Synthesis of indole derivatives as prevalent moieties present in selected alkaloids

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Indoles are a significant heterocyclic system in natural products and drugs. They are important types of molecules and natural products and play a main role in cell biology. The application of indole derivatives as biologically active compounds for the treatment of cancer cells, microbes, and different types of disorders in the human body has attracted increasing attention in recent years. Indoles, both natural and synthetic, show various biologically vital properties. Owing to the importance of this significant ring system, the investigation of novel methods of synthesis have attracted the attention of the chemical community. In this review, we aim to highlight the construction of indoles as a moiety in selected alkaloids.

1. Introduction

Indoles are a significant type of heterocycle as they are found in proteins in the form of amino acids, such as tryptophan. They are also present in several drugs, such as indomethacin and the notorious LSD, and several plants such as strychnine. The incorporation of an indole core, a biologically known pharmacophore in medicinal molecules, means it is a useful heterocyclic that can bear a number of biological properties. Compounds containing the indole nucleus exhibit several different biological properties, including anti-cancer, anti-fungal, anti-HIV, anti-inflammatory, anti-viral, anti-tubercular, anti-microbial, and anti-diabetic activities, and also photochemotherapeutic properties.

Natural products have been renowned as the source of several active ingredients of medicines. The currently approved natural-product-based drugs have been reported broadly in previous reviews. They contain compounds from plants (such as huperzine, elliptinium and galantamine), animals (ziconotide and exenatide), microbes (daptomycin) and also synthetic or semi-synthetic compounds that rely on naturally occurring compounds (for example everolimus, micafungin, telithromycin, caspofungin and tigecycline). They have various therapeutic indications, for example, they have anti-diabetic, anti-infective, and anti-cancer properties and so on.

Alkaloids occur as secondary metabolites in plants. They are recognized as nitrogen-containing natural biologically active compounds. Chemically, alkaloids are a class of nitrogen-containing compounds, which may contain one or more nitrogen atoms (in heterocyclic rings). In general, alkaloids are basic in nature and are typically obtained from plant sources.
There are numerous commercially available drugs available, that are alkaloid based in nature.\(^{10}\)

Indole alkaloids contain indoles that are bicyclic in structure, comprising a six membered benzene ring fused to a five-membered nitrogen bearing pyrrole ring. This pyrrole ring has a nitrogen atom, which results in the basic properties of indole alkaloids, making them pharmacologically active.\(^{11}\)

Indole alkaloids are broadly distributed in plants belonging to the families of Loganiaceae, Apocynaceae, Nyssaceae and Rubiaceae. Significant indole alkaloids that have been extracted from plants include the anti-hypertensive drug, reserpine from *Rauwolfia serpentina*\(^{12}\) and also the potent anti-tumor drugs, vincristine and vinblastine, obtained from *Catharanthus roseus*.

Various indole alkaloids exert significant pharmacological properties, but quite diverse influences can be attained even from alkaloids of one genus, for example the *Strychnos* alkaloid strychnine can strongly affect muscle contraction, whereas the toxiferines serve as muscle relaxants.\(^{13}\)

The indole unit is a near-ubiquitous component of biologically potent naturally occurring compounds. For instance, melatonin (1) is a hormone known in plants, animals, and microbes, in which the difference in duration of melatonin production each day, is used as a seasonal clock in animals.\(^{14}\) Tryptophan (2), a vital amino acid, partakes in various critical biological processes.\(^{15}\) Serotonin or 5-hydroxytryptamine (5-HT) (3), which is biochemically obtained from tryptophan, is known as a neurotransmitter and is found in all bilateral animals.\(^{16}\)

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**Fig. 1** The structures of natural products and drugs that possess indole moieties.

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In addition, the indole unit is recognized as one of the most significant moieties for drug discovery, and it has attracted the attention of researchers for generations. Reserpine (4), an indole alkaloid, is utilized in the treatment of high blood pressure and also in the treatment of severe agitation in patients that have mental disorders. Ajmalicine (5), an indole alkaloid which is present in various plants, is an anti-hypertensive drug that is utilized for the treatment of high blood pressure. Vinblastine (6) is applied for the treatment of various kinds of cancer, such as Kaposi’s sarcoma, Hodgkin’s disease, non-Hodgkin’s lymphoma, and testicular or breast cancer (Fig. 1).
Various methods have been reported for the synthesis of indoles, for example modern versions of classical synthesis methods (named reactions along with indole synthesis) such as: Bartoli indole synthesis, Hemetsberger indole synthesis, Bischler indole synthesis, Julia indole synthesis, Larock indole synthesis, Nenitzescu indole synthesis, Madelung indole synthesis, Reissert indole synthesis and the most important one, Fischer indole synthesis. Other methods involve the transformation of heterocycles, the conversion of indolines into indoles, the synthesis of \( \sigma \)-alkynylanilines, the reduction of oxindoles to indoles, synthetic methods using arynes, the reductive cyclization of nitrobenzene derivatives and catalysis using \( N \)-heterocyclic carbenes.

Owing to the importance of the indole as a scaffold in natural products and biologically active compounds, a plethora of reviews and several chapters have been published in this field. In a continuation of our interest in heterocyclic chemistry and the applications of named reactions in the total synthesis of natural products, in this review we aim to highlight the synthesis of indoles as a moiety in selected alkaloids.

2. Synthesis of indole moieties in alkaloids via named reactions

2.1. Fischer indole synthesis

Murrayanine is the main compound extracted from *Murraya Koenigii* in 1965 by Chakraborty. Murrayanine shows various anti-mycobacterial, anti-oxidant, and anti-fungal activities. *Murraya Koenigii* Spreng, an aromatic plant belonging to the family Rutaceae, is usually identified as the curry leaf tree. Notably, it has been utilized in sub-tropical and tropical Asia as a folk medicine. This tonic plant has been employed for the treatment of different disease conditions and has been demonstrated to have a potential role as a remedy for cancer.
and also inflammation. Moreover, the leaf extracts of *M. Koenigii* are broadly utilized as having anti-fungal,\(^7\) anti-diabetic,\(^8\) anti-inflammatory\(^9\) and anti-oxidant properties.\(^{10}\) In 1968, Chakraborty and co-workers reported\(^{11}\) the total synthesis of murrayanine (12). The total synthesis of murrayanine (12) started with the Japp–Klingemann reaction of phenyldiazonium chloride (7) and 2-hydroxymethylene-5-methylcyclohexanone (8) affording hydrazine 9. Then, the Fischer indole synthesis of hydrazine 9 using HOAc/HCl under reflux gives 1-oxo-3-methyl-1,2,3,4-tetrahydrocarbazole (10). The latter, after three synthetic steps, gives benzylic alcohol 11, which was oxidized using manganese dioxide in carbon tetrachloride to afford murrayanine (12) (Scheme 1).\(^{12}\) In addition, some alternative methods for the synthesis of murrayanine (12), including some with better overall yields, have been reported.\(^{13-18}\)

Pyrido[3,2-α]carbazole alkaloids are very stimulating owing to their structural aspects, and also because of their valuable biological properties.\(^{19-24}\) In 1968, Chakraborty *et al.* isolated murrayacine (18) from two different natural sources including *Clausena heptaphylla*\(^{25}\) and *Murraya koenigii*.\(^{26}\) The total synthesis of murrayacine (18) was achieved and reported by Chakraborty *et al.* in 1973.\(^{27}\) Using this method, the total synthesis of murrayacine (18) commenced with the reaction between 4-hydroxymethyl-3-hydroxyaniline (13) and formylcyclohexanone (14) via the Japp–Klingemann reaction, which afforded cyclohexane-1,2-dione 4-hydroxymethyl-3-hydroxyphenylhydrazone (15). The latter, through indolization in the presence of a mixture of glacial HOAc and HCl, provided the indole-2-hydroxy-3-hydroxymethyl-8-oxo-5,6,7,8-tetrahydrocarbazole (16). The latter afforded chromenoindole 17 after six steps. Finally, oxidation of the chromenoindole 17

Scheme 4 Total synthesis of makaluvamine D (37).
produced the natural product murrayacine (18) (Scheme 2). In addition, some alternative synthesis methods for murrayacine (18), some of which have better overall yields, have been reported.

_Evodia rutaecarpa_ has been used in Chinese medical practice for a long time has been utilized for the treatment of inflammation-related symptoms. Rutaecarpine is an alkaloid extracted from _Evodia rutaecarpa_. Investigations have demonstrated that this anti-inflammatory function is owed to its component rutaecarpine, which shows potent COX-2 inhibited activity. Moreover, rutaecarpine has other functions, for example, it has analgesic, vasorelaxing, anti-anoxic, anti-platelet and cytotoxic properties.

In 1971, vasicolinone (26), an quinazoline alkaloid, was extracted from the leaves of the Indian plant _Adhatoda vasica_ Nees (Acanthaceae). Both kinds of alkaloids have attracted significant attention because of their pharmacological properties. Rutaecarpine is one of the component parts of traditional ancient Chinese herbal medicine. In 1992, Hermecz and co-worker achieved and reported the total synthesis of rutaecarpine (24) and vasicolinone (26) through Fischer indolization of 3-(phenylhydrazonomethyl)pyrroloquinazolinone (22) under thermal and acidic reaction conditions, respectively. This research group attempted the total synthesis of rutaecarpine (24) and vasicolinone (26). The total syntheses of these two natural products started with deoxyvasicinone (21). Anthranilic acid (19) and 2-pyrrolidone (20) were reacted together via Kametani’s method using thionyl chloride (SOCl2) and gave the deoxyvasicinone alkaloid (21) in a high yield (93% yield), after two steps this yielded hydrazone 22. A solution of the hydrazone 22 in Dowtherm A was heated to above 160 °C, and the produced rutaecarpine (24) was slowly precipitated, upon recrystallization from dimethylformamide (DMF), the target natural product rutaecarpine (24) was provided in a moderate yield (49%).

In addition, under acidic reaction conditions, upon the protonation of spiroindoleninpyrroloquinazolinone (23) on the indolenine nitrogen, underwent a retrograde aldol reaction to afford the ring-opened pyrroloquinazolinone (25). In the following, after hydrolysis of the formamide substituent, the natural product vasicolinone (26) was quantitatively provided.
from pyrroloquinazolinone 25 using dimethylation of the amino group with 37% aqueous formaldehyde (HCHO) using sodium cyanoborohydride (NaBH₃CN) in acetonitrile at room temperature¹⁰⁹ (Scheme 3).¹⁰⁹

A class of very cytotoxic metabolites that possess the pyrrolo[4,3,2-de]quinoline framework were discovered upon examining the marine sources of anti-neoplastic agents.¹¹⁰ These contain the discorhabdins,¹¹¹ prianosins,¹¹² isobatzellines, batzelines,¹¹³ and damirones,¹¹⁴ all extracted in 1991 from sponges, and also wakayin, isolated from the Fijian ascidian Clauelina sp.¹¹⁵ Other members of the pyrroloiminoquinone family were identified by Ireland in 1993 from the Fijian sponge Zyzzya cf. marsailis.¹¹⁶ These materials, called makaluvamines, have been known to contain outstanding and potentially significant biological properties, for example inhibition of the function of mammalian topoisomerase II. Moreover, they show strong in vitro cytotoxicity towards the human colon tumor cell line HCT 116. The synthesis of the pyrrolo[4,3,2-de]quinoline system, that is typical of a class of marine alkaloids that contains the discorhabdins, prianosins, and also other anti-neoplastic agents, was demonstrated in 1994 by White et al.¹¹⁷ This method is represented in the total synthesis of makaluvamine D (37), a topoisomerase II inhibitor extracted from the sponge Zyzzya cf. marsailis. The total synthesis of makaluvamine D (37) starts from 2,3-dimethoxybenzoic acid (27) and within five steps affords (3,4-dimethoxyphenyl)hydrazine (28). The latter was reacted with dihydrofuran¹¹⁸ and provided a 1 : 1 mixture of the tetrahydrofuran (THF) 29 and the hydrazone 30 (as an E/Z mixture). The mixture was exposed to Fischer indolization reaction conditions in the presence of ZnCl₂ and gave the desired tryptophol 31, accompanied by the 4,5-dimethoxyindole derivative 32. Next, the elimination of 32 from the
corresponding product 31 proved difficult, and to prevent losses during purification, the mixture of 31 and 32 was directly sulfonated using excess p-toluenesulfonyl chloride. The bissulfonfonyl derivative 33 was provided in a satisfactory yield. The latter afforded tosylate 34 after five steps. In the following, the condensation reaction of 34 with tyramine was correspondingly productive, affording 35. In addition, further prolonged exposure to tyramine under reflux in EtOH eliminated the N-tosyl substituent from 35 and resulted in makaluvamine D (37) (Scheme 4).

In 1995, Osada and co-workers isolated tryprostatins A and B from the fermentation broth of *Aspergillus fumigatus* BM939. Tryprostatin A (44) possesses promising attributes, as it selectively stops the cell cycle in tsFT210 cells in the mitotic phase. Stimulating biological activity, along with a seemingly simple structure, has motivated the synthetic community, and various total syntheses have been demonstrated. In 1997, Cook and co-workers achieved and reported the enantiospecific total synthesis of tryprostatin A (44) through a regiospecific bromination method as a key step. The total synthesis of tryprostatin A (44) started with the reaction of *m*-anisidine (38) with NaNO2 and concentrated aqueous hydrochloric acid, followed by the addition of the anion of ethyl α-ethylacetoacetate, and the Japp–Klingmann azo-ester intermediate was obtained.

![Scheme 8](image-url)
Once this intermediate was heated in a solution of ethanolic HCl, a mixture of ethyl 6-methoxy-3-methylindole-2-carboxylate \(39a\) and its 4-methoxy isomer \(39b\) (10 : 1) was provided. The corresponding 6-methoxyindole isomer \(39a\) was separated from the mixture through facile crystallization and a four synthetic steps gave 3-(bromomethyl)indole (\(40\)). The latter was coupled with the anion of the Schollkopf chiral auxiliary \(41\) (obtained from \( \beta \)-valine),\(^{124}\) and the corresponding trans dia stereomer \(42\) was obtained as the sole product. After four steps the latter yielded dipeptide \(43\), which was heated at 160 °C (neat) and gave tryprostatin A (\(44\)) (Scheme 5).\(^{123}\)

The acetylcholinesterase inhibitors physovenine (\(48\)) and physostigmin\(^{125,126}\) contain basic furo- and pyrrolidinoindoline scaffolds, respectively. Pyrrolidinoindoline natural products, which contain the C-3a functionalized hexahydropyrrolo[2,3-b] indole ring scaffold, have been extracted from various natural sources and show diverse biological properties.\(^{127}\) The Physostigma genus (Fabaceae) produces a class of indole alkaloids involving physostigmine as the major basic component. Physovenine, one of the minor alkaloids of a similar plant, and a C-ring oxygenated analogue of physostigmine, was in turn structurally identified in 1964.\(^{128}\) Two of the alkaloids, (--)physostigmine and (--)physovenine exhibited strong anti-acetylcholinesterase (AChE) properties upon examination in vitro, and could be used to measure the inhibition of AChE by human erythrocytes.\(^{129}\) In 2010, Garg et al. demonstrated a convergent approach for the construction of the fused indoline ring scaffold found in a multitude of bioactive compounds. This approach includes the condensation reaction of hydrazines with latent aldehydes to eventually provide indoline-comprising products by using an interrupted Fischer indolization sequence.\(^{130}\)

This research group tried to demonstrate the formal synthesis of physovenine (\(48\)). Based on this approach, the formal synthesis of physovenine (\(48\)) was commenced from the Fischer indole synthesis of hydrazine \(45\) and lactol \(46\) in HAOc, which afforded furoindoline \(47\). The latter, after two steps (in a 55% yield), was transformed to physovenine (\(48\))\(^{131}\) (Scheme 6).\(^{130}\)

The formal total synthesis of (--)debromoflasumarine B (\(55\)) starting from pyrrolidinone \(49\)\(^{132}\) afforded hemiaminal \(50\) in two steps. The latter with 1-allyl-1-phenylhydrazine (\(51\)) in acetic acid/water at 100 °C assisted the key condensation/sigmatropic rearrangement to provide bis(allylated)pyrrolidinoindoline \(52\). Next, the reaction of compound \(52\) with 2-methyl-2-butene (\(53\)) using Grubbs’ second generation catalyst yielded the bis(pre nylated) derivative \(54\), which was transformed into (--)debromoflasumarine B (\(55\)) through reduction with Red-Al. It is worth mentioning that compound \(54\) has formerly been transformed into debromoflasumarine B (\(55\)) via reduction using lithium aluminum hydride\(^{133}\) (Scheme 7).\(^{130}\)

Colegate and co-workers isolated a furanobisindole alkaloid, called phalarine (\(63\)) from \( \textit{Phalaris coerulescens} \).\(^{134}\) Its structure was identified using a distinctive tricyclic propeller unit building block fused to a piperidine core and a multiply substituted indole scaffold via successive tetrafunctionalized stereogenic centers at C4a and C9a. However, the biological properties of \(63\) have not been previously reported, and the typical structure attracted the attention of various synthetic chemists,\(^{135,136}\) and their attempts resulted in the seminal

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**Scheme 9** Total synthesis of lycogarubin C (\(67\)) and lycogalic acid A (\(68\)).
enantioselective total synthesis of 63 by Danishefsky and Chen. In 2010, Danishefsky et al. demonstrated the Pictet-Spengler reaction for C2-aryl indoles, and effectively separated the elusive azaspiroindolenine intermediate of the Pictet-Spengler reaction. Total synthesis of phalarine (63) was commenced from β-carboline 56 and after 11 steps afforded the intermediate 57. The latter, using p-toluenesulfonic acid in toluene, gave the corresponding indole product 58 (5% yield), benzofuro[3,2-b]indole 59 (17% yield), benzofuro[3,2-b]indol-8-amine 60 (18% yield), and diindole-2-carboxylate 61 (9% yield). In the following, compound 60 gave diindole 62 after three steps. Upon installation of the gramine side chain on 62 using N,N-dimethylmethylene ammonium chloride in acetic acid, and elimination of the tosyl masking group, phalarine (63) was afforded (Scheme 8).

The natural products of lycogarubin C (67) and lycogalic acid A (68) were identified in 1994. They were extracted individually by Steglich and Akazawa from Lycogala epidendrum, a slime mold. Moreover, lycogalic acid, referred to as chromopyrrolic acid (CPA), has been identified as the usual intermediate in the biosynthesis of the indolo[2,3-a]carbazole alkaloids containing staurosporine and rebeccamycin; these show a broad range of properties as inhibitors of protein kinases and also topoisomerase I.

Lycogarubin C (67) and lycogalic acid A (68) are naturally occurring key marine compounds that are utilized in investigations into the inhibitor of DNA topoisomerase-I. In 2010, Zhixiang et al. demonstrated that lycogarubin C was synthesized from (but-3-ynyl)(tert-butyl)dimethylsilane as a starting precursor in eight steps, through the following key steps: a hetero-/retro-Diels-Alder reaction, the reduction of 1,2-diazine, Swern oxidation, and also Fischer indole synthesis.

The total synthesis of lycogarubin C (67) and lycogalic acid A (68) was commenced from (but-3-yn-1-yloxy)(tert-butyl)dime-thylsilane (64), and after seven synthetic steps, gave 1-(tert-butyl) 2,5-dimethyl 3,4-bis[2-oxoethyl]-1H-pyrrole-1,2,5-tricarboxylate (65). Then, the Fischer indole synthesis of 65 with phenyl hydrazine (66) using PPA in THF under reflux, afforded lycogarubin C (67) in a satisfactory yield (49% yield). Lastly, lycogalic acid A (68) was synthesized from lycogarubin C (67) using potassium hydroxide in THF and H2O under reflux (Scheme 9).

Minfiensine (75), an indole alkaloid that possesses important biological properties, such as anti-cancer activities, was initially extracted and isolated by Massiot et al. in 1989 from the African plant Strychnos minfensi. In 2011, Zhang et al. demonstrated the short total synthesis of (±)-minfiensine. This method involves a Fischer indole synthesis, a Heck alkylation of an intermediate ketone enolate, transformation of a ketone carbonyl into an epoxide, and also conversion of an epoxide into an allylic alcohol. The total synthesis of minfiensine (75) commenced with the Fischer indole synthesis. The

![Scheme 10](total synthesis of (±)-minfiensine (75))
Scheme 11  Total synthesis of (±)-aspidophylline A (84).

Scheme 12  Total synthesis of (+)-scholarisine A (90).
condensation reaction of phenylhydrazine (66) and 1,4-cyclohexadiene monoethylenecatetral (69) at ambient temperature followed by heating (at 190°C for 4.5 h) provided the anticipated indole product 70 in a good yield (89% yield), a further three steps gave the aldehyde 71. Then, the reductive amination of aldehyde 71 using NaBH₄ and 2-iodocrotylamine (72) in MeOH at ambient temperature afforded (Z)-2-iodobut-2-en-1-ol (73) in a good yield (86%). The latter after five steps afforded the allyl alcohol 74. After hydrolysis of the carbamide group in 74 using NaOH, minfensine (75) was synthesized in a good yield (82%) (Scheme 10).

(±)-Aspidophylline A (84) was extracted from *Malayan Kopsia singapurensis* by Kam and co-workers in 2007. It is known to reverse drug resistance in resistant KB cells. In 2011, Garg and co-worker reported the total synthesis of (±)-aspidophylline A (84), which is one of various complex furoindoline-containing alkaloids. This pathway contains various main conversions, comprising the Heck cyclization to assemble the [3.3.1]-bicyclic motif, as well as a late-stage interrupted Fischer indolization to provide the furoindoline and form the pentacyclic building block natural product. The total synthesis of (±)-aspidophylline A (84) started with the Diels–Alder adduct 78 that was prepared from the thermal Diels–Alder reaction of maleic anhydride (77) and pyridinone 76. Bicycle 78 furnished lactone 79 within 15 steps. The Fischer indolization reaction between ketoster 79 and phenylhydrazine using trifluoroacetic acid (TFA) in dichloroethane (DCE) at 40°C provided the intermediate 81, probably through intermediate 80. In the following, the elimination of the solvent and the addition of potassium carbonate in methanol under heating resulted in lactone methanolysis and cyclization (transition structure 82) and gave pentacycle 83. The elimination of the tosyl masking substituent of 83 and formylation gave (±)-aspidophylline A (84). As a result, the total synthesis of (±)-aspidophylline A (84) was performed in 18 steps from the Diels–Alder adduct 78 (Scheme 11).

The scholarisines belong to the family of akuammiline alkaloids. Scholarisine A, a monoterpenoid indole alkaloid, having an unprecedented framework with a bridged lactone embedded in a cage like building block, was first extracted in 2008 by Luo et al. from the leaves of *Alstonia scholaris*. The majority of Dengtaiye components are indole alkaloids, in which four major bioactive compounds, comprising vallesamine, scholarisine, 19-epischolarisine, and picrinine show important analgesic, anti-fertility, antibacterial, anti-asthmatic, antitumor and anti-tussive bioactivities. In 2012, Smith et al. reported an effective total synthesis of (+)-scholarisine A (90) through a 20-step reaction. Highlights of the reaction are a reductive cyclization including a nitrile and an epoxide, a modified Fischer indole reaction, a late-stage oxidative lactonization, and an intramolecular cyclization providing the indolene ring system of (+)-scholarisine A. The total synthesis of (+)-scholarisine A (90) was commenced from bicyclic lactone (–)–85, and after six steps gave the ketone (+)–86. Next, a Fischer synthesis using 1-benzyl-1-phenylhydrazine (87) (pyridine-HCl, 110°C) gave the masked indole lactone (–)–88. After 12 steps the latter gave indolenine (+)–89. Elimination of the trifluoroacetyl substituent in 89 with a 1:2 mixture of saturated aqueous potassium carbonate and MeOH, followed by aliphatic amine oxidation with iodosobenzene (PHIO) in CH₂Cl₂ afforded the natural product (+)-scholarisine A (90) (Scheme 12).

The asymmetric total synthesis of (+)-scholarisine A (90) was achieved and reported in 2013 by Smith et al. The key steps involve a novel cyclization, a modified Fischer indolization; an oxidative lactonization and a late-stage cyclization. The total synthesis of (+)-scholarisine A (90) was commenced from the commercially available anhydride 91 and after 12 steps this gave the ketone (+)–86. The latter was reacted with benzyl phenylhydrazine using a slightly acidic medium of pyridine/HCl.

![Scheme 13](image_url)
hydrochloric acid at 110 °C overnight to give the benzyl-protected indole (−)-88 in a good yield (>70%). Next, after 11 steps, the latter gave indolenine 89. In the following, the elimination of the trifluoroacetyl group in 89 was easily accomplished using a mixture of saturated aqueous potassium carbonate and MeOH (1:2) to provide the desired free amine. Finally, oxidation with iodosobenzene (PhIO) in CH₂Cl₂ completed the synthesis of (+)-scholarisine A (90) (Scheme 13).

The communesin family of naturally occurring compounds and perophoramidine are prevalent goals for chemical synthesis. Two indole alkaloids, including perophoramidine and communesin, that have unique molecular frameworks were extracted in 1993 and 2002 from ascidian Perophora namei and a strain of Penicillium sp., respectively. Both the indole alkaloids contain an analogous polycyclic scaffold comprising two vicinal quaternary centers and having a moderately inverted stereochemistry at the 4-position of the part-saturated quinoline scaffold. It is worth mentioning that perophoramidine 96 is cytotoxic against the HCT116 colon cancer cell line. In 2012, Garg et al. demonstrated a short strategy for the total synthesis of the communesin alkaloids and perophoramidine. This approach relies on the usage of the interrupted Fischer indolization to construct the tetracyclic indoline unit of the naturally occurring compounds. The synthesis of perophoramidine 96 started with the reaction of hydrazine 45 and N, O-acetal 93 using HOAc in H₂O at 75 °C via Fischer indole synthesis to provide the tetracyclic indoline 94. It is worth mentioning that the carbamylated N, O-acetal 93 was used in this approach as it was known to be more easily removed in comparison with the N-Ts group. Next, the tetracyclic indoline 94 afforded imine 95 within two steps as an intermediate for the synthesis of perophoramidine 96 (Scheme 14).

Dictyodendrins A–E were extracted from the marine sponge Dictyodendrilla verongiformis collected off the southern Japanese coast in 2003 by Matsunaga and Fusetani. These natural products contain an exclusive pyrrolo[2,3-c]carbazole unit, and at least one sulfate substituent in their periphery structure. In addition, these alkaloids display a telomerase inhibitory property. As telomerase is overexpressed in most tumor cell lines, telomerase inhibition signifies a unique favorable approach for the establishment of cancer chemotherapy. Jia and co-workers in 2014 revealed a complete elucidation for the short total synthesis of dictyodendrins E. The total synthesis of dictyodendrins E (105) started from the Ullmann coupling reaction of p-iodoanisole (97) and 1,3-dinitrobenzene (98), and afforded biphenyl 99, after a further three steps the iodide 100 was obtained. Next, the Ullmann coupling reaction of iodide 100 using BocNHNH₂ provided the corresponding Boc-masked phenylhydrazine 101 in a satisfactory yield (57%). Then, the Fischer indole synthesis of Boc-masked phenylhydrazine 101 and ketone 102 afforded indole 103. Upon four steps, phenol 104 was provided from indole 103. Finally, dictyodendrins E (105) were successfully synthesized after four synthetic steps ((1) CI₂SO₃, CH₂CCL₃; (2) BCl₃, TBAI; (3) Zn, HCO₂NH₄; (4) 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), room temperature) from phenol 104 (Scheme 15).

In 2015, Tokuyama reported the total synthesis of the biosynthetically-related monoterpene indole alkaloid (−)-mersicarpine (110). An azepino[3,2-b]indole intermediate was synthesized through d’Angelo’s enantioselective Michael addition, Fischer indole synthesis, and DIBALH-catalyzed reductive ring-expansion reaction. The total synthesis of (−)-mersicarpine...
(110) began from the optically active cyclohexanone 106. The Fischer indole synthesis of the optically active cyclohexanone 106 and phenylhydrazine hydrochloride (107) by using methanesulfonic acid (MsOH) under reflux in MeOH gave the corresponding tricyclic indole (−)-108 in a good yield (84% yield). Indole (−)-108 after six steps, gave azepinoindole 109. The latter, after autoxidation of the resultant 109 and reductive treatment with dimethyl sulfide completed the total synthesis of (−)-mersicarpine (110). As a result, the total synthesis of (−)-mersicarpine (110) was accomplished in a six-pot/nine-step sequence with a 21% overall yield (Scheme 16)."
Scheme 16  Total synthesis of (-)-mersicarpine (110).

Scheme 17  Synthesis of the unit structure of racemosin B (117) and asteropusazole (118).
The indolo[3,2-a]carbazole framework, one of the isomeric indolocarbazoles, is naturally occurring and was first reported in 2002. Three members of this family, including asteropusazole A, B and ancorinazole were extracted from marine sponges by Wright and co-workers in 2013. The first results of the cytotoxicity and anti-microbial assays demonstrated that asteropusazole A is a medicinal candidate that can be used to target psychiatric and neurological disorders. In 2016, Kotha et al. reported a novel synthetic approach to indolocarbazoles using a two-fold Fischer indolization under eco-friendly reaction conditions using N,N-dimethyl urea and L- (+)-tartaric acid. In this method, atom economical reactions, such as ring-closing metathesis, enyne-metathesis, and also the Diels-Alder reaction have been utilized as key steps.

The unit structure of asteropusazole (118) and racemosin B (117) was synthesized using Fischer indolization of cyclohexanone 113 and N-methylphenylhydrazine (112) (prepared from the commercially available aniline derivative 111) that afforded carbazole 114. Using the DDQ oxidation reaction, 111 gave the keto derivative 115. Lastly, the N-masked indole derivative 115 was treated with N-methylphenylhydrazine 112 to afford the highly aromatized product 116 in a moderate yield (51% yield), which is an intermediate for the synthesis of asteropusazole (118) and racemosin B (117) (Scheme 17). Scholarisine K and A belong to the family of akuammiline alkaloids. Scholarisine K (123) and alstolactine A (125) were extracted by Luo and co-workers in 2015 from Alstonia scholaris. The first enantioselective total synthesis of scholarisine K (123) and alstolactine A (125) were performed in 2017 by Gao et al. The key aspects of these syntheses are the ring closure metathesis and also an intramolecular Heck reaction to make the 1,3-bridged [3,3,1] bicycle (C–D ring), the intramolecular alkylation reaction was followed by the Fischer indolization reaction to make the basic framework of the akuammilines, and also the bioinspired, acid-improved epoxide opening/lactonization to form the second lactone ring of alstolactine A. The total synthesis of scholarisine K (123), and alstolactine A (125) started with aldehyde 119, which after more
than 14 steps afforded the corresponding lactone 120. The latter was converted to indolenine 121 through a Fischer indolization. After five steps indolenine 121 gave epoxide 122. The removal of N-Cbz under Pd(OH)₂/C and reductive amination in two steps (with 79% yield) provided scholarisine K (123). Moreover, indolenine 121, after more than six steps, gave epoxide 124.

Scheme 19  Total synthesis of (−)-quebrachamine (132), (−)-pyrifolidine (133), (−)-aspidospermine (134), (+)-aspidospermidine (135) and (+)-vincadifformine (136).
Based on similar transformations, the natural product alston lactine A (125) was provided by replacing the Cbz with a methyl group (Scheme 18).  

(-)-Pyridofidine was first extracted by Svoboda et al. from the leaves of Aspidosperma quebracho blanco (Apocynaceae) in 1973. The consistently strategic total syntheses of Aspidosperma alkaloids (+)-vincadifformine (136), (-)-quebrachamine (132), (+)-aspidospermidine (135), (-)-aspidospermine (134), (-)-pyridofidine (133), and also nine others using the effectively generated tricyclic ketone 129 were demonstrated in 2017 by Jiang et al. Key aspects of these synthetic methods are the stereoselective intermolecular [4 + 2] cycloaddition, a palladium/C-mediated hydrogenation/deprotection/amidation cascade method and also the Fischer indolization reaction. The total synthesis of (+)-vincadifformine (136), (+)-aspidospermidine (135), (-)-aspidospermine (134), (-)-pyridofidine (133), and (-)-quebrachamine (132) were started from the cycloaddition of 3-ethyl-5-bromo-2-pyrene 126 and enecarbamate (5)-127 that afforded the exo-bridged tricyclic lactone 128 (54% yield, 77% brsm) with an exo/endo selectivity of 7 : 1. The latter, after more than nine steps, gave the tricyclic ketone 129. Next, the reaction of ketone 129 with phenylhydrazine (66), 2-methoxyphenylhydrazine (130), or 2,3-dimethoxyphenylhydrazine (28) via a Fischer indole cyclization gave (+)-dehydroadiospermidine (131a) (71% yield), (+)-dehydroadecatryptopospermidine (131b) (66% yield) and (+)-dehydroaspidospermidine (131c) (46% yield), respectively. Natural products (+)-vincadifformine (136), (+)-aspidospermidine (135), and (-)-quebrachamine (132) were synthesized from 131a (via different routes). 

Moreover, the total synthesis of (-)-aspidospermine (134) was accomplished in two steps from 131b and also the total synthesis of (-)-pyridofidine (133) was performed in two steps from 131c. As a result, the total synthesis of (+)-vincadifformine (136) (4.4% overall yield), (+)-aspidospermidine (135) (7.1% overall yield), (-)-aspidospermine (134) (3.8% overall yield), (-)-pyridofidine (133) (3.7% overall yield), and (-)-quebrachamine (132) (4.3% overall yield) were accomplished from the cycloaddition of 3-ethyl-5-bromo-2-pyrene 126 and enecarbamate (5)-127 (Scheme 19).  

(-)-Goniomitine, extracted in 1987 by Randriambola et al. from the bark of Gonomia Malagasy, is distinguished from other Aspidosperma alkaloids by its distinctive aminal-comprising tetracyclic unit. In 2017, Stoltz et al. demonstrated a Fischer indolization method to form a key tricyclic intermediate dihydropyrrolo[1,2-a]indole (140) to give (-)-goniomitine (142) in three steps from commercially available precursors. The synthesis of (-)-goniomitine (142) started from 1,3-cyclohexanedione (137), which provided the corresponding C-alkylated product 139 in a satisfactory yield (70% yield) as the enol tautomer. Upon examining various reaction conditions for the Fischer indolization reaction, it was identified that exposing enol-139 to 2N HCl under reflux in toluene gives the key product dihydropyrrolo[1,2-a]indoline (140), although in an inadequate range of 10–33% yield. After three steps the latter afforded lactam 141 that is an intermediate for the synthesis of (-)-goniomitine (142) (Scheme 20). 

Carbazole alkaloids exhibit various biological and pharmacological properties. In addition, they have potential uses in electroluminescent materials, especially electrical, thermal, and also optical properties. Chlorine C (153) and clausine M (155) were extracted from Clausena excavata by Huang and co-workers in 1996. The sienanol carbazole alkaloid (150) extracted from Murraya siamensis exhibited biological properties, for example anti-HIV properties. In addition, clauszinol K (152) and clausine N (154), extracted from the stem bark of Clausena excavata, have been applied in traditional medicine as a detoxification agent and also for the treatment of snake bites. In addition, they show powerful anti-cancer, anti-bacterial, and anti-oxidant properties. Glycozolicine (156) was isolated for the first time in 1992 from the roots of Glycosmis pentaphylla by Chakraborty and co-workers. Furthermore, cytotoxic carbazole alkaloids; claurail A (148a) and clausenial (148b) were extracted from
the roots of *Clausena harmandiana* (*Rutaceae*) and the leaves of *Clausena heptaphylla*, respectively. Clauraila A (148a) demonstrated an important selective cytotoxicity towards human lung cancer cells (NCIC-H187) and is utilized in Thai folk medicine for the treatment of stomach aches, headaches, and also stomach sickness.²⁰³
In 2017, Lokhande et al. reported the synthesis of 7-oxygenated carbazole alkaloids through a Fischer–Borsche ring and metal-free reaction conditions. The key step includes the aromatization and a one-pot iodination procedure for functionalization of the Fischer–Borsche ring with molecular iodine. A suitably oxygenated functionality has been introduced to the Fischer–Borsche ring through this approach to produce clauszoline K (152), clausine M (155), clausine N (154), siamenol (153), and strictamine (166), (-)-2(S)-cathafoline (167), (-)-Ψ-akuammigine (169) and (+)-akuammiline (171).
(150), glycozolicine (156), clauraila A (148a) and clausenal (148b). The total synthesis of clauszoline K (152), glycozolicine (156), clausine C (153), clausine N (154), clausine M (155), clauraila A (148a), clausenal (148b) and also the formal synthesis of siamenol (150) were started from the reaction of (3-methoxy/3-bromo)phenylhydrazine 143a/143b and 4-methylcyclohexanone/4-propionylcyclohexan-1-one 144a/144b under reflux in HOAc via the Fischer–Borsche method, which delivered tetrahydrocarbazoles 145a/146a or 145b/146b. Next, compounds 147a and b were synthesized from tetrahydrocarbazoles 145a and 146a in four steps. Finally, the oxidation of carbazoles 147a and b using DDQ in MeOH/H2O yielded clauraila A (148a) and clausenal (148b). In addition, the total synthesis of glycozolicine (156) was performed in two steps (aromatization and displacement) from tetrahydrocarbazole 146a (Scheme 21).

On the other hand, a two steps tetrahydrocarbazole 145a gave the monoiodinated carbazoles 149 or 151 (using different routes). Then, the substrate 151, through an oxidation reaction in the presence of DDQ in MeOH/H2O, afforded clauszoline-K (152). Lastly, the formal synthesis of siamenol (150) was accomplished from monoiodinated carbazole 149. In the following, clausine C (153) was synthesized from ester 145b, in two steps. Moreover, the reaction of 153 with sodium hydroxide in MeOH gave the clausine N (154) in a 100% yield.

On the other hand, the elimination of the methyl group in clausine C (153) using BBr3 in dichloromethane, gave the natural product clausine M (155) in a satisfactory yield (75% yield) (Scheme 21). Some alternative synthesis methods for these carbazole alkaloids, some of which have better overall yields, have been reported.

The akuammiline alkaloids, a significant class of naturally occurring compounds, were extracted from plants found in Africa, India, and Southeast Asia. (+)-Strictamine (166) was extracted in 1966 by Schnoes from the plant *Rhazya stricta*, and (−)-2(S)-cathafoline (167) was isolated in 2014 from *Alstonia macrophylla*. (−)-2(S)-Cathafoline (167) exhibited satisfactory activity in overturning drug resistance in vincristine resistant KB cells. (+)-Akuammiline (171) was extracted together with (−)-Ψ-akuammigine (169) in 1932 by Henry. (−)-Ψ-Akuammigine (169) was extracted from *Picralima klaineana* in 1932. Biological investigations demonstrated favorable activity for use as an anti-inflammatory agent. In 2018, Garg et al. demonstrated the initial total synthesis of (+)-strictamine (166), (−)-2(S)-cathafoline (167), (−)-Ψ-akuammigine (169) and (+)-akuammiline (171). This methodology is based on the establishment of the reductive interrupted Fischer indolization reaction to form a pentacyclic intermediate having five contiguous stereocenters, as well as late-stage construction of the methanoquinolizidine building block through a deprotection cyclization cascade reaction. The total synthesis of
(−)-Ψ-akuammigine (169) and (+)-akuammilide (171) feature the initial constructions of akuammiline alkaloids comprising both a methanoquinolizidine unit and vicinal quaternary centers. Moreover, this group demonstrated the bioinspired reductive rearrangements of (+)-strictamine (166) and (+)-akuammiline (171) to give (−)-10-demethoxyvincorine and also a novel equivalent thereof.

In this method, the total synthesis of (+)-strictamine (166), (−)-2(S)-cathafoline (167), (−)-Ψ-akuammigine (169) and (+)-akuammiline (171), began with the palladium-mediated Trost desymmetrization of sulfonamide 158 and dibenzoate 157 and providing the alcohol 160. The latter, after 12 steps, gave ketolactone 161, and through the Fischer indolization reaction in the presence of trifluoroacetic acid in 1,2-dichloroethane this afforded the indolenine lactone 162. The latter in the presence of triethylsilane and additional trifluoroacetic acid under stirring at 23 °C afforded the reductive Fischer indolization product 164 in a good yield (83% yield). In the following, indoline 164, after seven steps gave the alkyl chloride 165, which after oxidation, followed by deprotection-cyclization afforded the natural product (+)-strictamine (166). Similarly, compound 165, after N-methylation and deprotection-cyclization afforded (−)-2(S)-cathafoline (167).

Furthermore, indoline 164, after seven steps, gave furindoline alcohol 168. The latter, after two steps, yielded the natural product (−)-Ψ-akuammigine (169).

![Scheme 24](image)
after six steps, afforded aldehyde 170. Finally, aldehyde 170 after four steps yielded (+)-akuammiline (171) (Scheme 22). Various carbazole alkaloids have been extracted from terrestrial plants. In addition, numerous carbazole alkaloids have been found in various streptomycillin and algae species. In 1979, 6-chlorohyellazole and hyellazole were the first carbazole alkaloids extracted from the blue-green alga *Hyella caesipitosa*. In 2018, Chakraborty and co-worker demonstrated

**Scheme 25**  Total synthesis of (-)-minovincine (190) and (-)-aspidofractinine (195).
the total synthesis of marine natural alkaloids chlorohyellazole and hyellazole. In this route, the total synthesis of hyellazole (180) and 4-deoxycarbazomycin B (181) were commenced from 2-methyl-3-nitroaniline (172), which after ten steps afforded 2-bromo-4-methoxy-3-methylaniline hydrochloride (173). The latter, using NaNO2 and diluted HCl in 0–5 °C afforded 2-bromo-4-methoxy-3-methylbenzene diazonium chloride (174), which using the Japp–Klingemann coupling reaction with 2-formylenoohexanone (175) provided functionalized phenylhydrazonocyclohexanone (176). Fischer indole cyclization of 176 in the presence of glacial AcOH and a concentrated HCl mixture afforded 1-ketotetrahydrocarbazole (177).209 The latter, after two steps including a Wolff–Kishner reduction and aromatization, gave a mixture of 3-methoxy-2-methyl-9H-carbazole (178) with an 11% yield and 1-bromo-3-methoxy-2-methyl-9H-carbazole (179) with a 65% yield. Finally, the Suzuki cross-coupling reaction of carbazole 179, phenylboronic acid and methylboronic acid, respectively, in the presence of a palladium catalyst, afforded the natural products hyellazole (180) and 4-deoxycarbazomycin B (181) (Scheme 23).208 Some alternative synthetic methods for hyellazole (180), chlorohyellazole, and 4-deoxycarbazomycin B (181), some of which have better overall yields, have been reported.210–218

Fontanesines A–C, bearing both quinazoline and the pyrano[3,2-e]indole framework, were extracted from the leaf fractions and stem bark of Conocarpus fontanesianus that were gathered in Brazil by Queiroz and co-workers in 2016.219 These alkaloids have not been completely examined biologically, owing to restricted accessibility. Fontanesines are a rare type of pyrano[3,2-e]indoloquinazoline alkaloid. However, although pyrano[3,2-e]indoloquinazoline alkaloids have not been reported previously. A previous investigation on the leaf extracts of C. fontanesianus stated their cytotoxic, anti-fungal, and also anti-microbial activities, but the potent principles were not developed.209 In 2019, Abe et al. reported220 a short synthesis of pyrano[3,2-e]indole alkaloid fontanesine B via a Fischer indolization. The isomer of fontanesine B exhibited a greater anti-proliferative property in comparison with the natural product, fontanesine B (187). The total synthesis of fontanesine B (187) was started from 4-acetamidophenyl acetal (182), which after seven steps gave the arlyhydrazone 183. The reaction between arlyhydrazone 183 and quinazolinone 185 (prepared from isatoic anhydride (184) in five steps) using acetic acid afforded hydrazone 186 in a moderate yield (50% yield). In the following, the extraordinary Fischer indolization of hydrazone 186 was examined. It was found that the pyran ring was injured under the acidic conditions, thus establishment of the Fischer indolization using the hydrazone containing pyran scaffold is fairly stimulating. Hence, examination using different acids was performed, it was found that acetic acid and propionic acid were appropriate for improving the Fisher indolization and the pyran-ring and alkene remained intact. Hydrazine 186 under reflux in acetic acid gave a mixture of 187 and 188 in a satisfactory yield (71% yield, 187/188 = 25 : 75). Among the various acids, propionic acid was the most effective acid at providing the desired cyclized products (88% yield, 187/188 = 33 : 67) (Scheme 24).221

The Tabernaemontana genus belongs to the family Apocynaceae containing various species distributed throughout subtropical and tropical regions of the world, including Brazil.222 (±)-Minovincine was extracted from Tabernaemontana riedelii by Szántay in 1997.223 Aspidofrutacin-type alkaloids were extracted from the leaf extract of Kopsia teoi by Kam and co-workers in 1997.224 In 2020, Soós and co-workers demonstrated225 the eight-step synthesis of (−)-minovincine (190) and (−)-aspidofrutacin (195) using simply accessible reagents and a catalyst. A key aspect of the methodology was the application of the chain of cascade reactions to quickly make the penta- and hexacyclic building blocks. These cascade conversions involved the organocatalytic Michael–Aldol condensation, a multistep anionic Michael–S,2 cascade reaction and also a Mannich reaction interrupted Fischer indolization. The total synthesis of (−)-minovincine (190) began with the formation of tricyclic 186, which was provided using the Michael addition–Aldol condensation organocascade reaction of the Nazarov reagent 184 and ω-chloro-formylpentenoate 185 (ref. 226) in three steps. Then, by using the selective deprotection of the t-Bu-ester, the resultant β-oxo carboxylic acid was decarboxylated in situ and gave ketone 187 in a high yield (95% yield). Then, reaction of product 187 with phenylhydrazine (66) gave aspidospermane-type indolene 189 (50% yields) and its structural isomer 188 (31%, yields) respectively. Finally, after two steps, pentacyclic 189 gave (−)-minovincine (190). As a result, (−)-minovincine (190) was synthesized in eight steps with an 11% overall yield. On the other hand, after three steps the tricyclic ketone 186 afforded the C-5 acetyl functionalized tricyclic ketone 191. Next, the Fischer indoleMannich cascade reaction occurred efficiently to give the relevant oxoaspidofrutacin 194 in a moderate yield (55% yield) (alongside its isomer 192) through a recognized indolene intermediate 193. Finally, substrate 194 was submitted to hydrazine to provide the (−)-aspidofrutacin (195) in a high yield (89% yield). As a result, (−)-aspidofrutacin (195) was synthesized in eight steps with a 19% overall yield (Scheme 25).225

The genus Strychnos, the biggest genus of the family Loganiaceae, was identified by Linnaeus on the basis of Strychnos nux vomica, the type species, and Strychnos colubrina.227 The uleine-type alkaloids constitute a significant subgroup of the Strychnos alkaloids that are identified by the 1-methylcholanoazocino[4,3-b]indole scaffold as having an ethyl substituent at the bridging carbon atom. Uleine was extracted by Schmutz et al. from Aspidosperma ulei MgP228 and its accurate structure was suggested by Warnhoef and Buchi in the late 1950s.229 (−)-Tubifolidine was extracted from the Strychnos species by Amat and co-workers in 1997.230 In 2020, Cho and co-workers reported231 the enantioselective synthesis of (±)-uleine (204) and (−)-tubifolidine (210). The regioselective construction of enol triflates from 2-aza bicyclo[3.3.1]nonan ketones and also indolizations of the resulting ene-hydrizades permitted the effective formation of key indole intermediates, assisting the total synthesis of the desired natural alkaloids. The total synthesis of (±)-uleine (204) was commenced from the key chiral...
Cyclohexenone 197 prepared in a 93% enantiomeric excess (ee) by using modification of the process previously published by Ma et al. from ethyl (E)-4-oxopent-2-enoate (196). In the following, compound 197, after five steps, afforded the bicyclic ketone 198. The latter was reacted with potassium tert-butoxide and the Comins’ reagent at −78 °C in THF/DMF (1 : 6) to provide enol triflate 199 as the main product, together with trace quantities of 199′, which was exposed to the two-step indolization reaction for the end-game synthesis of (+)-uleine (204). In this route, the carbon–nitrogen coupling of 199 and 199′ with phenyl hydrazide 200 afforded enehydrazides 201 and 201′ as an inseparable 37 : 1 mixture in a satisfactory yield (71% total yield). Next, indolization was applied in the presence of zinc chloride by heating to 90 °C in toluene using a molecular sieve, which afforded the corresponding indole 202 (76% yield) and its isomer 202′ (3% yield), after separation. After a further two steps, indol 202 gave (+)-dasycarpidone (203), and after the addition of MeLi and the subsequent dehydration reaction (+)-uleine (204) was yielded. As a result, (+)-uleine (204) was synthesized in 12 steps from cyclohexenone 197 with a 9.2% total yield (Scheme 26).

The formal synthesis of (−)-tubifolidine (210) was started from cyclohexenone 205 in an enantiomerically enriched form with a high ee (98% ee). After five steps cyclohexenone 205, afforded the corresponding ketone 206. After two steps the latter gave enehydrazides 207 and 207′ as an inseparable 21 : 1 mixture. Submission to the zinc-catalyzed indolization reaction gave indole 208 in a good yield (74% yield). Then, the indole intermediate 208, after six steps, including the protection of the indole nitrogen, elimination of the methoxymethyl (MOM) substituent, pyridinium chlorochromate (PCC) oxidation, Wittig olefination, palladium-mediated hydrogenation, and N-alkylation afforded the recognized indole intermediate 209, this

Scheme 26  Total synthesis of (+)-uleine (204).
was formerly transformed to (−)-tubifolidine (210) (Scheme 27).

The paraherquamides are an uncommon family of naturally occurring fungal compounds that include a bicyclo[2.2.2]diazaoctane unit structure, a spiro-oxindole, and a functionalized proline scaffold. Among them, paraherquamide A, was extracted from cultures of *Penicillium paraherquei* by Yamazaki et al. in 1981. VM55599, a minor metabolite from culture extracts of a *Penicillium* spp. was isolated in 1993 by Everett et al. Sarpong et al. in 2020 demonstrated a full explanation of the investigations into reverse-prenylated indole alkaloids containing a bicyclo[2.2.2] unit. A different pathway was described that led to the formation of (+)-VM-55599, paraherquamide and premalbrancheamide. An intramolecular Dieckmann cyclization of an isocyanate and an enolate was utilized to make the bicyclo[2.2.2]diazaoctane unit. The pentacyclic indole framework was formed via a one-pot Hoffman rearrangement and Fischer indolization synthesis. The total synthesis of paraherquamide (219), (+)-VM-55599 (220) and premalbrancheamide (216) were started from enone 211 (prepared in gram-scale amounts from 1-tert-butyl 2-ethyl-3-oxopyrrolidine-1,2-dicarboxylate in nine steps with a 37% overall yield). In the following, enone 211, after three steps, gave isocyanate 212. The latter, using H2SO4, was transformed into the relevant ammonium intermediate 213 that was exposed to phenylhydrazine (66) to influence Fischer indolization, affording pentacyclic indole 214 in a single-pot operation. Next, the latter, after three steps, gave ketone 215, which after two steps (Wolff–Kishner reduction and chemoselective reduction of the tertiary amide) gave the natural product premalbrancheamide (216). Moreover, ketone 215, after two steps, afforded a mixture of the exocyclic alkene (217) and endocyclic alkene (218) in a 71% yield (1:2 mixture). Hydrogenation of the mixture of alkenes (*i.e.*, 217 and 218) using Pd/C and chemoselective tertiary amide reduction using DIBAL-H gave the natural products paraherquamide (219) and (+)-VM-55599 (220) (Scheme 28).

In 2020, Varga et al. demonstrated a unique reductive interrupted Fischer indolization method for the short synthesis of the 20-oxoaspidospermidine scaffold. This fast complexity producing pathway covers the route towards different dihydroindole *Aspidosperma* alkaloids having various C-5 side chain redox patterns. The end-game redox modulations were performed by using a modified Wolff-Kishner reaction and also a photo-Wolff rearrangement, allowing the total synthesis of (−)-aspidospermidine (229), (−)-limaspermidine (232), and also (+)-17-demethoxy-N-acetylcylindrocarine (231). The total synthesis of (−)-aspidospermidine (229), (−)-limaspermidine (232), and (+)-17-demethoxy-N-acetylcylindrocarine (231) were

![Scheme 27](image-url)  
**Scheme 27** The formal synthesis of (−)-tubifolidine (210).
started from the reaction of tert-butyl 3-oxopent-4-enoate (221) and methyl 5-chloro-2-formylpentanoate (222), that afforded 1,3-dicarboxylate 223. The latter, after three steps, gave the stereochemically complex intermediate 225. It was found that the chemoselective reduction of the imine scaffold is similar to a Meerwein–Ponndorf–Verley type reduction,240 in which the hydride source was the sacrificial alcohol solvent. Based on this result, isopropanol was used as a solvent to increase the

Scheme 28  Total synthesis of preparherquamide (219), (+)-VM-55599 (220) and premalbrancheamide (216).
efficiency of the reductive conversion and elevate the reaction temperature from 85 to 115 °C. Pleasantly, these modifications afforded the corresponding pentacyle 228 as the main product (63% yield) along with the 3H-indole 227 (32% yield), the side-product of Fischer indolization. After three steps, ester 230 was synthesized from the key intermediate 20-oxoaspidospermidine (228). Then, ester 230, after two steps including reduction and removal, yielded (−)-limaspermidine (232). Moreover, ester 230, after treatment using TFA and Ac₂O, gave (+)-17-demethoxy-N-acetylcylindrocarine (231).

In the following, the intermediate 228, after two steps (modification of the original Stork–Dolfini synthesis) afforded the natural product (−)-aspidospermidine (229). Notably, the total synthesis of (−)-aspidospermidine (229) was performed in eight reaction vessels with an overall yield of 14%. In addition, the total synthesis of (−)-limaspermidine (232) was performed in 12 steps and gave an overall yield of 7%. Moreover, the total synthesis of (+)-17-demethoxy-N-acetylcylindrocarine (231) was accomplished in 12 steps with a 5% overall yield (Scheme 29).

Scheme 29  Total synthesis of (−)-aspidospermidine (229), (+)-17-demethoxy-N-acetylcylindrocarine (231) and (−)-limaspermidine (232).
2.2. Larock indole synthesis

Sarpagine and Ajmaline are biogenetically correlated alkaloids that have been extracted from different species of *Rauwolfia* that are generally dispersed throughout Africa and Asia. These plants are broadly utilized in folk Chinese medicine for the treatment of neuralgia, hypertension, and migraines. (+)-12-Methoxy-\(N\)-methylvellosimine (239) and (+)-12-

Scheme 30  Total synthesis of (+)-12-methoxy-\(N\)_methylvellosimine (239), (+)-12-methoxyaffinisine (240) and (-)-fuchsiaefoline (242).
methoxyaffinisine (240) were extracted by Kato and co-workers in 2002 from the bark of *Rauwolfia bahiensis*. In addition, (−)-fuchsiaefoline (242) was extracted from *Peschiera fuchsiaefolia* in 1987 by Reis and co-worker. Cook and co-workers in 2004 demonstrated that the asymmetric synthesis of 7-methoxy-D-tryptophan ethyl ester (237) was accomplished by a combination of the Larock heteroannulation reaction with a Schollkopf-based chiral auxiliary in a satisfactory yield. Next, this ester 237 was used in the initial total synthesis of (+)-12-methoxy-Nα-methylvellosimine (239), (+)-12-methoxyaffinisine (240), and (−)-fuchsiaefoline (242) using the regiospecific and stereospecific approach with very high overall yield. The enantioselective Pictet–Spengler reaction, and also the enolate-driven Pd-mediated cross coupling reactions, acted as key steps. Based on this method, the total synthesis of (+)-12-methoxy-Nα-methylvellosimine (239), (+)-12-methoxyaffinisine (240) and (−)-fuchsiaefoline (242) were started from the Larock heteroannulation of 2-iodo-6-methoxyaniline (233) and the propargyl-functionalized Schollkopf chiral auxiliary 234 using palladium(II) acetate, potassium carbonate, and lithium.

Scheme 31  Total synthesis of 9-methoxygeissoschizol (247), 9-methoxy-Nβ-methylgeissoschizol (248), and mitragynine (250).
chloride in DMF at 100 °C. The ratio of the corresponding indole 235 to the byproduct 236 was identified on the basis of the integration of the proton at C3 in the 1H-NMR spectrum of the crude reaction mixture. The ratio was increased to 15 : 1 (235 : 236) when a 2% catalyst was used rather than a 5% catalyst (palladium(II) acetate). The corresponding indole 235 was isolated from the side-product 236 by using flash chromatography. In the following, after seven steps, indole 235 gave the pentacyclic ketone 238. The latter was transformed into 12-methoxy-Nα-methylvellosimine 239 through a Wittig reaction and hydrolysis. Next, the aldehyde 239 was reduced using sodium borohydride and gave 12-methoxyaffinisine 240 in a high yield (95% yield). On the other hand, the aldehyde group for the intermediate 239, using iodine (I2) and potassium hydroxide in ethanol, was oxidized to the ethyl ester 241. Finally, quaternization of the Nα nitrogen function in ester 241 using methyl iodide afforded the Nα-methiodide salt that was transformed into the chloride 242 after reacting with silver chloride in ethanol (Scheme 30). Moreover, this alkaloid was synthesized by this research group in 2006.

Scheme 32 Total synthesis of 9-methoxygeissoschizol (247), 9-methoxy-Nα-methylgeissoschizol (248), and mitragynine (250).
Kratom is the usual name of *Mitragyne speciosa Korth*, found in Thailand, which can be utilized as an opium substitute by chewing, smoking, or drinking a broth form of the kratom leaves. Noticeably, the alkaloid content of the leaves of the *Mitragyne speciosa* is about 0.5%, about half of which contains mitragynine (250). However, the structural identification of 250 contains a rich history, the actual structure of 250 was definitely determined by Zacharias in 1964. The formal

Scheme 33  Total synthesis of chloropeptin II (259) and chloropeptin I (260).
investigation of the pharmacology of mitragynine (250) demonstrated that it was a central nervous system (CNS) stimulant.\textsuperscript{253} Then, \textit{in vivo} and \textit{in vitro} investigations showed mitragynine mostly acted on the \(\mu\)-opioid receptors.\textsuperscript{234} Cook and co-workers in 2007 demonstrated\textsuperscript{255} an asymmetric approach for the formation of 4-methoxytryptophan through a regiospecific Larock heteroannulation. This method was used for the first total synthesis of 9-methoxygeissoschizol (247), 9-methoxy-
$N_\theta$-methylgeissoschizol (248), and also the total synthesis of mitragynine (250). The total synthesis of mitragynine (250), 9-methoxygeissoschizol (247), and 9-methoxy-$N_\theta$-methylgeissoschizol (248) began from the Larock heteroannulation of Boc-masked 2-iodo-3-methoxyaniline (243) and the TES alkyne 244 (ref. 257) using palladium(0) acetate, potassium carbonate, and lithium chloride in DMF at 100 °C, which afforded the corresponding indole 245 in an 82% yield. The latter, after 12 steps, gave the 9-methoxy-substituted tetracyclic intermediate 246. In the following, ester 246 was reduced using lithium aluminium hydride and afforded 9-methoxygeissoschizol (247) in a high yield (90% yield). Next, 9-methoxy-$N_\theta$-methylgeissoschizol (248) was provided through the $N_\theta$-methylolation of compound 247 with MeI and followed by exchange of the iodide to the chloride in the presence of silver carbonate (Scheme 31). On the other hand, after two steps, ester 246 gave the corresponding ester 249. Lastly, ester 249 was exposed to formylation, and the Boc substituent was removed in ethyl acetate that had been saturated with HCl gas. Lastly, acetal construction and potassium tert-butoxide catalyzed the removal of methanol and afforded the natural product mitragynine (250) (Scheme 31).

In the following, this method was used in 2009 for the total synthesis of mitragynine (250), 9-methoxygeissoschizol (247), and 9-methoxy-$N_\theta$-methylgeissoschizol (248) by Cook and co-workers. This research group demonstrated the total synthesis of these alkaloids through the Mori–Ban–Hegedus indole synthesis. The total synthesis of mitragynine (250), 9-methoxygeissoschizol (247), and 9-methoxy-$N_\theta$-methylgeissoschizol (248) were started from easily accessible aryl iodide 243 that was exposed to the allylic alkylation and the Mori–Ban–Hegedus indole synthesis and afforded a 1 : 1 mixture of 3-methylindoline (252) and 3-methylindolone 251. To diminish the isomerization of the 3-methylindoline (252) to the 3-methylindolone 251 in the Mori–Ban–Hegedus indole synthesis, it was essential to change the base from K$_2$CO$_3$ to Ag$_2$CO$_3$. Pleasantly, upon using Ag$_2$CO$_3$ in the Heck reaction, this approach was much quicker, and the reaction could be performed at ambient temperature. The 3-methyleneindoline (252) was provided, along with a trace quantity of the 3-methylindolone 251. In the following, 3-methyleneindoline 252, upon four steps, gave the optically active 4-methoxytryptophan ethyl ester (253). The latter, after 11 steps, gave the chiral tetracyclic ester 246. Next, the reduction of the ester 246 in the presence of LiAlH$_4$ in THF at room temperature provided 9-methoxygeissoschizol (247) in a high yield (90% yield). Then, methylation of compound 247 using MeI and the exchange of the iodide anion to the chloride anion using silver chloride afforded 9-methoxy-$N_\theta$-methylgeissoschizol (248).

On the other hand, after 16 steps the optically active 4-methoxytryptophan ethyl ester (253) gave enol 254. The latter was reacted with HCl (g) in ethyl acetate to eliminate the Boc substituent, and this was followed by reaction with anhydrous methanolic HCl solution using trimethyl orthoformate to give the desired acetal intermediate. The acetal was dissolved in DMF and treated with potassium tert-butoxide and provided mitragynine (250) (Scheme 32).

Complestatin (259, chloropeptin II) was first revealed in 1980 as an inhibitor of the alternate pathway of human complement. Then, the first results of its activity against HIV infectivity and its cytopathic effects were revealed. In the following, Omura demonstrated the separation of both chloropeptin I (256) and chloropeptin II (259) from Streptomyces sp. In 2009, Boger and co-workers reported the first total synthesis of chloropeptin II (259, complestatin). Key to this method is the usage of an intramolecular Larock indole synthesis. The first macrocyclization, using conditions that allow application of 2-bromoaniline and incorporating a removable terminal alkyne group (-SiEt$_3$), sterically dictates the indole cyclization regioselectivity. The total synthesis of chloropeptin II (complestatin) (259) and chloropeptin I (260) commenced from 3-iodo-4,5-dimethoxybenzaldehyde (255),...
which after 12 steps afforded the cyclization substrate 256. The reaction of 256 with palladium(II) acetate in the presence of the bidentate ligand Dt-BPF and the soluble base triethylamine under reflux in toluene/acetonitrile (1 : 1, 1 mM at 110 °C for 1 h) efficiently afforded indole 257 (71% yield) and its (S)-atropisomer (not shown) in a superb, combined yield (89% yield) using a reaction which enables whole cyclization regioselectivity and a good atropdiastereoselectivity (4 : 1 R : S) to select the natural isomer. After 11 steps, indole 257 provided the penultimate precursor 258. Next, deprotection of 258 to afford 259 was performed with LiOH (THF/H2O at 0 °C for 3 h, 60% yield) in a reaction in which the indole N-acyetyl substituent was eliminated quicker (<30 min) than the methyl ester hydrolysis. However, this group did not perform the reaction on a preparative scale affording an isolated yield, the clean acid-mediated transformation of 259 to 260 was performed on a small scale with both synthetic and authentic 259 and checked using liquid chromatography mass spectrometry. The two examples acted in a similar way giving 260 as the sole product, and the optimum results were obtained when it was performed with trifluoroacetic acid (50%)/H2O at 50 °C proceeding at a rate that could be easily observed (5 hours, vs. <5–15 min with neat trifluoroacetic acid at 50 °C (ref. 266)) (Scheme 33).

This method was also used for the total synthesis of chloropeptin II 259 and chloropeptin I 260 by Boger et al. in 2010. This research group used 3-iodo-4,5-dimethoxybenzaldehyde (255) as a starting material thus, chloropeptin II (259) and chloropeptin I (260) were synthesized in 22 and 23 synthetic steps, respectively.

The simplest members of the hexahydropyrrolo[2,3-b]indole alkaloids are flustramines, which exhibit noteworthy biological properties.268 (−)-Flustramine B and (−)-debromoflustramine B were extracted from the marine hydroid Flustra foliacea in 1979 by Carle and co-worker.269 (−)-Flustramine B has been known to show muscle relaxant activity, influencing both smooth and skeletal muscles.270

Scheme 36  Total synthesis of (+)-terreusinone (286).
Indole, bearing a quaternary carbon prenylated at C-3a, is the defining structural aspect of these alkaloids and thus various effective approaches have been reported for their synthesis. In 2009, Kobayashi and co-workers reported the total synthesis of (+)-terreusminone B (267) through a one-pot intramolecular Ullmann coupling reaction and Claisen rearrangement. The enantioselective total synthesis of (+)-terreusminone B (267) was started from the reaction of the iodoaniline derivative (brominated iodoaniline 264 was synthesized from o-nitroaniline (263) in four steps) and silyl acetylene 262 having a chiral center (synthesized from (+)-linalool (261) in three steps). The Larock indole synthesis, using the iodoaniline derivative 264 and silyl acetylene 262, was accomplished in the presence of lithium chloride, potassium carbonate (K2CO3), triphenylphosphine, and palladium(II) acetate in DMF at 100 °C and gave the desired silyl indole 265. The latter, after 12 steps,

Scheme 37 Bidirectional synthesis of (+)-terreusminone (286).
afforded \((-\)-flustramine B (266). Lastly, the latter was reacted with \(\text{AlH}_3\cdot\text{EtNMe}_2\) (1.5 equiv.) at ambient temperature to decrease the unreacted lactum carbonyl substituent. As a result, \((-\)-flustramine B (267) was synthesized in a high yield (93% yield) (Scheme 34). In this method, the enantioselective total synthesis of \((-\)-debramotoflustramine B was started from \((R)\)-\((-\)-linalool (261), which after three steps gave the non-racemic silylalkyne 262. The Pd-mediated Larock indole synthesis was performed using Walsh’s reaction conditions. Next, the reaction of 262 with \(\text{N-benzyl-ortho-iodoaniline (269)}\) in DMF at 100 °C in the presence of palladium(II) acetate and triphenylphosphine using

![Scheme 38](image)

Scheme 38. Total synthesis of dictyodendrin B (297) and the formal synthesis of dictyodendrin E (105).
lithium chloride and potassium carbonate gave the 2-silylindole 270 in a good yield (82% yield). It should be mentioned that the N-benzyl-ortho-iodoanilines 269 were synthesized through the reductive amination reaction of benzaldehyde and iodoaniline using sodium cyanoborohydride (NaBH₃CN) and zinc chloride in methanol. In the following, the iodosilylation of 2-silylindole 270 using ICl and also the elimination of the TMS substituent with tetra-n-butylammonium fluoride afforded the tertiary allylic alcohol (R)-271 with a high ee (97% ee) and a satisfactory yield (58%). The latter, after nine steps, gave the hexahydropyrrolo[2,3-b]indole derivative 272. Lastly, reductive debenzylation of 272 using Na in liquid NH₃ and quenching of the resultant amide anion with prenyl bromide led to the total synthesis of (−)-debronnolustramine B (55) in a high yield (93%) (Scheme 34).²⁷³

Most of the iboga alkaloids were extracted by Sundberg and co-workers in 2002 from the Tabernaemontana or Tabernanthe species of plants from the Apocynaceae family. Ibogaine (278a) is known as a naturally occurring plant indole alkaloid of the iboga family.²⁷⁶ Members of this group of alkaloids contain a typical bridgehead nitrogen comprising a tricyclic building block by the fusion of a seven-membered indoloazepine ring, along with a rigid isoquinuclidine ring. Ibogaine shows various pharmacological activities and it has been under active examination as an anti-addictive agent.²⁷⁴ In 2012, Sinha and Jana demonstrated²⁷⁵ the effective total synthesis of ibogaine (278a), epiibogaine (278b) and their analogues. An intramolecular reductive-Heck type cyclization reaction was applied for the formation of a seven-membered indoloazepine ring to provide the iboga-skeleton. Larock’s heteroannulation reaction was used for the formation of an appropriately functionalized indole and also the Diels–Alder reaction was used for the formation of the isoquinuclidine ring. The total synthesis of ibogaine (278a) and epiibogaine (278b) were commenced from Larock’s heteroannulation reaction of 4-methoxy-2-iodoaniline (274) (prepared in three steps from m-iodophenol (273)) and disilylated alkyne 275 that gave the 5-methoxy-2,3-disubstituted indole 276.²⁷⁶ The latter, after five steps, gave compounds 277a and 277b. Lastly, the reductive Heck coupling reaction of 277a and 277b was performed individually in DMF and afforded...
ibogaine (278a) in a moderate yield (66% yields) and also epi-
ibogaine (278b) in a 55% yield. As a result, ibogaine (278a) (9.8%) and epiibogaine (278b) (9.7%) were synthesized from 4-
methoxy-2-iodoaniline (274) in an overall yield of 19.5% (Scheme 35).

The natural product, terreusinone was extracted in 2003 by
Son and co-workers from the algicolous marine fungus Asper-
gillus terreus. Terreusinone includes a pyrrolo[2,3-
f]indole-4,8-
dione ring scaffold. Terreusinone exhibits significant UV-A
masking properties, indicating terreusinone may act to shield
the host organism from the destructive influences of solar UV
radiation. The initial synthesis of (+)-terreusinone (286) was
reported in 2011 by Sperry and Wang. Key steps involve
a one-pot Larock indolization-Sonogashira coupling and the
hydroamination of an unfunctionalized ortho-alkynylaniline
mediated by a cationic Au(i) complex. The total synthesis of
(+)-terreusinone (286) was started from 2-methoxy-4-
nitroaniline, which after three steps gave bromide 280
and 1,2-dibromide 281 in a 2 : 1 ratio. Then, dibromide 280 was
exposed to an excess of (R)-283 (prepared from racemic
propargylic alcohol (±)-282 in two steps) through Sen-
anyake’s modified Larock indolization reaction. Both the
Larock indolization and also the Sonogashira coupling reaction
afforded indole 284 in a low yield (26% yields). The latter, after
three steps, gave pyrroloindole 285. Upon oxidation of 285 with
Frémy’s salt under buffered conditions, (+)-terreusinone (286)
was provided in a good yield. This synthetic method was per-
formed in eight steps from commercially available starting
precursors (Scheme 36).

An effective, bidirectional synthesis of the photoprotecting
dipyrrolobenzoquinone (+)-terreusinone (286) was performed
by Sperry and Wang in 2012. Key steps involve a Cu- and
amine-free double Sonogashira reaction between an electron-
rich 1,4-dibromide and a masked propargylic alcohol and also
pyrrolo[2,3-f]indole construction through double hydro-
amination mediated by Echavarren’s cationic Au(i) complex.
Based on this method, the bidirectional synthesis of (+)-ter-
reusinone (286) was commenced from the double Sonogashira
reaction of the newly synthesized electron-rich 2,5-dibromo-3-
methoxy-1,4-dianiline (287) and an excess of propargylic

Scheme 40  Formal synthesis of dictyodendrins C (305).
alcohol (R)-283 with Pd(OAc)$_2$, 1,1'-bis(di-tert-butylphosphino)ferrocene and K$_2$CO$_3$ in N-methyl-2-pyrrolidone at 138 °C (for 2 h), which afforded the double Sonogashira product 288. It should be mentioned that 2,5-dibromo-3-methoxy1,4-dianiline (287) was easily provided by using the simple reduction of p-nitroaniline (280). Next, the double hydroamination reaction
of compound 288 using Echavarren’s cationic Au(I) complex (acetonitrile)[(2-biphenyl)di-tert-butylphosphine]gold(I) hexafluoroantimonate (289) gave the pyrrolo[2,3-f]indole 290. It is worth mentioning that the desilylation of 290 did not perform as well as expected, returning only satisfactory yields of the desired pyrrolo[2,3-f]indole 285 with a yield of 43% over two steps from 288 (path A, Scheme 37).

In the following, in an effort to increase the above mentioned yield, initially the order of synthetic steps (from 288 → 285) was reversed and the desilylation was accomplished. However, the deprotection of 288 into 291 was performed and gave a very high yield, the double hydroamination of 287 to afford 285 was low yielding, meaning this alternate route afforded 285 in a 22% yield from 288 (path B, Scheme 37). Nevertheless, the two distinct routes depicted in Scheme 37 demonstrate the formal synthesis of the natural product (+)-286.

Moreover, this method was applied by Sperry and Wang in 2013 for the total synthesis of (+)-terreusinone (286), that commenced from a one-pot Larock–Sonogashira coupling reaction. The short synthesis of dictyodendrins B (297) and E (105) was accomplished in just 9 and 11 steps by Jia and co-workers in 2013. The very convergent methodology used a Pd-mediated Larock indole synthesis and a Pd-catalyzed one-pot consecutive Buchwald–Hartwig amination/C–H activation reaction as key steps. The total synthesis of dictyodendrin B (297) and the formal synthesis of dictyodendrin E (105) were commenced from the iodonitration of aniline 292. In this route, aniline 292, in the presence of iodine monochloride (ICl), afforded o-idoaniline (293) in a good yield (83% yield). The o-idoaniline (293) and alkynyl ketone 294 were reacted under Larock reaction conditions (palladium(II) acetate, triphenylphosphine, sodium carbonate, lithium chloride, and DMF at 100 °C). Pleasantly, the reaction was very regioselective and afforded the corresponding indole 295 as the only regioisomer, although in a poorer yield (44% yield). The latter, after four steps comprising N-alkylation, bromination, a Buchwald–Hartwig amination/C–H activation reaction, and elimination by using hydrogenolysis, yielded compound 296. Next, the latter was easily transformed into...
dictyodendrin B (297), after a three-step sequence. Therefore, the total synthesis of dictyodendrin B (297) was accomplished in only nine steps and a 27% overall yield from aniline 292. On the other hand, indole 295, after nine steps, gave dictyodendrin E (105). Thus, the total synthesis of dictyodendrin E (105) was accomplished in only 11 steps and with a 29% overall yield from aniline 292 (Scheme 38).

In 2014, Jia et al. published a complete explanation of the short total synthesis of dictyodendrins B and also the formal synthesis of dictyodendrin C. In this method, a palladium-catalyzed Larock indole synthesis was utilized to make the very functionalized indole unit, and a Pd-catalyzed one-pot sequential Buchwald–Hartwig amination/C–H activation reaction was utilized to form the key pyrrolo[2,3-c]carbazole unit. The total synthesis of dictyodendrins B (297) began with the Ullmann coupling reaction of p-iodoanisole (97) and 1,3-dinitrobenzene (98), that afforded bipheny 99. The latter, after three steps, gave o-iodoaniline 298. In the following, the reaction of o-iodoaniline 298 and alkyne 299 through the Larock indole reaction afforded the corresponding indole 300. Finally, after three steps [(1) ClSO3, CH2CCl3; (2) HCl, TBAI; (3) Zn, HCO2NH4], the total synthesis of dictyodendrins B (297) was performed successfully (Scheme 39).

Moreover, the formal synthesis of dictyodendrins C (305) was commenced from the Ullmann coupling reaction of p-iodoanisole (97) and 1,3-dinitrobenzene (98), that afforded aniline 99. After four steps aniline 99 gave o-iodoaniline 302. Then, the reaction of o-iodoaniline 302 with alkyne 299 using the Larock indole reaction afforded the corresponding indole 303. The latter, after four steps, gave phenol 304, which after several steps afforded dictyodendrins C (305). As a result, the formal synthesis of dictyodendrins C (305) was accomplished in a 14% overall yield (Scheme 40).

Fargesine, an N-oxide alkaloid, was extracted by Zhu and co-workers from the stem and root of *Evodia fargesii* Dode, in which fruits are used in folk medicine for pain relief from bellyache. In 2013, Jia et al. developed the commonly used methodology for the formation of 3,4-fused tricyclic indoles through an intramolecular Larock indolization reaction. The total synthesis of fargesine (312) began with the reductive coupling reaction of aldehyde 306 and the primary amine 307.
Scheme 45  Total synthesis of isonauclefidine triflate (335) and the formal synthesis of norepiisogeissoschizoate (336).

Scheme 46  Formal synthesis of mitragynine (250).
that afforded the secondary amine 308. The latter, after two steps, gave 2-idoaniline (309). The intramolecular Larock indolization reaction of 309 gave the corresponding tricyclic product 310 in an almost quantitative yield. The latter, after three steps including selective elimination of the Boc substituent on N, reductive amination and oxidation, yielded the desired N-oxide 311. Finally, removal of the Boc group on the oxygen of 311 under basic conditions afforded fargesine (312). As a result, the total synthesis of fargesine (312) was performed in eight steps with a 15% overall yield (Scheme 41).

β-Carbolines, a large group of natural indole alkaloids, contain a tricyclic pyrido-3,4-indole ring, analogous to the

Scheme 47  Asymmetric total synthesis of dragmacidin D (349).
tryptamine structure.295 β-Carboline alkaloids were initially found in *Peganum harmala* that grows in Central Africa, Asia, and also South America. Indolopyridocoline (319), was extracted in 1965 by Kaschnitz from the bark of *Gonioma kamassi* E. Mey.296 The commonly used synthetic method for β-carboline-containing alkaloids was reported in 2014 by Bannister and Pan.297 Two sequential Pd-catalyzed methods, a Sonagashira coupling reaction and a Larock indole annulation reaction, are the key steps. This research group tried to synthesize indolopyridocoline (319), norketoyobyrine (323), demethoxy carbonyl dihydrogambirtannine (324), ruteacarpine (329), isonaucleolidine triflate (335), norepisigossoschizoate (336) and mitragynine (250). The total synthesis of indolopyridocoline (319) began with the Sonogashira coupling reaction of butyne-1-ol (313) and 2-bromopyridine (314), that afforded the corresponding alkyne (315). Then, the Larock indole annulation reaction of alkyne (315) and 2-bromoaniline (316) using palladium(II) acetate, 1,10-bis(diphenylphosphino) ferrocene (dppf), and potassium bicarbonate (KHCO₃) in DMF at 110 °C gave the desired indole (317) with a 95% yield and a high regioselectivity. The latter, after two steps, involving the conversion of the alcohol (317) to a triflate (318) and the oxidation of tetracycle (318), gave indolopyridocoline (319) (Scheme 42).297

(−)-Demethoxy carbonyl dihydrogambirtannine (324) was extracted in 1973 by Peube-Locou from the leaves of *Ochrosia lifiiana* and also *Ochrosia miana* (Apocynaceae).298 Norketoyobyrine (323) and isonaucleolidine (335) were extracted in 2011 by Xu and co-workers from the bark of *Anthocephalus chinensis*.299 The genus *Anthocephalus*, a member of the tribe Naucleaceae in the family Rubiaceae, is known in southern China and southern Asia. Their barks have been utilized for treating blood diseases, uterine complaints, dysentery and leprosy in ‘Ayurvedo’, an ancient Indian form of medicine.300 The total syntheses of norketoyobyrine (323) and demethoxy carbonyl dihydrogambirtannine (324) were started from the Sonogashira coupling reaction of isoquinolin-3-yl triflate (320) and butyne-1-
ol (313) that afforded alkyne 321. The Larock indolization of alkyne 321 and 2-bromoaniline (316) afforded the corresponding indole isoquinoline 322. In the following, indole isoquinoline 322, after two synthetic steps containing cyclization and oxidation, gave norketoyobyrine (323). In addition, indole isoquinoline 322, after two steps involving cyclization.
Scheme 51  Total synthesis of festuclavine (370), pyroclavine (371), pibocin A (373), 9-deacetoxyfumigaclavine C (372), fumigaclavine G (374) and dihydrosetoclavine (369).
and reduction, yielded demethoxycarbonyl dihydrogambirtannine (324) (Scheme 43). In addition, the alternative synthesis of demethoxycarbonyl-dihydrogambirtannine (324) and norketoyobyrine (323) have been reported.\textsuperscript{301,302}

Furthermore, the total synthesis of rutaecarpine (329) was started from the Sonogashira reaction of methyl ether 325 which contained a chloro group and butyne-1-ol (313) that gave alkyne 326. The Larock indolization afforded a regiosomeric mixture that exhibited a preference for the desired 2-heteroaryl indole product 328. Potassium bicarbonate as a base afforded an 8 : 1 preference for 328 in a very good yield (82%). Next, the cyclization of 328 using HCl/n-butanol showed a preference for rutaecarpine (329) (16 : 1, 81% yield) (Scheme 44).\textsuperscript{297}

The total synthesis of isonaucleidine triflate (335) and the formal synthesis of norepiisogeissoschizoate (336) began with the Sonogashira coupling of the tert-butyl ester functionalized chloropyridine 331 and butyne-1-ol (313) that afforded the corresponding alkyne 332. Then, the Larock reaction of alkyne 332 and 2-bromoaniline (316) provided indole 333, which after the cyclization reaction gave tetracycle 334. Finally, isonaucleidine triflate (335) was provided from the reaction of tetracycle 334 in the presence of TFA. Moreover, the formal synthesis of norepiisogeissoschizoate (336) was accomplished after three steps from tetracycle 334 (ref. 303) (Scheme 45).\textsuperscript{297}

Dragmacidin D (349), a secondary metabolite, was extracted by Wright and co-workers in 1992 from a deep-water marine sponge of the genus Spongosorites.\textsuperscript{305} Dragmacidin D was known to be an active inhibitor of the serine/threonine phosphatases PP2A and PP1. Additional biological properties that have been reported for the dragmacidins involve anti-bacterial, anti-viral, and anti-fungal properties, and also \textit{in vitro} cytotoxicity against A549 human lung, HCT-8 human colon and P388 murine leukemia.\textsuperscript{306} In 2015, Zakarian \textit{et al.} reported the enantioselective synthesis of dragmacidin D (349) in 10 steps.\textsuperscript{307}

The asymmetric total synthesis of dragmacidin D (349) was achieved from the central heteroannulation of propanoate 343 (prepared in four steps from 4-methoxy-2-bromoacetic acid 341) and pyrazine 344 (prepared in four steps from 2,6-dichloropyrazine (342)) in the presence of the [1,1\textsuperscript{0}-bis(di-tert-butylphosphino)ferrocene] PdCl\textsubscript{2} catalyst 345 (central Larock indole synthesis) and afforded the 2,3,4,7-tetrasubstituted indole 346. The latter, after three steps, gave the thioester 347. Finally, the total synthesis of dragmacidin D (349) was completed after two additional steps, including the CuOAc-mediated acyl cross-

**Scheme 52** Total synthesis of (−)-aspergilazine A (379).
coupling reaction of the thioester 347 with stannane 348 (bearing a guanidinyl) and the cyclocondensation of the resulting guanidinylmethyl ketone using acidic conditions in the presence of trifluoroacetic acid in dichloromethane. Upon purification by using reverse-phase preparative high performance liquid chromatography (HPLC), 15 mg of the trifluoroacetic acid salt of synthetic dragmacidin D (349) was isolated as a brownish red foam (Scheme 47).

Indole alkaloids bearing a 3α-amino-hexahydropyrrolo[2,3-b]indole motif were found in various natural products. Among the alkaloids in this family, psychotriasine (355) was extracted from *Psychotria calocarpa* in 2010 by Hao et al. In 2015, Deng et al. demonstrated the total synthesis of (−)-psychotriasine (355), which relied on the advanced intermediates of 3α-amino-hexahydropyrrolo[2,3-b]indole. To make these structural scaffolds, a cascade reaction containing a BINOL-derived phosphoric anion-paired catalyst for asymmetric or diastereoselective azo-coupling/iminium-cyclizations was established. Other key steps of the synthesis include a sterically hindered amination using hypervalent iodine reagents and the Larock annulation. The asymmetric total synthesis of (−)-psychotriasine (355) was started from 3α-amino-hexahydropyrrolo[2,3-b]indole 350. The latter, after two steps, gave tetrahydropyrrolo[2,3-b]indole 351. Then, the Larock cyclization of 351 and an identified alkyne framework (N-(methoxycarbonyl)-4-(trimethylsilyl)-3-butynamylamine) (352), using a palladium(0) acetate catalyst, Dt-BPF ligand, potassium carbonate additive and N-methyl-2-pyrrolidone, provided the tryptamine dimer compound 353 in a good yield (83% yield). Then, N-deprotection was used to remove the Bz group using Dibal-H and carbamation of the amine using CICO₂Me gave 354 in a 64% yield (over two steps). Finally, N-deprotection of 354 to remove the Boc group using trifluoroacetic acid and further reduction using Red-Al provided the desired natural product (−)-psychotriasine (355) at >96% ee (Scheme 48). It is worth mentioning that

\[
\text{Scheme 53 Total synthesis of 2,4-dimethylindole (382), 4-(hydroxymethyl)-2-methylinde (386) and 4-(methoxymethyl)-2-methylinde (388).}
\]
its structure was revised in 2010 by de Lera and co-worker upon total synthesis.102 The total synthesis of (+)-pestalazine B (358) was commenced from the easily accessible compound 356, and after three steps afforded compound 357. Lastly, the Larock annulation of 357, with the sterically bulky ligand Dr-BPF, afforded (+)-pestalazine B (358) in a 16.2% overall yield over this four-step total synthesis (from the known compound 356) (Scheme 49).

The ergot alkaloids manufactured by the fungus Claviceps purpurea are a different group of naturally occurring indole compounds that show a wide range of powerful pharmacological properties.113,114 Among the ergot alkaloids (EAs) family of naturally occurring compounds, ergotamine is the most broadly identified member and various semisynthetic derivatives have been clinically utilized for treating various neurological diseases. In 2015, Boger et al. demonstrated106 that the total synthesis of dihydrolysergic acid (363) and dihydrolysergol (364) relied on a palladium (0)-mediated intramolecular Larock indole cyclization for the formation of the tricyclic indole and also a consequently inverse electron demand Diels–Alder reaction. The total synthesis of dihydrolysergic acid (363) and dihydrolysergol (364) were commenced from 2-bromoaniline (359). The latter, after five steps, gave homopropargylic alcohol 360, that through an intramolecular palladium(0)-mediated Larock indole annulation gave the tricyclic indole 361. The latter, after eight steps yielded the intermediate 362, which after hydrolysis of the methyl ester (1 N NaOH/MeOH at 40 °C, 3 h) afforded dihydrolysergic acid (363). Moreover, reduction of the intermediate 362 (using LiAlH₄, THF at 0 °C) yielded dihydrolysergol (364) (Scheme 50).116

An efficient method for the total synthesis of eight ergot alkaloids was reported in 2017 by Jia et al.117 This method permits the first total synthesis of pyroclavine (371), pibocin (373), 9-deacetoxyfumigaclavine C (372), fumigaclavine G (374), festuclavine (370), and dihydrosetoclavine (369). The key aspect of the synthesis is the usage of a palladium-mediated intramolecular Larock indole annulation/Tsuji–Trost allylation cascade to make the tetracyclic unit in one step. The total synthesis of festuclavine (370), pyroclavine (371), pibocin A (373), 9-deacetoxyfumigaclavine C (372), fumigaclavine G (374) and dihydrosetoclavine (369) began with bromide 365. After six steps, 365 gave homopropargylic amines 366a and b. In the following, the intramolecular palladium-mediated Larock indole annulation of 366a was accomplished using palladium(η) acetate and Me-phos at 100 °C and provided the corresponding tricyclic indole 367 in a high yield (92% yield). Astonishingly, when the reaction was performed on a gram scale, an undesired tetracyclic compound 368 was obtained in a small quantity. It should be mentioned that compound 368 most probably occurred as a result of using the Tsuji–Trost allylation of the tricyclic indole 367. Meanwhile, compound 368 could be utilized as an advanced intermediate to simplify the synthesis and reduce the synthetic pathway, additional optimization of the cascade reaction of 366a to increase the yield of 368 was examined. When the reaction was performed using palladium(η) acetate (0.3 equiv.) and Me-phos (0.9 equiv.), the desired compound 368 was provided in a good yield (65% yield) along with 25% of 367. Following this, the tetracyclic basic framework 368, after four steps, gave dihydrosetoclavine (369).117

In addition, the total synthesis of festuclavine (370) and pyroclavine (371) were started from bromide 365, and after six steps gave 366a and b. After reacting Pd(OAc)₂ (20 mol%) and Me-phos (40 mol%), K₂CO₃, and LiCl in DMF at 100 °C, 366a and b afforded 367, and after a further five steps these gave compounds 370 and 371. In the following, this research group examined the formation of pibocin A (373), 9-deacetoxyfumigaclavine C (372) and fumigaclavine G (374) using the direct functionalization of 370 and 371. The chemoselective bromination reaction of the 2-position of festuclavine (370) using N-bromosuccinimide yielded pibocin A (373) in a good yield (80% yield). Moreover, the chlorination of 370 with tert-butyl hypochlorite and reaction with prenyl-9-BBN using triethylamine gave 9-deacetoxyfumigaclavine C (372) in a good yield (80% yield). Similarly, pyroclavine (371) was converted to

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![Scheme 54](image-url)  
**Scheme 54** Total synthesis of (±)-trans-trikentrin A (393).
Aspergillus A, dimerized by two diketopiperazines cores through an unusual N-1 to C-6 linkage, was extracted in 2012 by Gu and co-workers from the marine-derived fungus Aspergillus taichungensis ZHN-7-07. The fungal strain Aspergillus taichungensis ZHN-7-07 along with the mangrove plant Acrostichum auratum, are members of the Aspergillus Candidi family. In 2016, Reisman et al. demonstrated the total synthesis of the bisindole natural product (−)-aspergilazine A (379). The total synthesis of the dimeric diketopiperazine natural product (−)-aspergilazine A (379) began with a Buchwald–Hartwig coupling reaction between 1-bromo-2-iodobenzene (375) and diamine 376, which afforded dibromide (377). Next, exposure of a mixture of dibromide 377 and alkyne 378 to Pd[P(t-Bu)3]2 and Cy2NMe in 1,4-dioxane at 80 °C provided bis(triethylsilyl)(−)-aspergilazine A in a satisfactory yield (62% isolated yield), demonstrating an average reaction proficiency of 79% per indolization. Finally, HCl-catalyzed desilylation efficiently provided the natural product (−)-aspergilazine A (379) (Scheme 52).

2.3. Bartoli indole synthesis

In 2001, Dobbs demonstrated a concise and effective method for the synthesis of 2,4-dimethylindole (382), 4-(hydroxymethyl)-2-methyldole (386) and 4-(methoxymethyl)-2-methyldole (388). These alkaloids were previously extracted and reported in 1994 by Sterner and co-workers from two species of European Basidiomycetes (Tricholoma sciodes and Tricholoma virgatum). Tricholoma is one of the well-known genera of the Basidiomycota division. However, several species of this genus have been utilized as culinary mushrooms, only a few insignificant investigations have been performed exploring the phenolic contents of the Tricholoma genus and also their biological properties. The total synthesis of 2,4-dimethylindole (382), 4-(hydroxymethyl)-2-methyldole (386), and 4-(methoxymethyl)-2-methyldole (388) started from 4-bromo-3-nitrotoluene (380). The straight reaction between isopropenylmagnesium bromide and 4-bromo-3-nitrotoluene (380) via Bartoli reaction conditions in THF at −40 °C gave 2,4-dimethyl-7-bromoindole (381) in a satisfactory yield (67% yield). As with the examination reactions, the radical reduction was performed almost quantitatively (94% yield) to afford 2,4-dimethylindole (382) in moderate yields (62% overall yield).

Furthermore, the radical benzylic bromination reaction of 4-bromo-3-nitrotoluene (380) yielded 4-bromo-3-nitromethylen benzene (383) in very high yields (>85% yield). The latter was exposed to the Bartoli reaction again using isopropenylmagnesium bromide, to give 7-bromo-4-(bromomethyl)-2-methyldole (384) in a good yield (61% yield). In the following, the reaction of compound 384 with H2O (under acidic reaction conditions) afforded 7-bromo-4-(hydroxymethyl)-2-methyldole (385) in very good yields (88%) and this was transformed into the alkaloid 4-(hydroxymethyl)-2-methyldole (386) by using radical reduction (91% yield) (41% overall yields). In addition, the reaction of 7-bromo-4-(bromomethyl)-2-methyldole (384) with NaOMe provided 7-bromo-4-(methoxymethyl)-2-methyldole (387) in good yields (76% yields) and this was again reduced quantitatively with tributyltin hydride (Bu3SnH) (94% yield) to afford 4-(methoxymethyl)-2-methyldole (388) in a moderate overall yield (37%) (Scheme 53).

The family of trikentrins and herbindoles have the most noticeable features of an unusual class of naturally occurring indole alkaloid compounds, in which annulation takes place around the benzene core. These biologically potent compounds are attractive structures. The trikentrins were extracted from the marine sponge Trikentron flabelliforme by Capon et al. in 1986. The herbindoles were discovered by Scheuer from the Australian sponge Axinella sp. and contain both anti-feedant and cytotoxict activities. Silva and Craveiro in 2008 reported an efficient method to synthesize the polyalkylated indole (±)-trans-trikentrin A (393). The synthesis of this alkaloid involves a Tl(III)-catalyzed ring contraction reaction to provide the trans-1,3-difunctionalized five-membered ring through...
a diastereoselective method. Other key steps are Bartoli’s reaction and a Heck coupling reaction. The total synthesis of (±)-trans-trikentrin A (393) started from acetophenone 389 and after three steps gave 1-bromo-4-ethyl-2-nitrobenzene (390) in good yields (79% overall yield). The latter was reacted with CH$_2$CHMgBr in THF to afford the bromo-indole 391 via a Bartoli indole synthesis. In the following, after 14 synthetic steps, indole 391 yielded the corresponding dihydrocyclopentag[indole 392, containing the trans-1,3-five-membered ring.$^{131}$ Then, compound 392, after three steps, including tosylation, and the reduction and removal of the Boc substituent, gave (±)-trans-trikentrin A (393) (Scheme 54).$^{130}$

In 2009, Buszek and co-workers demonstrated$^{132}$ an effective nine-step total synthesis of the annulated indole natural products (±)-cis-trikentrin A (398) and (±)-herbindole A (403) through an intermolecular Diels–Alder cycloaddition using the established indole aryne (indolyne) approach as the key step. This approach enables the trikentrins and the related herbindoles to be quickly admitted. The essential 6,7-indolyne material was easily generated through a Bartoli indole synthesis using functionalized vinyl magnesium bromide and nitrobenzenes. This research group tried to provide (±)-cis-trikentrin A (398) and (±)-herbindole A (403). The total synthesis of (±)-cis-trikentrin A (398) was started from 4-ethylaniline (394) and after two steps, including nitration diazotization and bromination, afforded o-dibromide 395. The Bartoli indole synthesis using vinyl magnesium bromide and THF at $-40^\circ$C was progressed uneventfully and afforded the corresponding indole 396 in a moderate yield (52% yield). The latter, after five steps comprising protection, cycloaddition, osmylation, oxidative removal, and concomitant desilylation, provided the desired dithioacetal 397. Lastly, upon Raney Ni reduction of 397, the natural product (±)-cis-trikentrin A (398) was synthesized successfully (Scheme 55).$^{132}$

In addition, the total synthesis of (±)-herbindole A (403) began from 3,4-dimethylaniline (399) and after two steps, including nitration, diazotization and bromination, gave o-dibromide (400). Pleasantly, the Bartoli approach provided the corresponding indole 401, but in a moderate yield (36% yield). The latter, after five steps including N-silylation, a Diels–Alder reaction, osmylation, oxidative removal, and a thioacetalization reaction was converted into etrahydrocyclopentag[indole 402. Lastly, Raney Ni reduction of 402 gave the racemic herbindole A (403). As a result, (±)-herbindole A (403) was synthesized efficiently in nine steps from 3,4-dimethylaniline (399) (Scheme 56).$^{133}$

2.4. Madelung indole synthesis

Mersicarpine was isolated from the stem-bark extracts of the Kopsia fruticosa and Kopsia arborea by Kam et al. in 2004.$^{134}$ Mersicarpine contains a typical seven-membered cyclic imine fused along with indoline and δ-lactam.$^{134,135}$ The monoterpene indole alkaloids represent a significant family of naturally occurring compounds with a rich structural diversity. Different compounds in this class show strong biological activities.$^{136}$ Various methods for the total synthesis have been reported, involving Kerr’s first total synthesis of (±)-mersicarpine$^{137}$ and Fukuyama’s first total synthesis of (−)-Mersicarpine (110).$^{138}$

The mersicarpine and leuconoxine are structurally complex and biologically fascinating aspido-sperma-derived monoterpene indole alkaloids.$^{139}$ (−)-Scholarisine G (415),$^{139}$ (+)-melodidine E (416)$^{140}$ and (−)-leuconoxine (417)$^{141}$ are pentacyclic alkaloids containing a stimulating [5.5.6.6]diazafenestrane unit$^{142}$ that possesses two or three contiguous quaternary stereogenic centers. (−)-Mersicarpine (110),$^{139}$ however, contains a fused tetracyclic 6/5/6/7 ring scaffold, identified by an unusual tetrahydro-2H-azepine ring and also a hemiaminal scaffold.$^{143-146}$ In 2019, Wang and co-worker reported$^{147}$ a unified approach for the asymmetric synthesis of (−)-scholarisine G (415), (+)-melodidine E (416), (−)-leuconoxine (417) and (−)-mersicarpine (110) from the 2-alkylated indole intermediate. The total synthesis of (−)-scholarisine G (415), (+)-melodidine E (416), (−)-leuconoxine (417) and (−)-mersicarpine (110) began with o-toluidine (404). The key Smith-modified Madelung indole synthesis was commenced with
Scheme 57  Total synthesis of (−)-scholarisine G (415), (+)-melodinine E (416), (−)-leuconoxine (417) and (−)-mersicarpine (110).
the formation of N-silylated o-toluidine (405) by treating o-toluidine (404) in the presence of a stoichiometric quantity of n-BuLi and was quenched with chlorotrimethylsilane ((Me)3SiCl). Without separation, this intermediate was subjected to sec-butyl lithium solution at a low temperature to make a reactive lithium dianion (406). After slow addition of lactone (+)-409, the cascade acylation/heteroatom Peterson olefination/isomerization reactions progressed effortlessly to yield the 2-quantenary carbon functionalized indole (−)-412 in an overall yield of 85%. It should be mentioned that lactone (+)-409 was synthesized in a good yield (72% yield) and with a good ee (89% ee) from the reaction of 3-ethylerethydro-2H-pyrane-2-one (407) and allyl methyl carbonate (408) using a Pd catalyst and the (R)-DM-BINAP ligand.44 Next, after four steps indole (−)-412 gave the keto hemiaminal 413. In the following, after a Staudinger-aza-Wittig cyclization reaction, the keto hemiaminal 413 yielded (−)-mersicarpine (110). Moreover, Zhu’s intermediate 414, after six steps, was obtained from indole (−)-412. Zhu’s intermediate 414 provided the natural product (−)-scholarisine G (415) after an LDA-promoted intramolecular aldol cyclization. Then, the reaction of (−)-scholarisine G (415) with the Burgess reagent in acetonitrile at 70 °C yielded (−)-melodinine E (416) in a high yield (99%). In the following, the hydrogenation of (−)-melodidine E (416) provided another member, (−)-leuconoxine (417), in a high yield (94%). In addition, (−)-mersicarpine (110) was synthesized using five steps from indole (−)-412 (Scheme 57).447

2.5. Buchwald-modification of the classical Fischer indolization

Alkaloids containing β-carboline have been extracted both from marine and terrestrial sources.448 Haploscleridamine is a unique tryptamine-derived alkaloid extracted from a marine sponge of the order Haplosclerida gathered in Palau and was reported in 2002 by Faulkner et al.449 This unique β-tetrahydrocarboline has been shown to prevent cathepsin K, a cysteine protease that results in osteoporosis, and therefore this natural product can act as the main compound in the establishment of treatment methods for this disease. In 2019, Lovely et al. reported the enantioselective total synthesis of the imidazole comprising a β-carboline natural product, and (−)-haploscleridamine (421) from the histidine methyl ester (418). Key to the effective assembly of this alkaloid is a ring-closing metathesis reaction of an imidazole resulting in an allylic alcohol to give 3-piperidinone. In addition, the usage of the Buchwald-modification of the classical Fischer indolization and deprotection of the N-tosyl scaffold supplied haploscleridamine. Based on this method, the total synthesis of (−)-haploscleridamine (421) started with the histidine methyl ester (418) and after seven steps this gave piperidinone (419). The latter, through Buchwald modification of the Fischer indole reaction, afforded the indole product (420). Then, after subjecting tosyllamid (420) to reductive detosylation with Mg in MeOH,451 (−)-haploscleridamine (421) was obtained in a satisfactory yield (Scheme 58).452

2.6. Batcho–Leimgruber indole formation

In 2013, Buszek and co-workers demonstrated an effective total synthesis of the annulated indole natural product (±)-cis-trikentrin B (427) by using a regioselectively constructed 6,7-indole aryn cycladdition from 5,6,7-tribromoindole. The unaffected C-5 bromine was successively utilized for a Stille cross-coupling reaction to make the butenyl side chain and
complete the synthesis. This methodology gives enables the triketrins and the relevant herbindoles to be quickly admitted. The requisite 5,6,7-indole aryne precursor was synthesized through the Leimgruber–Batcho indole synthesis. The total synthesis of (±)-cis-trikentrin B (427) started with p-toluidine (422) and after four steps yielded the enamine intermediate 423, which was instantaneously utilized without separation for the next step. An iron(III) chloride-mediated reaction with hydrazine hydrate in MeOH at 60 °C consistently gave the corresponding 5,6,7-tribromoindole (424) (Leimgruber–Batcho indole synthesis). The latter, after seven steps, gave the corresponding indole 425. Lastly, Stille cross-coupling of indole 425 and the vinyl tin reagent 426 in the presence of triphenylarsine and Pd2(dba)3 using MWI easily gave racemic cis-trikentrin B (427) in a satisfactory yield (73% yield) (Scheme 59).\textsuperscript{354}

Indiacen A and B\textsuperscript{355} are prenyl indoles and were the initially identified secondary metabolites extracted from the bacterium Sandaracinus amylolyticus in 2012 by Müller et al. belonging to a novel species of myxobacteria. These secondary metabolites,
indiacen A and its chloro analogue indiacen B, exhibit anti-microbial properties. These are known to be potent against Gram-positive and Gram-negative bacteria and also the fungus Mucor hiemalis. Indiacen B (433) is a 3-formylindole derivative having a dienyl chloride side chain. The natural product indiacen B from the myxobacterium Sandaracinus amylolyticus was produced for the first time, revealing its anti-microbial properties. The E-configuration of the chloroalkene scaffold of indiacen B was proved using X-ray analysis. In 2015, Lindel et al. demonstrated that the total synthesis of indiacen B (433) began from 2-methyl-3-nitroaniline (428), and using sodium nitrite (NaNO₂) and potassium iodide (KI) afforded the 1-iodo-2-methyl-3-nitrobenezene 429. The latter, through the Batcho-Leimgruber method (using dimethylformamide dimethyl acetal (DMFDM) and titanium(III) chloride), gave 4-iodoindole (430), and after two steps this afforded the indole 431. Finally, indiacen B (433) (29%) and its Z-isomer 432 (14%) were synthesized successfully from indole 431 (using POCl₃ in DMF at 0 °C) (Scheme 60).
2.7. Cadogan-Sundberg and SnCl₂-mediated reductive cyclization

The phytoalexins are a different group of naturally occurring compounds, which are produced in plants in response to a pathogenic challenge. The indole-comprising phytoalexins are denoted as the indole phytoalexins⁴⁵⁸ or the crucifer wasabi phytoalexins.⁴⁵⁹ These phytoalexins have been extracted from cruciferous plants, comprising cabbage, broccoli, mustard, cauliflower and wasabi (Wasabia japonica, syn. Eutrema wasabi).⁴⁶⁰,⁴⁶¹ The initial wasabi phytoalexin, methyl 1-methoxyindole-3-carboxylate (437), was extracted, identified, and manufactured by Soledade et al.⁴⁶² In 2013, Peet et al. reported the total synthesis of phytoalexin (437). Two synthetic methods have been utilized for the formation of the wasabi indole phytoalexin (437)⁴⁶³. The total synthesis of phytoalexin (437) began with 2-nitrophenylacetic acid (434). The reaction of methyl 2-nitrophenylacetic acid (434) with formaldehyde (HCHO), tetrabutylammonium iodide (n-Bu₄NI) and K₂CO₃ in toluene provided 2-(2-nitrophenyl)acrylate (435) in a good yield (85% yield). Then, phytoalexin (437) was synthesized in a good yield (85%) from 435 using modified Cadogan-Sundberg conditions,⁴⁶⁴ for instance, using trimethylphosphite (P(OCH₃)₃) instead of triethylphosphite (P(OEt)₃).

In the second route for the synthesis of 437, acrylate 435 was used. The reaction of 435 in the presence of SnCl₂ and NaOAc in THF provided methyl 1-hydroxyindole-3-carboxylate (436) in a good yield (88%). Finally, the methylation reaction of compound 436 using MeI afforded phytoalexin (437) in a high yield (97%). Based on these methods, phytoalexin (437) was synthesized in yields of 72% and 73%, respectively, that are the maximum yields obtained for all the different synthetic pathways (Scheme 61).⁴⁶³

2.8. Hemetsberger-Knittel reaction

Lyngbyatoxin A (442) was extracted in 1979 by Moore et al. from the lipid extract of sea weed.⁴⁶⁵ Lyngbyatoxin A (442) is an effective tumor promoter and similar to other indolactam alkaloids, applies its biological properties via the activation of the protein kinase C (PKC). In 2006, Tanner and Vital demonstrated⁴⁶⁷ that indole 441, an advanced intermediate for the asymmetric total synthesis of lyngbyatoxin A (442), was synthesized from allylic alcohol 439 in nine steps and with a high ee (>95% ee). The effective and very asymmetric construction of the all-carbon quaternary stereocentre of

![Scheme 63 Total synthesis of rizatriptan (447).](image)

![Scheme 64 Formal synthesis of (+)-aspidospermidine (135).](image)
lyngbyatoxin A (442) started with the allylic alcohol 439 (prepared from p-aminoacetophenone 438 in four steps), which after eight steps gave azide 440. This was performed by heating compound 440 in xylene, that efficiently gave indole 441 in a satisfactory yield (69% yield). The latter is appropriately functionalized so as to permit its transformation into

Scheme 65  Total synthesis of the tetracyclic indole alkaloid ht-13-A (455).

heating compound 440 in xylene, that efficiently gave indole 441 in a satisfactory yield (69% yield). The latter is appropriately functionalized so as to permit its transformation into

Scheme 66  Synthetic studies towards jerantinine E (459).

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lyngbyatoxin A: the C-3 indolic position is essentially nucleophilic, and the bromine at C-4 gives an appropriate handle for insertion of the amino group; moreover, the TBDMS-masked alcohol scaffold permits the formation of the linalyl appendage (Scheme 62).

### 3. Miscellaneous

Rizatriptan, an active selective 5-HT 1B/1D receptor agonist, has been proven to be clinically valuable for the treatment of migraines. Rizatriptan selectively limits isolated human middle meningeal arteries and prevents neurogenic dural extravasation and also vasodilatation. In 2015, Zhu et al. achieved and reported the total synthesis of rizatriptan (447). The reaction of the o-nitrostyrenes using aqueous titanium(III) chloride solution at ambient temperature gives indoles via a formal reductive C(sp²)–H amination reaction. β,β-Difunctionalized o-nitrostyrenes, 2,3-difunctionalized indoles were provided through a domino sequential reaction involving a reduction/cyclization/migration reaction. This approach was utilized as a key step in the short synthesis of rizatriptan and also the formal total synthesis of aspidospermidine. In this route, the synthesis of rizatriptan (447) began with the regioselective Heck reaction of aryl triflate 443 and but-3-en-1-ol (444), which after three steps afforded the triazole 445. The titanium(III) chloride-improved reductive cyclization of 445 gave the corresponding indole 446 (51% yield), which was transformed to rizatriptan (447) (Scheme 63).

The formal total synthesis of (+)-aspidospermidine (135) began with ketone 448. A solution of compound 448 in acetonitrile was stirred at room temperature to give tetrahydrocarbazolone 449 in a satisfactory yield (70% yield). The latter was then transformed into (+)-aspidospermidine (135) (Scheme 64).

Tetracyclic indole alkaloids were extracted from a genus of the bacteria Streptomyces sp. (PA-48561) by Yasui and Kamiguchi in 2000. In 2016, Söderberg et al. reported the total synthesis of furostifoline (463) (Scheme 67).

### Scheme 67  Total synthesis of furostifoline (463).

![Scheme 67](image)

### Scheme 68  Formal synthesis of 0231B (468).

![Scheme 68](image)
synthesis of the tetracyclic indole alkaloid ht-13-A (455) from 3(R)-t-butyldimethylsilyloxyprolidin-2-one. The main steps in this method are a Lewis acid catalyzed acyliminium ion allylation reaction, a Mitsunobu reaction, a Pd-mediated Stille–Kelly intramolecular cross coupling, and also a CO catalyzed Pd-mediated reductive N-heterocyclization. The total synthesis of ht-13-A (455) was commenced from the Mitsunobu reaction between the pyrrolidines 451 (prepared from 3(R)-t-butyldimethylsilyloxyprolidin-2-one (450) (in four steps) and 2-bromo-3-nitrophenol (452), which after two steps afforded the tricyclic compound 453. The Pd-mediated reductive N-heterocyclization of 453 using CO afforded the desired tetracyclic indole 454. Lastly, the reduction of the methoxycarbonyl substituent to a methyl substituent with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) in toluene afforded ht-13-A (455) in a very good yield (Scheme 65).374

Kam et al. in 2008 reported375 the extraction of seven indole alkaloids, jerantinines A–G of the Aspidosperma type from an examination of the leaf extract of a similar species.376 The jerantinines exhibited a noteworthy cytotoxicity against human KB
In 2017, Magauer et al. demonstrated the establishment of an enantioselective and very convergent three-component synthesis of the functionalized ABC ring scaffold of the *Aspidosperma* alkaloid jerantinine E. This synthetic methodology was achieved for fast formation of the tricyclic tetrahydrocarbazolone unit through a Pd-mediated amination and oxidative indole construction. In addition, a secondary amine framework, which includes all carbon atoms of the D and E ring of the natural product can be formed in three additional steps. Synthetic investigations for jerantinine E (459) began with 1,4-cyclohexanediol monoethyleneacetal (69), which after six steps gave cyclohex-2-en-1-one 456. The latter, through oxidative indole construction in the presence of Pd(OAc)$_2$ and Cu(OAc)$_2$, provided tetrahydrocarbazolone 457. In the following, benzyl protection of the tetrahydrocarbazolone 457 afforded tetrahydrocarbazolone 458, that is an intermediate for the formation of jerantinine E (459) (Scheme 66).

Furostifoline (463), the furo[3,2-α]carbazole alkaloid, was extracted by Furukawa et al. in 1990 (ref. 380) from the root bark of *Murraya euchrestifolia* Hayata and is utilized in Chinese traditional medicine. The first total synthesis of furostifoline (463) was reported in 1996 (ref. 382) and the optimum synthetic

**Scheme 71** Total synthesis of indole-3-acetonitrile-4-methoxy-2-C-β-D-glucopyranoside (487).
route to furostifoline (463) was reported in 2000 by Knölker and Fröhner. Furostifoline is a carbazole alkaloid having a furo [3,2-a]carbazole building block. In 2002, Yasuhara et al. demonstrated that furostifoline was synthesized in four steps with a 10% overall yield from 2-acetyl-3-bromofuran (460). The total synthesis of furostifoline (463) began from 2-acetyl-3-bromofuran (460) and after two steps, including the Wittig reaction and the Sonogashira reaction afforded 2-(isopropenyl)-3-[2-ethoxycarbonylamino]phenylethynyl]furan (461). Next, the tetra-n-butylammonium fluoride-improved cyclization of 461 in THF under reflux conditions afforded a mixture of 2-[[isopropenyl]furanyl]indole (462). Thus, it was proposed that the photocyclization triggered the polymerization of 462 and afforded the natural product furostifoline (463) in a low yield (24%) (Scheme 67). The inhibitors of 3z-hydroxysteroid dehydrogenase, 0231A and 0231B, were extracted in 2001 by Gräfe from a fermentation broth of Streptomyces sp. HKI0231. Meanwhile 3z-hydroxysteroid dehydrogenase is an enzyme related to inflammatory processes, these compounds are favorable as main structures for anti-inflammatory agents. An advanced intermediate in the Nakatsuka synthesis of 0231B was synthesized through a fluoride-catalyzed indole construction in the key step. It is worth mentioning that both Pd-based methods and hydride-based methods were unsuccessful in forming the indole. The formal synthesis of 0231B (468) was commenced from 2-hydroxy-5-methyl-3-nitrobenzaldehyde (464) and after three

Scheme 72 Formal synthesis of (±)-herbindole B (491) and (±)-cis-trikentrin A (398).
steps afforded acetamide 465. Auspiciously, the reaction of acetylene 465 with tetrabutylammonium fluoride (TBAF) in THF under refluxing conditions provided indole 466 in a satisfactory yield (yield). After two steps, enone 467 was furnished, and gave 0231B (468) (after six steps)\(^{389}\) (Scheme 68).\(^{388}\)

In addition, the formal synthesis of 0231B (468) was commenced from the Sonogashira coupling reaction of triflate 469 and trimethylsilylacetylene (470) and afforded acetylene 471. Fluoride-catalyzed cyclization, desilylation and also deacetylation occurred in a one-pot reaction and resulted in the transformation of 471 into indole 472 in a moderate yield (34%). After two steps, enone 473 was provided, and then gave 0231B (468) (after six steps) (Scheme 69).\(^{389}\)

Pyrido[3,4-b]indoles, frequently identified as β-carbolines, are the key structural scaffolds of different biologically significant alkaloids of synthetic and natural origins.\(^{390,391}\) Naturally occurring compounds bearing a β-carboline core have been extracted from terrestrial plants and several marine invertebrates and their biological activities change from interactions with the benzodiazepine receptor to powerful anti-viral, anti-tumor, and anti-microbial properties.\(^{392-394}\) Eudistomin U (478) was extracted in 1994 by Badre and co-workers from the Caribbean ascidian Lissoclinum fragile and exhibited anti-microbial and DNA binding properties.\(^{395-397}\) A flexible method for the synthesis of functionalized β- and γ-carbolines relied on the transition metal mediated [2 + 2 + 2] cycloadition reactions of substituted yne-ynamides and methylcyanofornate was achieved and reported by Witulski et al. in 2011.\(^{398}\) The flexibility of this unique reaction sequence is shown by its use in the total synthesis of the marine natural product eudistomin U (478). The total synthesis of eudistomin U (478) was commenced from 2-iodoaniline (474) that after three steps yielded yne-ynamide 475. Next, the Cp*RuCl(cod)-mediated [2 + 2 + 2] cycloadition of 475 using methylcyanofornate led to the β-carboline ester 476 (94% yield), which was saponified using \textit{in situ} elimination of the N-carboline and N-indolyl tosyl substituents to afford the β-carboline carboxylic acid 477 in a high yield (96% yield). Lastly, decarboxylation of 477 using Cu powder under microwave irradiation (MWI) gave eudistomin U (478) in a high yield (88%) (Scheme 70).\(^{398}\)

C-aryl glycosides, a class of naturally occurring compounds, show a variety of significant biological activities.\(^{399}\) A number of members of this family exhibit strong anti-viral, anti-biotic, and anti-tumor activities, and there is also sufficient experimental proof that C-aryl glycosides bind duplex DNA.\(^{400}\) Two alkaloids extracted from the roots of the plant Isatis indigotica contain an...
Scheme 74  Total synthesis of (+)-vinblastine (514).
indole-C-glycoside unit. Indole-3-acetonitrile-4-methoxy-2-C-\(\beta\)-n-glucopyranoside (487) exhibits a cytotoxic property against human liver cancer HepG2 cells and also human myeloid leukemia HL60 cells. In 2012, Minehan and Yapremyan demonstrated that indole-3-acetonitrile-4-methoxy-2-C-\(\beta\)-n-glucopyranoside (487), a unique C-glycoside from *Isatis indigotica* that has significant cytotoxic properties, can be synthesized in ten steps from ethynyl-\(\beta\)-C-glycoside (481) and 2-iodo-3-nitrophenyl acetate (482). Noticeably, key steps in the synthesis involve a Sonogashira coupling reaction and a copper(i) iodide-catalyzed indole construction. The total synthesis of indole-3-acetonitrile-4-methoxy-2-C-\(\beta\)-n-glucopyranoside (487) was commenced from the Sonogashira reaction between acetoxyaryl iodide 482 (obtained from 2-amino-3-nitrophenol (480) in two steps), and alkyne 481 (obtained from dextrose 479 in seven steps), and gave the corresponding alkyne 483. The latter, after three steps including amination, hydroxy methylolation, and reduction, provided aniline 484. Next, a base-catalyzed indolation reaction was investigated using Nockel’s t-BuOK-NMP system. The reaction of compound 484 in the presence of t-BuOK in N-methyl-2-pyrrolidone gave variable amounts of indole C-glycoside 485 with yields of 33–55%. In the following, indole C-glycoside 485 after four steps gave nitrile 486. The elimination of the silyl ether masking groups was performed using TBAF in THF and provided indole-3-acetonitrile-4-methoxy-2-C-\(\beta\)-n-glucopyranoside (487) in satisfactory yields (72%) (Scheme 71). Duerer et al. 2016 demonstrated the formal synthesis of the indole alkaloids (±)-cis-trikentren A (398) and (±)-herbinderdole B (491) from the usual meso-hydroquinone intermediate synthesized by a Ru-mediated \(2 + 2 + 1 + 1\) cycloaddition. Key steps involve a sterically demanding Buchwald–Hartwig amination and also a distinctive C(sp\(^3\))-H amination/indole construction. The formal synthesis of (±)-herbinderdole B (491) and (±)-cis-trikentren A (398) began with the bicyclic alkene 488, which after six steps afforded anilide triflamide 489 and triflamide (492) through two different routes. In the following, anilide triflamide 489, through straight indole construction by using the C-H activation method, gave indole 490 in a satisfactory yield (66%), in which one carbon–nitrogen bond and one carbon–carbon double bond were formed. Next, after more than eight steps, indole 490 gave (±)-herbinderdole B\(^{496}\) (491). On the other hand, triflamide 492 was exposed to the indolization reaction and the desired indole 493 was obtained in a satisfactory yield (61%), in which one carbon–nitrogen bond and one carbon–carbon double bond were constructed (average yield of 78% per event). Finally, after more than eight steps, (±)-cis-trikentren A (398) was synthesized successfully from indole 493 (Scheme 72).

Catharanthine is a significant member of the *Iboga* class of alkaloids. Catharanthine was extracted in 1985 by Raucher and Bray from the leaves of *Catharanthus roseus*. Catharanthine *Catharanthus roseus* includes more than 400 valuable alkaloids, for example vinblastine, vincristine, catharanthine, yohimbine, tabersonine, lochnerine, ajmalicine, vindosine, vindoline and vindolincine. Catharanthine has noteworthy biological functions as it has anti-cancer properties. A stereoregulated total synthesis of (±)-catharanthine (502) was accomplished in 1999 by Fukuyama and Reding. The key step includes the radical-catalyzed cyclization of a variety of substituted intermediates to provide the desired indole. The cyclization reaction employs a facile phosphorus-based radical-reducing agent. The total synthesis of (±)-catharanthine (502) begins with the carbodiimide coupling of cis-2-alkenyl aniline 497 (prepared as a single diastereomer from quinoline 495 in three synthetic steps with a 42% overall yield) and endo-lactone 496 (prepared from diethyl ethosymethenemonalontate 494 in four steps). This reaction yielded anilide iodolactone 498, which after three steps gave 2-alkenylothioanilide 499. The cyclization reaction using stoichiometric azobisisobutyronitrile (AIBN), excess aqueous hypophosphorous acid (\(\text{H}_2\text{PO}_2\)) and \(\text{Et}_3\text{N}\) under reflux in 1-propanol consistently gave the corresponding indole 500 in a 40–50% yield. After two further steps, 500 gave intermediate 501. Next, the benzyl carbamate was eliminated under mild conditions and very selective reaction conditions\(^{413}\) to directly give (±)-catharanthine (502) (Scheme 73). Vinblastine is a well known chemotherapeutic agent utilized for the treatment of cancer. This natural product was recognized for the first time as a myelosuppressive agent by Noble’s group in 1958 during the investigation of anti-diabetic agents in *Catharanthus roseus*\(^{414}\). Individually, researchers at Eli Lilly demonstrated that extracts of *Catharanthus roseus* influenced activity against P-1534 leukemia in mice, and also extracted vinblastine as a potent unit in 1959. In 2010, Yokoshima et al. reported a stereoregulated total synthesis of (+)-vinblastine (514). The synthesis of the upper half specifies the stereocontrolled formation of the tertiary alcohol via a 1,3-dipolar cycloaddition of nitrile oxide and a Baeyer–Villiger oxidation, a simple indole construction using the radical cyclization of \(\sigma\)-alkenylothioanilide, and also the macrocyclization of 2-nitrobenzenesulfonamide. The essential coupling reaction of the upper half with synthetic vindoline was effectively accomplished to provide the coupling product in an approximately quantitative yield, and subsequent conversions afforded (+)-vinblastine (514). The total synthesis of (+)-vinblastine (514) started with the construction of the lower half, vindoline (507). The synthesis of the lower half was achieved using a Mitsunobu coupling reaction of indole 505 (prepared from 7-mesyloxquinoline (503) in seven steps) and 2,4-dinitrobenzenesulfonamide (chiral amine) 506 (prepared from 2-pentenal (504) in six steps), which after over three steps afforded vindoline (507). On the other hand, the upper unit 511 was synthesized from \(\text{n}\)-butyraldehyde (508) and after 16 steps gave the alkenylothioanilides 509. Then, numerous conditions were examined, and it was found that using THF as a solvent inhibited the isomerization to provide indole 510 in a satisfactory yield (67%) yield. The latter, after nine steps, gave the upper unit 511. Then, the chlorination of 511 using tert-butyl hypochlorite gave chloroindolenine, which was concisely proven using a neutral silica gel column to eliminate the excess quantity of the reagent. The chloroindolenine and synthetic vindoline (0.9 equivalents) were dissolved in \(\text{CH}_2\text{Cl}_2\) and reacted with trifluoroacetic acid (\(\text{CF}_3\text{CO}_2\)H) to give the corresponding coupled product 512 in a high yield (97%) as a single isomer.
which after two synthetic steps provided the secondary amine 513. Lastly, the latter using NaHCO₃ in isopropyl alcohol (i-PrOH) and H₂O gave (+)-vinblastine (514) in a moderate yield (66% yield) (Scheme 74).419

4. Conclusion

In summary, indoles represent one of the most significant privileged motifs in drug discovery. Indoles and their derivatives have the exclusive property of mimicking the structure of peptides and can bind reversibly to enzymes, giving incredible opportunities to identify unique drugs that possess various modes of action. In addition, there are a remarkable number of approved indole-comprised drugs on the market. With the improvement in synthetic approaches, the separation of unique compounds from natural sources bearing indole frameworks is another ongoing and increasing area of investigation. The investigation of these novel molecules and the study of their properties and potential applications in the reaction of various diseases is another synergistic feature of the significance of the organic synthesis of indoles. Fischer indole synthesis is an essential reaction used in many natural product syntheses. This important named reaction is broadly used for installing the indole ring. In this review, we aim to demonstrate various methods used for synthesizing indoles as a moiety in selected alkaloids.

Conflicts of interest

There are no conflicts to declare.

References

1 V. Sharma, P. Kumar and D. Pathak, *J. Heterocycl. Chem.*, 2010, 47, 491–502.
2 E. Abele, R. Abele, O. Dzenitis and E. Lukevics, *Chem. Heterocycl. Compd.*, 2003, 39, 3–35.
3 H. Fanwar, R. Verma, V. Srivastava and A. Kumar, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 2006, 45, 2099.
4 Y.-Y. Li, H.-S. Wu, L. Tang, C.-R. Feng, J.-H. Yu, Y. Li, Y.-S. Yang, B. Yang and Q.-J. He, *J. Pharmacol. Res.*, 2007, 56, 335–343.
5 P. Barraja, L. Sciacibica, P. Diana, A. Lauria, A. Montalbano, A. M. Almerico, G. Dattolo, G. Cirrinicone, S. Disarò and G. Basso, *Bioorg. Med. Chem. Lett.*, 2005, 15, 2291–2294.
6 K. S. Lam, *Trends Microbiol.*, 2007, 15, 279–289.
7 M. S. Butler, *Nat. Prod. Rep.*, 2008, 25, 475–516.
8 D. J. Newman and G. M. Cragg, *J. Nat. Prod.*, 2007, 70, 461–477.
9 B. Debnath, W. S. Singh, M. Das, S. Goswami, M. K. Singh, D. Maiti and K. Manna, *Mater. Today Chem.*, 2018, 9, 56–72.
10 B. Debnath, M. Uddin, P. Patari, M. Das, D. Maiti and K. Manna, *Int. J. Pharm. Pharm. Sci.*, 2015, 7, 223–227.
11 M. El-Sayed and R. Verpoorte, *Phytochem. Rev.*, 2007, 6, 277–305.
12 S. Sagi, B. Avula, Y.-H. Wang and I. A. Khan, *Anal. Bioanal. Chem.*, 2016, 408, 177–190.
13 N. K. Kaushik, N. Kaushik, P. Attril, N. Kumar, C. H. Kim, A. K. Verma and E. H. Choi, *Molecules*, 2013, 18, 6620–6662.
14 L. B. Diss, S. D. Robinson, Y. Wu, S. Fidalgo, M. S. Yeoman and B. A. Patel, *ACS Chem. Neurosci.*, 2013, 4, 879–887.
15 M.-Z. Zhang, N. Mulolland, D. Beattie, D. Irwin, Y.-C. Gu, Q. Chen, G.-F. Yang and J. Clough, *Eur. J. Med. Chem.*, 2013, 63, 22–32.
16 S. N. Young, *J. Neuropsychiatry Clin. Neurosci.*, 2007, 32, 394.
17 S. A. Patil, R. Patil and D. D. Miller, *Future Med. Chem.*, 2012, 4, 2085–2115.
18 F.-E. Chen and J. Huang, *Chem. Rev.*, 2005, 105, 4671–4706.
19 W. Kurz, K. Chatson, F. Constabel, J. Kutney, L. Choi, P. Kolodziejczyk, S. Sleigh, K. Stuart and B. Worth, *Planta Med.*, 1981, 42, 22–31.
20 H. Ishikawa, D. A. Colby and D. L. Boger, *J. Am. Chem. Soc.*, 2008, 130, 420–421.
21 G. Bartoli, R. Tearndi, A. Medici and G. Rosini, *J. Chem. Soc., Perkin Trans. 1.*, 1978, 692–696.
22 H. Hemsztberger and D. Knittel, *Monatsh. Chem.*, 1972, 103, 194–204.
23 A. Bischler and P. Fireman, *Ber. Dtsch. Chem. Ges.*, 1893, 26, 1336–1349.
24 J.-B. Baudin and S. A. Julia, *Tetrahedron Lett.*, 1986, 27, 837–840.
25 R. C. Larock and S. Babu, *Tetrahedron Lett.*, 1987, 28, 5291–5294.
26 C. Nenitzescu, *Bull. Assoc. Chim.*, 1929, 11, 37–43.
27 W. Madelung, *Ber. Dtsch. Chem. Ges.*, 1912, 45, 1128–1134.
28 W. Noland and F. Baude, *Org. Synth.*, 1973, 5, 567–571.
29 E. Fischer and F. Jourdan, *Ber. Dtsch. Chem. Ges.*, 1883, 16, 2241–2245.
30 A. Kuznetsov, A. Makarov, A. E. Rubtsov, A. V. Butin and V. Gevorgyan, *J. Org. Chem.*, 2013, 78, 12144–12153.
31 T. Chandra, S. Zou and K. L. Brown, *Tetrahedron Lett.*, 2004, 45, 7783–7786.
32 A. Carpita and A. Ribecai, *Tetrahedron Lett.*, 2009, 50, 6877–6881.
33 W. Wierenga, J. Griffin and M. A. Warpehoski, *Tetrahedron Lett.*, 1983, 24, 2437–2440.
34 D. Hong, Z. Chen, X. Lin and Y. Wang, *Org. Lett.*, 2010, 12, 4608–4611.
35 R. Umeda, Y. Nishimoto and T. Mashino, *Heterocycles*, 2013, 87, 1241–1247.
36 M. T. Hovey, C. T. Check, A. F. Sipher and K. A. Scheidt, *Angew. Chem., Int. Ed.*, 2014, 126, 9757–9761.
37 J. J. Li, *Name reactions in heterocyclic chemistry*, John Wiley & Sons, 2004.
38 J. P. Kutney, in *The Total Synthesis of Natural Products*, 2007, vol. 3, pp. 273–438.
39 S. M. Bronner, G. V. J. Im and N. K. Garg, in *Heterocycles in Natural Product Synthesis*, 2011, pp. 221–265, DOI: 10.1002/1987527634880.ch7.
40 D. L. Hughes, *Org. Prep. Proced. Int.*, 1993, 25, 607–632.
41 R. McDanell, A. E. M. McLean, A. B. Hanley, R. K. Heaney and G. R. Fenwick, *Food Chem. Toxicol.*, 1988, 26, 59–70.
42 R. Dalpozzo and G. Bartoli, *Curr. Org. Chem.*, 2005, 9, 163–178.
