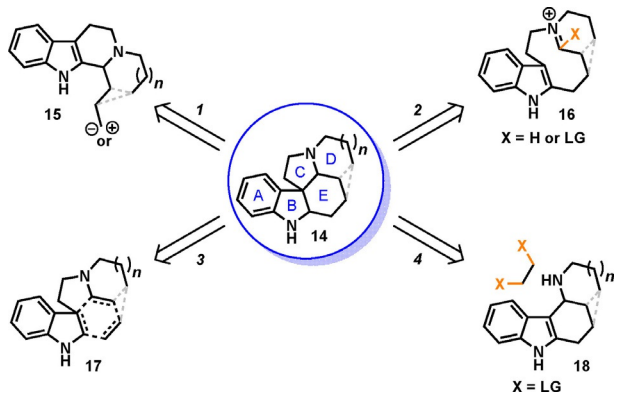

Scheme 2. Dearomatization strategies towards the pentacyclic backbone of *Aspidosperma* and *Strychnos* alkaloids divided into four classes.

ples are organized into four main categories (Scheme 2): 1) dearomative ring contractions of β-carbolines **15**, 2) electrophilic aromatic additions (**16**), 3) cycloadditions (**17**), and 4) C-ring formation (**18**). We primarily discuss the dearomative strategies used and will not focus on an in-depth discussion of the entire synthetic route.

2. Dearomative 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.[6] By treatment of β-carboline **20** with $BF_3{\cdot}OEt_2$ 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 enantioenriched **27** (85% *ee*).[8] 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 $BF_3{\cdot}OEt_2$ induced dearomatization reported by Harley-Mason proceeded in low yields. Switching to triflic acid gave the pentacycle **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 (±)-vindoline (**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 diastereoisomers 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 S_N2-type mechanism. After the rearrangement, a Krapcho decarboxylation mediated by the liberated NaCl occurs under the

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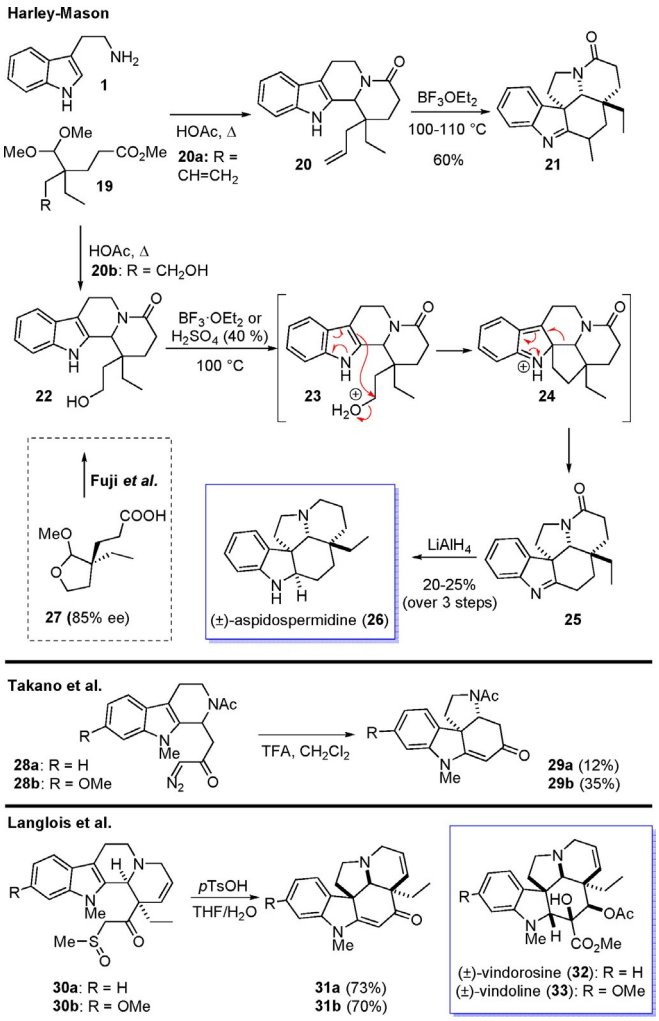
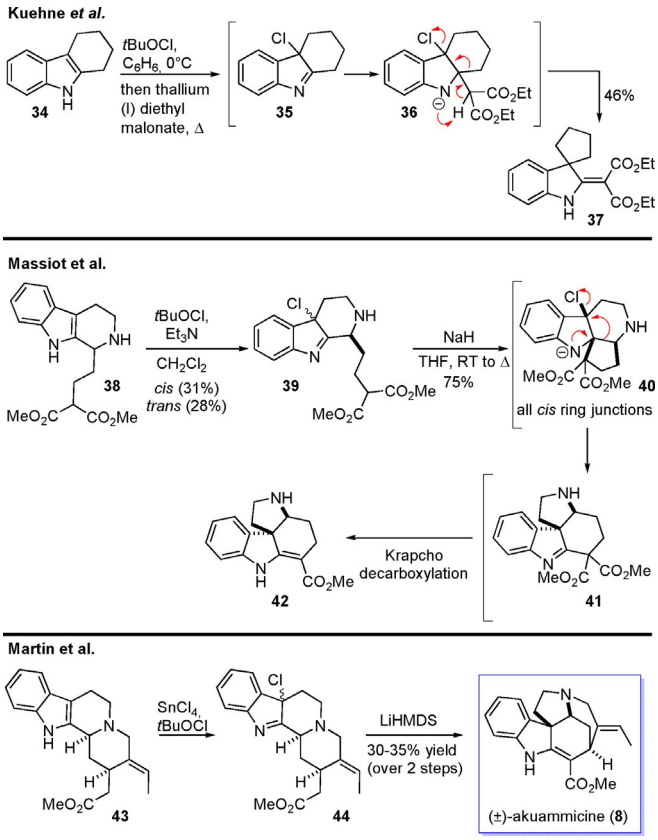
Eelco Ruijter obtained his PhD from the Vrije Universiteit Amsterdam and the Leibniz Institute of Plant Biochemistry (Halle/Saale, D) in 2005. After a postdoctoral stay at Utrecht University (2004–2006) with Profs. Liskamp and Heck, he was appointed assistant professor of organic chemistry at the Vrije Universiteit Amsterdam and received tenure in 2012. In 2018, he was promoted to associate professor. His research interests include the development of synthetic methods based on cascade reactions and homogeneous catalysis for the efficient and sustainable production of high-added-value molecules.

Romano Orru completed his PhD in organic chemistry at the Agricultural University of Wageningen, The Netherlands. From 1996 to 2000 he worked at the Technical as well as at the Karl-Franszens University of Graz, Austria on synthetic applications of biotransformations. In 2000, he returned to the Netherlands, and was appointed Assistant Professor and later Associate Professor (2003) of Synthetic & Bioorganic Chemistry at Vrije University in Amsterdam. Since 2007, he holds the Chair of Synthetic & Bioorganic Chemistry. His research focuses on the utilization of one-pot cascade reactions and multicomponent reactions to improve the efficiency, sustainability and precision of organic compound synthesis.



Scheme 3. Dearomatizations of β-carbolines based on electrophilic aromatic substitutions towards spiroindolines (Harley-Mason, Takano and Langlois et al.). An asymmetric approach was found by Fuji et al.



Scheme 4. Biomimetic dearomatization of β-carbolines by indole C3 chlorination (Kuehne, Massiot and Martin et al.).

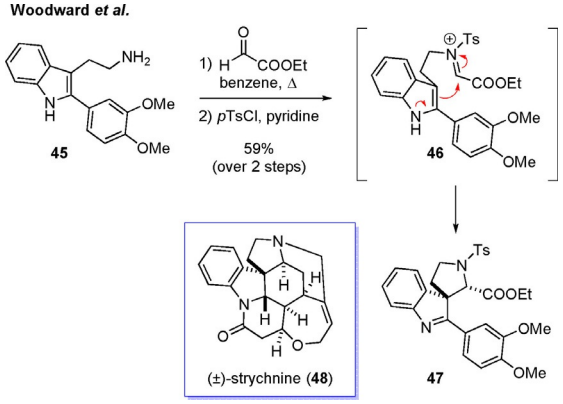
reaction conditions to afford tetracycle **43**. Martin et al. later have translated this strategy into a remarkable biomimetic synthesis of (±)-akuammicine starting from **43**.[14] Also in this procedure, only one diastereoisomer of the 3-chloroindolenine intermediate was susceptible to spirocyclization.

3. Electrophilic Aromatic Additions

3.1. Pictet–Spengler-type cyclizations with C2 substituents

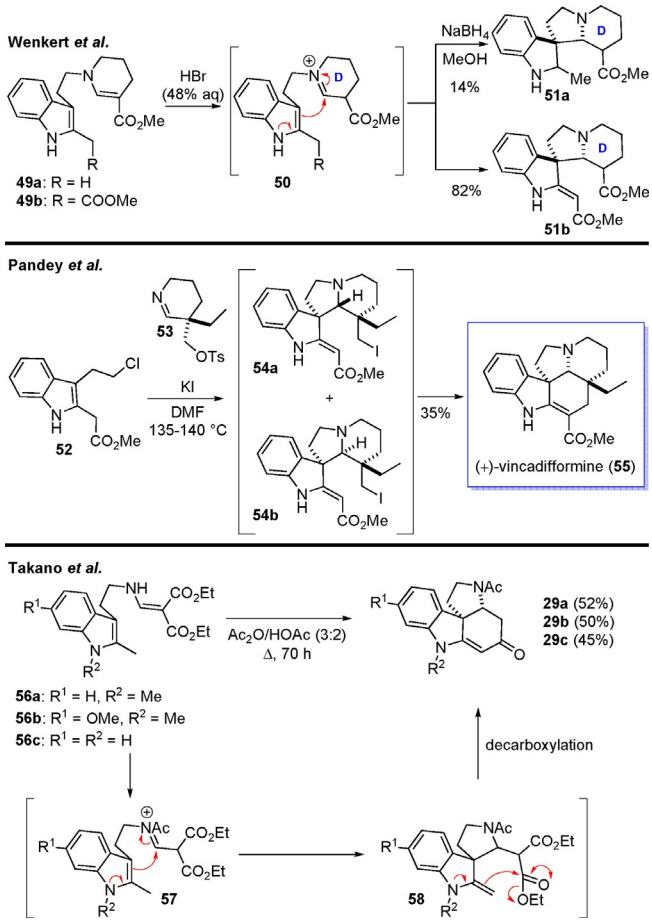
In the early days of natural product synthesis, Woodward et al. have been the first to tackle a complex indole monoterpenoid alkaloid, that is, strychnine (**48**). The structure of strychnine had been elucidated after more than 100 years of extensive spectroscopic and synthetic studies following the 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.[3] 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,[15] were corroborated by his group in the total



Scheme 5. The first total synthesis of (±)-strychnine by Woodward et al. through a dearomative Pictet–Spengler reaction.

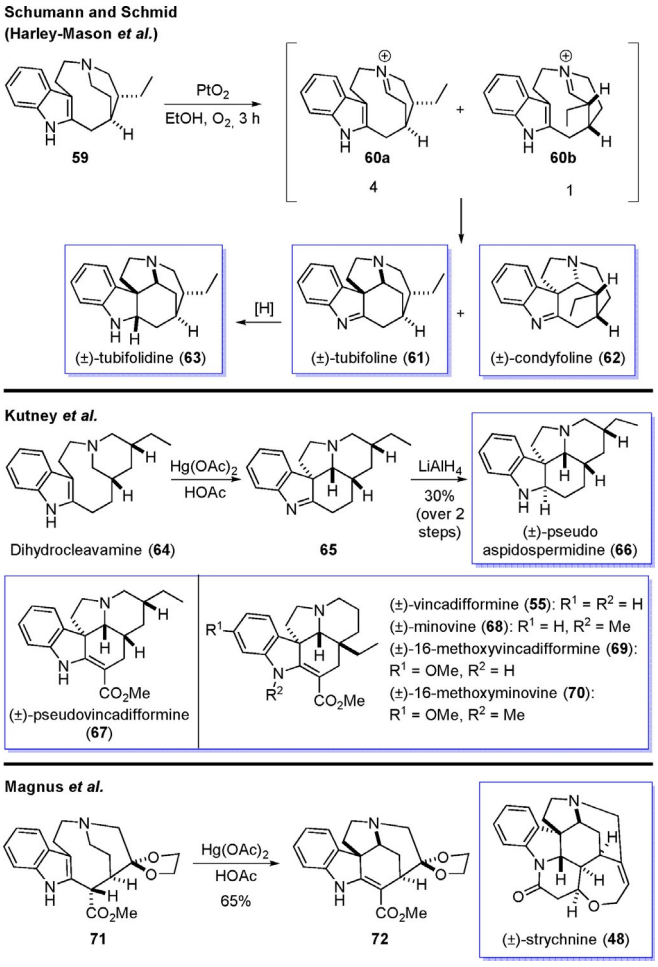
synthesis of the pentacyclic core of *Aspidosperma* and *Strychnos* alkaloids (Scheme 6).[16] Wenkert's strategy took advantage of tetrahydropyridines **49** as substrates for key Pictet–Spengler type spirocyclizations. The dearomative cyclization of **49a** in



Scheme 6. Pictet–Spengler approaches of preformed imines/enamines (Wenkert, Pandey and Takano et al.).

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.[17] By mixing optically pure tetrahydropyridine **53** (>99% *ee*) and indole **52** in DMF in the presence of potassium iodide 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**.[8] 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.

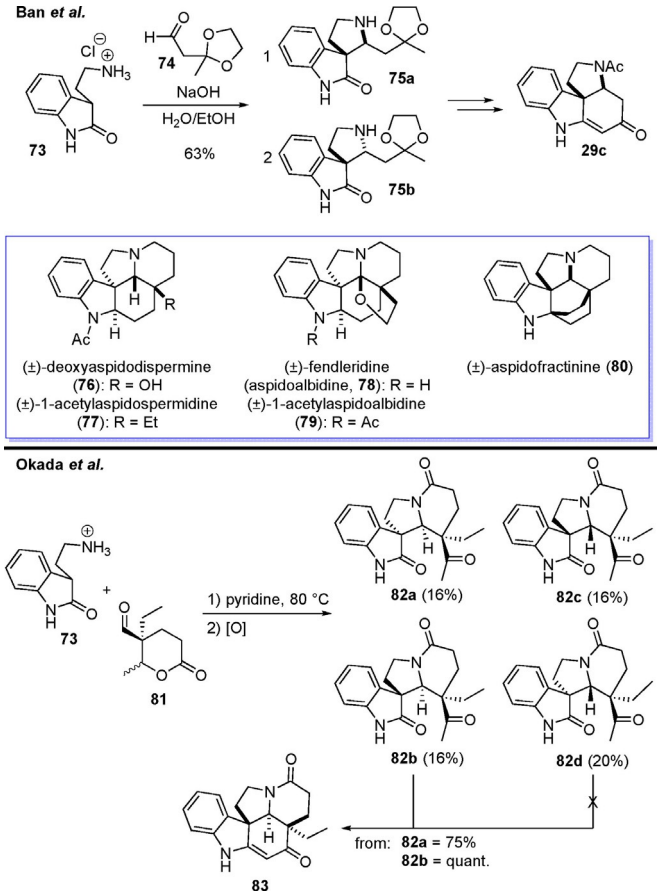
Rather than condensation of aldehydes and tryptamines to generate the iminium ion, Schumann and Schmid have used platinum(IV) oxide catalyzed oxidation of **59** to obtain a mixture of (±)-tubifoline (**61**) and (±)-condyfoline (**62**, Scheme 7).[18] The regioselectivity is directed by steric repulsion 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.[19] Subsequent reduction of spiroindolenine **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.[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.[21] As in the oxidation of **59**, a mixture of isomeric oxidation products formed



Scheme 7. PtO_2 or $Hg(OAc)_2$ oxidations to facilitate the Pictet–Spengler reactions (Schumann/Schmid and Kutney et al.). Magnus et al. applied this strategy in the second total synthesis of (±)-strychnine.

upon treatment of **71** with mercuric acetate in acetic acid, however, the undesired minor isomer formed in undefined small amounts.

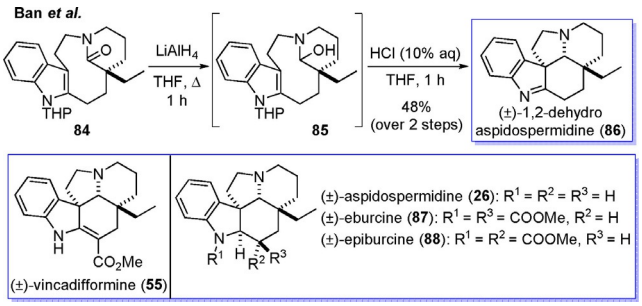
Instead of using a carbon substituent at the indole C2 position, Ban et al. have chosen to use 2-hydroxytryptamine (Scheme 8).[22] Considering the alkaline reaction conditions,



Scheme 8. Pictet–Spengler reactions from 2-hydroxytryptamine (Ban et al.). Okada et al. demonstrated an asymmetric approach.

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] Although dearomatization using the optically enriched aldehyde **81** gave a mixture of stereoisomers **82a–d**, the authors managed to isolate all four of them after a difficult purification. Both **82a** and **82b** could be conveniently transformed to pentacycle **83**, which is a common intermediate in several syntheses by Ban and co-workers.[23]

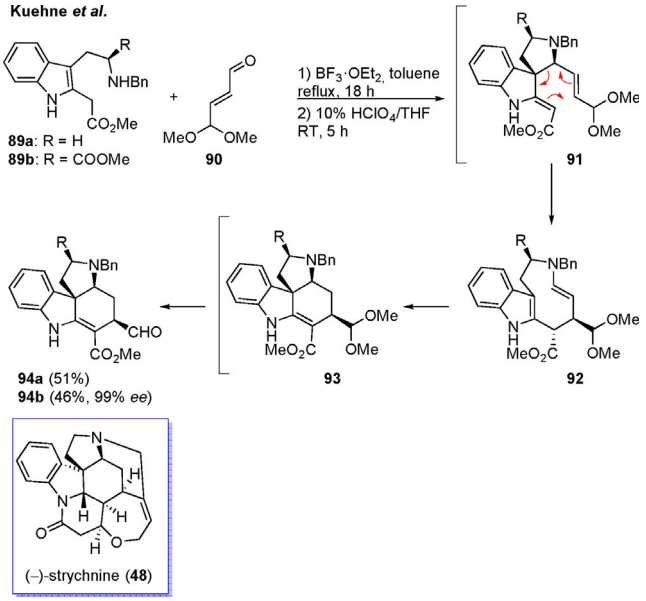
Ban et al. have also developed a reduction strategy to the *Aspidosperma* alkaloid core (Scheme 9).[25] Tetracyclic lactam **84** was first selectively reduced to hemiaminal **85**. Next, treatment with hydrochloric acid removed the THP group and triggered the dearomatization step in a transannular Pictet–Spengler re-



Scheme 9. Pictet–Spengler reactions initiated by reduction of cyclic lactams (Ban et al.).

action 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**

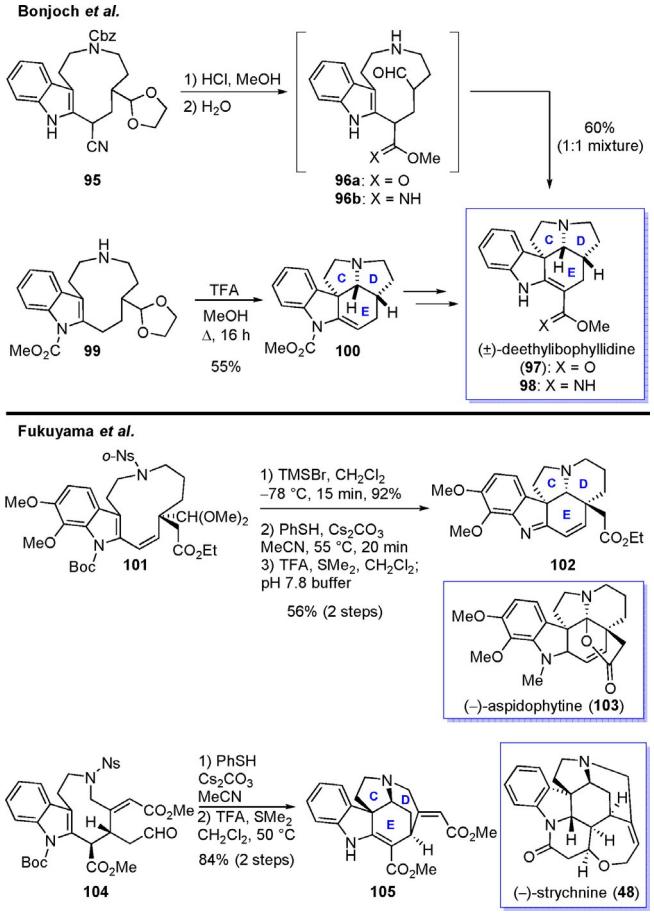


Scheme 10. Pictet–Spengler/[3,3]-sigmatropic rearrangement/Pictet–Spengler cascade reactions (Kuehne et al.).

were activated by BF_3·OEt_2 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

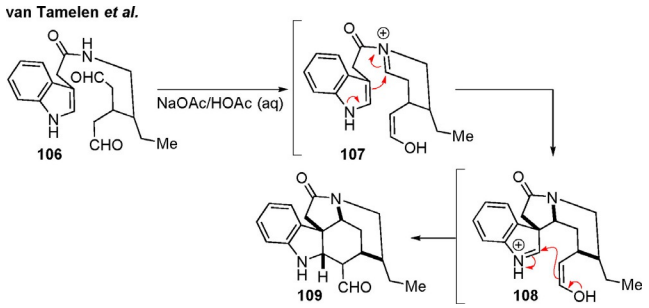
Pictet–Spengler reaction to obtain deethylibophyllidine (**97**; Scheme 11).[28] In a direct approach, the tricyclic **95** should undergo a series of chemical transformations, including deprotection, conversion of the nitrile to the methyl ester, and a Pictet–Spengler reaction. The double cyclization 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**[29] and **104**,[30] the Pictet–Spengler cyclization can proceed with complete diastereoselectivity. The authors applied this strategy in the total synthesis of (−)-aspidophytine (**103**) and (−)-strychnine.



Scheme 11. Efficient assembly of the CDE-rings through Pictet–Spengler reactions of ten-membered cyclic amines (Bonjoch et al.). Fukuyama applied this approach in the asymmetric synthesis of (−)-aspidophytine and (−)-strychnine. TMSBr = trimethylsilyl bromide.

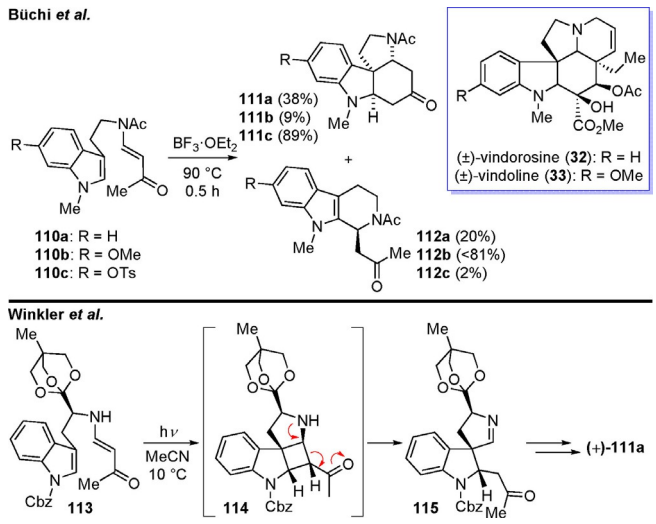
3.2. Pictet–Spengler-type cyclizations followed by trapping of the iminium intermediate

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 dearomatized indolenine 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).[31] 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.



Scheme 12. Pictet–Spengler/Mannich cascade towards the *Strychnos* core (van Tamelen et al.).

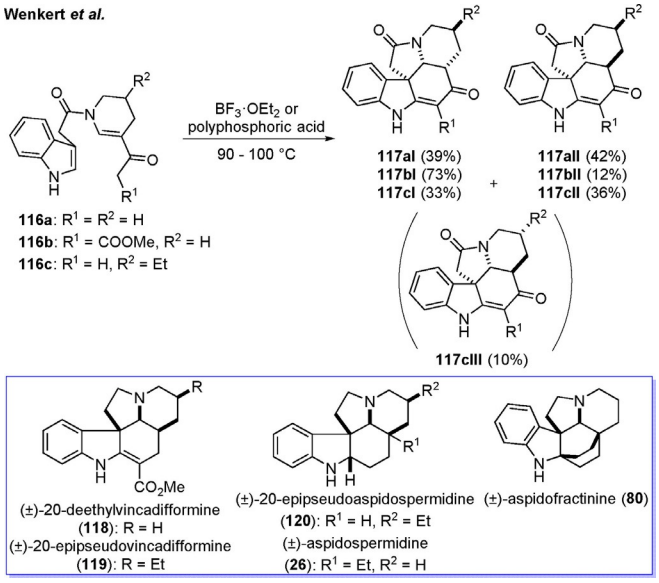
In 1971, Büchi et al. have reported an elegant Pictet–Spengler/Mannich cascade approach {which may also be considered as a formal [4+2] cycloaddition}.[32] Initial attempts with the enamine derived from a condensation reaction of N1-methyl tryptamine and 3-oxobutanal were unsuccessful. However, reaction of the acetylated analogue **110a** in $BF_3{\cdot}OEt_2$ 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.[23i,33] 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.[34] 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



Scheme 13. Synthesis of Buchi's ketones (Büchi and Winkler et al.).

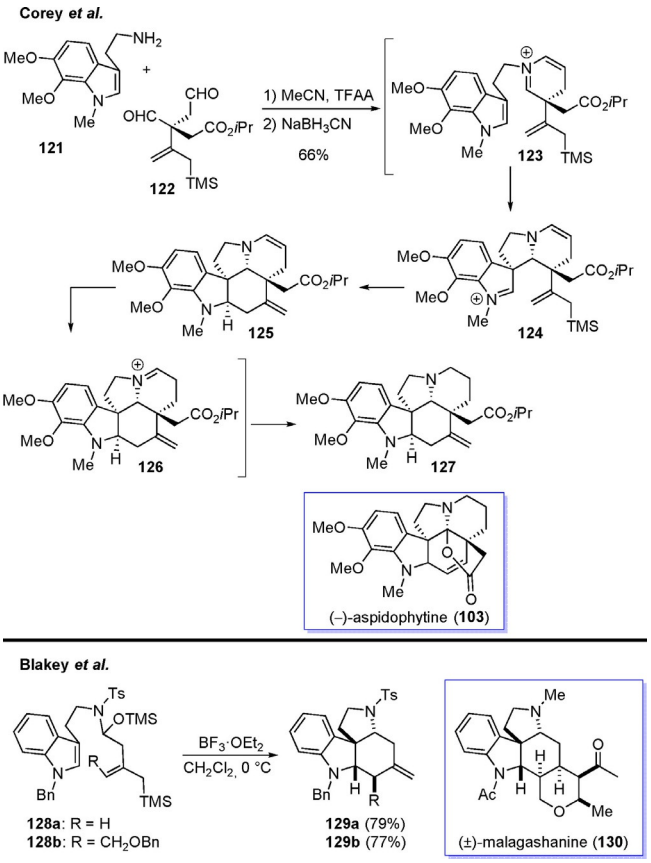
Büchi's ketone (+)-**111a**, the authors performed a Mannich cyclization, followed by fragmentation of the OBO ester.

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 $BF_3{\cdot}OEt_2$ or polyphosphoric acid at 100 °C to obtain diastereomeric mixtures of **117**. Although they are not formed selectively, **117al-cl** have been employed in the synthesis of several indoline alkaloids.



Scheme 14. Synthesis of the pentacyclic framework of *Aspidosperma*-type alkaloids (Wenkert et al.).

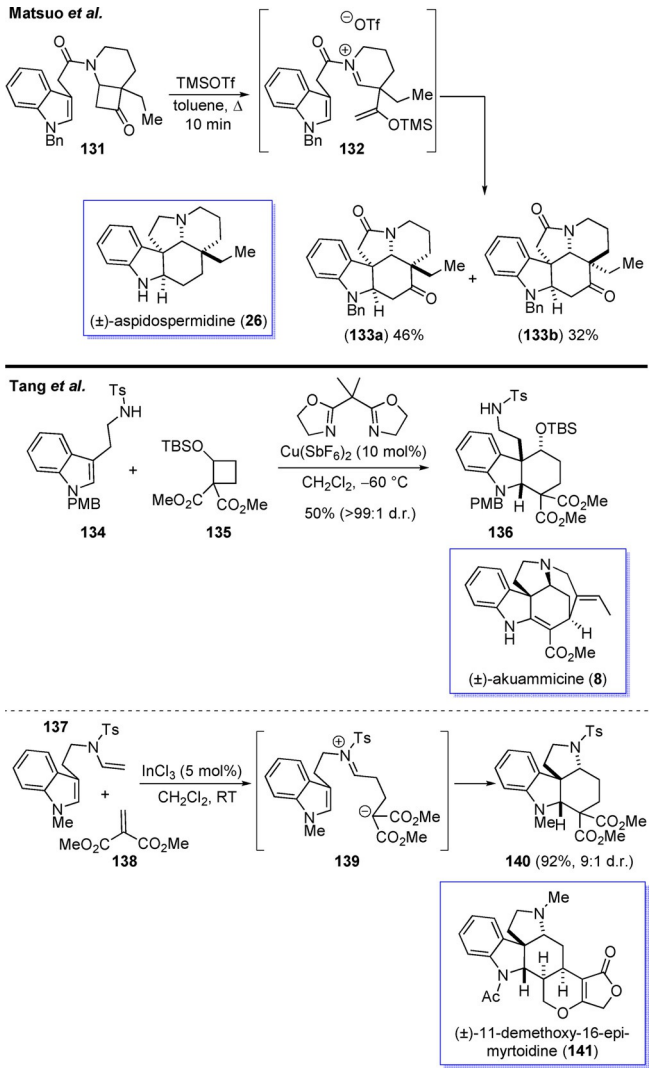
An elegant approach using an aza-Sakurai reaction to install the spiroindoline structure has been reported by the group of Corey (Scheme 15).[36] The required rather complex dialdehyde **122** was obtained optically enriched (97% *ee*) and reacted with tryptamine derivative **121**. In the presence of triflic anhydride



Scheme 15. Pictet–Spengler/aza-Sakurai cascades towards (−)-aspidophytine (Corey et al.) and (±)-malagashanine (Blakey et al.).

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 $NaBH_3CN$. 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 (**130**). The difference in diastereomeric outcome between substrates **121** and **128** in the Pictet–Spengler/aza-Sakurai cascade is presumably caused by the dihydropyridinium ring that is present in **123**, directing the stereochemistry into the more stable all *cis* ring junction of **127**.

Recently, Matsuo and co-workers have reported an alternative cycloaddition procedure employing donor–acceptor cyclobutanes in combination with indoles (Scheme 16).[38] They found that for intermolecular [4+2]-cycloadditions, the temperature should be maintained between −78 and −45 °C, whereas $TiCl_4$ should be used for optimal yields. To apply their method in the total synthesis of (±)-aspidospermidine, the authors used an intramolecular approach with cyclobutanone **131**. However, after further optimization, more suitable conditions were found (TMSOTf in refluxing toluene). A major disadvant-



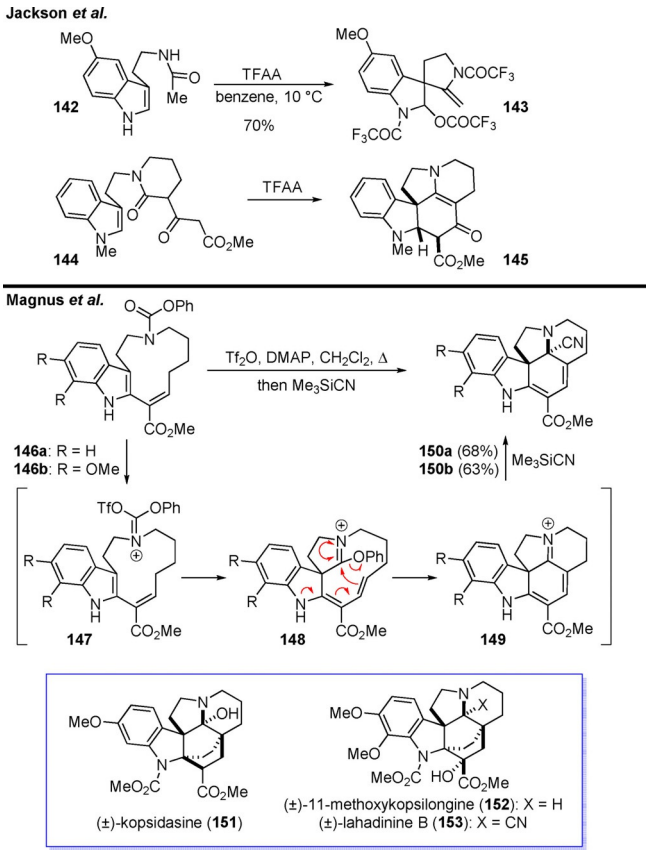
Scheme 16. Donor–acceptor cyclobutanes in indole dearomatization reactions (Matsuo and Tang et al.). TMSOTf = trimethylsilyl trifluoromethanesulfonate; TBS = *tert*-butyldimethylsilyl.

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 diastereoisomer. Similarly, Tang and co-workers have developed an intermolecular annulation of malonate-derived donor-acceptor cyclobutanes (**135**).[39] The authors achieved mild activation by Cu^{II} catalysis in good diastereoselectivity. Advantageously, indoline **136**, which was their building block for the total synthesis of (±)-akuammicine, 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**.[40] 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-demethoxy-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).[41]



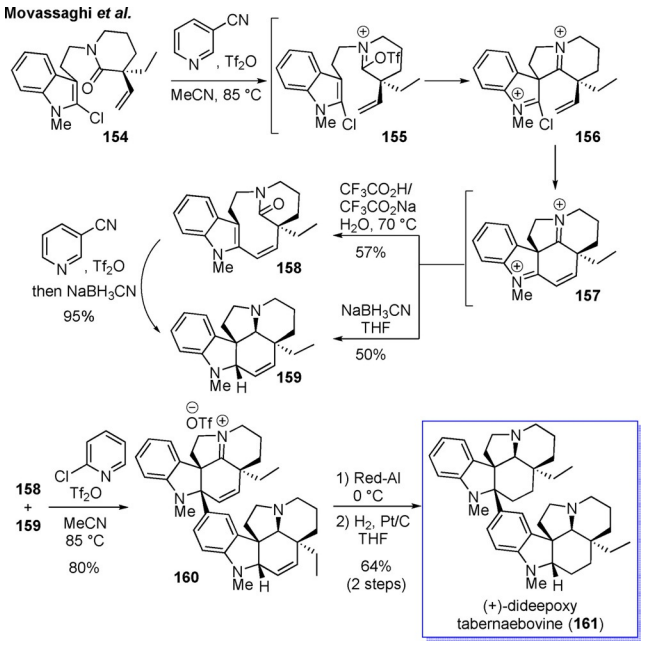
Scheme 17. Interrupted Bischler–Napieralski cyclizations towards the pentacyclic backbone of *Aspidosperma* alkaloids (Jackson and Magnus et al.). DMAP = 4-dimethylaminopyridine.

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**.[42] 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

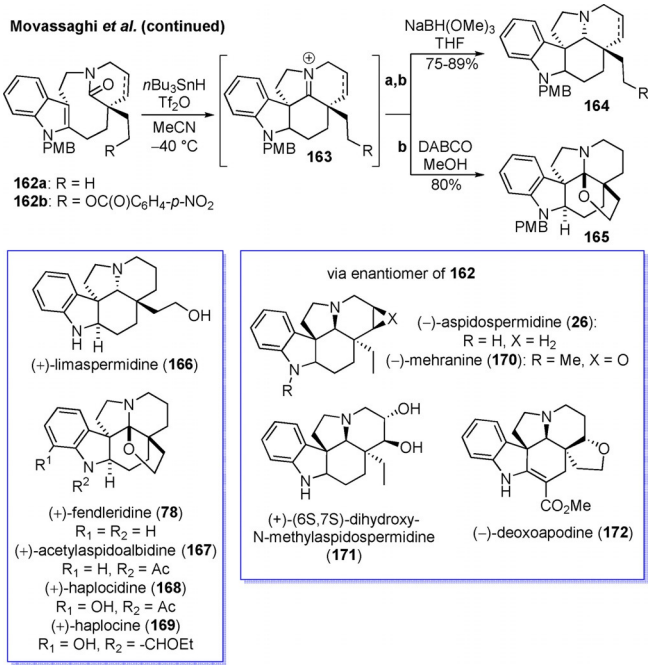
Kopsia alkaloids.[43] In their approach, starting from 11-membered ring system **146**, activation of the carbamate triggers an interrupted Bischler-Napieralski cyclization. After this a vinylogous enamine addition to the resulting imidate gave pentacyclic dienes **149**. After the conversion to iminium ions **149** was complete, a Strecker reaction by in situ treatment with trimethylsilyl cyanide (TMSCN) results in the formation of aminonitriles **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 $AgBF_4$-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).[44] 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 rearomatization/dearomatization 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 (+)-dideepoxytabernaebovine (**161**).



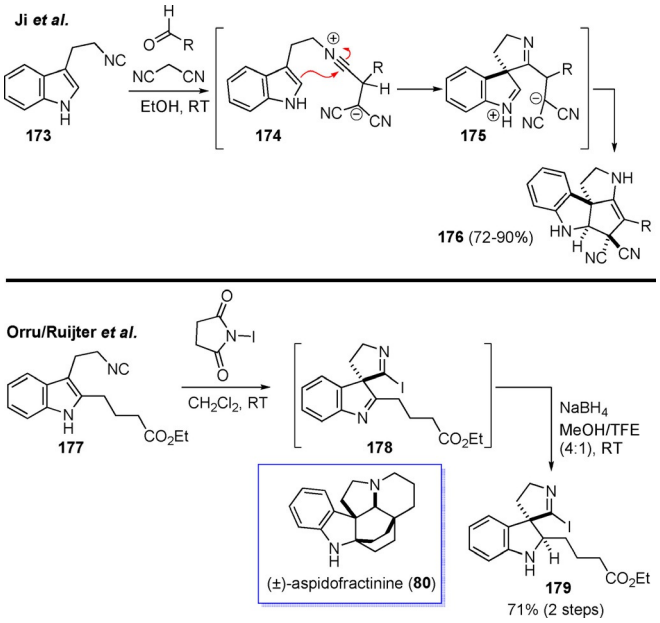
Scheme 18. Interrupted Bischler–Napieralski cyclizations in the synthesis of (+)-dideepoxytabernaebovine (Movassaghi et al.).

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,[45] biocatalytic kinetic resolution[46] or enantioselective ring-closing metathesis (RCM) mediated desymmetrization[47] was employed to access enantioenriched lactam **162** as starting material.



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.

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).[48] After in situ condensation of aldehydes with malonitrile, a nucleophilic addition of isocyanide **173** generates nitrilium ion **174**. The indole C3 position subsequently intercepts the nitrilium ion to form spiroindolenine **175**. 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.[49] We have reported *N*-iodosuccinimide (NIS) as a compatible electrophile in iodospirocyclization reactions.[49c] The resulting products, especially regarding the imidoyl iodide 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**).

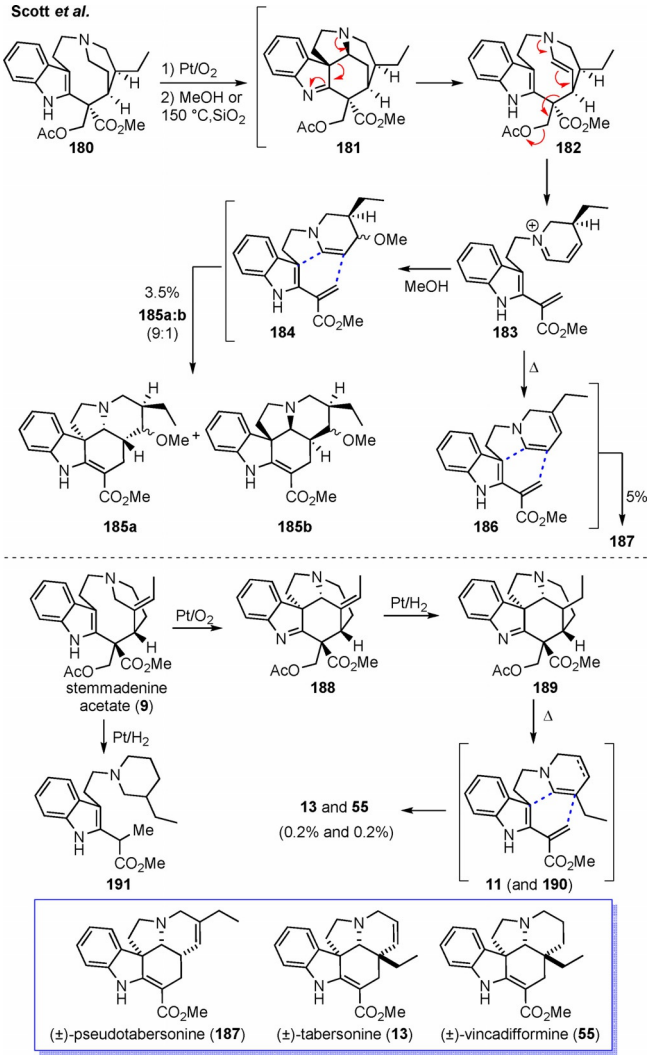


Scheme 20. Tryptamine-derived isocyanides in dearomatization strategies towards spiroindolines (Ji and Orru/Ruijter et al.).

4. Cycloadditions

4.1. Normal electron-demand Diels–Alder reactions

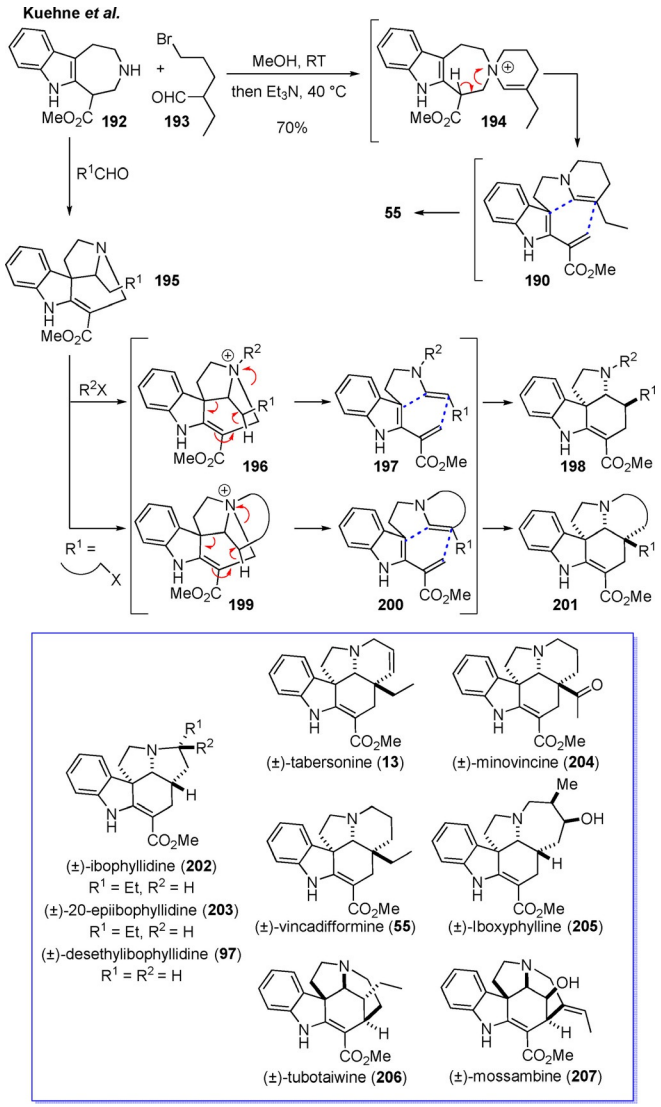
The *Aspidosperma*-type alkaloids biosynthetically originate from an enzyme-catalyzed [4+2]-cycloaddition of stemmadenine acetate (**9**). This has been first established by Scott and co-workers in 1968 in several studies on stemmadenine and analogues.[50a] After serious criticism by Smith and Poisson 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).[50] Upon platinum-catalyzed oxidation of **180** to 19,20- dihydropreakuammicine acetate (**181**), followed by methanolysis (4 h, room temperature), a 9:1 diastereomeric mixture of **185 a** and **185 b** 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 hydrogenated [Pt, H_2 (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.



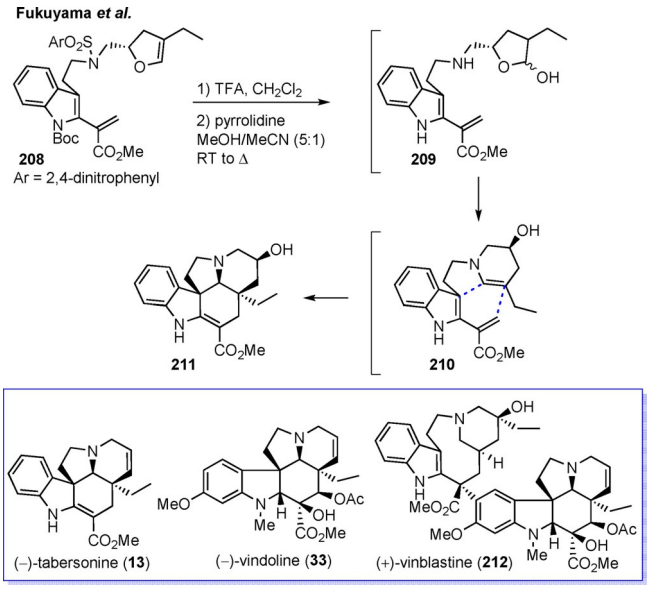
Scheme 21. Biomimetic studies by Scott et al. in finding proof of the biosynthetic [4+2]-cycloaddition (Diels–Alder reaction) towards *Aspidosperma* alkaloids.

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).[51] 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,[52] 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.[53]

A more selective approach based on chiral sulfonamide **208** has been successfully applied by Fukuyama and co-workers in



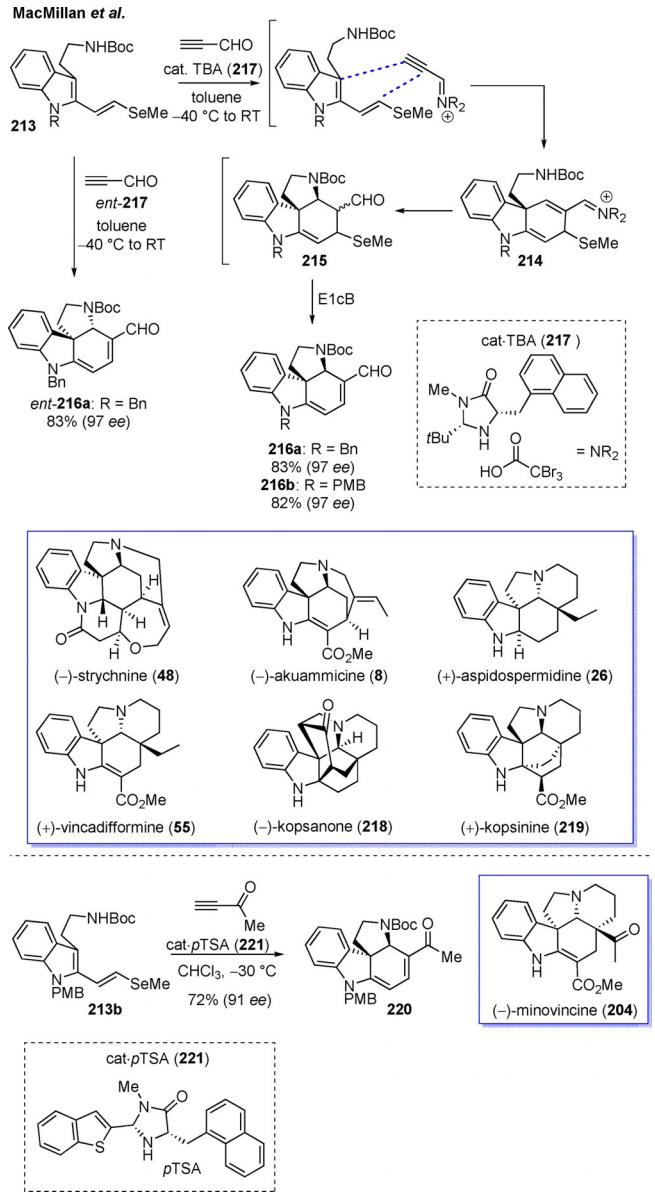
Scheme 22. Biomimetic approaches of Kuehne et al. through [4+2]-cycloaddition towards *Aspidosperma* and *Strychnos* alkaloids.



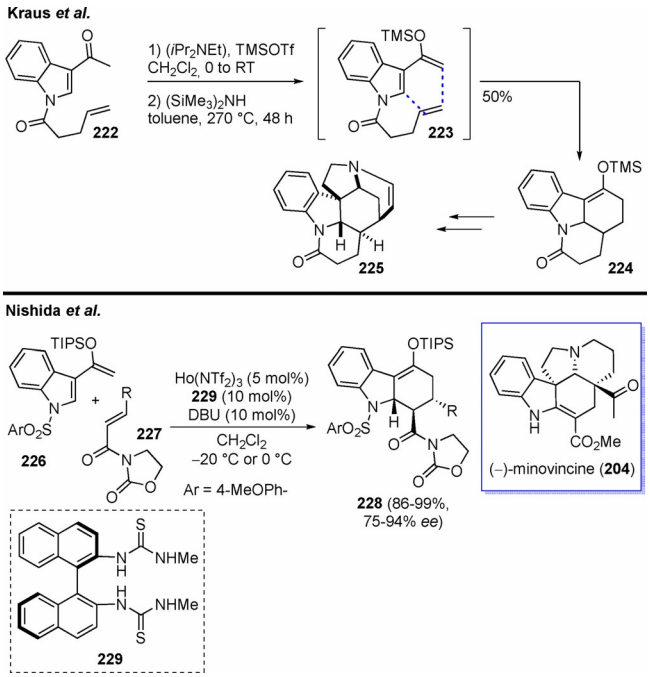
Scheme 23. An asymmetric alternative by Fukuyama and co-workers based on the biosynthetic [4+2]-cycloaddition to *Aspidosperma* alkaloids.

the asymmetric total synthesis of (−)-vindoline and (+)-vinblastine (Scheme 23).[54] After the inspiring work by the group of Kuehne, other syntheses have been developed that convert trienes similar to **190**.[55] Even quite recently, this biomimetic strategy has been again exploited by Oguri and co-workers (in 2014)[55e] and Dixon and co-workers (in 2016).[55f] Although most indole dearomatization strategies towards the *Aspidosperma* or *Strychnos* alkaloids are in general not enantioselective, MacMillan and co-workers have been the first to develop an catalytic asymmetric dearomatization approach (Scheme 24).[56] As one of the pioneers of asymmetric organocatalysis, they used this expertise in the asymmetric total synthesis of six indole alkaloids, hence developing arguably the most elegant approach towards the *Aspidosperma* and *Strychnos* 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 propynal in the presence of imidazolidinone catalyst **217**, a domino process provides tetracyclic indolines **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.[56b] 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/Mannich cyclization process. As a result, several catalytic asymmetric conjugate additions of C2-substituted tryptamines to propargylic aldehydes and ketones have been developed.[57]

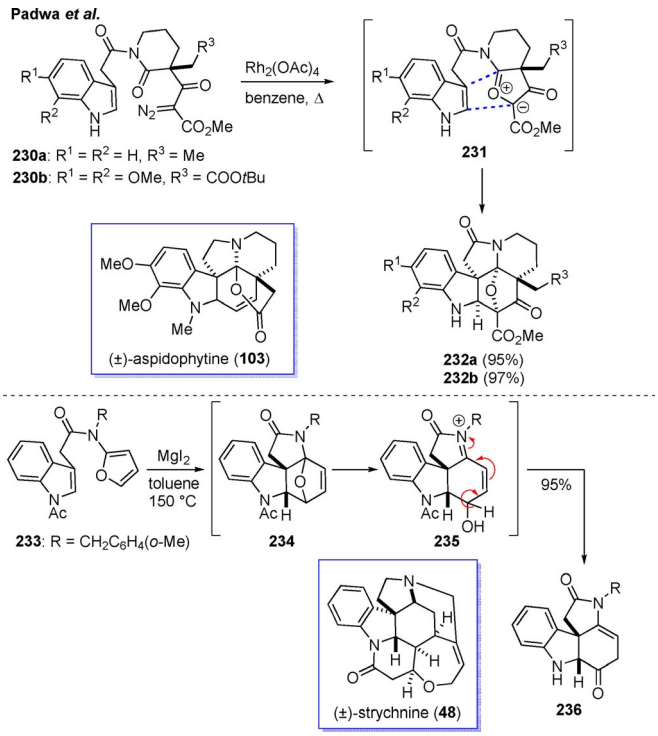
As an alternative to the biomimetic Diels–Alder approach, Kraus et al. have developed an intramolecular [4+2]-cycloaddition (Scheme 25).[58] Diels–Alder substrate **223** was obtained efficiently from 3-acetylindole, by first tethering the dienophile followed by conversion of ketone **222** to silyl 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 reactions, 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 backbone of strychnine. Recently, based on the strategy of Kraus et al., Nishida and co-workers have developed an intermolecular enantioselective Diels–Alder approach catalyzed by a chiral holmium complex.[59] 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 24. Efficient organocatalyzed cascade reactions by MacMillan and co-workers based on intermolecular [4+2] cycloadditions. TBA = tribromoacetic acid.



Scheme 25. Intra-and intermolecular Diels–Alder reactions of 3-vinylindoles (Kraus and Nishida et al.).



Scheme 26. 1,3-dipolar cycloadditions and Diels–Alder reactions (Padwa et al.).

good yields (86–99%) and with high *ee* (up to 94%). This catalytic enantioselective approach was applied in the total synthesis of (–)-minovincine.

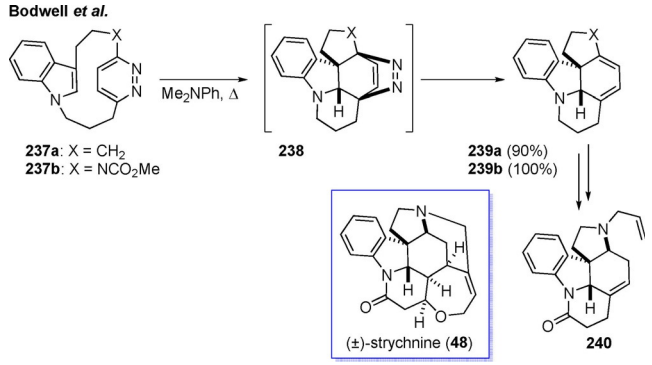
4.2. Indole as the dienophile/dipolarophile

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).[60] Based on earlier findings in generating mesoionic oxazolium ylides in situ under Rh^{II} 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 from 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.[61] 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^{II}-catalyzed 1,3-dipolar cycloaddition, Padwa et al. have moved to 2-aminofuran **233** in the synthesis of tetracyclic backbone **236**.[62] This involves the dearomatization 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 dearomatization 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 MgI_2.[63] The authors did not include any additional details on how they developed this catalyst and furthermore do not comment on the necessity of MgI_2 or any alternative catalyst in other communications.

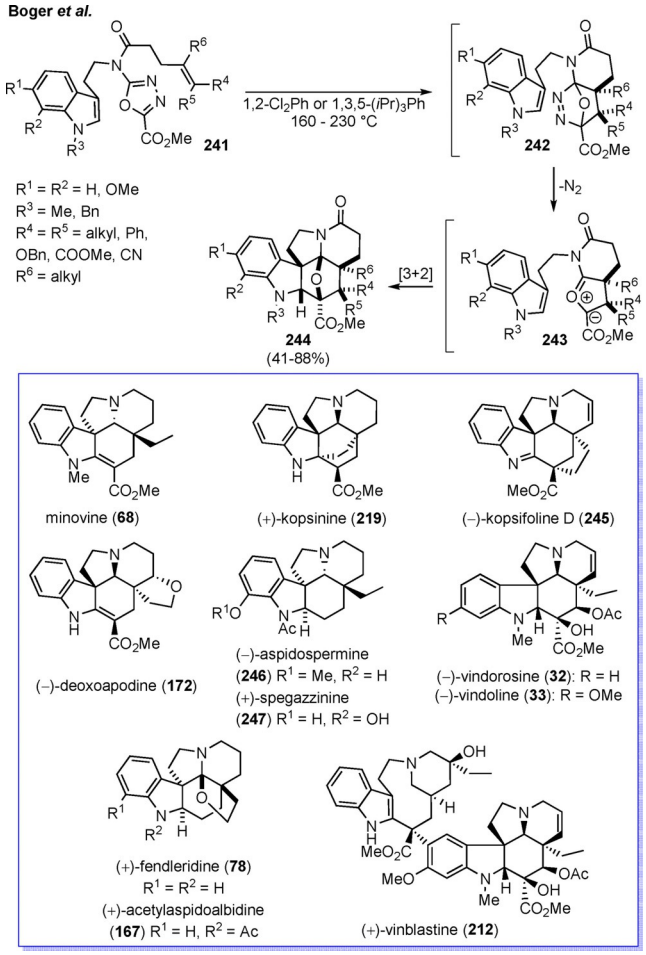
In 2001, just before Padwa et al. demonstrated the cycloaddition of 2-aminofuran tethered indoles, Bodwell and Li had already demonstrated an inverse electron-demand Diels–Alder approach.[64] By tethering pyridazines to indoles (**237**), they ingeniously made use of the electron deficiency of pyridazines (Scheme 27). Following the cycloaddition, release of N_2 gener-



Scheme 27. Diels–Alder reactions with pyridazines (Bodwell et al.).

ates pentacycle **239**. With **237a** (X = CH_2), 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 = NCO_2Me) 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.[65]

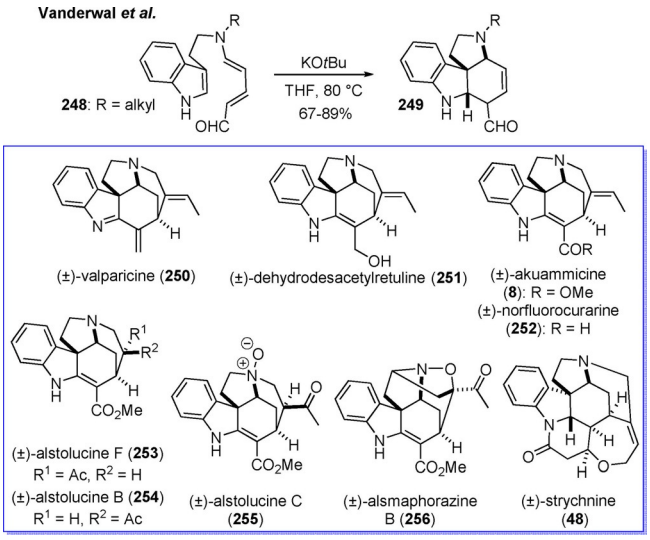
Shortly after Bodwell's strategy, Boger and co-workers have entered the field of monoterpene indole synthesis with a highly efficient cycloaddition cascade approach.[66] Inspired by the 1,3-dipolar cycloaddition strategy of Padwa, and perhaps also of the work of Bodwell et al., Boger has introduced a 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-triisopropylbenzene, oxadiazole **241** first undergoes an inverse electron-demand Diels–Alder reac-



Scheme 28. Tandem [4+2]/[3+2] cycloadditions (Boger et al.).

tion. Loss of N_2 then generates ylide **243**, which sets the stage for a 1,3-dipolar cycloaddition with the indole. In four straightforward steps 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 towards 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.[67] Next to optical resolution, the authors have also devised an asymmetric approach to obtain enantioenriched natural products by incorporating a chiral center on the D-ring.

An alternative cycloaddition approach has been found by the group of Vanderwal, who has made efficient use of Zincke aldehydes **248** (Scheme 29).[68] 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 led to decomposition of the starting material. In several

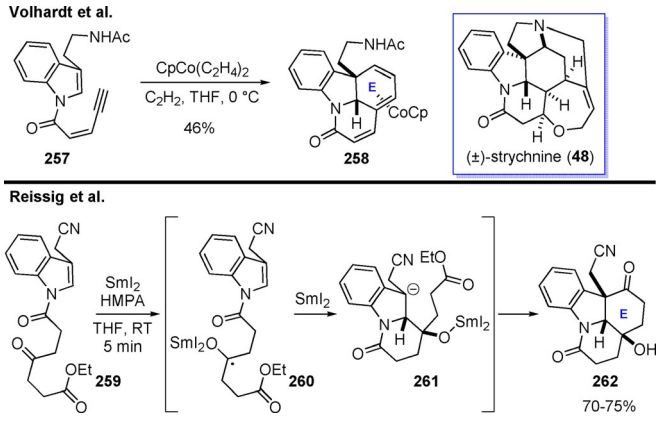


Scheme 29. Employment of Zincke aldehydes in Diels–Alder reactions towards tetracyclic indolines (Vanderwal et al.).

reports, Vanderwal has described the synthetic versatility of the tetracyclic building block **249** towards several *Strychnos* alkaloids.[69] 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).[70] By using N1 tethered alkynes in combination with external alkynes or C3 tethered alkynes, a [2+2+2] cycloaddition is initiated by $CpCo(C_2H_4)_2$. This method was applied to the total synthesis of (±)-strychnine. Starting from **257**, dearomatization through [2+2+2] cycloaddition gave indoline **258** as a single diastereomer of its CoCp complex in 46% yield.

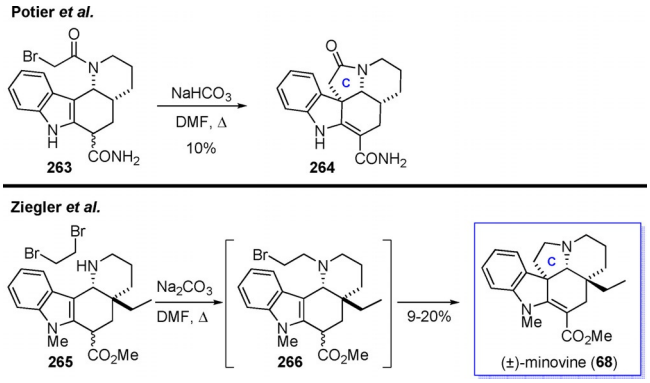


Scheme 30. Other approaches based on Co^{I}-mediated cycloadditions (Volhardt et al.) and Sm^{II}-mediated cascade cyclizations (Reissig et al.). HMPA = hexamethylphosphoramide.

Reissig and co-workers have obtained a similar synthetic intermediate through a SmI_2-mediated cascade cyclization from N1 tethered ketoester **259**.[71] SmI_2 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 Sm^{II} 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 diastereoisomer. The authors also applied this strategy in the formal total synthesis of (±)-strychnine.

5. Dearomative Assembly of the C-Ring

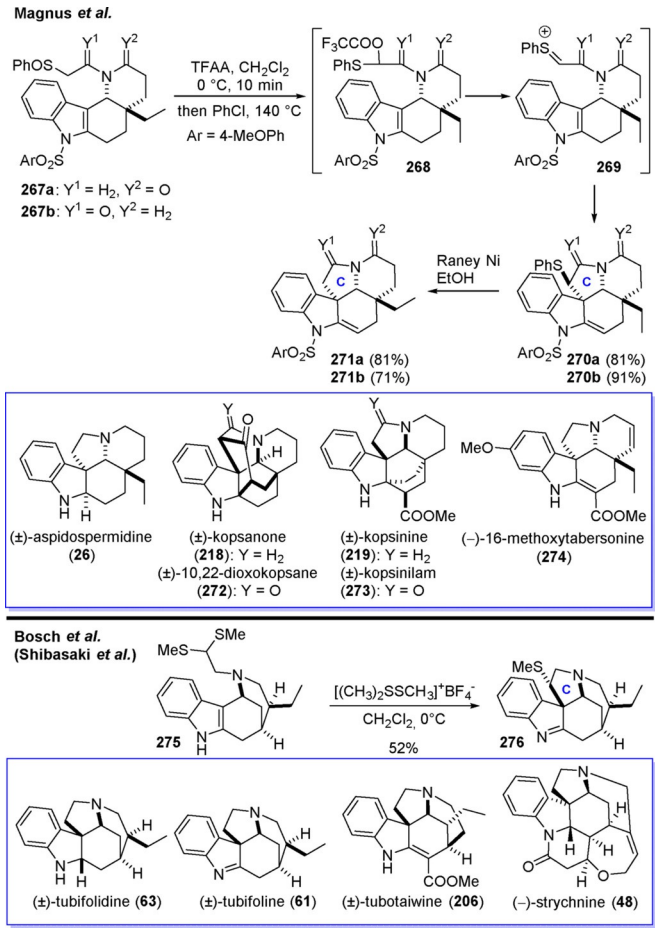
A retrosynthetic disconnection of the C-ring of the pentacyclic core of *Aspidosperma* and *Strychnos* alkaloids at first sight seems trivial. Nevertheless, this transformation should be deemed difficult, given the poor yields in separate communications of Potier and co-workers[72] and Ziegler et al.,[73] based on a seemingly straightforward dearomative S_N2 cyclization (Scheme 31).



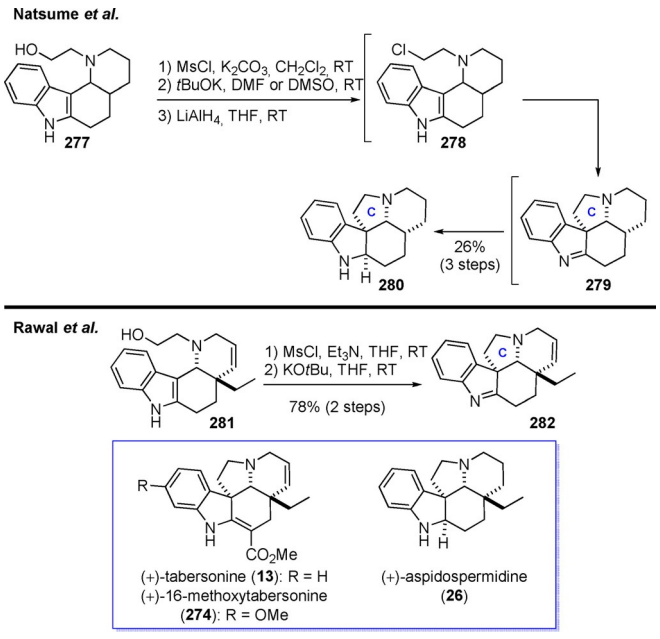
Scheme 31. First reported dearomative construction of the C-ring via S_N2 cyclizations (Potier and Ziegler et al.).

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).[74] 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.[75] 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.[76]

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).[77] After

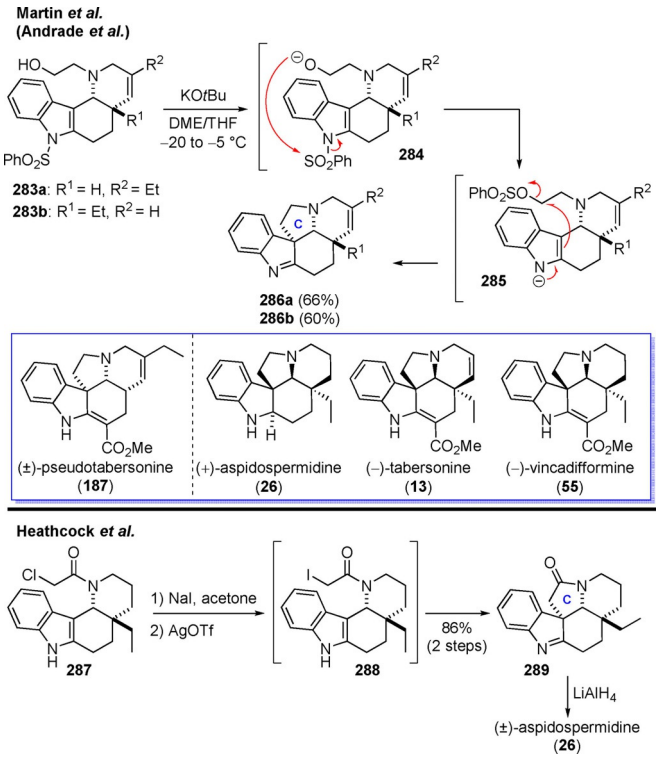


Scheme 32. 1,2-additions on sulfonium ions in *Aspidosperma* (Magnus et al.) and *Strychnos* alkaloids (Bosch et al.).



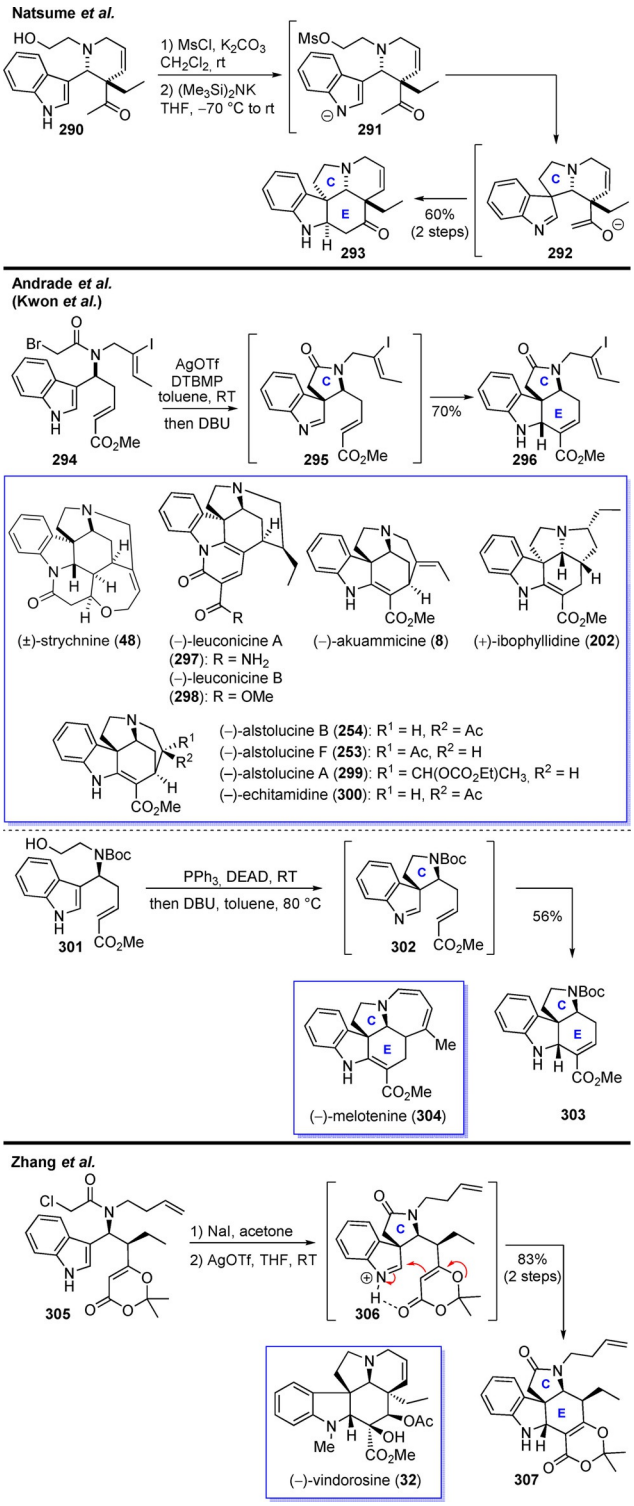
Scheme 33. Dearomative S_N2 cyclization to construct the C-ring (Natsume, and Rawal et al.).

slightly modifying the reaction conditions, Rawal and co-workers have improved this transformation and the analogous pentacycle **282** was obtained in 78% yield.[78] This two-step sequence is the most frequently found approach in the literature to construct the C-ring.[79] Martin et al. cleverly employed this principle by using alcohol **283** under basic conditions, allowing a sulfonyl transfer activating both the indole C3 position and the resulting sulfonate to promote an S_N2 cyclization (Scheme 34).[80] Alternatively to 2-hydroxyethyl substituents, Heathcock et al. showed that α-chloroamide **287** could be used under Finkelstein conditions to construct the C-ring.[81] However, this requires reduction of the amide to reach the pentacyclic core of the *Aspidosperma* alkaloids. Alternative routes involving carbene chemistry[82] and radical chemistry[83] were developed by others.



Scheme 34. Dearomative S_N2 cyclization to construct the C-ring (Martin and Heathcock et al.). DME = 1,2-dimethoxyethane.

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).[84] In the presence of potassium bis(trimethylsilyl)amide (KHMDS) at −70 °C, a dearomative S_N2 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.[85] 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



Scheme 35. Double cascade reactions to construct both the C- and E-ring systems in *Aspidosperma* and *Strychnos* alkaloids (Natsume, Andrade, and Zhang et al.). DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine; DEAD = diethyl azodicarboxylate.

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.[86]

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. Dearomatization 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 monoterpenoid 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 dearomative 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 dearomative strategies towards *Aspidosperma* and *Strychnos* alkaloid synthesis.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkaloids · biomimetic synthesis · dearomatization · indoles · natural product synthesis

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