RSC Advances

REVIEW

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2021, **11**, 33540

Synthesis of indole derivatives as prevalent moieties present in selected alkaloids

Majid M. Heravi,* Zahra Amiri, Kosar Kafshdarzadeh and Vahideh Zadsirjan*

Received 6th August 2021
Accepted 10th September 2021

DOI: 10.1039/d1ra05972f

rsc.li/rsc-advances

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.[1] 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.[2] 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,[3] anti-hypertensive,[2] and anti-diabetic activities,[4] and also photochemotherapeutic properties.[5]

Department of Chemistry, School of Physics and Chemistry, Alzahra University, Vanak, Tehran, Iran. E-mail: mmh1331@yahoo.com; mmheravi@alzahra.ac.ir; z_zadsirjan@yahoo.com; Fax: +98 2188041344; Tel: +98 9121329147

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.[6–8] 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.[9] 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.

Majid M. Heravi was born in 1952 in Mashhad, Iran. He received his BSc degree from the National University of Iran in 1975, his MSc and PhD degrees from Salford University, England, in 1977 and 1980. He started his career as a research fellow in Daroupakhsh in 1981 and joined as an assistant professor at Ferdowsi University of Mashhad. In 1999 he moved to Alzahra University of Tehran. He has so far published 880 ISI cited papers including 12 chapters in Advances in heterocyclic chemistry and one chapter in Alkaloids and also three books (published by Elsevier).

Zahra Amiri was born in Lorestan, Iran and received her BSc degree in Pure Chemistry from Lorestan University. Currently, she is MSc student in Organic Chemistry at Alzahra University under the supervision of Professor Majid M. Heravi. Her research interests focus on heterocyclic chemistry, catalysis, organic methodology and green synthetic organic chemistry.

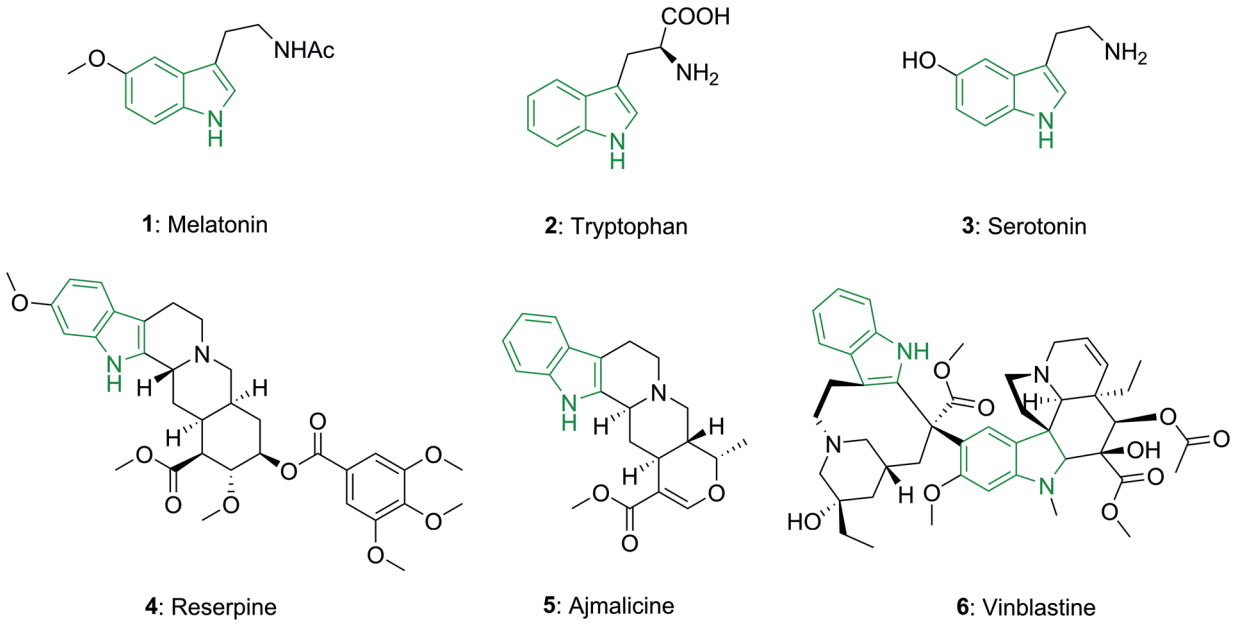


Fig. 1 The structures of natural products and drugs that possess indole moieties.

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]

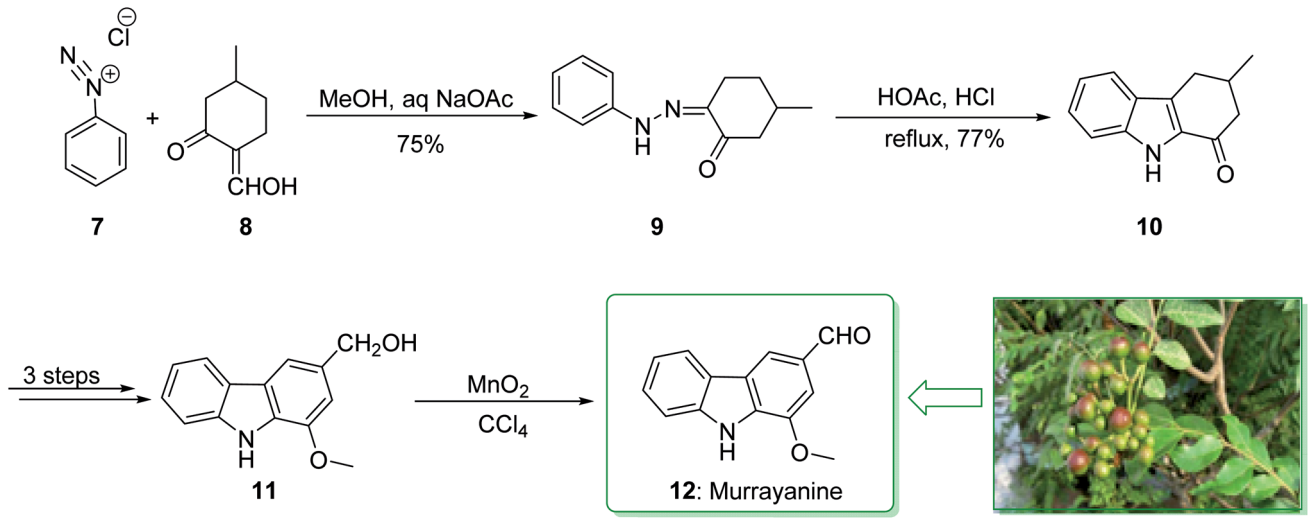
Indole alkaloids are broadly distributed in plants belonging to the families of Loganiaceae, Apocynaceae, Nyssaceae and Rubiaceae. Significant indole alkaloids that have been extracted from plants include the anti-hypertensive drug, reserpine from *Rauwolfia serpentine*[12] and also the potent anti-tumor 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]

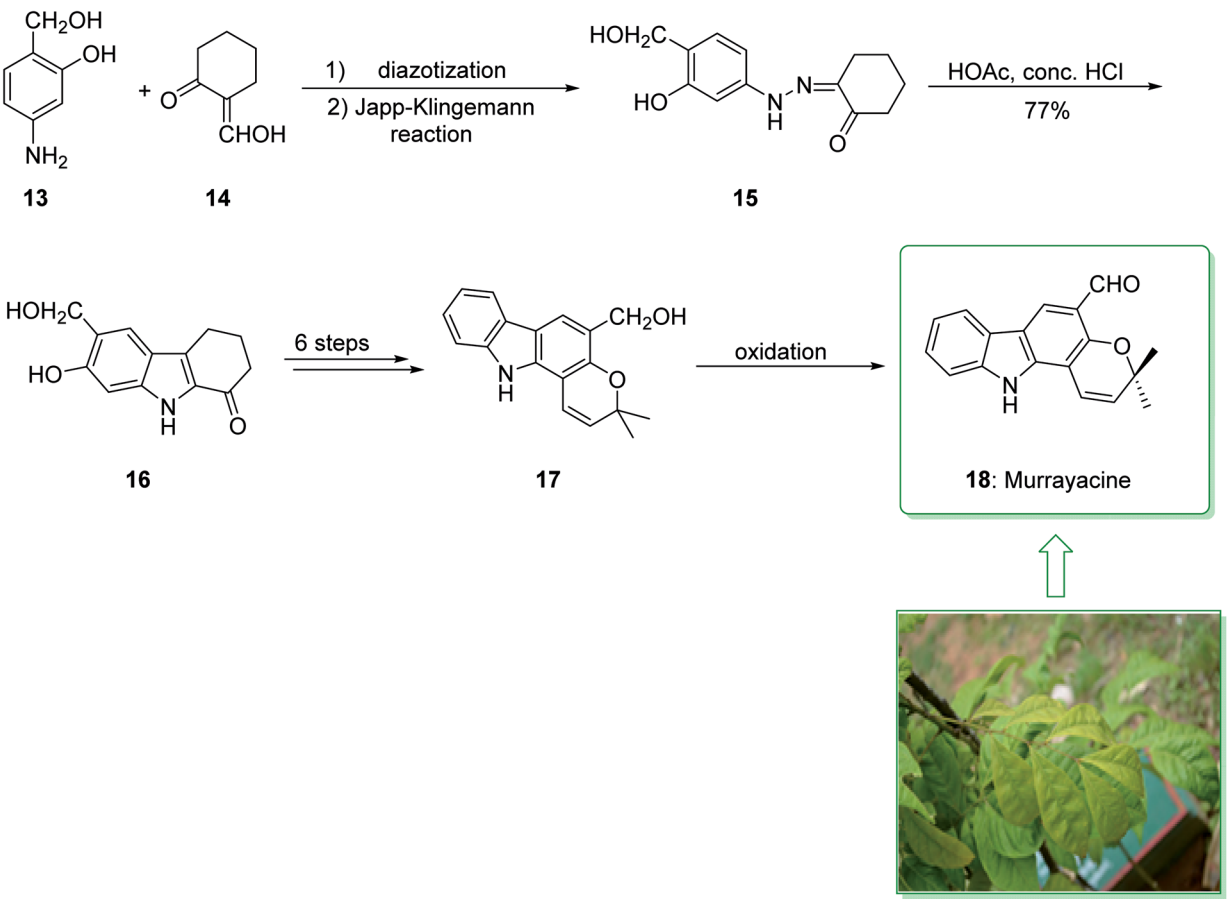
Kosar Kafshdarzadeh was born in 1995 in Karaj, Iran. She received her BSc degree in Applied Chemistry from University of Tehran in 2018. Since 2018, she is MSc student in Organic Chemistry at Alzahra University under the supervision of Professor Majid M. Heravi. Her research focuses on heterocyclic chemistry, catalysis, organic methodology and green synthetic organic chemistry.

Vahideh Zadsirjan was born in 1979 in Shiraz. She received her BSc in Pure Chemistry from Kharazmi University in 2002, and her MSc in 2007 and PhD degrees in organic chemistry in 2016 under the supervision of Professor Majid M. Heravi from Alzahra University Tehran, Iran. Her research is focused on heterocyclic chemistry, catalysis, organic methodology and green synthetic organic chemistry. He has so far published 80 ISI cited papers including one chapter in Advances in heterocyclic chemistry book series published by Elsevier) and one chapter in Alkaloids, and also two books (published by Elsevier).

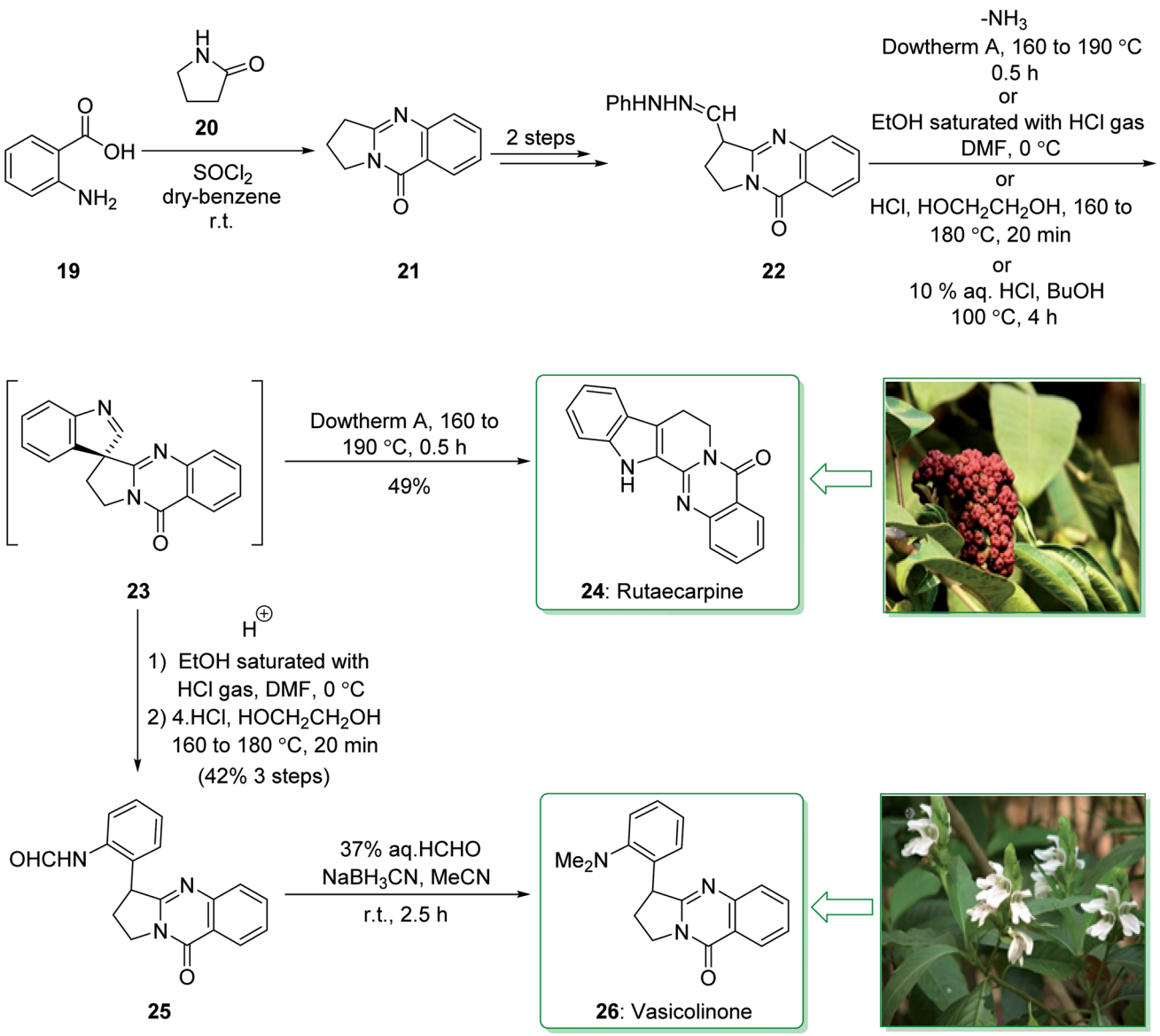


Scheme 1 Total synthesis of murrayanine (12).

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.[17] 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.[18] 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.[19] 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).[20]



Scheme 2 Total synthesis of murrayacine (18).



Scheme 3 Total synthesis of rutaecarpine (24) and vasicolinone (26).

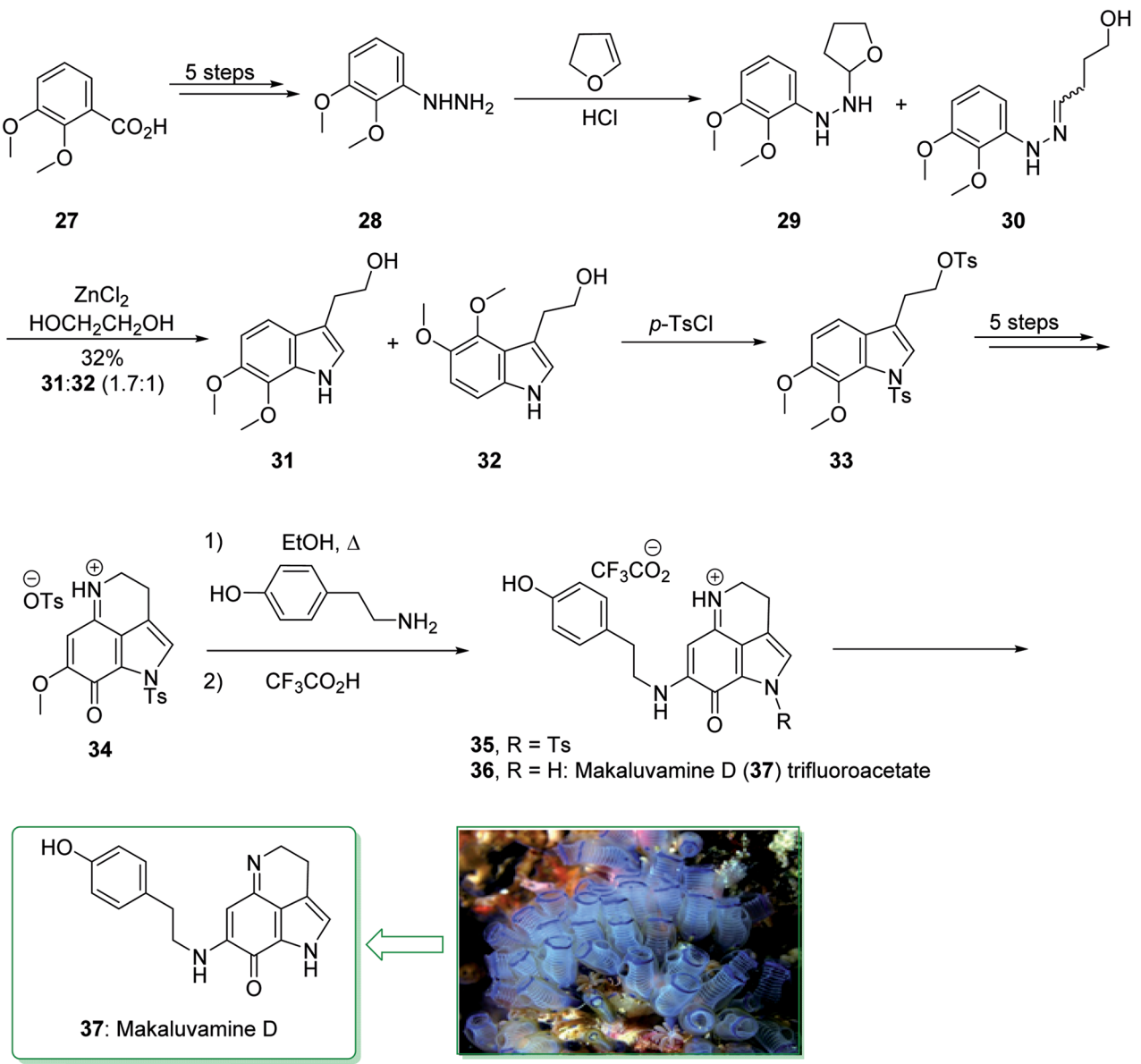
Various methods have been reported for the synthesis of indoles, for example modern versions of classical synthesis methods (named reactions along with indole synthesis) such as: Bartoli indole synthesis,[21] Hemetsberger indole synthesis,[22] Bischler indole synthesis,[23] Julia indole synthesis,[24] Larock indole synthesis,[25] Nenitzescu indole synthesis,[26] Madelung indole synthesis,[27] Reissert indole synthesis[28] and the most important one, Fischer indole synthesis.[29] Other methods involve the transformation of heterocycles,[30] the conversion of indolines into indoles,[31] the synthesis of *o*-alkynylanilines,[32] the reduction of oxindoles to indoles,[33] synthetic methods using arynes,[34] the reductive cyclization of nitrobenzene derivatives[35] and catalysis using *N*-heterocyclic carbenes.[36]

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.[37–64] In a continuation of our interest in heterocyclic chemistry[65–67] and the applications of named reactions in the total synthesis of natural products,[68–75] 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

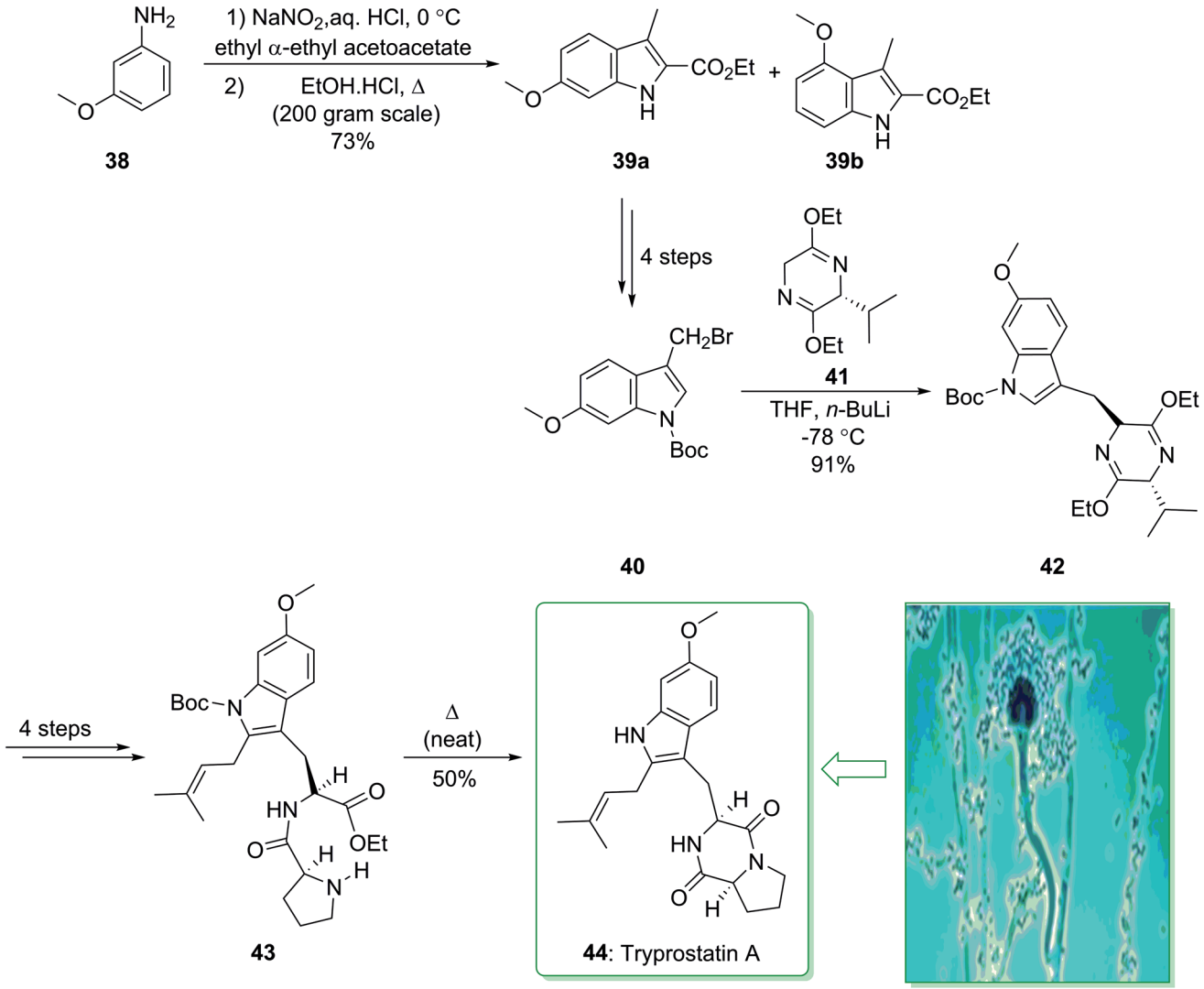
Murrayanine is the main compound extracted from *Murraya Koenigii* in 1965 by Chakraborty. Murrayanine shows various anti-mycobacterial, anti-oxidant, and anti-fungal activities. *Murraya Koenigii* Spreng, an aromatic plant belonging to the family *Rutaceae*, is usually identified as the curry leaf tree. Notably, it has been utilized in sub-tropical and tropical Asia as a folk medicine.[76] This tonic plant has been employed for the treatment of different disease conditions[77] and has been demonstrated to have a potential role as a remedy for cancer[78]



Scheme 4 Total synthesis of makaluvamine D (37).

and also inflammation. Moreover, the leaf extracts of *M. Koenigii* are broadly utilized as having anti-fungal,[79] anti-diabetic,[80] anti-inflammatory[81] and anti-oxidant properties.[82] In 1968, Chakraborty and co-workers reported[83] 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).[83] In addition, some alternative methods for the synthesis of murrayanine (**12**), including some with better overall yields, have been reported.[84–89]

Pyrano[3,2-*a*]carbazole alkaloids are very stimulating owing to their structural aspects, and also because of their valuable biological properties.[90–94] In 1968, Chakraborty *et al.* isolated murrayacine (**18**) from two different natural sources including *Clausena heptaphylla*[95] and *Murraya koenigii.*96 The total synthesis of murrayacine (**18**) was achieved and reported by Chakraborty *et al.* in 1973.[97] 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**

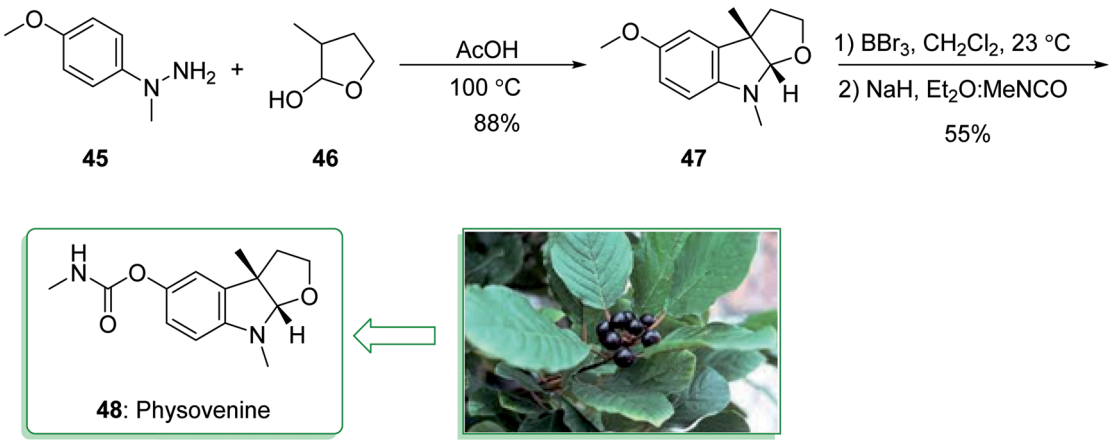


Scheme 5 Total synthesis of tryprostatin A (**44**).

produced the natural product murrayacine (**18**) (Scheme 2).[97] In addition, some alternative synthesis methods for murrayacine (**18**), some of which have better overall yields, have been reported.[98–100]

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*.[101] 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.[102] In 1971, vasicolinone (**26**), an quinazoline alkaloid, was extracted from the leaves of the Indian plant *Adhatoda uasica* Nees (Acanthaceae).[103] Both kinds of alkaloids have attracted significant attention because of their pharmacological properties.[104,105] Rutaecarpine is one of the component parts of traditional ancient Chinese herbal medicine.[106] In 1992, Hermecz and co-worker achieved and reported[106] 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,[107] using thionyl chloride ($SOCl_2$) and gave the deoxyvasicinone alkaloid (**21**) in a high yield (93% yield),[108] 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%).

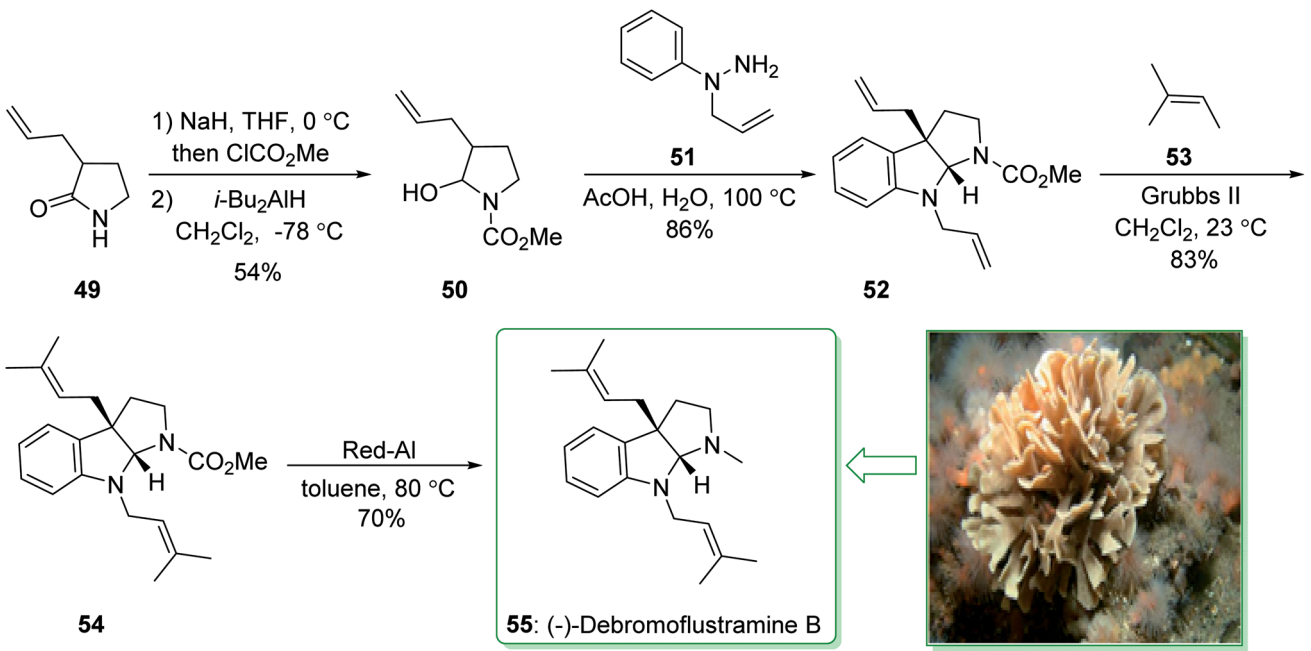
In addition, under acidic reaction conditions, upon the protonation of spiroindoleninpyrroloquinazolinone **23** on the indolenine nitrogen, **23** underwent a retrograde aldol reaction to afford the ring-opened pyrroloquinazolinone **25**. In the following, after hydrolysis of the formamide substituent, the natural product vasicolinone (**26**) was quantitatively provided



Scheme 6 Formal synthesis of physovenine (**48**).

from pyrroloquinazolinone **25** using dimethylation of the amino group with 37% aqueous formaldehyde (HCHO) using sodium cyanoborohydride ($NaBH_3CN$) in acetonitrile at room temperature[109] (Scheme 3).[106]

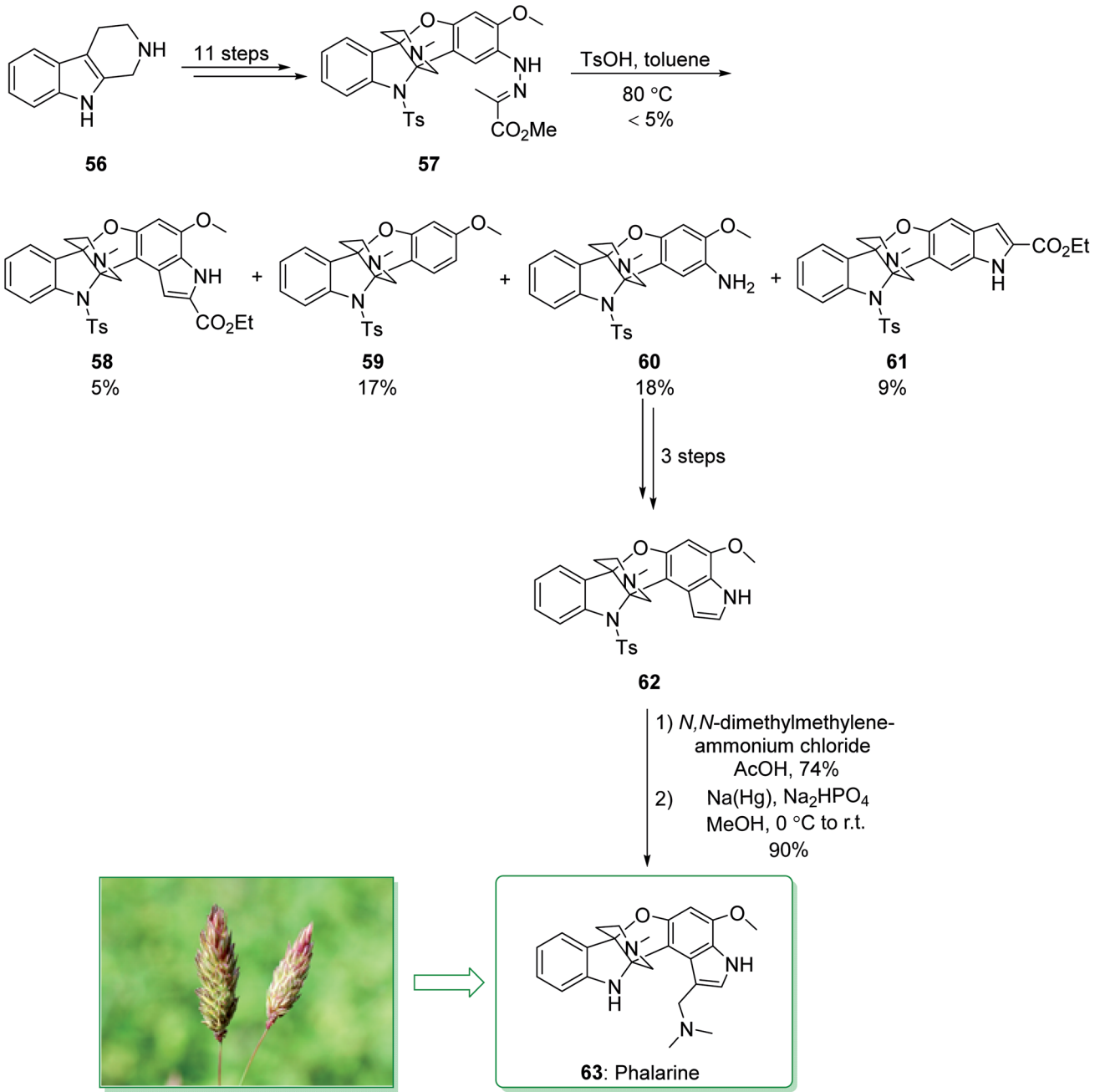
A class of very cytotoxic metabolites that possess the pyrrolo[4,3,2-*de*]quinoline framework were discovered upon examining the marine sources of anti-neoplastic agents.[110] These contain the discorhabdins,[111] prianosins,[112] isobatzellines, batzellines,[113] and damirones,[114] all extracted in 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 dihydrofuran[118] 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 $ZnCl_2$ and gave the desired tryptophol **31**, accompanied by the 4,5-dimethoxyindole derivative **32**. Next, the elimination of **32** from the



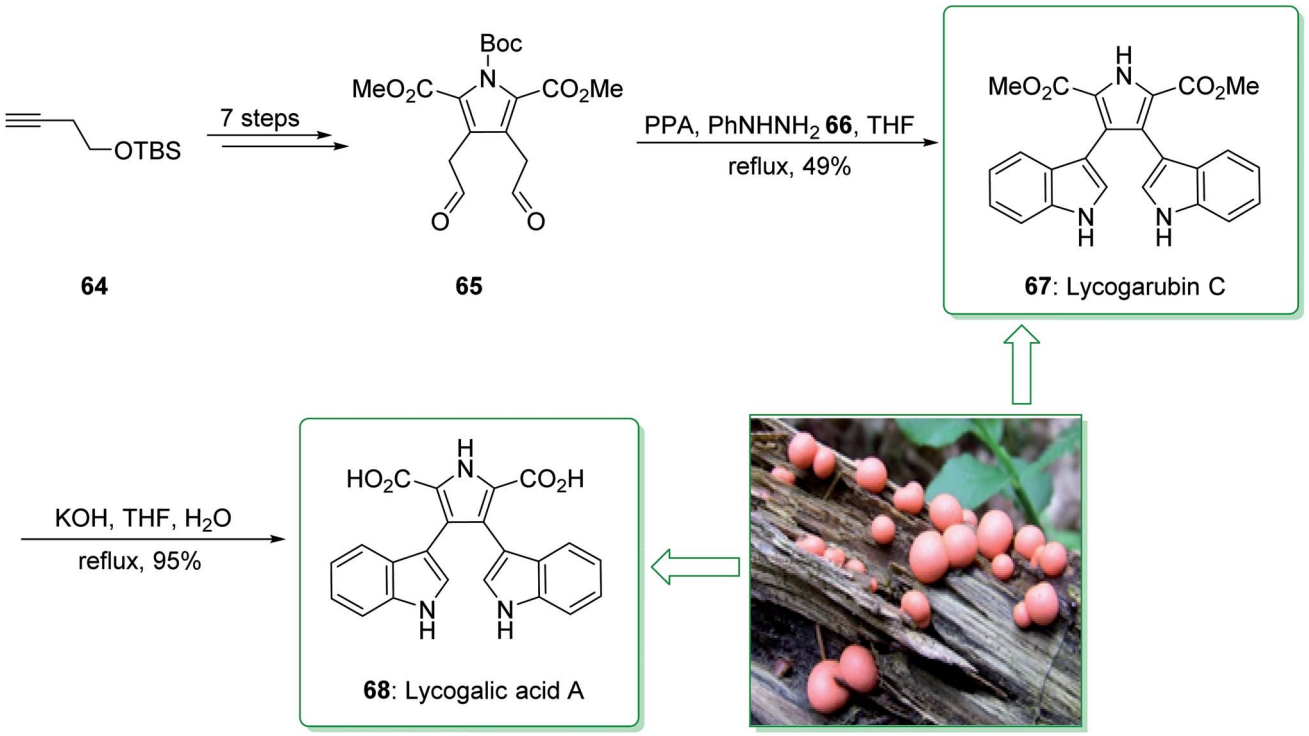
Scheme 7 Formal synthesis of (−)-debromoflustramine B (**55**).

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 bissulfonyl 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).[117]

In 1995, Osada and co-workers isolated tryprostatins A and B from the fermentation broth of *Aspergillus fumigatus* BM939.[119] Tryprostatin A (**44**) possesses promising attributes, as it selectively stops the cell cycle in tsFT210 cells in the mitotic phase.[120] Stimulating biological activity, along with a seemingly simple structure, has motivated the synthetic community, and various total syntheses have been demonstrated.[121,122] In 1997, Cook and co-workers achieved and reported[123] 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 $NaNO_2$ 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 Total synthesis of phalarine (**63**).



Scheme 9 Total synthesis of lycogarubin C (**67**) and lycogalic acid (**68**).

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 after four synthetic steps gave 3-(bromomethyl)indole (**40**). The latter was coupled with the anion of the Schollkopf chiral auxiliary **41** (obtained from D-valine),[124] and the corresponding trans diastereomer **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 (−)-debromoflustramine 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(prenylated) derivative **54**, which was transformed into (−)-debromoflustramine B (**55**) through reduction with Red-Al. It is worth mentioning that compound **54** has formerly been transformed into debromoflustramine B (**55**) *via* reduction using lithium aluminum hydride[133] (Scheme 7).[130]

Colegate and co-workers isolated a furanobisindole alkaloid, called phalarine (**63**) from *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

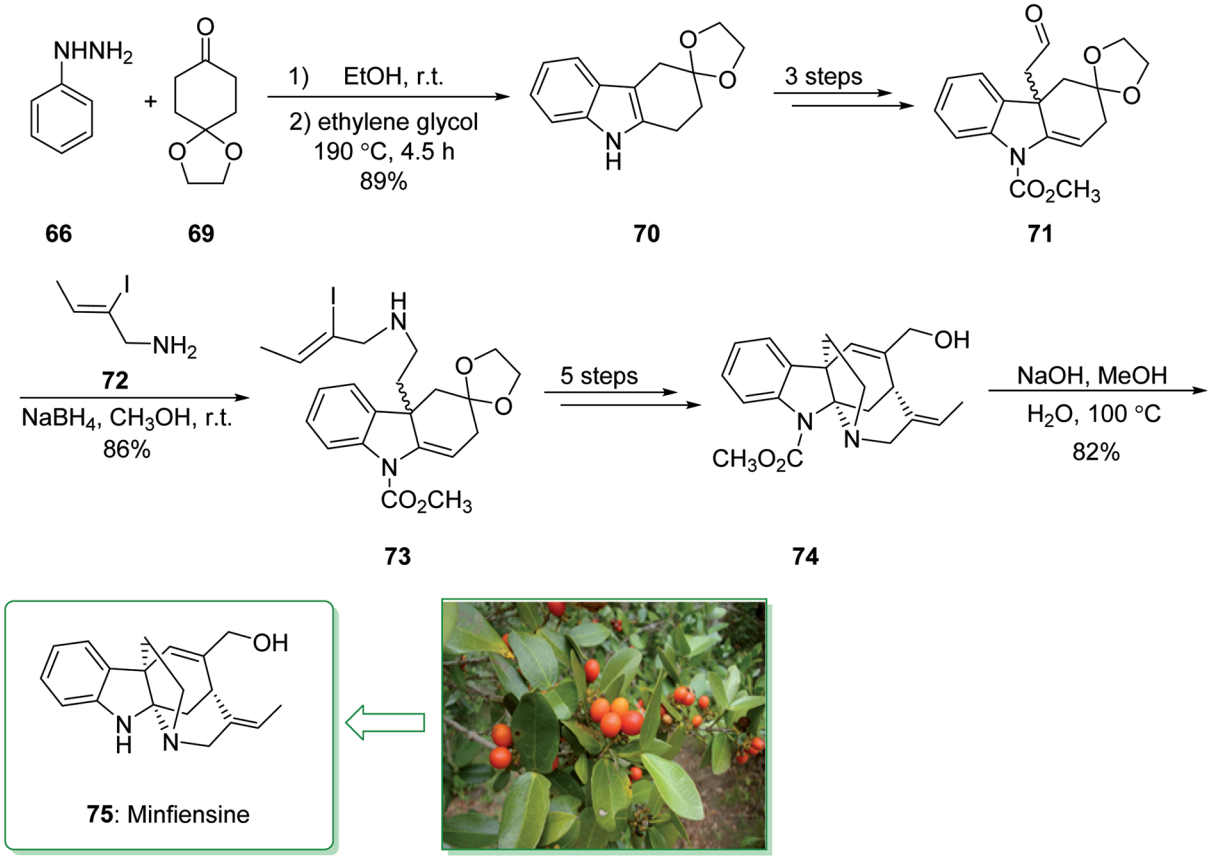
enantioselective total synthesis of **63** by Danishefsky[137] and Chen.[138] In 2010, Danishefsky *et al.* demonstrated[136] the Pictet–Spengler reaction for C_2-aryl indoles, and effectively separated the elusive azaspiroindolenine intermediate of the Pictet–Spengler reaction. Total synthesis of phalarine (**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).[136]

The natural products of lycogarubin C (**67**) and lycogalic acid (**68**) were identified in 1994. They were extracted individually by Steglich[139] and Akazawa[140] from *Lycogala epidendrum*, a slime mold. Moreover, lycogalic acid, referred to as chromopyrrolic acid (CPA),[141–143] 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.[91]

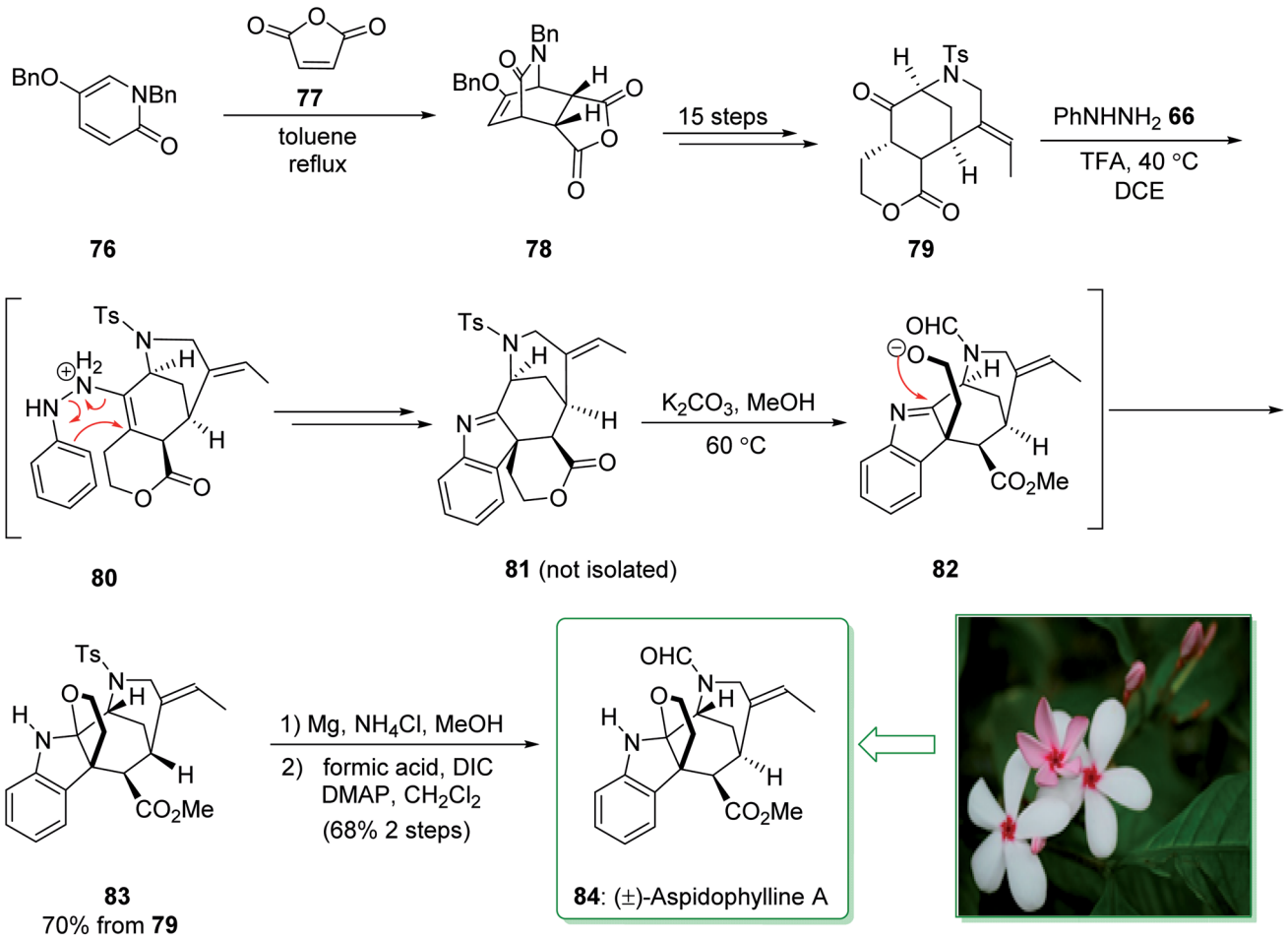
Lycogarubin C (**67**) and lycogalic acid A (**68**) are naturally occurring key marine compounds that are utilized in investigations into the inhibitor of DNA topoisomerase-I. In 2010, Zhixiang *et al.* demonstrated that lycogarubin C was synthesized from (but-3-ynyloxy)(*tert*-butyl)dimethylsilane 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.[144]

The total synthesis of lycogarubin C (**67**) and lycogalic acid A (**68**) was commenced from (but-3-yn-1-yloxy)(*tert*-butyl)dimethylsilane (**64**), and after seven synthetic steps, gave 1-(*tert*-butyl) 2,5-dimethyl 3,4-bis(2-oxoethyl)-1*H*-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 H_2O under reflux (Scheme 9).[144]

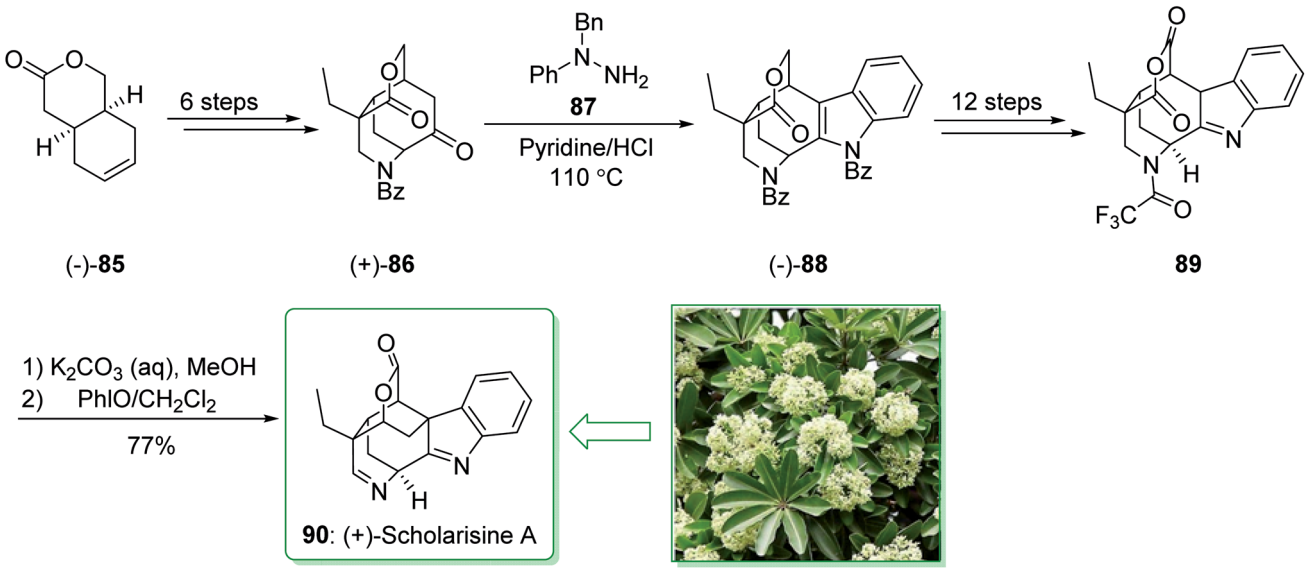
Minfiensine (**75**), an indole alkaloid that possesses important biological properties, such as anti-cancer activities, was initially extracted and isolated by Massiot *et al.* in 1989 from the African plant *Strychnos minfiensis*.[145,146] In 2011, Zhang *et al.* demonstrated[147] the short total synthesis 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**).



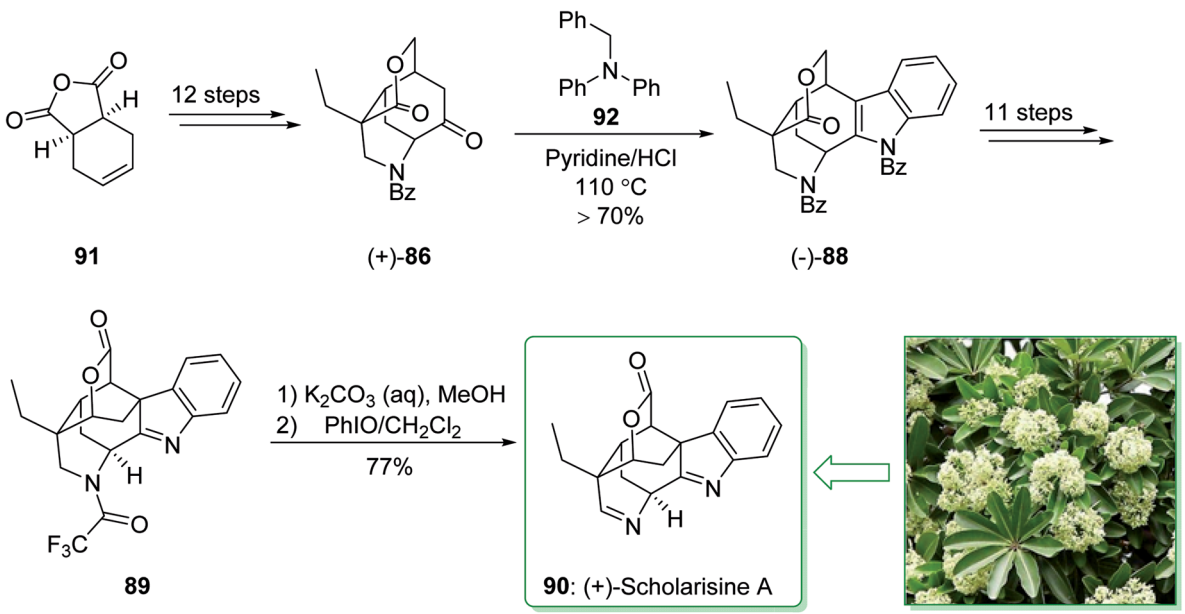
Scheme 12 Total synthesis of (+)-scholarisine A (**90**).

condensation reaction of phenylhydrazine (**66**) and 1,4-cyclohexanedione monoethyleneacetal (**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 $NaBH_4$ and 2-iodocrotylamine (**72**) in MeOH at ambient temperature afforded (*Z*)-2-iodobut-2-en-1-ol (**73**)[148] 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, minfiensine (**75**) was synthesized in a good yield (82%) (Scheme 10).[147]

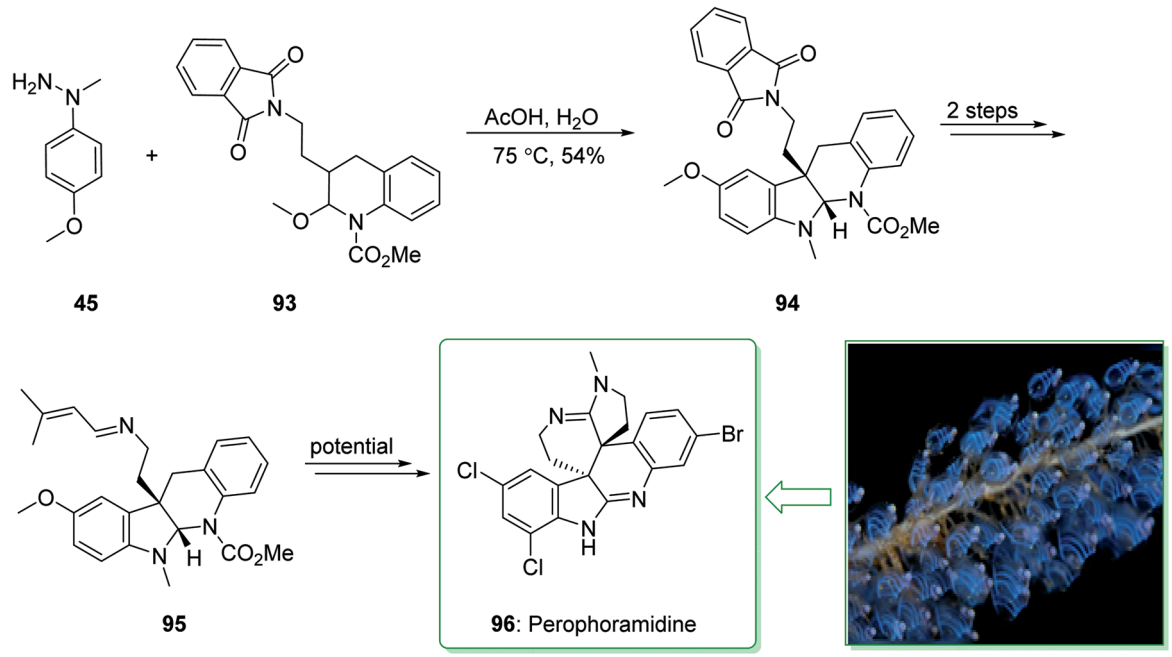
(±)-Aspidophylline A (**84**) was extracted from *Malayan Kopsia* singapurensis by Kam and co-workers in 2007. It is known to reverse drug resistance in resistant KB cells.[149] In 2011, Garg and co-worker reported[150] the total synthesis of (±)-aspidophylline A (**84**), which is one of various complex 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**.[151] Bicycle **78** furnished lactone **79** within 15 steps. The Fischer indolization reaction between ketoester **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).[150]

The scholarisines belong to the family of akuammiline alkaloids.[152] 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*.[153] 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.[154,155] In 2012, Smith *et al.* reported[156] 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 indolenine 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 CH_2Cl_2, afforded the natural product (+)-scholarisine A (**90**) (Scheme 12).[156]

The asymmetric total synthesis of (+)-scholarisine A (**90**) was achieved and reported in 2013 by Smith *et al.*[157] 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/



Scheme 13 Total synthesis of (+)-scholarisine A (**90**).



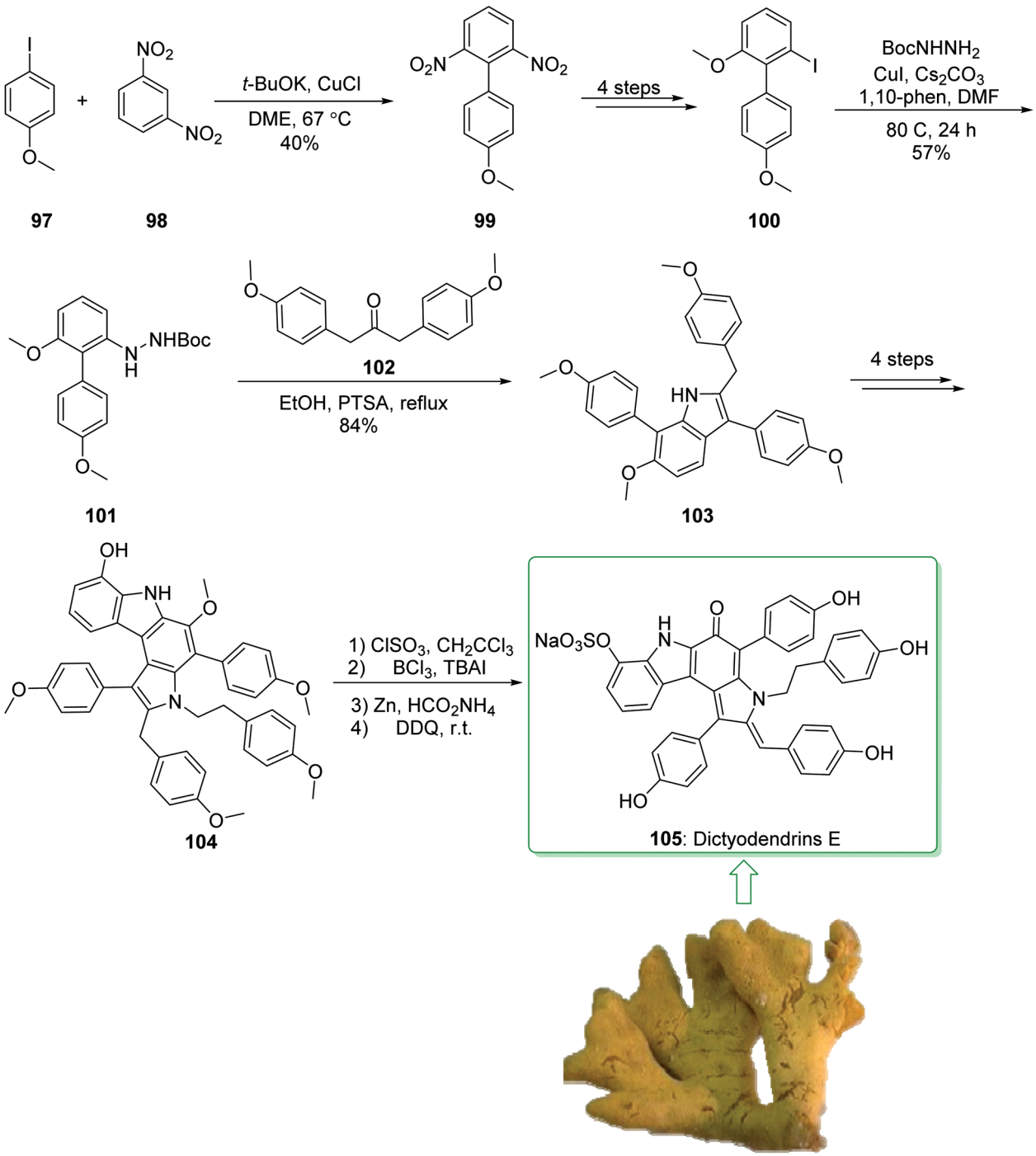
Scheme 14 The total synthesis of perophoramidine (**96**).

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)[158] in CH_2Cl_2 completed the synthesis of (+)-scholarisine A (**90**) (Scheme 13).[157]

The communesin family of naturally occurring compounds and perophoramidine are prevalent goals for chemical synthesis.[159,160] Two indole alkaloids, including perophoramidine[161] and communesin,[162] 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.[161] In 2012, Garg *et al.* demonstrated[163] 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 H_2O 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).[163]

Dictyodendrins A–E were extracted from the marine sponge *Dictyodendrilla verongiformis* collected off the southern Japanese coast in 2003 by Matsunaga and Fusetani.[164] 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,[165] telomerase inhibition signifies a unique favorable approach for the establishment of cancer chemotherapy.[166] Jia and co-workers in 2014 revealed[167] 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 $BocNHNH_2$ 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) $ClSO_3$, CH_2CCl_3; (2) BCl_3, TBAI; (3) Zn, HCO_2NH_4; (4) 2,3-dichloro-5,6-dicyano1,4-benzoquinone (DDQ), room temperature) from phenol **104** (Scheme 15).[167]

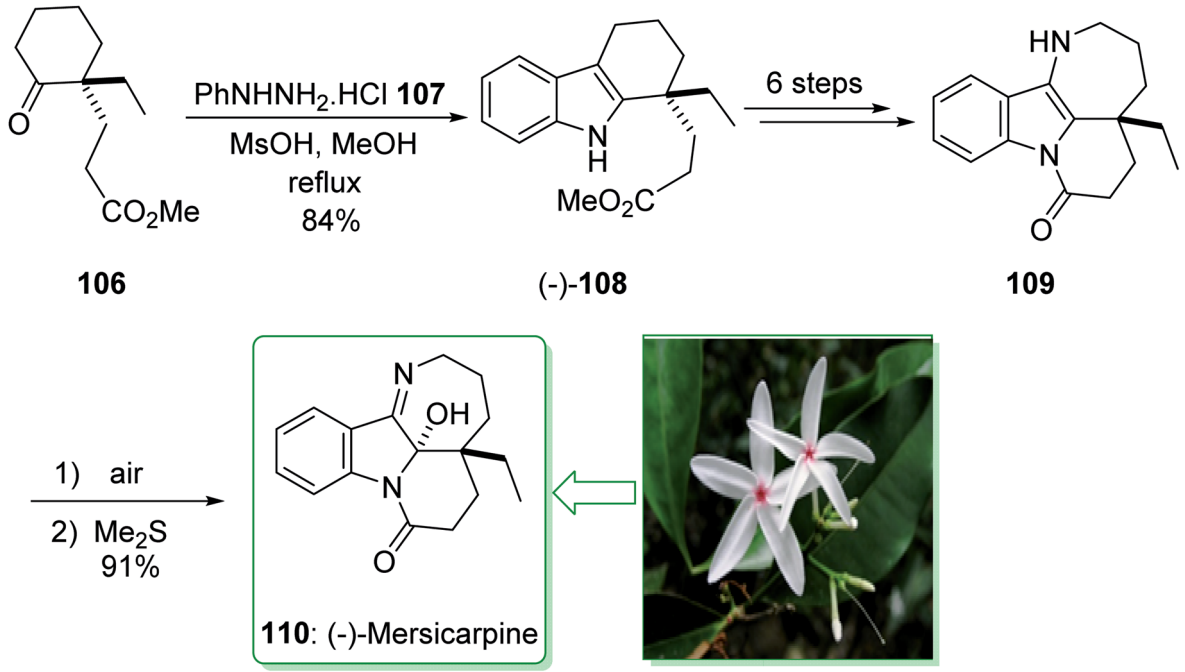
In 2015, Tokuyama reported[168] the total synthesis of the biosynthetically-related monoterpene indole alkaloid (−)-mersicarpine (**110**). An azepino[3,2-*b*]indole intermediate was synthesized through d'Angelo's enantioselective Michael addition, Fischer indole synthesis, and DIBALH-catalyzed reductive ring-expansion reaction. The total synthesis of (−)-mersicarpine



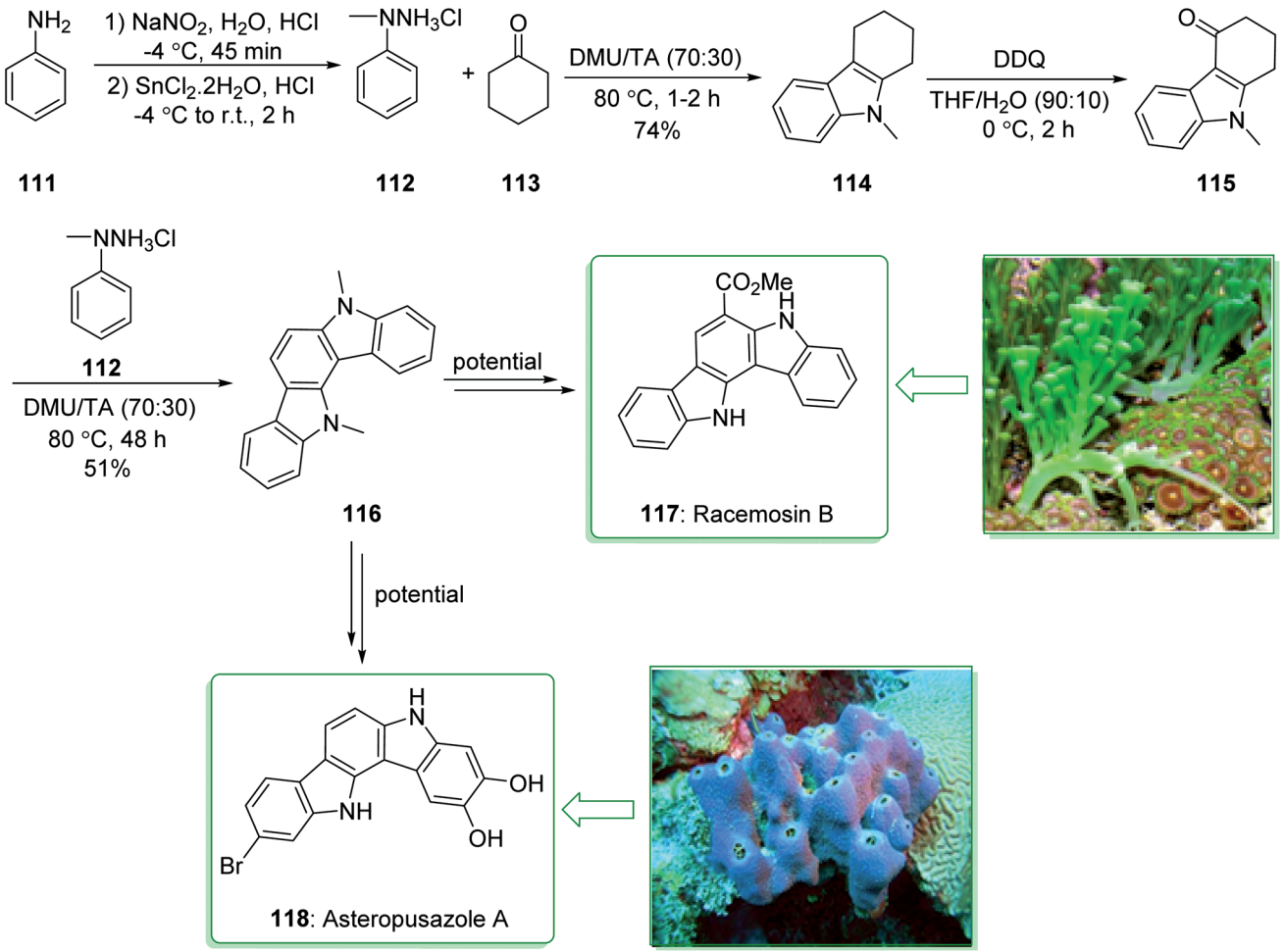
Scheme 15 Total synthesis of dictyodendrins E (**105**).

(**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).[168]

Indolocarbazoles and carbazoles are known to be present in various natural products that are used as significant drugs.[91,169,170] Owing to their auspicious anti-microbial, anti-fungal, anti-hypertensive and anti-cancer properties the chemistry of indolo[2,3-*a*]carbazoles has been broadly investigated.[171] Racemosin B (**117**) was extracted in 2013 by Guo and co-workers from the green alga *Caulerpa racemosa*, along with the most frequently encountered pigment in the genus *Caulerpa*,



Scheme 16 Total synthesis of (−)-mersicarpine (**110**).

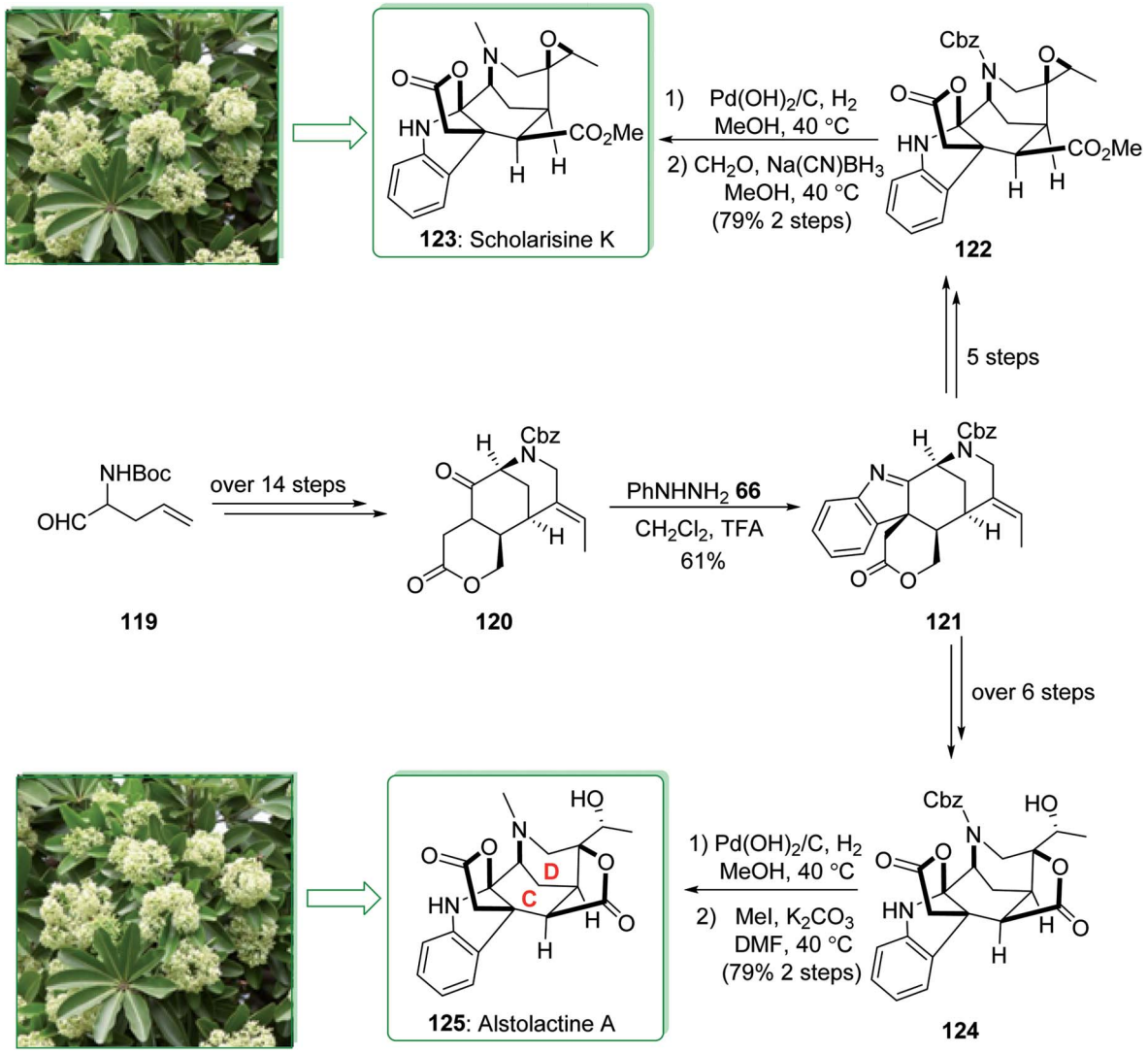


Scheme 17 Synthesis of the unit structure of racemosin B (**117**) and asteropusazole (**118**).

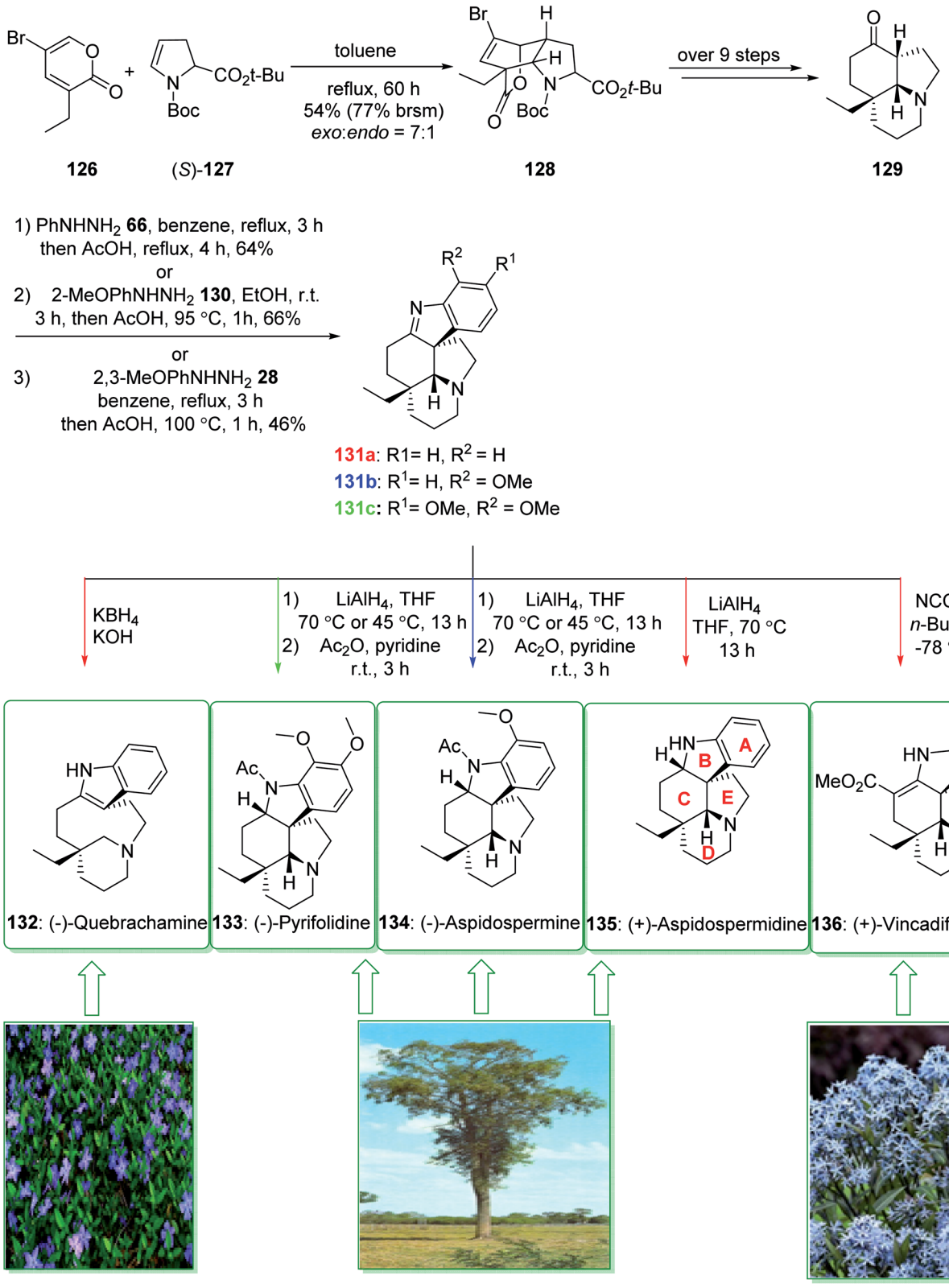
caulerpin.[172] The indolo[3,2-*a*]carbazole framework, one of the isomeric indolocarbazoles, is naturally occurring and was first reported in 2002.[173] Three members of this family, including asteropusazole A, B and ancorinazole were extracted from marine sponges by Wright and co-workers in 2013. The 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.[174] In 2016, Kotha *et al.* reported[175] 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**)[176] 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).[175]

Scholarisine K and A belong to the family of akuammiline alkaloids.[152] Scholarisine K (**123**) and alstolactine A (**125**) were extracted by Luo and co-workers in 2015 from *Alstonia scholaris*.[177,178] The first enantioselective total synthesis of scholarisine K (**123**) and alstolactine A (**125**) were performed in 2017 by Gao *et al.*[179] 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

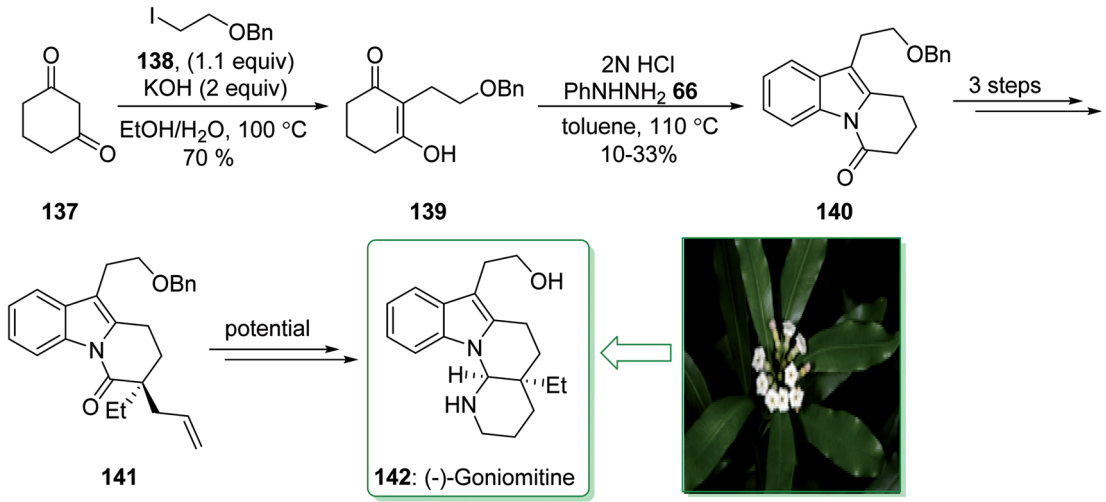


Scheme 18 Total synthesis of scholarisine K (**123**) and alstolactine A (**125**).



Scheme 19 Total synthesis of (−)-quebrachamine (**132**), (−)-pyrifolidine (**133**), (−)-aspidospermine (**134**), (+)-aspidospermidine (**135**) and (+)-vincadifformine (**136**).

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 20 Synthesis of (−)-goniomitine (**142**).

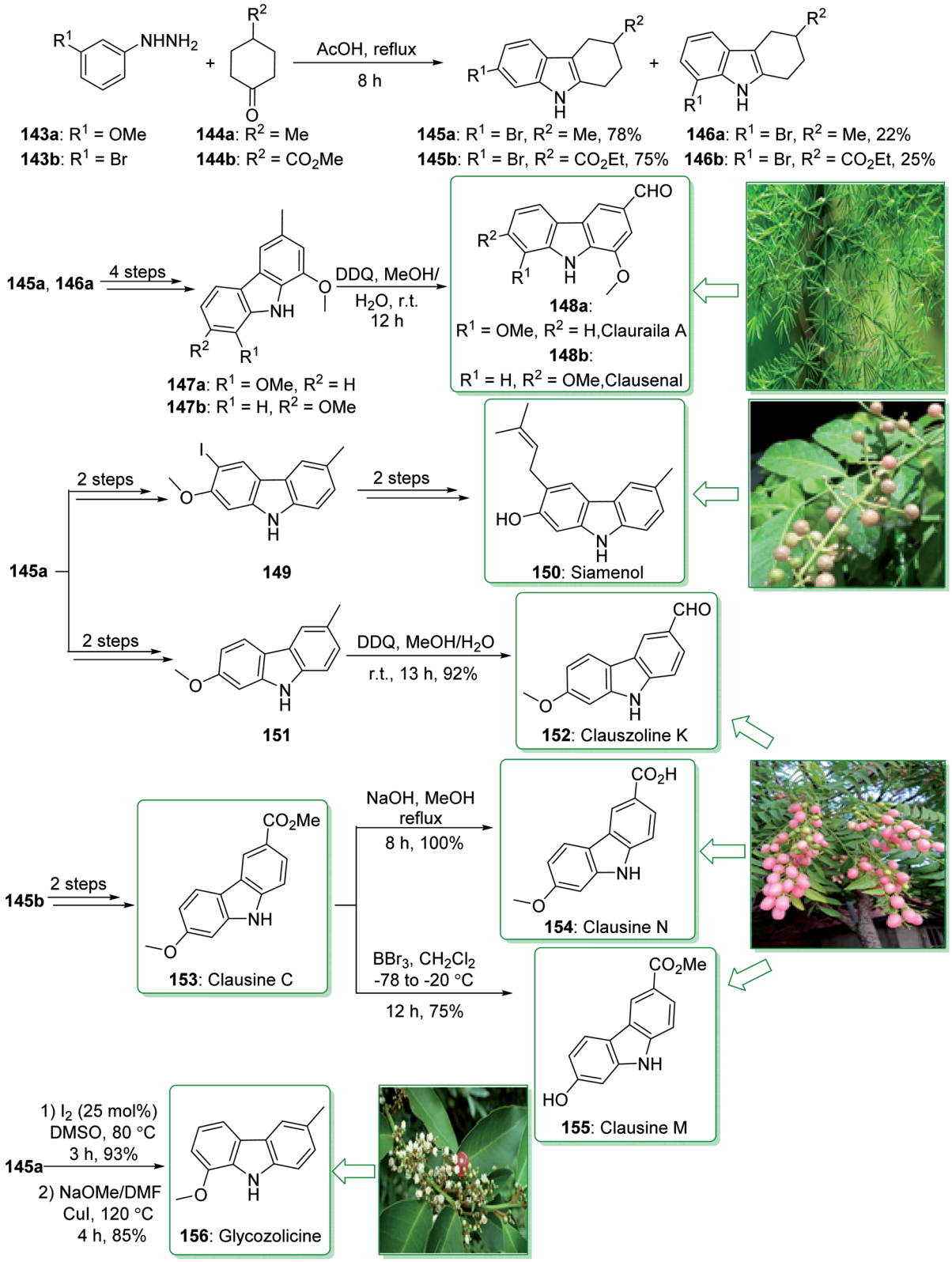
Based on similar transformations, the natural product alstolactine A (**125**) was provided by replacing the Cbz with a methyl group (Scheme 18).[179]

(−)-Pyrifolidine was first extracted by Svoboda *et al.* from the leaves of *Aspidospermu quebrucho blunco* (Apocynaceae) in 1973.[180] The consistently strategic total syntheses of *Aspidosperma* alkaloids (+)-vincadifformine (**136**), (−)-quebrachamine (**132**), (+)-aspidospermidine (**135**), (−)-aspidospermine (**134**), (−)-pyrifolidine (**133**), and also nine others using the effectively generated tricyclic ketone **129** were demonstrated in 2017 by Jiang *et al.*[181] 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**), (−)-pyrifolidine (**133**), and (−)-quebrachamine (**132**) were started from the cycloaddition of 3-ethyl-5-bromo-2-pyrone **126** and enecarbamate (*S*)-**127** that afforded the *exo*-bridged tricyclic-clactone **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-methoxylphenyldrazine (**130**), or 2,3-dimethoxyphenylhydrazine (**28**) *via* a Fischer indole cyclization gave (+)-dehydroaspidospermidine (**131a)** (71% yield),[182] (+)-dehydrodeacetylaspidospermine (**131b**) (66% yield)[183] and (+)-dehydrodeacetylpyrifolidine (**131c**) (46% yield), respectively. Natural products (+)-vincadifformine (**136**), (+)-aspidospermidine (**135**), and (−)-quebrachamine (**132**) were synthesized from **131a** (*via* different routes).[181]

Moreover, the total synthesis of (−)-aspidospermine (**134**) was accomplished in two steps from **131b** and also the total synthesis of (−)-pyrifolidine (**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), (−)-pyrifolidine (**133**) (3.7% overall yield), and (−)-quebrachamine (**132**) (4.3% overall yield) were accomplished from the cycloaddition of 3-ethyl-5-bromo-2-pyrone **126** and enecarbamate (*S*)-**127** (Scheme 19).[181]

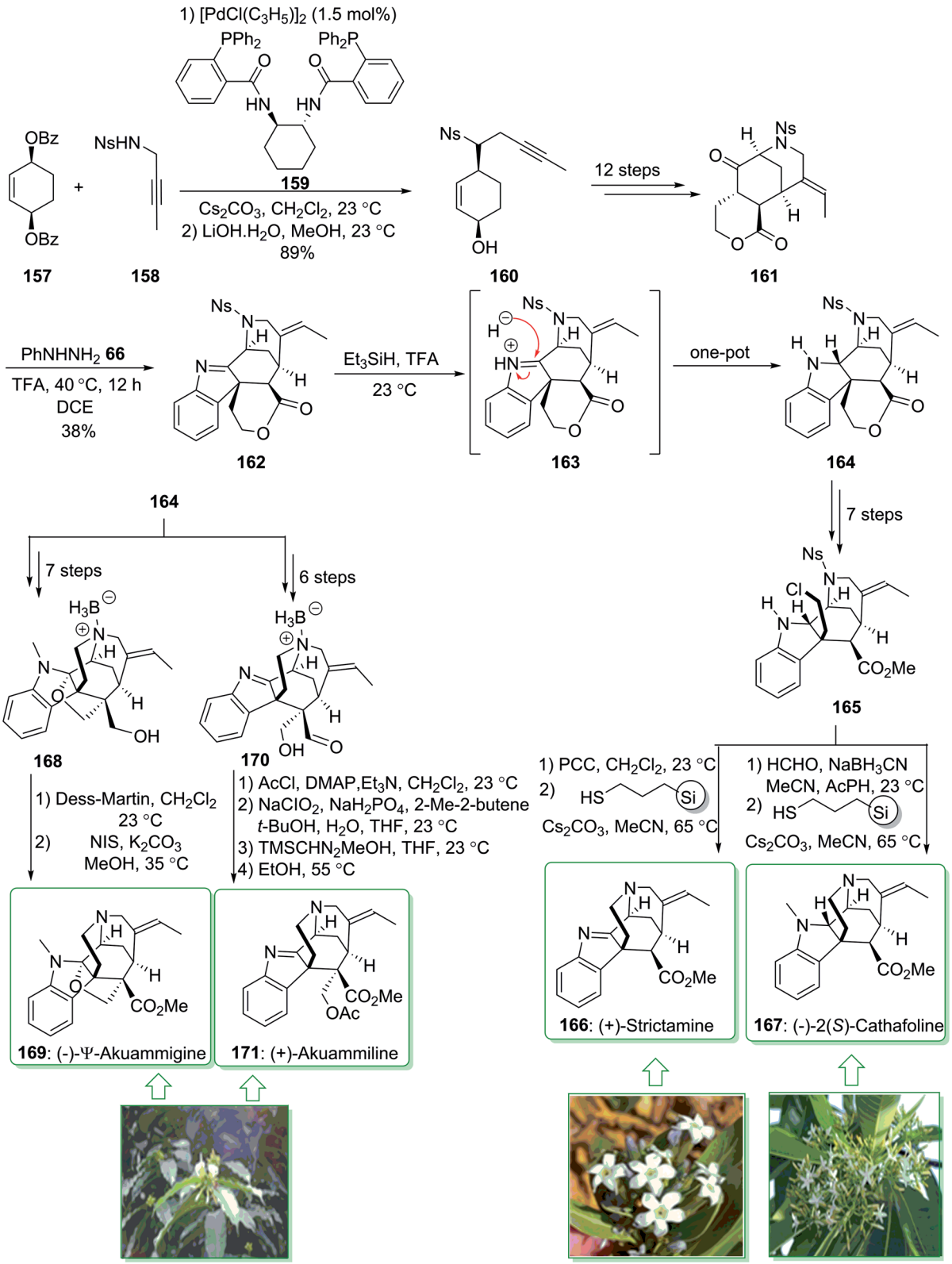
(−)-Goniomitine, extracted in 1987 by Randriambola *et al.* from the bark of *Gonomia Malagasy*, is distinguished from other *Aspidosperma* alkaloids by its distinctive aminal-comprising tetracyclic unit.[184] In 2017, Stoltz *et al.* demonstrated[185] a Fischer indolization method to form a key tricyclic intermediate dihydropyrido[1,2-*a*]indolone (**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 dihydropyrido[1,2-*a*]indolone (**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).[185]

Carbazole alkaloids exhibit various biological and pharmacological properties. In addition, they have potential uses in electroluminescent materials, especially electrical, thermal, and also optical properties.[91,186] Clausine C (**153**) and clausine M (**155**) were extracted from *Clausena excavate* by Huang and co-workers in 1996.[187] The siamenol carbazole alkaloid (**150**) extracted from *Murraya siamensis* exhibited biological properties, for example anti-HIV properties.[173] In addition, clauszoline K (**152**) and clausine N (**154**), extracted from the stem bark of *Clausena excavate*, have been applied in traditional medicine as a detoxification agent and also for the treatment of snake bites.[188] In addition, they show powerful anti-cancer, anti-bacterial, and anti-oxidant properties.[189] Glycozolicine (**156**) was isolated for the first time in 1992 from the roots of *Glycosmis pentaphylla* by Chakraborty and co-workers.[190] Furthermore, cytotoxic carbazole alkaloids; clauraila A (**148a**) and clausenal (**148b**) were extracted from



Scheme 21 Total synthesis of clauszoline-K (**152**), glycozolicine (**156**), clausine C (**153**), clausine N (**154**), clausine M (**155**), clauraila A (**148a**), clausenal (**148b**) and the formal synthesis of siamenol (**150**).

the roots of *Clausena harmandiana* (*Rutaceae*)[191] and the leaves of *Clausena heptaphylla*,[192] 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.[193]



Scheme 22 The total synthesis of (+)-strictamine (**166**), (−)-2(*S*)-cathafoline (**167**), (−)-Ψ-akuammigine (**169**) and (+)-akuammiline (**171**).

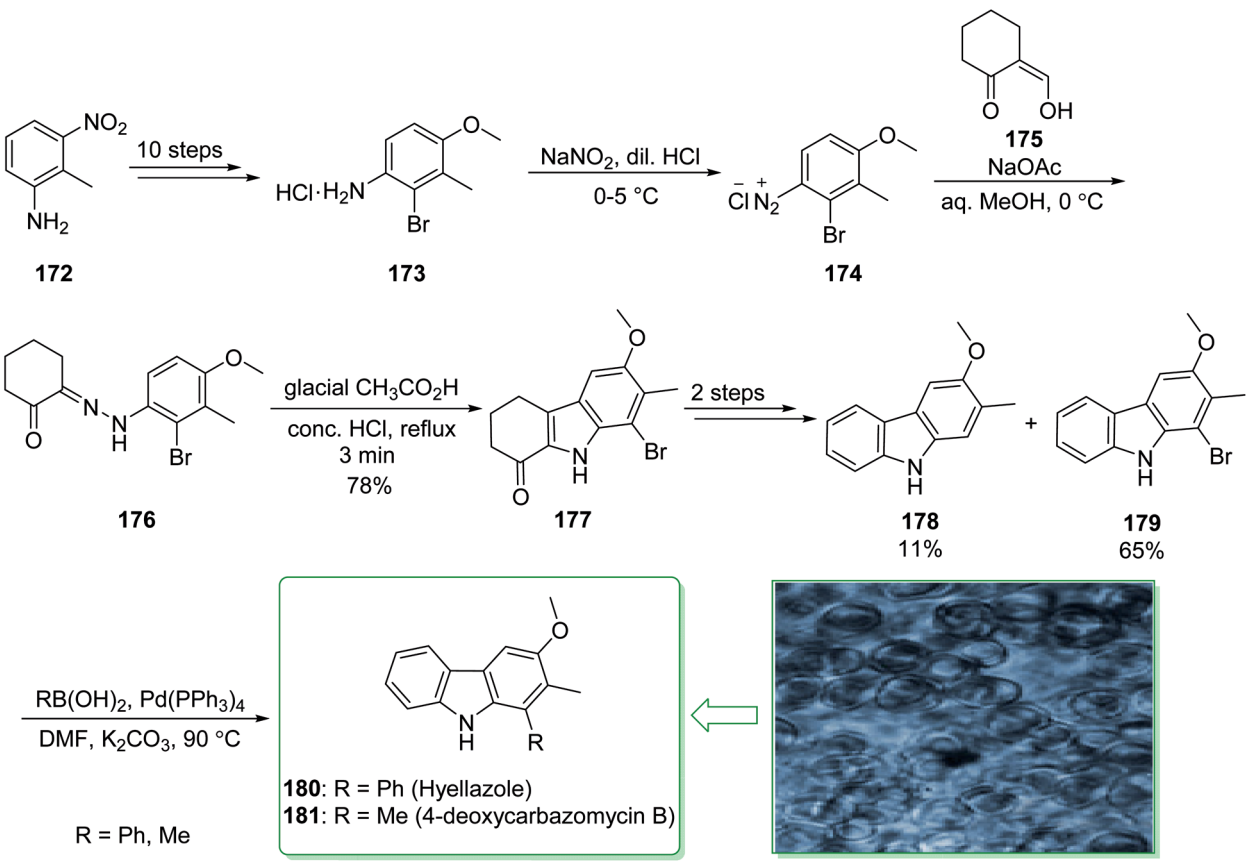
In 2017, Lokhande *et al.* reported[194] the synthesis of 7-oxygenated carbazole alkaloids through a Fischer–Borsche ring and metal-free reaction conditions. The key step includes the aromatization and a one-pot iodination procedure for functionalization of the Fischer–Borsche ring with molecular iodine. 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

(**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/H_2O 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).[194]

On the other hand, after 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[195] in MeOH/H_2O, afforded clauszoline-K (**152**). Lastly, the formal synthesis of siamenol (**150**) was accomplished from monoiodinated carbazole **149**.[194] 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 BBr_3 in dichloromethane, gave the natural product clausine M (**155**) in a satisfactory yield (75% yield) (Scheme 21).[194] Some alternative synthesis methods for these carbazole alkaloids, some of which have better overall yields, have been reported.[196–199]

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*,[200] and (−)-2(*S*)-cathafoline (**167**) was isolated in 2014 from *Alstonia macrophylla*.[201] (−)-2(*S*)-Cathafoline (**167**) exhibited satisfactory activity in overturning drug resistance in vincristine resistant KB cells.[200–202] (+)-Akuammiline (**171**) was extracted together with (−)-Ψ-akuammigine (**169**) in 1932 by Henry. (−)-Ψ-Akuammigine (**169**) was extracted from *Picralima klaineana* in 1932.[203] Biological investigations demonstrated favorable activity for use as an anti-inflammatory agent.[204] In 2018, Garg *et al.* demonstrated[205] 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

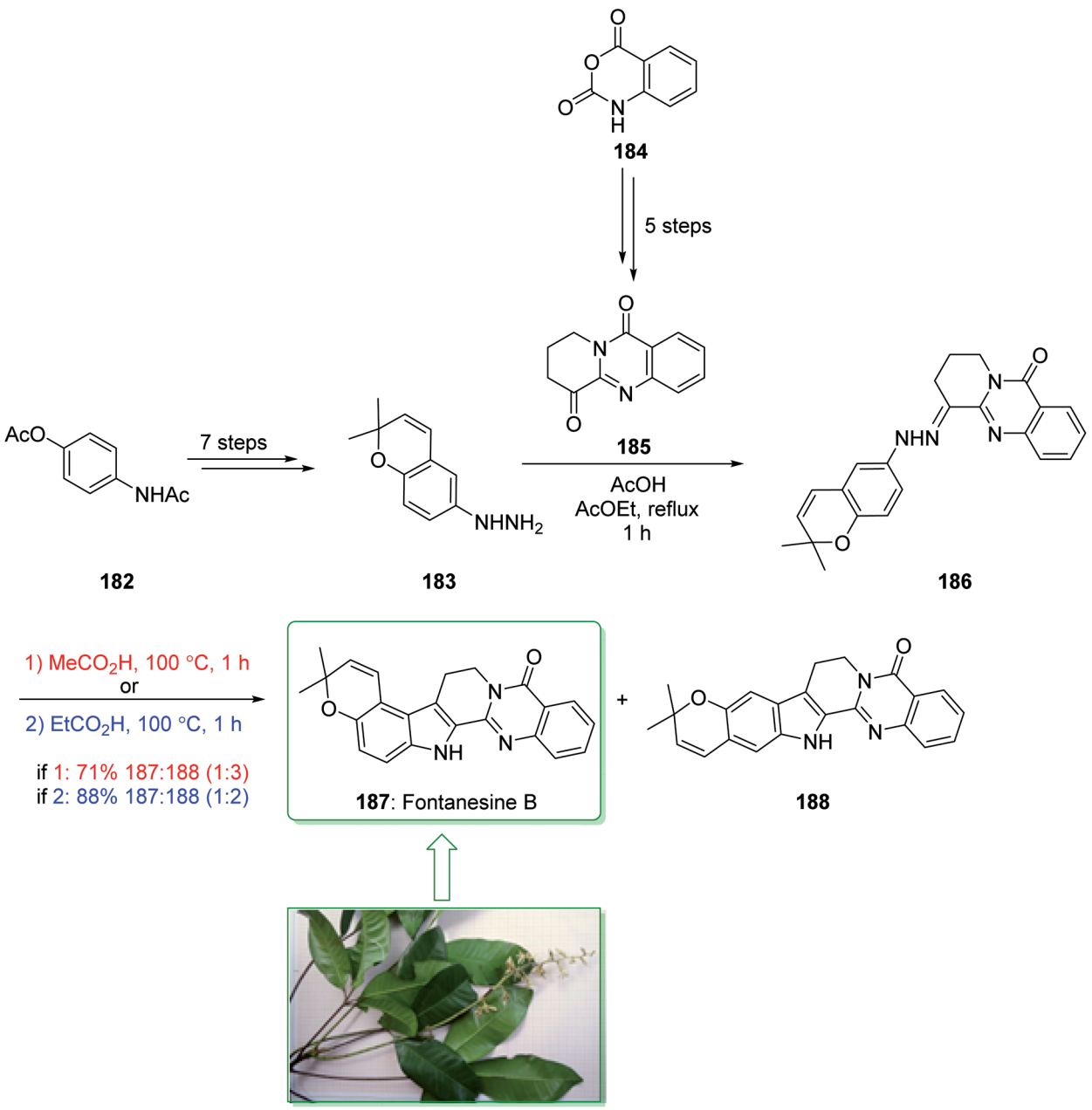


Scheme 23 The total synthesis of hyellazole (**180**) and 4-deoxycarbazomycin B (**181**).

(−)-Ψ-akuammigine (**169**) and (+)-akuammiline (**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 yielded the natural product (+)-strictamine (**166**). Similarly, compound **165**, after *N*-methylation and deprotection–cyclization afforded (−)-2(*S*)-cathafoline (**167**).

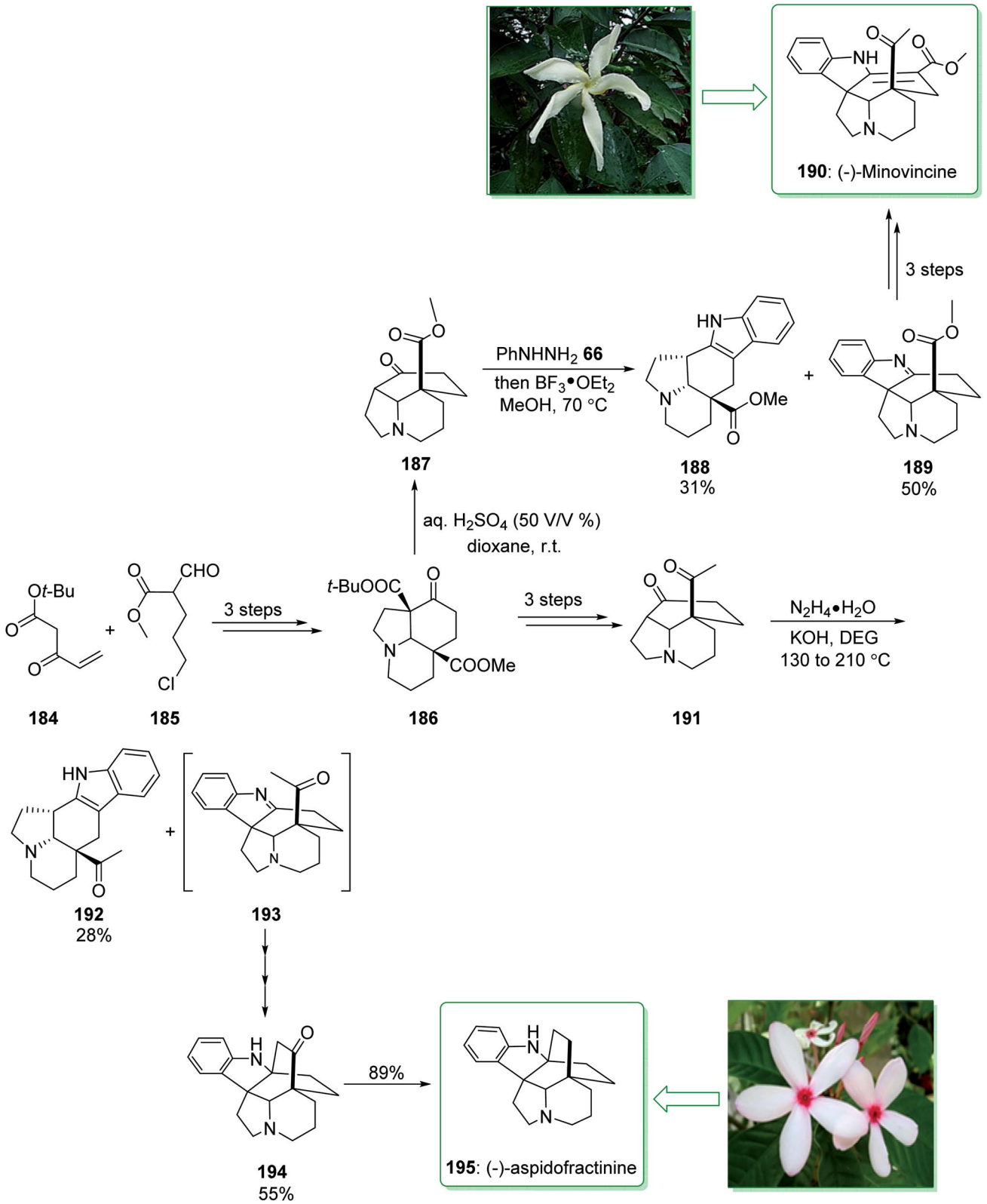
Furthermore, indoline **164**, after seven steps, gave furoindoline alcohol **168**. The latter, after two steps, yielded the natural product (−)-Ψ-akuammigine (**169**). Moreover, indoline



Scheme 24 Total synthesis of fontanesine B (**187**).

164, after six steps, afforded aldehyde **170**. Finally, aldehyde **170** after four steps yielded (+)-akuammiline (**171**) (Scheme 22).[205]

Various carbazole alkaloids have been extracted from terrestrial plants. In addition, numerous carbazole alkaloids have been found in various streptomycillin and algae species.[206] In 1979, 6-chlorohyellazole and hyellazole were the first carbazole alkaloids extracted from the blue-green alga *Hyella caespitosa*.[207] In 2018, Chakraborty and co-worker demonstrated[208]



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 $NaNO_2$ 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-formylcyclohexanone (**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-9*H*-carbazole (**178**) with an 11% yield and 1-bromo-3-methoxy-2-methyl-9*H*-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]

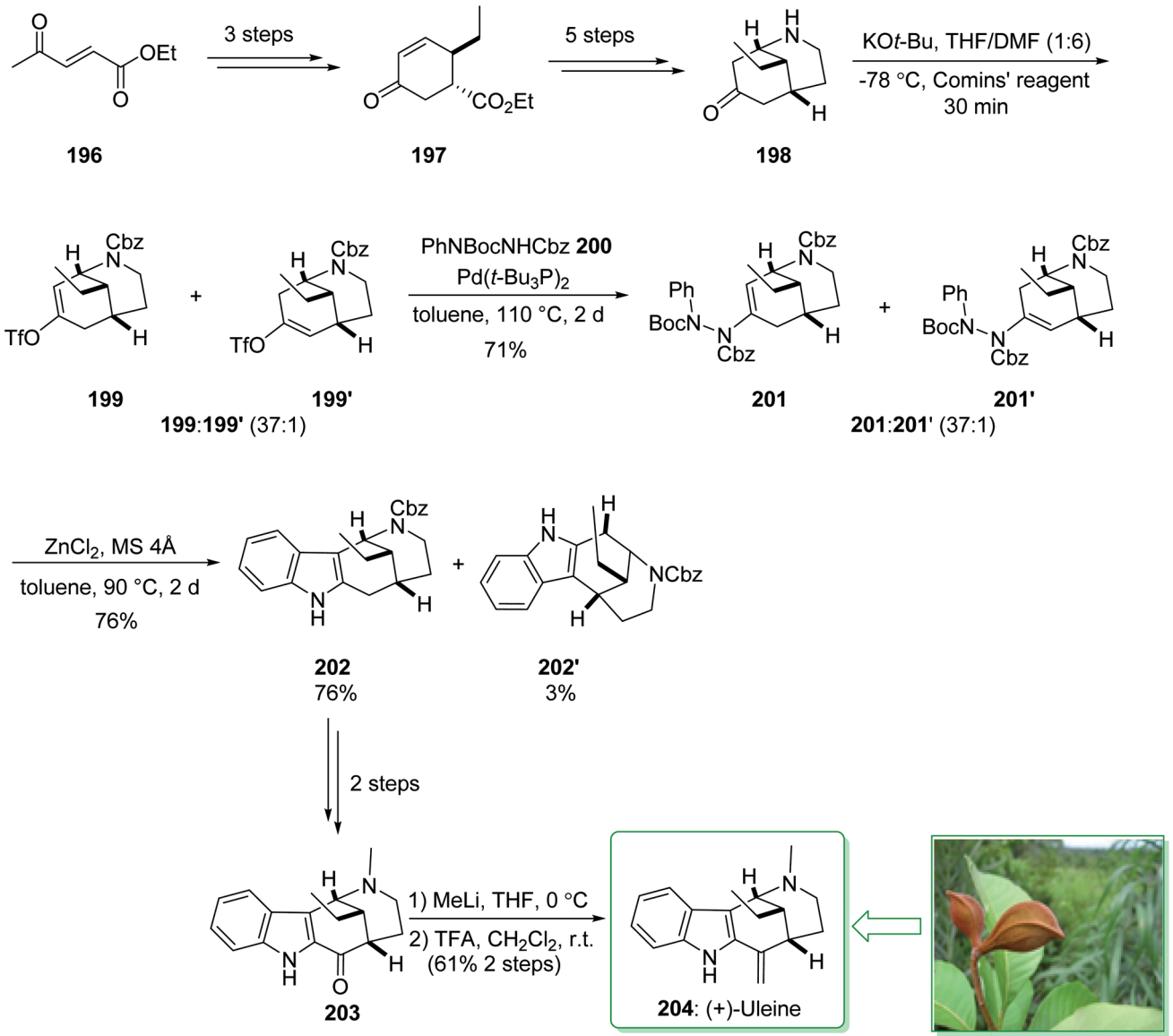
Fontanesines A–C, bearing both quinazoline and the pyrano[3,2-*e*] indole framework, were extracted from the leaf fractions and stem bark of *Conchocarpus fontanesianus* that were gathered in Brazil by Queiroz and co-workers in 2016.[219] These alkaloids have not been completely examined biologically, owing to restricted accessibility. Fontanesines are a rare type of pyrano[3,2-*e*]indoloquinazoline alkaloid. However, although pyranocarbazole and pyranoindole alkaloids have been widely prepared,[91,94] 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.[220] In 2019, Abe *et al.* reported[221] 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 acetate (**182**), which after seven steps gave the arylhydrazine **183**. The reaction between arylhydrazine **183** and quinazolinone **185** (prepared from isatoic anhydride (**184**) in five steps) using acetic acid afforded hydrazine **186** in a moderate yield (50% yield). In the following, the extraordinary Fischer indolization of hydrazine **186** was examined. It was found that the pyran ring was injured under the acidic conditions, thus establishment of the Fischer indolization using the hydrazine 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] Aspidofractinine-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 demonstrated[225] the eight-step synthesis of (−)-minovincine (**190**) and (−)-aspidofractinine (**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_N2 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 indolenine **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 oxoaspidofractinine **194** in a moderate yield (55% yield) (alongside its isomer **192**) through a recognized indolenine intermediate **193**. Finally, substrate **194** was submitted to hydrazine to provide the (−)-aspidofractinine (**195**) in a high yield (89% yield). As a result, (−)-aspidofractinine (**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 uomica*, the type species, and *Strychnos colubrina*.[227] The uleine-type alkaloids constitute a significant subgroup of the *Strychnos* alkaloids that are identified by the 1,5-methanoazocino[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 Mgf*[228] and its accurate structure was suggested by Warnhoft 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 reported[231] the enantioselective synthesis of (+)-uleine (**204**) and (−)-tubifolidine (**210**). The regioselective construction of enol triflates from 2-azabicyclo[3.3.1]nonane ketones and also indolizations of the resulting ene-hydrazides 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**).[232] 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).[231]

The formal synthesis of (−)-tubifolidine (**210**) was started from cyclohexenone **205** in an enantiomerically enriched form with a high ee (98% ee).[233] After five steps cyclohexenone **205**, afforded the corresponding ketone **206**. After two steps the latter gave ene-hydrazides **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).[231] 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

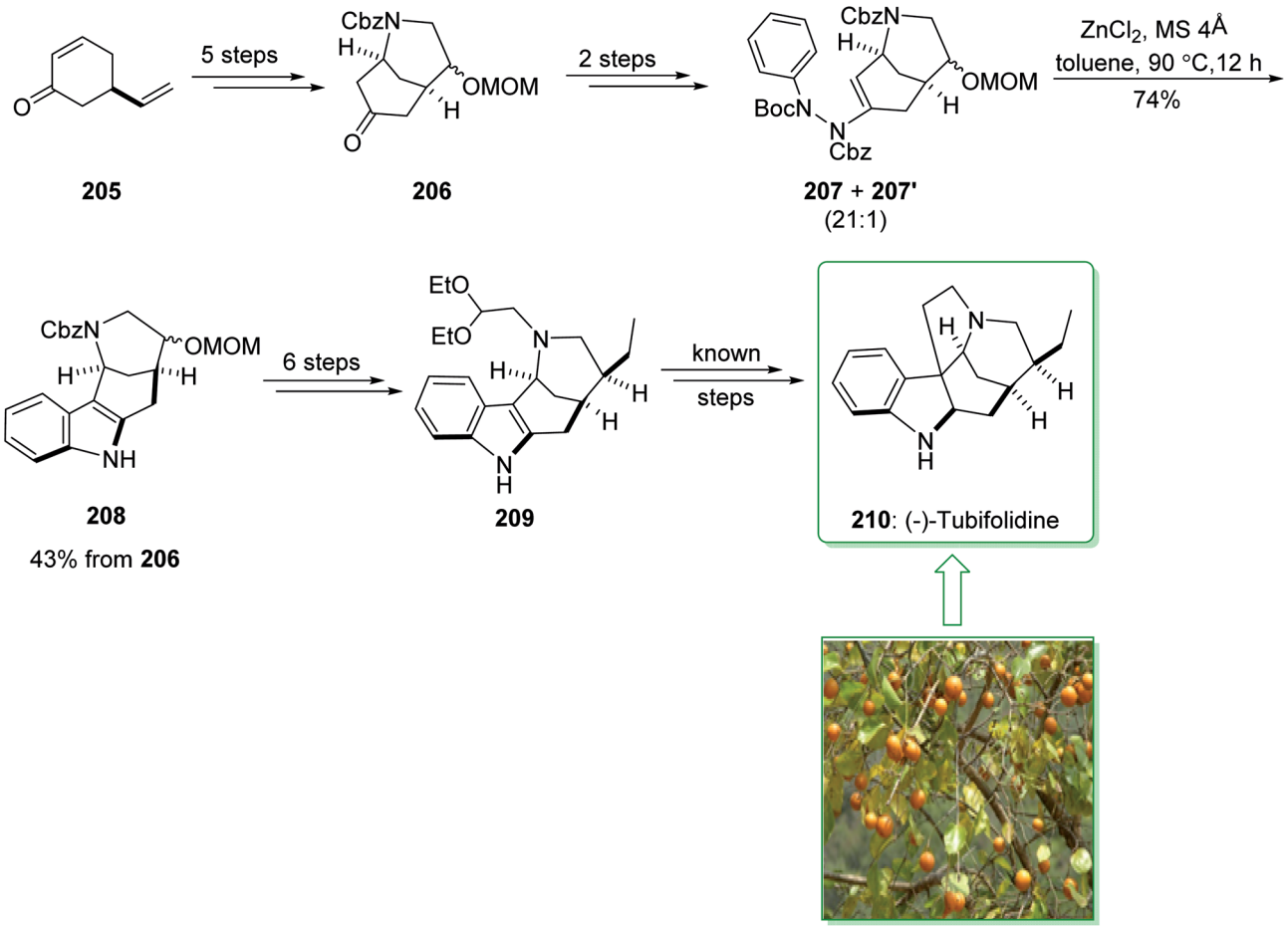


Scheme 26 Total synthesis of (+)-uleine (**204**).

was formerly transformed to (−)-tubifolidine (**210**) (Scheme 27).[234]

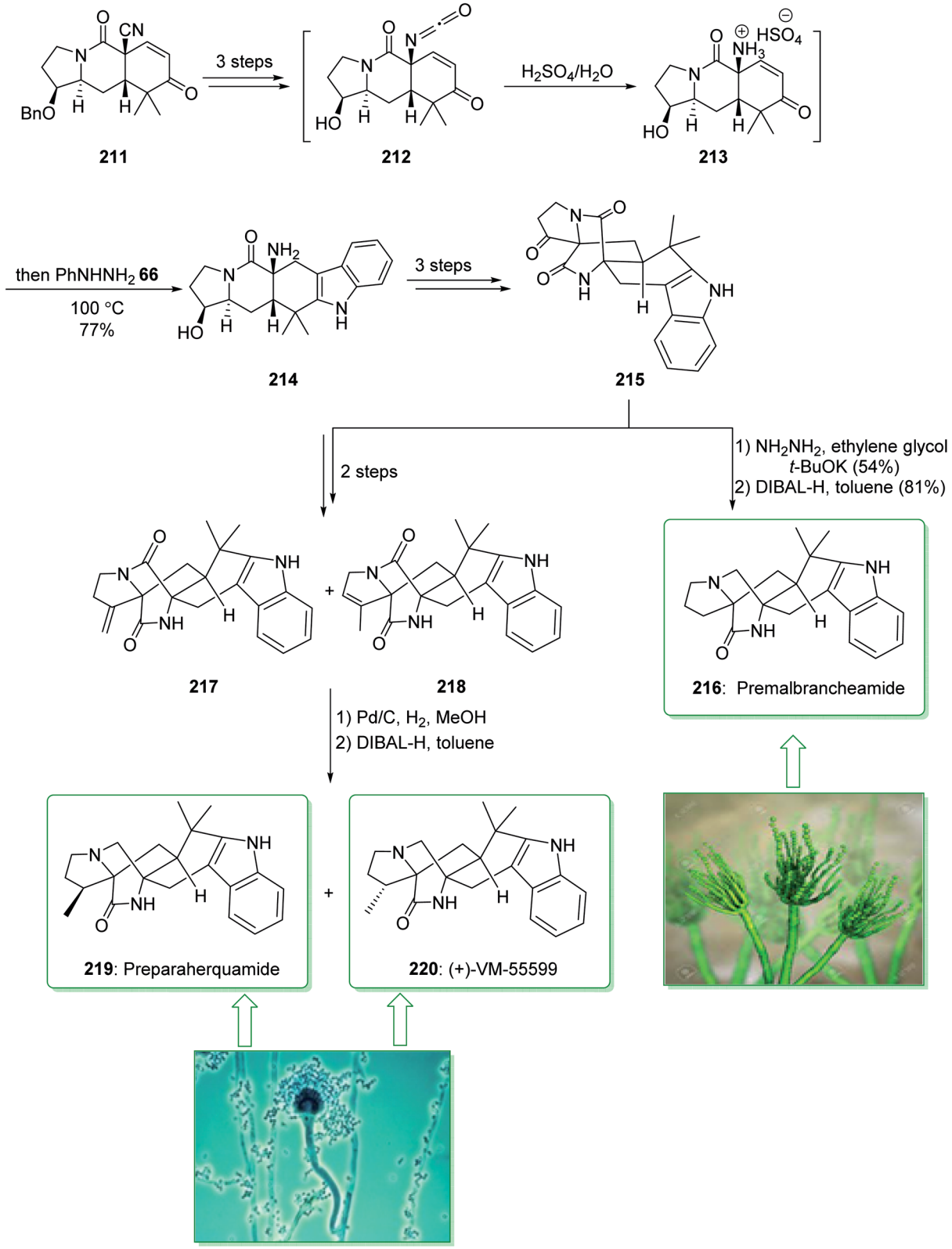
The paraherquamides are an uncommon family of naturally occurring fungal compounds that include a bicyclo[2.2.2]diazaoctane unit structure, a spiro-oxindole, and a functionalized proline scaffold. Among them, paraherquamide A, was extracted from cultures of *Penicillium paraherquei* by Yamazaki *et al.* in 1981.[235] VM55599, a minor metabolite from culture extracts of a *Penicillium* spp. was isolated in 1993 by Everett *et al.*[236] Sarpong *et al.* in 2020 demonstrated[237] 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, preparaherquamide 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 indole synthesis. The total synthesis of preparaherquamide (**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).[238] In the following, enone **211**, after three steps, gave isocyanate **212**. The latter, using H_2SO_4, 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 preparaherquamide (**219**) and (+)-VM-55599 (**220**) (Scheme 28).[237]

In 2020, Varga *et al.* demonstrated[239] 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**).[239] The total synthesis of (−)-aspidospermidine (**229**), (−)-limaspermidine (**232**), and (+)-17-demethoxy-*N*-acetylcylindrocarine (**231**) were



Scheme 27 The formal synthesis of (−)-tubifolidine (**210**).

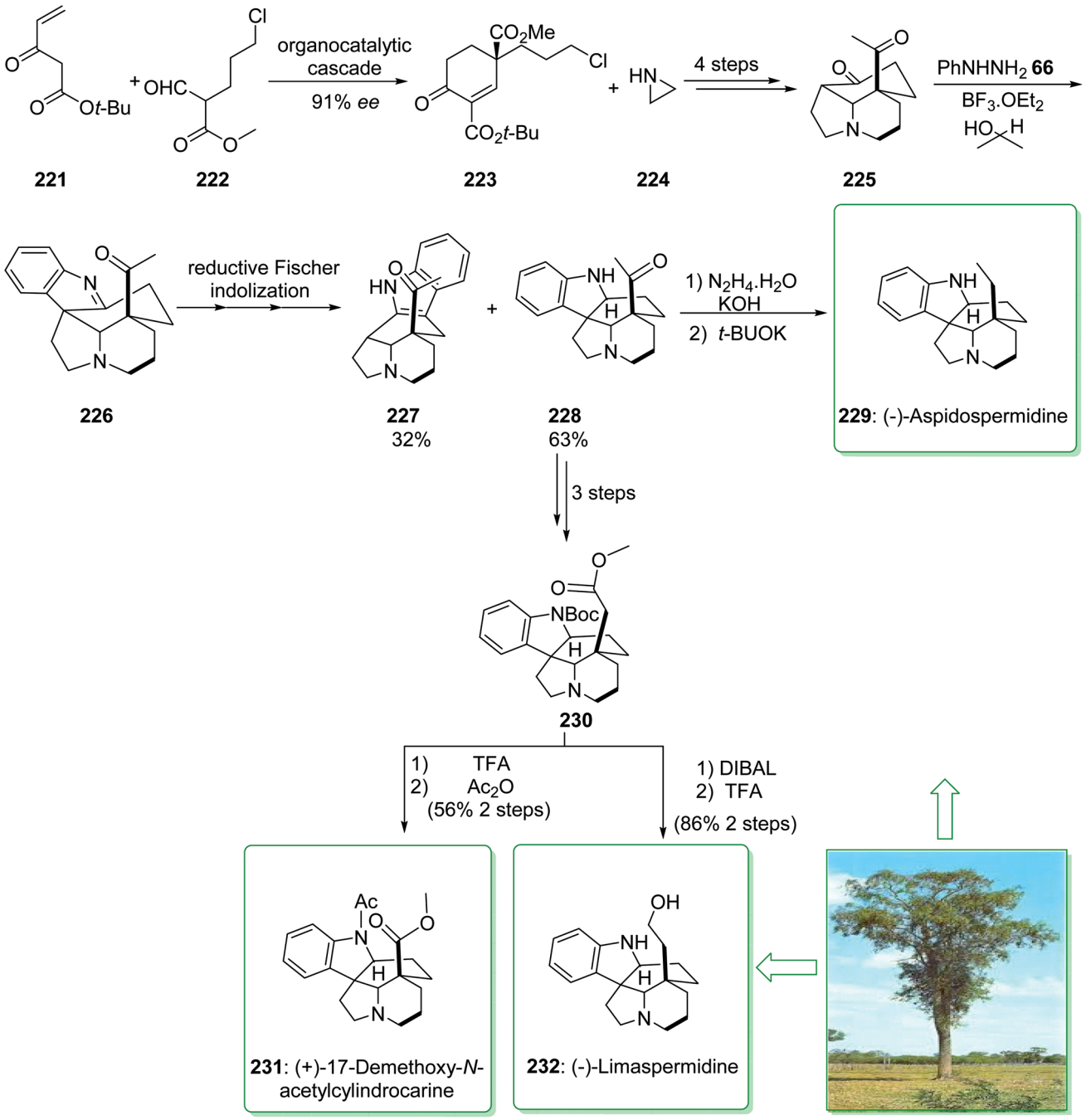
started from the reaction of *tert*-butyl 3-oxopent-4-enoate (**221**) and methyl 5-chloro-2-formylpentanoate (**222**), that afforded 1,3-dicarboxylate **223**. The latter, after three steps, gave the stereochemically complex intermediate **225**. It was found that the chemoselective reduction of the 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 preparaherquamide (**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 pentacycle **228** as the main product (63% yield) along with the 3*H*-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 Ac_2O, gave (+)-17-demethoxy-*N*-acetylcylindrocarine (**231**).

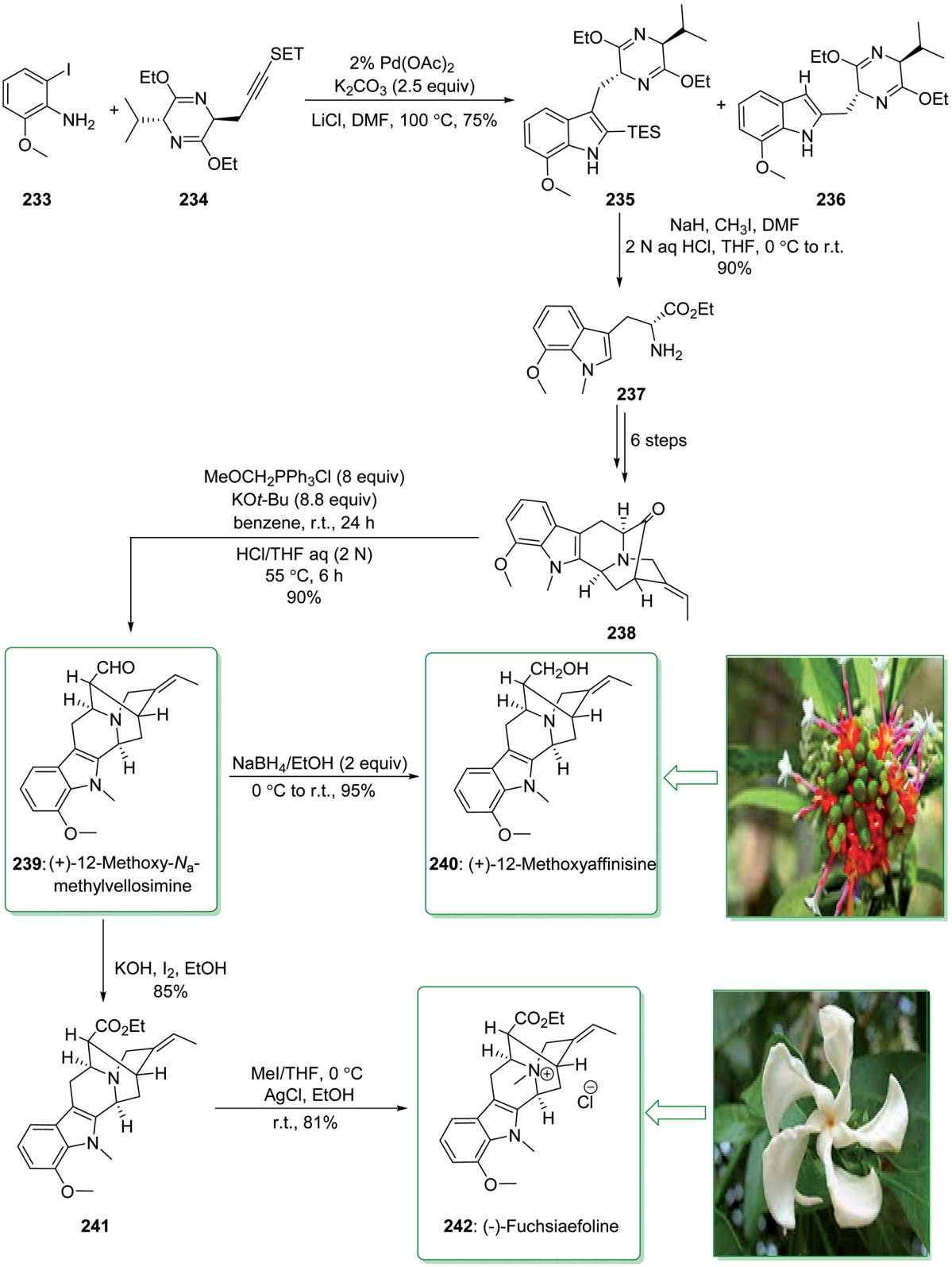
In the following, the intermediate **228**, after two steps (modification of the original Stork–Dolfini synthesis) afforded the natural product (−)-aspidospermidine (**229**). Notably, the total synthesis of (−)-aspidospermidine (**229**) was performed in eight reaction vessels with an overall yield 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).[239]



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

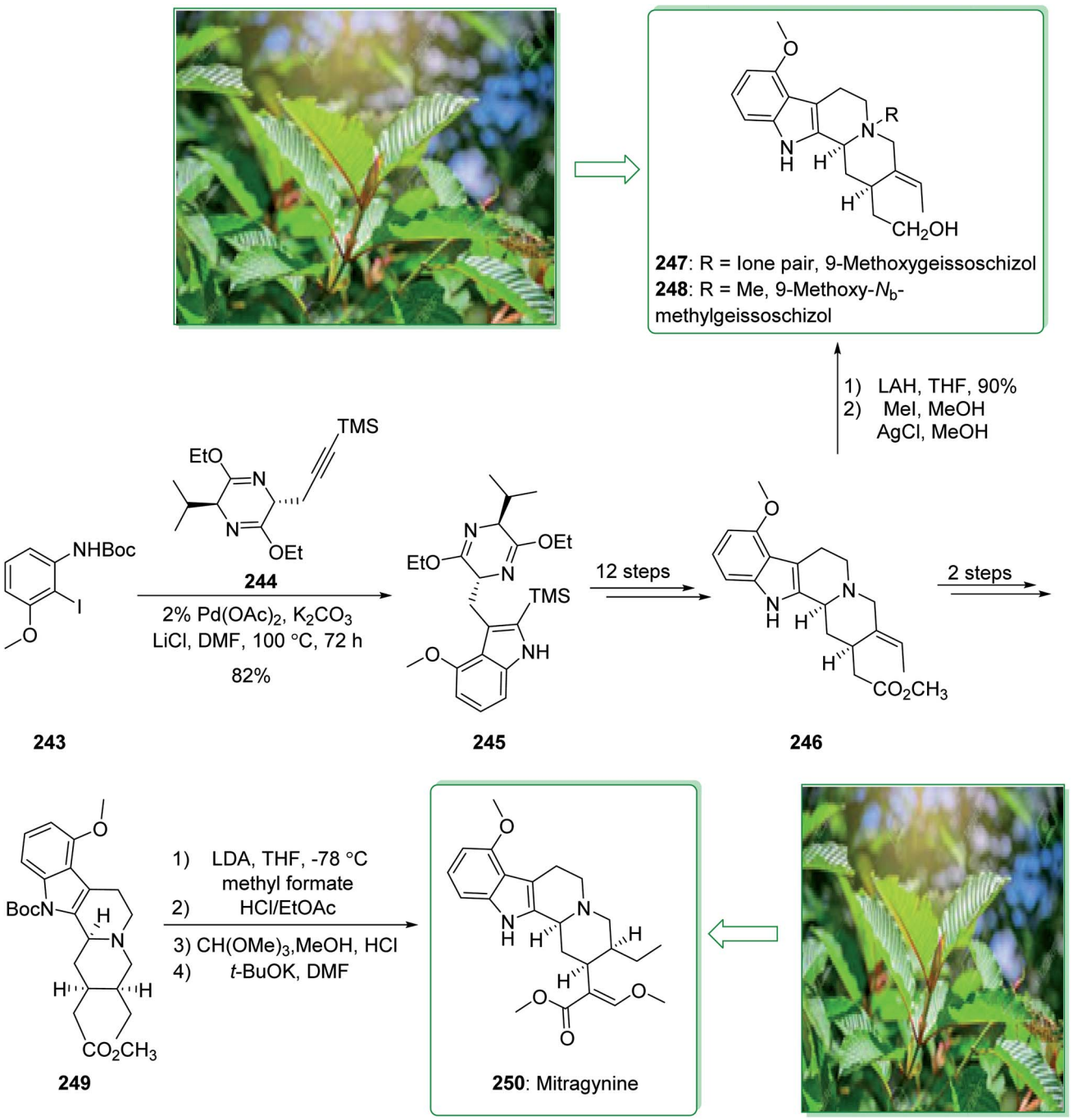
2.2. Larock indole synthesis

Sarpagine and Ajmaline are biogenetically correlated alkaloids that have been extracted from different species of *Rauwolfia* that are generally dispersed throughout Africa and Asia.[241,242] These plants are broadly utilized in folk Chinese medicine for the treatment of neuralgia, hypertension,[243] and migraines.[244] (+)-12-Methoxy-N_a-methylvellosimine (**239**) and (+)-12-



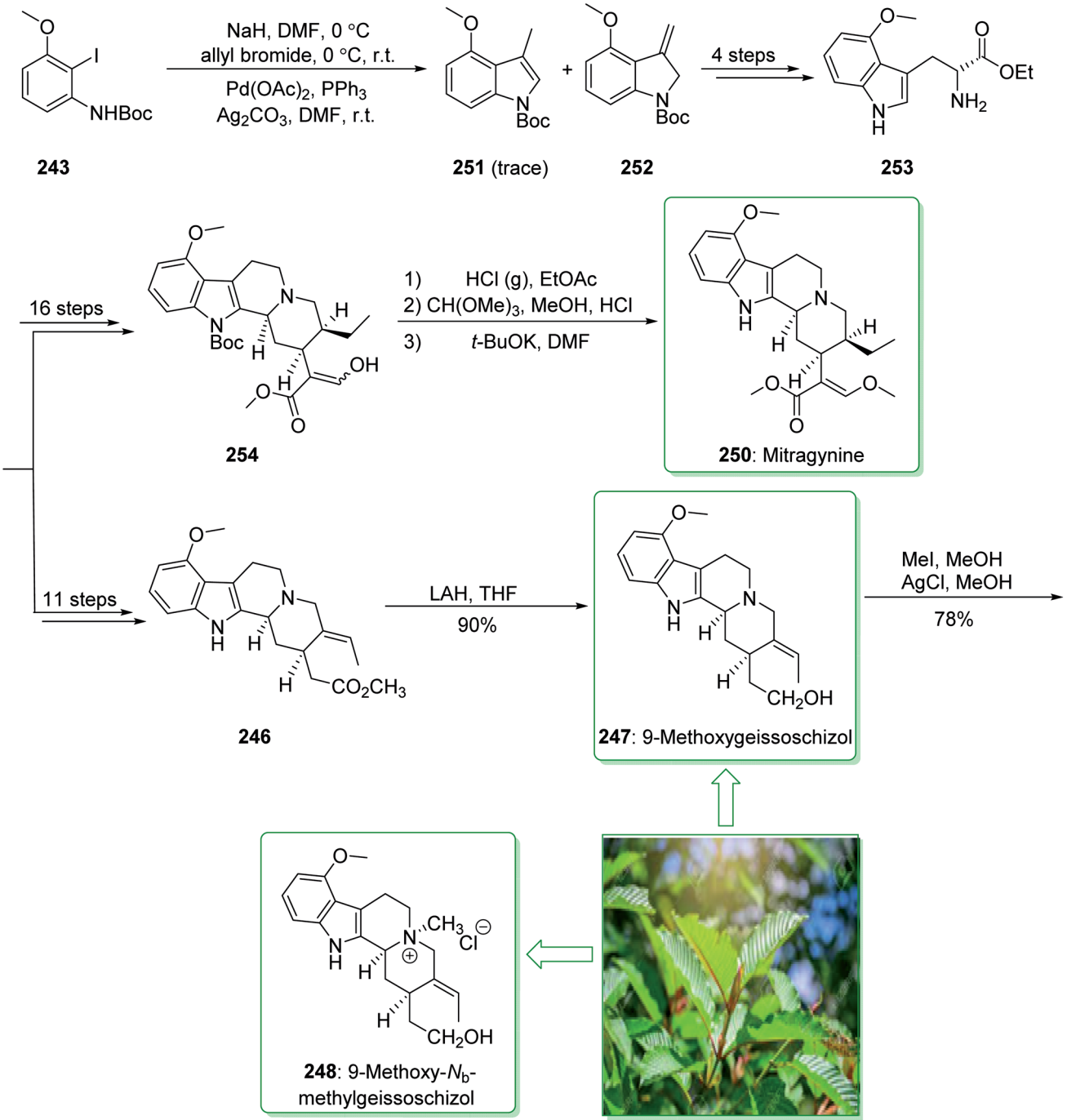
Scheme 30 Total synthesis of (+)-12-methoxy-N_a-methylvellosimine (**239**), (+)-12-methoxyaffinisine (**240**) and (−)-fuchsiaefoline (**242**).

methoxyaffinisine (**240**) were extracted by Kato and co-workers in 2002 from the bark of *Rauwolfia bahiensis*.[245] In addition, (−)-fuchsiaefoline (**242**) was extracted from *Peschiera fuchsiaefolia* in 1987 by Reis and co-worker.[246] Cook and co-workers in 2004 demonstrated[247] 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-N_a-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-N_a-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



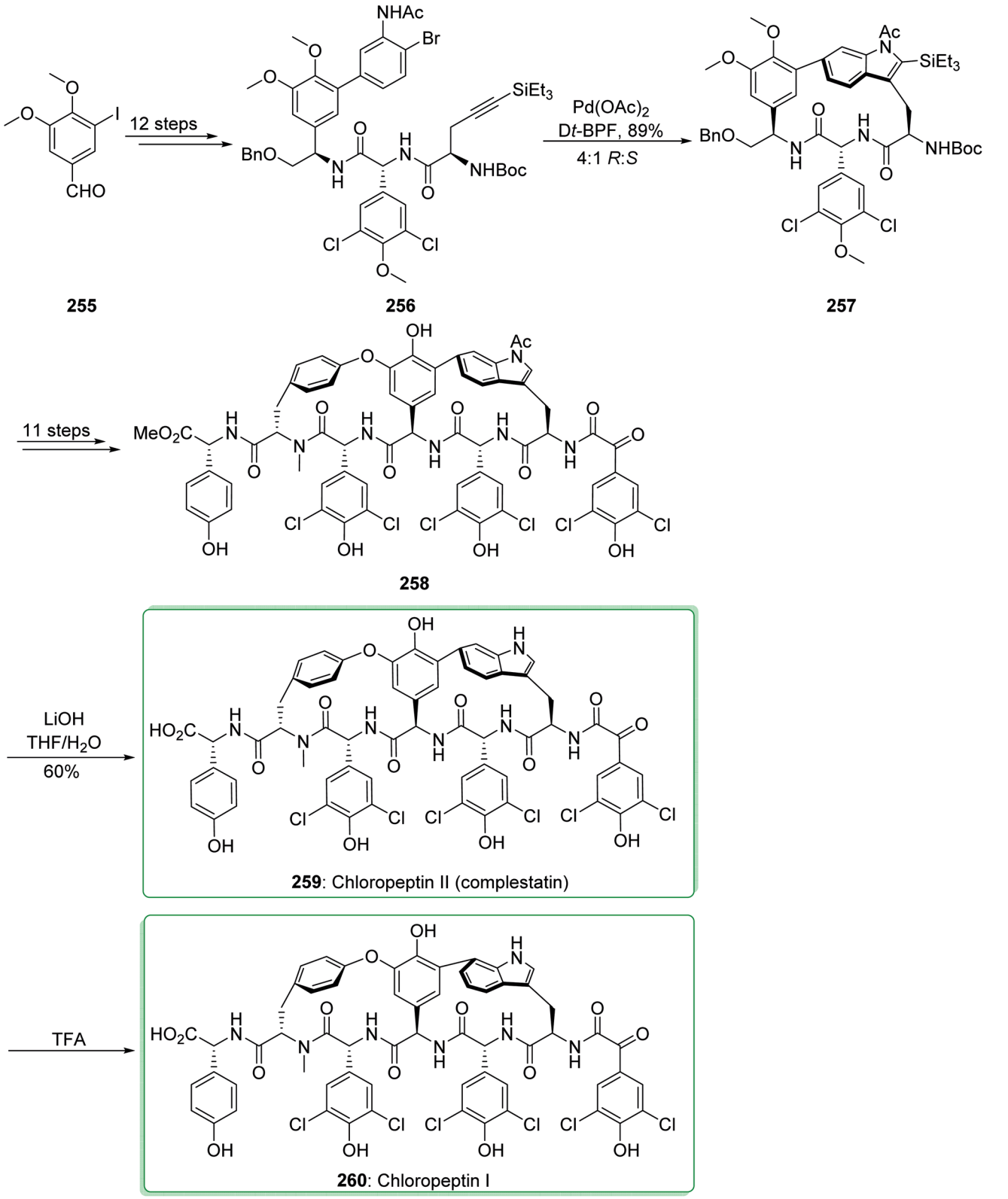
Scheme 31 Total synthesis of 9-methoxygeissoschizol (**247**), 9-methoxy-N_b-methylgeissoschizol (**248**), and mitragynine (**250**).

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 ^{1}H-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-N_a-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 (I_2) and potassium hydroxide in ethanol, was oxidized to the ethyl ester **241.**[248] Finally, quaternization of the N_b nitrogen function in ester **241** using methyl iodide afforded the N_b-methiodide salt that was transformed into the chloride **242** after reacting with silver chloride in ethanol (Scheme 30).[247] Moreover, this alkaloid was synthesized by this research group in 2006.[249]

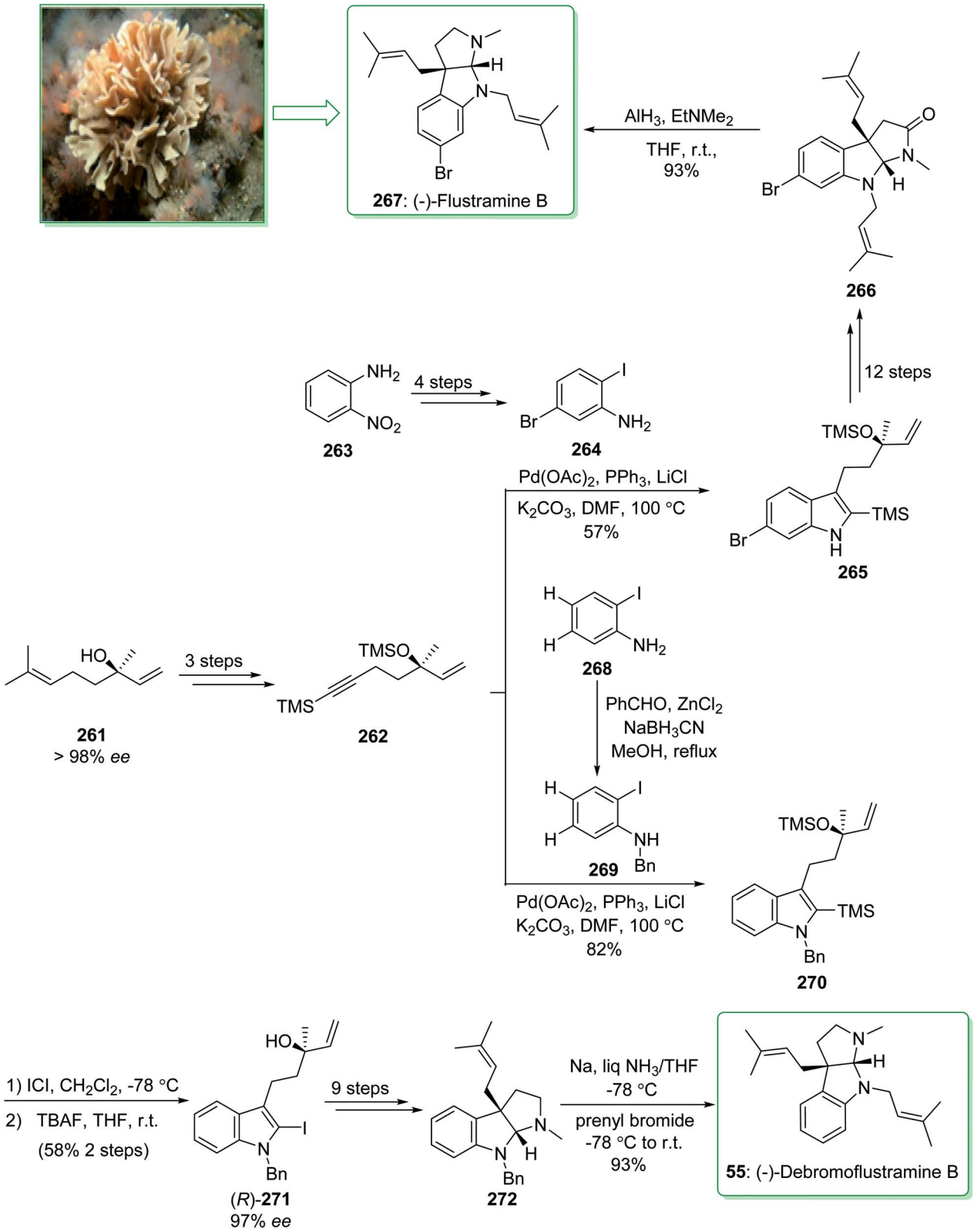


Scheme 32 Total synthesis of 9-methoxygeissoschizol (**247**), 9-methoxy-N_b-methylgeissoschizol (**248**), and mitragynine (**250**).

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,[250,251] the actual structure of **250** was definitely determined by Zacharias in 1964.[252] The formal

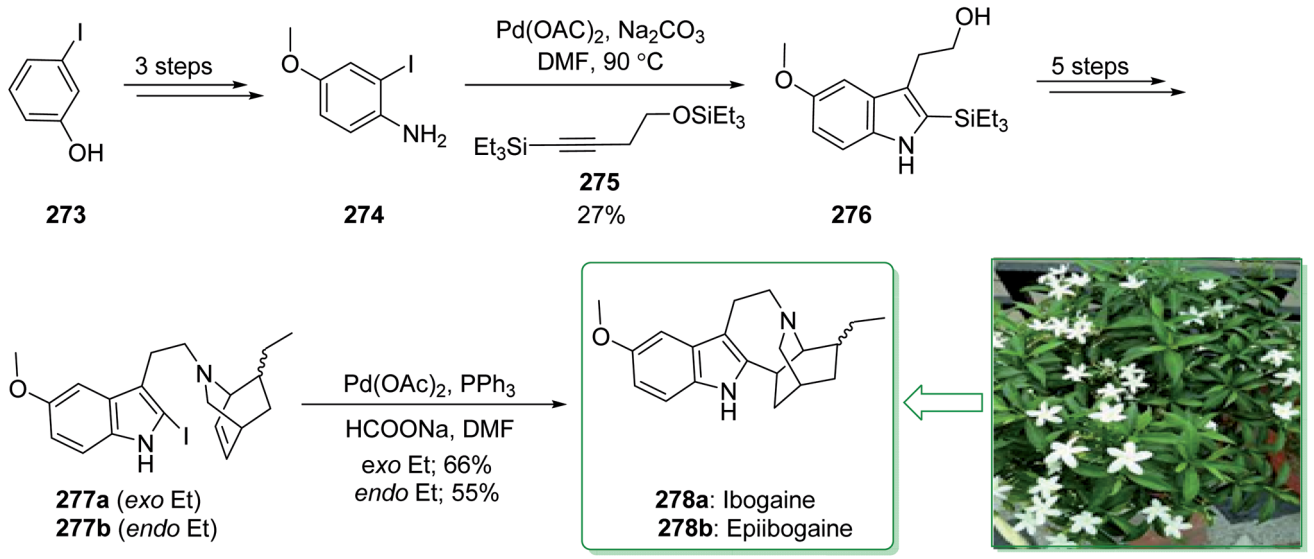


Scheme 33 Total synthesis of chloropeptin II (**259**) and chloropeptin I (**260**).



Scheme 34 Enantioselective total synthesis of (−)-flustramine B (**267**) and (−)-debromoflustramine B (**55**).

investigation of the pharmacology of mitragynine (**250**) demonstrated that it was a central nervous system (CNS) stimulant.[253] Then, *in vivo* and *in vitro* investigations showed mitragynine mostly acted on the μ-opioid receptors.[254] Cook and co-workers in 2007 demonstrated[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-



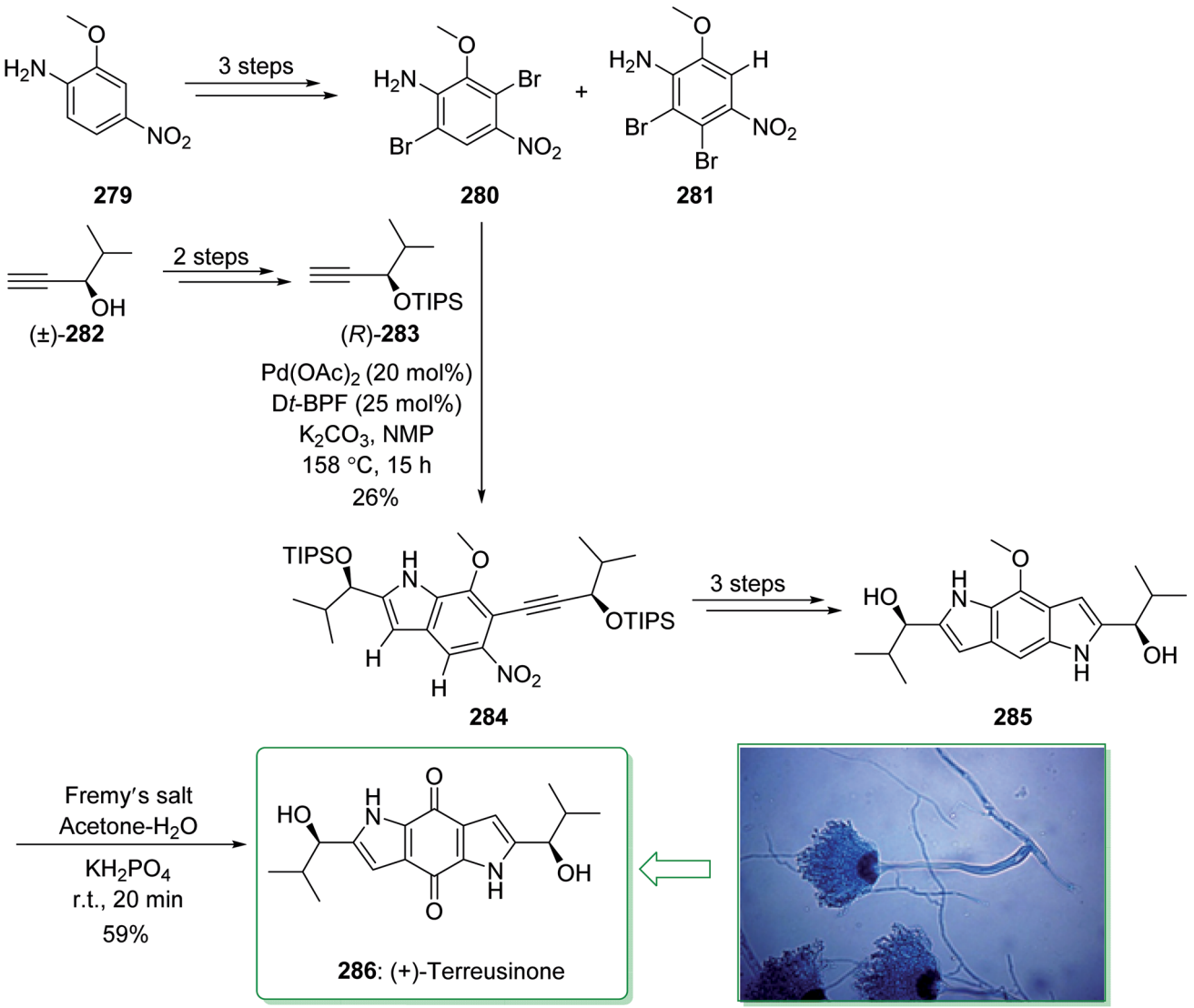
Scheme 35 Total synthesis of ibogaine (**278a**) and epiibogaine (**278b**).

N_b-methylgeissoschizol (**248**), and also the total synthesis of mitragynine (**250**). The total synthesis of mitragynine (**250**), 9-methoxygeissoschizol (**247**), and 9-methoxy-N_b-methylgeissoschizol (**248**) began from the Larock heteroannulation of Boc-masked 2-iodo-3-methoxyaniline (**243**)[256] and the TES alkyne **244** (ref. 257) using palladium(II) 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 aluminum hydride and afforded 9-methoxygeissoschizol (**247**) in a high yield (90% yield). Next, 9-methoxy-N_b-methylgeissoschizol (**248**) was provided through the N_b methylation of compound **247** with MeI and followed by exchange of the iodide to the chloride in the presence of silver chloride (Scheme 31).[255] 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_b-methylgeissoschizol (**248**) by Cook and co-workers.[258] 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_b-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-methylindole **251**. To diminish the isomerization of the 3-methyleneindoline (**252**) to the 3-methylindole **251** in the Mori–Ban–Hegedus indole synthesis, it was essential to change the base from K_2CO_3 to Ag_2CO_3.[259] Pleasantly, upon using Ag_2CO_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-methylindole **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_b-methylgeissoschizol (**248**).[258]

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.[260] Then, the first results of its activity against HIV infectivity and its cytopathic effects were revealed.[261–263] In the following, Omura demonstrated the separation of both chloropeptin I (**260**) and chloropeptin II (**259**) from *Streptomyces* sp. In 2009, Boger and co-workers reported[264] 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.[265] The total synthesis of chloropeptin II (complestatin) (**259**) and chloropeptin I (**260**) commenced from 3-iodo-4,5-dimethoxybenzaldehyde (**255**),

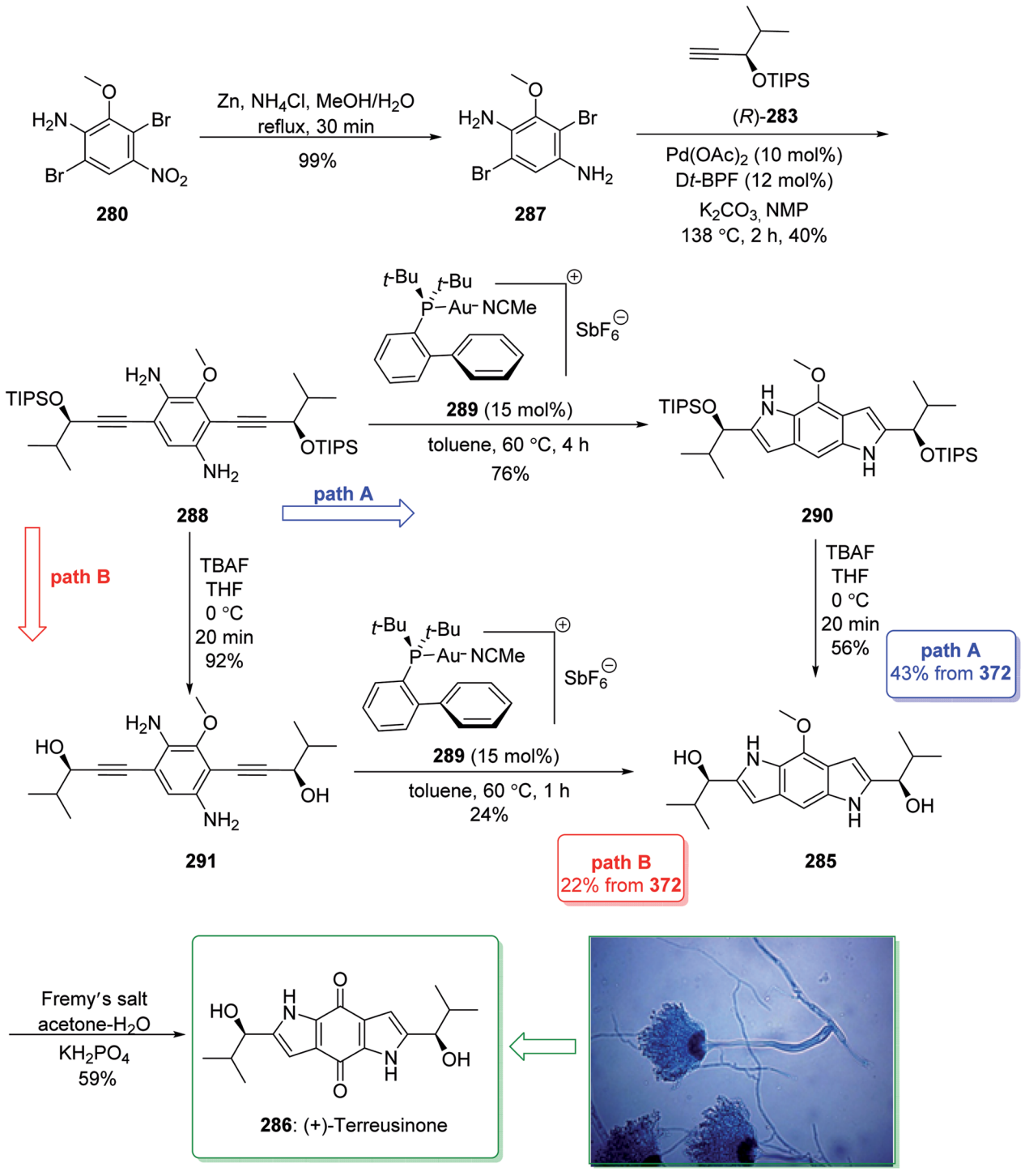


Scheme 36 Total synthesis of (+)-terreusinone (**286**).

which after 12 steps afforded the cyclization substrate **256.** The reaction of **256** with palladium(II) acetate in the presence of the bidentate ligand D*t*-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/H_2O at 0 °C for 3 h, 60% yield) in a reaction in which the indole *N*-acetyl 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%)/H_2O 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).[264]

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.[267]

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 byrozoan *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] The hexahydropyrrolo[2,3-*b*]

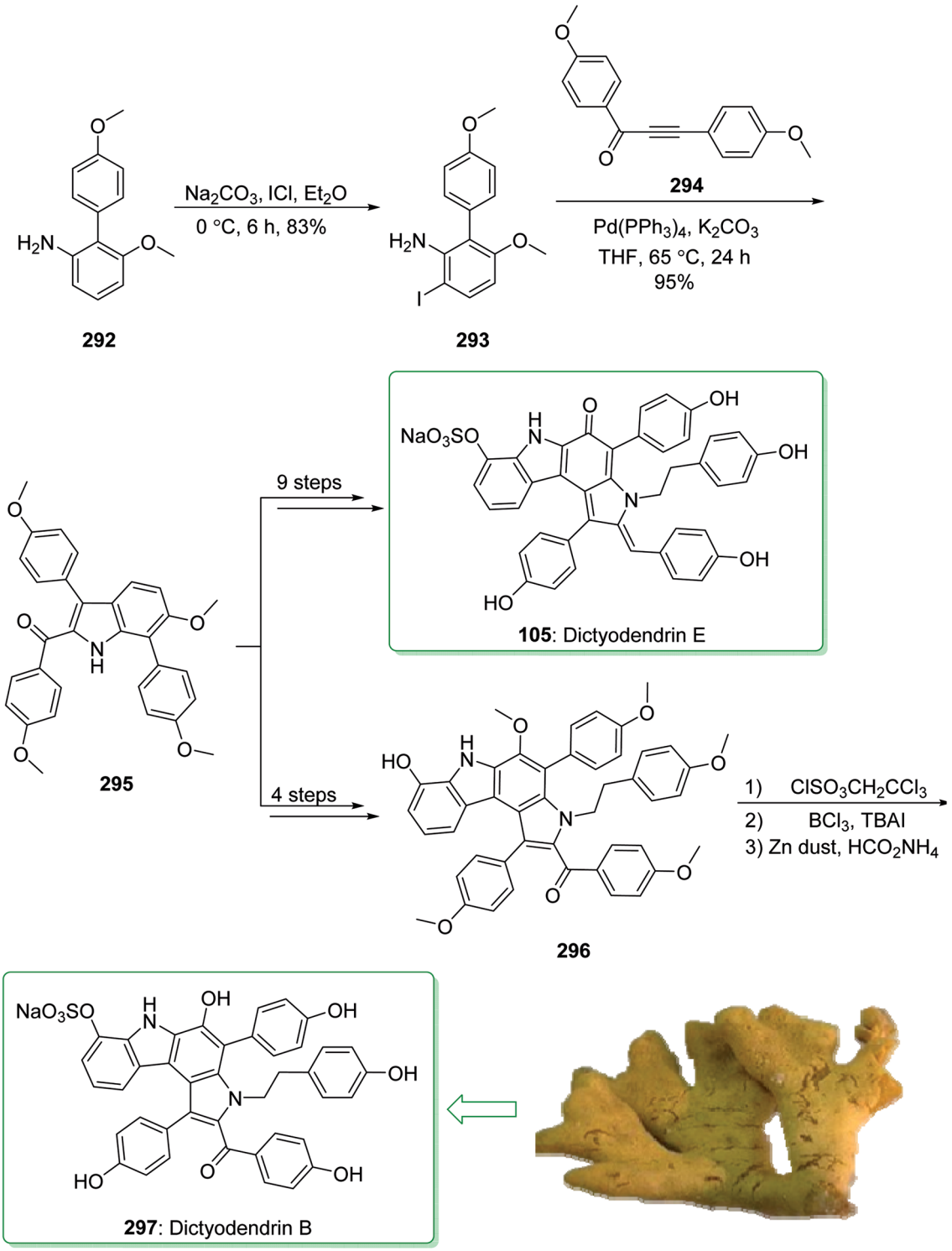


Scheme 37 Bidirectional synthesis of (+)-terreusinone (**286**).

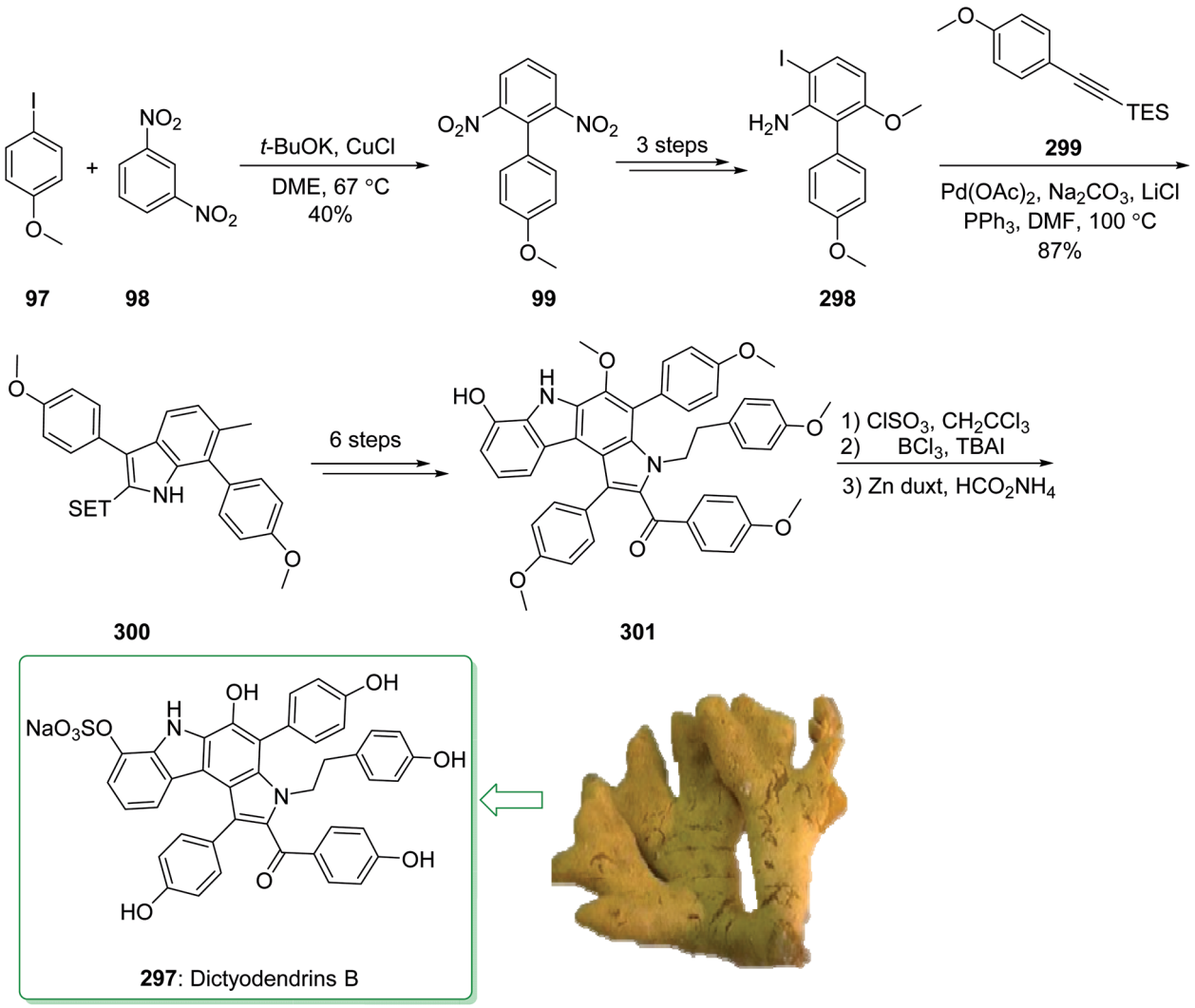
indole, bearing a quaternary carbon prenylated at C-3a, is the defining structural aspect of these alkaloids and thus various effective approaches have been reported for their synthesis.[271] In 2009, Kobayashi and co-workers reported[272] the total synthesis of (−)-flustramine B (**267**) through a one-pot intramolecular Ullmann coupling reaction and Claisen rearrangement. The enantioselective total synthesis of (−)-flustramine B (**267**) was started from the reaction of the iodoaniline derivative **264** (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 (K_2CO_3), triphenylphosphine, and palladium(II) acetate in DMF at 100 °C and gave the desired silyl indole **265**. The latter, after 12 steps,

afforded (−)-flustramide B (**266**). Lastly, the latter was reacted with $AlH_3 \cdot EtNMe_2$ (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).[272]

The enantioselective total synthesis of (−)-debromoflustramine B (**55**) was performed by Kobayashi and co-workers in 2013.[273] In this method, the enantioselective total synthesis of (−)-debromoflustramine 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.[274] Next, the reaction of **262** with *N*-benzyl-*ortho*-iodoaniline (**269**) in DMF at 100 °C in the presence of palladium(II) acetate and triphenylphosphine using



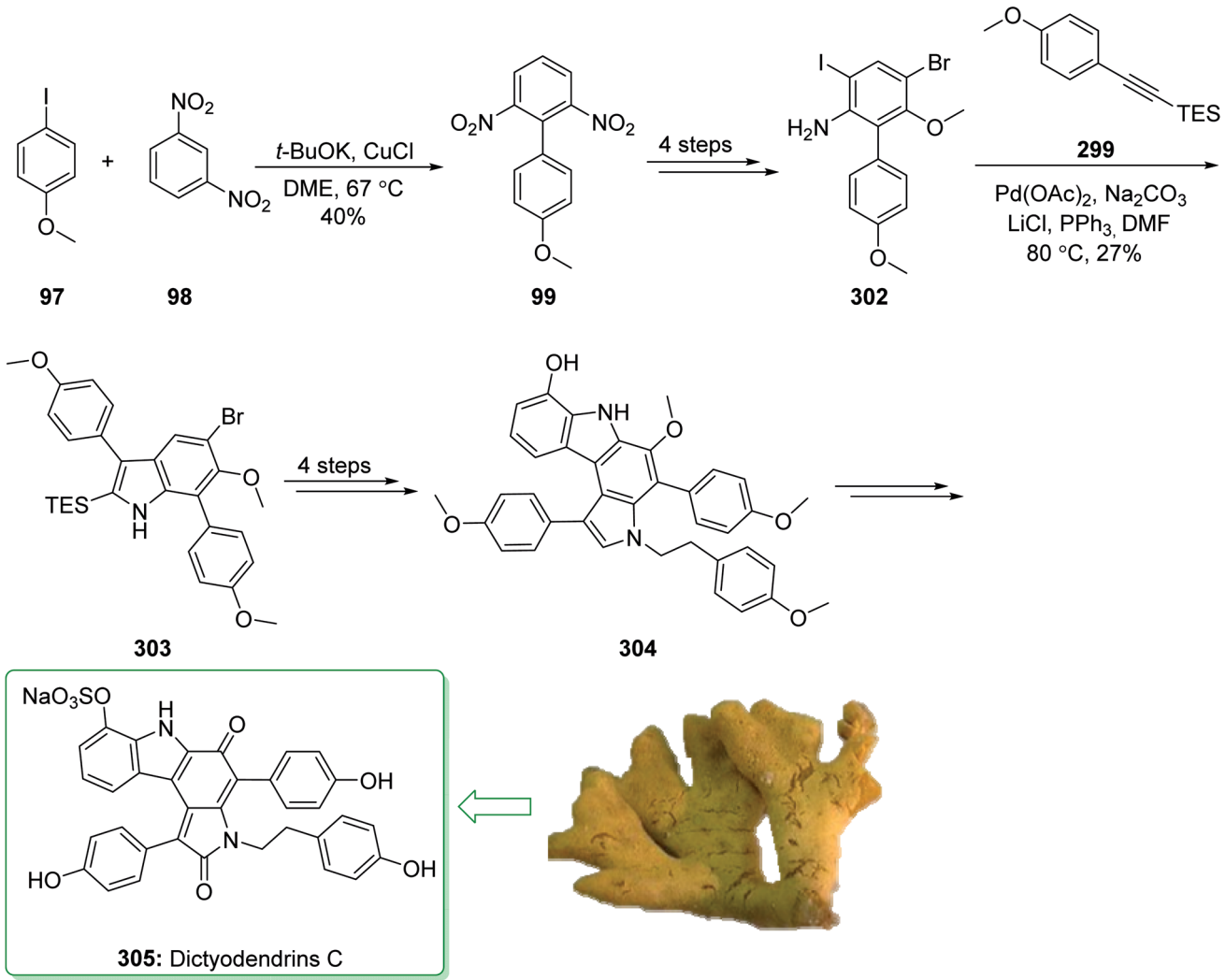
Scheme 38 Total synthesis of dictyodendrin B (**297**) and the formal synthesis of dictyodendrin E (**105**).



Scheme 39 Total synthesis of dictyodendrins B (**297**).

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 ($NaBH_3CN$) and zinc chloride in methanol.[275] In the following, the iododesilylation 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 NH_3 and quenching of the resultant amide anion with prenyl bromide led to the total synthesis of (−)-debromoflustramine 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.[277] In 2012, Sinha and Jana demonstrated[278] 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**.[279] 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

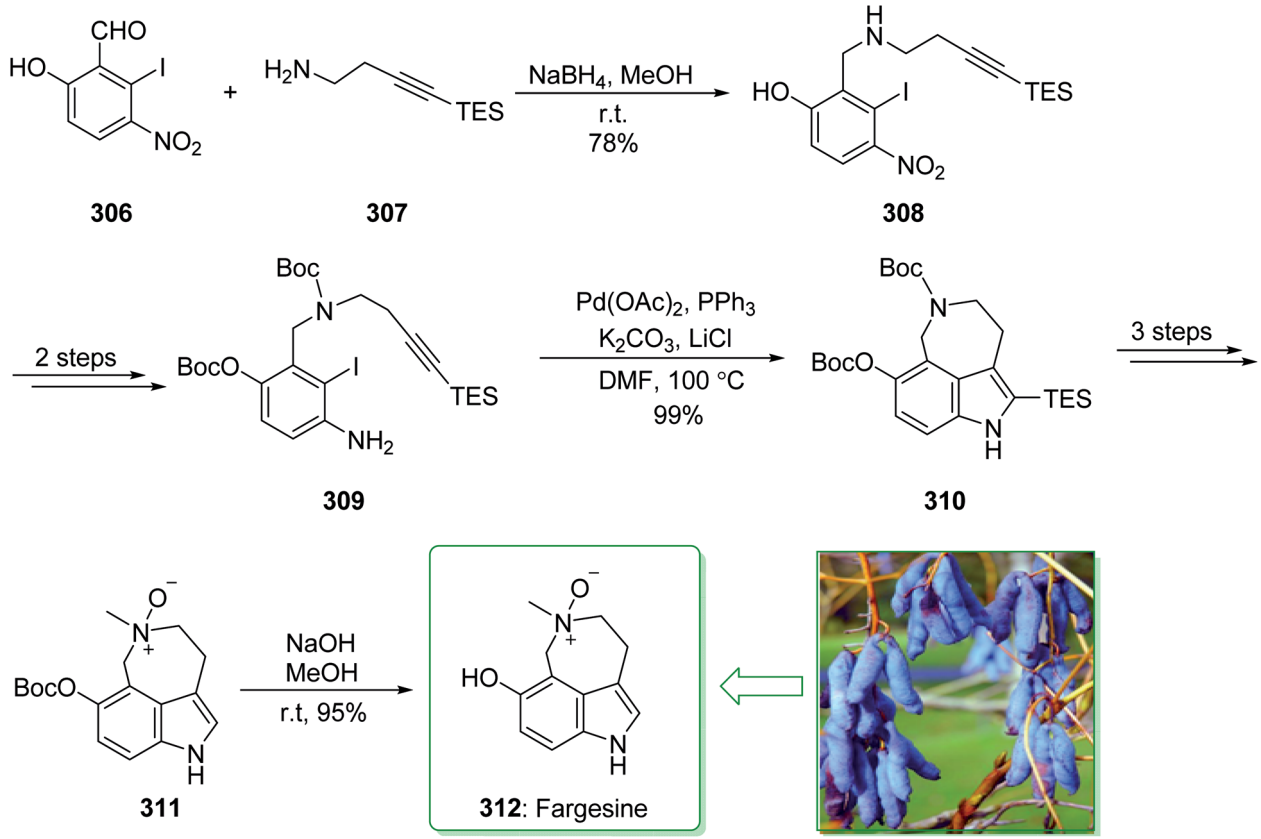


Scheme 40 Formal synthesis of dictyodendrins C (**305**).

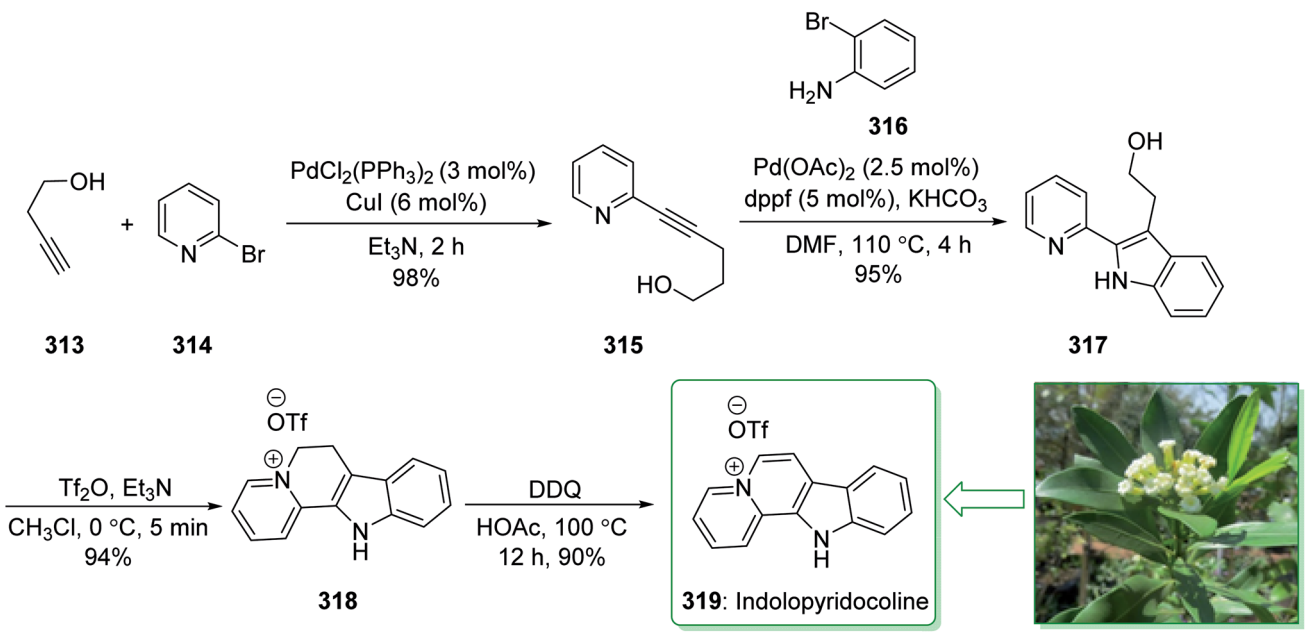
ibogaine (**278a**) in a moderate yield (66% yields) and also epiibogaine (**278b**) in a 55% yield. As a result, ibogaine (**278a**) (9.8%) and epiibogaine (**278b**) (9.7%) were synthesized from 4-methoxy-2-iodoaniline (**274**) in an overall yield of 19.5% (Scheme 35).[278]

The natural product, terreusinone was extracted in 2003 by Son and co-workers from the algicolous marine fungus *Aspergillus terreus.*[280] 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.[281,282] The initial synthesis of (+)-terreusinone (**286**) was reported in 2011 by Sperry and Wang.[283] 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 **279**, 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)[284] through Senanayake's modified Larock indolization reaction.[285] 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 performed in eight steps from commercially available starting precursors (Scheme 36).[283]

An effective, bidirectional synthesis of the photoprotecting dipyrrolobenzoquinone (+)-terreusinone (**286**) was performed by Sperry and Wang in 2012.[286] 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 hydroamination mediated by Echavarren's cationic Au(I) complex. Based on this method, the bidirectional synthesis of (+)-terreusinone (**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

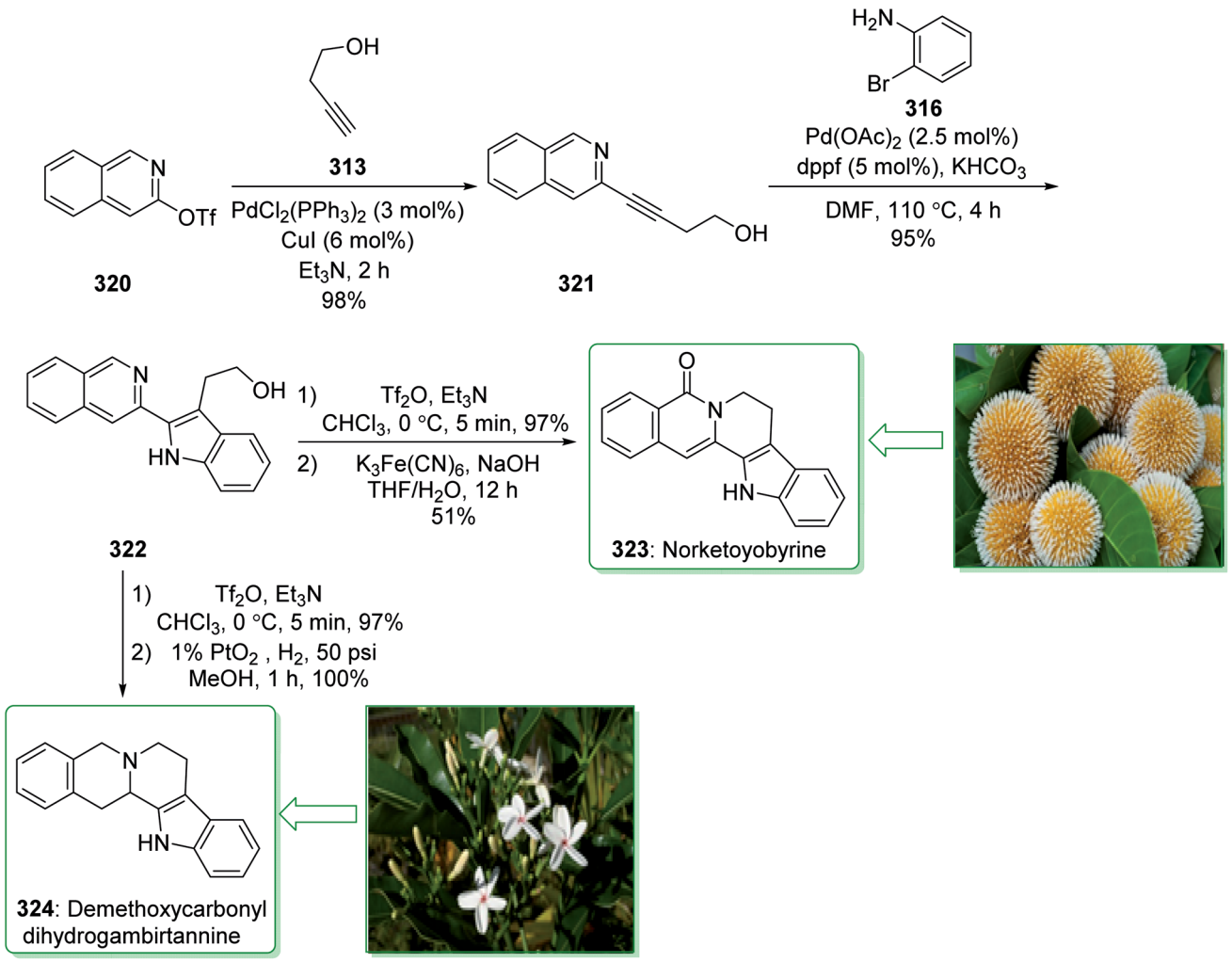


Scheme 41 Total synthesis of fargesine (**312**).



Scheme 42 Total synthesis of indolopyridocoline (**319**).

alcohol (*R*)-**283** with $Pd(OAc)_2$, 1,1′-bis(di-*tert*-butylphosphino) ferrocene and K_2CO_3 in *N*-methyl-2-pyrrolidone at 138 °C (for 2 h),[287,288] 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**).[283] Next, the double hydroamination reaction



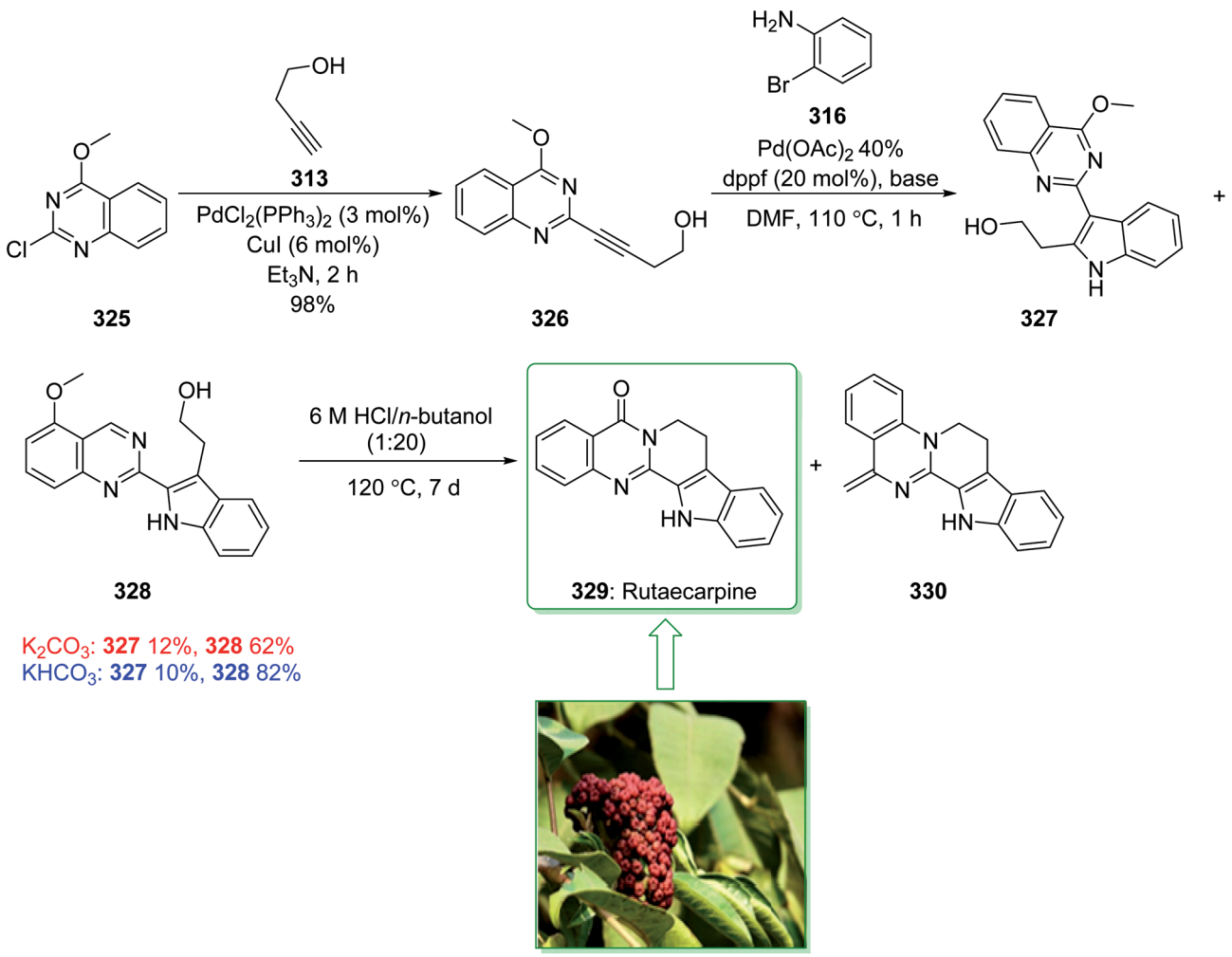
Scheme 43 Total synthesis of norketoyobyrine (**323**) and demethoxycarbonyl dihydrogambirtannine (**324**).

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**.[286] The pyrrolo[2,3-*f*]indole **285** was oxidized and afforded terreusinone [(+)-**286**] (Scheme 37).[283]

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.[289]

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.[290] 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 iodination of aniline **292**. In this route, aniline **292**, in the presence of iodine monochloride (ICl), afforded *o*-iodoaniline (**293**) in a good yield (83% yield). The *o*-iodoaniline (**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



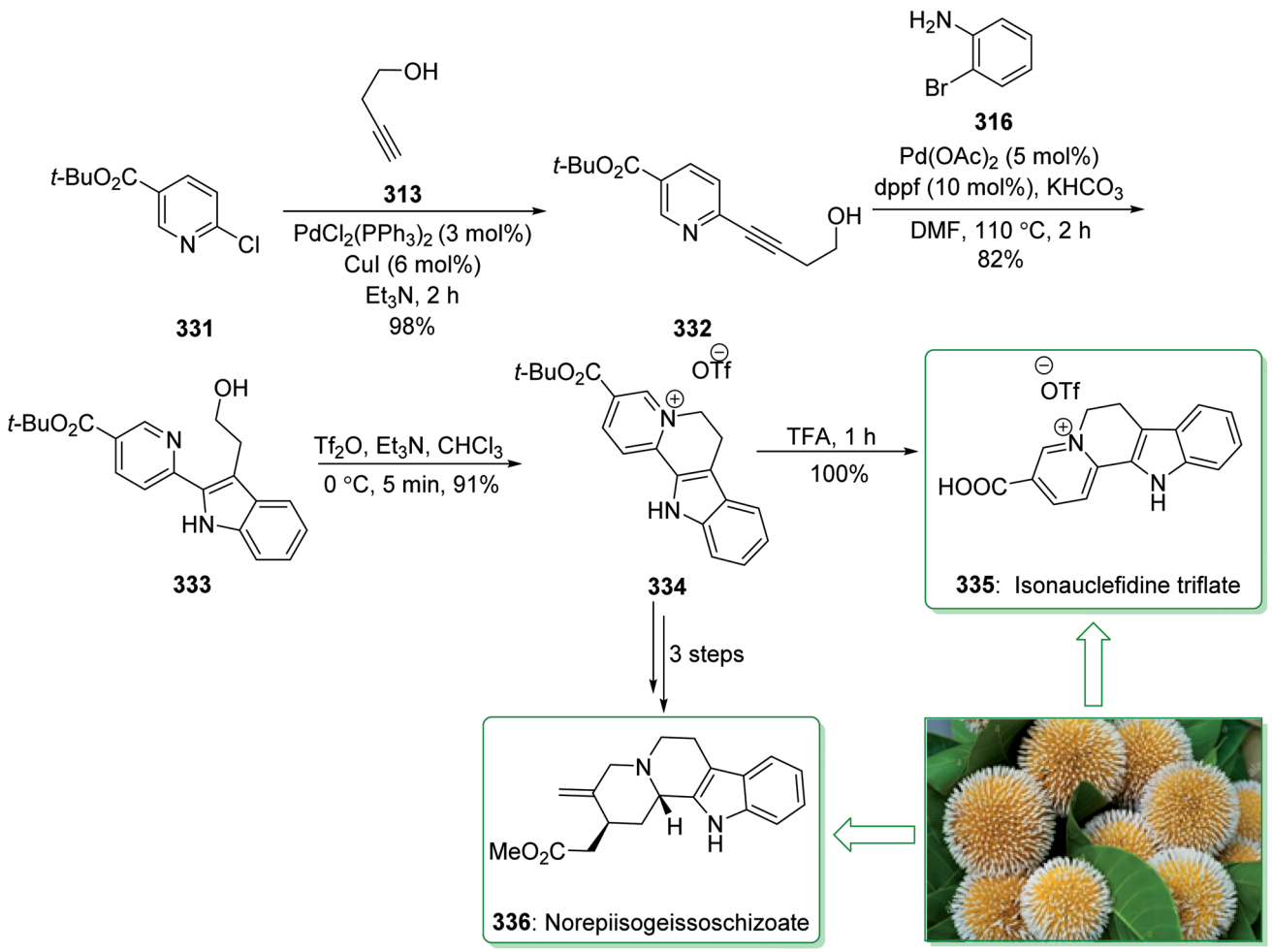
Scheme 44 Total synthesis of rutaecarpine (**329**).

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**.[290] On the other hand, indole **295**, after nine steps, gave dictyodendrin E (**105**).[291] 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).

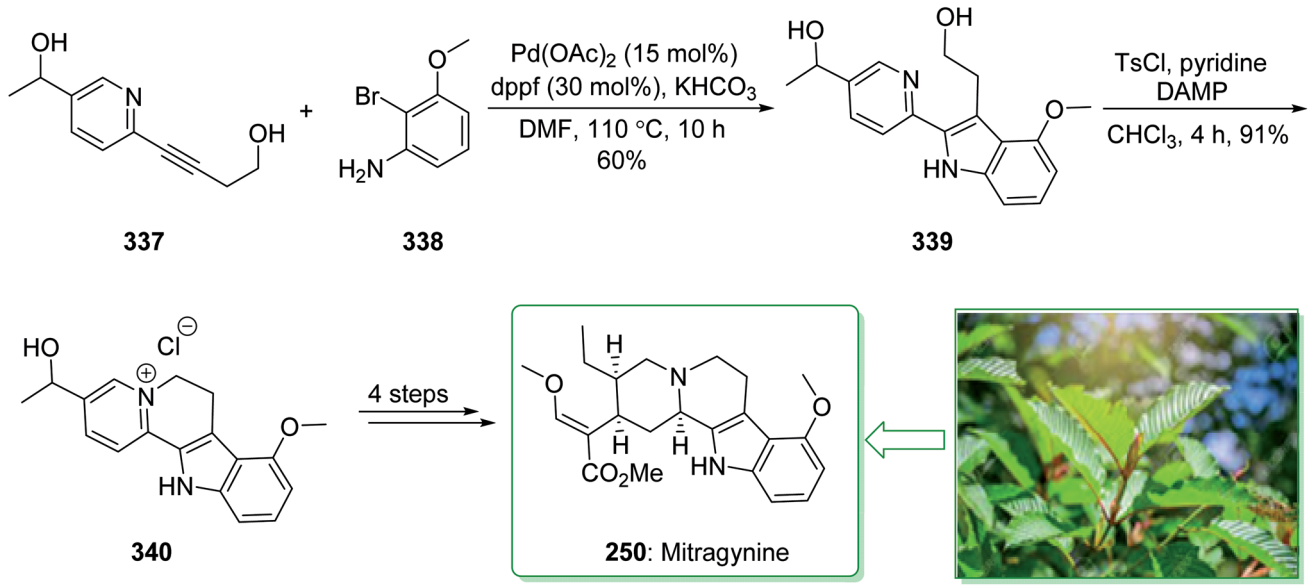
In 2014, Jia *et al.* published[167] a complete explanation of the short total synthesis of dictyodendrins B and also the formal synthesis of dictyodendrin C. In this method, a palladium-catalyzed Larock indole synthesis was utilized to make the very functionalized indole unit, and a Pd-catalyzed one-pot 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 biphenyl **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 reaction afforded the corresponding indole **300** in a good yield (87% yield). After six steps, phenol **301** was provided from indole **300**. Finally, after three steps ((1) $ClSO_3$, CH_2CCl_3; (2) BCl_3, TBAI; (3) Zn, HCO_2NH_4), the total synthesis of dictyodendrins B (**297**) was performed successfully (Scheme 39).[167]

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).[292]

Fargesine, an *N*-oxide alkaloid, was extracted by Zhu and coworkers from the stem and root of *Evodia fargesii* Dode, in which fruits are used in folk medicine for pain relief from bellyache.[293] In 2013, Jia *et al.* developed[294] 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**



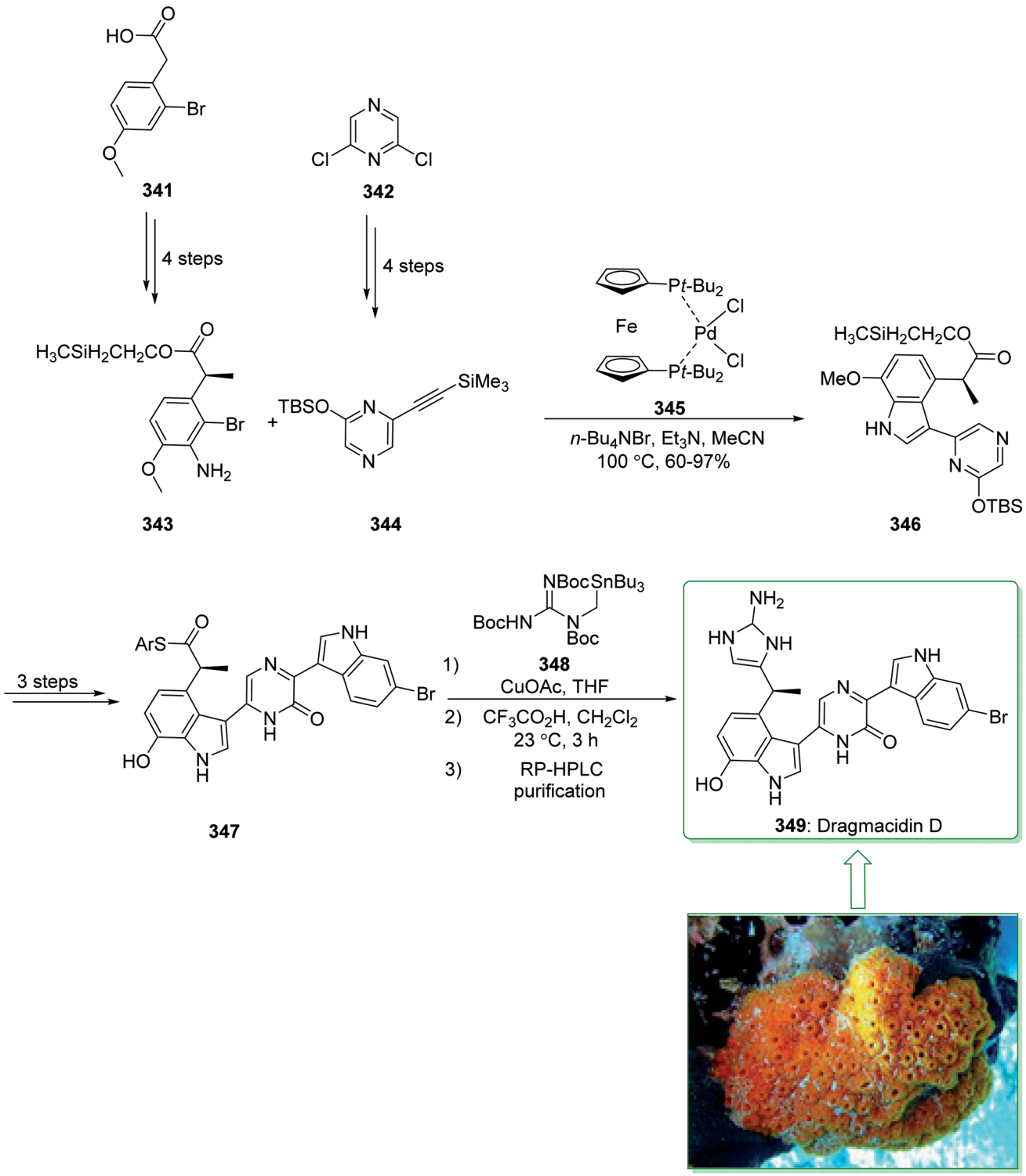
Scheme 45 Total synthesis of isonauclefidine triflate (335) and the formal synthesis of norepiisogeissoschizoate (336).



Scheme 46 Formal synthesis of mitragynine (250).

that afforded the secondary amine **308**. The latter, after two steps, gave 2-iodoaniline (**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).[294]

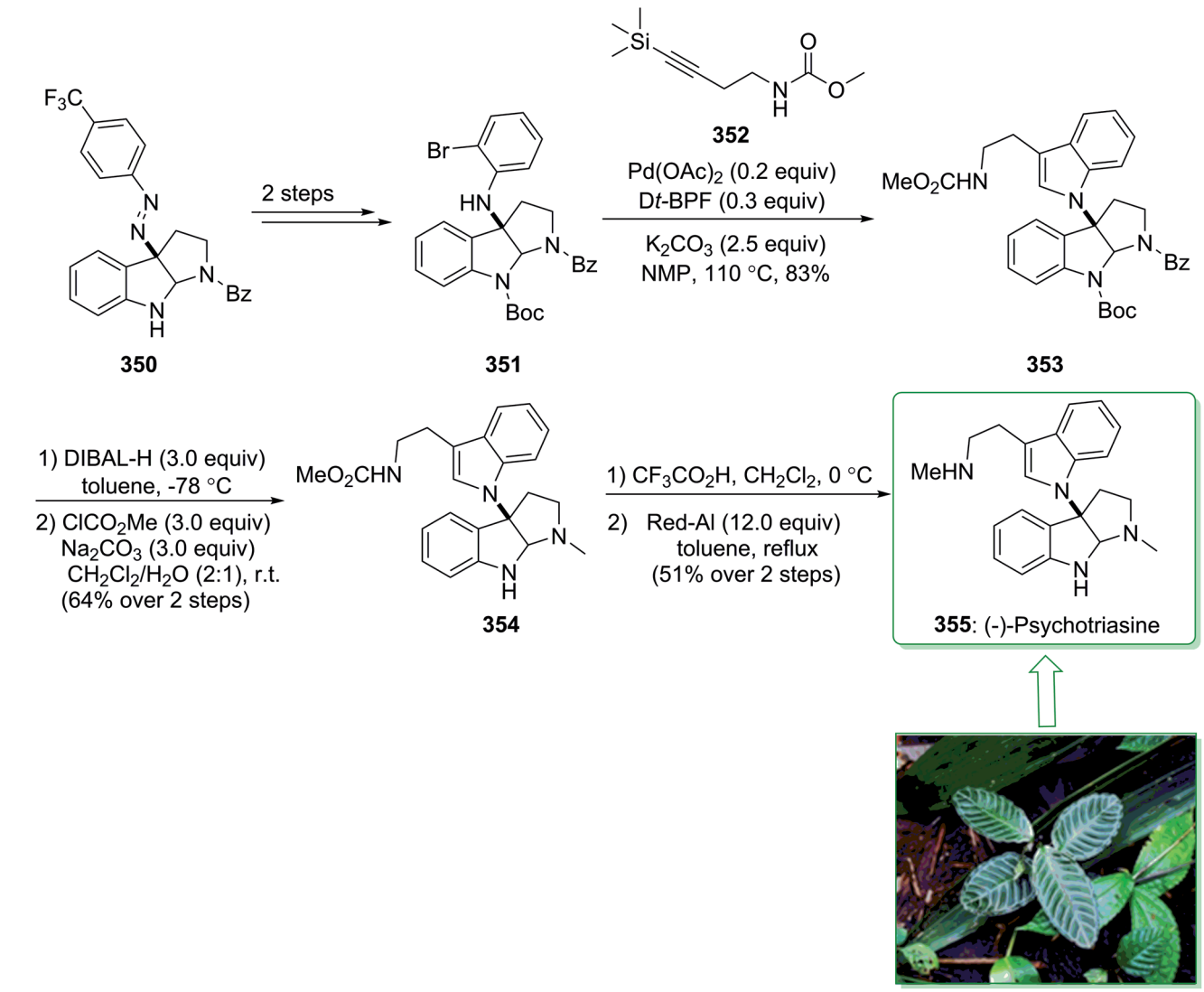
β-Carbolines, a large group of natural indole alkaloids, contain a tricyclic pyrido-3,4-indole ring, analogous to the



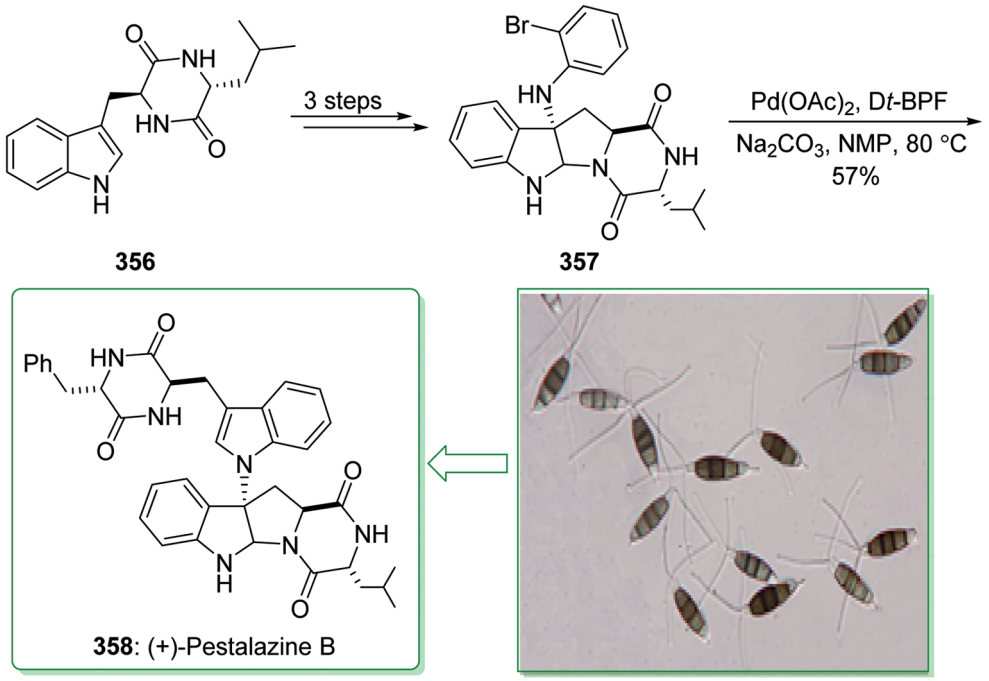
Scheme 47 Asymmetric total synthesis of dragmacidin D (**349**).

tryptamine structure.[295] β-Carbolines 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**), demethoxycarbonyl dihydrogambirtannine (**324**), rutaecarpine (**329**), isonauclefidine triflate (**335**), norepiisogeissoschizoate (**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, 1,1′bis(diphenylphosphino) ferrocene (dppf), and potassium bicarbonate ($KHCO_3$) 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]

(−)-Demethoxycarbonyldihydrogambirtannine (**324**) was extracted in 1973 by Peube–Locou from the leaves of *Ochrosia lifuana* and also *Ochrosia miana* (Apocynaceae).[298] Norketoyobyrine (**323**) and isonauclefidine (**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 demethoxycarbonyl dihydrogambirtannine (**324**) were started from the Sonogashira coupling reaction of isoquinolin-3-yl trifiate (**320**) and butyne-1-

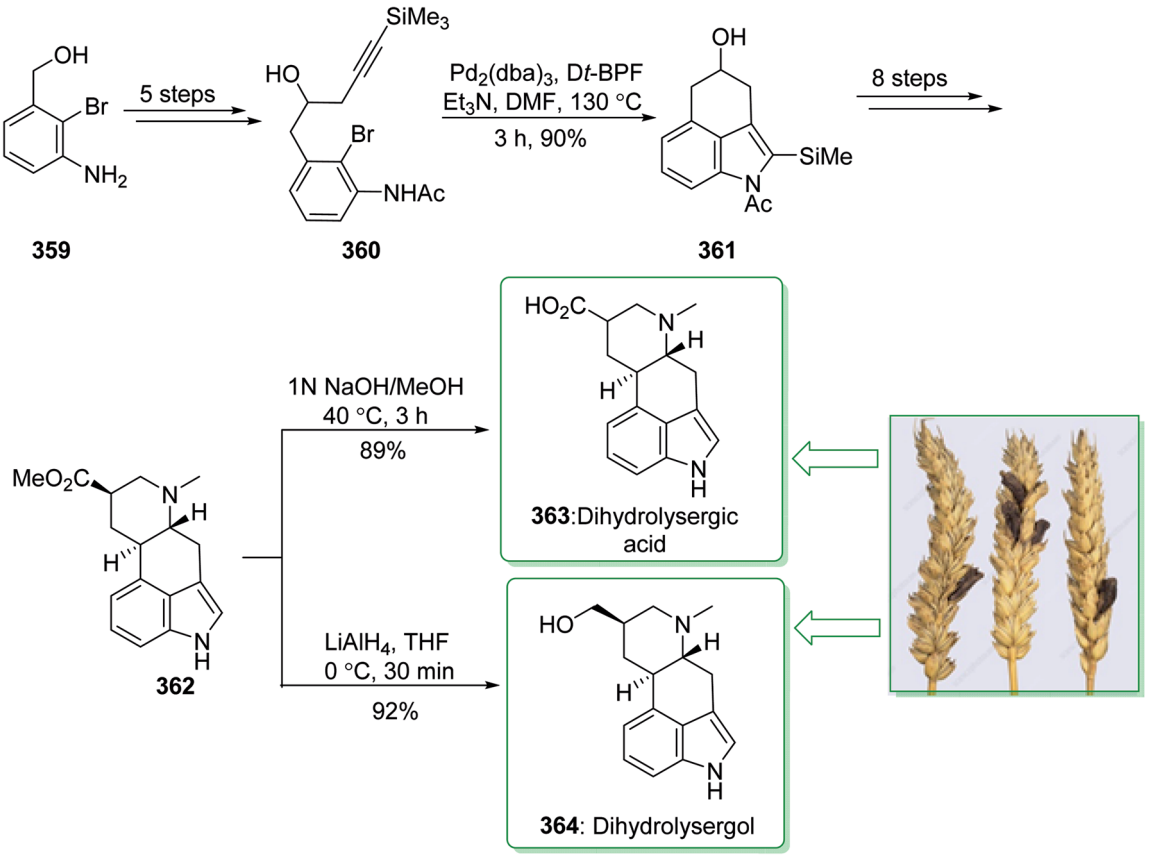


Scheme 48 Asymmetric total synthesis of (−)-psychotriasine (**355**).

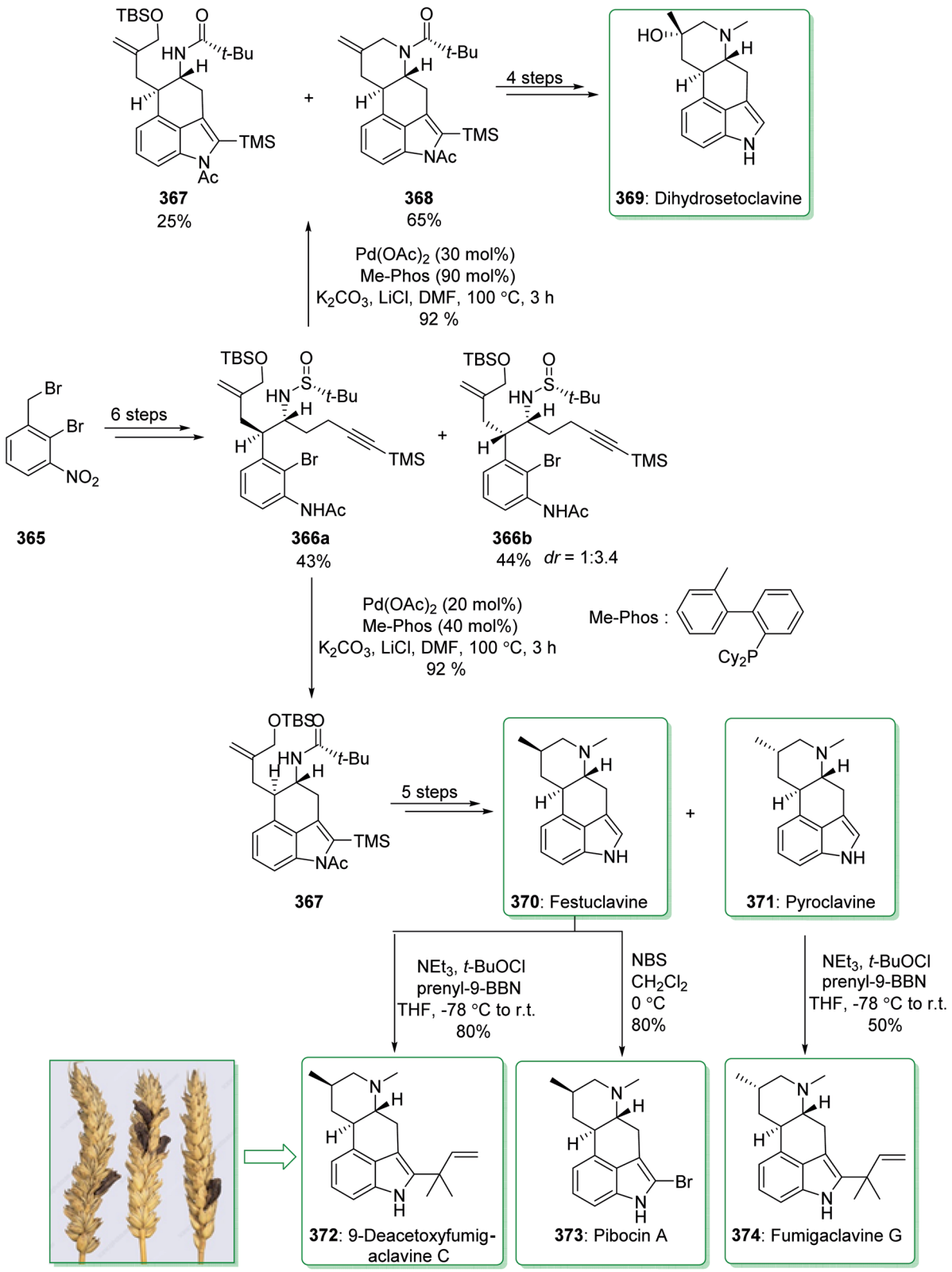


Scheme 49 Total synthesis of (+)-pestalazine B (**358**).

ol (**313**) that afforded alkyne **321**.[297] 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 50 Total synthesis of dihydrolysergic acid (**363**) and dihydrolysergol (**364**).



Scheme 51 Total synthesis of festuclavine (**370**), pyroclavine (**371**), pibocin A (**373**), 9-deacetoxyfumigaclavine C (**372**), fumigaclavine G (**374**) and dihydrosetoclavine (**369**).

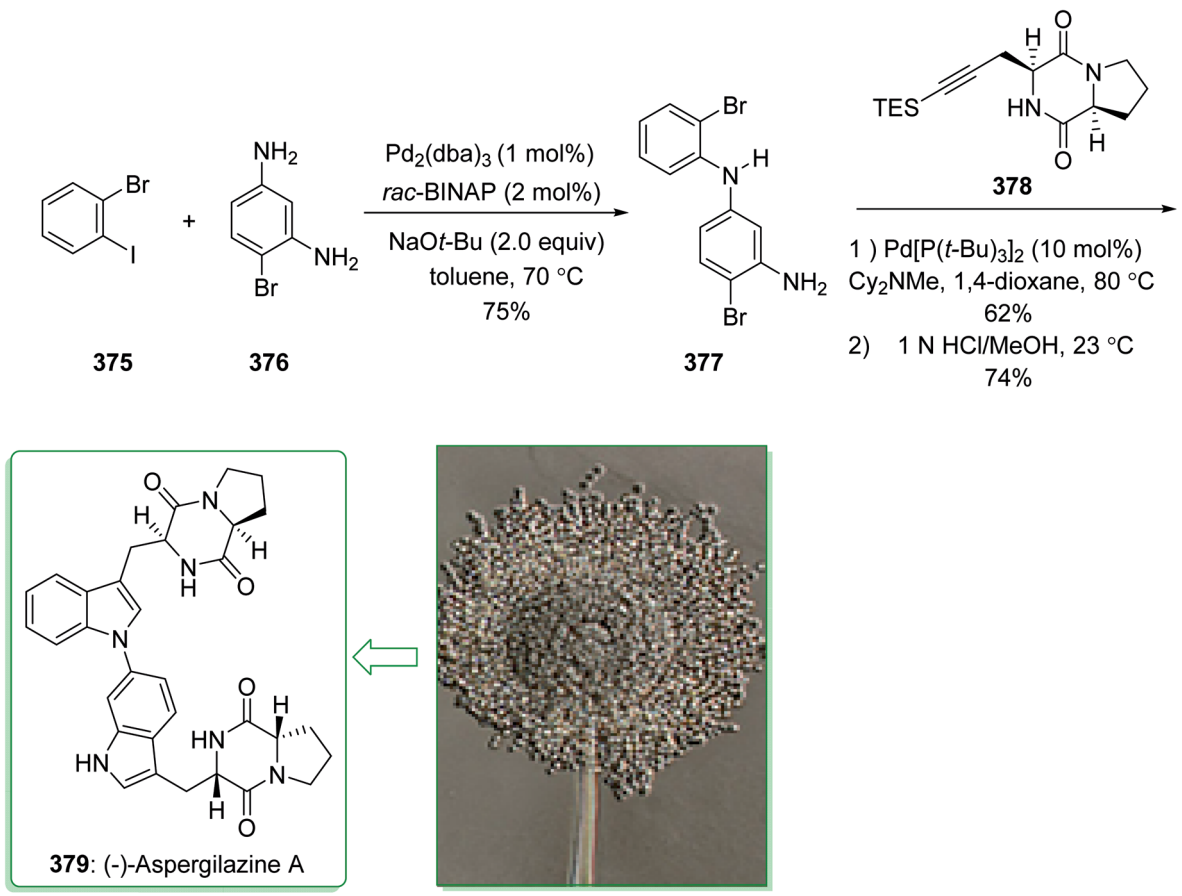
and reduction, yielded demethoxycarbonyl dihydrogambirtannine (**324**) (Scheme 43). In addition, the alternative synthesis of demethoxycarbonyl-dihydrogambirtannine (**324**) and norketoyobyrine (**323**) have been reported.[301,302]

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 regioisomeric 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).[297]

The total synthesis of isonauclefidine 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, isonauclefidine 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).[297]

Furthermore, the formal synthesis of mitragynine (**250**) started with the Larock indolization of alcohol **337** and electron-rich aniline **338**, which yielded the corresponding tetracycle **340**. The latter after four steps gave mitragynine (**250**)[304] (Scheme 46).[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*.[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 *in vitro* cytotoxicity against A549 human lung, HCT-8 human colon and P388 murine leukemia.[306] In 2015, Zakarian *et al.* reported the enantioselective synthesis of dragmacidin D (**349**) in 10 steps.[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′-bis(di-*tert*-butylphosphino)ferrocene] $PdCl_2$ 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-

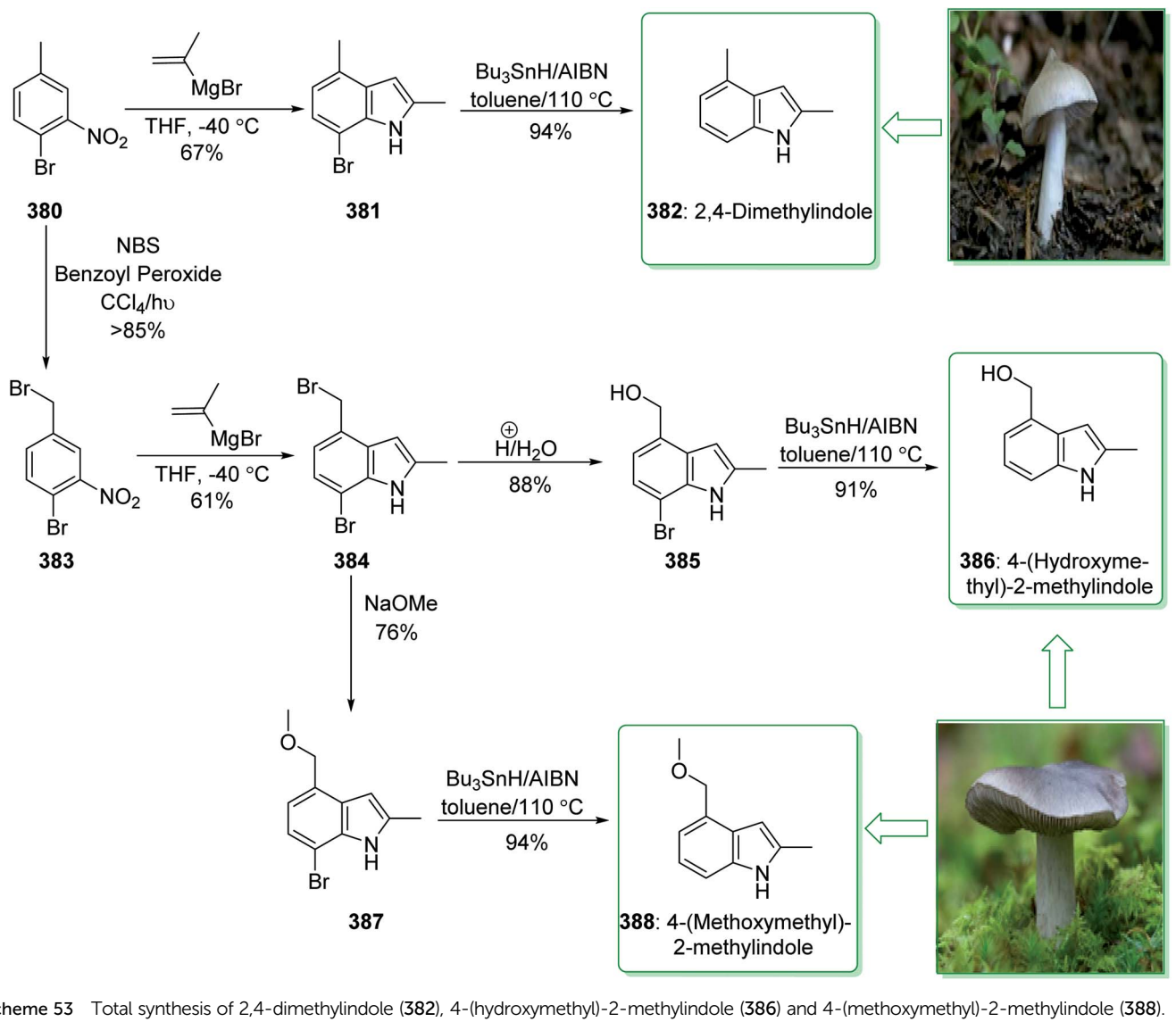


Scheme 52 Total synthesis of (−)-aspergilazine A (**379**).

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).[307]

Indole alkaloids bearing a 3α-amino-hexahydropyrrolo-[2,3-*b*]indole motif were found in various natural products.[308] Among the alkaloids in this family, psychotriasine (**355**) was extracted from *Psychotria calocarpa* in 2010 by Hao *et al.*[309] In 2015, Deng *et al.* demonstrated[310] 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-butynylamine) (**352**), using a palladium(II) acetate catalyst, D*t*-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 $ClCO_2Me$ 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).[310]

(+)-Pestalazine B (**358**) containing a C3(sp^3)–N1 bridge was initially extracted from the plant pathogenic fungus *Pestalotiopsis theae* in 2008 by Ding *et al.*[311] It is worth mentioning that



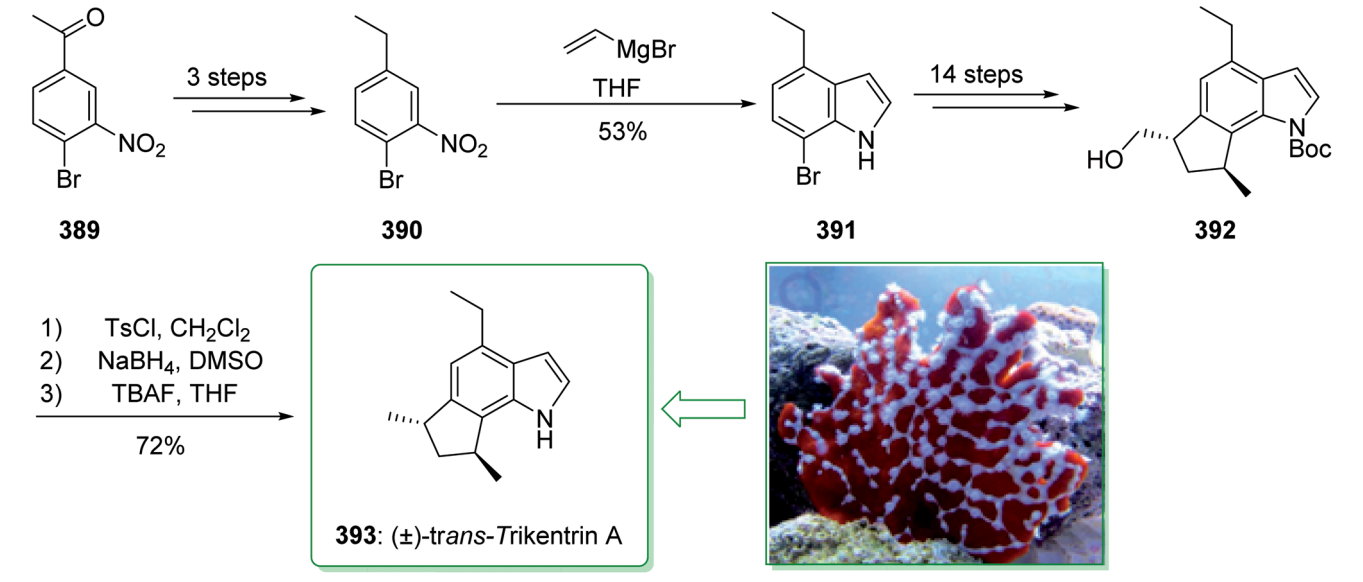
Scheme 53 Total synthesis of 2,4-dimethylindole (**382**), 4-(hydroxymethyl)-2-methylindole (**386**) and 4-(methoxymethyl)-2-methylindole (**388**).

its structure was revised in 2010 by de Lera and co-worker upon total synthesis.[312] 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 D*t*-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.[313,314] Among the ergot alkaloids (EAs) family of naturally occurring compounds, lysergic acid[315] is the most broadly identified member and various semisynthetic derivatives have been clinically utilized for treating various neurological diseases. In 2015, Boger *et al.* demonstrated[316] 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 $LiAlH_4$, THF at 0 °C) yielded dihydrolysergol (**364**) (Scheme 50).[316]

An efficient method for the total synthesis of eight ergot alkaloids was reported in 2017 by Jia *et al.*[317] 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(II) 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(II) 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**).[317]

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%), K_2CO_3, 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



Scheme 54 Total synthesis of (±)-*trans*-trikentrin A (**393**).

fumigaclavine G (**374**) in a satisfactory yield (50% yield) (Scheme 51).[317]

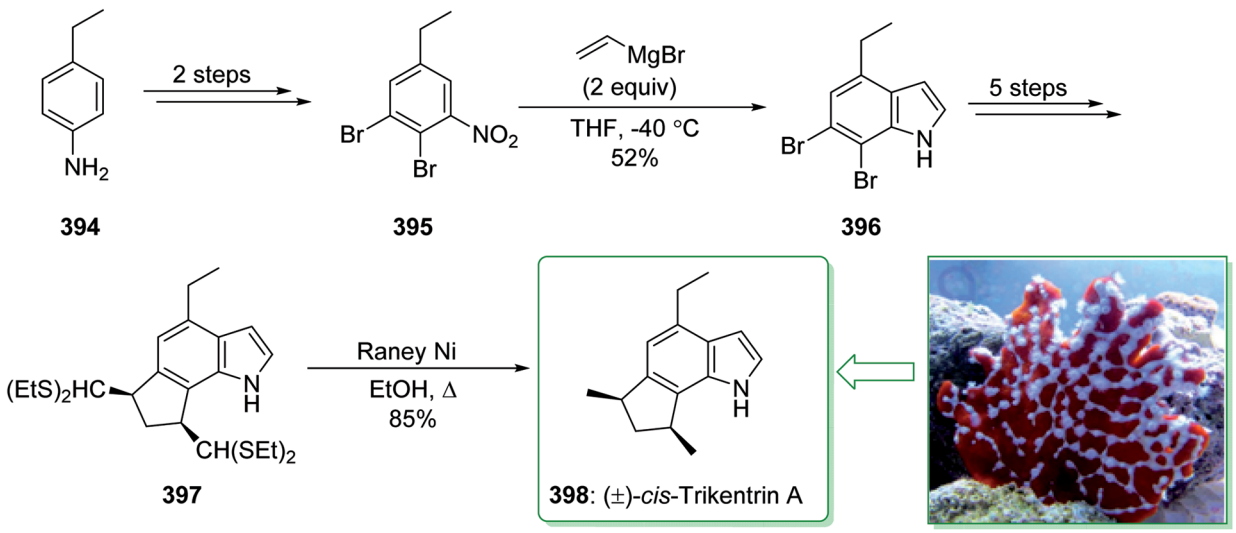
Aspergilazine A, dimerized by two diketopiperazines cores through an unusual N-1 to C-6 linkage, was extracted in 2012 by Gu and co-workers from the marine-derived fungus *Aspergillus taichungensis* ZHN-7-07.[318] The fungal strain *Aspergillus taichungensis* ZHN-7-07 along with the mangrove plant *Acrostichum aureum*, are members of the *Aspergillus Candidi* family.[319,320] In 2016, Reisman *et al.* demonstrated the total synthesis of the bisindole natural product (−)-aspergilazine A (**379**).[321] 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 Cy$_2$NMe 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).[321]

2.3. Bartoli indole synthesis

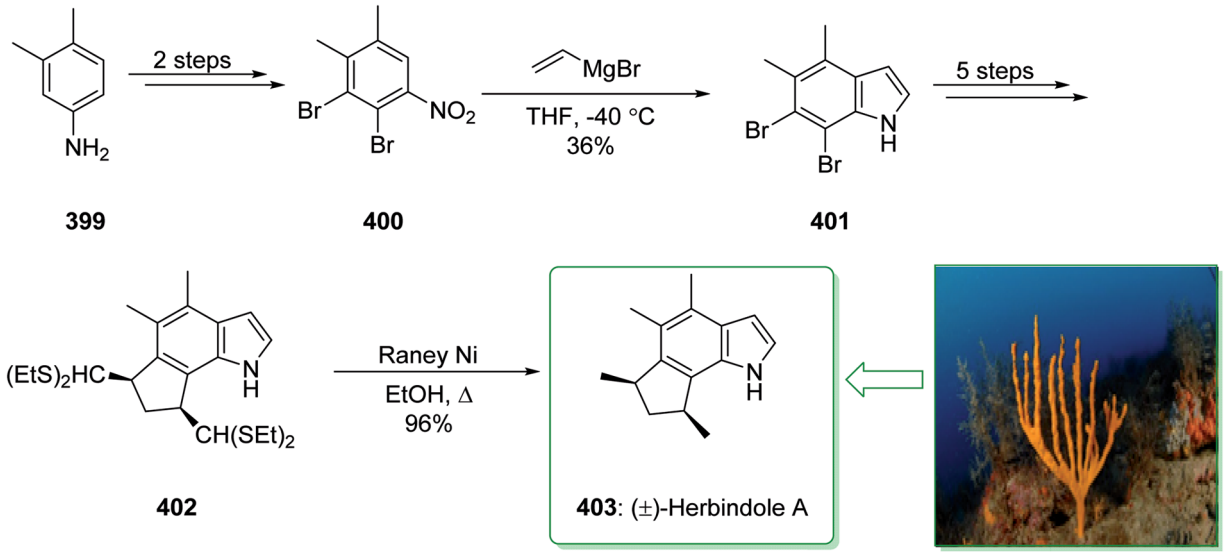
In 2001, Dobbs demonstrated[322] a concise and effective method for the synthesis of 2,4-dimethylindole (**382**), 4-(hydroxymethyl)-2-methylindole (**386**) and 4-(methoxymethyl)-2-methylindole (**388**). These alkaloids were previously extracted and reported in 1994 by Sterner and co-workers from two species of European Basidomycetes (*Tricholoma sciodes* and *Tricholoma virgatum*).[323] *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.[324] The total synthesis of 2,4-dimethylindole (**382**), 4-(hydroxymethyl)-2-methylindole (**386**), and 4-(methoxymethyl)-2-methylindole (**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).[322] 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-nitro-1-bromomethylbenzene (**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-methylindole (**384**) in a good yield (61% yield). In the following, the reaction of compound **384** with H_2O (under acidic reaction conditions) afforded 7-bromo-4-(hydroxymethyl)-2-methylindole (**385**) in very good yields (88% yields) and this was transformed into the alkaloid 4-(hydroxymethyl)-2-methylindole (**386**) by using radical reduction (91% yield) (41% overall yields). In addition, the reaction of 7-bromo-4-(bromomethyl)-2-methylindole (**384**) with NaOMe provided 7-bromo-4-(methoxymethyl)-2-methylindole (**387**) in good yields (76% yields) and this was again reduced quantitatively with tributyltin hydride (Bu_3SnH) (94% yield) to afford 4-(methoxymethyl)-2-methylindole (**388**) in a moderate overall yield (37%) (Scheme 53).[322]

The family of trikentrins,[325] and herbindoles[326] 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.[327] The trikentrins were extracted from the marine sponge *Trikentrion flabelliforme* by Capon *et al.* in 1986.[328] The herbindoles were discovered by Scheuer from the Australian sponge *Axinella* sp. and contain both anti-feedant and cytotoxic activities.[329] Silva and Craveiro in 2008 reported[330] 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



Scheme 55 Total synthesis of (±)-*cis*-trikentrin A (**398**).



Scheme 56 Total synthesis of (±)-herbindole A (**403**).

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 $CH_2CHMgBr$ 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 dihydrocyclopenta[*g*] indole **392**, containing the *trans*-1,3 five-membered ring.[331] Then, compound **392**, after three steps, including tosylation, and the reduction and removal of the Boc substituent, gave (±)-*trans*-trikentrin A (**393**) (Scheme 54).[330]

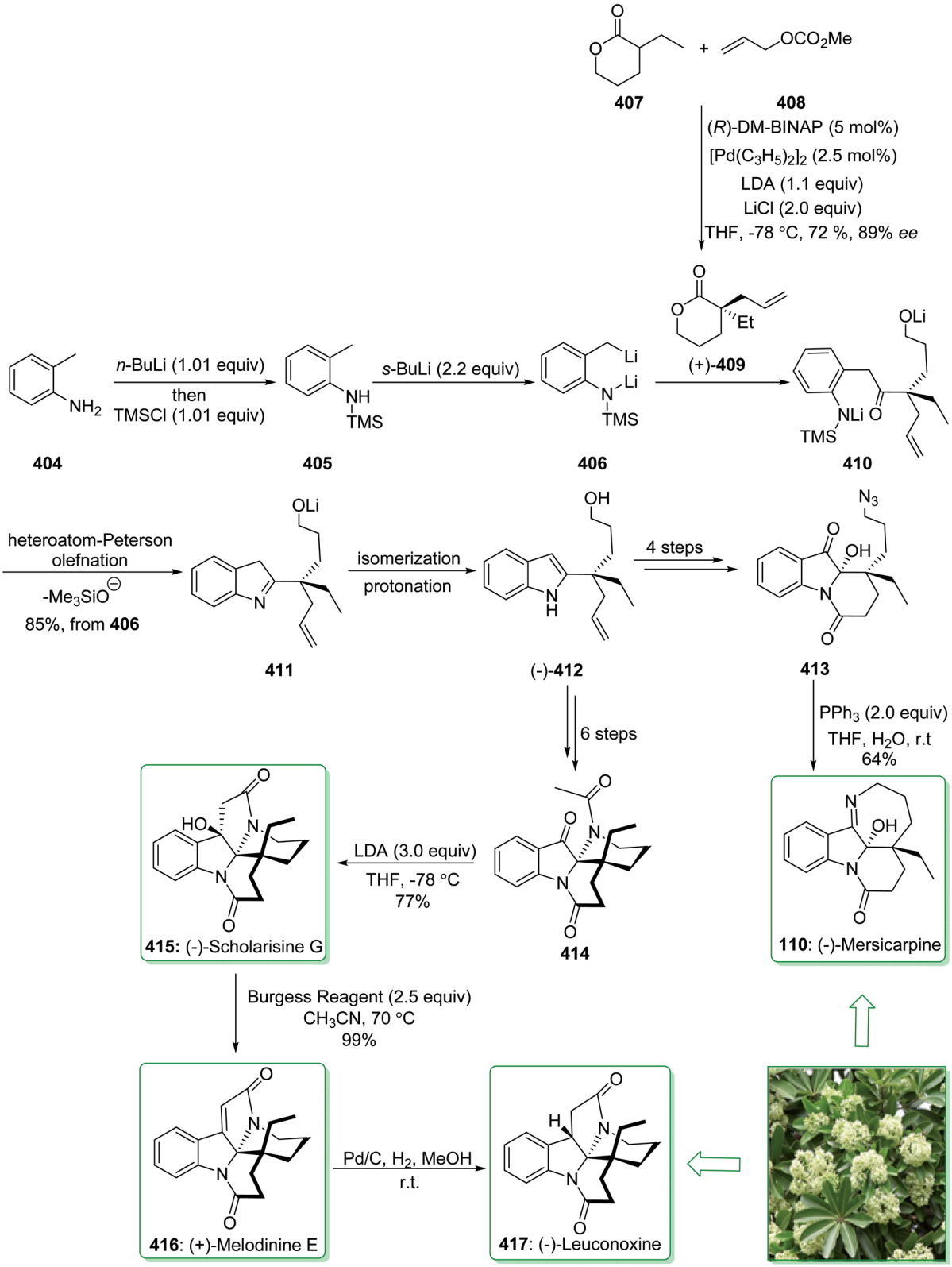
In 2009, Buszek and co-workers demonstrated[332] an effective nine-step total synthesis of the annulated indole natural products (±)-*cis*-trikentrin A (**398**) and (±)-herbindole A (**403**) through an intermolecular Diels–Alder cycloaddition using the established indole aryne (indolyne) approach as 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 °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).[332]

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 etrahydrocyclopenta[*g*]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).[332]

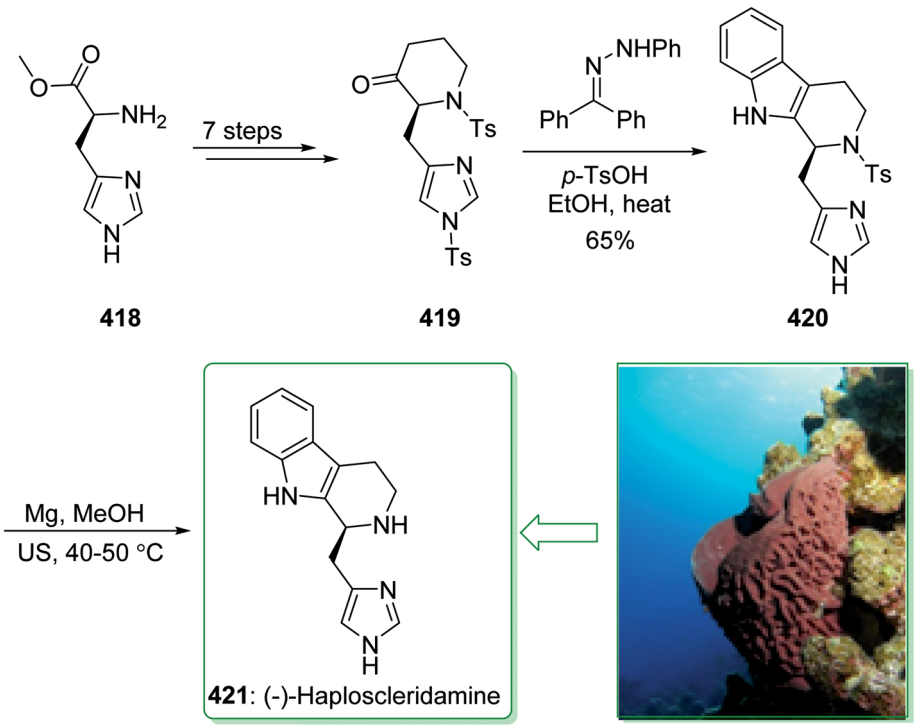
2.4. Madelung indole synthesis

Mersicarpine was isolated from the stem-bark extracts of the *Kopsia fruticosa* and *Kopsia arborea* by Kam *et al.* in 2004.[333] Mersicarpine contains a typical seven-membered cyclic imine fused along with indoline and δ-lactam.[334,335] 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.[336] Various methods for the total synthesis have been reported, involving Kerr's first total synthesis of (±)-mersicarpine[337] and Fukuyama's first total synthesis of (−)-Mersicarpine (**110**).[338]

The mersicarpine and leuconoxine are structurally complex and biologically fascinating aspido-sperma-derived monoterpene indole alkaloids.[55] (−)-Scholarisine G (**415**),[339] (+)-melodinine E (**416**)[340] and (−)-leuconoxine (**417**)[341] are pentacyclic alkaloids containing a stimulating [5.5.6.6]diazafenestrane unit[342] that possesses two or three contiguous quaternary stereogenic centers. (−)-Mersicarpine (**110**),[333] however, contains a fused tetracyclic 6/5/6/7 ring scaffold, identified by an unusual tetrahydro-2*H*-azepine ring and also a hemiaminal scaffold.[343–346] In 2019, Wang and co-worker reported[347] a unified approach for the asymmetric synthesis of (−)-scholarisine G (**415**), (+)-melodinine E (**416**), (−)-leuconoxine (**417**) and (−)-mersicarpine (**110**) from the 2-alkylated indole intermediate. The total synthesis of (−)-scholarisine G (**415**), (+)-melodinine 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**).



Scheme 58 Total synthesis of (−)-haploscleridamine (**421**).

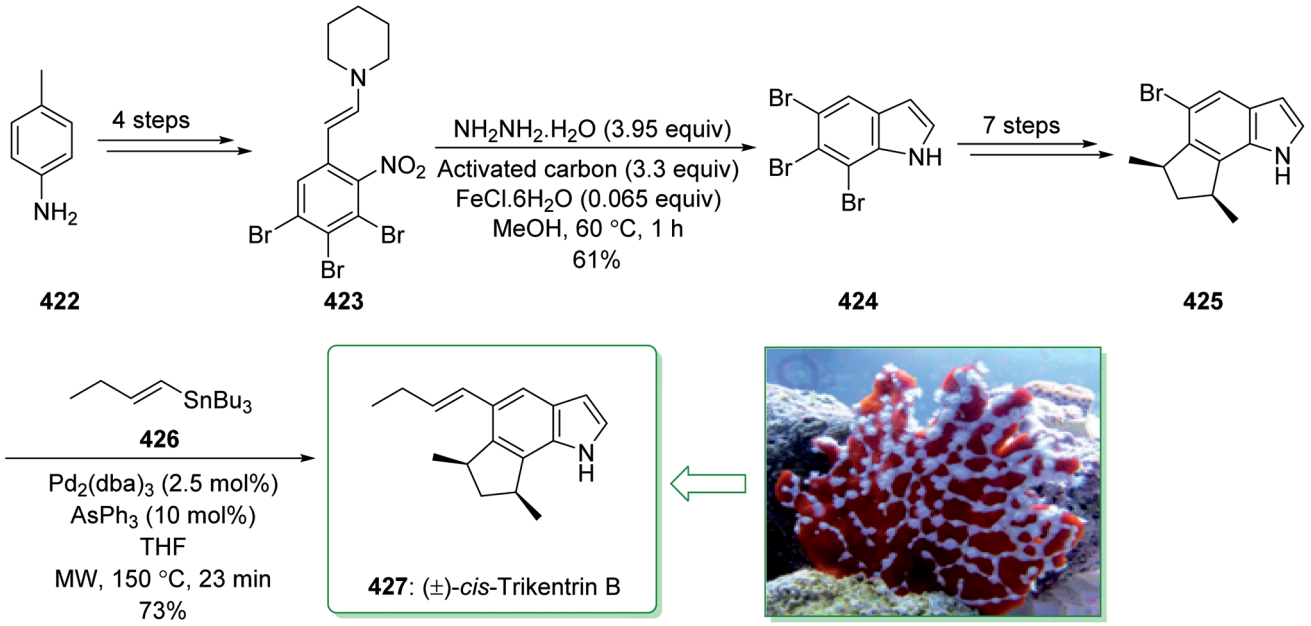
the formation of *N*-silylated *o*-toluidine (**405**) by treating *o*-toluidine (**404**) in the presence of a stoichiometric quantity of *n*-BuLi and was quenched with chlorotrimethylsilane ($(Me)_3SiCl$). Without separation, this intermediate was subjected to *sec*-butyllithium solution at a low temperature 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-ethyltetrahydro-2*H*-pyran-2-one (**407**) and allyl methyl carbonate (**408**) using a Pd catalyst and the (*R*)-DM-BINAP ligand.[348] 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 (+)-melodinine 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).[347]

2.5. Buchwald-modification of the classical Fischer indolization

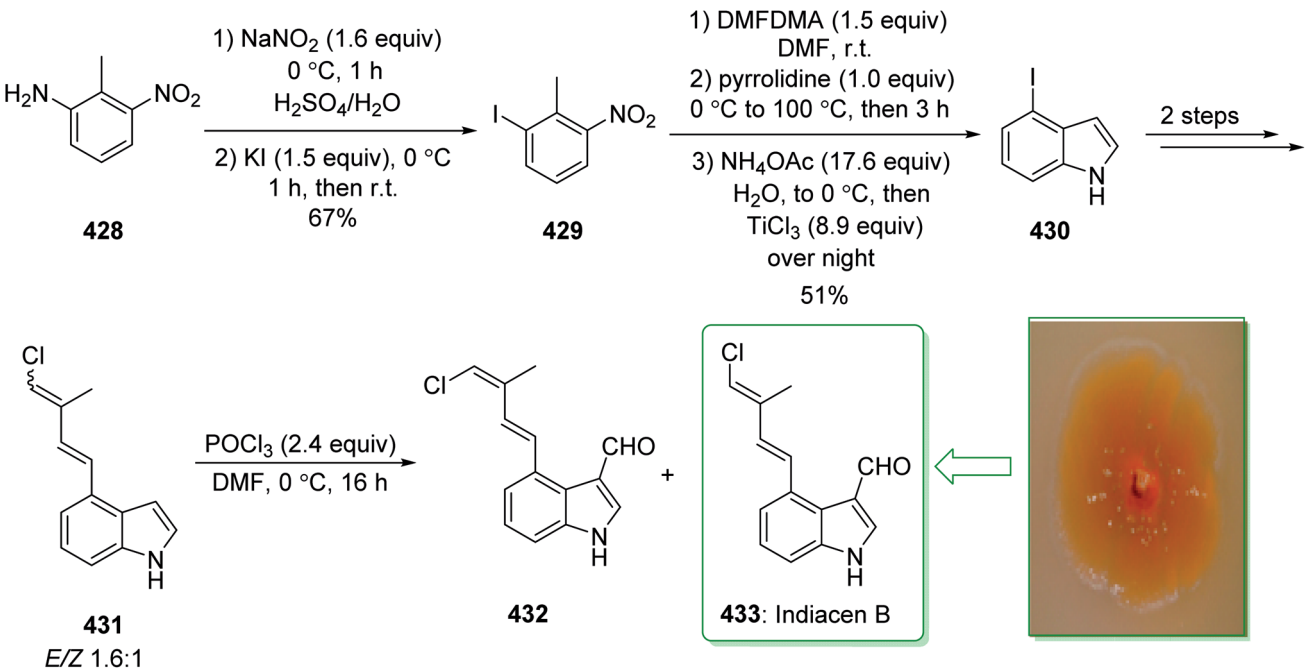
Alkaloids containing β-carboline have been extracted both from marine and terrestrial sources.[349] Haploscleridamine is a unique tryptamine-derived alkaloid[350] extracted from a marine sponge of the order *Haplisclerida* gathered in Palau and was reported in 2002 by Faulkner *et al.*[351] This unique 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[352] 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 tosylamide **420** to reductive detosylation with Mg in MeOH,[353] (−)-haploscleridamine (**421**) was obtained in a satisfactory yield (Scheme 58).[352]

2.6. Batcho–Leimgruber indole formation

In 2013, Buszek and co-workers demonstrated[354] an effective total synthesis of the annulated indole natural product (±)-*cis*-trikentrin B (**427**) by using a regioselectively constructed 6,7-indole aryne cycloaddition 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



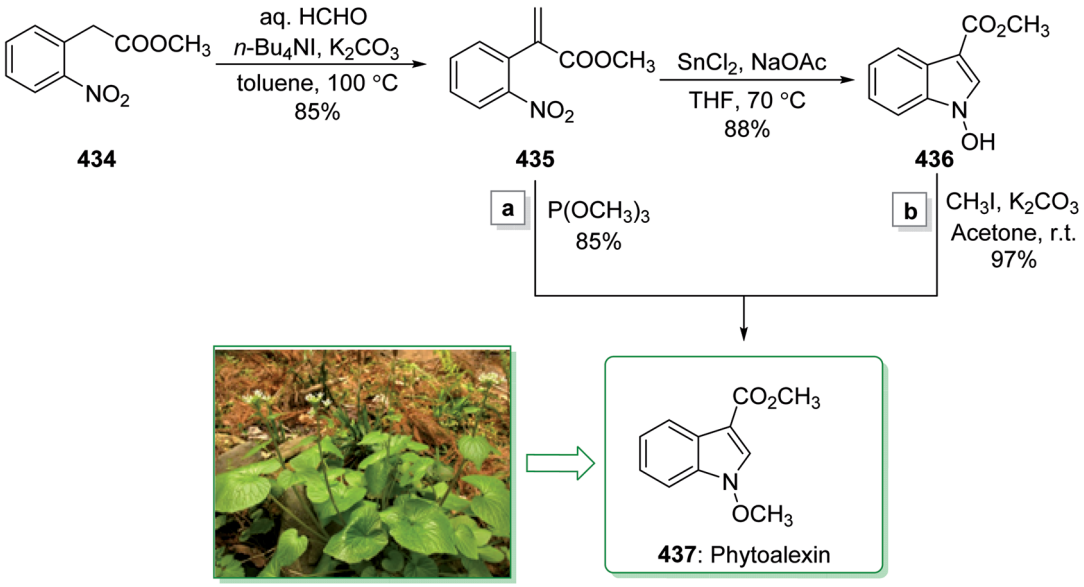
Scheme 59 Total synthesis of (±)-*cis*-trikentrin B (**427**).



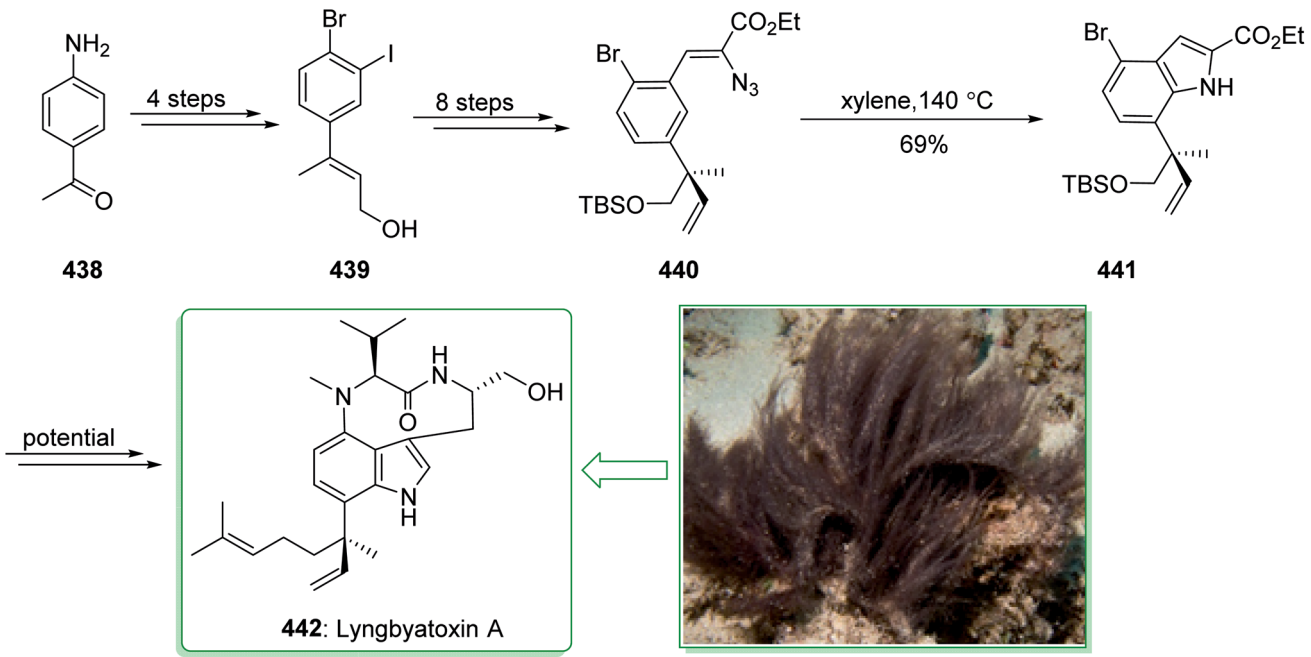
Scheme 60 Total synthesis of indiacen B (**433**).

complete the synthesis. This methodology gives enables the trikentrins 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 $Pd_2(dba)_3$ using MWI easily gave racemic *cis*-trikentrin B (**427**) in a satisfactory yield (73% yield) (Scheme 59).[354]

Indiacen A and B[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,



Scheme 61 Synthesis of phytoalexin (**437**).



Scheme 62 Asymmetric construction of the all-carbon quaternary stereocentre of lyngbyatoxin A (**442**).

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.[356] 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.[357] In 2015, Lindel *et al.* demonstrated[357] that the total synthesis of indiacen B (**433**) began from 2-methyl-3-nitroaniline (**428**), and using sodium nitrite ($NaNO_2$) and potassium iodide (KI) afforded the 1-iodo-2-methyl-3-nitrobenzene **429**. The latter, through the Batcho–Leimgruber method (using dimethylformamide dimethyl acetal (DMFDMA) 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 $POCl_3$ in DMF at 0 °C) (Scheme 60).[357]

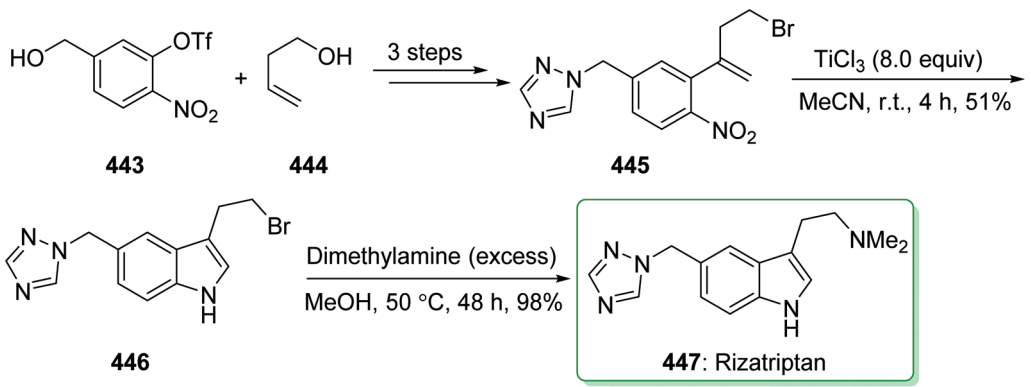
2.7. Cadogan–Sundberg and $SnCl_2$-mediated reductive cyclization

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 phytoalexins[358] or the crucifer wasabi phytoalexins.[359] These phytoalexins have been extracted from cruciferous plants, comprising cabbage, broccoli, mustard, cauliflower and wasabi (*Wasabia japonica*, *syn*. *Eutrema wasabi*).[360,361] The initial wasabi phytoalexin, methyl 1-methoxyindole-3-carboxylate (**437**), was extracted, identified, and manufactured by Soledade *et al.*[362] 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**).[363] 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-Bu_4NI) and K_2CO_3 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,[364] for instance, using trimethylphosphite ($P(OCH_3)_3$) instead of triethylphosphite ($P(OEt)_3$).

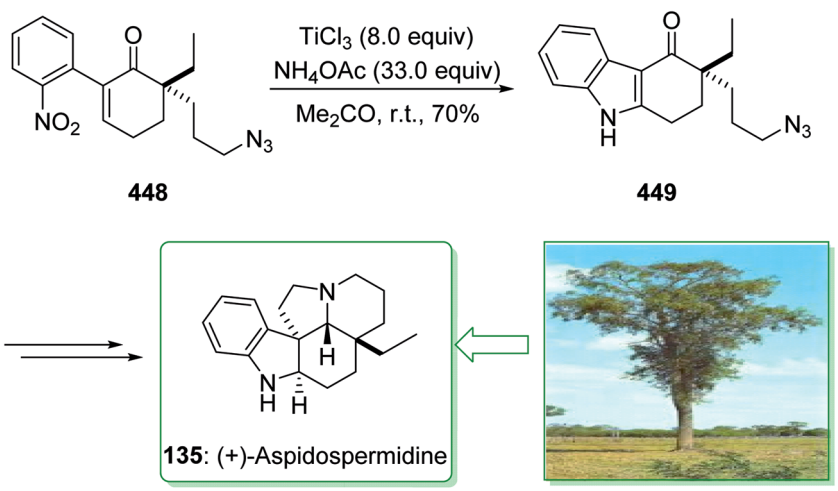
In the second route for the synthesis of **437**, acrylate **435** was used. The reaction of **435** in the presence of $SnCl_2$ and NaOAc in THF provided methyl 1-hydroxyindole-3-carboxylate (**436**) in a good yield (88%). Finally, the methylation reaction of compound **436** using MeI afforded phytoalexin (**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).[363]

2.8. Hemetsberger–Knittel reaction

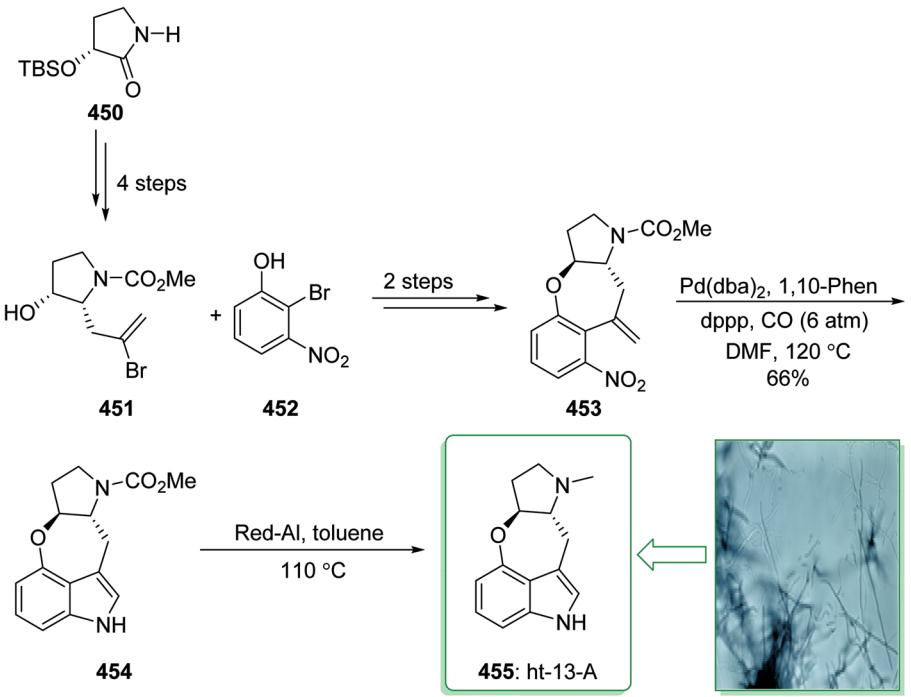
Lyngbyatoxin A (**442**) was extracted in 1979 by Moore *et al.* from the lipid extract of sea weed.[365] Lyngbyatoxin A (**442**) is an effective tumor promoter[366] and similar to other indolactam alkaloids, applies its biological properties *via* the activation of the protein kinase C (PKC). In 2006, Tanner and Vital demonstrated[367] 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**).

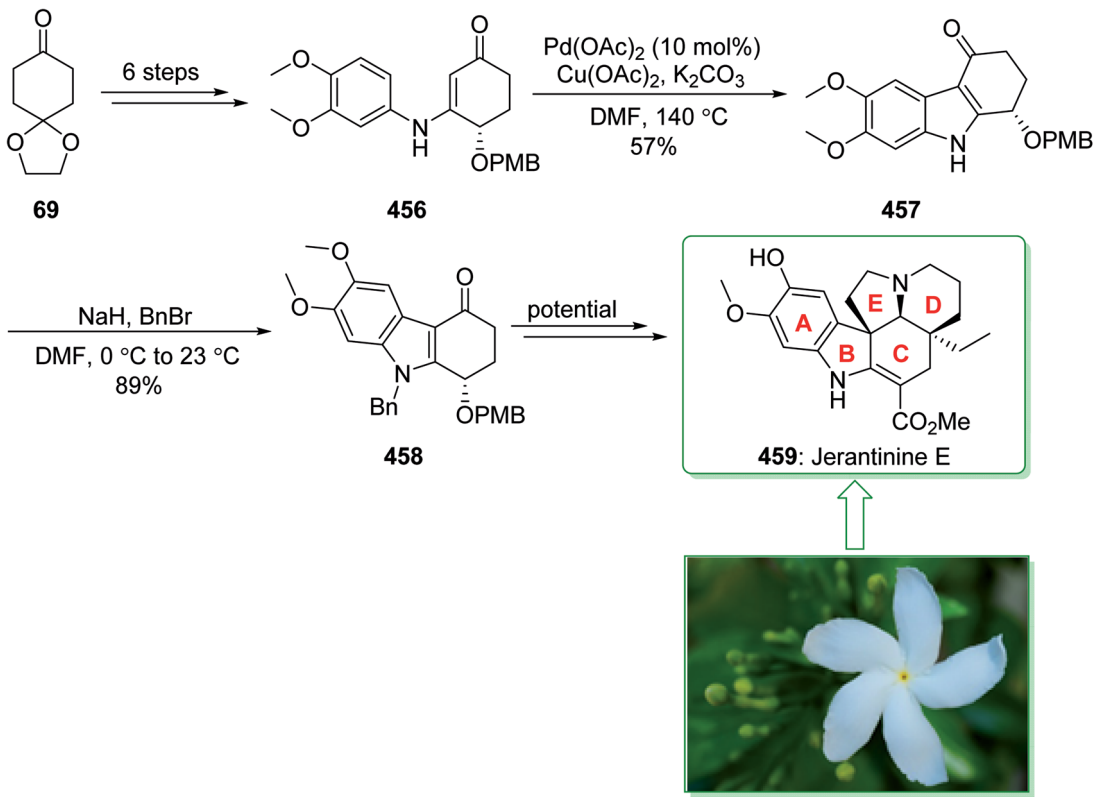


Scheme 64 Formal synthesis of (+)-aspidospermidine (**135**).

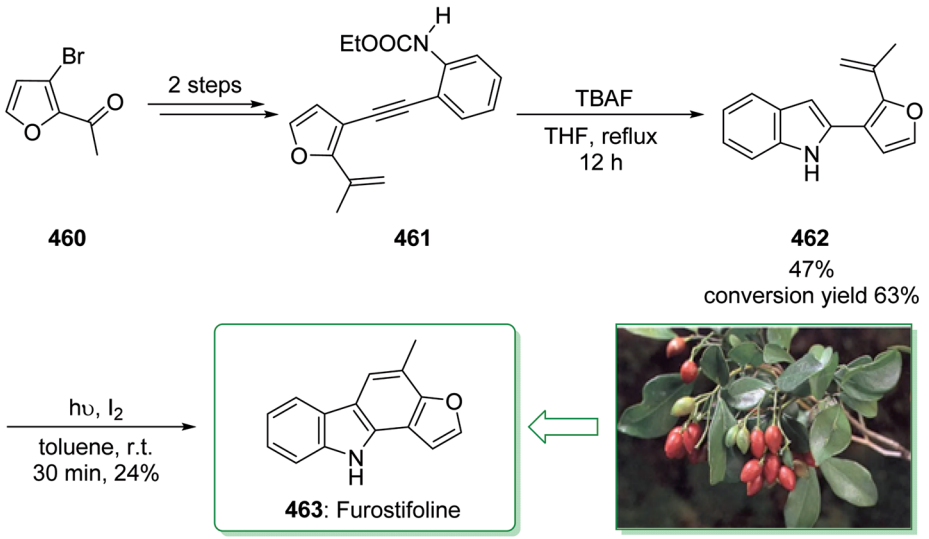


Scheme 65 Total synthesis of the tetracyclic indole alkaloid ht-13-A (**455**).

lyngbyatoxin A (**442**) started with the allylic alcohol **439** (prepared from *p*-aminoacetophenone **438** in four steps), which after eight steps gave azide **440**.[368] 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 66 Synthetic studies towards jerantinine E (**459**).



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

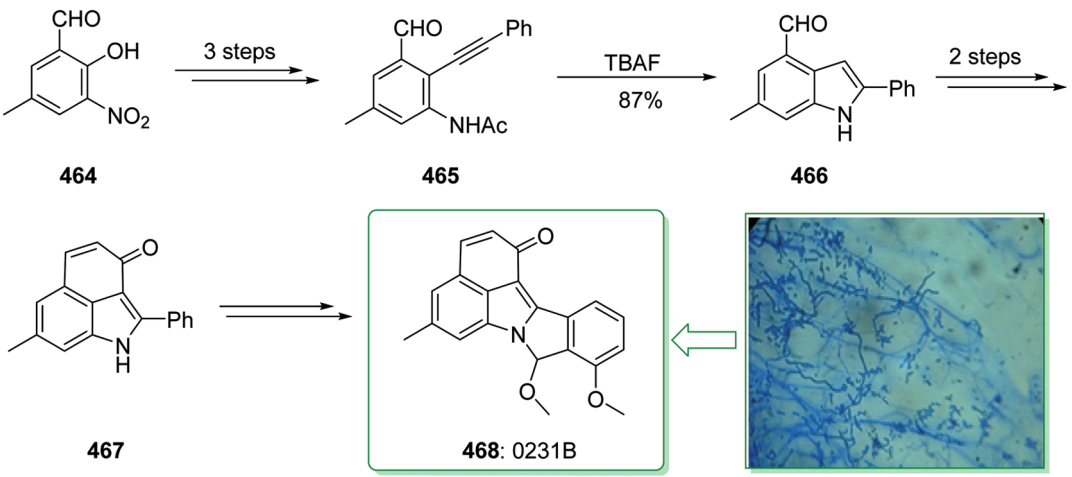
lyngbyatoxin A: the C-3 indolic position is essentially nucleophilic, and the bromine at C-4 gives an appropriate handle for insertion of the amino group; moreover, the TBDMS-masked alcohol scaffold permits the formation of the linalyl appendage (Scheme 62).[367]

3. Miscellaneous

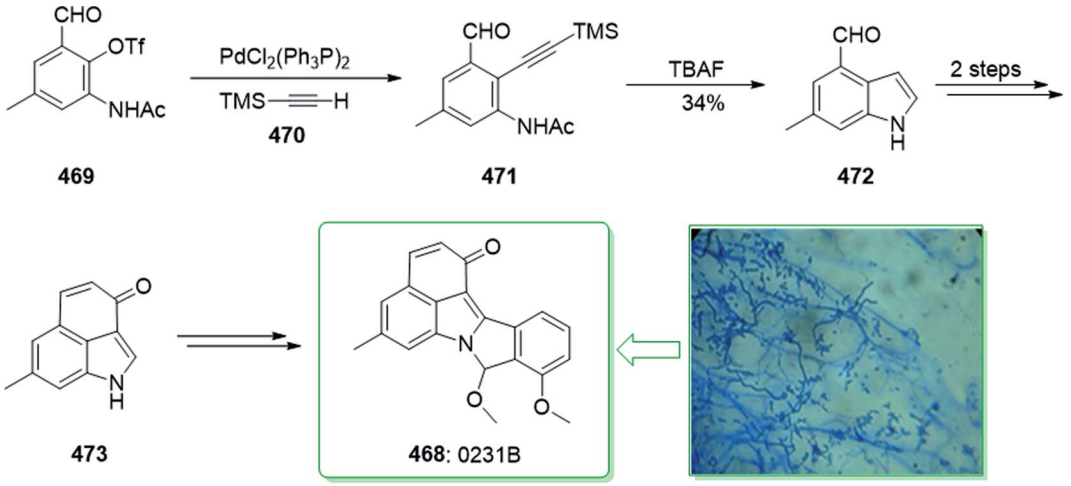
Rizatriptan, an active selective 5-HT 1B/1D receptor agonist, has been proven to be clinically valuable for the treatment of migraines.[369] Rizatriptan selectively limits isolated human middle meningeal arteries and prevents neurogenic dural extravasation and also vasodilatation.[370] In 2015, Zhu *et al.* achieved and reported[371] 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(sp^2)–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).[371]

The formal total synthesis of (+)-aspidospermidine (**135**) began with ketone **448**. A solution of compound **448** in acetone-ammonium acetate with titanium(III) chloride was stirred at room temperature to give tetrahydrocarbazolone **449** in a satisfactory yield (70% yield). The latter was then transformed into (+)-aspidospermidine (**135**)[372] (Scheme 64).[371]

Tetracyclic indole alkaloids were extracted from a genus of the bacteria *Streptomyces* sp. (PA-48561) by Yasui and Kamiguchi in 2000.[373] In 2016, Söderberg. *et al.* reported[374] the total



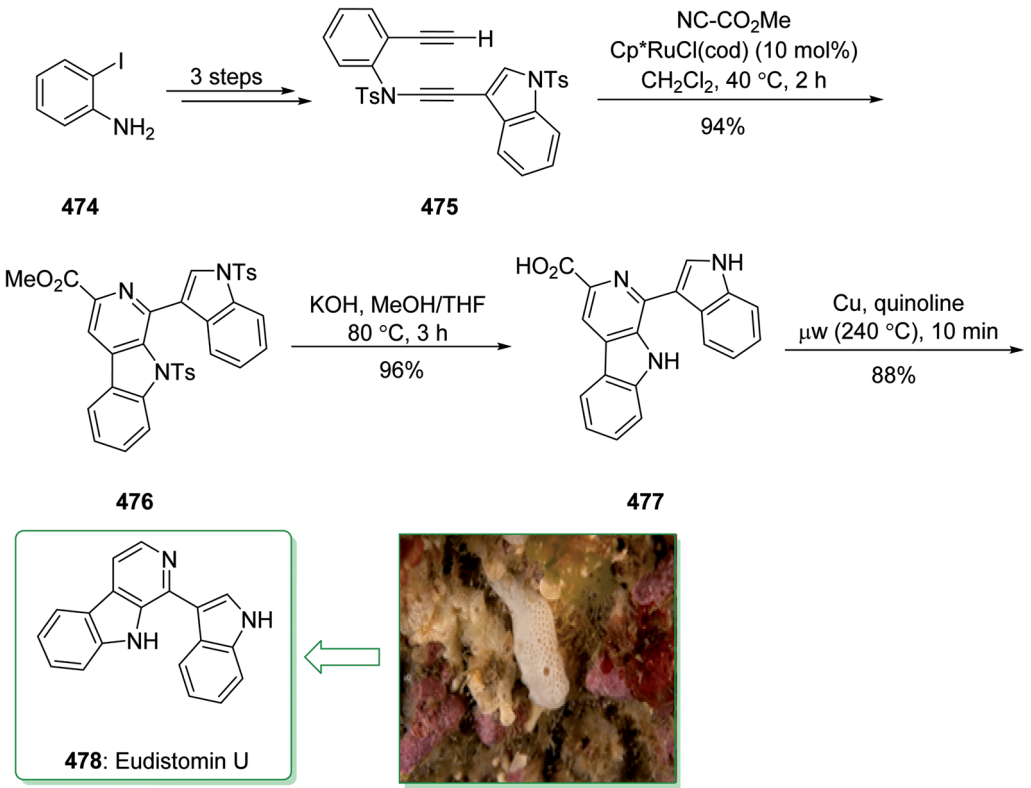
Scheme 68 Formal synthesis of 0231B (**468**).



Scheme 69 Formal synthesis of 0231B (**468**).

synthesis of the tetracyclic indole alkaloid ht-13-A (**455**) from 3(*R*)-*t*-butyldimethylsilyloxypyrrolidin-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*-butyldimethylsilyloxypyrrolidin-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]

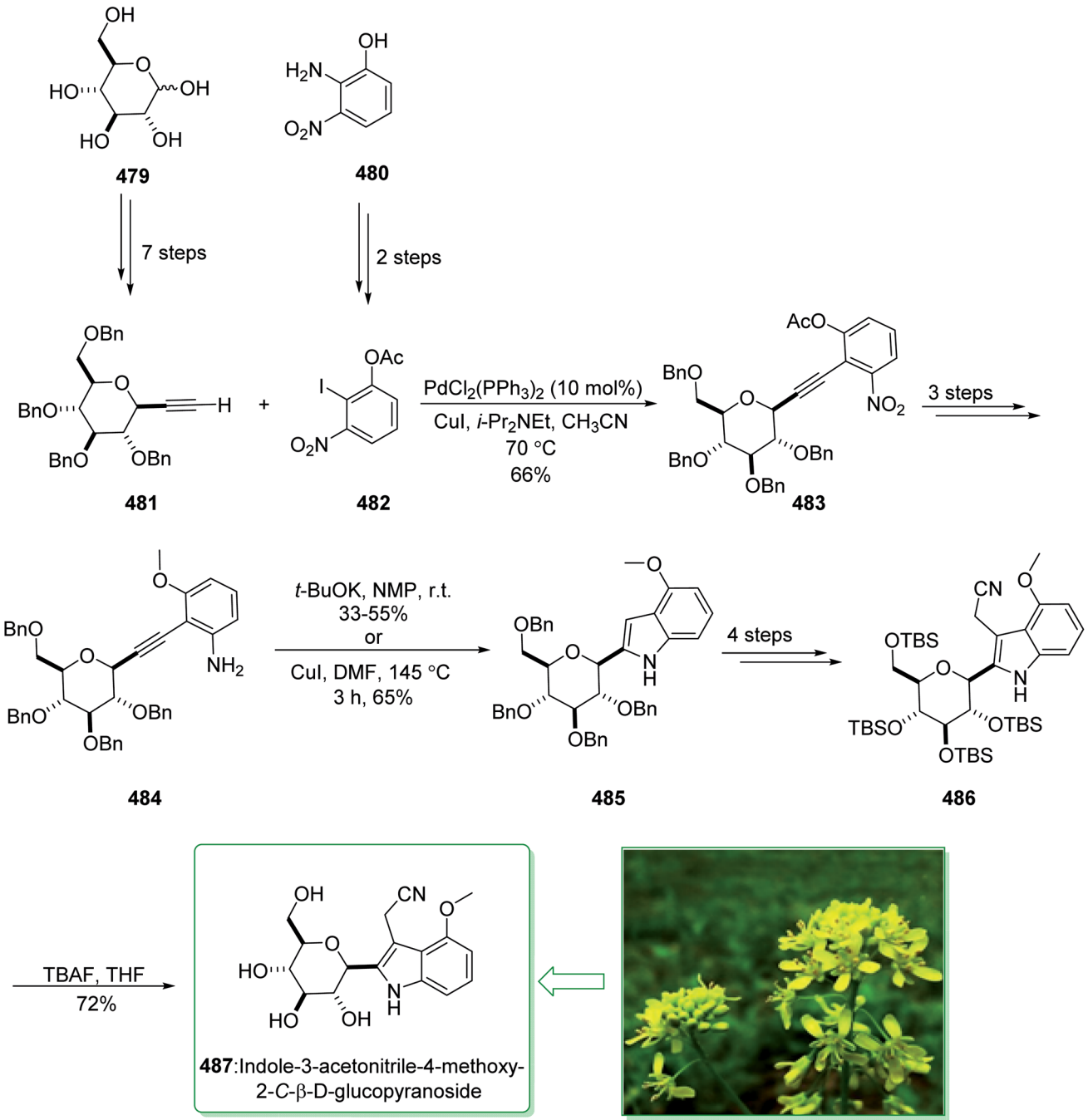
Kam *et al.* in 2008 reported[375] the extraction of seven indole alkaloids, jerantinines A–G of the *Aspidosperma* type from an examination of the leaf extract of a similar species.[376] The jerantinines exhibited a noteworthy cytotoxicity against human KB



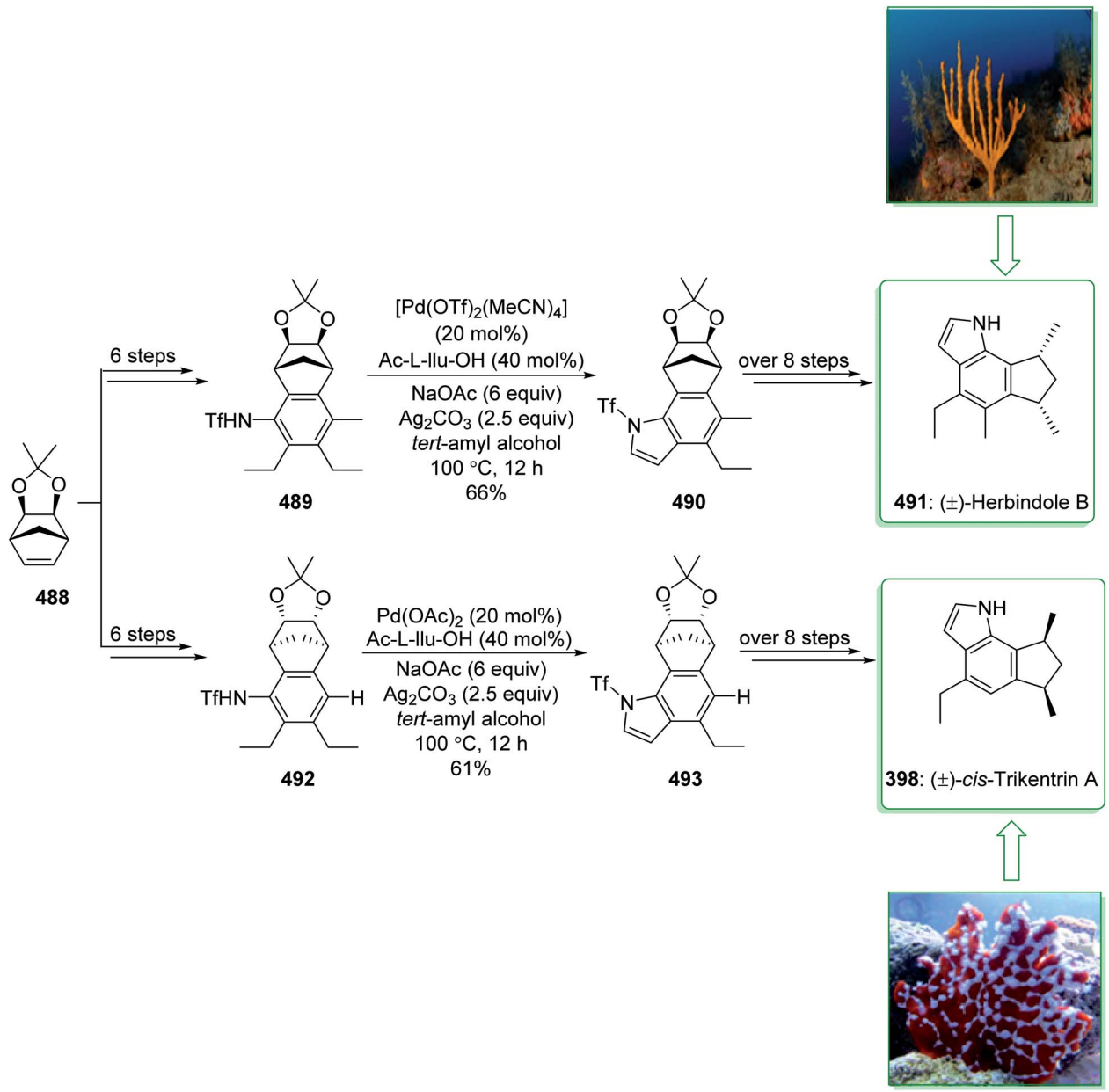
Scheme 70 Total synthesis of eudistomin U (**478**).

cells.[377] In 2017, Magauer *et al.* demonstrated[378] 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-cyclohexanedione monoethyleneacetal (**69**), which after six steps gave cyclohex-2-en-1-one **456**. The latter, through oxidative indole construction[379] 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).[378]

Furostifoline (**463**), the furo[3,2-*a*]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.[381] The first total synthesis of furostifoline (**463**) was reported in 1996 (ref. 382) and the optimum synthetic



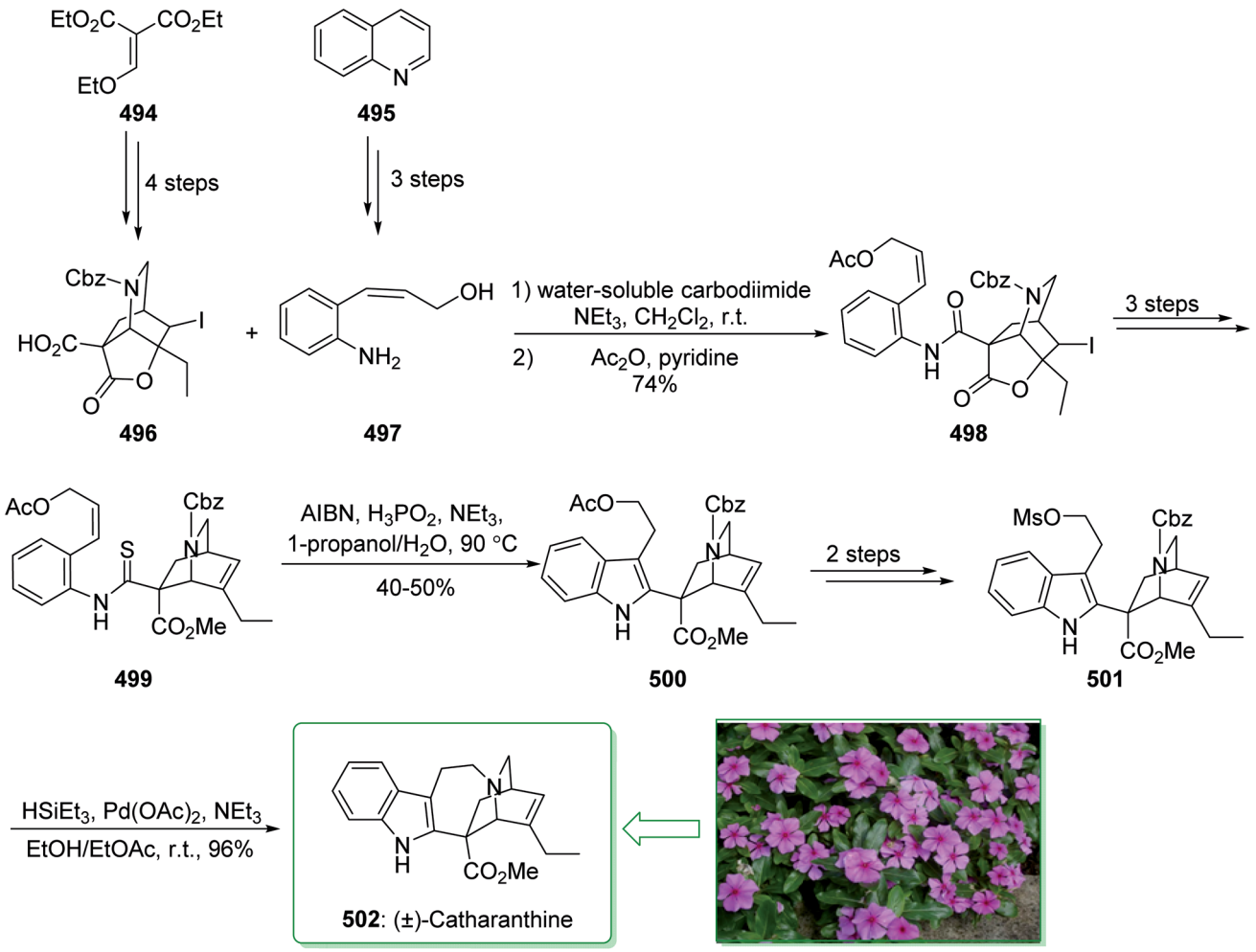
Scheme 71 Total synthesis of indole-3-acetonitrile-4-methoxy-2-*C*-β-D-glucopyranoside (**487**).



Scheme 72 Formal synthesis of (±)-herbindole B (**491**) and (±)-*cis*-trikentrin A (**398**).

route to furostifoline (**463**) was reported in 2000 by Knölker and Fröhner.[383] Furostifoline is a carbazole alkaloid having a furo [3,2-*a*]carbazole building block.[384,385] In 2002, Yasuhara *et al.* demonstrated[386] 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).[386]

The inhibitors of 3α-hydroxysteroid dehydrogenase, 0231A and 0231B, were extracted in 2001 by Gräafe from a fermentation broth of *Streptomyces* sp. HKI0231. Meanwhile 3α-hydroxysteroid dehydrogenase is an enzyme related to inflammatory processes, these compounds are favorable as main structures for anti-inflammatory agents.[387] 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.[388] The formal synthesis of 0231B (**468**) was commenced from 2-hydroxy-5-methyl-3-nitrobenzaldehyde (**464**) and after three



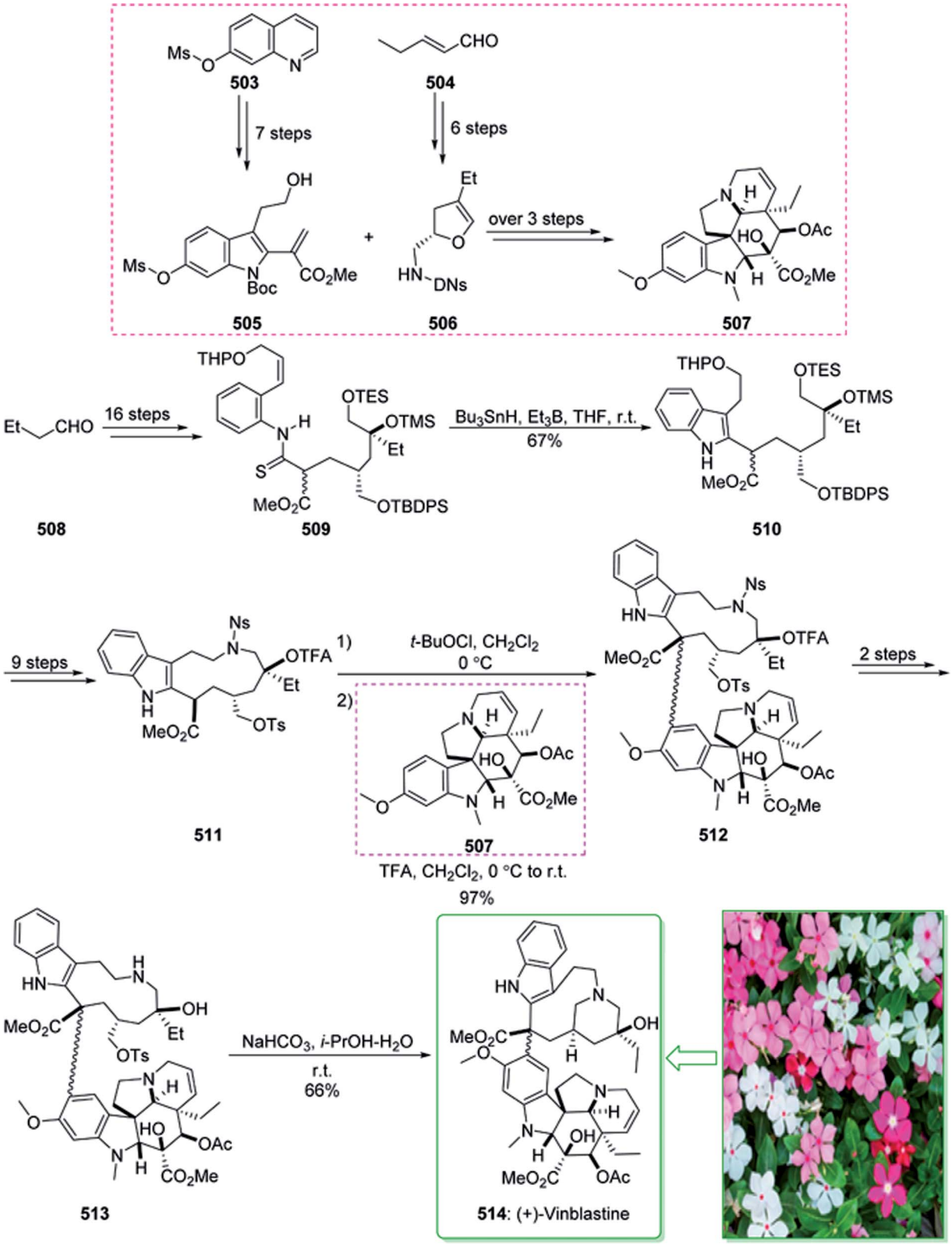
Scheme 73 Total synthesis of (±)-catharanthine (**502**).

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] cycloaddition reactions of substituted yne-ynamides and methylcyanoformate 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] cycloaddition of **475** using methylcyanoformate led to the β-carboline ester **476** (94% yield), which was saponificated using *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,[400] and there is also sufficient experimental proof that *C*-aryl glycosides bind duplex DNA.[401] Two alkaloids extracted from the roots of the plant *Isatis indigotica* contain an



Scheme 74 Total synthesis of (+)-vinblastine (514).

indole-*C*-glycoside unit.[402] Indole-3-acetonitrile-4-methoxy-2-*C*-β-D-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[403] that indole-3-acetonitrile-4-methoxy-2-*C*-β-D-glucopyranoside (**487**), a unique *C*-glycoside from *Isatis indigotica* that has significant cytotoxic properties, can be synthesized in ten steps from ethynyl-β-*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*-β-D-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 aminolysis, hydroxyl methylation, and reduction, provided aniline **484**. Next, a base-catalyzed indolization reaction was investigated using Knochel's *t*-BuOK-NMP system.[404] 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*-β-D-glucopyranoside (**487**) in satisfactory yields (72%) (Scheme 71).[403]

Dueber *et al.* 2016 demonstrated[405] the formal synthesis of the indole alkaloids (±)-*cis*-trikentrin A (**398**) and (±)-herbindole 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 (±)-herbindole B (**491**) and (±)-*cis*-trikentrin A (**398**) began with the bicyclic alkene **488**, which after six steps afforded aniline triflamide **489** and triflamide (**492**) through two different routes. In the following, aniline 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 (±)-herbindole B[406] (**491**).[405]

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*-trikentrin A (**398**) was synthesized successfully from indole **493** (Scheme 72).

Catharanthine is a significant member of the *Iboga* class of alkaloids.[407,408] Catharanthine was extracted in 1985 by Raucher and Bray[409] from the leaves of *Catharanthus roseous*.[410,411] *Catharanthus roseus* includes more than 400 valuable alkaloids, for example vinblastine, vincristine, catharanthine, yohimbine, tabersonine, lochnericine, ajmalicine, vindosine, vindoline and vindolicine.[412] Catharanthine has noteworthy biological functions as it has anti-cancer properties.[413] A stereocontrolled total synthesis of (±)-catharanthine (**502**) was accomplished in 1999 by Fukuyama and Reding.[414] 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 ethoxymethylenemalonate **494** in four steps). This reaction yielded anilide iodolactone **498**, which after three steps gave 2-alkenylthioanilide **499**. The cyclization reaction using stoichiometric azobisisobutyronitrile (AIBN), excess aqueous hypophosphorous acid (H_3PO_2) and Et_3N 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[415] to directly give (±)-catharanthine (**502**) (Scheme 73).[414]

Vinblastine[416] 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*.[417] 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.[418] In 2010, Yokoshima *et al.* reported[419] a stereocontrolled total synthesis of (+)-vinblastine (**514**). The synthesis of the upper half specifies the stereoselective 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 *o*-alkenylthioanilide, 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-mesyloxyquinoline (**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**).[419] On the other hand, the upper unit **511** was synthesized from *n*-butyraldehyde (**508**) and after 16 steps gave the alkenylthioanilides **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 CH_2Cl_2 and reacted with trifluoroacetic acid (CF_3CO_2H) 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 $NaHCO_3$ in isopropyl alcohol (i-PrOH) and H_2O 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. Panwar, 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. Sciabica, P. Diana, A. Lauria, A. Montalbano, A. M. Almerico, G. Dattolo, G. Cirrincione, 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. Attri, 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. Mulholland, 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. Leardini, A. Medici and G. Rosini, *J. Chem. Soc., Perkin Trans. 1*, 1978, 692–696.
22 H. Hemetsberger 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. Y. J. Im and N. K. Garg, in *Heterocycles in Natural Product Synthesis*, 2011, pp. 221–265, DOI: 10.1002/9783527634880.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.

43 S. Cacchi and G. Fabrizi, *Chem. Rev.*, 2011, **111**, PR215–PR283.
44 M. Shiri, *Chem. Rev.*, 2012, **112**, 3508–3549.
45 D. F. Taber and P. K. Tirunahari, *Tetrahedron*, 2011, **67**, 7195.
46 M.-Z. Zhang, Q. Chen and G.-F. Yang, *Eur. J. Med. Chem.*, 2015, **89**, 421–441.
47 H. A. Hamid, A. N. Ramli and M. M. Yusoff, *Front. Pharmacol.*, 2017, **8**, 96.
48 K. Hemalatha, G. Madhumitha and S. M. Roopan, *Chem. Sci. Rev. Lett.*, 2013, **2**, 287–292.
49 B. M. Trost and M. K. Brennan, *Synthesis*, 2009, **2009**, 3003–3025.
50 G. W. Gribble, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1045–1075, DOI: 10.1039/A909834H.
51 M. Inman and C. Moody, *Chem. Sci.*, 2013, **4**, 29–41.
52 F. Wu, P. Kerčmar, C. Zhang and J. Stöckigt, in *The Alkaloids*, ed. H.-J. Knölker, Academic Press, London, 2016, vol. 76, pp. 1–61.
53 G. L. Adams and A. B. Smith III, in *The Alkaloids*, ed. H.-J. Knölker, Academic Press, London, 2016, vol. 76, pp. 171–257.
54 M. Kitajima and H. Takayama, in *The Alkaloids*, ed. H.-J. Knölker, Academic Press, London, 2016, vol. 76, pp. 259–310.
55 M. Pfaffenbach and T. Gaich, in *The Alkaloids*, ed. H.-J. Knölker, Academic Press, London, 2017, vol. 77, pp. 1–84.
56 S. Arai, M. Nakajima and A. Nishida, in *The Alkaloids*, ed. H.-J. Knölker, Academic Press, London, 2017, vol. 78, pp. 167–204.
57 C. Xia and X. Tong, in *Alkaloids Chem. Biol.*, ed. H.-J. Knölker, Academic Press, London, 2018, vol. 79, pp. 139–189.
58 J. D. Mason and S. M. Weinreb, in *The Alkaloids*, ed. H.-J. Knölker, Academic Press, London, 2019, vol. 81, pp. 115–150.
59 M. G. Kalshetti and N. P. Argade, in *The Alkaloids*, ed. H.-J. Knölker, Academic Press, London, 2020, vol. 83, pp. 187–223.
60 S. C. Taylor and S. M. Weinreb, in *The Alkaloids*, ed. H.-J. Knölker, Academic Press, London, 2021, vol. 85, pp. 177–222.
61 N. R. Tasker, P. Wipf, S. C. Taylor and S. M. Weinreb, in *The Alkaloids*, ed. H.-J. Knölker, Academic Press, London, 2021, vol. 85, pp. 1–112.
62 G. W. Gribble, *Pure Appl. Chem.*, 2003, **75**, 1417–1432.
63 S. Agarwal, S. Cammerer, S. Filali, W. Frohner, J. Knoll, M. P. Krahl, K. R. Reddy and H.-J. Knolker, *Curr. Org. Chem.*, 2005, **9**, 1601–1614.
64 G. R. Humphrey and J. T. Kuethe, *Chem. Rev.*, 2006, **106**, 2875–2911.
65 S. Khaghaninejad and M. M. Heravi, *Adv. Heterocycl. Chem.*, 2014, **111**, 95–146.
66 M. M. Heravi and T. Alishiri, *Adv. Heterocycl. Chem.*, 2014, **113**, 1–66.
67 M. M. Heravi and V. F. Vavsari, *Adv. Heterocycl. Chem.*, 2015, **114**, 77–145.
68 M. M. Heravi and V. F. Vavsari, *RSC Adv.*, 2015, **5**, 50890–50912.
69 A. Taheri Kal Koshvandi, M. M. Heravi and T. Momeni, *Appl. Organomet. Chem.*, 2018, **32**, e4210.
70 M. M. Heravi and L. Mohammadkhani, *J. Organomet. Chem.*, 2018, **869**, 106–200.
71 M. M. Heravi, T. B. Lashaki, B. Fattahi and V. Zadsirjan, *RSC Adv.*, 2018, **8**, 6634–6659.
72 M. M. Heravi, V. Zadsirjan and M. Malmir, *Molecules*, 2018, **23**, 943.
73 M. M. Heravi, V. Zadsirjan, K. Kafshdarzadeh and Z. Amiri, *Asian J. Org. Chem.*, 2020, **9**, 1999–2034.
74 M. M. Heravi, S. Rohani, V. Zadsirjan and N. Zahedi, *RSC Adv.*, 2017, **7**, 52852–52887.
75 M. M. Heravi, V. Zadsirjan, H. Hamidi, M. Daraie and T. Momeni, in *The Alkaloids*, ed. H.-J. Knölker, Elsevier, Academic Press, London, 2020, vol. 84, pp. 201–334.
76 L. Wei, Y. Z. Wang and Z. Y. Li, *BMC Plant Biol.*, 2012, **14**, 190–197.
77 S. Syam, A. B. Abdul, M. Sukari, S. Mohan, S. I. Abdelwahab and T. S. Wah, *Molecules*, 2011, **16**, 7155–7170.
78 S. Mohan, S. I. Abdelwahab, S.-C. Cheah, M. A. Sukari, S. Syam, N. Shamsuddin and M. Rais Mustafa, *Evid Based Complement Alternat Med.*, 2013, vol. 2013.
79 K. Das, D. Chakraborty and P. Bose, *Experientia*, 1965, **21**, 340.
80 A. C. Adebajo, G. Olayiwola, J. Eugen Verspohl, E. O. Iwalewa, N. Omisore, D. Bergenthal, V. Kumar and S. Kolawole Adesina, *Pharm. Biol.*, 2005, **42**, 610–620.
81 S. Gupta, M. George, M. Singhal, G. N. Sharma and V. Garg, *J. Adv. Pharm. Technol. Res.*, 2010, **1**, 68.
82 R. S. Ramsewak, M. G. Nair, G. M. Strasburg, D. L. DeWitt and J. L. Nitiss, *J. Agric. Food Chem.*, 1999, **47**, 444–447.
83 D. P. Chakraborty and B. Chowdhury, *J. Org. Chem.*, 1968, **33**, 1265–1268.
84 T. Martin and C. J. Moody, *J. Chem. Soc., Perkin Trans. 1*, 1988, 235–240, DOI: 10.1039/P19880000235.
85 H.-J. Knölker and M. Bauermeister, *J. Chem. Soc., Chem. Commun.*, 1990, 664–665, DOI: 10.1039/C39900000664.
86 H.-J. Knölker and M. Bauermeister, *Tetrahedron*, 1993, **49**, 11221–11236.
87 H.-J. Knölker and M. Wolpert, *Tetrahedron*, 2003, **59**, 5317–5322.
88 P. Bernal and J. Tamariz, *Helv. Chim. Acta*, 2007, **90**, 1449–1454.
89 C. Börger, O. Kataeva and H.-J. Knölker, *Org. Biomol. Chem.*, 2012, **10**, 7269–7273.
90 H. Knölker and K. R. Reddy, in *The Alkaloids*, ed. G. A. Cordell, Academic Press, Amsterdam, 2008, vol. 65, pp. 1–430.
91 H.-J. Knölker and K. R. Reddy, *Chem. Rev.*, 2002, **102**, 4303–4428.
92 H.-J. Knolker, *Curr. Org. Synth.*, 2004, **1**, 309–331.
93 I. Bauer and H.-J. Knölker, *Top. Curr. Chem.*, 2012, **309**, 203–253.
94 A. W. Schmidt, K. R. Reddy and H.-J. Knölker, *Chem. Rev.*, 2012, **112**, 3193–3328.

95 S. Ray and D. Chakraborty, *Phytochemistry*, 1976, **15**, 356.
96 D. Chakraborty and K. Das, *Chem. Commun.*, 1968, 967.
97 D. P. Chakraborty, A. Islam and P. Bhattacharyya, *J. Org. Chem.*, 1973, **38**, 2728–2729.
98 H.-J. Knölker and C. Hofmann, *Tetrahedron Lett.*, 1996, **37**, 7947–7950.
99 K. K. Gruner, T. Hopfmann, K. Matsumoto, A. Jäger, T. Katsuki and H.-J. Knölker, *Org. Biomol. Chem.*, 2011, **9**, 2057–2061.
100 R. Hesse, K. K. Gruner, O. Kataeva, A. W. Schmidt and H. J. Knölker, *Chem.–Eur. J.*, 2013, **19**, 14098–14111.
101 W.-F. Chiou, C.-J. Chou, J.-F. Liao, A. Y.-C. Sham and C.-F. Chen, *Eur. J. Pharmacol.*, 1994, **257**, 59–66.
102 J.-F. Liao, W.-F. Chiou, Y.-C. Shen, G.-J. Wang and C.-F. Chen, *Chin. Med.*, 2011, **6**, 1–8.
103 S. Johne, D. Gröger and M. Hesse, *Helv. Chim. Acta*, 1971, **54**, 826–834.
104 A. Amin, D. Mehta and S. Samarth, *Prog. Drug Res.*, 1970, 218–268.
105 N. Shoji, A. Umeyama, T. Takemoto, A. Kajiwara and Y. Ohizumi, *J. Pharm. Sci.*, 1986, **75**, 612–613.
106 J. Kökösi, G. Szász and I. Hermecz, *Tetrahedron Lett.*, 1992, **33**, 2995–2998.
107 T. Kametani, T. Higa, C. Van Loc, M. Ihara, M. Koizumi and K. Fukumoto, *J. Am. Chem. Soc.*, 1976, **98**, 6186–6188.
108 T. Kametani, C. Van Loc, T. Higa, M. Koizumi, M. Ihara and K. Fukumoto, *J. Am. Chem. Soc.*, 1977, **99**, 2306–2309.
109 C. Kaneko, T. Chiba, K. Kasai and C. Miwa, *Heterocycles*, 1985, **23**, 1385–1390.
110 T. F. Molinski, *Chem. Rev.*, 1993, **93**, 1825–1838.
111 N. B. Perry, J. W. Blunt, M. H. G. Munro, T. Higa and R. Sakai, *J. Org. Chem.*, 1988, **53**, 4127–4128.
112 J. F. Cheng, Y. Ohizumi, M. R. Walchli, H. Nakamura, Y. Hirata, T. Sasaki and J. Kobayashi, *J. Org. Chem.*, 1988, **53**, 4621–4624.
113 S. Sakemi, H. H. Sun, C. W. Jefford and G. Bernardinelli, *Tetrahedron Lett.*, 1989, **30**, 2517–2520.
114 D. B. Stierle and D. J. Faulkner, *J. Nat. Prod.*, 1991, **54**, 1131–1133.
115 B. R. Copp, C. M. Ireland and L. R. Barrows, *J. Org. Chem.*, 1991, **56**, 4596–4597.
116 D. C. Radisky, E. S. Radisky, L. R. Barrows, B. R. Copp, R. A. Kramer and C. M. Ireland, *J. Am. Chem. Soc.*, 1993, **115**, 1632–1638.
117 J. D. White, K. M. Yager and T. Yakura, *J. Am. Chem. Soc.*, 1994, **116**, 1831–1838.
118 B. Mckittrick, A. Failli, R. J. Steffan, R. M. Soll, P. Hughes, J. Schmid, A. A. Asselin, C. Shaw, R. Noureldin and G. Gavin, *J. Heterocycl. Chem.*, 1990, **27**, 2151–2163.
119 C.-B. Cui, H. Kakeya, G. Okada, R. Onose, M. Ubukata, I. Takahashi, K. Isono and H. Osada, *J. Antibiot.*, 1995, **48**, 1382–1384.
120 T. Usui, M. Kondoh, C.-B. Cui, T. Mayumi and H. Osada, *Biochem. J.*, 1998, **333**, 543–548.
121 A. S. P. Cardoso, M. M. B. Marques, N. Srinivasan, S. Prabhakar, A. M. Lobo and H. S. Rzepa, *Org. Biomol. Chem.*, 2006, **4**, 3966–3972.
122 S. Zhao, K. S. Smith, A. M. Deveau, C. M. Dieckhaus, M. A. Johnson, T. L. Macdonald and J. M. Cook, *J. Med. Chem.*, 2002, **45**, 1559–1562.
123 T. Gan, R. Liu, P. Yu, S. Zhao and J. M. Cook, *J. Org. Chem.*, 1997, **62**, 9298–9304.
124 M. S. Allen, L. K. Hamaker, A. J. La Loggia and J. M. Cook, *Synth. Commun.*, 1992, **22**, 2077–2102.
125 S. Takano and K. Ogasawara, *Alkaloids*, 1990, **36**, 225–251.
126 D. J. Triggle and R. Filler, *CNS Drug Rev.*, 1998, **4**, 87–136.
127 U. Anthoni, C. Christophersen and P. Nielsen, *Alkaloids: Chemical and Biological Perspectives*, Wiley, New York, 1999.
128 B. Robinson, *J. Chem. Soc.*, 1964, 1503–1506, DOI: 10.1039/JR9640001503.
129 F. J. Dale and B. Robinson, *J. Pharm. Pharmacol.*, 1970, **22**, 889–896.
130 A. W. Schammel, B. W. Boal, L. Zu, T. Mesganaw and N. K. Garg, *Tetrahedron*, 2010, **66**, 4687–4695.
131 T. Matsuura, L. E. Overman and D. J. Poon, *J. Am. Chem. Soc.*, 1998, **120**, 6500–6503.
132 N. Khoukhi, M. Vaultier and R. Carrie, *Tetrahedron*, 1987, **43**, 1811–1822.
133 A. V. Dix, C. M. Meseck, A. J. Lowe and M. O. Mitchell, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 2522–2524.
134 P. A. Cockrum, S. M. Colegate, J. A. Edgar, K. Flower, D. Gardner and R. I. Willing, *Phytochemistry*, 1999, **51**, 153–157.
135 C. Li, C. Chan, A. C. Heimann and S. J. Danishefsky, *Angew. Chem., Int. Ed.*, 2007, **46**, 1444–1447.
136 J. D. Trzupek, C. Li, C. Chan, B. M. Crowley, A. C. Heimann and S. J. Danishefsky, *Pure Appl. Chem.*, 2010, **82**, 1735–1748.
137 J. D. Trzupek, D. Lee, B. M. Crowley, V. M. Marathias and S. J. Danishefsky, *J. Am. Chem. Soc.*, 2010, **132**, 8506–8512.
138 H. Ding and D. Y. K. Chen, *Angew. Chem., Int. Ed.*, 2011, **123**, 702–705.
139 R. Fröde, C. Hinze, I. Josten, B. Schmidt, B. Steffan and W. Steglich, *Tetrahedron Lett.*, 1994, **35**, 1689–1690.
140 T. Hashimoto, Y. Akiyo, K. Akazawa, S. Takaoka, M. Tori and Y. Asakawa, *Tetrahedron Lett.*, 1994, **35**, 2559–2560.
141 C. Sánchez, A. F. Braña, C. Méndez and J. A. Salas, *ChemBioChem*, 2006, **7**, 1231–1240.
142 T. Nishizawa, S. Grüschow, D.-H. E. Jayamaha, C. Nishizawa-Harada and D. H. Sherman, *J. Am. Chem. Soc.*, 2006, **128**, 724–725.
143 A. R. Howard-Jones and C. T. Walsh, *J. Am. Chem. Soc.*, 2006, **128**, 12289–12298.
144 N. Zhou, Q. Shi and Z. Xie, *Chin. J. Org. Chem.*, 2014, **34**, 1104–1109.
145 G. Massiot, P. Thépenier, M.-J. Jacquier, L. Le Men-Olivier and C. Delaude, *Heterocycles*, 1989, **29**, 1435–1438.
146 A. Ramírez and S. García-Rubio, *Curr. Med. Chem.*, 2003, **10**, 1891–1915.
147 P. Liu, J. Wang, J. Zhang and F. G. Qiu, *Org. Lett.*, 2011, **13**, 6426–6428.
148 M. E. Krafft and J. W. Cran, *Synlett*, 2005, **2005**, 1263–1266.

149 G. Subramaniam, O. Hiraku, M. Hayashi, T. Koyano, K. Komiyama and T.-S. Kam, *J. Nat. Prod.*, 2007, **70**, 1783–1789.
150 L. Zu, B. W. Boal and N. K. Garg, *J. Am. Chem. Soc.*, 2011, **133**, 8877–8879.
151 C. Herdeis and C. Hartke, *Heterocycles*, 1989, **29**, 287–296.
152 G. L. Adams and A. B. Smith III, *The chemistry of the akuammiline alkaloids*, Academic Press, London, 2016.
153 X.-H. Cai, Q.-G. Tan, Y.-P. Liu, T. Feng, Z.-Z. Du, W.-Q. Li and X.-D. Luo, *Org. Lett.*, 2008, **10**, 577–580.
154 P. Kamarajan, N. Sekar, V. Mathuram and S. Govindasamy, *Biochem. Int.*, 1991, **25**, 491–498.
155 X.-H. Cai, Z.-Z. Du and X.-D. Luo, *Org. Lett.*, 2007, **9**, 1817–1820.
156 G. L. Adams, P. J. Carroll and A. B. Smith III, *J. Am. Chem. Soc.*, 2012, **134**, 4037–4040.
157 G. L. Adams, P. J. Carroll and A. B. Smith III, *J. Am. Chem. Soc.*, 2013, **135**, 519–528.
158 P. Müller and D. M. Gilabert, *Tetrahedron*, 1988, **44**, 7171–7175.
159 Z. Zuo and D. Ma, *Isr. J. Chem.*, 2011, **51**, 434–441.
160 D. Zhang, H. Song and Y. Qin, *Acc. Chem. Res.*, 2011, **44**, 447–457.
161 S. M. Verbitski, C. L. Mayne, R. A. Davis, G. P. Concepcion and C. M. Ireland, *J. Org. Chem.*, 2002, **67**, 7124–7126.
162 A. Numata, C. Takahashi, Y. Ito, T. Takada, K. Kawai, Y. Usami, E. Matsumura, M. Imachi, T. Ito and T. Hasegawa, *Tetrahedron Lett.*, 1993, **34**, 2355–2358.
163 A. W. Schammel, G. Chiou and N. K. Garg, *Org. Lett.*, 2012, **14**, 4556–4559.
164 K. Warabi, S. Matsunaga, R. W. van Soest and N. Fusetani, *J. Org. Chem.*, 2003, **68**, 2765–2770.
165 F. Lavelle, J.-F. Riou, A. Laoui and P. Mailliet, *Crit. Rev. Oncol. Hematol.*, 2000, **34**, 111–126.
166 S. M. Gowan, J. R. Harrison, L. Patterson, M. Valenti, S. Neidle and L. R. Kelland, *Mol. Pharmacol.*, 2002, **61**, 1154–1162.
167 P. Tao, J. Liang and Y. Jia, *Eur. J. Org. Chem.*, 2014, **2014**, 5735–5748.
168 H. Tokuyama, *J. Synth. Org. Chem., Jpn.*, 2015, **73**, 1120–1129.
169 T. J. Hagen, K. Narayanan, J. Names and J. M. Cook, *J. Org. Chem.*, 1989, **54**, 2170–2178.
170 T. Janosik, N. Wahlström and J. Bergman, *Tetrahedron*, 2008, **39**, 9159–9180.
171 M. Prudhomme, *Eur. J. Med. Chem.*, 2003, **38**, 123–140.
172 D.-Q. Liu, S.-C. Mao, H.-Y. Zhang, X.-Q. Yu, M.-T. Feng, B. Wang, L.-H. Feng and Y.-W. Guo, *Fitoterapia*, 2013, **91**, 15–20.
173 K. M. Meragelman, L. M. West, P. T. Northcote, L. K. Pannell, T. C. McKee and M. R. Boyd, *J. Org. Chem.*, 2002, **67**, 6671–6677.
174 F. Russell, D. Harmody, P. J. McCarthy, S. A. Pomponi and A. E. Wright, *J. Nat. Prod.*, 2013, **76**, 1989–1992.
175 S. Kotha, M. Saifuddin and V. R. Aswar, *Org. Biomol. Chem.*, 2016, **14**, 9868–9873.
176 D. Zhao, Z. Shi and F. Glorius, *Angew. Chem., Int. Ed.*, 2013, **52**, 12426–12429.
177 X.-W. Yang, X.-D. Luo, P. K. Lunga, Y.-L. Zhao, X.-J. Qin, Y.-Y. Chen, L. Liu, X.-N. Li and Y.-P. Liu, *Tetrahedron*, 2015, **71**, 3694–3698.
178 X.-W. Yang, X.-J. Qin, Y.-L. Zhao, P. K. Lunga, X.-N. Li, S.-Z. Jiang, G.-G. Cheng, Y.-P. Liu and X.-D. Luo, *Tetrahedron Lett.*, 2014, **55**, 4593–4596.
179 D. Wang, M. Hou, Y. Ji and S. Gao, *Org. Lett.*, 2017, **19**, 1922–1925.
180 R. Lyon, H. Fong, N. Farnsworth and G. Svoboda, *J. Pharm. Sci.*, 1973, **62**, 218–221.
181 N. Wang, S. Du, D. Li and X. Jiang, *Org. Lett.*, 2017, **19**, 3167–3170.
182 G. Stork and J. E. Dolfini, *J. Am. Chem. Soc.*, 1963, **85**, 2872–2873.
183 I. Coldham, A. J. Burrell, L. E. White, H. Adams and N. Oram, *Angew. Chem., Int. Ed.*, 2007, **46**, 6159–6162.
184 L. Randriambola, J.-C. Quirion, C. Kan-Fan and H.-P. Husson, *Tetrahedron Lett.*, 1987, **28**, 2123–2126.
185 B. P. Pritchett, J. Kikuchi, Y. Numajiri and B. M. Stoltz, *Heterocycles*, 2017, **95**, 1245.
186 H.-J. Knolker, *Curr. Org. Chem.*, 2004, **1**, 309–331.
187 T.-S. Wu, S.-C. Huang and P.-L. Wu, *Phytochemistry*, 1996, **43**, 1427–1429.
188 S.-C. Huang, P.-L. Wu and T.-S. Wu, *Phytochemistry*, 1997, **44**, 179–181.
189 I. A. Arbab, A. B. Abdul, M. Aspollah, S. I. Abdelwahab, M. Y. Ibrahim and Z. Ali, *J. Med. Plants Res.*, 2012, **6**, 5107–5118.
190 A. Chakraborty, B. Chowdhury, S. Jash, G. Biswas, S. Bhattacharyya and P. Bhattacharyya, *Phytochemistry*, 1992, **31**, 2503–2505.
191 U. Songsiang, T. Thongthoom, C. Boonyarat and C. Yenjai, *J. Nat. Prod.*, 2011, **74**, 208–212.
192 A. Chakraborty, C. Saha, G. Podder, B. Chowdhury and P. Bhattacharyya, *Phytochemistry*, 1995, **38**, 787–789.
193 R. Bautista, A. Benavides, H. A. Jiménez-Vázquez and J. Tamariz, *Nat. Prod. Res.*, 2013, **27**, 1749–1756.
194 M. S. Naykode, S. D. Tambe and P. D. Lokhande, *ChemistrySelect*, 2017, **2**, 567–570.
195 Y. Yang, T. J. L. Mustard, P. H.-Y. Cheong and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2013, **52**, 14098–14102.
196 M. P. Krahl, A. Jäger, T. Krause and H.-J. Knölker, *Org. Biomol. Chem.*, 2006, **4**, 3215–3219.
197 M. Fuchsenberger, R. Forke and H.-J. Knölker, *Synlett*, 2011, **22**, 2056–2058.
198 C. Schuster, C. Börger, K. K. Julich-Gruner, R. Hesse, A. Jäger, G. Kaufmann, A. W. Schmidt and H. J. Knölker, *Eur. J. Org. Chem.*, 2014, **2014**, 4741–4752.
199 A. Kishonti, A. Jäger and H. J. Knölker, *Eur. J. Org. Chem.*, 2020, **2020**, 5572–5579.
200 H. Schnoes, K. Biemann, J. Mokry, I. Kompis, A. Chatterjee and G. Ganguli, *J. Org. Chem.*, 1966, **31**, 1641–1642.
201 S.-H. Lim, Y.-Y. Low, S. K. Sinniah, K.-T. Yong, K.-S. Sim and T.-S. Kam, *Phytochemistry*, 2014, **98**, 204–215.

202 Y. Ahmad, K. Fatima, J. L. Occolowitz, B. A. Solheim, J. Clardy, R. L. Garnick and P. W. Le Quesne, *J. Am. Chem. Soc.*, 1977, **99**, 1943–1946.
203 T. A. Henry, *J. Chem. Soc.*, 1932, 2759–2768.
204 M. Duwiejua, E. Woode and D. Obiri, *J. Ethnopharmacol.*, 2002, **81**, 73–79.
205 E. Picazo, L. A. Morrill, R. B. Susick, J. Moreno, J. M. Smith and N. K. Garg, *J. Am. Chem. Soc.*, 2018, **140**, 6483–6492.
206 D. Chakraborty and S. Roy, *Progress in the chemistry of organic natural products*, Springer, Wien, 1991.
207 J. Cardellina, *Tetrahedron Lett.*, 1979, **20**, 4915–4916.
208 S. Chakraborty and C. Saha, *Eur. J. Org. Chem.*, 2018, **2018**, 2013–2021.
209 S. Chakraborty and C. Saha, *Eur. J. Org. Chem.*, 2013, **2013**, 5731–5736.
210 H. J. Knölker, M. Bauermeister, D. Bläser, R. Boese and J. B. Pannek, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 223–225.
211 C. J. Moody and P. Shah, *J. Chem. Soc., Perkin Trans. 1*, 1989, 2463–2471.
212 H.-J. Knölker, M. Bauermeister, P. Jörn-Bernd, D. Bläser and R. Boese, *Tetrahedron*, 1993, **49**, 841–862.
213 S. Hibino, A. Tonari, T. Choshi and E. Sugino, *Heterocycles*, 1993, **35**, 441–444.
214 E. M. Beccalli, A. Marchesini and T. Pilati, *J. Chem. Soc., Perkin Trans. 1*, 1994, 579–587.
215 H.-J. Knölker, E. Baum and T. Hopfmann, *Tetrahedron Lett.*, 1995, **36**, 5339–5342.
216 T. Choshi, T. Sada, H. Fujimoto, C. Nagayama, E. Sugino and S. Hibino, *J. Org. Chem.*, 1997, **62**, 2535–2543.
217 H.-J. Knölker, E. Baum and T. Hopfmann, *Tetrahedron*, 1999, **55**, 10391–10412.
218 H.-J. Knoelker, W. Froehner and R. Heinrich, *Synlett*, 2004, **2004**, 2705–2708.
219 R. S. A. Cabral, P.-M. Allard, L. Marcourt, M. C. u. M. Young, E. F. Queiroz and J.-L. Wolfender, *J. Nat. Prod.*, 2016, **79**, 2270–2278.
220 D. G. Agripino, M. E. L. Lima, M. R. d. Silva, C. I. Meda, V. d. S. Bolzani, I. Cordeiro, M. C. M. Young and P. R. H. Moreno, *Biota Neotrop.*, 2004, **4**, 1–15.
221 T. Abe, T. Itoh and M. Terasaki, *Helv. Chim. Acta*, 2019, **102**, e1900116.
222 F. F. Marinho, A. O. Simões, T. Barcellos and S. Moura, *Fitoterapia*, 2016, **114**, 127–137.
223 G. Kalaus, I. Juhász, I. Greiner, M. Kajtár-Peredy, J. Brlik, L. Szabó and C. Szántay, *J. Org. Chem.*, 1997, **62**, 9188–9191.
224 T.-S. Kam, K. Yoganathan and S.-L. Mok, *Phytochemistry*, 1997, **46**, 789–792.
225 T. Soós, S. Varga, P. Angyal, G. Martin, O. Egyed and T. Holczbauer, *Angew. Chem., Int. Ed.*, 2020, **132**, 13649–13653.
226 B. Berkes, K. Ozsváth, L. Molnár, T. Gáti, T. Holczbauer, G. Kardos and T. Soós, *Chem.–Eur. J.*, 2016, **22**, 18101–18106.
227 F. Ohiri, R. Verpoorte and A. B. Svendsen, *J. Ethnopharmacol.*, 1983, **9**, 167–223.
228 J. Schmutz, F. Hunziker and R. Hirt, *Helv. Chim. Acta*, 1957, **40**, 1189–1200.
229 G. Büchi and E. Warnhoff, *J. Am. Chem. Soc.*, 1959, **81**, 4433–4434.
230 M. Amat, M.-D. Coll, J. Bosch, E. Espinosa and E. Molins, *Tetrahedron: Asymmetry*, 1997, **8**, 935–948.
231 D.-H. Kim, J.-H. Kim, T.-H. Jeon and C.-G. Cho, *Org. Lett.*, 2020, **22**, 3464–3468.
232 J. Wang, A. Ma and D. Ma, *Org. Lett.*, 2008, **10**, 5425–5428.
233 E. E. Robinson and R. J. Thomson, *J. Am. Chem. Soc.*, 2018, **140**, 1956–1965.
234 M. Amat, A. Linares and J. Bosch, *J. Org. Chem.*, 1990, **55**, 6299–6312.
235 M. Yamazaki, E. Okuyama, M. Kobayashi and H. Inoue, *Tetrahedron Lett.*, 1981, **22**, 135–136.
236 S. E. Blanchflower, R. M. Banks, J. R. Everett and C. Reading, *J. Antibiot.*, 1993, **46**, 1355–1363.
237 J. B. Roque, E. V. Mercado-Marin, S. C. Richter, D. P. de Sant'Ana, K. Mukai, Y. Ye and R. Sarpong, *Chem. Sci.*, 2020, **11**, 5929–5934.
238 E. V. Mercado-Marin and R. Sarpong, *Chem. Sci.*, 2015, **6**, 5048–5052.
239 G. B. Martin, P. T. Angyal, O. Egyed, S. R. Varga and T. Soós, *Org. Lett.*, 2020, **22**, 4675–4679.
240 J. S. Cha, *Org. Process Res. Dev.*, 2006, **5**, 1032–1053.
241 A. Chatterjee and S. Bandyopadhyay, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 1979, **18**, 87–88.
242 H. Arthur, S. Johns, J. Lamberton and S. Loo, *Aust. J. Chem.*, 1968, **21**, 1399–1401.
243 M. Lin, B.-Q. Yang and D.-Q. Yu, *Acta Pharm. Sin.*, 1986, **21**, 114–118.
244 D. Ponglux, S. Wongseripipatana, S. Subhadhirasakul, H. Takayama, M. Yokota, K. Ogata, C. Phisalaphong, N. Aimi and S.-I. Sakai, *Tetrahedron*, 1988, **44**, 5075–5094.
245 L. Kato, R. M. Braga, I. Koch and L. S. Kinoshita, *Phytochemistry*, 2002, **60**, 315–320.
246 R. M. Braga and F. D. A. Reis, *Phytochemistry*, 1987, **26**, 833–836.
247 H. Zhou, X. Liao and J. M. Cook, *Org. Lett.*, 2004, **6**, 249–252.
248 S. Yamada, D. Morizono and K. Yamamoto, *Tetrahedron Lett.*, 1992, **33**, 4329–4332.
249 H. Zhou, X. Liao, W. Yin, J. Ma and J. M. Cook, *J. Org. Chem.*, 2006, **71**, 251–259.
250 D. Hooper, *Pharm. J.*, 1907, **78**, 453.
251 E. Field, *J. Chem. Soc., Trans.*, 1921, **119**, 887–891.
252 D. Zacharias, R. Rosenstein and G. Jeffrey, *Acta Crystallogr.*, 1965, **18**, 1039–1043.
253 K. L. Jansen and C. J. Prast, *J. Ethnopharmacol.*, 1988, **23**, 115–119.
254 K. Matsumoto, M. Mizowaki, T. Suchitra, H. Takayama, S.-i. Sakai, N. Aimi and H. Watanabe, *Life Sci.*, 1996, **59**, 1149–1155.
255 J. Ma, W. Yin, H. Zhou and J. M. Cook, *Org. Lett.*, 2007, **9**, 3491–3494.
256 Y. Kondo, S. Kojima and T. Sakamoto, *J. Org. Chem.*, 1997, **62**, 6507–6511.
257 C. Ma, X. Liu, X. Li, J. Flippen-Anderson, S. Yu and J. M. Cook, *J. Org. Chem.*, 2001, **66**, 4525–4542.

258 J. Ma, W. Yin, H. Zhou, X. Liao and J. M. Cook, *J. Org. Chem.*, 2009, **74**, 264–273.
259 T. Sakamoto, Y. Kondo, M. Uchiyama and H. Yamanaka, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1941–1942.
260 I. Kaneko, D. T. Fearon and K. Austen, *J. Immunol.*, 1980, **124**, 1194–1198.
261 K. Momota, I. Kaneko, S. Kimura, K. Mitamura and K. Shimada, *Biochem. Biophys. Res. Commun.*, 1991, **179**, 243–250.
262 I. Kaneko, K. Kamoshida and S. Takahashi, *J. Antibiot.*, 1989, **42**, 236–241.
263 H. Seto, T. Fujioka, K. Furihata, I. Kaneko and S. Takahashi, *Tetrahedron Lett.*, 1989, **30**, 4987–4990.
264 J. Garfunkle, F. S. Kimball, J. D. Trzupek, S. Takizawa, H. Shimamura, M. Tomishima and D. L. Boger, *J. Am. Chem. Soc.*, 2009, **131**, 16036–16038.
265 T. Jeschke, D. Wensbo, U. Annby, S. Gronowitz and L. A. Cohen, *Tetrahedron Lett.*, 1993, **34**, 6471–6474.
266 V. R. Hegde, P. Dai, M. Patel and V. P. Gullo, *Tetrahedron Lett.*, 1998, **39**, 5683–5684.
267 H. Shimamura, S. P. Breazzano, J. Garfunkle, F. S. Kimball, J. D. Trzupek and D. L. Boger, *J. Am. Chem. Soc.*, 2010, **132**, 7776–7783.
268 L. Peters, G. M. König, H. Terlau and A. D. Wright, *J. Nat. Prod.*, 2002, **65**, 1633–1637.
269 J. S. Carle and C. Christophersen, *J. Am. Chem. Soc.*, 1979, **101**, 4012–4013.
270 T. Sjöblom, L. Bohlin and C. Christophersen, *Acta Pharm. Suec.*, 1983, **20**, 415–418.
271 P. López-Alvarado, E. Caballero, C. Avendaño and J. C. Menéndez, *Org. Lett.*, 2006, **8**, 4303–4306.
272 T. Hirano, K. Iwakiri and H. Miyamoto, *Heterocycles*, 2009, **79**, 805–820.
273 H. Miyamoto, T. Hirano, Y. Okawa, A. Nakazaki and S. Kobayashi, *Tetrahedron*, 2013, **69**, 9481–9493.
274 T. F. Walsh, R. B. Toupence, F. Ujjainwalla, J. R. Young and M. T. Goulet, *Tetrahedron*, 2001, **57**, 5233–5241.
275 D. E. Lizos and J. A. Murphy, *Org. Biomol. Chem.*, 2003, **1**, 117–122.
276 R. J. Sundberg and S. Q. Smith, *Alkaloids*, 2002, **59**, 281.
277 C. Gallo, P. Renzi, S. Loizzo, A. Loizzo and A. Capasso, *Pharmacology*, 2009, **3**, 906–920.
278 G. K. Jana and S. Sinha, *Tetrahedron*, 2012, **68**, 7155–7165.
279 D. L. Moody, M. Dyba, T. Kosakowska-Cholody, N. I. Tarasova and C. J. Michejda, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 2380–2384.
280 S. M. Lee, X. F. Li, H. Jiang, J. G. Cheng, S. Seong, H. D. Choi and B. W. Son, *Tetrahedron Lett.*, 2003, **44**, 7707–7710.
281 Q. Gao and F. Garcia-Pichel, *Nat. Rev. Microbiol.*, 2011, **9**, 791–802.
282 E. P. Balskus, R. J. Case and C. T. Walsh, *FEMS Microbiol. Ecol.*, 2011, **77**, 322–332.
283 C. Wang and J. Sperry, *Org. Lett.*, 2011, **13**, 6444–6447.
284 C. Raminelli, J. V. Comasseto, L. H. Andrade and A. L. Porto, *Tetrahedron: Asymmetry*, 2004, **15**, 3117–3122.
285 M. Shen, G. Li, B. Z. Lu, A. Hossain, F. Roschangar, V. Farina and C. H. Senanayake, *Org. Lett.*, 2004, **6**, 4129–4132.
286 C. Wang and J. Sperry, *Synlett*, 2012, **23**, 1824–1828.
287 T. Kunisue, Z. Chen, G. M. Buck Louis, R. Sundaram, M. L. Hediger, L. Sun and K. Kannan, *Environ. Sci. Technol.*, 2012, **46**, 4624–4632.
288 S. E. Cross, M. S. Roberts, R. Jiang and H. A. E. Benson, *J. Invest. Dermatol.*, 2001, **117**, 147–150.
289 C. Wang and J. Sperry, *Tetrahedron*, 2013, **69**, 4563–4577.
290 J. Liang, W. Hu, P. Tao and Y. Jia, *J. Org. Chem.*, 2013, **78**, 5810–5815.
291 S. Hirao, Y. Yoshinaga, M. Iwao and F. Ishibashi, *Tetrahedron Lett.*, 2010, **51**, 533–536.
292 P. Buchgraber, M. M. Domostoj, B. Scheiper, C. Wirtz, R. Mynott, J. Rust and A. Fürstner, *Tetrahedron*, 2009, **65**, 6519–6534.
293 S.-J. Qu, Q.-W. Liu, C.-H. Tan, S.-H. Jiang and D.-Y. Zhu, *Planta Med.*, 2006, **72**, 264–266.
294 D. Shan, Y. Gao and Y. Jia, *Angew. Chem., Int. Ed.*, 2013, **52**, 4902–4905.
295 P. Heshmati, M. Nasehi and M. R. Zarrindast, *J. Paramed. Sci.*, 2014, **5**, 99–104.
296 R. Kaschnitz and G. Spiteller, *Monatsh. Chem.*, 1965, **96**, 909–921.
297 X. Pan and T. D. Bannister, *Org. Lett.*, 2014, **16**, 6124–6127.
298 N. Peube-Locou, M. Plat and M. Koch, *Phytochemistry*, 1973, **12**, 199.
299 X. Y. Xu, X. H. Yang, S. Z. Li and Q. S. Song, *Helv. Chim. Acta*, 2011, **94**, 1470–1476.
300 I. Kitagawa, H. Wei, S. Nagao, T. Mahmud, K. Hori, M. Kobayashi, T. Uji and H. Shibuya, *Chem. Pharm. Bull.*, 1996, **44**, 1162–1167.
301 H. J. Knölker, H. Goesmann and R. Klauss, *Angew. Chem., Int. Ed.*, 1999, **38**, 702–705.
302 H.-J. Knölker and S. Cämmerer, *Tetrahedron Lett.*, 2000, **41**, 5035–5038.
303 A. Stoit and U. Pandit, *Heterocycles*, 1987, **25**, 7–10.
304 I. P. Kerschgens, E. Claveau, M. J. Wanner, S. Ingemann, J. H. van Maarseveen and H. Hiemstra, *Chem. Commun.*, 2012, **48**, 12243–12245.
305 A. E. Wright, S. A. Pomponi, S. S. Cross and P. McCarthy, *J. Org. Chem.*, 1992, **57**, 4772–4775.
306 N. K. Garg and B. M. Stoltz, *Chem. Commun.*, 2006, 3769–3779.
307 J. J. Jackson, H. Kobayashi, S. D. Steffens and A. Zakarian, *Angew. Chem., Int. Ed.*, 2015, **54**, 9971–9975.
308 P. Ruiz-Sanchis, S. A. Savina, F. Albericio and M. Álvarez, *Chem.–Eur. J.*, 2011, **17**, 1388–1408.
309 H. Zhou, H. P. He, Y. H. Wang and X. J. Hao, *Helv. Chim. Acta*, 2010, **93**, 1650–1652.
310 Q. Li, T. Xia, L. Yao, H. Deng and X. Liao, *Chem. Sci.*, 2015, **6**, 3599–3605.
311 G. Ding, L. Jiang, L. Guo, X. Chen, H. Zhang and Y. Che, *J. Nat. Prod.*, 2008, **71**, 1861–1865.
312 C. Pérez-Balado and Á. R. de Lera, *Org. Biomol. Chem.*, 2010, **8**, 5179–5186.

313 A. N. de Groot, P. W. van Dongen, T. B. Vree, Y. A. Hekster and J. van Roosmalen, *Drugs*, 1998, **56**, 523–535.
314 N. R. Tasker and P. Wipf, in *The Alkaloids*, ed. H.-J. Knölker, Academic Press, London, 2021, vol. 85, pp. 1–112.
315 A. Stoll, *Helv. Chim. Acta*, 1949, **32**, 506.
316 K. Lee, Y. B. Poudel, C. M. Glinkerman and D. L. Boger, *Tetrahedron*, 2015, **71**, 5897–5905.
317 H. Liu, X. Zhang, D. Shan, M. Pitchakuntla, Y. Ma and Y. Jia, *Org. Lett.*, 2017, **19**, 3323–3326.
318 S. Cai, X. Kong, W. Wang, H. Zhou, T. Zhu, D. Li and Q. Gu, *Tetrahedron Lett.*, 2012, **53**, 2615–2617.
319 T. Yaguchi, A. Someya and S.-i. Udagawa, *Mycoscience*, 1995, **36**, 421–424.
320 J. Varga, J. C. Frisvad and R. A. Samson, *Stud. Mycol.*, 2007, **59**, 75–88.
321 K. V. Chuang, M. E. Kieffer and S. E. Reisman, *Org. Lett.*, 2016, **18**, 4750–4753.
322 A. Dobbs, *J. Org. Chem.*, 2001, **66**, 638–641.
323 L. Garlaschelli, Z. Pang, O. Sterner and G. Vidari, *Tetrahedron*, 1994, **50**, 3571–3574.
324 G. Tel, M. Apaydın, M. E. Duru and M. Öztürk, *Food Anal. Methods*, 2012, **5**, 495–504.
325 T. Yasukouchi and K. Kanematsu, *Tetrahedron Lett.*, 1989, **30**, 6559–6562.
326 N. Saito, T. Ichimaru and Y. Sato, *Org. Lett.*, 2012, **14**, 1914–1917.
327 R. J. Huntley and R. L. Funk, *Org. Lett.*, 2006, **8**, 3403–3406.
328 R. J. Capon, J. K. Macleod and P. J. Scammells, *Tetrahedron*, 1986, **42**, 6545–6550.
329 R. Herb, A. R. Carroll, W. Y. Yoshida, P. J. Scheuer and V. J. Paul, *Tetrahedron*, 1990, **46**, 3089–3092.
330 L. F. Silva Jr and M. V. Craveiro, *Org. Lett.*, 2008, **10**, 5417–5420.
331 L. F. Silva Jr, M. V. Craveiro and M. T. Gambardella, *Synthesis*, 2007, **2007**, 3851–3857.
332 K. R. Buszek, N. Brown and D. Luo, *Org. Lett.*, 2009, **11**, 201–204.
333 T.-S. Kam, G. Subramaniam, K.-H. Lim and Y.-M. Choo, *Tetrahedron Lett.*, 2004, **45**, 5995–5998.
334 Z. Li and G. Liang, *Tetrahedron Lett.*, 2013, **54**, 242–244.
335 D. V. Patil, M. A. Cavitt, P. Grzybowski and S. France, *Chem. Commun.*, 2011, **47**, 10278–10280.
336 M. Ishikura, K. Yamada and T. Abe, *Nat. Prod. Rep.*, 2010, **27**, 1630–1680.
337 J. Magolan, C. A. Carson and M. A. Kerr, *Org. Lett.*, 2008, **10**, 1437–1440.
338 R. Nakajima, T. Ogino, S. Yokoshima and T. Fukuyama, *J. Am. Chem. Soc.*, 2010, **132**, 1236–1237.
339 T. Feng, X.-H. Cai, P.-J. Zhao, Z.-Z. Du, W.-Q. Li and X.-D. Luo, *Planta Med.*, 2009, **75**, 1537–1541.
340 T. Feng, X.-H. Cai, Y.-P. Liu, Y. Li, Y.-Y. Wang and X.-D. Luo, *J. Nat. Prod.*, 2010, **73**, 22–26.
341 S.-H. Lim, K.-M. Sim, Z. Abdullah, O. Hiraku, M. Hayashi, K. Komiyama and T.-S. Kam, *J. Nat. Prod.*, 2007, **70**, 1380–1383.
342 R. Keese, *Chem. Rev.*, 2006, **106**, 4787–4808.
343 Z. Xu, Q. Wang and J. Zhu, *J. Am. Chem. Soc.*, 2013, **135**, 19127–19130.
344 Y. Iwama, K. Okano, K. Sugimoto and H. Tokuyama, *Chem.–Eur. J.*, 2013, **19**, 9325–9334.
345 A. Biechy and S. Z. Zard, *Org. Lett.*, 2009, **11**, 2800–2803.
346 M. Pfaffenbach and T. Gaich, *Chem.–Eur. J.*, 2016, **22**, 3600–3610.
347 Y. Liu and H. Wang, *Chem. Commun.*, 2019, **55**, 3544–3547.
348 X.-H. Li, S.-L. Wan, D. Chen, Q. R. Liu, C. H. Ding, P. Fang and X. L. Hou, *Synthesis*, 2016, **48**, 1568–1572.
349 J. W. Blunt, A. R. Carroll, B. R. Copp, R. A. Davis, R. A. Keyzers and M. R. Prinsep, *Nat. Prod. Rep.*, 2018, **35**, 8–53.
350 R. G. Berlinck, A. F. Bertonha, M. Takaki and J. P. Rodriguez, *Nat. Prod. Rep.*, 2017, **34**, 1264–1301.
351 A. D. Patil, A. J. Freyer, B. Carte, P. B. Taylor, R. K. Johnson and D. J. Faulkner, *J. Nat. Prod.*, 2002, **65**, 628–629.
352 M. S. Roy, X. Meng, K. Koda, S. Rasapalli, D. Gout and C. J. Lovely, *Tetrahedron Lett.*, 2019, **60**, 979–982.
353 H. L. Maia, L. S. Monteiro and J. Sebastião, *Eur. J. Org. Chem.*, 2001, **2001**, 1967–1970.
354 N. Chandrasoma, N. Brown, A. Brassfield, A. Nerurkar, S. Suarez and K. R. Buszek, *Tetrahedron Lett.*, 2013, **54**, 913–917.
355 H. Steinmetz, K. I. Mohr, W. Zander, R. Jansen, K. Gerth and R. Müller, *J. Nat. Prod.*, 2012, **75**, 1803–1805.
356 K. J. Weissman and R. Müller, *Bioorg. Med. Chem.*, 2009, **17**, 2121–2136.
357 N. Marsch, P. G. Jones and T. Lindel, *Beilstein J. Org. Chem.*, 2015, **11**, 1700–1706.
358 R. Mezencev, M. Galizzi, P. Kutschy and R. Docampo, *Exp. Parasitol.*, 2009, **122**, 66–69.
359 M. S. C. Pedras and S. Montaut, *Chem. Commun.*, 2004, 452–453.
360 M. S. C. Pedras, M. G. Sarwar, M. Suchy and A. M. Adio, *Phytochemistry*, 2006, **67**, 1503–1509.
361 M. S. C. Pedras, J. L. Sorensen, F. I. Okanga and I. L. Zaharia, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 3015–3020.
362 M. S. C. Pedras and J. L. Sorensen, *Phytochemistry*, 1998, **49**, 1959–1965.
363 B. Li, J. D. Williams and N. P. Peet, *Tetrahedron Lett.*, 2013, **54**, 3124–3126.
364 M. Kaur and R. Kumar, *ChemistrySelect*, 2018, **3**, 5330–5340.
365 J. H. Cardellina, F.-J. Marner and R. E. Moore, *Science*, 1979, **204**, 193–195.
366 H. Fujiki and T. Sugimura, *Cancer Surv.*, 1983, **2**, 539–556.
367 P. Vital and D. Tanner, *Org. Biomol. Chem.*, 2006, **4**, 4292–4298.
368 H. Hemetsberger, D. Knittel and H. Weidmann, *Monatsh. Chem.*, 1970, **101**, 161–165.
369 W. H. Visser, G. M. Terwindt, S. A. Reines, K. Jiang, C. R. Lines and M. D. Ferrari, *Arch. Neurol.*, 1996, **53**, 1132–1137.
370 M. J. Cumberbatch, R. G. Hill and R. J. Hargreaves, *Eur. J. Pharmacol.*, 1997, **328**, 37–40.
371 S. Tong, Z. Xu, M. Mamboury, Q. Wang and J. Zhu, *Angew. Chem., Int. Ed.*, 2015, **127**, 11975–11978.

372 Y. Yang, Y. Bai, S. Sun and M. Dai, *Org. Lett.*, 2014, **16**, 6216–6219.
373 T. Kamigauchi and M. Yasui, PCT Int. Appl., WO 2000059909, [CAN 133:267009], 2000.
374 Y. Zhang, I. W. McArdle, J. W. Hubbard, N. G. Akhmedov and B. C. Söderberg, *Tetrahedron Lett.*, 2016, **57**, 2865–2867.
375 T.-S. Kam, K.-M. Sim, H.-S. Pang, T. Koyano, M. Hayashi and K. Komiyama, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 4487–4489.
376 K.-H. Lim, O. Hiraku, K. Komiyama and T.-S. Kam, *J. Nat. Prod.*, 2008, **71**, 1591–1594.
377 R. Frei, D. Staedler, A. Raja, R. Franke, F. Sasse, S. Gerber-Lemaire and J. Waser, *Angew. Chem., Int. Ed.*, 2013, **52**, 13373–13376.
378 T. Huber, T. A. Preuhs, C. K. Gerlinger and T. Magauer, *J. Org. Chem.*, 2017, **82**, 7410–7419.
379 J. J. Neumann, S. Rakshit, T. Dröge, S. Würtz and F. Glorius, *Chem.–Eur. J.*, 2011, **17**, 7298–7303.
380 C. Ito and h. Furukawa, *Chem. Pharm. Bull.*, 1990, **38**, 1548–1550.
381 W. Frohner, M. P. Krahl, K. R. Reddy and H.-J. Knölker, *Heterocycles*, 2004, **63**, 2393–2407.
382 H.-J. Knölker and W. Fröhner, *Tetrahedron Lett.*, 1996, **37**, 9183–9186.
383 H.-J. Knölker and W. Froehner, *Synthesis*, 2000, **2000**, 2131–2136.
384 T. Soós, G. Timári and G. Hajós, *Tetrahedron Lett.*, 1999, **40**, 8607–8609.
385 G. Timári, T. Soós, G. Hajós, A. Messmer, J. Nacsa and J. Molnár, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 2831–2836.
386 A. Yasuhara, N. Suzuki and T. Sakamoto, *Chem. Pharm. Bull.*, 2002, **50**, 143–145.
387 P. Kleinwaechter, B. Schlegel, I. Groth, A. Haertl and U. Graefe, *J. Antibiot.*, 2001, **54**, 510–512.
388 G. A. Kraus and T. Wu, *Tetrahedron*, 2005, **61**, 9502–9505.
389 T. Komoda and S.-i. Nakatsuka, *Heterocycl. Commun.*, 2003, **9**, 119–122.
390 E. Magnier and Y. Langlois, *Tetrahedron*, 1998, **54**, IN6201–IN6202.
391 R. Cao, W. Peng, Z. Wang and A. Xu, *Curr. Med. Chem.*, 2007, **14**, 479–500.
392 R. Sakai, T. Higa, C. W. Jefford and G. Bernardinelli, *J. Am. Chem. Soc.*, 1986, **108**, 6404–6405.
393 M. Cain, R. W. Weber, F. Guzman, J. M. Cook, S. A. Barker, K. C. Rice, J. N. Crawley, S. M. Paul and P. Skolnick, *J. Med. Chem.*, 1982, **25**, 1081–1091.
394 W. D. Inman, W. M. Bray, N. C. Gassner, R. S. Lokey, K. Tenney, Y. Y. Shen, K. TenDyke, T. Suh and P. Crews, *J. Nat. Prod.*, 2010, **73**, 255–257.
395 A. Badre, A. Boulanger, E. Abou-Mansour, B. Banaigs, G. Combaut and C. Francisco, *J. Nat. Prod.*, 1994, **57**, 528–533.
396 P. Molina, P. M. Fresneda and S. García-Zafra, *Tetrahedron Lett.*, 1995, **36**, 3581–3582.
397 P. Rocca, F. Marsais, A. Godard, G. Quéguiner, L. Adams and B. Alo, *Tetrahedron Lett.*, 1995, **36**, 7085–7088.
398 F. Nissen, V. Richard, C. Alayrac and B. Witulski, *Chem. Commun.*, 2011, **47**, 6656–6658.
399 M. R. Hansen and L. H. Hurley, *Acc. Chem. Res.*, 1996, **29**, 249–258.
400 U. Hacksell and G. D. Daves, *Prog. Med. Chem.*, 1985, **22**, 1–65.
401 V. Murray, A. G. Moore, C. Matias and G. Wickham, *Biochim. Biophys. Acta, Gene Struct. Expression*, 1995, **1261**, 195–200.
402 Y. Wu, Z.-X. Zhang, H. Hu, D. Li, G. Qiu, X. Hu and X. He, *Fitoterapia*, 2011, **82**, 288–292.
403 A. Yepremyan and T. G. Minehan, *Org. Biomol. Chem.*, 2012, **10**, 5194–5196.
404 A. L. Rodriguez, C. Koradin, W. Dohle and P. Knochel, *Angew. Chem., Int. Ed.*, 2000, **39**, 2488–2490.
405 R. A. Leal, C. Bischof, Y. V. Lee, S. Sawano, C. C. McAtee, L. N. Latimer, Z. N. Russ, J. E. Dueber, J. Q. Yu and R. Sarpong, *Angew. Chem., Int. Ed.*, 2016, **55**, 11824–11828.
406 S. K. Jackson and M. A. Kerr, *J. Org. Chem.*, 2007, **72**, 1405–1411.
407 G. Büchi, D. Coffen, K. Kocsis, P. Sonnet and F. E. Ziegler, *J. Am. Chem. Soc.*, 1966, **88**, 3099–3109.
408 M. Gorman, N. Neuss, G. H. Svoboda, A. J. Barnes and N. J. Cone, *J. Am. Pharm. Assoc., Sci. Ed.*, 1959, **48**, 256–257.
409 S. Raucher and B. L. Bray, *J. Org. Chem.*, 1985, **50**, 3236–3237.
410 R. Noble, 1964.
411 G. R. Dwivedi, R. Tyagi, S. Gupta, S. Tripathi, S. Pati, S. K. Srivastava, M. P. Darokar and A. Sharma, *J. Biomol. Struct. Dyn.*, 2018, **36**, 4270–4284.
412 S. Das and A. B. Sharangi, *J. Pharmacogn. Phytochem.*, 2017, **6**, 1695–1701.
413 M. Sottomayor and A. R. Barceló, in *Stud. Nat. Prod. Chem.*, Elsevier, 2006, vol. 33, pp. 813–857.
414 M. T. Reding and T. Fukuyama, *Org. Lett.*, 1999, **1**, 973–976.
415 M. Sakaitani, K. Hori and Y. Ohfune, *Tetrahedron Lett.*, 1988, **29**, 2983–2984.
416 A. Brossi and M. Suffness, *The Alkaloids: Antitumor Bisindole Alkaloids from Catharanthus roseus*, Academic Press, New York, 1990.
417 R. Noble, C. T. Beer and J. H. Cutts, *Ann. N. Y. Acad. Sci.*, 1958, **76**, 882.
418 G. H. Svoboda, N. Neuss and M. Gorman, *J. Am. Pharm. Assoc., Sci. Ed.*, 1959, **48**, 659–666.
419 S. Yokoshima, H. Tokuyama and T. Fukuyama, *Chem. Rec.*, 2010, **10**, 101–118.