Simple indole alkaloids and those with a nonrearranged monoterpenoid unit

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Covering: 2008 to 2009

This review covers the literature on simple indole alkaloids and those with a nonrearranged monoterpenoid unit, and includes newly isolated alkaloids, structure determinations, total syntheses and biological activities.

1 Introduction

This review covers the literature on simple indole alkaloids and those with a nonrearranged monoterpenoid unit from the beginning of 2008 to the end of 2009. In this series, marine natural products and peptide alkaloids have been also surveyed. As a result, there will be some overlap with marine alkaloids and peptide alkaloids containing the indole ring. Reviews on thaxtomin phytotoxins,[1] progress towards the total synthesis of calothrixins,[2] synthesis of carbazole alkaloids,[3] nomofungin and communesin,[4] copper-catalyzed synthesis of indole alkaloids,[5] a new strategy for the synthesis of hexahydropyrroloindole alkaloids,[6] asymmetric syntheses of oxindole and indole spirocyclic alkaloids,[7] and recent progress in the chemistry and applications of indolocarbazoles[8] have appeared during the review period.

2 Simple indole alkaloids

2.1 Non-tryptamines

Six new bromoindole alkaloids, aplicyanins A–F (**1–6**), have been isolated from the CH_2Cl_2–MeOH extract of the tunicate *Aplidium cyaneum* collected in Antarctica. Cytotoxic and antimitotic activities were found for compounds **2**, **4**, **5** and **6**.[9]

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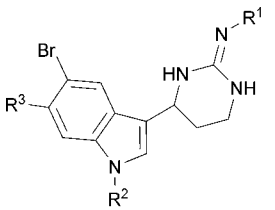
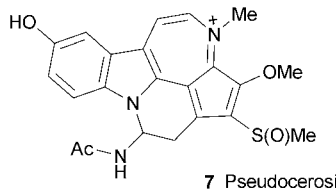
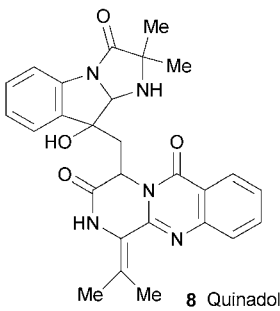
An indolic azafulvene alkaloid, pseudocerosine (**7**), has been obtained from the marine flatworm *Pseudoceros indicus*, collected in the mangrove forests of Palau, Chuuk and Pohnapei (Micronesia).[10]



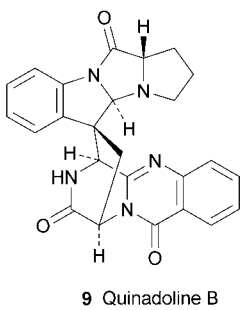
1 Aplicyanin A ($R^1 = R^2 = R^3 = H$)
2 Aplicyanin B ($R^1 = Ac$ $R^2 = R^3 = H$)
3 Aplicyanin C ($R^1 = H$ $R^2 = OMe$ $R^3 = H$)
4 Aplicyanin D ($R^1 = OH$ $R^2 = H$ $R^3 = Me$)
5 Aplicyanin E ($R^1 = H$ $R^2 = OMe$ $R^3 = Br$)
6 Aplicyanin F ($R^1 = Ac$ $R^2 = OMe$ $R^3 = Br$)



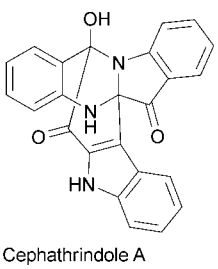
7 Pseudocerosine



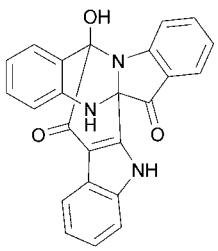
8 Quinadoline A



9 Quinadoline B



10 Cephathrindole A

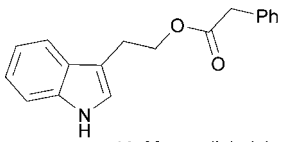


11 Cephathrindole B

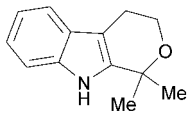
Two new fungal metabolites, quinadolines A (**8**) and B (**9**), have been isolated from the culture broth of *Aspergillus* sp. FKI-1746, and the absolute stereochemistry of **9** was determined.[11]

Two new indolotryptanthrin alkaloids, cephathrindoles A (**10**) and B (**11**), have been isolated from *Cephalantheropsis gracilis* (Orchidaceae).[12]

Two new indole alkaloids, monaspiloindole (**12**) and monaspyranoindole (**13**), have been obtained from the EtOAc-soluble fraction of the MeOH extract of the mycelia of *Monascus pilosus* BCRC 38072.[13]



12 Monaspiloindole



13 Monaspyranoindole

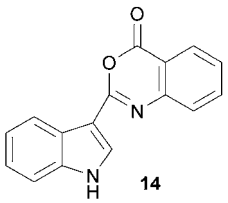
Minoru Ishikura

Minoru Ishikura was born in Hokkaido, Japan. He graduated from the Graduate School of Pharmaceutical Sciences, Hokkaido University, and received his Ph.D. degree under the supervision of Professor Yoshio Ban in 1982. He then worked at Faculty of Pharmaceutical Sciences, Health Sciences University of Hokkaido, and became a Full Professor in 2001. He spent the years 1985–1986 as a postdoctoral fellow at University of California, San Diego, with Professor Ernest Wenkert. His main research interests are the development of synthetic methods using organometallic reagents and the syntheses of bioactive natural products.

Koji Yamada

Koji Yamada was born in Niigata, Japan. He graduated in 1995 from Toyama Medical and Pharmaceutical University, and worked at Faculty of Pharmaceutical Sciences, Kanazawa University (1995–2006). He received his Ph.D. degree from Kanazawa University under the supervision of Professor Masanori Somei in 2003, and worked as a research fellow with Professor Kuo-Hsiung Lee at University of North Carolina (2005). Since then, he has been an Associate Professor at the Faculty of Pharmaceutical Sciences, Health Sciences University of Hokkaido. His current research is the synthesis of biologically active natural products and related compounds.

The originally proposed structure of cephalandole A (**14**), obtained from the MeOH extract of the Taiwanese orchid *Cephalantheropsis gracilis* (Orchidaceae), has been revised to the structure **15**.[14]



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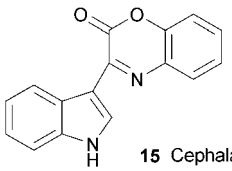
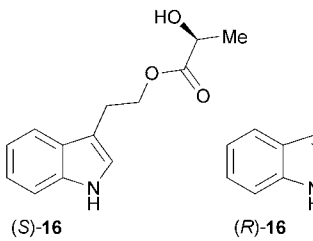


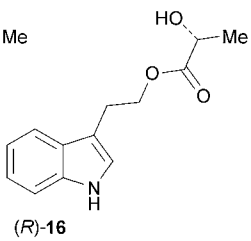
15 Cephalandole A

Three new indole derivatives (*S*)-**16**, (*R*)-**16** and **17**, have been obtained from the culture filtrate of marine sponge-derived yeast HO-25 strain. The absolute configurations of **16** were determined, and all compounds exhibited weak radical-scavenging activities.[15]

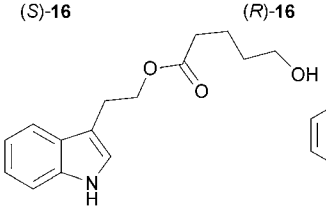
A cytotoxic alkaloid, mansouramycin D (**18**), has been isolated from the ethyl acetate extract of the marine-derived *Streptomyces* sp. isolate Mei37.[16]



(*S*)-**16**



(*R*)-**16**



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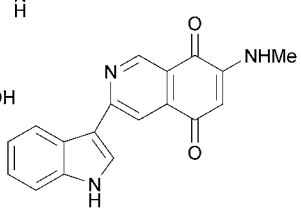
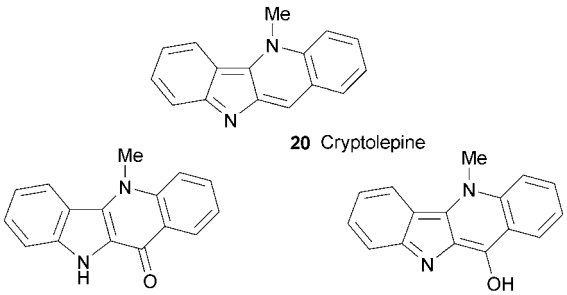


18 Mansouramycin D

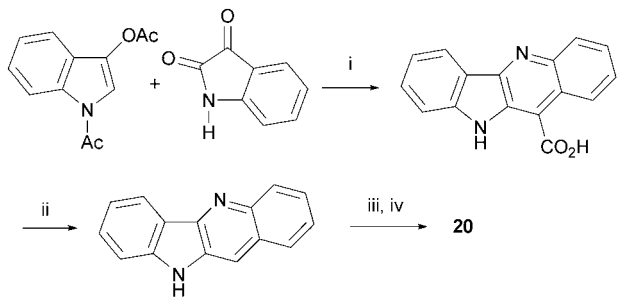
Takumi Abe

Takumi Abe was born in Hokkaido, Japan. He graduated from the Graduate School of Pharmaceutical Sciences, Hokkaido University, and received his Ph.D. degree under the supervision of Professor Shunichi Hashimoto in 2007. He then worked at the Faculty of Pharmaceutical Sciences, Health Sciences University of Hokkaido. In 2009, he worked as a postdoctoral fellow with Professor Kim D. Janda at the Scripps Research Institute, La Jolla, California. He is interested in developing synthetic reactions catalyzed by transition metal complexes and their synthetic applications.

The intercalating and antimalarial drugs cryptolepine (**20**) and cryptolepinone (**21**) have been isolated from the decoction of the roots of the West Africa climbing shrubs *Cryptolepis sanguinolenta* and *Cryptolepis triangularis*. The relative stability between cryptolepinone (the keto form) (**21**) and 11-hydroxycryptolepine (the enol form) (**22**) was investigated based on semiempirical molecular orbital calculations, which showed that **21** is more stable than **22** in various solvents.[17]

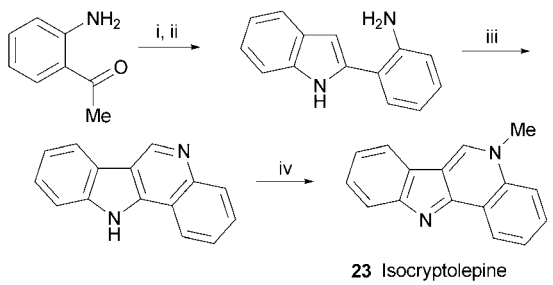


Cryptolepine (**20**) has been synthesized by the condensation of isatin with 1-acetyl-1*H*-indol-3-yl acetate under microwave irradiation (Scheme 1).[18]



Scheme 1 *Reagents and conditions*: i, aq. KOH, microwave, reflux, 16 min; ii, Ph_2O, 250 °C, 4 h; iii, MeI, microwave, 4 min; iv, 5% aq. Na_2CO_3, SiO_2.

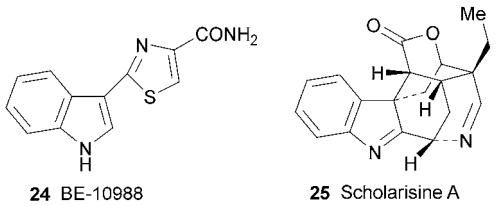
Isocryptolepine (**23**), isolated from the roots of the plant *Cryptolepis sanguinolenta*, displays antimalarial properties. Syntheses of **23** and its analogues have been carried out using a modified Pictet–Spengler reaction (Scheme 2).[19]



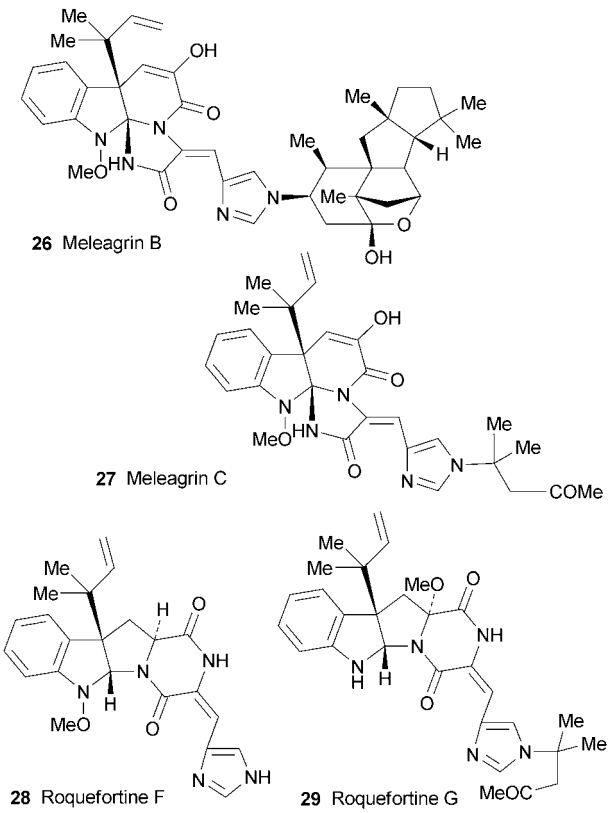
Scheme 2 *Reagents and conditions*: i, $PhNHNH_2$, AcOH, EtOH, 6 h; ii, PPA, 100 °C, 10 min; iii, $(HCHO)_n$, TFA, MeCN, sealed tube, 80 °C, 2 h; iv, MeI, toluene, reflux, 2 h.

The biosynthetic origin of the tumor-inhibitory thiazolylindole, BE-10988 (**24**) obtained from the culture broth of the *Streptomyces* sp. BA10988, has been investigated – the results indicated that tryptophan and a related metabolite serve as biosynthetic precursors.[20]

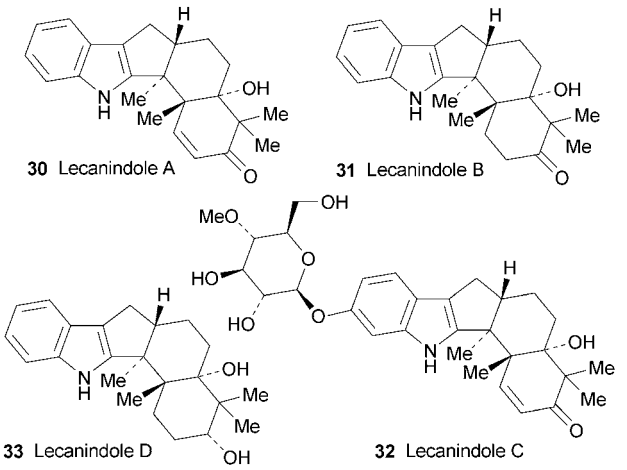
A novel cage-like indole alkaloid, scholarisine A (**25**), has been isolated from the leaves of *Alstonia scholaris* collected in Simao of Yunnan, China.[21]



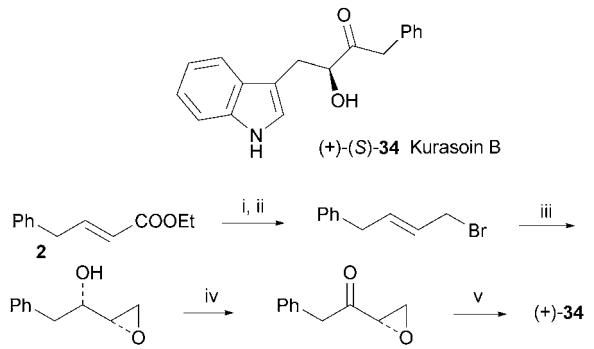
Two meleagrin analogs, meleagrins B (**26**) and C (**27**), and two diketopiperazines, roquefortines F (**28**) and G (**29**), have been isolated from a deep ocean sediment derived fungus, *Penicillium* sp. The cytotoxicity of the new compounds against the HL-60, A-549, BEL-7402 and MOLT-4 cell lines was evaluated.[22]



Four indolosesquiterpenes, lecanindoles A (**30**), B (**31**), C (**32**) and D (**33**), have been isolated from fermentations of the terrestrial fungus *Verticillium lecanii* 6144. Lecanindole D (**33**) exhibited a potent and selective progesterone receptor agonist activity.[23]



(+)-(*S*)-Kurasoin B (**34**), isolated from the fermentation broth of the soil fungus *Paecilomyces* sp. FO-3684, is a protein farnesyl transerase (PFTase) inhibitor and has potential as an anticancer drug. Two enantioselective syntheses of (+)-(*S*)-**34** have been reported. The synthesis of (+)-(*S*)-**34** has been achieved from (2*E*)-ethyl 4-phenylbut-2-enoate in 5 steps using asymmetric Sharpless dihydroxylation to establish the stereocenters and $Yb(OTf)_3$-catalyzed regioselective coupling (Scheme 3).[24]

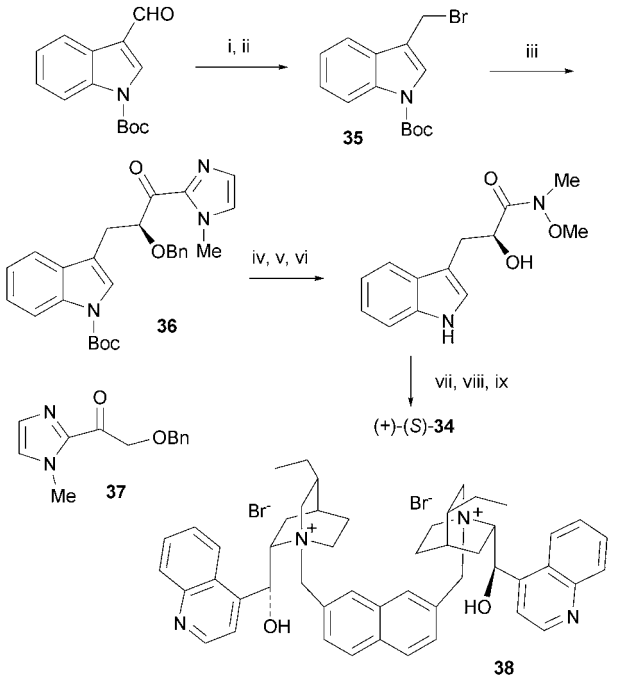


Scheme 3 *Reagents and conditions*: i, DIBAL, CH_2Cl_2, 0 °C, 2 h, then rt, 0.5 h; ii,Ph_3P, NBS, CH_2Cl_2, −15 °C, 0.5 h, then rt, 45 min; iii, $K_3Fe(CN)_6$, K_2CO_3, $NaHCO_3$, $MeSO_2NH_2$, $(DHQ)_2PHAL$, K_2OsO_4, *t*-BuOH–H_2O (1 : 1), 0 °C, 24 h, then K_2CO_3, MeOH, rt, 10 h; iv, CrO_3, H_2SO_4, acetone, rt, 30 min, 95% ee; v, indole, $Yb(OTf)_3$ (20 ml%), 1,2-dichloroethane, 50 °C, 4 h.

An asymmetric alkylation of **35** with **37** using cinchonidine-based PTC **38** has been employed as the key step to produce **36** in near-quantitative yield and complete selectivity. Then, **36** was converted to (+)-(*S*)-**34** without racemization (Scheme 4).[25]

The first total synthesis of racemic actinophyllic acid (**39**), isolated from the H_2O–MeOH extracts of the tree *Alstonia actinophylla* collected on the Cape York Peninsula, Queensland, Australia, has been achieved through aza-Cope–Mannich rearrangement of the formaldiminium ion.[26] The absolute configuration of (−)-actinophyllic acid (**39**) was assigned based on investigation of the methyl ester (−)-**40** (Scheme 5).[27]

A concise synthesis of (−)-indolmycin (**42**), an antibiotic isolated from the African strain of *Streptomyces albus*, has been achieved



Scheme 4 *Reagents and conditions*: i, $NaBH_4$; ii, PBr_3, Et_2O; iii, **37**, CsOH, **38** (10 mol%), CH_2Cl_2, −40 °C, 28 h, 99% ee; iv, MeOTf, MeCN, MeOH, DBU, 6 h; v, BCl_3; vi, $AlMe_3$, HN(OMe)Me; vii, TESCl, imidazole; viii, BnMgCl, THF; ix, TBAF.

through Pd-catalyzed reaction of optically active alkyne with 2-iodoaniline, followed by reaction with guanidine (Scheme 6).[28]

The total synthesis of (±)-goniomitine (**43**), isolated from the root bark of *Gonioma malagasy*, has been achieved starting from δ-valerolactam, which included a formal [3 + 2] cycloaddition between nitrile and cyclopropane (Scheme 7).[29]

The first total synthesis of (±)-mersicarpine (**44**), isolated from the *Kopsia* genus of plants, has been achieved through $Mn(OAc)_3$-mediated radical cyclization of a β-diketone and oxidation of an *N*-arylindole (Scheme 8).[30]

A formal synthesis of (±)−**44** has been completed, in which the key intermediate was prepared through an intramolecular radical addition–radical cyclization cascade (Scheme 9).[31]

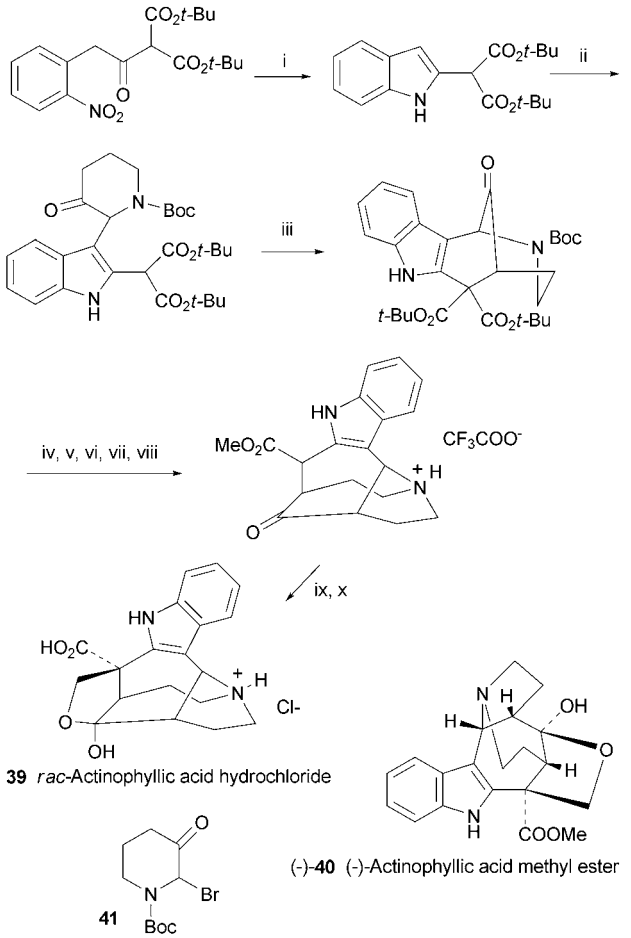
A total synthesis of polyalkylated indole (±)-*trans*-trikentrin A (*trans*-**45**) has been developed *via* a thallium(III)-mediated ring contraction process to obtain the *trans*-1,3-disubstituted five-membered ring as the key features (Scheme 10).[32]

Total syntheses of (±)-*cis*-trikentrin A (*cis*-**45**) and (±)-herbindole (**46**) have been accomplished through an intramolecular Diels–Alder reaction using an indole aryne (Scheme 11).[33]

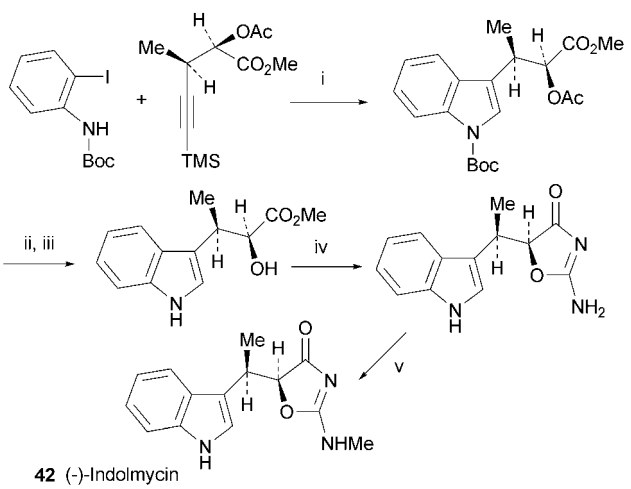
A short and improved access to (±)-*cis*-**45** has been developed using an efficient tandem 6,7-indolyne cycloaddition–Negishi coupling reaction (Scheme 12).[34]

The first total synthesis of (±)-apparicine (**47**), isolated from *Aspidosperma dasycarpon*, has been developed through an indole-templated ring-closing metathesis and a vinyl halide Heck cyclization (Scheme 13).[35]

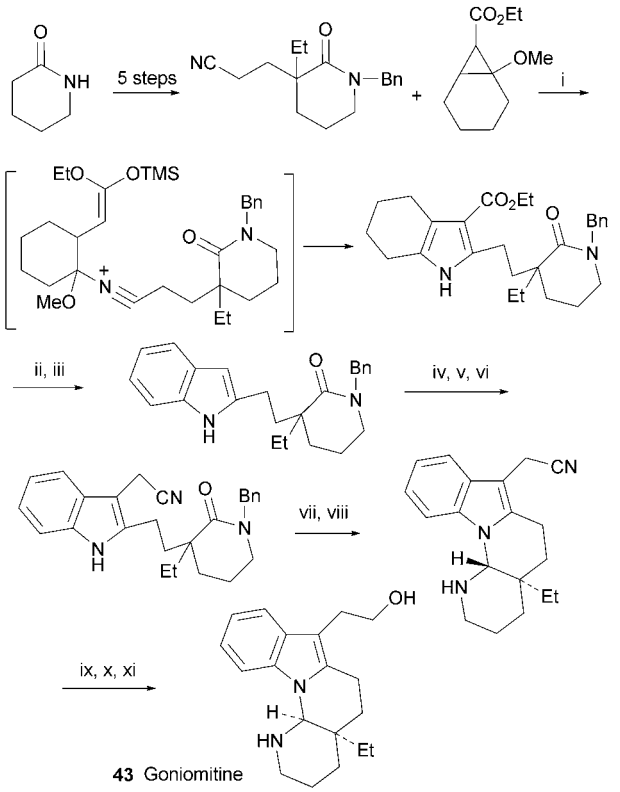
Enantioselective total synthesis of (−)-16-*epi*-silicine (**49**), isolated from *Pandaca caducifolia*, has been completed through a stereoselective conjugate addition and alkylation of a phenylglycinol-derived bicyclic lactam as the key step (Scheme 14).[36]



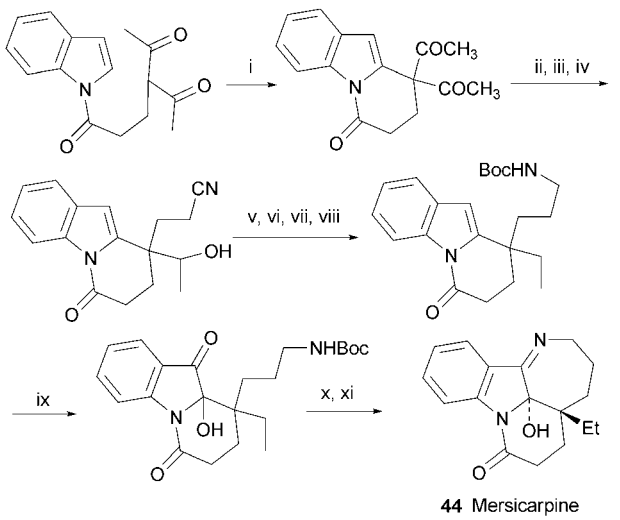
Scheme 5 *Reagents and conditions*: i, $Pd(OH)_2/C$, H_2, *i*-PrOH, rt; ii, **41**, DMF, rt; iii, LDA, $[Fe(DMF)_3Cl_2][FeCl_4]$, THF, −78 °C to rt; iv, $CeCl_3$, CH_2=CHMgBr, THF, −78 °C; v, TFA, rt; vi, $(CH_2O)_n$, MeCN, 70 °C; vii, 0.5 M HCl, MeOH, then aq. Na_2CO_3; viii, TFA; ix, LDA, CH_2O, THF, −78 °C, then TFA; x, 4 M HCl, 70 °C.



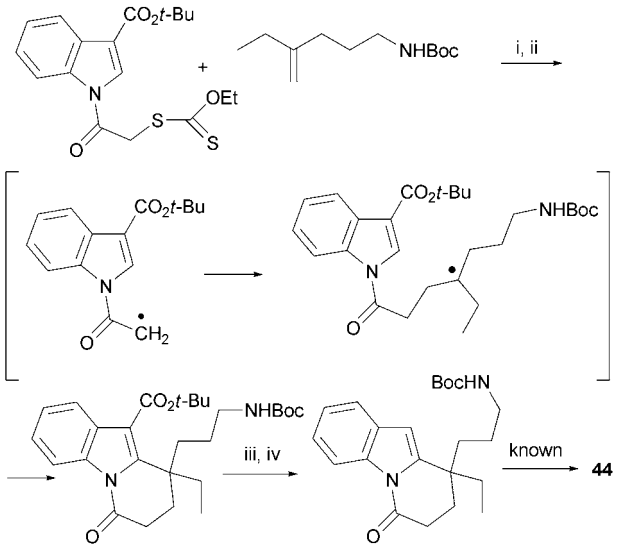
Scheme 6 *Reagents and conditions*: i, $Pd(OAc)_2$, Ph_3P, Et_4NCl, *i*-Pr_2NEt; ii, TFA, CH_2Cl_2; iii,K_2CO_3, MeOH; iv, guanidine hydrochloride, *t*-BuOK, *t*-BuOH, 4 Å MS; v, 40% aq. $MeNH_2$.



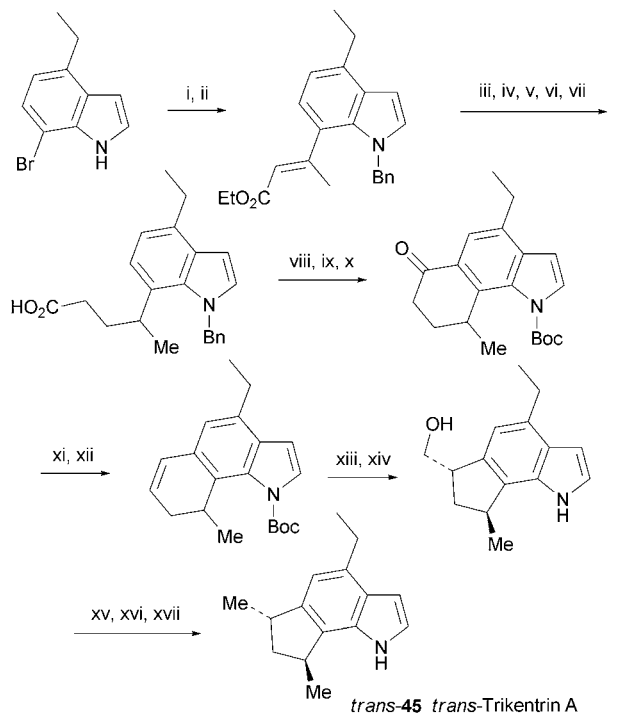
Scheme 7 *Reagents and conditions*: i, TMSOTf, $EtNO_2$; ii, Pd/C, mesitylene; iii, NaOH, EtOH/H_2O, 150 °C, MW; iv, $[Me_2N{=}CH_2]^+Cl^-$; v, MeI, MeOH; vi, NaCN, DMF; vii, Na, NH_3, THF; viii, $POCl_3$, toluene, then $NaBH_4$, MeOH; ix, DIBAL, CH_2Cl_2, then aq. H_2SO_4; x, $NaBH_4$, EtOH; xi, *p*-TsOH, Et_3N, MeOH.



Scheme 8 *Reagents and conditions*: i, $Mn(OAc)_3$, AcOH, reflux; ii, $NaHCO_3$, MeOH; iii, acrylonitrile, *t*-BuOK, THF; iv, $NaBH_4$, THF; v, NaH, CS_2, MeI, THF; vi, DME, 170 °C, MW; vii, H_2, PtO_2, $CHCl_3$, EtOH; viii, Boc_2O, Et_3N, CH_2Cl_2; ix, Oxone, acetone, TBAS, EDTA, CH_3CN, H_2O; x, TBSOTf, 2,6-lutidine, CH_2Cl_2; xi, TBAF, THF.

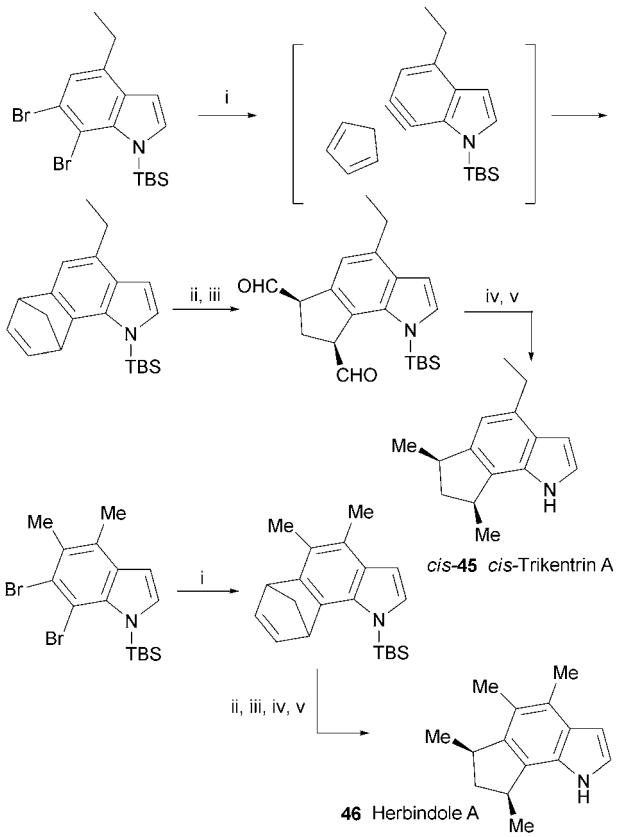


Scheme 9 *Reagents and conditions*: i, lauroyl peroxide, 1,2-dichloroethane; ii, MnO_2; iii, TFA, toluene; iv, Boc_2O, Et_3N.

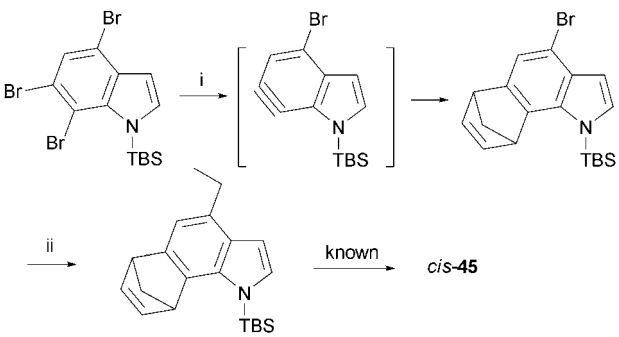


Scheme 10 *Reagents and conditions*: i, KOH, benzyl bromide; ii, ethyl crotonate, $PdCl_2$, P(*o*-tolyl)$_3$, Et_3N; iii, Mg, MeOH; iv, DIBAL; v, MsCl, pyridine; vi, KCN, DMSO; vii, KOH, ethylene glycol; viii, TFAA, TFA; ix, $AlCl_3$, anisole; x, Boc_2O; xi, $NaBH_4$, MeOH; xii, H_3PO_4, DMF; xiii, TTN, CH_3CN, −40 °C, 3 min; xiv, $NaBH_4$, −40 °C to −20 °C; xv, TsCl, CH_2Cl_2; xvi, $NaBH_4$, DMSO; xvii, TBAF, THF.

Physovenine (**50**) with a furoindoline ring system is a minor component of the calabar bean alkaloids, and has anti-cholinergic and nicotic activities. A Wittig olefination–Claisen rearrangement process was used for the total synthesis of (±)-**50** (Scheme 15).[37]



Scheme 11 *Reagents and conditions*: i, cyclopentadiene, *n*-BuLi, toluene, −78 °C to rt; ii, OsO_4, NMO, THF, H_2O; iii, $NaIO_4$, THF, H_2O; iv, EtSH, $BF_3 \cdot OEt_2$, −78 °C to 0 °C; v, Raney® Ni, EtOH, reflux.

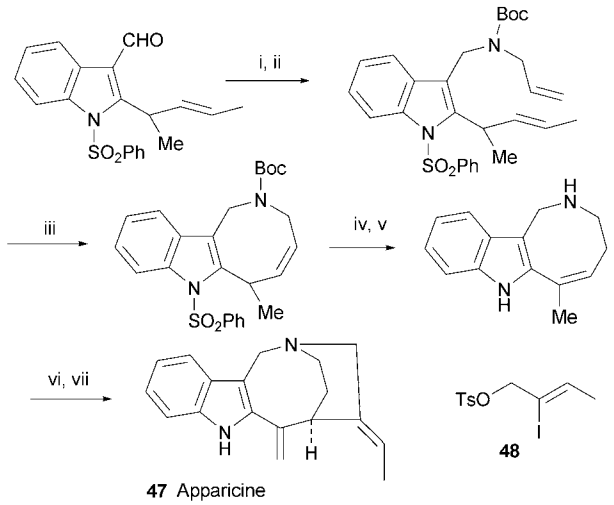


Scheme 12 *Reagents and conditions*: i, *n*-BuLi, toluene, −78 °C to rt, 2 h; ii, Et_2Zn, $Pd(dba)_3$, P(*t*-Bu)$_3 \cdot HBF_4$, THF, 65 °C, 1 h.

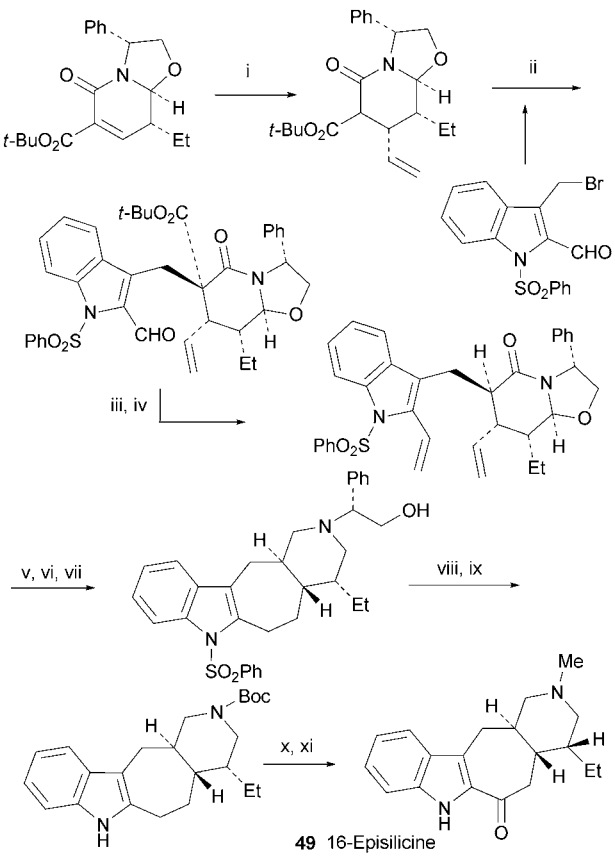
A total synthesis of a marine alkaloid (±)-**51**, isolated from a red marine organism, the tunicate *Dendrodoa grossularia*, has been achieved through a novel twist on an oxazole rearrangement (Scheme 16).[38]

Total syntheses of (*R*)-convolutamydines A (**52**), B (**53**) and E (**54**) have been achieved through a catalytic enantioselective aldol condensation of isatin with acetone and acetaldehyde in the presence of *N*-(2-thiophene-sulfonyl)prolinamide (**55**) as an organocatalyst (Scheme 17).[39]

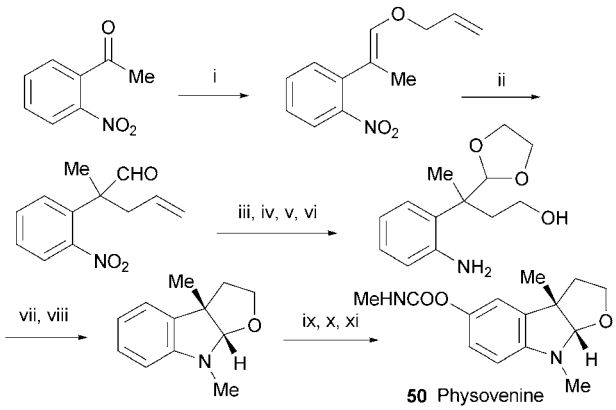
Soulieotine (**56**), isolated from a traditional Chinese medicine *Souliea vaginata*, has been synthesized by Pd-catalyzed



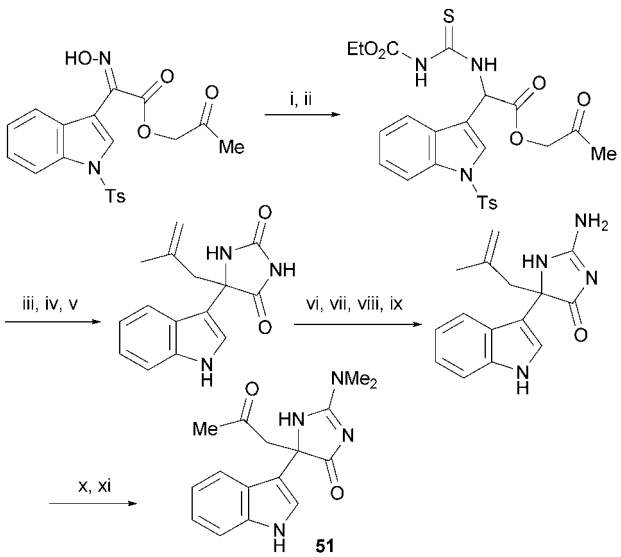
Scheme 13 *Reagents and conditions*: i, allylamine, $NaBH(OAc)_3$, AcOH, CH_2Cl_2, rt; ii, Boc_2O, MeOH, Et_3N, reflux; iii, second-generation Grubbs' catalyst, CH_2Cl_2, reflux; iv, *t*-BuOK, THF, reflux; v, 1 M HCl, MeOH, rt; vi, **48**, *i*-Pr_2NEt, CH_2Cl_2, CH_3CN, rt; vii, $Pd(OAc)_2$, Ag_2CO_3, Et_3N, toluene, 80 °C.



Scheme 14 *Reagents and conditions*: i, CH_2=CHMgBr, CuI, LiCl, TMSCl, THF, −78 °C, 16 h; ii, NaH, DMF, rt, 20 h; iii, $[Ph_3PCH_3]^+Br^-$, KHMDS, THF, reflux, 6 h; iv, TFA, CH_2Cl_2, rt, 1 h, then toluene, reflux, 15 h; v, second-generation Grubbs' catalyst, toluene, reflux; vi,H_2, PtO_2, EtOAc, rt, 24 h; vii, $AlCl_3$, $LiAlH_4$, THF, −78 °C to 0 °C, 3 h; viii, Mg, MeOH, rt, 6 h; ix, H_2, $Pd(OH)_2$, Boc_2O, EtOAc, rt, 24 h; x, I_2O_5, THF, H_2O; xi, TFA, THF, then MeI.



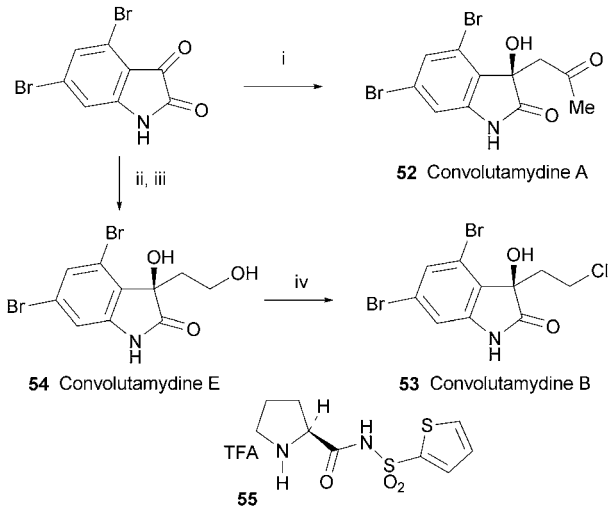
Scheme 15 *Reagents and conditions*: i, $[Ph_3PCH_2OCH_2CH{=}CH_2]^+Cl^-$, *t*-BuONa, THF, 0 °C; ii, xylene, reflux; iii, $(CH_2OH)_2$, *p*-TsOH, toluene, reflux, rt; iv, O_3, Me_2S, CH_2Cl_2; v, $NaBH_4$, THF, H_2O; vi, Raney® Ni, H_2, MeOH; vii, *p*-TsOH, THF, H_2O, reflux; viii, HCHO, H_2, Pd/C, AcOEt, rt; ix, NBS, DMF, 0 °C; x, CuI, NaOMe, reflux; xi, BBr_3, $MeNH_2$, $CO(COCl_3)_2$, toluene, reflux, NaH, MeNCO.



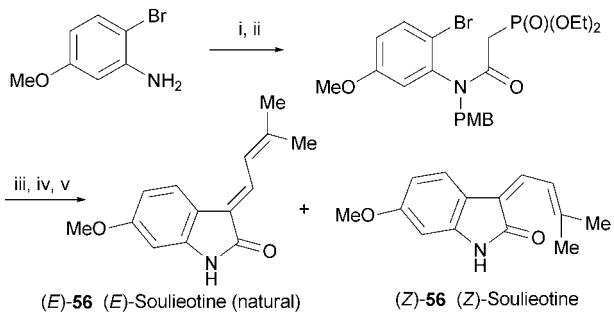
Scheme 16 *Reagents and conditions*: i, Zn, AcOH, 0 °C, 2 h; ii, EtO-CONCS, CH_2Cl_2, rt, 16 h; iii, EDCI, Et_3N, CH_2Cl_2, 0 °C to reflux, 9 h; iv, NaOMe, MeOH, rt, 4 h; v, aq. HCl, 5 min; vi, Lawesson's reagent, toluene, reflux; vii, MeI, DMAP, *i*-$PrNEt_2$, CH_2Cl_2, rt, 2 h; viii, Me_2NH, THF, sealed tube, 75 °C, 14 h; ix, KOEt, EtOH, reflux, 24 h; x, OsO_4, NMO, rt, 4 h; xi, $NaIO_4$, 0 °C, 2 h.

intramolecular enolate arylation followed by an *in situ* Horner–Wardsworth–Emmons olefination. The natural product is the *E*-isomer, and its structure was unambiguously established by X-ray crystallography (Scheme 18).[40]

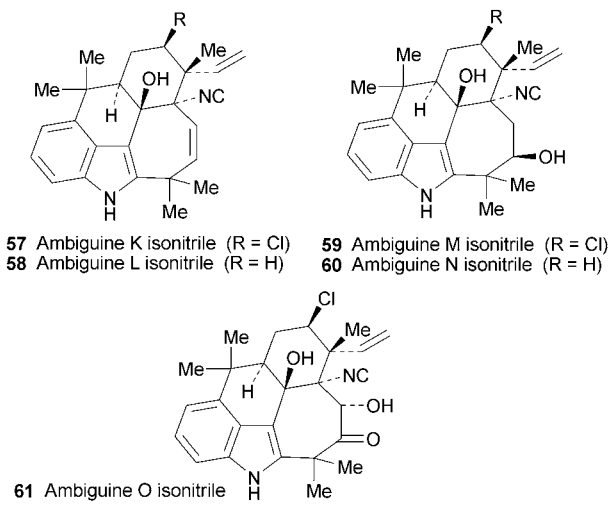
Five new antibacterial ambiguine K–O isonitriles (**57–61**) have been isolated from the cultured cyanobacterium *Fischerella ambigua* by bioassay-guided fractionation, and the absolute stereoconfiguration of **57** was determined by X-ray crystallography. All compounds were evaluated for their antibacterial activities.[41]

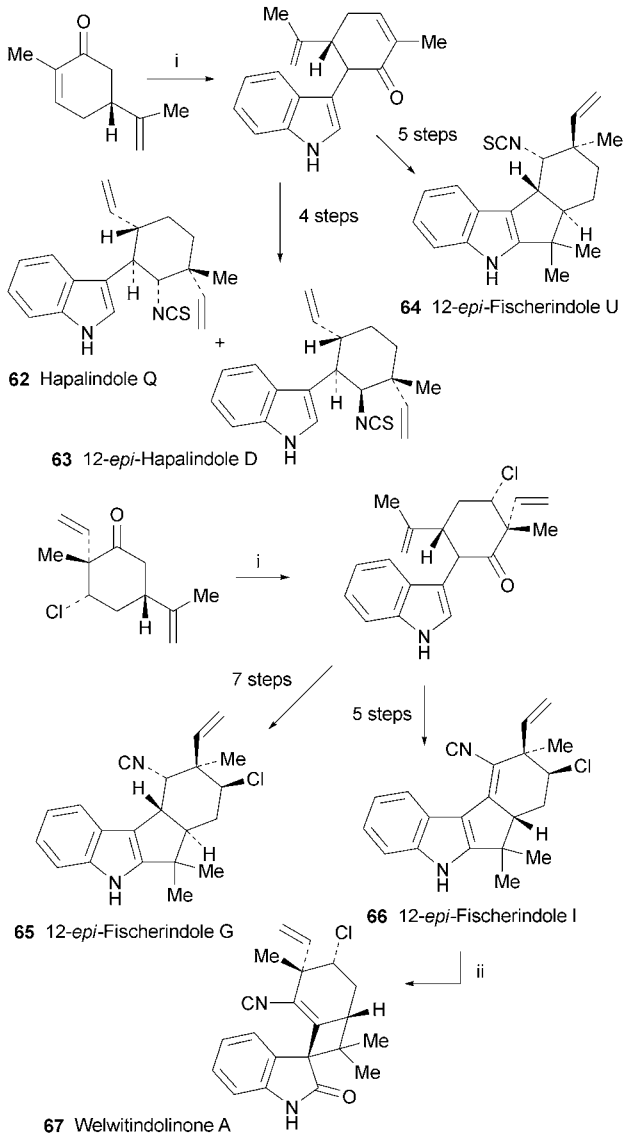


Scheme 17 *Reagents and conditions*: i, **55** (10 mol%), acetone, H_2O, 47 h, rt, 97% ee; ii, **55** (10 mol%), acetaldehyde, THF, rt, 48 h, 92% ee; iii, $NaBH_3CN$, AcOH; iv, TsCl, pyridine, 75 °C, 7 h.



Scheme 18 *Reagents and conditions*: i, *p*-anisaldehyde, TFA, $NaBH(OAc)_3$; ii, $(EtO)_2P(O)CH_2COCl$, DMAP; iii, $Pd(PPh_3)_4$, KDMO, THF, microwave; iv, 3-methylbutenal; v, anisole, TFA.





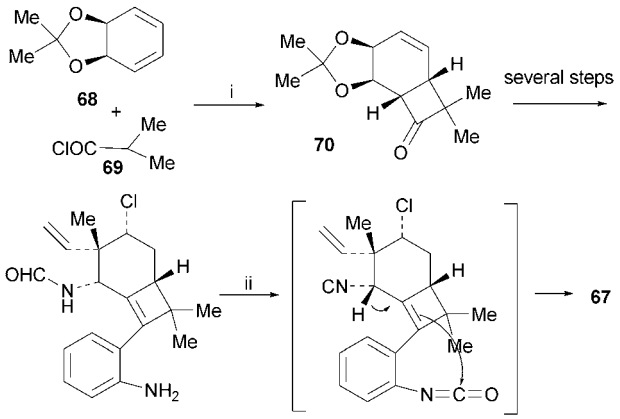
Scheme 19 *Reagents and conditions*: i, indole, LHMDS, THF, −78 °C, 30 min, then copper(II) 2-ethylhexanoate, THF, −78 °C to 23 °C, 20 min; ii, XeF_2, MeCN, H_2O, 23 °C, 5 min.

Full details have been provided for the syntheses of hapalindole Q (**62**), 12-*epi*-hapalindole D (**63**), 12-*epi*-fischerindole U (**64**), 12-*epi*-fischerindole G (**65**), 12-*epi*-fischerindole I (**66**) and welwitindolinone A (**67**) using oxidative indole coupling with ketones as the key step (Scheme 19).[42]

A full account of the total synthesis of (±)-**67** from ketone **70**, available from regio- and diastereoselective [2 + 2] ketene cycloaddition between **68** and **69**, has been reported (Scheme 20).[43]

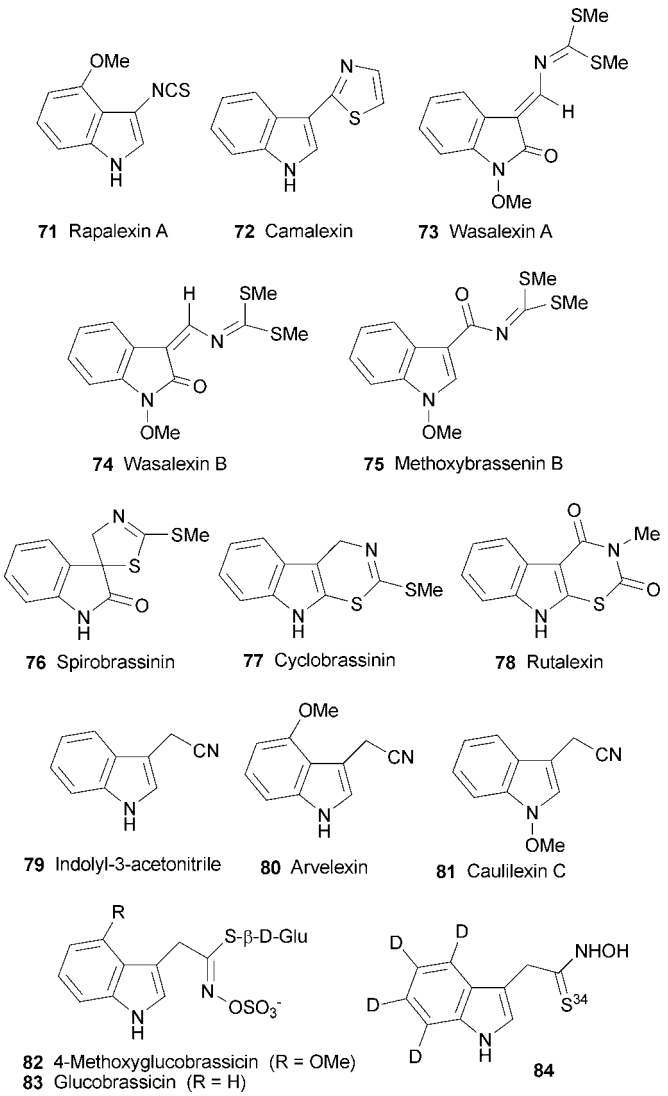
2.1.1 Indole phytoalexins. Phytoalexins are chemical defences produced *de novo* by plants to ward off pathogens and other stresses. Upon investigation of phytoalexin production using wild crucifers sprayed with a $CuCl_2$ solution, *Arabidopsis thaliana* produced rapalexin A (**71**) and camalexin (**72**), while *Thellungiella halophila* produced **71**, wasalexins A (**73**) and B (**74**), and methoxybrassenin B (**75**).[44]

When *Brassica rapa* was inoculated with either different races of the biotroph *Albugo candida* or sprayed with a $CuCl_2$ solution,



Scheme 20 *Reagents and conditions*: i, Et_3N, THF, reflux; ii, $COCl_2$, Et_3N, then LHMDS, THF, −78 °C.

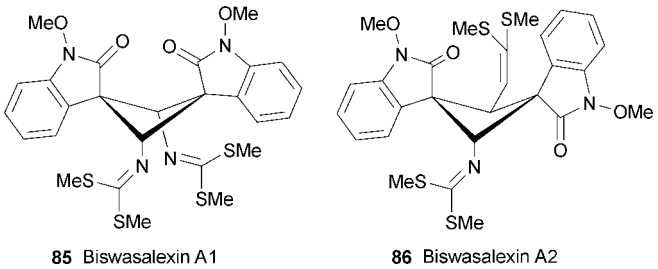
phytoalexins (spirobrassinin (**76**), cyclobrassinin (**77**) and rutalexin (**78**)) and phytoanticipins (indolyl-3-acetonitrile (**79**), arvelexin (**80**), caulilexin C (**81**) and 4-methoxyglucobrassicin (**82**)) were produced in response to both biotic and abiotic elicitation.[45]



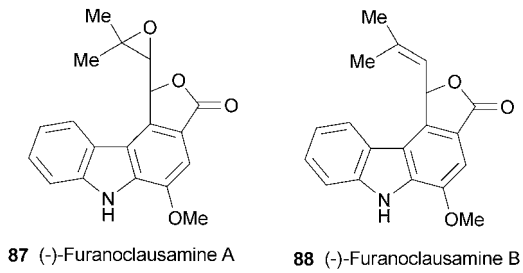
Biosynthetic pathways of crucifer phytoalexins have been investigated based on the incorporation of labelled compound [4′,5′,6′,7′-$^2H_4$]indolyl-3-[^{34}S]acetothiohydroxamic acid (**84**) into **77**, **76** and glucobrassinin (**83**).[46]

A review on the evolution of biosynthetic pathways of thiazolylindoles (camalexin (**72**) and structurally related compounds) has appeared.[47]

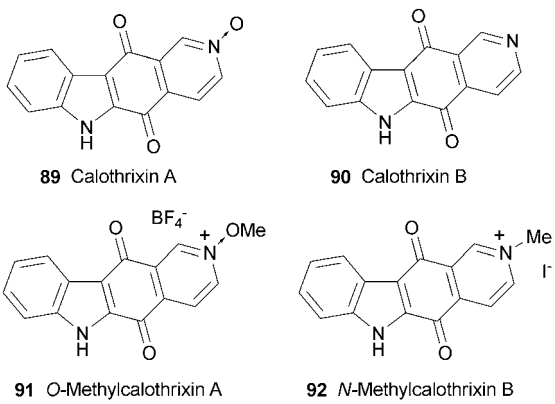
The production of phytoalexins in *Thellungiella halophila* exposed to UV radiation has been investigated, which led to the isolation of two metabolites, biswasalexins A1 (**85**) and A2 (**86**).[48]



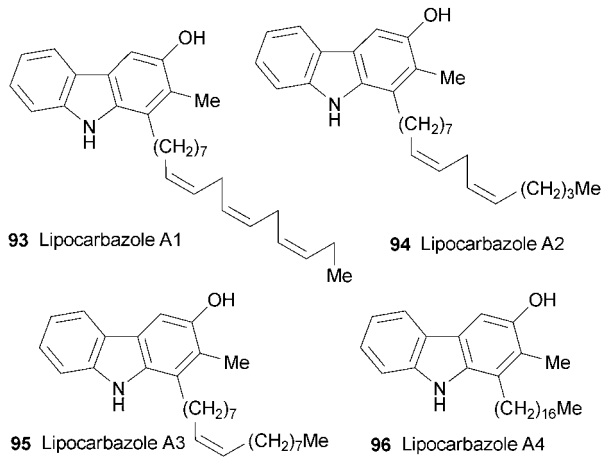
2.1.2 Carbazoles. Two new γ-lactone carbazole alkaloids, (−)-furanoclausamines A (**87**) and B (**88**), have been obtained from the stems of *Clausena anisata* collected in Thailand, along with eight known alkaloids.[49]



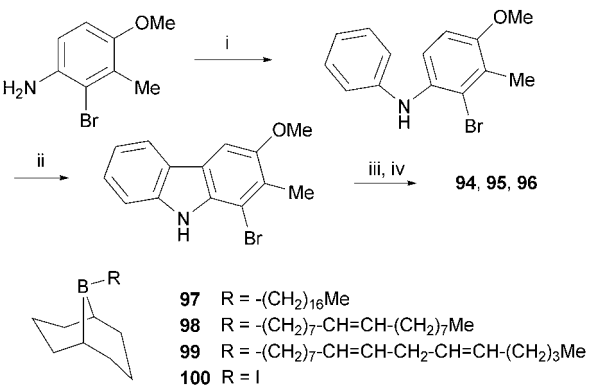
Calothrixins A (**89**) and B (**90**) have been converted to the corresponding *O*-methyl (**91**) and *N*-methyl (**92**) derivatives, respectively. All four compounds were found to act as poisons of DNA topoisomerase I, and three compounds (**89**, **90** and **92**) exhibited cytotoxicity toward cultured CEM leukemia cells.[50]



Four new secondary metabolites with a carbazole moiety, lipocarbazoles A1 (**93**), A2 (**94**), A3 (**95**) and A4 (**96**), have been isolated from the fermentation foam of the actinomycete *Tsukamurella pseudospumae* strain Acta 1857. Compounds **95** and **96** showed a slightly better activity for scavenging the DPPH radical in MeOH than ascorbic acid.[51]



Lipocarbazoles A2 (**94**), A3 (**95**) and A4 (**96**) have been synthesized through a sequence of three Pd-mediated coupling reactions (Scheme 21).[52]

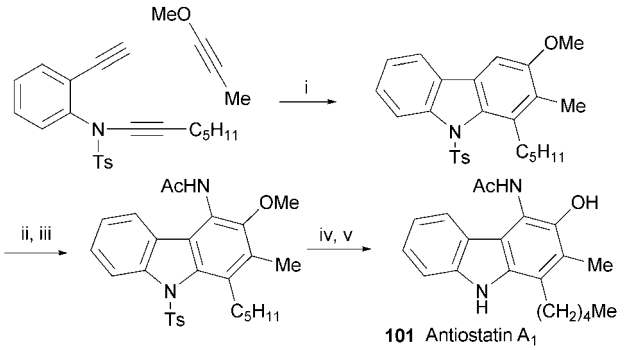


Scheme 21 *Reagents and conditions*: i, PhOTf, $Pd(OAc)_2$, BINAP, Cs_2CO_3, toluene, 100 °C, 24 h; ii, $Pd(OAc)_2$, AcOH, 100 °C, 24 h; iii, **97**, **98** or **99**, $PdCl_2$(dppf), 3 N NaOH, THF, 65 °C, 1 h; iv, **100**, hexane, rt, 5 min.

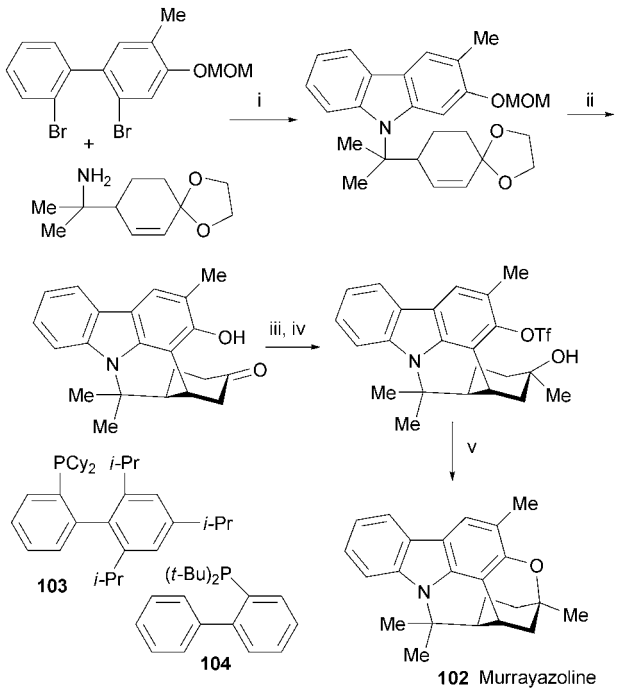
Antiostatin A_1 (**101**) has been isolated from *Streptomyces cyaneus* 2007-SV1 and showed significant inhibitory effects against free radical-induced lipid peroxidation. In addition, he first total synthesis of **101** was achieved through Rh-catalyzed cross-alkyne cyclotrimerization and Pd-catalyzed amidation reactions (Scheme 22).[53]

The total synthesis of (±)-murrayazoline (**102**), obtained from the genus *Murraya*, has been achieved through the double *N*-arylation of a sterically hindered amine, and intramolecular Friedel–Crafts-type Michael addition and Pd-catalyzed C–O coupling reactions (Scheme 23).[54]

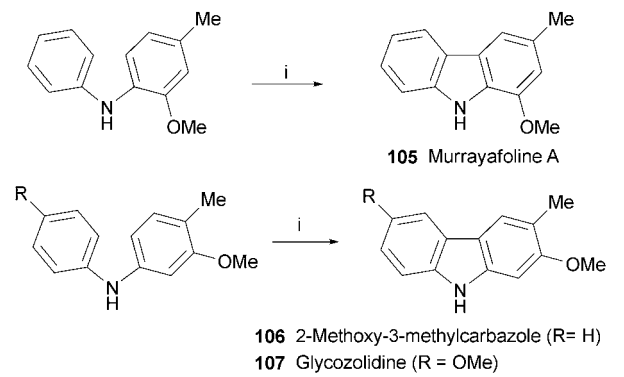
A mild methodology for the synthesis of three oxygenated carbazoles, murrayafoline A (**105**), 2-methoxy-3-methylcarbazole (**106**) and glycozolidine (**107**), has been developed



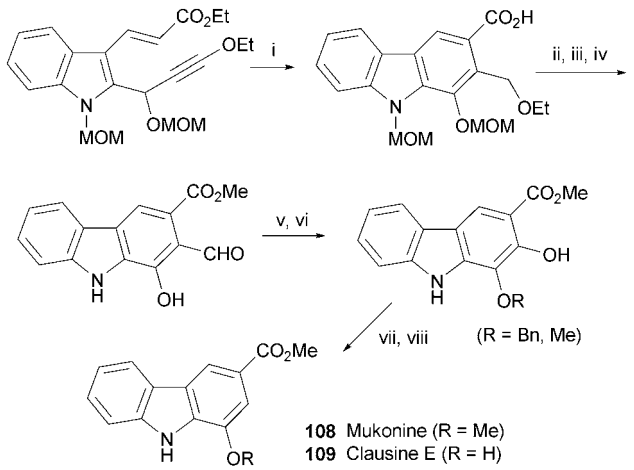
Scheme 22 *Reagents and conditions*: i, $RhCl(PPh_3)_2$, toluene, rt, 2 d; ii, NBS, MeCN, rt, 12 h; iii, $AcNH_2$, $Pd_2(dba)_3$, Xantphos, dioxane, 100 °C; iv, TBAF, THF, reflux, 30 h; v, BBr_3, CH_2Cl_2, −78 °C to rt.



Scheme 23 *Reagents and conditions*: i, $Pd_2(dba)_3$, **103**, *t*-BuONa, toluene, 130 °C, 13 h; ii, $Sc(OTf)_3$, $ClCH_2CH_2Cl$, H_2O, sealed tube, 120 °C, 36 h; iii, Tf_2O, Et_3N, DMAP, CH_2Cl_2; iv, MeMgBr, Et_2O, −78 °C to rt; v, $Pd(OAc)_2$, **104**, Cs_2CO_3, sealed tube, toluene, 120 °C, 20 h.



Scheme 24 *Reagents and conditions*: i, $Pd(OAc)_2$, $Cu(OAc)_2$, MW (100 W, 130 °C, 1 h), DMF.



Scheme 25 *Reagents and conditions*: i, *t*-BuOK, THF, *t*-BuOH, 90 °C, 1 h; ii, MeI, NaOH, HMPA, rt, 1 h; iii, DDQ, CH_2Cl_2, 50 °C, 24 h; iv, 6 M HCl, ethylene glycol, THF, 60 °C, 7 h; v, MeI or BnBr, K_2CO_3, DMF, 0 °C, 12 h; vi, MCPBA, KF, CH_2Cl_2, rt, 1 h; vii, Tf_2NPh, NaH, THF, −30 °C, 3 h; viii, H_2, 10% Pd/C, EtOH, rt, 4 h.

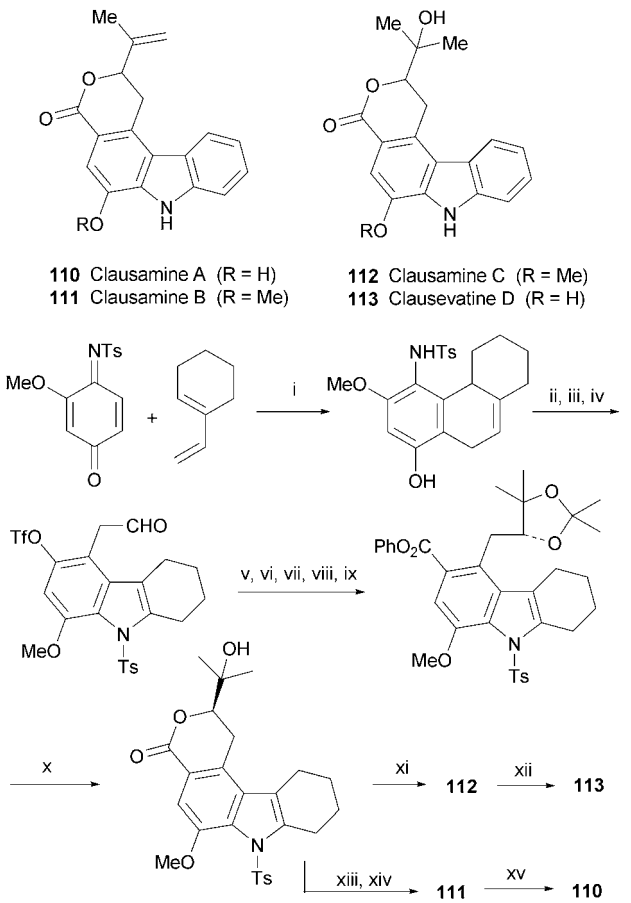
based on Pd-catalyzed microwave-assisted oxidative biaryl coupling under non-acidic conditions (Scheme 24).[55]

Two 1,3-disubstituted 1-oxygenated carbazole alkaloids, mukonine (**108**) and clausine E (clausoline I) (**109**), have been synthesized through an allene-mediated thermal electrocyclic reaction (Scheme 25).[56]

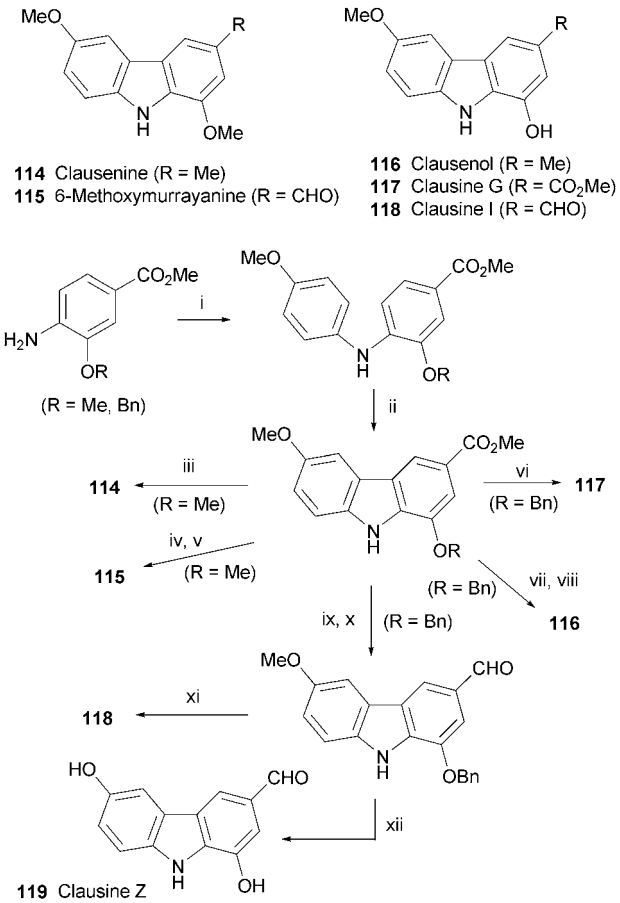
The first total syntheses of clausamines A (**110**), B (**111**) and C (**112**), and clausevatine D (**113**) have been achieved based on the Diels–Alder reaction between iminoquinone and cyclic diene as the key step (Scheme 26).[57]

A general route to oxygenated carbazole alkaloids has been developed by Knölker, based on Pd-catalyzed Buchwald–Hartwig coupling and Pd-catalyzed biaryl coupling reactions. Efficient syntheses of clausenine (**114**), 6-methoxymurrayanine (**115**) and clausenol (**116**), and the first total syntheses of clausine G (**117**), clausine I (**118**) and clausine Z (**119**), have been developed (Scheme 27).[58]

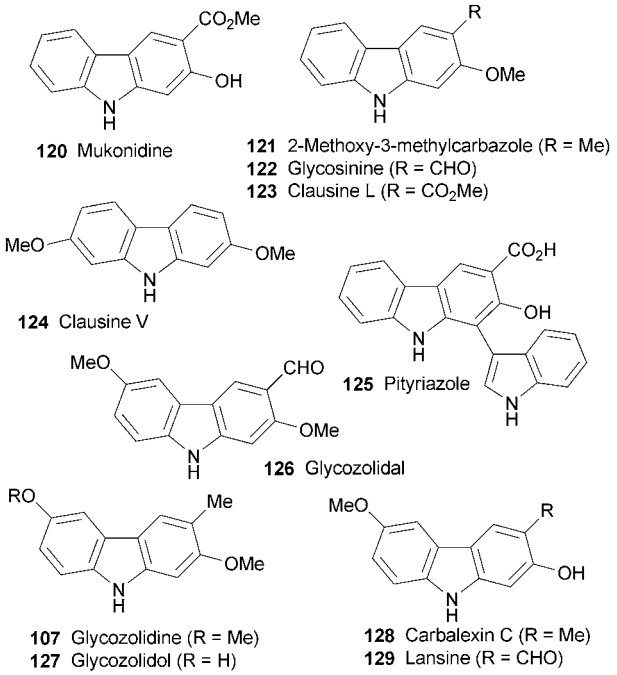
Using the Pd-catalyzed assembly of carbazoles, an efficient route to other oxygenated carbazole alkaloids (**120–129**) has also been developed.[59]



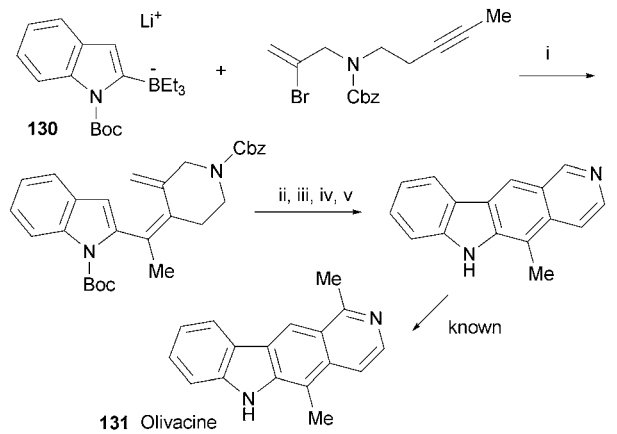
Scheme 26 *Reagents and conditions*: i, CH_2Cl_2, reflux, then DBU; ii, Tf_2O, pyridine; iii, OsO_4, NMO; iv, $NaIO_4$, SiO_2, then H_2SO_4; v, $[i\text{-}PrPPh_3]^+I^-$, *n*-BuLi, THF, 0 °C; vi, AD-mixβ; vii, TsOH, $CH_2{=}C(OMe)CH_3$; viii, $Pd(PPh_3)_4$, CO, phenol; ix, DDQ, benzene; x, TsOH, glycol; xi, TBAF; xii, BBr_3; xiii, Martin's sulfurane; xiv, TBAF; xv, BBr_3.



Scheme 27 *Reagents and conditions*: i, $Pd(OAc)_2$, *S*-Phos, Cs_2CO_3, 4-bromoanisole, toluene, 110 °C, 5 d; ii, $Pd(OAc)_2$, AcOH, 117 °C, 4 h; iii, $LiAlH_4$, THF, 67 °C, 4 h; iv, DIBAH, Et_2O, −78 °C, 3.5 h; v, MnO_2, CH_2Cl_2, rt, 24 h; vi, H_2, 10% Pd/C, CH_2Cl_2, MeOH, rt, 18 h; vii, $LiAlH_4$, THF, 67 °C, 7 h; viii, H_2, 10% Pd/C, CH_2Cl_2, MeOH, rt, 40 h; ix, DIBAH, Et_2O, −78 °C, 3.5 h; x, MnO_2, CH_2Cl_2, rt, 24 h; xi, $AlCl_3$, dioxane, 101 °C, 3 h; xii, BBr_3, CH_2Cl_2, −78 °C to rt, 24 h.

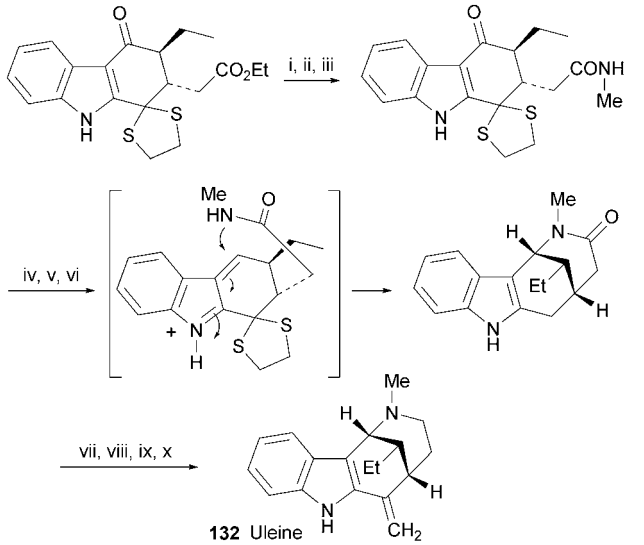


A short formal synthesis of olivacine (**131**) has been achieved using Pd-catalyzed tandem cyclization–cross-coupling of indolylborate (**130**) with vinyl bromide (Scheme 28).[60]

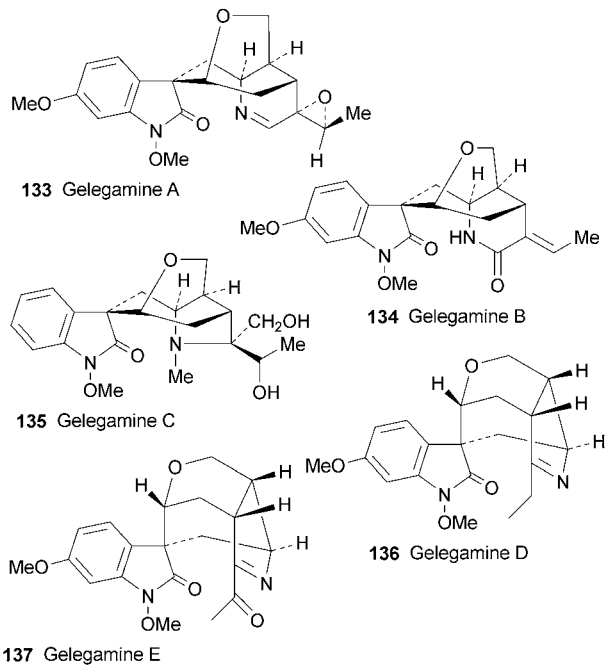


Scheme 28 *Reagents and conditions*: i, $PdCl_2(MeCN)_2$, THF, 60 °C; ii, *hv*, benzene; iii, 10% Pd/C, H_2, THF; iv, MnO_2, EtOAc, reflux; v, Cs_2CO_3, MeOH, THF, reflux.

A total synthesis of (±)-uleine (**132**) has been completed starting from tetrahydrocarbazole through an intramolecular Michael reaction (Scheme 29).[61]



Scheme 29 *Reagents and conditions*: i, 15% KOH; ii, $ClCO_2Et$, Et_3N, $CHCl_3$; iii, $MeNH_2$; iv, $BH_3{\cdot}SMe_2$; v, AcOH; vi, DDQ; vii, $PhI(OCOCF_3)_2$; viii, MeLi; ix, TFA, CH_2Cl_2; x, $LiAlH_4$.



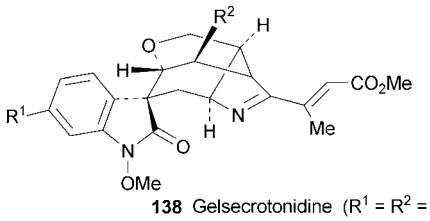
2.2 Tryptamines

Five new oxindole alkaloids, gelegamines A (**133**), B (**134**), C (**135**), D (**136**) and E (**137**), have been isolated from the roots of *Gelsemium elegans*. The absolute configurations of all compounds were established by biosynthetic consideration coupled with CD experiments.[62]

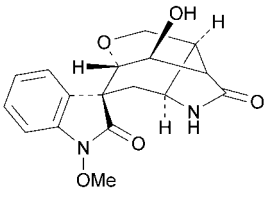
Four new gelsedine-type oxindole alkaloids, gelsecrotonidine (**138**), 14-hydroxygelsecrotonidine (**139**), 11-methoxygelsecrotonidine (**140**) and 14-hydroxygelsedilam (**141**), have been isolated from the leaves and branches of *Gelsemium elegans*.[63]

Two new oxindole alkaloids, gelseoxazolidinine (**142**) and gelsevanillidine (**143**), have been obtained from *Gelsemium elegans*.[64]

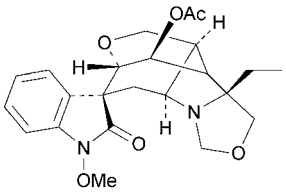
Two new 11-hydroxy-substituted gelsedine-type indole alkaloids, 11,14-dihydroxygelsenicine (**144**) and 11-hydroxygelsenicine (**145**), have been isolated from the EtOH extract of the stems of *Gelsemium elegans*. The configuration of **144** was determined by X-ray diffraction analysis.[65]



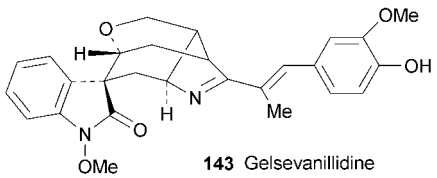
138 Gelsecrotonidine ($R^1 = R^2 = H$)
139 14-Hydroxygelsecrotonidine ($R^1 = OH$, $R^2 = H$)
140 11-Methoxygelsecrotonidine ($R^1 = H$, $R^2 = OMe$)



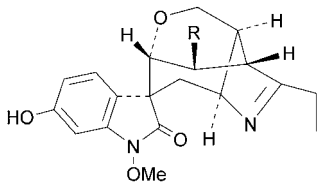
141 14-Hydroxygelsedilam



142 Gelseoxazolidinine



143 Gelsevanillidine

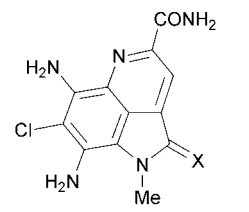


144 11,14-Dihydroxygelsenicine (R = OH)
145 11-Hydroxygelsenicine (R = H)

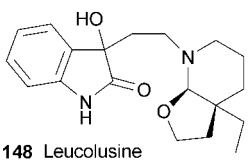
Ammosamides A (**146**) and B (**147**) have been obtained from *Streptomyces* strain CNR-698 isolated from bottom sediments collected in the Bahamas. Both compounds exhibited significant *in vitro* cytotoxicity against HCT-116 colon carcinoma.[66]

A tetracyclic ring-opened oxindole alkaloid, leucolusine (**148**), has been isolated from the Malayan species *Leuconotis griffithii*. A possible biosynthetic pathway from an *Aspidosperma* precursor was proposed.[67]

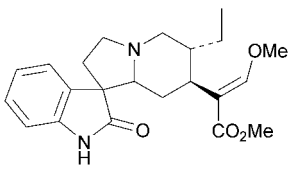
Rhynchophylline (**149**), a neuroprotective agent isolated from *Uncaria rhynchophylla*, has been shown to result slow voltage-gated K^+-channel inactivation.[68]



146 Ammosamide A (X = S)
147 Ammosamide B (R = O)

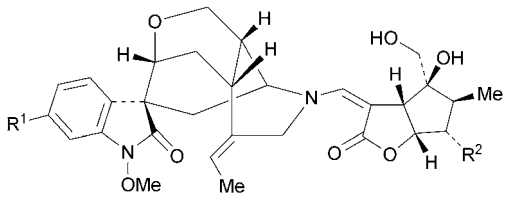


148 Leucolusine



149 Rhynchophylline

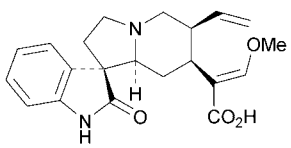
Two new oxindole alkaloids, rankiniridine (**150**) and humanteniridine (**151**), have been isolated from *Gelsemium rankinii* and *Gelsemium elegans*, respectively.[69]



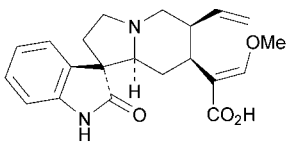
150 Rankiniridine ($R^1 = H$, $R^2 = OH$)
151 Humanteniridine ($R^1 = OMe$, $R^2 = H$)

Two new isomeric alkaloids, 18,19-dehydrocorynoxinic acid B (**152**) and 18,19-dehydrocorynoxinic acid (**153**), have been isolated from the $CHCl_3$ extract of the leaves of *Uncaria rhynchophylla*. These compounds showed weak inhibitory activity for lipopolysaccharide-induced NO release.[70]

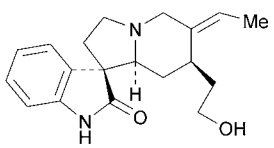
Four tetracyclic oxindole alkaloids, (7*R*)-geissoschizol oxindole (**154**), (7*S*)-geissoschizol oxindole (**155**), (7*R*,16*R*,19*E*)-isositsirikine oxindole (**156**) and (7*S*,16*R*,19*E*)-isositsirikine oxindole (**157**), have been isolated from Malayan *Tabernaemontana corymbosa*.[71]



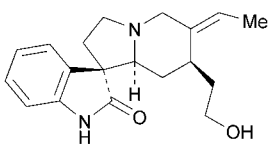
152 18,19-Dehydrocorynoxinic acid B



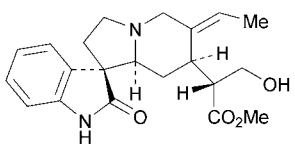
153 18,19-Dehydrocorynoxinic acid



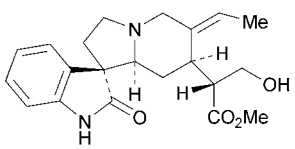
154 (7*R*)-Geissoschizol oxindole



155 (7*S*)-Geissoschizol oxindole



156 (7*R*,16*R*)-(19*E*)-Isositsirikine oxindole

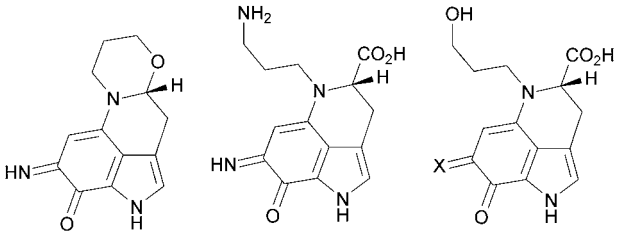


157 (7*S*,16*R*)-(19*E*)-Isositsirikine oxindole

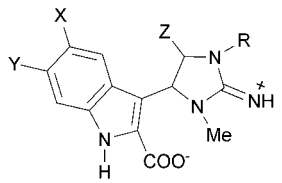
Four red pyrroloquinoline alkaloids, haematopodin B (**158**) and mycenarubins D (**159**), E (**160**) and F (**161**), have been isolated from the fruiting bodies of *Mycena haematopus*. The structures and the absolute configurations of **158–161** were determined.[72]

Novel cytotoxic indole-2-carboxylic acids, trachycladindoles A–G (**162–168**), have been isolated from a southern Australian marine sponge, *Trachycladus laevispirulifer*.[73]

A new antimalarial fungal polyketide, codinaeopsin (**169**), has been isolated from a fungal isolate collected from the White Yemeri tree (*Vochysia guatemalensis*) in Costa Rica.[74] Three novel eight-membered alkaloids, hicksoanes A (**170**), B (**171**) and C (**172**), have been isolated from

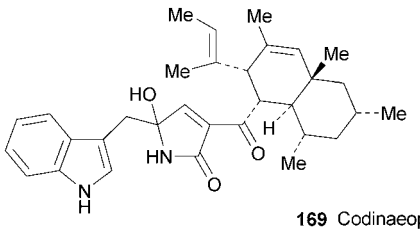


158 Haematopodin B **159** Mycenarubin D **160** Mycenarubin E (X = NH) **161** Mycenarubin F (X = O)

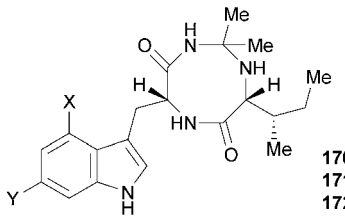


162 Trachycladindole A (X = Br Y = Z = R = H)
163 Trachycladindole B (X = Br Y = Z = H R = Me)
164 Trachycladindole C (X = Br Y = OH Z = R = H)
165 Trachycladindole D (X = Br Y = OH Z = H R = Me)
166 Trachycladindole E (X = Br Y = H Z = OH R = Me)
167 Trachycladindole F (X = Br Y = Z = OH R = Me)
168 Trachycladindole G (X = Y = Z = R = H)

the organic extracts of *Subergorgia hicksoni*, and the structures and the absolute configuration of **170–172** were determined.[75]



169 Codinaeopsin

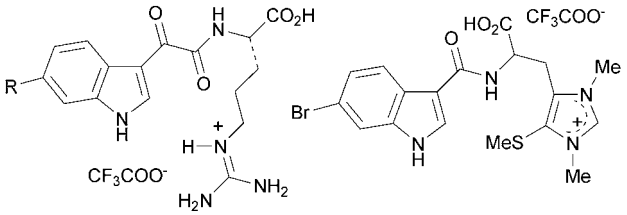


170 Hicksoane A (X = H Y = I)
171 Hicksoane B (X = I Y = H)
172 Hicksoane C (X = Y = I)

Three new indole alkaloids, leptoclinidamines A (**173**), B (**174**) and C (**175**), have been isolated from the Australian ascidian *Leptoclinides durus*. Compounds **173** and **175** were tested for antimalarial, antitrypanosomal and cytotoxic activity.[76]

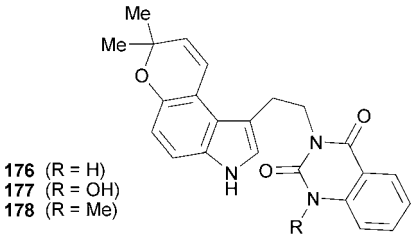
The methanol extract from stems of *Conchocarpus gaudichaudianus* yielded three new indole alkaloids, 3-(2-(7,7-dimethyl-3,7-dihydropyrano-[3,2-*e*]indol-1-yl)ethyl)quinazoline-2,4(1*H*,3*H*)dione (**176**), 3-(2-(7,7-dimethyl-3,7-dihydropyrano-[3,2-*e*]indol-1-yl)ethyl)-1-hydroxyquinazoline-2,4(1*H*,3*H*)dione (**177**) and 3-(2-(7,7-dimethyl-3,7-dihydropyrano-[3,2-*e*]indol-1-yl)ethyl)-1-methylquinazoline-2,4(1*H*,3*H*)dione (**178**).[77]

Six new alkaloids, notoamides F (**179**), G (**180**), H (**181**), I (**182**), J (**183**) and K (**184**), have been isolated from a marine-derived *Aspergillus* sp., and their absolute configurations were elucidated.[78]

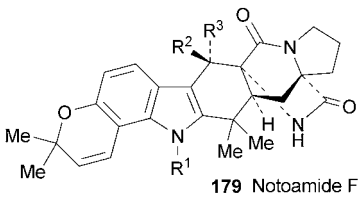


173 Leptoclinidamine A (R = H)
174 Leptoclinidamine B (R = OH)

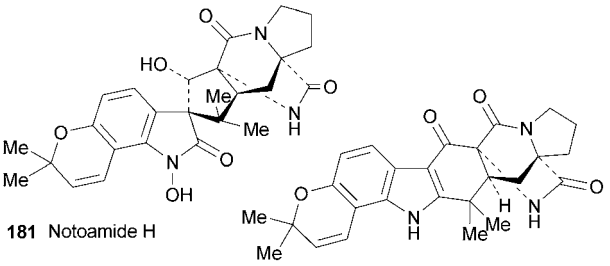
175 Leptoclinidamine C



176 (R = H)
177 (R = OH)
178 (R = Me)

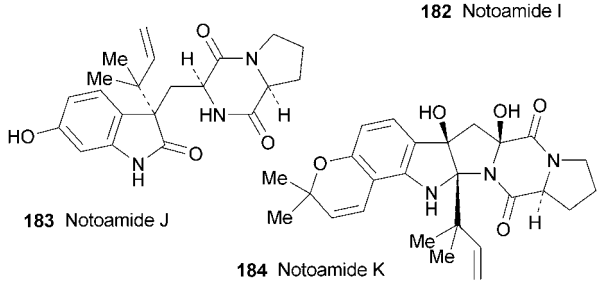


179 Notoamide F (R^1 = R^2 = H, R^3 = OMe)
180 Notoamide G (R^1 = OH, R^2 = H, R^3 = OMe)



181 Notoamide H

182 Notoamide I



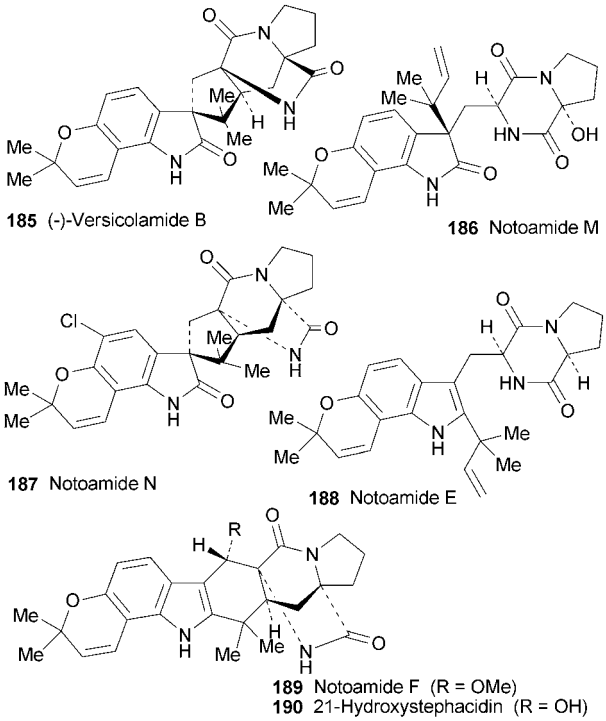
183 Notoamide J

184 Notoamide K

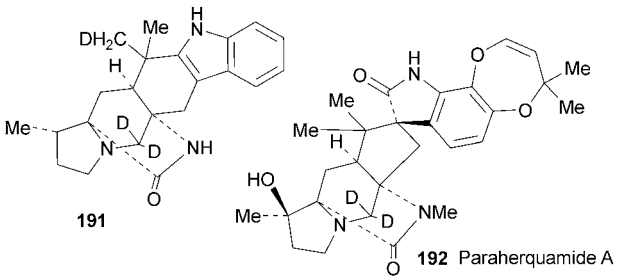
(−)-Versicolamide B (**185**), notoamide M (**186**) and notoamide N (**187**) have been isolated from a marine-derived *Aspergillus* species.[79]

Notoamide E (**188**), which has been postulated to be a putative biosynthetic precursor of notoamides, has been isolated from cultures of a marine-derived *Aspergillus* species.[80]

Isolation of notoamide F (**189**) and 21-hydroxystephacidin (**190**) from the cultivation medium of the marine-derived fungus *Aspergillus ostianus*, and the confirmation of their structures by X-ray crystallography, has been reported.[81]



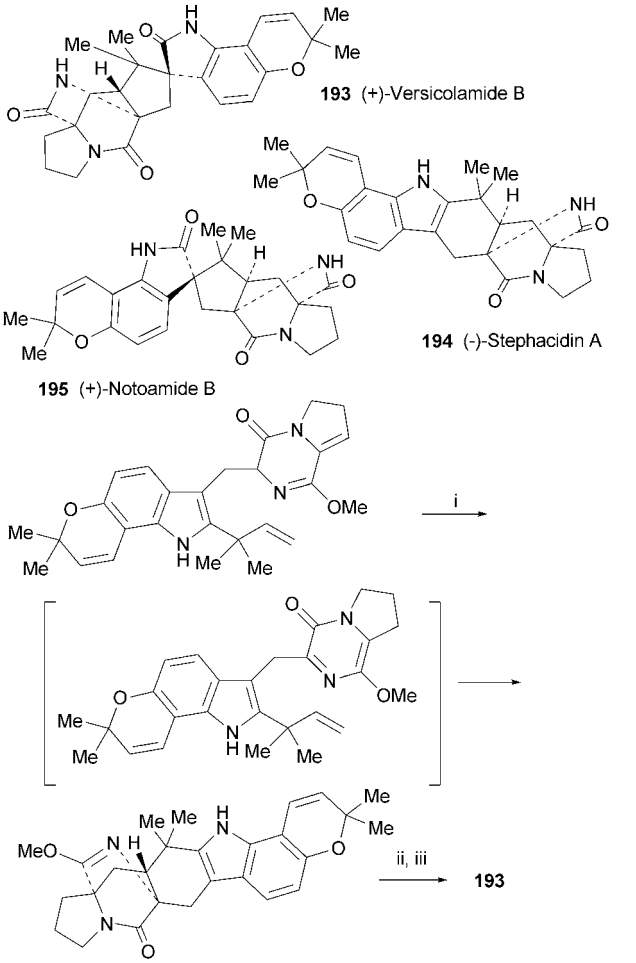
Triply deuterium-labeled 7-hydroxy-preparaherquamide (**191**) has been synthesized from 3-methylproline and tryptophan, and was subjected to a precursor incorporation experiment in the paraherquamide-producing *Penicillium fellutanum*. The isolated sample of paraherquamide A (**192**) revealed incorporation of one of the two germinal deuterons of the CD_2 group at C-12.[82]



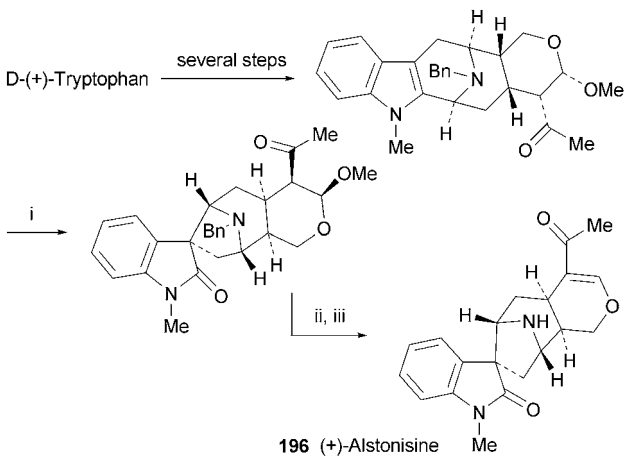
An isolate of *Aspergillus versicolor* NRRL 35600, obtained from a basidioma of *Ganoderma australe* collected in a Hawaiian forest, yielded (+)-versicolamide B (**193**); a biomimetic total synthesis of (±)-**193** was also achieved (Scheme 30). (−)-Stephacidin A (**194**) and (+)-notoamide B (**195**), both with the opposite absolute configuration to that previously reported, were also isolated from *Aspergillus versicolor*.[83]

The first enantioselective total synthesis of (+)-alstonisine (**196**) has been accomplished using a diastereoselective osmylation to construct spirocyclic oxindole as the key step. The structure was determined by NOE experiments and X-ray crystallography (Scheme 31).[84]

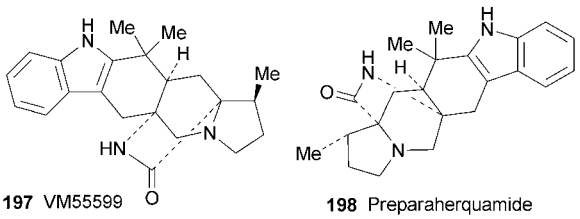
The secondary metabolites VM55599 (**197**) and preparaherquamide (**198**) have been identified as natural metabolites in a culture of *Penicillium fellutanum*, and **198** was also observed as a natural metabolite from *Aspergillus japonicus*.[85]



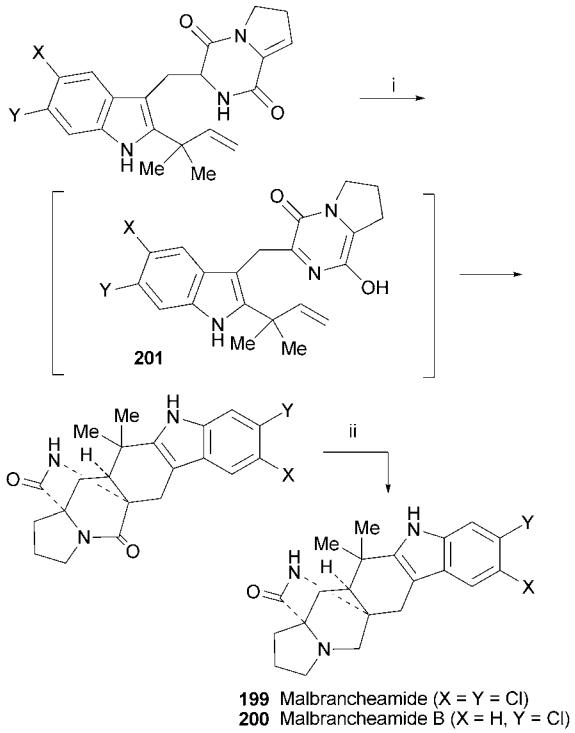
Scheme 30 *Reagents and conditions*: i, 20% NaOH, MeOH, 0 °C to rt, 6 h; ii, Davis' saccharine-derived oxaziridine, CH_2Cl_2, rt, 4 h; iii, 0.1 M HCl, THF, 0 °C, 5 h.



Scheme 31 *Reagents and conditions*: i, OsO_4, pyridine, THF, rt, 3 d, then aq. $NaHSO_3$, rt, 4 h; ii, $Pd(OH)_2/C$, H_2, EtOH, rt, 5 h; iii, 2 N NaOH, MeOH, rt, 2 h.



Biomimetic total syntheses of malbrancheamide (**199**) and malbrancheamide B (**200**), isolated from *Malbranchea aurantiaca* RRC1813, a fungus growing on bat detritus collected in a cave in Mexico, have been achieved through an intramolecular Diels–Alder reaction of 5-hydroxypyrazin-2(1*H*)-one **201** (Scheme 32).[86]



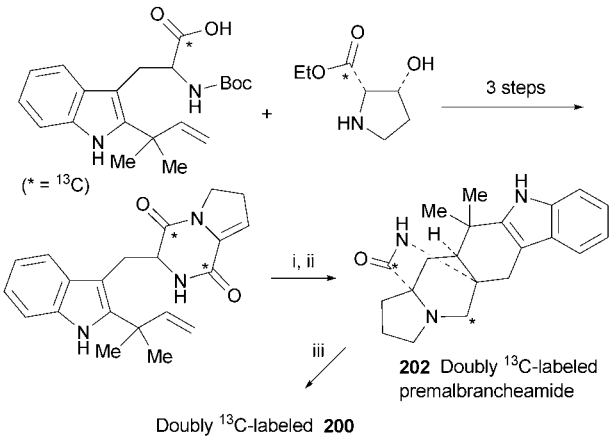
Scheme 32 *Reagents and conditions*: i, 20% aq. KOH, MeOH; ii, DIBAH, toluene.

Premalbrancheamide (**202**), a biosynthetic metabolite of **199** and **200**, has been synthesized in double ^{13}C-labeled form at the 4- and 5-positions *via* an intramolecular Diels–Alder reaction, and was subjected to biosynthetic incorporation experiments (Scheme 33).[87]

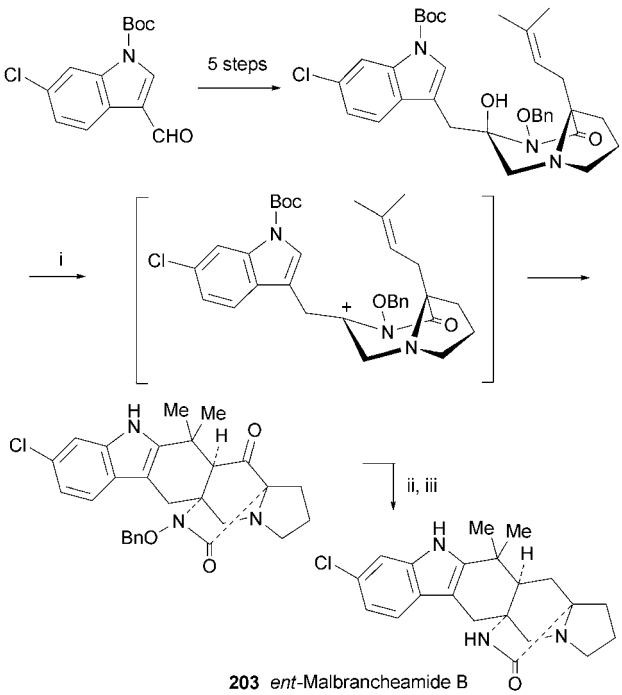
An enantioselective synthesis of *ent*-malbrancheamide B (**203**) has been achieved through double cyclization of hydroxydiketopiperazine *via* α-amino *N*-acyliminium species (Scheme 34).[88]

New members of the discorhabdin A- and B-type families, (+)-(6*R*,8*S*)-1-thiomethyldiscorhabdin G*/I (**204**) and both enantiomers of 16a,17a-dehydrodiscorhabdin W (**205**), have been isolated from New Zealand sponges of the genus *Latrunculia*.[89]

The first asymmetric total synthesis of (+)-prianosin B (**206**) has been achieved through the dehydrogenation of pyrroloiminoquinone (**207**), the known synthetic intermediate of discorhabdin A, as a key step (Scheme 35).[90]



Scheme 33 *Reagents and conditions*: i, 20% aq. KOH, MeOH; ii, DIBAH, toluene; iii, *Malbranchea aurantiaca*.

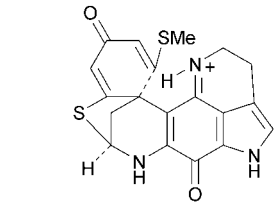


Scheme 34 *Reagents and conditions*: i, TMSOTf, CH_2Cl_2, 0 °C to rt; ii, SmI_2, LiCl, THF, rt; iii, DIBAH, toluene, rt.

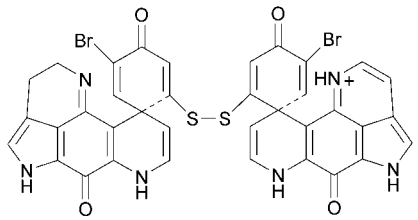
A concise total synthesis of a marine pyrroloiminoquinone alkaloid, tsitsikammamine A (**208**), has been developed through a Michael reaction between the indole dione **209** and 2′-amino-1-(4-methoxyphenyl)ethanol (**210**) (Scheme 36).[91]

Two enantioselective total syntheses of (−)-chaetominine (**211**), obtained from the solid-substrate culture of *Chaetomium* sp. IFB-E015, have appeared.[92,93] Evano's approach applied a copper(I)-mediated cyclization of iodotryptophanylalanine derivative leading to ABC-tricyclic ring system (Scheme 37).[92]

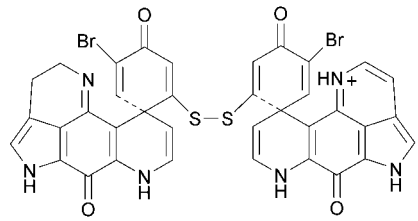
Papeo's strategy to (−)-**211** involved NCS-promoted *N*-acyl cyclization on indole ring as the key step to construct ABC-tricyclic ring system (Scheme 38).[93]



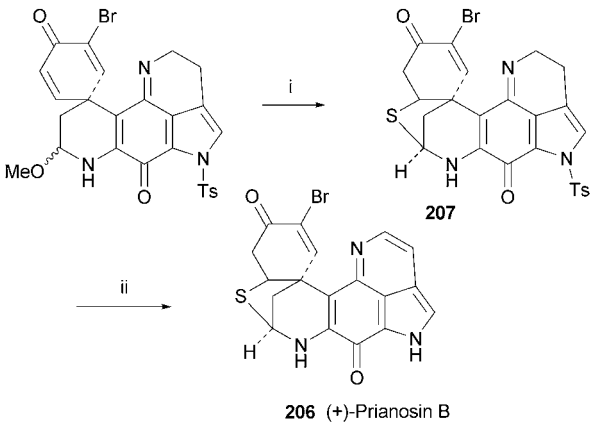
204 (+)-(6*R*,8*S*)-1-Thiomethyldiscorhabdin G*/I



(-)-**205** (-)-(6*S*,6a*S*)-16a,17a-Dehydeodiscorhabdin W



(+)-**205** (+)-(6*R*,6a*R*)-16a,17a-Dehydeodiscorhabdin W



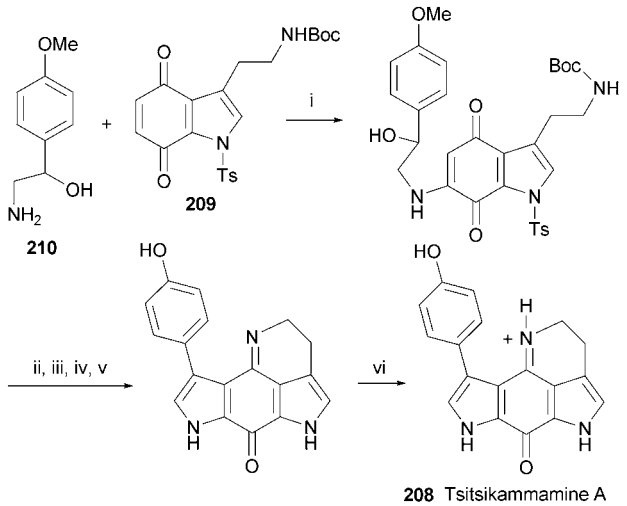
206 (+)-Prianosin B

Scheme 35 *Reagents and conditions*: i, *p*-MeOBnSH, 30% HBr–AcOH, CH_2Cl_2, then aq. $MeNH_2$; ii, NaN_3, DMF.

A pentacyclic indole alkaloid, serotobenine (**213**), has been isolated as the racemate from safflower seeds (*Carthamus tinctorius*). A total synthesis of (−)-**213** was accomplished by a Rh-catalyzed C–H insertion of **214** in a completely stereoselective manner as the key step (Scheme 39).[94]

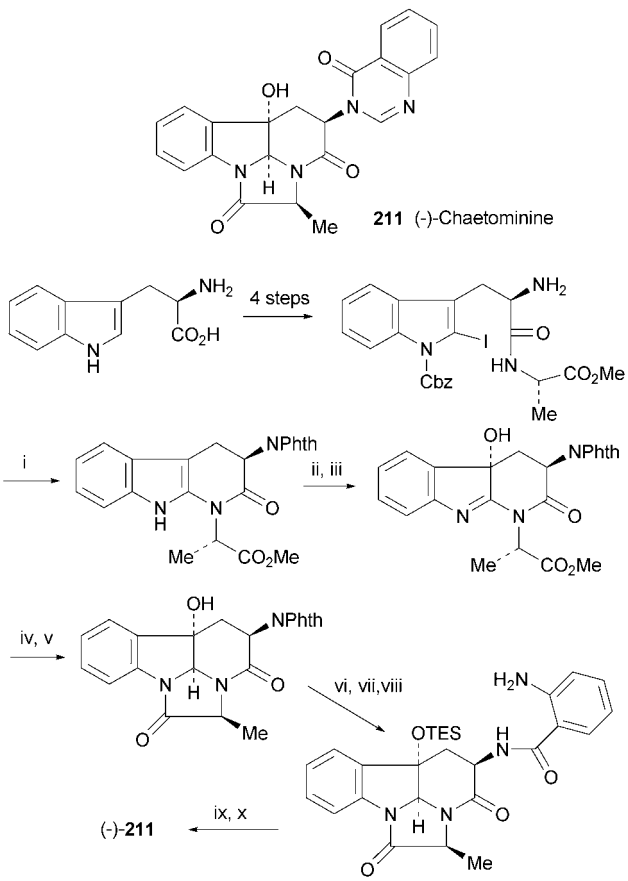
A total synthesis of (−)-*cis*-clavicipitic acid (*cis*-**216**) and (−)-*trans*-clavicipitic acid (*trans*-**216**) has been achieved starting from optically pure 4-chlorotryptophan through a Heck reaction and a stereoselective $Mg(ClO_4)_2$-mediated intramolecular aminoacylation step (Scheme 40).[95]

A concise total synthesis of (±)-aurantioclavine (**217**) has been completed in 3 steps from N^b-benzylserotonin through the base-promoted Pictet–Spengler reaction (Scheme 41).[96]



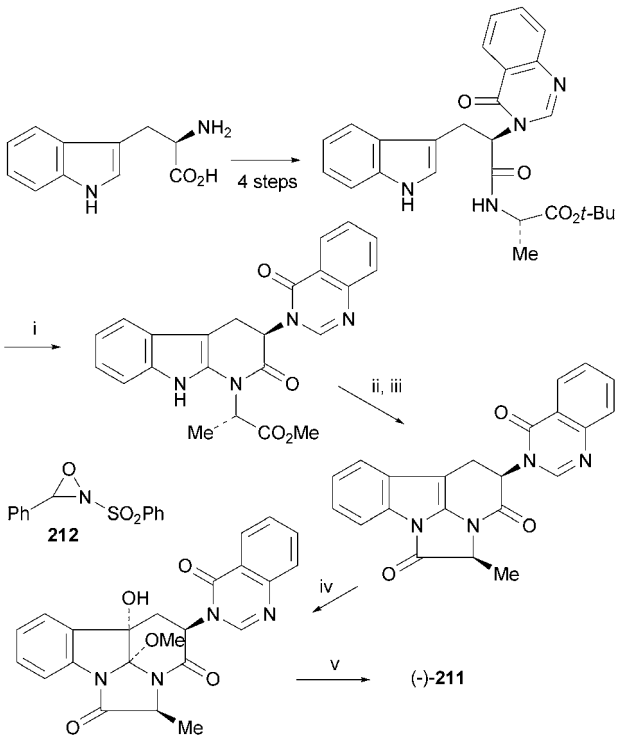
208 Tsitsikammamine A

Scheme 36 *Reagents and conditions*: i, EtOH, rt, 2 h; ii, TFA, CH_2Cl_2; iii, MnO_2, CH_2Cl_2, rt, overnight; iv, EtOH, 4 Å MS, reflux, 3 h; v, BBr_3, CH_2Cl_2, 4 h; vi, TFA.

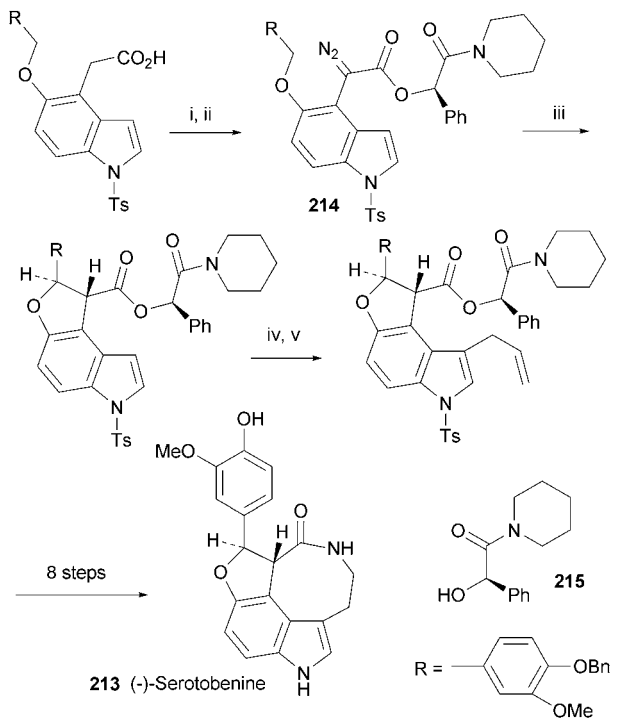


211 (-)-Chaetominine

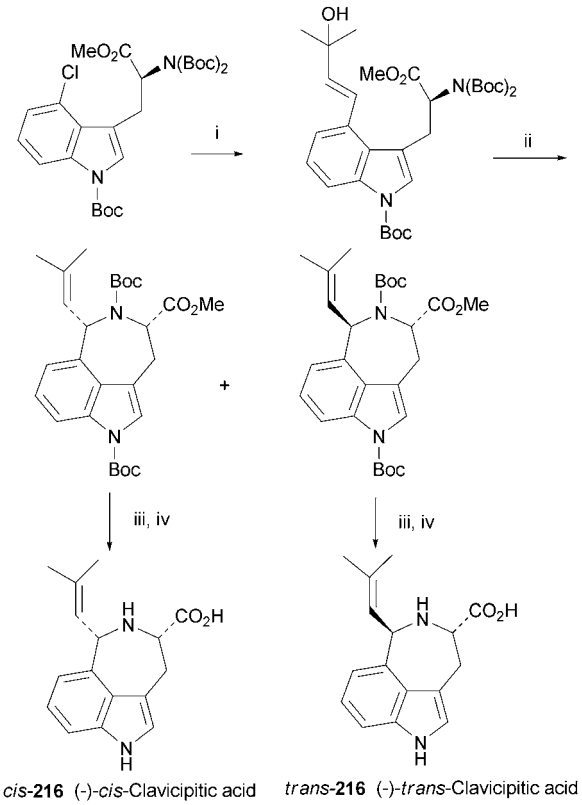
Scheme 37 *Reagents and conditions*: i, CuI, *trans*-*N*,*N*′′-dimethylcyclohexane-1,2-diamine, K_3PO_4, toluene, 110 °C; ii, H_2, Pd/C, MeOH, CH_2Cl_2; iii, DMDO, CH_2Cl_2; iv, $NaBH_3CN$, AcOH, MeOH; v, SiO_2, CH_2Cl_2, acetone, EtOH, NH_3; vi, TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt; vii, hydrazine hydrate, THF, EtOH, rt; viii, isatoic anhydride, benzene, reflux; ix, $CH(OEt)_3$, TsOH, benzene, reflux; x, HF, CH_3CN, rt



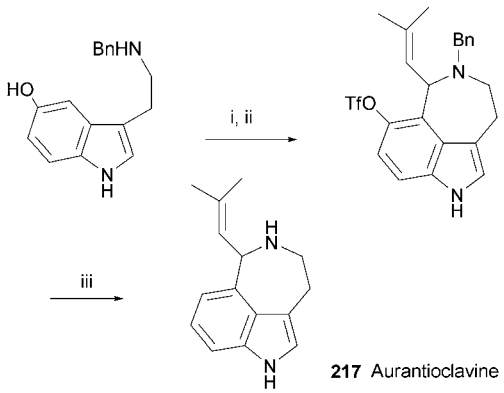
Scheme 38 *Reagents and conditions*: i, NCS, Et_3N, CH_2Cl_2; ii, TFA, CH_2Cl_2, rt; iii, $(COCl)_2$, *i*-Pr_2NEt, DMF, CH_2Cl_2, rt; iv, **212**, CH_2Cl_2, MeOH; v, Et_3SiH, CH_2Cl_2, TFA, rt.



Scheme 39 *Reagents and conditions*: i, **215**, EDCI, DMAP, CH_2Cl_2; ii, *p*-AcNH-C_6H_4-SO_2N_3, DBU, MeCN; iii, Rh_2(*S*-DOSP)$_4$, CH_2Cl_2; iv, NBS, CH_2Cl_2; v, allyltributyltin, Pd(dppf)$Cl_2 \cdot CH_2Cl_2$, toluene, 90 °C.



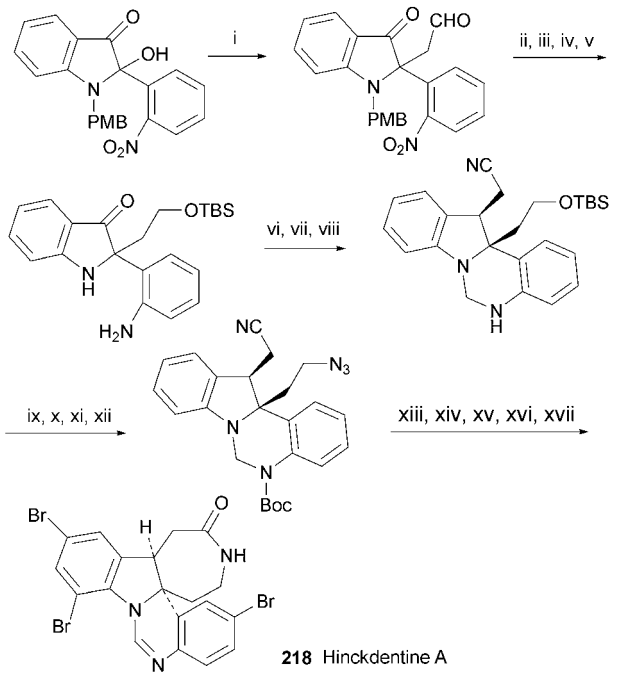
Scheme 40 *Reagents and conditions*: i, 2-methyl-3-buten-2-ol, $Pd(OAc)_2$, Cy_3P, K_2CO_3, dioxane, 120 °C, 12 h; ii, $Mg(ClO_4)_2$, CH_3CN, reflux, 2 h, *cis*/*trans* = 5 : 1; iii, TMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; iv, K_2CO_3, MeOH, H_2O, reflux, 2 d.



Scheme 41 *Reagents and conditions*: i, 3-methylbut-2-enal, Et_3N, MeOH, rt, 10 h; ii, Tf_2O, Et_3N, CH_2Cl_2; iii, Pd/C, HCO_2NH_4, MeOH, rt, 0.5 h.

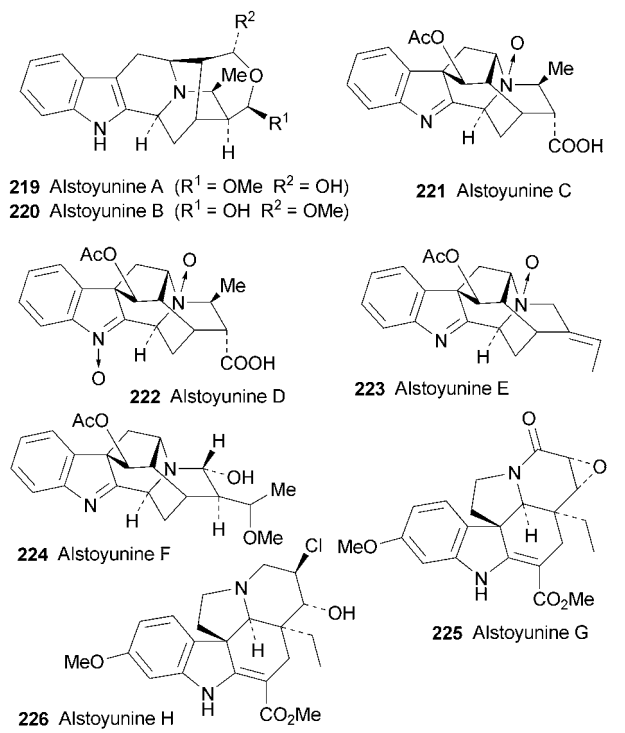
The total synthesis of (±)-hinckdentine A (**218**), isolated from the bryozoans *Hincksinoflustra denticulata*, has been performed through Mannich-type C–C bond formation upon 2-hydroxyindolin-3-one (Scheme 42).[97]

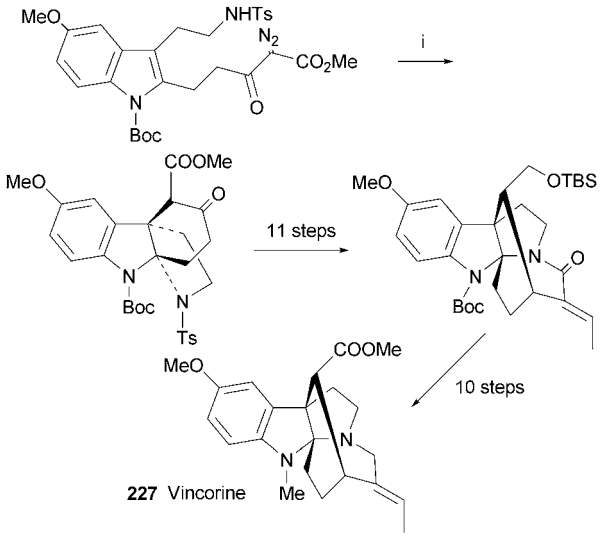
Eight new alkaloids, alstoyunines A–H (**219–226**), have been isolated from *Alstonia yunnanensis*, a medicinal plant used for the treatment of fever, headache and inflammation in the southwest of China.[98]



Scheme 42 *Reagents and conditions*: i, CH_2=CHOTMS, CSA, CH_2Cl_2, 0 °C; ii, $NaBH_4$, MeOH; iii, TBSCl, Et_3N, DMAP, CH_2Cl_2; iv, DDQ, $ClCH_2CH_2Cl$, H_2O; v, Zn, AcOH, CH_2Cl_2; vi, $CH(OMe)_3$, PPTS; vii, $(EtO)_2P(O)CH_2CN$, NaH, DMF; viii, Mg, MeOH; ix, Boc_2O, Et_3N, DMAP, MeCN; x, HF·pyr, THF; xi, MsCl, Et_3N, DMAP, CH_2Cl_2; xii, NaN_3, DMF; xiii, Ph_3P, THF, H_2O; xiv, $RuH_2(PPh_3)_4$, H_2O, DME; xv, NBS, THF; xvi, TFA, CH_2Cl_2; xvii, TPAP, NMO, MeCN.

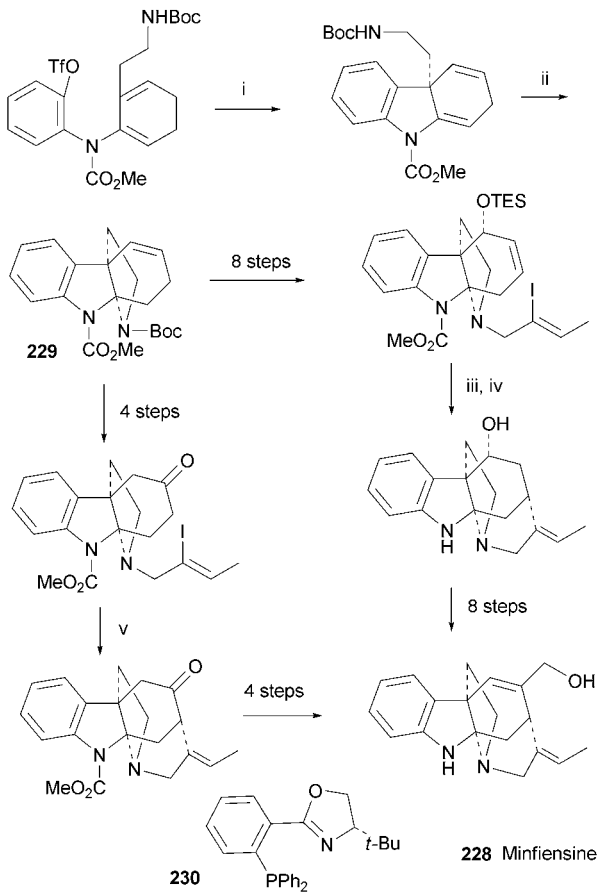
The first total synthesis of the akuammiline alkaloid, vincorine (**227**), has been accomplished using a one-pot, three-step cascade reaction (Scheme 43).[99]





Scheme 43 *Reagents and conditions*: i, CuOTf, CH_2Cl_2.

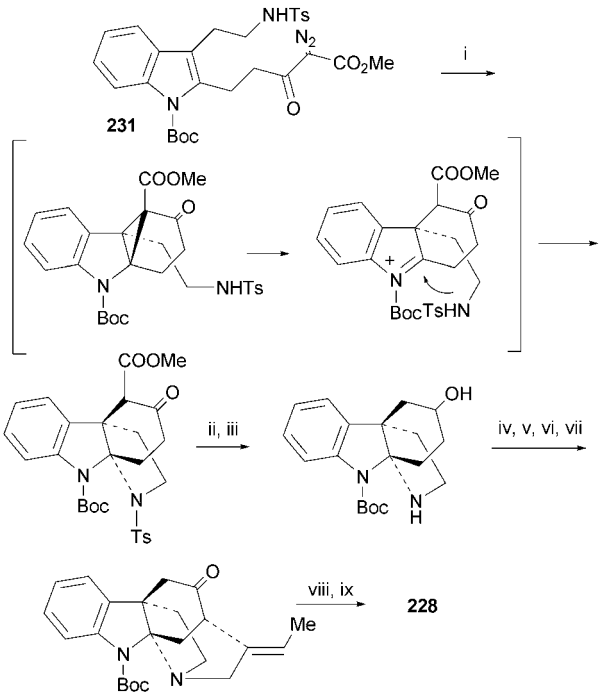
The first total synthesis of (+)-minfiensine (**228**), isolated from the African plant *Strychnos minfiensis*, has been completed. The key intermediate **229** was prepared through a cascade catalytic asymmetric Heck–iminium cyclization in high enantiomeric



Scheme 44 *Reagents and conditions*: i, $Pd(OAc)_2$, **230**, 1,2,2,6,6-pentamethylpiperidine, toluene, 100 °C, 70 h; ii, TFA, CH_2Cl_2; iii, $Pd(OAc)_2$, K_2CO_3, *n*-Bu_4NCl, HCO_2Na, DMF, 80 °C; iv, CsF, DMF; v, $PdCl_2(dppf)$, K_2CO_3, MeOH, 70 °C.

purity. Two sequences were developed to convert **229** to (+)-**228**. An intramolecular reductive Heck cyclization and an intramolecular Pd-catalyzed ketone enolate vinyl iodide coupling were employed in the first and the second approaches, respectively, to form the fifth ring of **228** (Scheme 44).[100]

(±)-Minfiensine (**228**) has been synthesized through a three-step, one-pot cascade reaction of diazoketone **231** including cyclopropanation, ring-opening and ring-closure as the key steps (Scheme 45).[101]



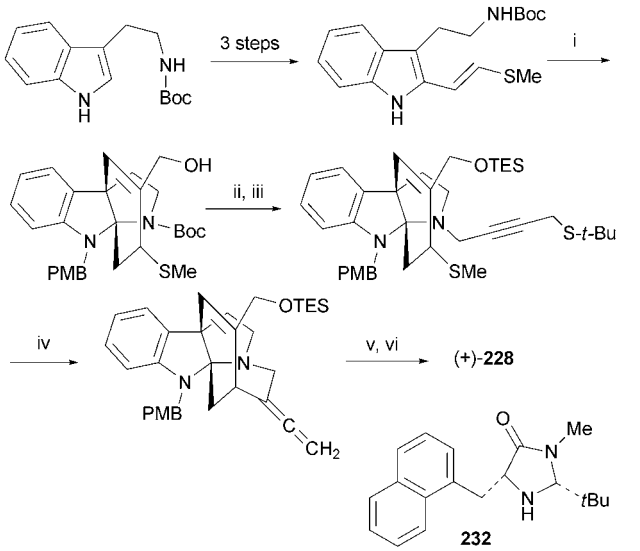
Scheme 45 *Reagents and conditions*: i, CuOTf, CH_2Cl_2; ii, LiCl, H_2O, DMSO, 130 °C, 7 h; iii, Na/Hg amalgam, NaH_2PO_4, MeOH, reflux, 24 h; iv, (*Z*)-2-iodo-2-butenyl mesylate, K_2CO_3, MeCN, 70 °C, 24 h; v, Dess–Martin reagent, CH_2Cl_2, 25 °C, 30 min; vi, $Pd(OAc)_2$, PPh_3, Bu_4NBr, K_2CO_3, DMF, H_2O, 70 °C, 12 h; vii, Comins' reagent, NaHDMS, THF, −78 °C, 20 min; viii, $Pd(PPh_3)_4$, Bu_3SnCH_2OH, LiCl, dioxane, MW, 1 h; ix, TMSOTf, CH_2Cl_2, 0 °C, 10 min.

A nine-step total synthesis of (+)-**228** has been completed from tryptamine. The key features of the approach involve a new cascade organocatalysis sequence to build the tetracyclic pyrroloindoline and a 6-*exo*-dig radical cyclization to assemble the final piperidynyl ring (Scheme 46).[102]

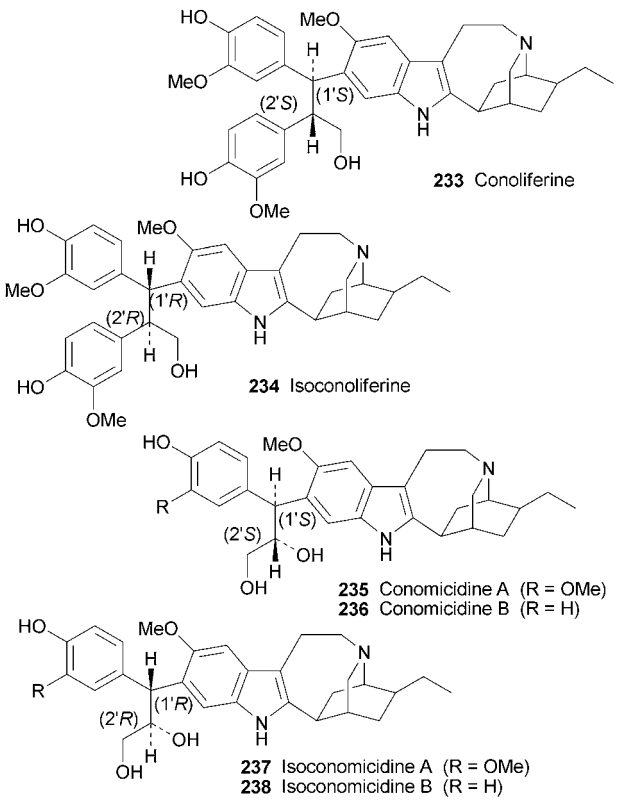
Conoliferine (**233**) and isoconoliferine (**234**), the first examples of alkaloid–lignan conjugates, have been isolated from the stem bark extract of *Tabernaemontana corymbosa* as an unresolvable mixture of (1′*S*,2′*S*)- and (1′*R*,2′*R*)-diastereomers.[103]

Conomicidines A (**235**) and B (**236**) have been isolated from the stem bark extract of *Tabernaemontana corymbosa* together with the diastereomeric isoconomicidines A (**237**) and B (**238**) as unresolvable 1 : 1 mixtures of (1′*S*,2′*S*)- and (1′*R*,2′*R*)-diastereomers.[104]

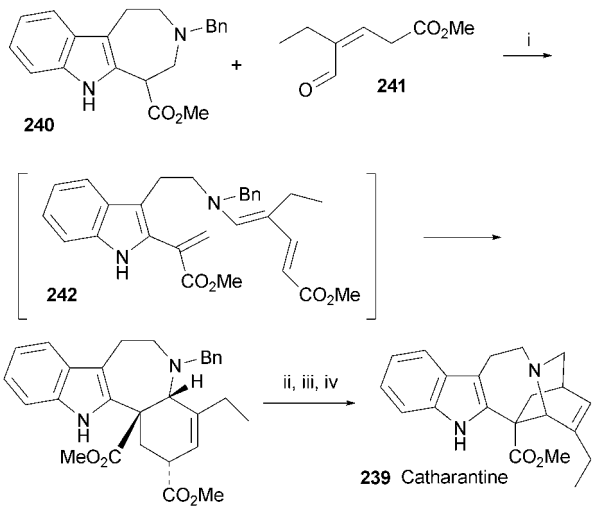
(±)-Catharanthine (**239**) has been synthesized by the reaction of azepinoindole **240** with crotonal **241** through transient formation of the indoloacrylate dienamine **242** and its intramolecular cyclization (Scheme 47).[105]



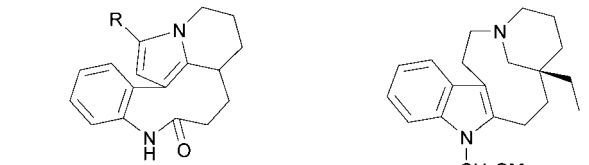
Scheme 46 *Reagents and conditions*: i, **232** (15 mol%), propynal, tribromoacetic acid (15 mol%), Et_2O, −40 °C, then $NaBH_4$, $CeCl_3$, MeOH, 96% ee; ii, TESOTf, MeCN, 0 °C; iii, 4-(*tert*-butylthio)-but-2-ynal, $NaBH(OAc)_3$, CH_2Cl_2, rt; iv, *tert*-Bu_3SnH, AIBN, toluene, 110 °C; v, Pd/C, H_2, THF, −15 °C; vi, PhSH, TFA, rt.



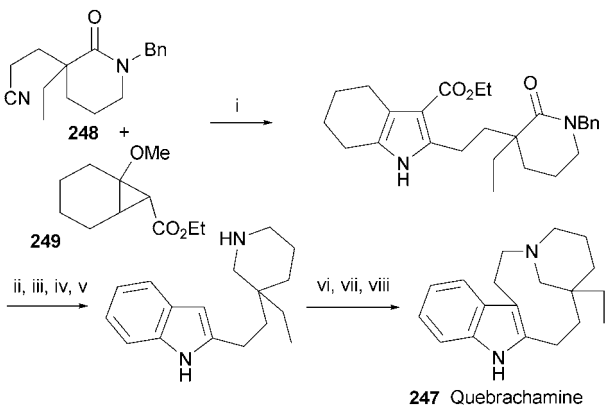
Three new rhazinilam-derived alkaloids, kopsiyunnanine C1 (**243**), C2 (**244**) and C3 (**245**), and a new quebrachamine-type alkaloid, kopsiyunnanine D (**246**), have been isolated from the aerial parts of Yunnan *Kopsia arborea*.[106]



Scheme 47 *Reagents and conditions*: i, benzoic acid, toluene, reflux, 48 h; ii, $NaBH_4$, THF, MeOH, 15–72 h; iii, TsCl, DMAP, THF, 3 h; iv, Pd/C, H_2, AcOH.



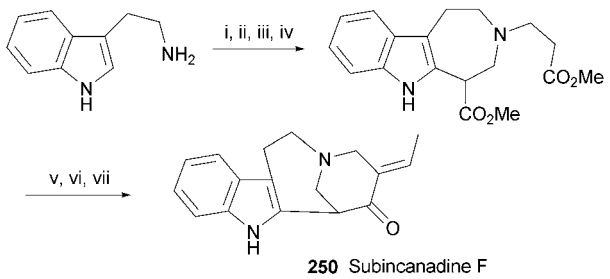
The total synthesis of (±)-quebrachamine (**247**) has been completed in 13 linear steps through a formal [3 + 2] dipolar cycloaddition between nitrile **248** and cyclopropane **249** (Scheme 48).[107]



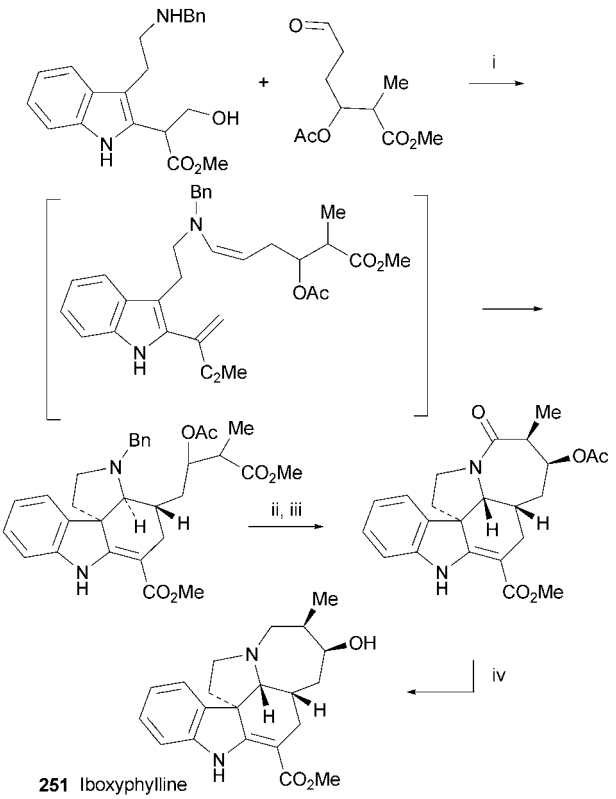
Scheme 48 *Reagents and conditions*: i, TMSOTf, $EtNO_2$; ii, Pd/C, mesitylene; iii, NaOH, EtOH, H_2O; iv, Na, NH_3, THF; v, Red-Al, THF; vi, $SnCl_4$, $ClCH_2COCl$, THF; vii, *hv*, EtOH, H_2O; viii, $LiAlH_4$, THF.

A protecting-group-free total synthesis of (±)-subincanadine F (**250**) has been completed in 7 steps from tryptamine using chemoselective Dieckmann condensation as the key step (Scheme 49).[108]

(±)-Iboxyphylline (**251**) has been synthesized from tryptamine and aldehyde using a intramolecular [4 + 2] cycloaddition of the intermediate enamine as the key step (Scheme 50).[109]



Scheme 49 *Reagents and conditions*: i, methyl bromoacetoacetate; ii, pyridine; iii, $NaBH_3CN$; iv, methyl acrylate; v, *t*-BuOK, THF; vi, LiOH, THF, H_2O; vii, MeCHO, $TiCl_4$, *i*-Pr_2NEt.

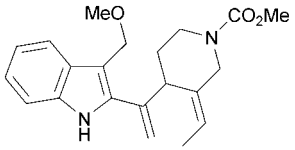


Scheme 50 *Reagents and conditions*: i, *p*-TsOH, toluene, reflux; ii, 10% Pd/C, H_2, AcOH, rt; iii, *p*-TsOH, toluene, reflux; iv, $LiAlH_4$, THF.

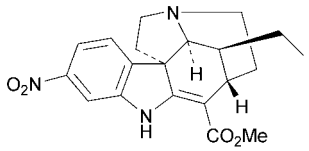
Three new monoterpenoid indole alkaloids, flabelliformine (**252**), 11-nitrotubotaiwine (**253**) and sodium dregaminate (**254**), have been isolated from the stems of *Ervatamia flabelliformis*, a common plant cultivated in Yunnan and Guangxi provinces in China.[110]

Bioassay-guided purification of the stem extracts of the Queensland tree *Ochrosia moorei* enabled the isolation of two new alkaloids, ochrosamines A (**255**) and B (**256**).[111]

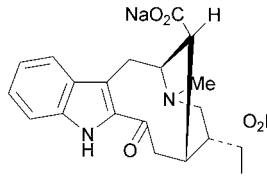
Seven new indole alkaloids of the *Strychnos*-type, leuconicines A–G (**257–263**), and a new eburnan alkaloid, (−)-eburnamaline (**264**), have been isolated from the stem-bark extract of two Malayan *Leuconosis* species. Compounds (**257–261**) showed multidrug resistance in vincristine-resistant KB cell.[112]



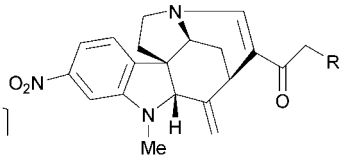
252 Flabelliformine



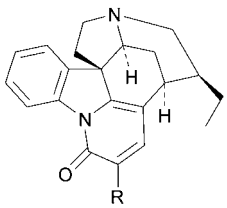
253 11-Nitrotubotaiwine

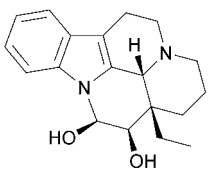


254 Sodium Dregaminate



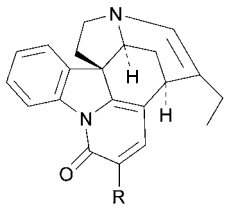
255 Ochrosamine A (R = OH)
256 Ochrosamine B (R = H)





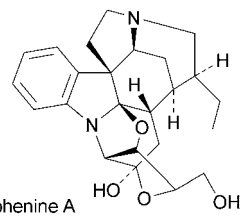
257 Leuconicine A (R = $CONH_2$)
258 Leuconicine B (R = CO_2Me)
262 Leuconicine F (R = $CONH_2$ *N*(4)-oxide)
263 Leuconicine G (R = CO_2Me *N*(4)-oxide)

264 Eburnamaline



259 Leuconicine C (R = $CONH_2$)
260 Leuconicine D (R = CO_2Me)
261 Leuconicine E (R = COOH)

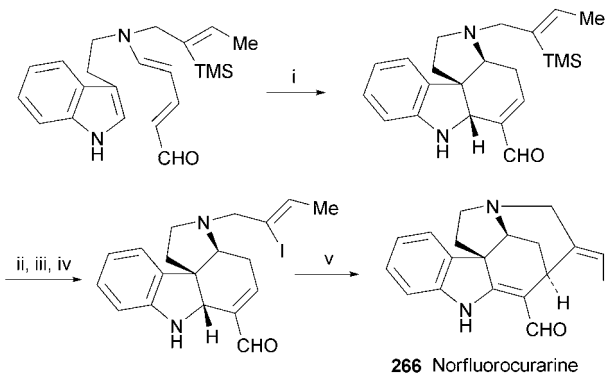
A photochemical study on *Melodinus henryi*, a cane distributed in China, Thailand and Burma that is used for treating meningitis and fracture, has led to the isolation of new indole alkaloid, melohenine A (**265**).[113]



265 Melohenine A

A concise total synthesis of the *Strychnos* alkaloid norfluorocurarine (**266**) has been completed using a base-mediated anionic bicyclization and an intramolecular Heck cyclization as the key step (Scheme 51).[114]

A general approach to the *Strychnos* alkaloids has been developed based on a [4 + 2] cycloaddition–rearrangement sequence as the key step. The total syntheses of (±)-strychnopivotine (**267**), (±)-tubifolidine (**268**), (±)-strychnine (**269**) and (±)-valparicine (**270**) have been achieved (Scheme 52).[115]



266 Norfluorocurarine

Scheme 51 *Reagents and conditions*: i, *t*-BuOK, THF, 80 °C; ii, TFAA; iii, NIS, AcOH, HFIP, CH_2Cl_2; iv, K_2CO_3, MeOH, H_2O; v, $Pd(PPh_3)_4$, PMP, MeCN, 70 °C.

(±)-Tubifoline (**272**) has been synthesized using Pd-catalyzed tandem cyclization–cross-coupling of indolylborate with vinyl bromide (Scheme 53).[116]

A new indole alkaloid, singaporentine A (**273**), has been obtained from the CH_2Cl_2 extract of the leaves of *Kopsia singapurensis* (Apocynaceae) with two known alkaloids.[117]

New methyl chanofruticosinate-type alkaloids, flavisiamines A (**274**), B (**275**), C (**276**) and D (**277**), have been isolated from *Kopsia flavida* (Apocynaceae).[118]

Flavisiamines E (**278**) and F (**279**) have been obtained from the leaves of *Kopsia flavida*, while an aspidofractinine-type alkaloid, fruticosiamine A (**280**), has been isolated from *Kopsia fruticosa*.[119]

The leaf extract of *Kopsia arborea* produced six new methyl chanofrutiosiate alkaloids, prunifolines A (**281**), B (**282**), C (**283**), D, E and F, and kopreasin A (**284**), along with known indole alkaloids. Prunifolines D, E and F are identical to flavisiamines A (**274**), D (**277**) and C (**276**), respectively.[120]

Two *seco*-tabersonine alkaloids, jerantiphyllines A (**285**) and B (**286**), have been isolated from the leaf extract of the Malayan *Tabernaemontana corymbosa*.[121]

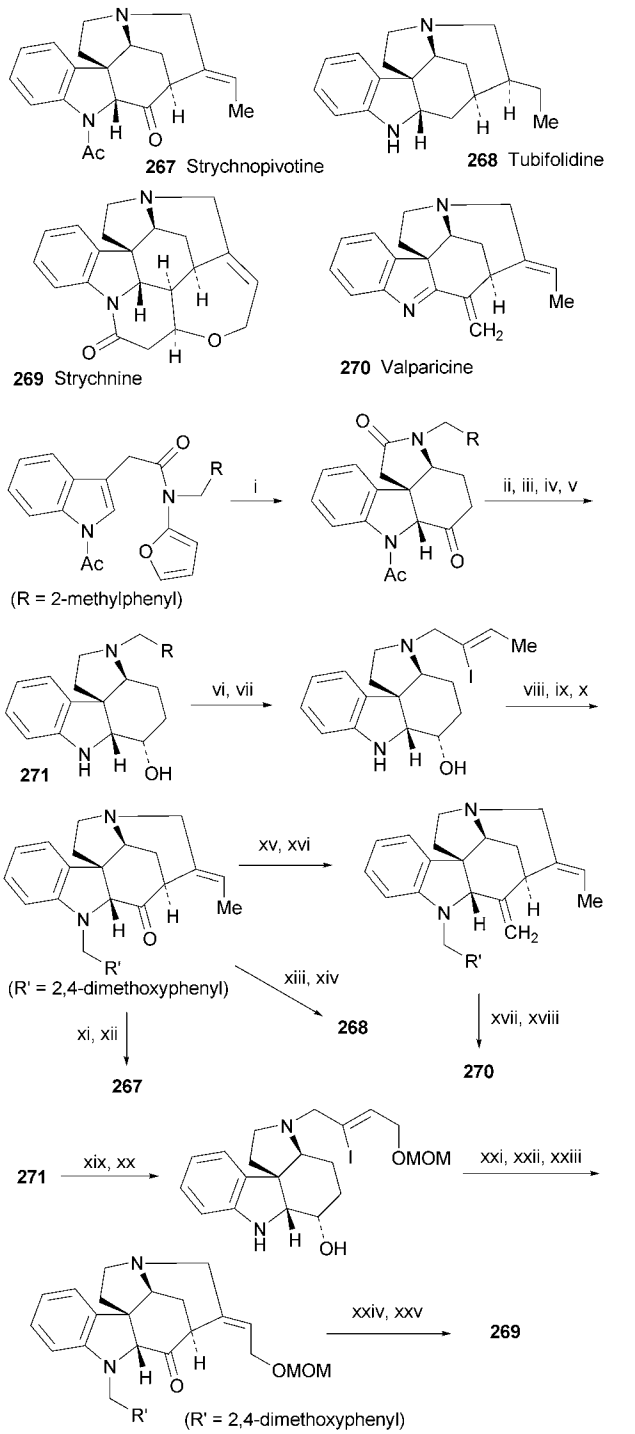
Five new alkaloids, kopsiloscine G (**287**), kopsidarine (**288**), kopsimaline F (**289**), kopsidine C *N*-oxide (**290**) and aspidophylline B (**291**), have been obtained from the leaf and stem-bark extract of Malaysian *Kopsia singapurensis* along with 17 known alkaloids.[122]

Ten new alkaloids, kopsimalines A–E (**292–296**), kopsinicine (**297**), kopsofinone (**298**) and kopsiloscines H–J (**299–301**), have been obtained from the leaf and stem-bark extract of Malaysian *Kopsia singapurensis*.[123]

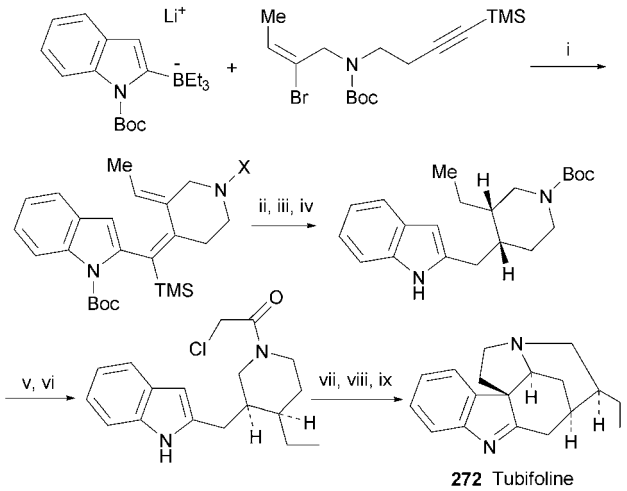
Two new alkaloids, 12-methoxykopsine (**302**) and danuphylline B (**303**), have been isolated from the leaf extract of Malayan *Kopsia arborea*. A partial synthesis of **303** has been carried out (Scheme 54).[124]

Seven new *Aspidosperma*-type alkaloids, jerantinines A–G (**304–310**), have been isolated from a leaf extract of the Malayan *Tabernaemontana corymbosa*. Five of the alkaloids (**304–308**) showed *in vitro* cytotoxicity against human KB cells.[125]

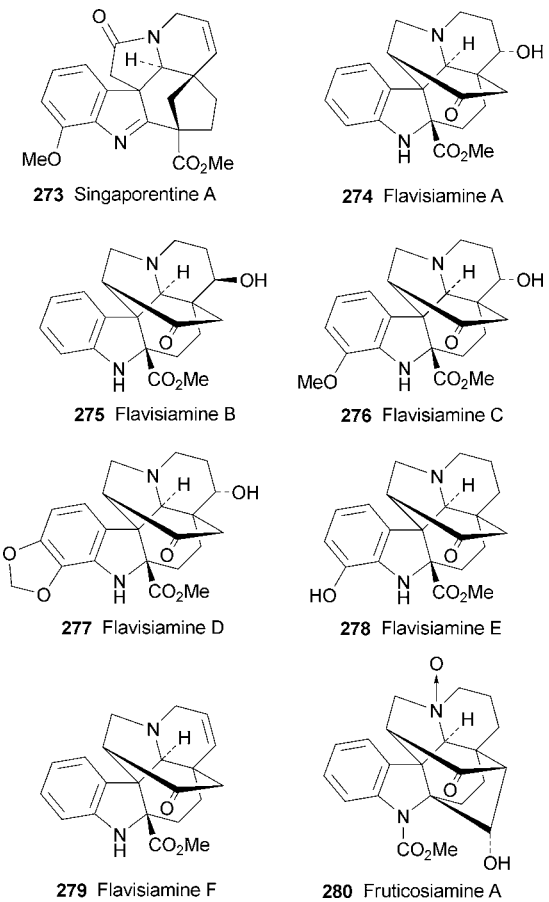
A total synthesis of (+)-aspidofractinine (**311**), isolated from the leaves of *Pleiocarpa tubicana* and *Aspidosperm refractum*, has been achieved using a stereoselective cyanate-to-isocyanate rearrangement, a ring-closing alkene metathesis and a chemoselective cycloaddition as the key features (Scheme 55).[126]

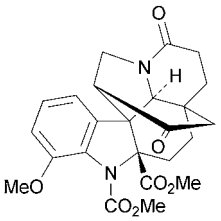


Scheme 52 *Reagents and conditions*: i, microwaves, 150 °C; ii, $NaBH_4$; iii, NaOMe; iv, $LiAlH_4$; v, $NaBH(OAc)_3$; vi, $Pd(OH)_2$, H_2; vii, (*Z*)-1-bromo-2-iodobut-2-ene; viii, AcOH, $NaBH(OAc)_3$, 2,4-dimethoxybenzaldehyde; ix, TPAP, NMO; x, $Pd(PPh_3)_4$, PhOK; xi, HCl; xii, Ac_2O; xiii, Na, NH_2NH_2; xiv, Pd/C, H_2, Na_2CO_3; xv, $LiCH_2SMe$, $CeCl_3$; xvi, KH; xvii, HCl; xviii, $CuBr_2$, NaO*t*Bu; xix, $Pd(OH)_2$, H_2; xx, (*Z*)-1-bromo-2-iodo-4-(methoxymethoxy)but-2-ene, K_2CO_3, DMF, H_2O; xxi, 2,4-dimethoxybenzaldehyde, $NaBH(OAc)_3$, AcOH; xxii, TPAP, NMO; xxiii, $Pd(PPh_3)_4$, PhO*t*Bu; xxiv, 3N HCl; xxv, $CH_2(COOH)_2$, Ac_2O, NaOAc, AcOH.

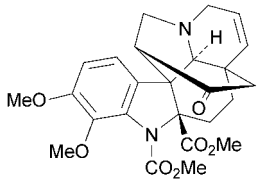


Scheme 53 *Reagents and conditions*: i, $Pd(OAc)_2$, P(*o*-Tol)$_3$, DME, reflux; ii, TBAF, THF, rt; iii, Cs_2CO_3, MeOH; iv, 10% Pd/C, H_2, EtOH; v, TMSCl, KI, CH_2Cl_2, rt; vi, $ClCH_2COCl$, Et_3N, CH_2Cl_2; vii, *hv*, EtOH; viii, $LiAlH_4$, THF; ix, PtO_2, O_2, EtOAc.

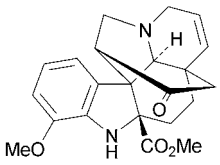




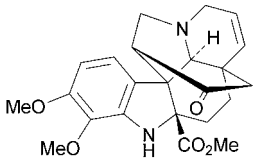
281 Prunifoline A



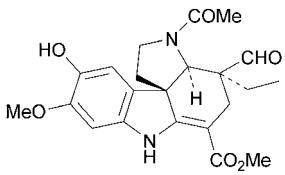
282 Prunifoline B



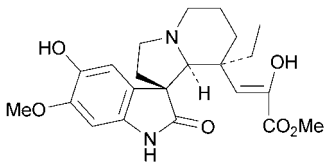
283 Prunifoline C



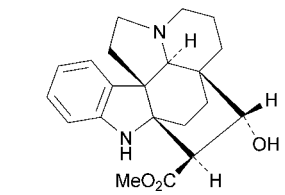
284 Kopreasin A



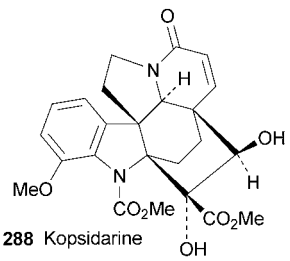
285 Jerantiphylline A



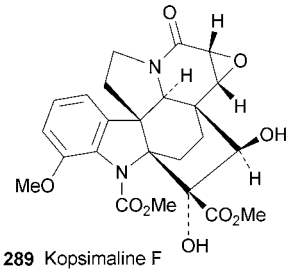
286 Jerantiphylline B



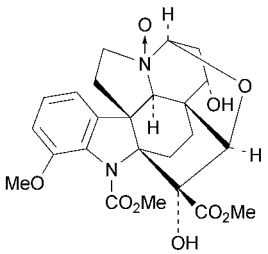
287 Kopsiloscine G



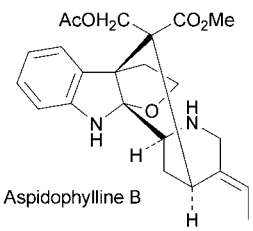
288 Kopsidarine



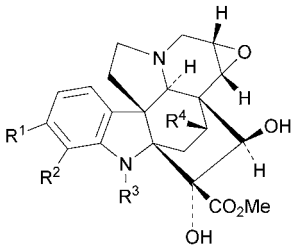
289 Kopsimaline F



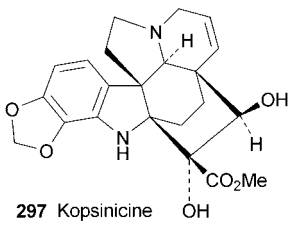
290 Kopsidine C *N*-oxide



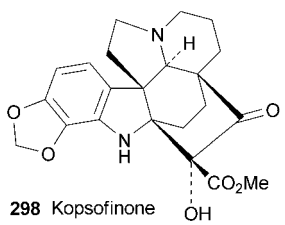
291 Aspidophylline B



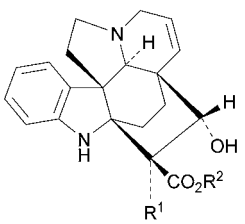
292 Kopsimaline A (R^1,R^2 = -OCH_2O-, R^3 = CO_2Me, R^4 = H)
293 Kopsimaline B (R^1= R^4 = H, R^2 = OH, R^3 = H)
294 Kopsimaline C (R^1= OMe, R^2 = OH, R^3 = CO_2Me, R^4 = H)
295 Kopsimaline D (R^1,R^2 = -OCH_2O-, R^3 = CO_2Me, R^4 = OH)
296 Kopsimaline E (R^1= R^4 = H, R^2 = OMe, R^3 = CO_2Me)



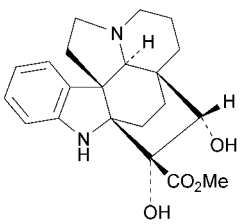
297 Kopsinicine



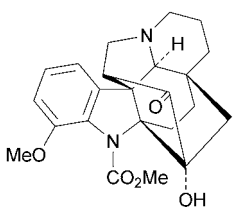
298 Kopsofinone



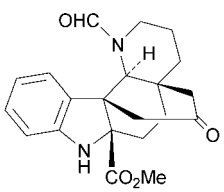
299 Kopsiloscine H (R^1 = OH, R^2 = Me)
300 Kopsiloscine J (R^1 = H, R^2 = Et)



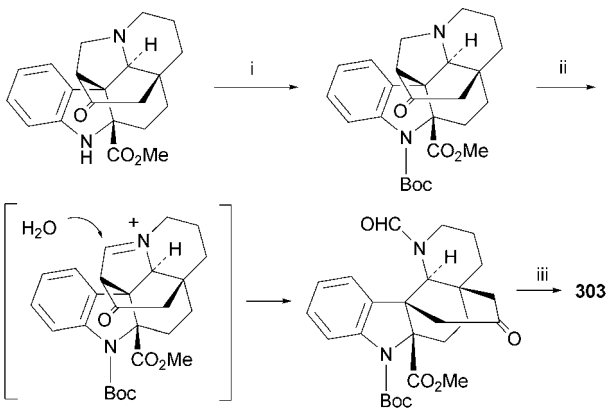
301 Kopsiloscine I



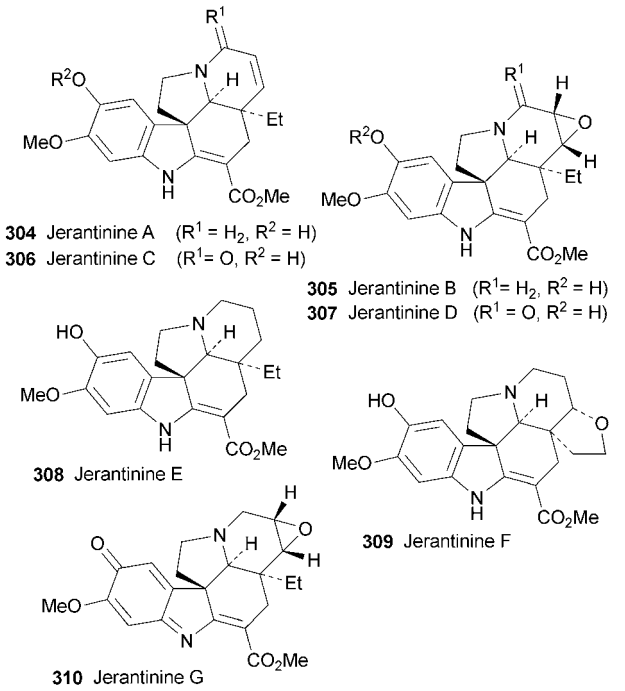
302 12-Methoxykopsine

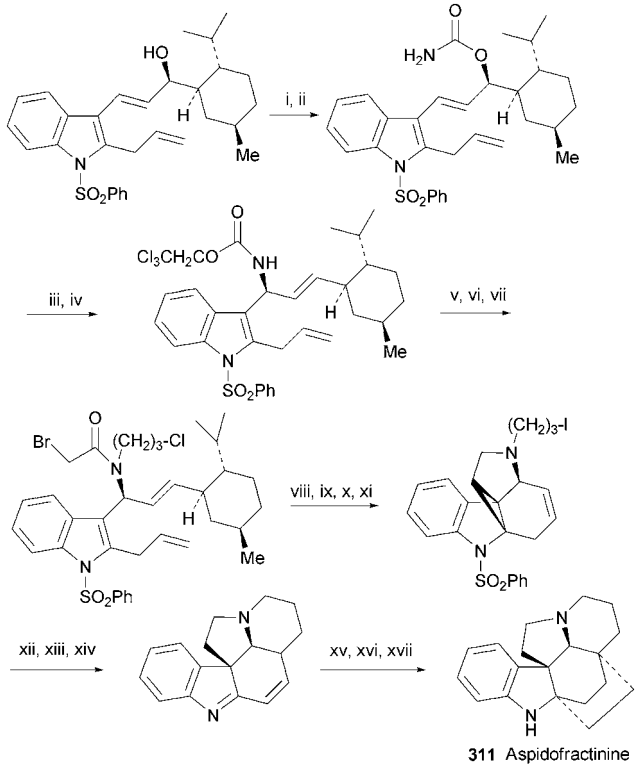


303 Danuphylline B



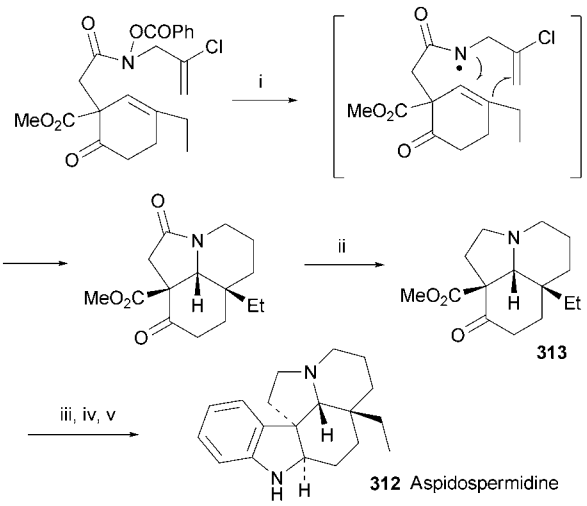
Scheme 54 *Reagents and conditions*: i, Boc_2O, NaHDMS, THF, rt; ii, anodic oxidation (Pt anode, 30% CH_2Cl_2–MeCN, 0.1 M Et_4NClO_4); iii, TMSOTf, CH_2Cl_2.





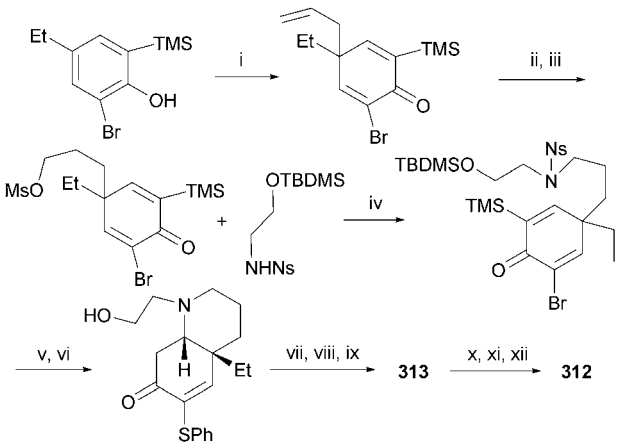
Scheme 55 *Reagents and conditions*: i, Cl_3CONCO, THF, 0 °C, 1 h; ii, MeOH, aq. K_2CO_3, 0 °C, 1 h; iii, TFAA, Et_3N, CH_2Cl_2, 0 °C; iv, Cl_3CCH_2OH; v, Zn, AcOH, THF, rt; vi, $I(CH_2)_3Cl$, K_2CO_3, MeCN; vii, $BrCH_2COCl$, Et_3N, CH_2Cl_2; viii, second-generation Grubbs' catalyst, CH_2Cl_2, rt; ix, $(TsNH)_2$, DBU, THF; x, CuOTf, CH_2Cl_2; xi, NaI, acetone; xii, *n*-Bu_3SnH, AIBN, benzene, reflux; xiii, anthracene, Na, DME, −70 °C; xiv, PhSe(O)OH, THF, pyridine, reflux; xv, phenylvinylsulfone, 5 h; xvi, Raney® Ni, *i*-PrOH, reflux; xvii, $LiAlH_4$, THF, reflux.

A detailed account of synthesis of (±)-aspidospermidine (**312**) has been provided, with the known tricyclic ketone (**313**) being assembled through an amidyl radical cascade (Scheme 56).[127]



Scheme 56 *Reagents and conditions*: i, *n*-Bu_3SnH, ACCN, $PhCF_3$, reflux; ii, 9-BBN, THF, reflux; iii, LiCl, DMF, 140 °C; iv, $PhNHNH_2$, AcOH; v, $NaBH_4$, MeOH.

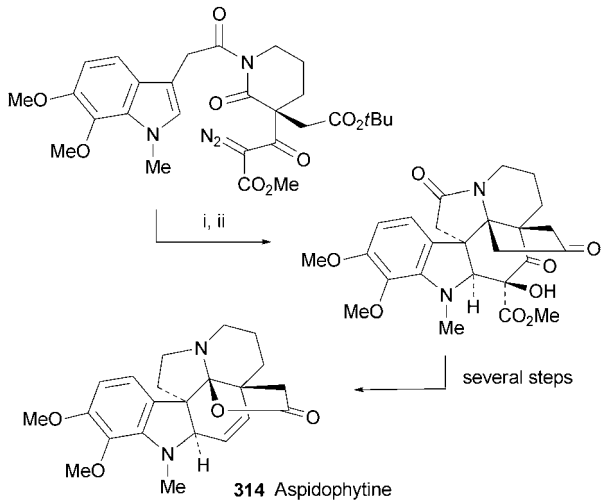
The tricyclic ketone **313** has also been constructed from a polysubstituted phenol *via* an oxidative Hosomi–Sakurai reaction and a Michael–retro-Michael process (Scheme 57).[128]



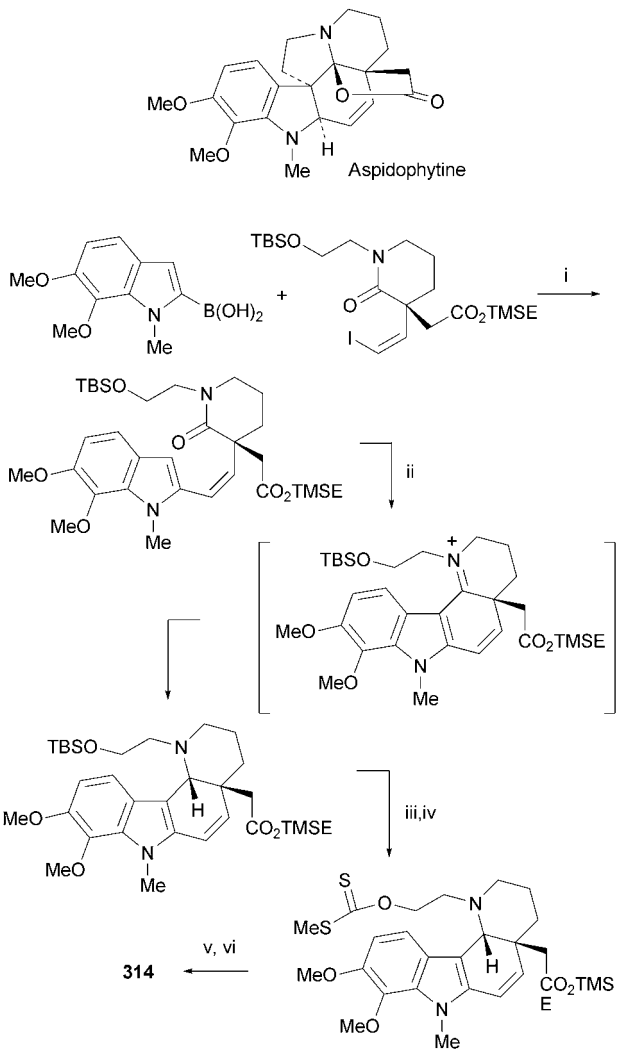
Scheme 57 *Reagents and conditions*: i, $PhI(OAc)_2$, HFIP, 0 °C, 15 min; ii, 9-BBN, THF, rt, 2 h, then H_2O_2, K_2CO_3, 0 °C, 5 min; iii, MsCl, lutidine, CH_2Cl_2, rt, 2 h; iv, NaH, DMF, 65 °C, 12 h; v, K_2CO_3, PhSH, MeCN, rt, 12 h; vi, TBAF, THF, rt, 5 h; vii, MsCl, Et_3N, CH_2Cl_2, rt, 2 h; viii, *t*-BuOK, toluene, rt, 12 h; ix, Raney® Ni, EtOH; x, $PhNHNH_2$, benzene, 80 °C, 2 h; xi, AcOH, 118 °C, 4 h; xii, $LiAlH_4$, THF, rt, 30 min.

Full details of the total synthesis of (±)-aspidophytine (**314**) using a Rh-catalyzed cycloaddition cascade as the key step have been reported (Scheme 58).[129]

An asymmetric total synthesis of **314** has been achieved by Nicolaou's group, which used Suzuki coupling, a reductive Vilsmeier–Haack-type cyclization and a 5-*exo*-trig radical cyclization (Scheme 59).[130]



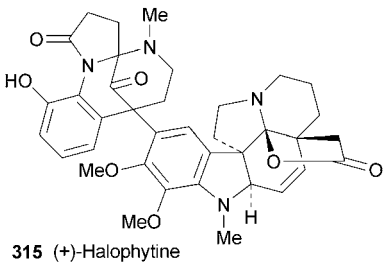
Scheme 58 *Reagents and conditions*: i, $Rh(OAc)_2$, benzene, reflux, 2 h; ii, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C to rt, overnight.

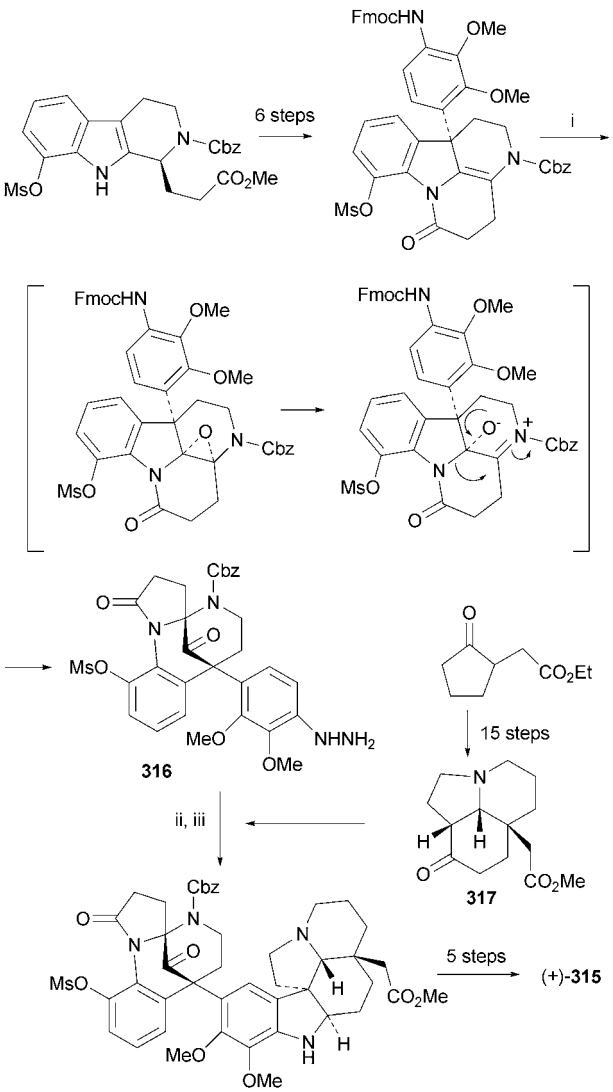


Scheme 59 *Reagents and conditions*: i, $PdCl_2(dppf)$, Cs_2CO_3, DMF, H_2O, rt, 12 h; ii, Tf_2O, DTBMP, CH_2Cl_2, rt, 30 min, then $NaBH_4$, MeOH, 0 °C, 15 min; iii, HF·pyridine, THF, rt, 1 h; iv, NaH, CS_2, THF, −78 °C to rt, 1 h, then MeI; v, Bu_3SnH, AIBN, benzene, 85 °C; vi, TBAF, THF, rt, 12 h, then $K_3Fe(CN)_6$, $NaHCO_3$, *t*-BuOH–H_2O (1 : 1), rt.

The heterodimeric alkaloid halophytine (**315**) has been isolated from the leaves of the Mexican plant *Halophyton cimicidum*, while an symmetric total synthesis of (+)-**315** has been accomplished by the groups of Tokuyama[131] and Nicolaou.[132] A mini-review of the total synthesis of (+)-**315** has appeared.[133]

Tokuyama's approach to (+)-**315** used Fischer indole synthesis between hydrazine **316** and tricyclic ketone **317** to assemble the

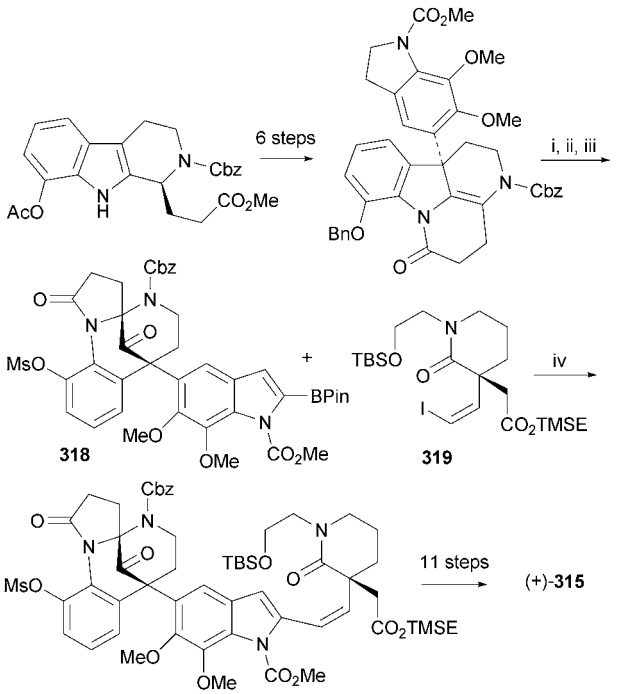




Scheme 60 *Reagents and conditions*: i, MCPBA, $NaHCO_3$, CH_2Cl_2, rt; ii, **317**, 50% aq, H_2SO_4, dioxane, 0 °C; iii, *p*-TsOH, *t*-BuOH, 80 °C.

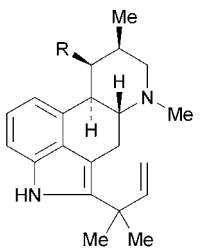
indole structure. Hydrazine **316** was elaborated from β-carboline *via* Friedel–Crafts alkylation and oxidative skeletal rearrangement (Scheme 60).[131]

Nicolaou's synthesis involved Suzuki–Miyaura coupling of iodide **319** with the left-hand domain of indole **318** derived from β-carboline through oxidative skeletal rearrangement, reductive Vilsmeier–Haack reaction and radical cyclization (Scheme 61).[132]



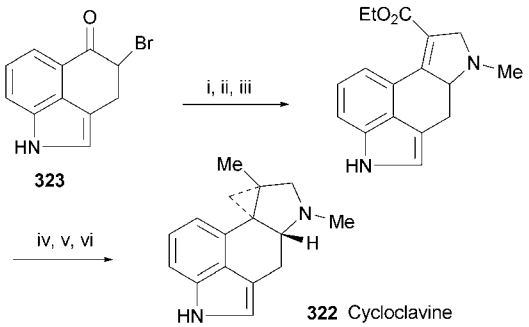
Scheme 61 *Reagents and conditions*: i, MCPBA, CH_2Cl_2, −5 °C, 12 h; ii, DDQ, benzene, 75 °C, 12 h; iii, LTMP, MeOBPin, THF, −100 °C, 15 min; iv, $Pd(dppf)Cl_2$, Ph_3As, TlOEt, DMSO, 23 °C, 1 h.

Two new alkaloids, 9-deacetylfumigaclavine C (**320**) and 9-deacetoxyfumigaclavine C (**321**), have been isolated from the culture of *Aspergillus fumigatus*. Compound (**321**) showed potent cytotoxicity against human leukemia cells (K562).[134]



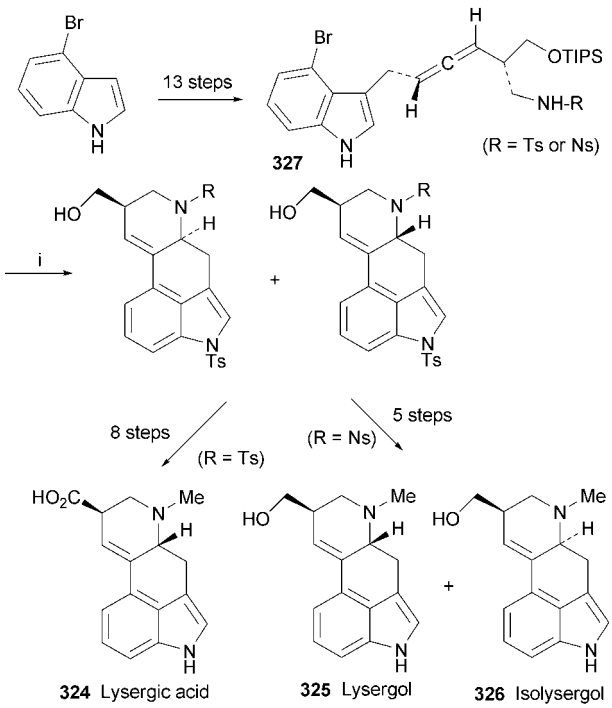
320 9-Deacetylfumigaclavine C (R = OH)
321 9-Deacetoxyfumigaclavine C (R = H)

The first total synthesis of a clavine-type ergot alkaloid, (±)-cycloclavine (**322**) isolated from the seeds of *Ipomea hildebrandtii*, has been performed, starting from 4-bromo-Uhle's ketone **323** in six steps (Scheme 62).[135]



Scheme 62 *Reagents and conditions*: i, $MeNHCH_2CH_2CO_2Et$, THF; ii, $(TMS)_2NLi$, THF; iii, $POCl_3$, pyridine; iv, $LiAlH_4$, Et_2O; v, SO_3, pyridine, THF, then $LiAlH_4$, Et_2O; vi, CH_2N_2, $Pd(OAc)_2$.

Total syntheses of the ergot alkaloids (±)-lysergic acid (**324**), (±)-lysergol (**325**) and (±)-isolysergol (**326**) have been achieved using Pd-catalyzed domino bicyclization of amino allenes **327** as the key step to construct the C/D ring (Scheme 63).[136]

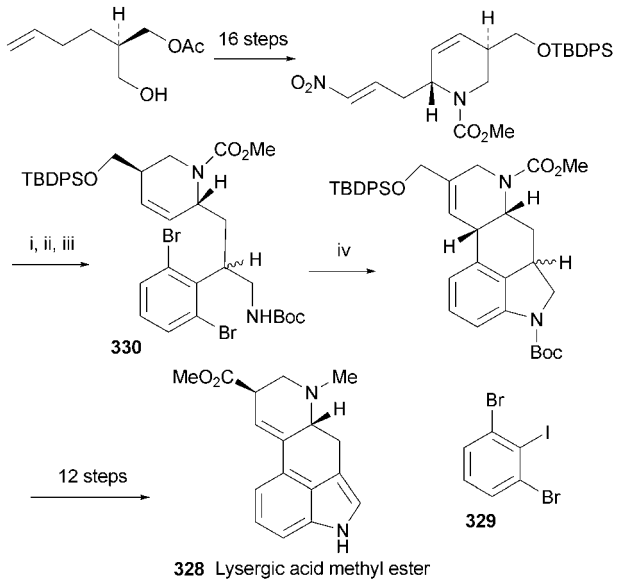


Scheme 63 *Reagents and conditions*: i, $Pd(PPh_3)_4$, K_2CO_3, DMF, 120 °C, 3.5 h.

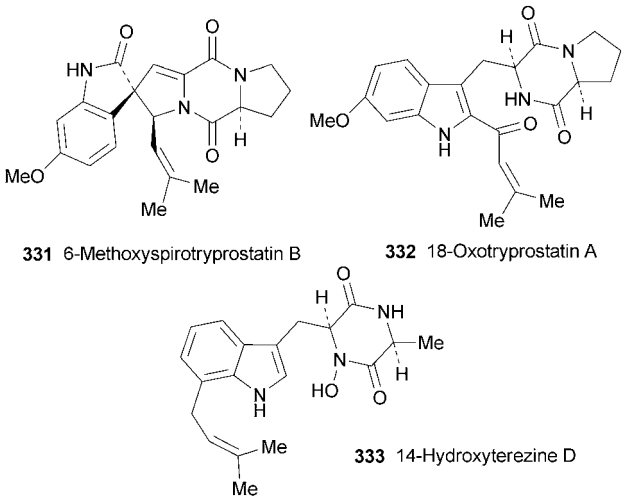
Asymmetric synthesis of (+)-lysergic acid methyl ester (**328**) has been completed using a one-pot Pd-mediated double cyclization of **330** involving Pd-mediated amination and intramolecular Heck reactions (Scheme 64).[137]

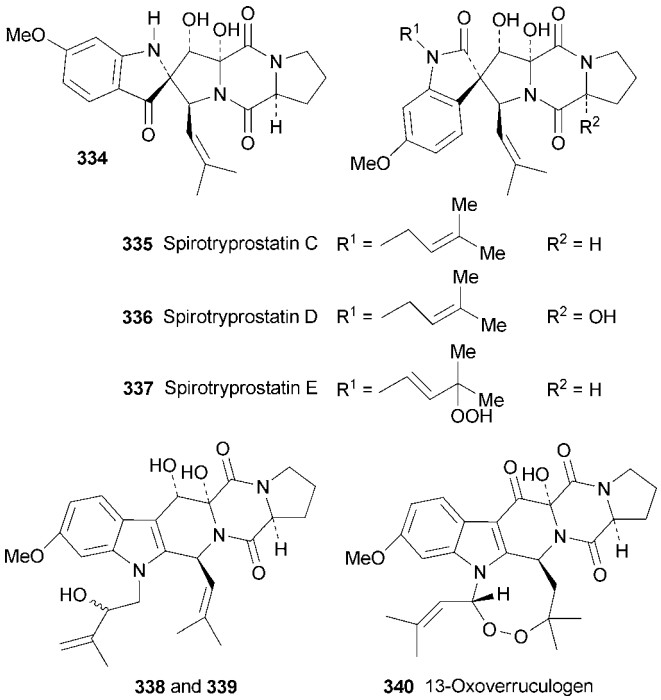
2.2.1 Piperazinediones. Three new diketopiperazine alkaloids, 6-methoxyspirotryprostatin B (**331**), 18-oxotryprostatin A (**332**) and 14-hydroxyterezine D (**333**), have been isolated from a marine-derived fungal strain, *Aspergillus sydowi* PFW-13.[138]

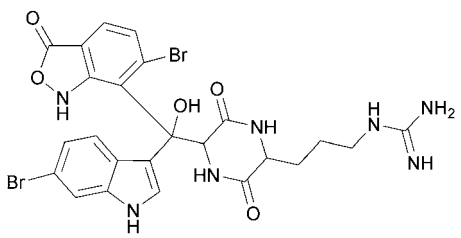
Seven new prenylated diketopiperazine alkaloids – **334**, spirotryprostatins C (**335**), D (**336**) and E (**337**), unnamed



Scheme 64 *Reagents and conditions*: i, **329**, *n*-BuLi, toluene, −78 °C; ii, Fe, $FeCl_2$, NH_4Cl, *i*-PrOH, H_2O, reflux; iii, Boc_2O, aq. $NaHCO_3$, CH_2Cl_2; iv, $Pd(OAc)_2$, PPh_3, Cs_2CO_3, Et_3N, EtCN, reflux.





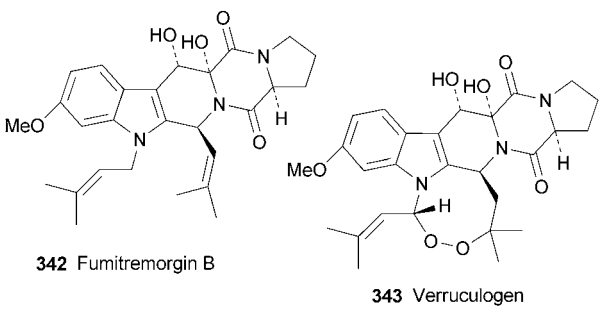


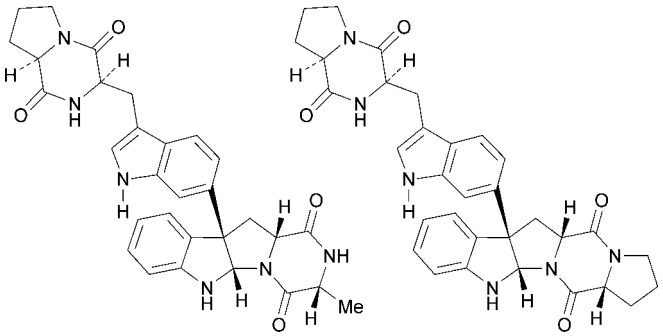
derivatives of fumitremorgin B (**338** and **339**) and 13-oxoverruculogen (**340**) – have been isolated from the holothurian-derived fungus *Aspergillus fumigatus*. Compounds **338** and **339** were epimers, with different chirality only on the side chain.[139]

A novel dibrominated alkaloid, bromobenzisoxazolone barettin (**341**), has been isolated from the marine sponge *Geodia barretti*, and this compound displayed settlement inhibition of barnacle larvae (*Balanus improvisus*).[140]

The cloning, overexpression and purification of a non-heme Fe(II) and α-ketoglutarate-dependent dioxygenase FtmOx1 from *Aspergillus fumigatus*, which catalyses the conversion of fumitremorgin B (**342**) to verruculogen (**343**), have been disclosed.[141]

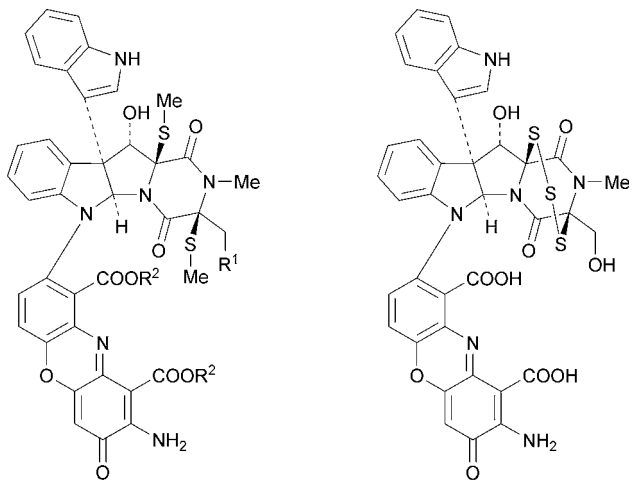
Two new dimeric diketopiperazines, naseseazines A (**344**) and B (**345**), have been obtained from a *Streptomyces* sp. (CMB-MQ030) isolated from a Fijian marine sediment.[142]





344 Naseseazine A **345** Naseseazine B

The fungus *Plectosphaerella cucumernia*, isolated from marine sediments collected in Barkley Sound, British Columbia, yielded three new alkaloids, plectosphaeroic acids A (**346**), B (**347**) and C (**348**). All compounds inhibited human indoleamine 2,3-dioxygenase (IDO).[143]

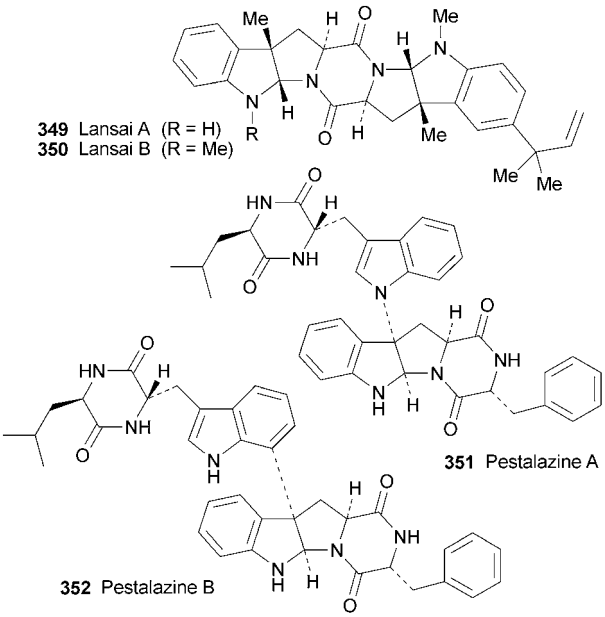


346 Plectosphaeroic acid A (R^1 = OH, R^2 = H)
347 Plectosphaeroic acid B (R^1 = R^2 = H)
348 Plectosphaeroic acid C

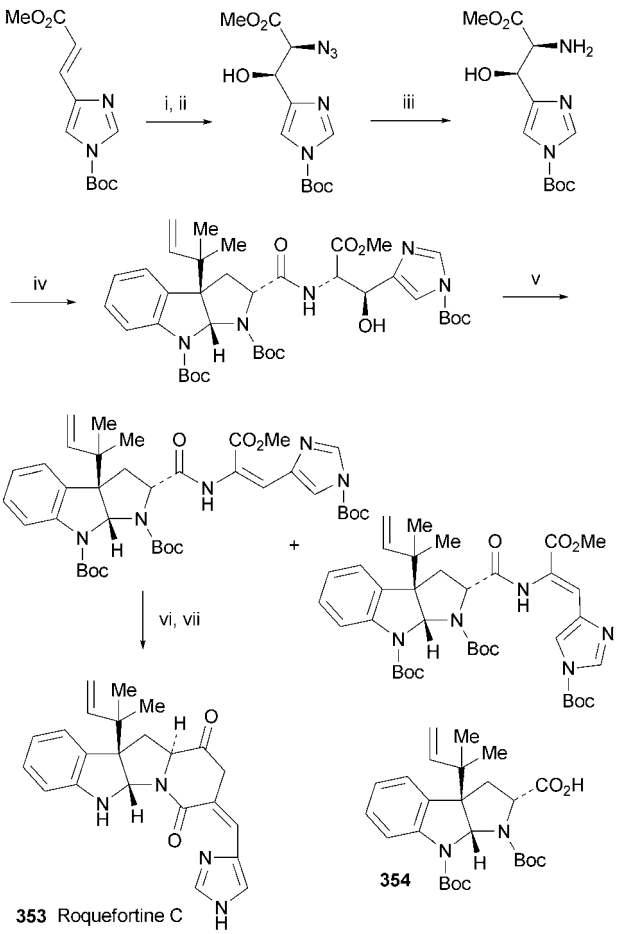
Two novel secondary metabolites, lansais A (**349**) and B (**350**), have been isolated from a culture of *Streptomyces* sp. SUC1, endophytic on the aerial roots of *Ficus benjamina*.[144] Two new diketopiperazine heterodimers, pestalazines A (**351**) and B (**352**), have been isolated from cultures of the plant pathogenic fungus *Pestalotiopsis theae* and the absolute configurations of these compounds were determined.[145]

The first total synthesis of roquefortine C (**353**), isolated from cultures of *Penicillium roqueforti*, has been achieved by implementation of a novel elimination strategy to construct the thermodynamically unstable *E*-dehydrohistidine moiety (Scheme 65).[146]

A total synthesis of the potent anti-MDR indole alkaloid (−)-ardeemin (**355**), isolated from the fermentation of a strain of *Aspergillus fischeri*, has been accomplished by using a three-step one-pot cascade reaction of **356** with diazoester (intermolecular cyclopropanation, ring-opening, ring-closure) as the key step (Scheme 66).[147]

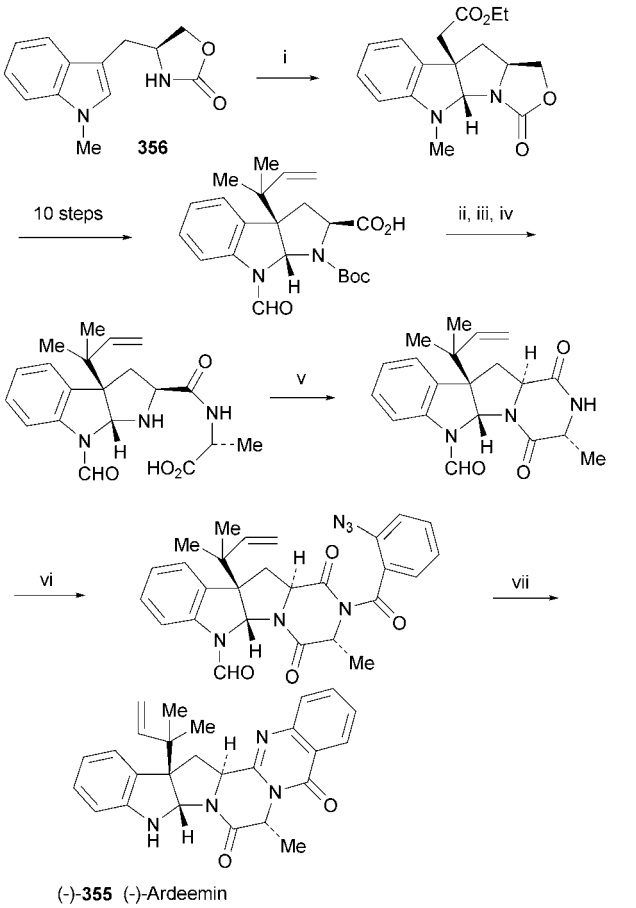


349 Lansai A (R = H)
350 Lansai B (R = Me)
351 Pestalazine A
352 Pestalazine B



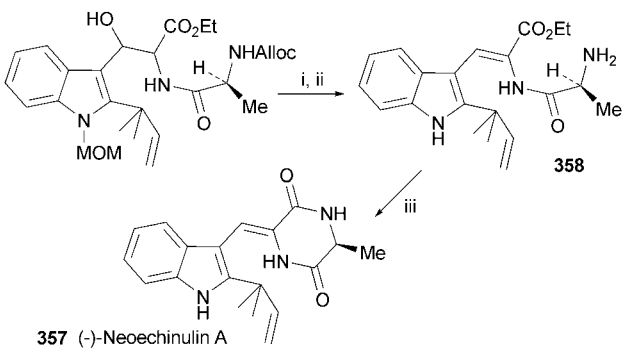
353 Roquefortine C
354

Scheme 65 *Reagents and conditions*: i, NBS, MeCN, H_2O; ii, NaN_3, DMF; iii, Pd/C, H_2, EtOAc; iv, **354**, HATU, *i*-Pr_2NEt; v, EDC, $CuCl_2$, toluene, 45 °C, 10 min; vi, TMSI, MeCN; vii, NH_4OH, MeOH.



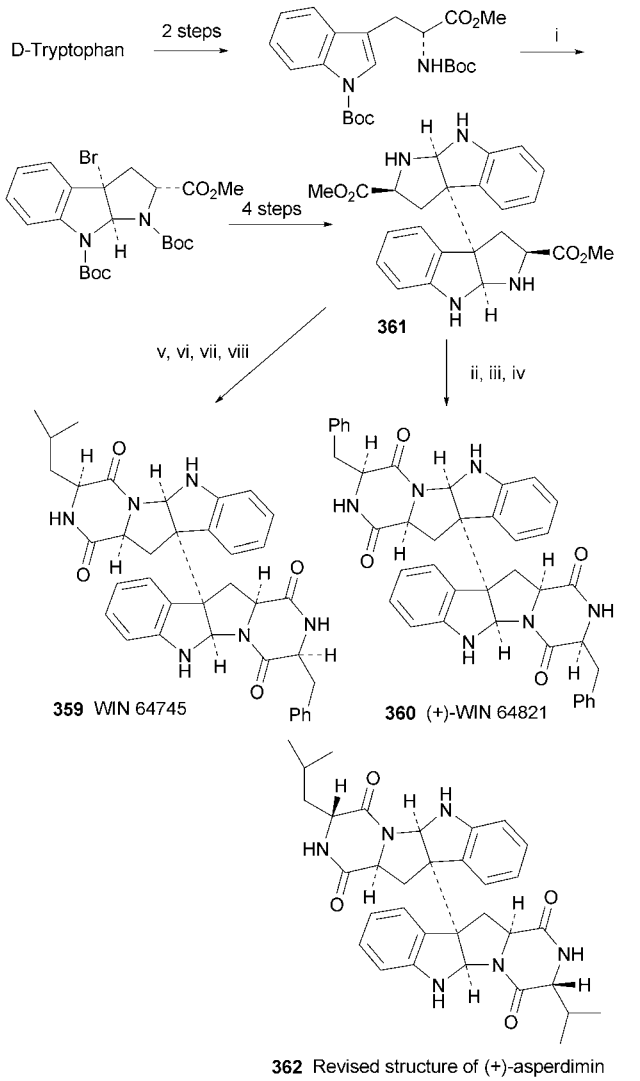
Scheme 66 *Reagents and conditions*: i, ethyl diazoacetate, Cu(OTf), toluene, rt; ii, $ClCO_2t$-Bu, Et_3N, D-Ala-OMe, CH_2Cl_2, 0 °C; iii, TMSI, MeCN, 0 °C; iv, LiOH, aq. MeOH; v, $ClCO_2t$-Bu, Et_3N, CH_2Cl_2, 0 °C to rt; vi, *n*-BuLi, *o*-azidobenzoic anhydride, THF, −78 °C; vii, *n*-Bu_3P, benzene, rt.

A total synthesis of (−)-neoechinulin A (**357**) has been achieved through the intramolecular cyclization of amide **358**, and the absolute configuration of **357** was determined (Scheme 67).[148]



Scheme 67 *Reagents and conditions*: i, 1 M HCl, EtOH; ii, $NaBH_4$, $Pd(PPh_3)_4$, THF; iii, toluene, 80 °C.

The first total syntheses of two dimeric diketopiperazine alkaloids, (+)-WIN 64821 (**360**) and (+)-WIN 64745 (**359**), have been achieved, using dimer **361** as a common intermediate. The enantiomeric dimer **361**, available from L-tryptophan, was converted to (+)-asperdimin



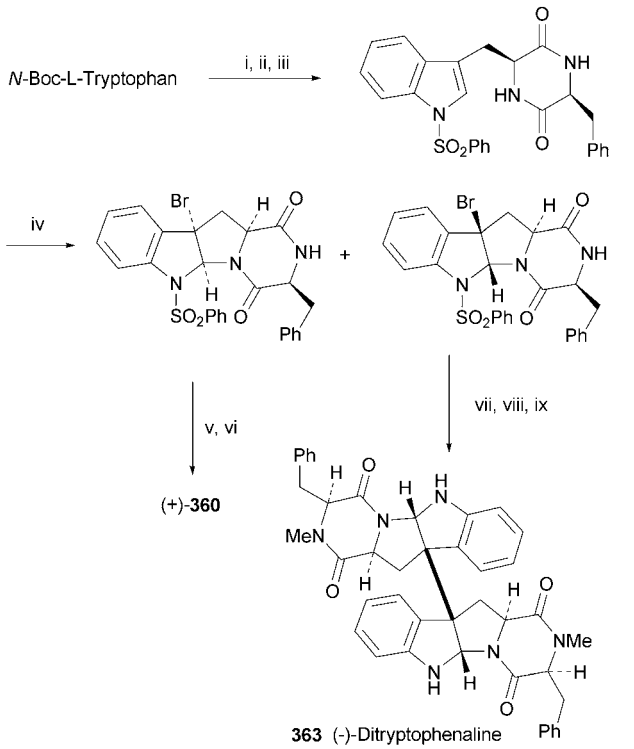
Scheme 68 *Reagents and conditions*: i, NBS, PPTS, CH_2Cl_2, rt; ii, *N*-Cbz-L-phenylalanine, HATU, Et_3N, DMF; iii, Pd/C, H_2, MeOH, rt; iv, 180 °C, 15 min; v, *N*-Cbz-L-leucine, HATU, Et_3N, DMF; vi, *N*-Cbz-L-phenylalanine, HATU, Et_3N, DMF, vii, Pd/C, H_2, MeOH, H_2O, rt; viii, 180 °C, 15 min.

through the same sequence, which also facilitated the structural revision of (+)-asperdimin (**362**) (Scheme 68).[149]

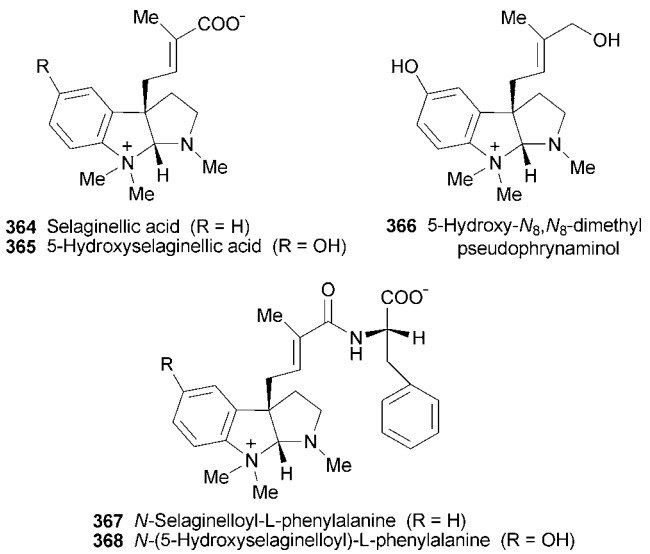
A concise approach to (+)−**360** and (−)-ditryptophenaline (**363**) has been developed based on the reductive dimerization of halogenated diketopiperazine available from L-tryptophan (Scheme 69).[150]

2.2.2 Pyrroloindoles. Five new pyrrolidinoindoline alkaloids, selaginellic acid (**364**), 5-hydroxyselaginellic acid (**365**), 5-hydroxy-N^8,N^8-dimethylpseudophrynaminol (**366**), *N*-selaginelloyl-L-phenylalanine (**367**) and *N*-(5-hydroxyselaginelloyl)-L-phenylalanine (**368**), have been isolated from the whole plant of *Selaginella moellendorfii*. A possible biosynthetic route from **364** was postulated and chemically mimicked.[151]

A novel hexacyclic indole alkaloid, conolutinine (**369**), has been isolated from Malayan *Tabernaemontana corymbosa*. A

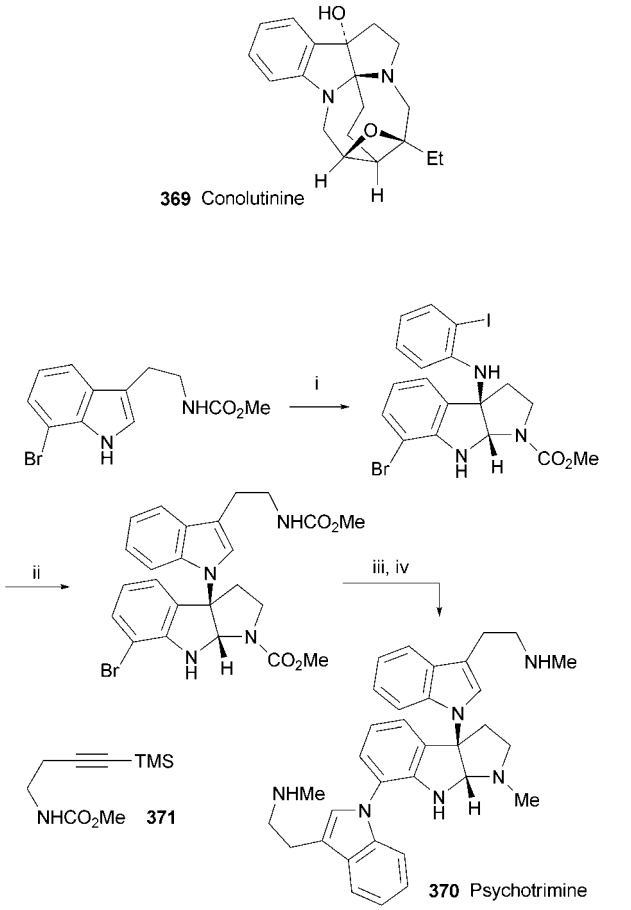


Scheme 69 *Reagents and conditions*: i, LHMDS, $PhSO_2Cl$, THF, −78 °C; ii, EDC·HCl, HOBt, Et_3N, CH_2Cl_2, rt; iii, TFA, CH_2Cl_2, 0 °C to rt; iv, Br_2, MeCN, 0 °C, 15 min; v, $CoCl(PPh_3)_3$, acetone, rt, 30 min; vi, SmI_2, NMP, *t*-BuOH, THF, 0 °C, 1 h; vii, MeI, K_2CO_3, acetone, rt, 3 d; viii, $CoCl(PPh_3)_3$, acetone, rt, 15 min; ix, SmI_2, NMP, *t*-BuOH, THF, 0 °C, 35 min.

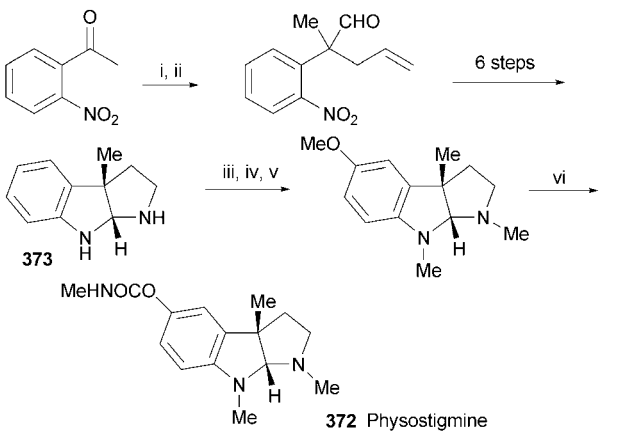


possible biosynthetic pathway from a cleavamine-type precursor was presented.[152]

A short and gram-scale synthesis of (±)-psychotrimine (**370**) has been completed from readily available 7-bromotryptamine in 4 steps (Scheme 70).[153]



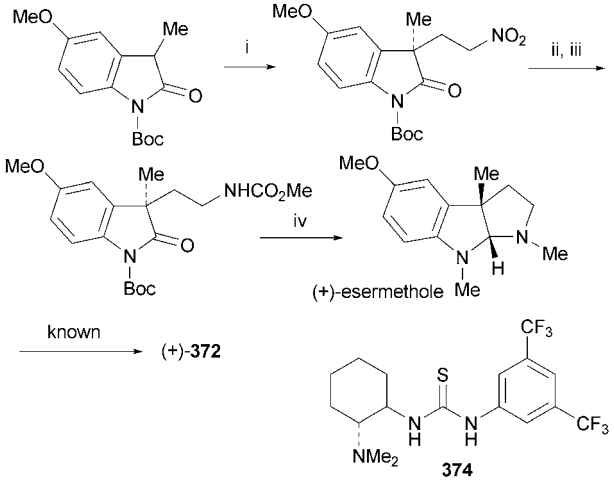
Scheme 70 *Reagents and conditions*: i, 2-iodoaniline, NIS, Et_3N; ii, **371**, $Pd(OAc)_2$, Na_2CO_3, LiCl; iii, CuI, K_2CO_3, *trans*-*N*,*N*′-dimethyl-1,2-cyclohexanediamine, N^b-(methoxycarbonyl)tryptamine, dioxane, 101 °C; iv, Red-Al, toluene, 110 °C, 30 min.



Scheme 71 *Reagents and conditions*: i, $[CH_2{=}CHCH_2OCH_2PPh_3]^+Cl^-$, *t*-BuONa, THF, 0 °C; ii, xylene, reflux; iii, HCHO, 10% Pd/C, H_2, EtOAc; iv, NBS, DMF, 0 °C; v, CuI, NaOMe, reflux; vi, BBr_3, CH_2Cl_2, 0 °C, then NaH, MeNCO.

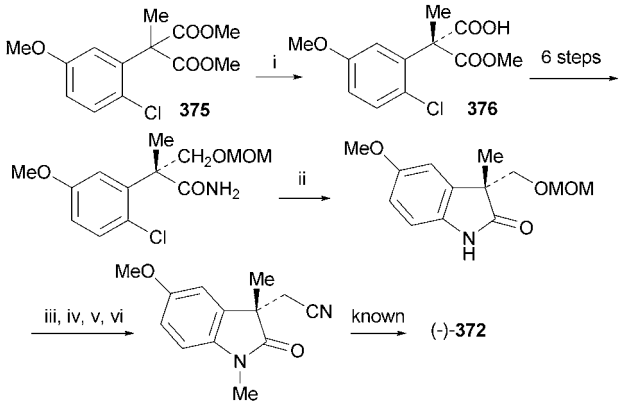
A total synthesis of (±)-physostigmine (**372**) has been achieved using the intermediate **373** available from 2-nitroacetophenone by the Wittig olefination–Claisen rearrangement (Scheme 71).[154]

Enantio- and diastereoselective addition of 2-oxindole to a nitroolefin in the presence of organocatalyst has been developed for a formal synthesis of (+)-**372** (Scheme 72).[155]



Scheme 72 *Reagents and conditions*: i, **374** (10 mol%), nitroethylene, THF, −15 °C, 96% ee; ii, Raney® Ni; iii, $ClCO_2Me$, *i*-Pr_2NEt; iv, $LiAlH_4$.

A formal synthesis of (−)-**372** has been completed. The key building block **376** was obtained by the PLE (pig liver esterase)-mediated hydrolysis of dimethyl malonate **375** (Scheme 73).[156]

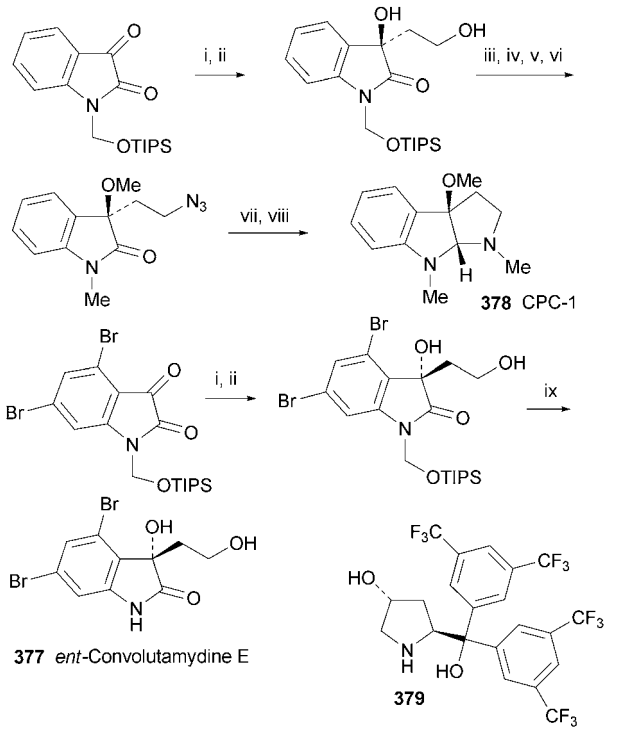


Scheme 73 *Reagents and conditions*: i, PLE, phosphate buffer (pH = 8), 30 °C, 2 d; ii, CuI, K_2CO_3, TMEDA, DMF, reflux, 12 h; iii, NaH, MeI, THF, 0 °C, 3 h; iv, HCl, MeOH, 50 °C, 12 h; v, PPh_3, imidazole, I_2, toluene, reflux, 12 h; vi, NaCN, DMSO, 80 °C, 12 h.

A 4-hydroxydiarylprolinol **379**-catalyzed asymmetric aldol reaction of isatins with acetaldehyde has been developed for the syntheses of *ent*-convolutamydine E (**377**) and CPC-1 (**378**) (Scheme 74).[157]

(±)-Flustramines A (**380**) and C (**381**), and (±)-flustramide A (**382**), have been synthesized from 3-oxoindolines through olefination–isomerization–Claisen rearrangement and reductive cyclization (Scheme 75).[158]

A total synthesis of flustramine B (**383**) has been developed, with a one-pot intramolecular Ullmann coupling and Claisen rearrangement as the key step (Scheme 76).[159]



Scheme 74 *Reagents and conditions*: i, acetaldehyde, **379** (30 mol%), $ClCH_2COOH$, DMF; ii, $NaBH_4$, MeOH, 85% ee; iii, MsCl, pyridine; iv, NaN_3, DMF, 60 °C; v, NH_4F, MeOH, 70 °C; vi, MeI, NaH, THF; vii, Red-Al, toluene; viii, HCHO, $NaBH_3CN$, MeOH; ix, NH_4F, MeOH, 70 °C.

Further studies on the marine bryozoan *Flustra foliacea*, collected from Canadian waters, produced 11 new flustramines F–P (**384–394**) along with known compounds. The dimers **393** and **394** may be isolation artifacts.[160]

The preparation of a collection of dictyodendrin and related compounds has been disclosed. It was also demonstrated that the compounds are capable of cleaving double-stranded DNA under oxidative conditions.[161]

2.2.3 β-Carbolines. A new anti-HIV alkaloid, drymaritin, has been isolated from *Drymaria diandra*. Based on synthetic studies and re-evaluation of the spectroscopic data, the putative structure of drymaritin (**395**) was revised to the structure identical to the known alkaloid cordatanine (**396**).[162]

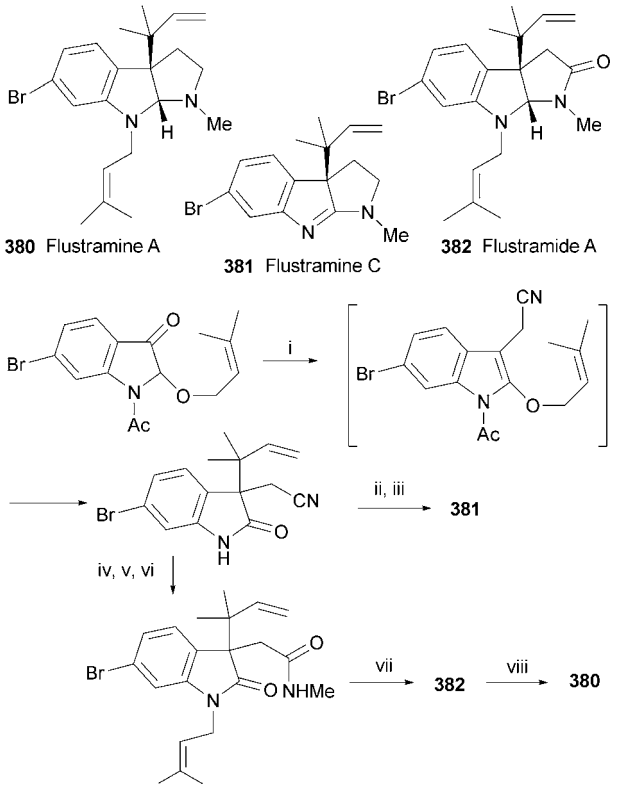
Two β-carboline compounds, **397** and **398**, have been obtained from the ethyl acetate extract of the terrestrial *Streptomyces* sp. isolate GW21/1313.[163]

The New Zealand marine bryozoan *Pterocella vesiculosa* has been found to produce a new alkaloid, 5-bromo-8-methoxy-1-methyl-β-carboline (**399**).[164]

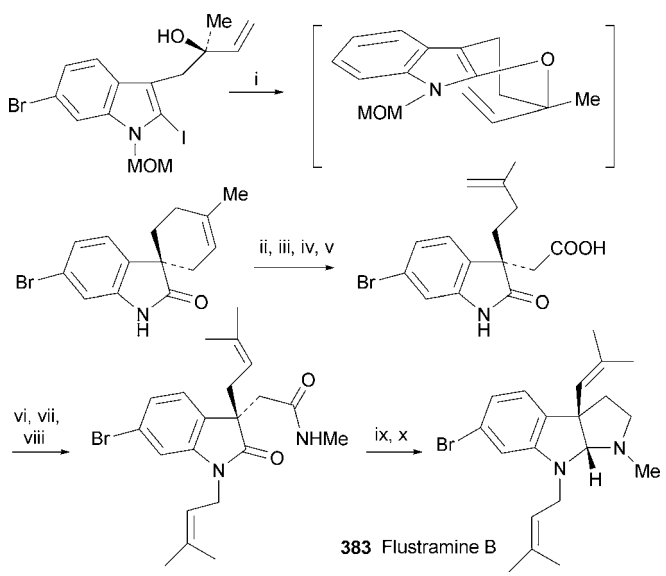
Three novel β-carbolines, tabernines A (**400**), B (**401**) and C (**402**), have been isolated from a MeOH extract of the leaves of *Tabernaemontana elegans*.[165]

Seven new β-carboline metabolites, eudistomins Y_1–Y_7 (**403–409**), have been isolated from a tunicate of the genus *Eudistoma* collected near Tong-Yeong City, Korea. Eudistomin Y_6 (**408**) exhibited moderate antibacterial activity against Gram-positive bacteria.[166]

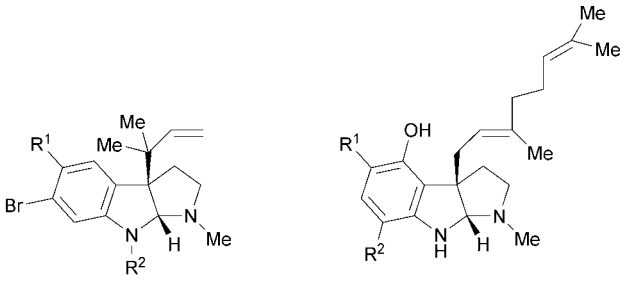
(+)-Anthocephalusine A (**410**) and (−)-3β-iso-dihydrocadambine-4-oxide (**411**) have been isolated from the leaves of *Anthocephalus chinensis* (Rubiaceae).[167]

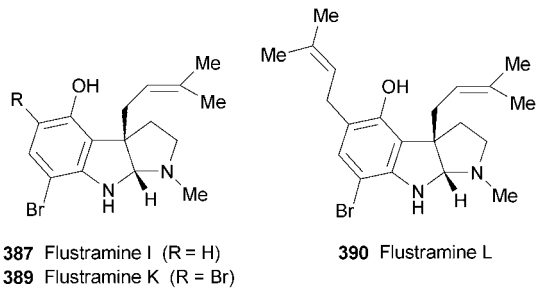


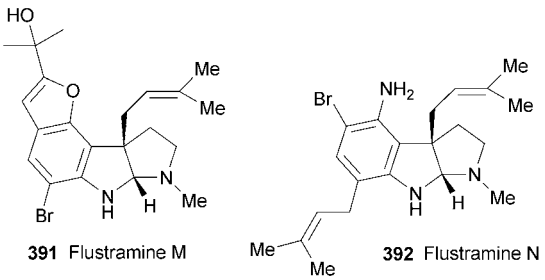
Scheme 75 *Reagents and conditions*: i, $(EtO)_2P(O)CH_2CN$, *t*-BuOK, DMF, −78 °C to rt; ii, Red-Al, toluene, 0 °C to rt; iii, MeI, Na_2CO_3, acetone, 55 °C; iv, prenyl bromide, NaH, DMF, 0 °C; v, NaOH, MeOH, reflux; vi, EDC, C_6F_5OH, Et_3N, THF, then $MeNH_2$, rt; vii, $AlH_3 \cdot NEtMe_2$, THF −15 °C; viii, $AlH_3 \cdot NEtMe_2$, THF, rt.

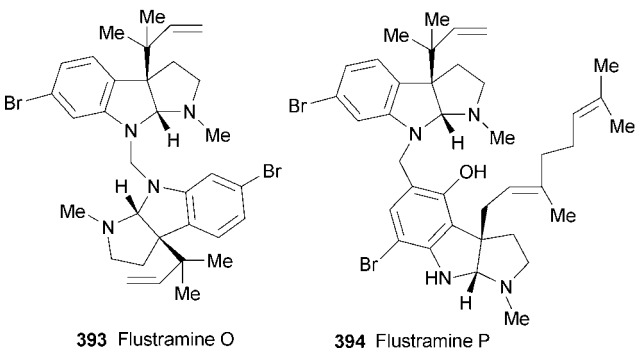


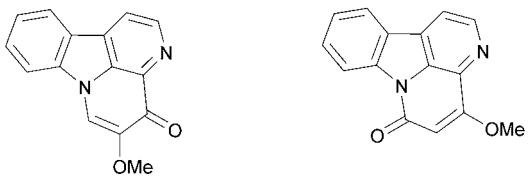
Scheme 76 *Reagents and conditions*: i, CuCl, 2-aminopyridine, NaOMe, MeOH, triglyme, 100 °C; ii, OsO_4, NMO, acetone, H_2O, rt; iii, $NaIO_4$, THF, H_2O, rt; iv, $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, H_2O, THF, rt; v, Ph_3PMeBr, *n*-BuLi, THF, −25 °C to rt; vi, H_2SO_4, then $MgSO_4$, dioxane, 60 °C; vii, prenyl bromide, K_2CO_3, acetone, reflux; viii, $MeNH_2$, MeOH, rt; ix, $AlH_3 \cdot NEtMe_2$, THF, −20 °C; x, $AlH_3 \cdot NEtMe_2$, THF, rt.

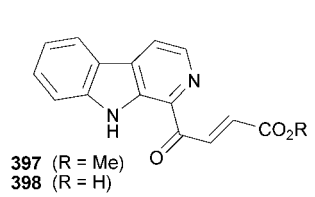




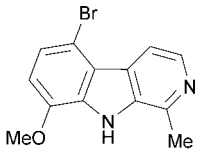




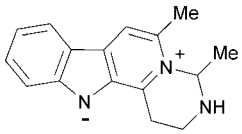




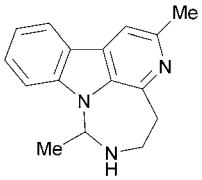
397 (R = Me)
398 (R = H)



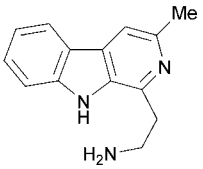
399



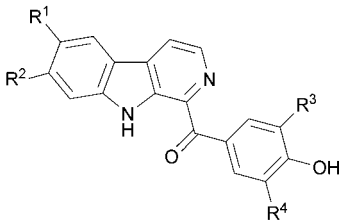
400 Tabernine A



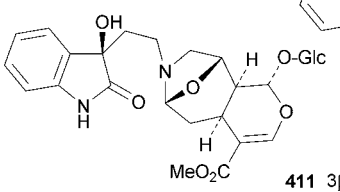
401 Tabernine B



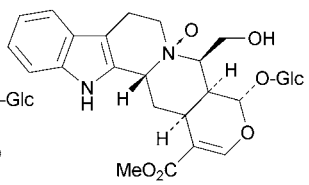
402 Tabernine C



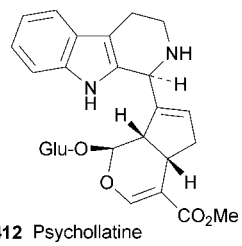
403 Eudistomin Y_1 ($R^1 = R^2 = R^3 = R^4 = H$)
404 Eudistomin Y_2 ($R^1 = Br$ $R^2 = R^3 = R^4 = H$)
405 Eudistomin Y_3 ($R^1 = R^2 = R^4 = H$ $R^3 = Br$)
406 Eudistomin Y_4 ($R^1 = R^3 = H$ $R^2 = R^4 = H$)
407 Eudistomin Y_5 ($R^1 = R^2 = H$ $R^3 = R^4 = Br$)
408 Eudistomin Y_6 ($R^1 = R^3 = R^4 = Br$ $R^2 = H$)
409 Eudistomin Y_7 ($R^1 = H$ $R^2 = R^3 = R^4 = Br$)



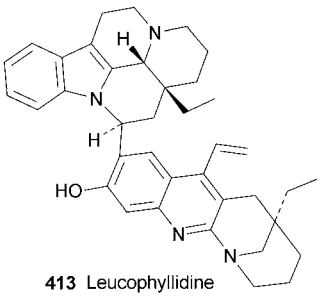
410 Anthocephalusine A



411 3β-Isodihydrocadambine-4-oxide



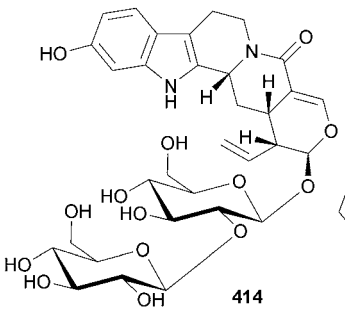
412 Psychollatine



413 Leucophyllidine

A monoterpene indole alkloid, (−)-psychollatine (**412**), has been obtained from the leaves of *Psychotria umbellata* leaves.[168]

(−)-Leucophyllidine (**413**) has been obtained as a minor alkaloid from the EtOH extract of the stem bark of *Leuconotis griffithii*. This compound showed cytotoxicity toward drug-sensitive as well as vincristine-resistant (VJ300) human KB cells.[169]



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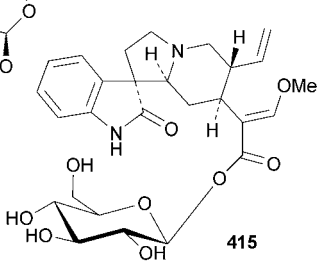
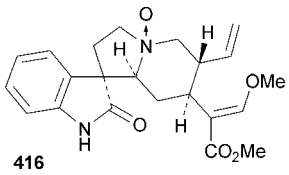


415



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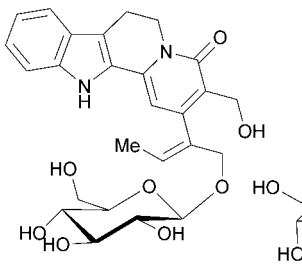
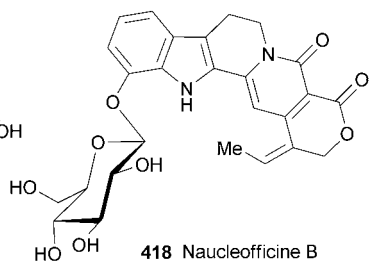
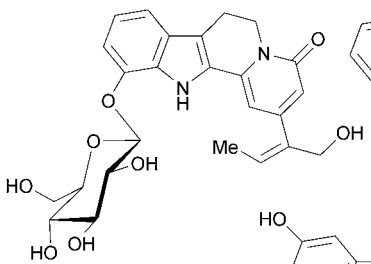


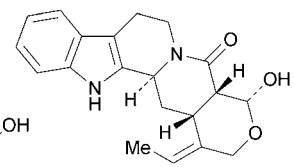
417 Naucleofficine A



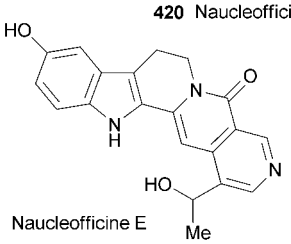
418 Naucleofficine B



419 Naucleofficine C



420 Naucleofficine D

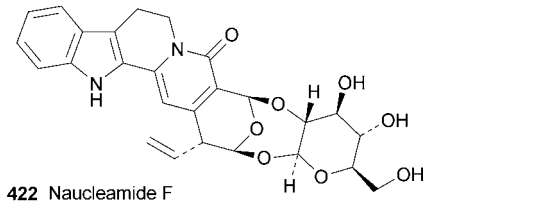


421 Naucleofficine E

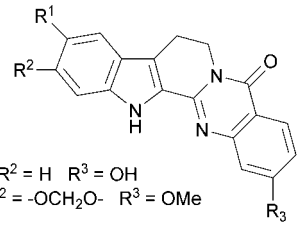
Three new alkaloids, 2′-*O*-β-D-glucopyranosyl-11-hydroxy-vincoside lactam (**414**), 22-*O*-demethyl-22-*O*-β-D-glucopyranosylisocorynoxeine (**415**) and (4*S*)-corynoxeine *N*-oxide (**416**), have been isolated from the leaves of *Uncaria rhynchophylla*. The compounds showed weak inhibitory activity on lipopolysaccharide (LPS)-induced NO release in N9 microglia cells.[170]

Five new indole alkaloids, naucleofficines A–E (**417–421**), have been obtained from the stems of *Nauclea officinalis*. All compounds showed weak to moderate inhibitory activity against *Plasmodium falciparum*.[171]

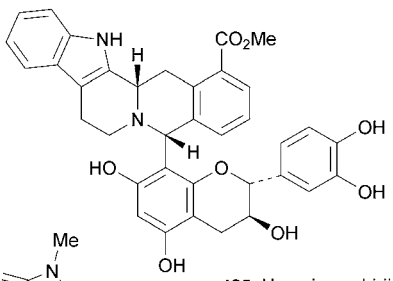
A new monoterpenoid indole alkaloid, (+)-naucleamide F (**422**), has been isolated from the bark and wood of *Nauclea latifolia*.[172]



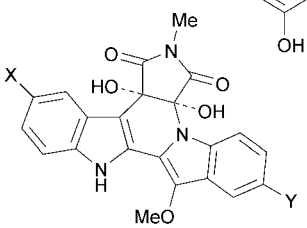
422 Naucleamide F



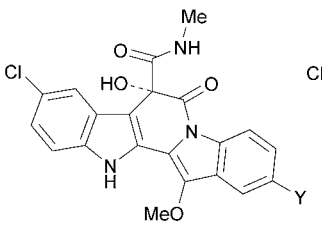
423 Orisuaveoline A $R^1 = R^2 = H$ $R^3 = OH$
424 Orisuaveoline B $R^1, R^2 = -OCH_2O-$ $R^3 = OMe$



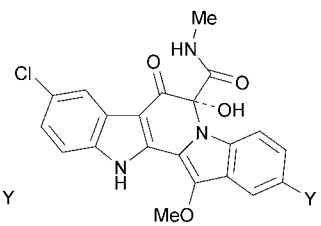
425 Uncariagambiriine



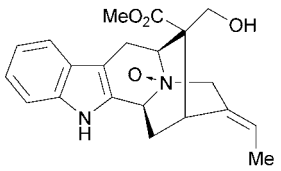
426 Cladoniamide A X = Cl Y = H
427 Cladoniamide B X = Y = Cl
428 Cladoniamide C X = Y = H



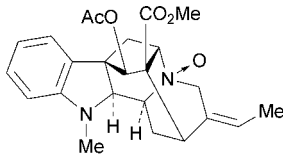
429 Cladoniamide D Y = H
430 Cladoniamide E Y = Cl



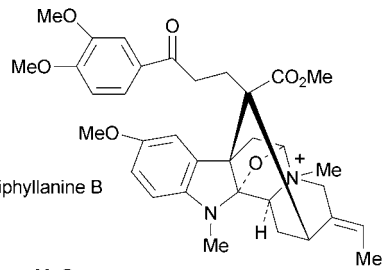
431 Cladoniamide F Y = H
432 Cladoniamide G Y = Cl



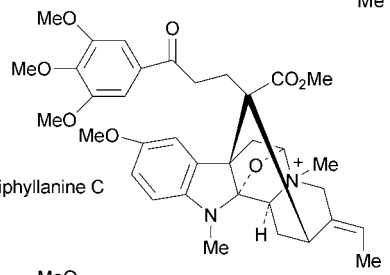
433 Akuammidine-*N*-oxide



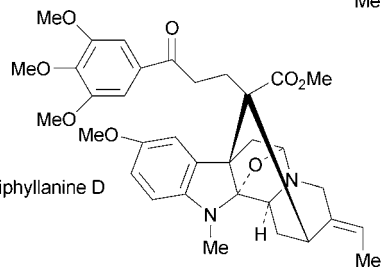
434 Alstiphyllanine A



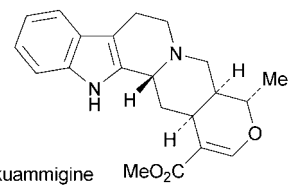
435 Alstiphyllanine B



436 Alstiphyllanine C



437 Alstiphyllanine D



438 Akuammigine

Two new β-indoloquinazoline alkaloids, orisuaveolines A (**423**) and B (**424**), have been isolated from *Oricia suaveolens*. Orisuaveoline B (**424**) was evaluated for oxidative burst inhibitory activity in a chemoluminescence assay and for cytotoxicity against A549 lung carcinoma cells.[173]

A new polyphenolic indole alkaloid, (−)-uncariagambiriine (**425**), has been obtained from an aqueous acetone homogenate of the leaves of *Uncaria gambir* (Rubiaceae) collected in Indonesia.[174]

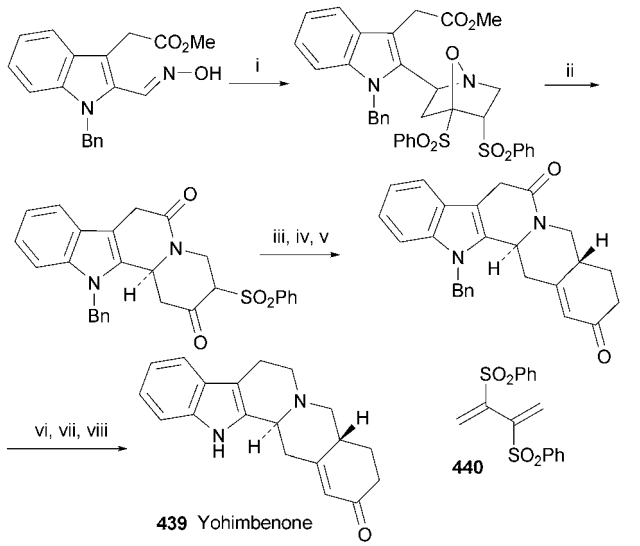
Investigation of extracts from cultures of *Streptomyces uncialis* resulted in the isolation of new alkaloids, cladoniamides A–G (**426–432**). Cladoniamide G (**432**) is cytotoxic to MCF-7 cells *in vitro*.[175]

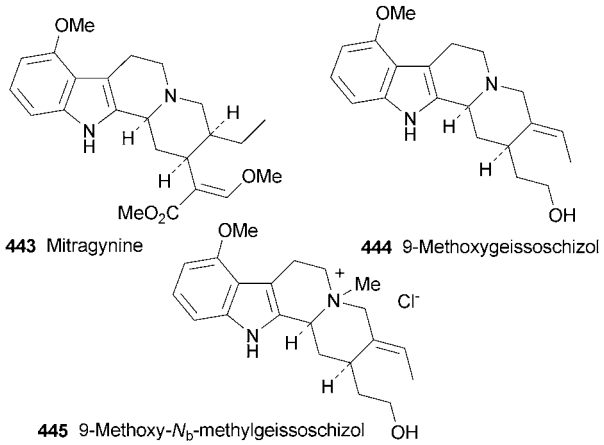
A new indole alkaloid, akuammidine-*N*-oxide (**433**), has been isolated from the leaves of *Alstonia scholaris* (Apocynaceae).[176]

Extracts of the leaves of *Alstonia macrophylla* produced four new alkaloids, alstiphyllanines A–D (**434–437**), and all compounds showed moderate antiplasmodial activity against *Plasmodium falciparum*.[177]

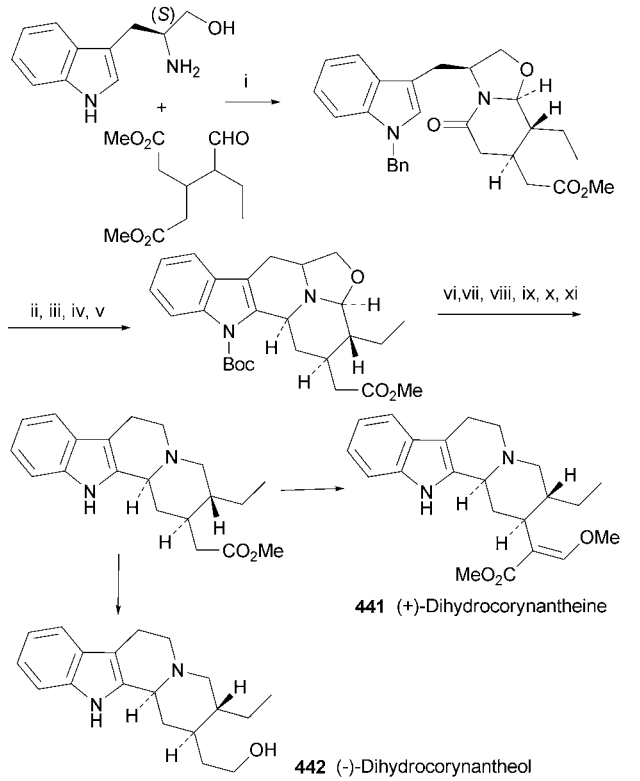
Akuammigine (**438**) has been isolated from young leaves of *Uncaria tomentosa*. The single-crystal X-ray data of akuammigine picrate hydrate confirmed the relative configuration.[178]

A total synthesis of (±)-yohimbenone (**439**) has been achieved through a conjugate addition–dipolar cycloaddition of 2,3-bis(phenylsulfonyl)-1,3-butadiene (**440**) with oxime as the key step (Scheme 77).[179]





Scheme 77 *Reagents and conditions*: i, **440**, toluene, reflux, 4 h; ii, 20% $Pd(OH)_2$, H_2, AcOH, EtOAc, sealed tube, 60 °C, 38 h; iii, methyl vinyl ketone, THF–MeOH (9 : 1), rt, 3 h, then Et_3N, 21 h; iv, *n*-Bu_3SnH, AIBN, toluene, reflux, 1 h; v, pyrrolidine, AcOH, CH_2Cl_2, rt, 68 h; vi, $LiAlH_4$, Et_2O, rt, 24 h; vii, MnO_2, CH_2Cl_2–THF (1 : 1), rt, 65 h; viii, $AlCl_3$, ultrasound, toluene, 5 h.



Scheme 78 *Reagents and conditions*: i, toluene, reflux, 4 h; ii, Lawesson's reagent, DME, reflux, 4 h; iii, BnBr, MeCN, reflux, 44 h; iv, $NaBH_4$, MeOH, −78 °C, 5 h; v, Boc_2O, DMAP, Et_3N, THF, 7 h; vi, BH_3, THF, −78 °C, 6 h; vii, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −50 °C, 20 h; viii, NH_2OH, pyridine, EtOH, reflux, 3 h; ix, Burgess reagent, CH_2Cl_2, rt, 4 h; x, $NaBH_3CN$, AcOH, MeCN; xi, HCOOH, rt, 40 h.

A enantioselective formal synthesis of (+)-dihycorynantheine (**441**) and (−)-dihydrocorynantheol (**442**) has been accomplished by the synthesis of a known synthetic precursor through a stereoselective cyclocondensation of (*S*)-tryptophanol with a racemic aldehyde and a stereoselective cyclization of the lactam (Scheme 78).[180]

Full details of the recently invented synthesis of 9-methoxy-substituted *Corynanthe* indole alkaloids, mitragynine (**443**), 9-methoxygeissoschizol (**444**) and 9-methoxy-N^b-methyl-geissoschizol (**445**), have appeared.[181]

Asymmetric syntheses of (−)-corynatheidol (**446**) and (−)-corynantheidine (**447**) have been achieved *via* one-pot azaelectrocyclization of 1-azatriene as the key step. The resulting tetracyclic aminoacetal (−)-**448** was transformed to (−)-**446** *via* (−)-**449**. Tetracyclic sulfide (−)-**449** was also converted to Cook's precursor **450** for the synthesis of (−)-**447** (Scheme 79).[182]

(−)-Arboricine (**451**), isolated from the leaves of *Kopsia arborea*, has been synthesized using an asymmetric organocatalytic Pictet–Spengler reaction and a diaselective Pd-catalyzed iodoalkene–enolate cyclization (Scheme 80).[183]

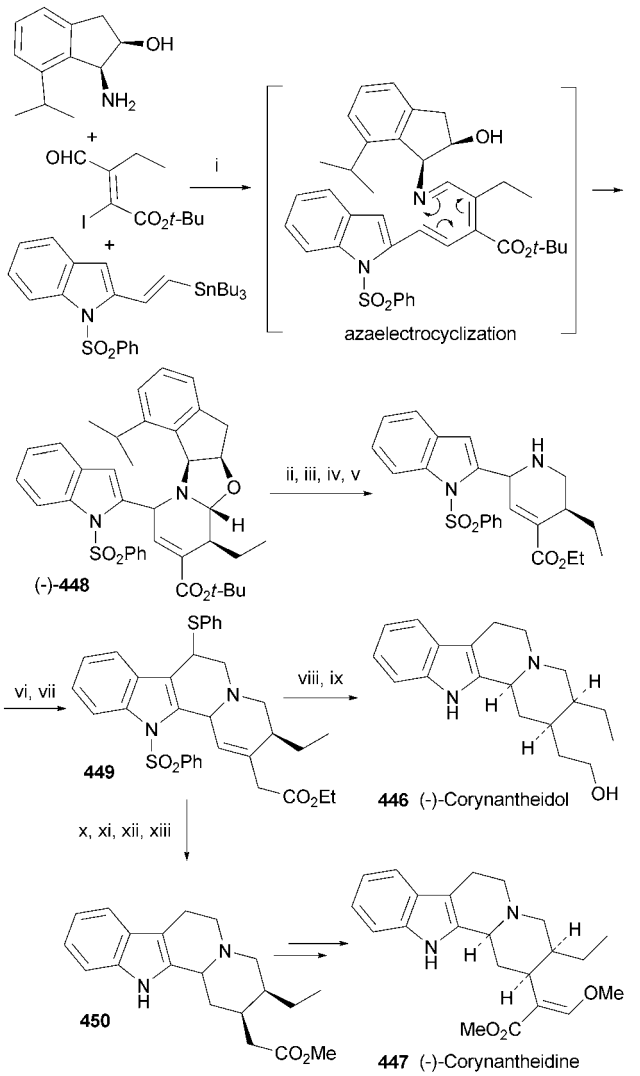
Catalytic asymmetric synthesis of (+)-yohimbine (**453**) has been achieved through a highly enantioselective thiourea **454**-catalyzed acyl-Pictet–Spengler reaction and a substrate-controlled intramolecular Diels–Alder reaction (Scheme 81).[184]

A biomimetic synthesis of (±)-tangutorine (**456**), isolated from *Nitraria tangutorum*, has been achieved in 3 steps from glutaraldehyde based on a new biosynthetic hypothesis (Scheme 82).[185]

Full details of the first total synthesis of (−)-isocyclocapitelline (**457**) and (−)-isochrysotricine (**458**), obtained from *Hedyotis capitellata* (Rubiaceae) has appeared. The key step is an Au-catalyzed cycloisomerization of a dihydroxyallene.[186]

A total synthesis of the reported tetrahydro-β-carboline structure of eudistomidin B (**459**), isolated from the Okinawan tunicate *Eudistoma glaucus*, has been achieved through an intramolecular Pictet–Spengler cyclization strategy. However, the data reported for the natural product were different to those of the synthetic compound (Scheme 83).[187]

Enantioselective syntheses of (+)-trypargine (**460**), isolated from the African frog *Kassia senegalensis*, and (+)-crispine E (**461**), obtained from *Carduus crispus*, have been achieved

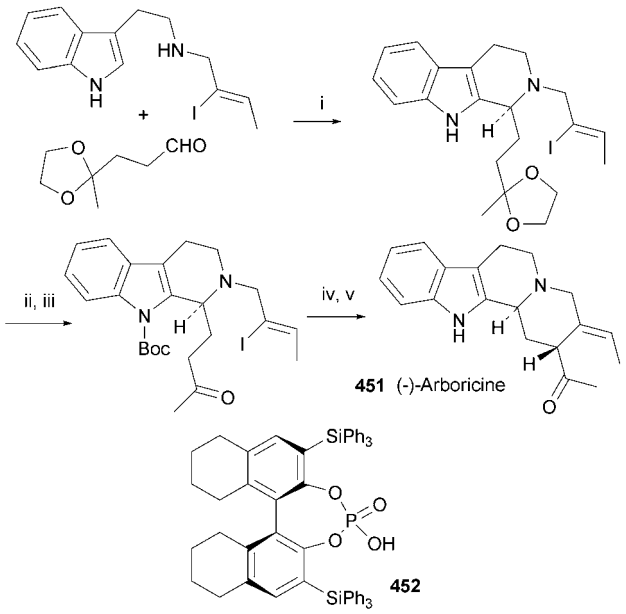


Scheme 79 *Reagents and conditions*: i, 5 Å MS, dioxane, 80 °C, 0.5 h, then $Pd_2(dba)_3$, trifurylphosphine, LiCl, reflux, 11 h; ii, DIBAL, CH_2Cl_2, −78 °C, 15 min; iii, ClCOOEt, pyridine, THF, −20 °C, 15 min, then rt, 0.5 h; iv, $Pd(OAc)_2$, Ph_3P, CO, EtOH, 50 °C, 18 h; v, $Pb(OAc)_4$, *n*-$PrNH_2$, $CHCl_3$, −50 °C, 0.5 h; vi, CH_2=CHS(O)Ph, MeOH, reflux, 27 h; vii, TMSOTf, DIPEA, CH_2Cl_2, rt, 0.5 h; viii, Li, NH_3, THF, −78 °C, then −33 °C; ix, H_2, PtO_2, MeOH, rt, 0.5 h; x, $Ba(OH)_2$, H_2O, THF, MeOH, 50 °C, 0.5 h; xi, Li, NH_3, THF, −78 °C, then −33 °C; xii, $SOCl_2$, MeOH, reflux, 1h; xiii, H_2, PtO_2, MeOH, rt, 0.5 h.

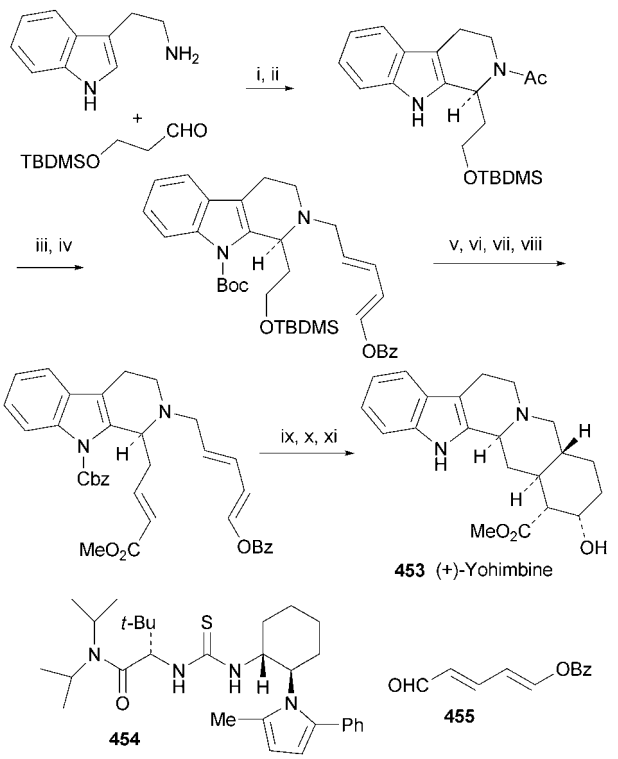
through asymmetric transfer hydrogenation of imines under Noyori conditions (Scheme 84).[188]

Enantioselective synthesis of dichotomine C (**463**), obtained from *Stellaria dichotoma*, has been achieved through microwave-assisted thermal electrocyclic reaction of azahexatriene and Sharpless asymmetric dihydroxylation (Scheme 85).[189]

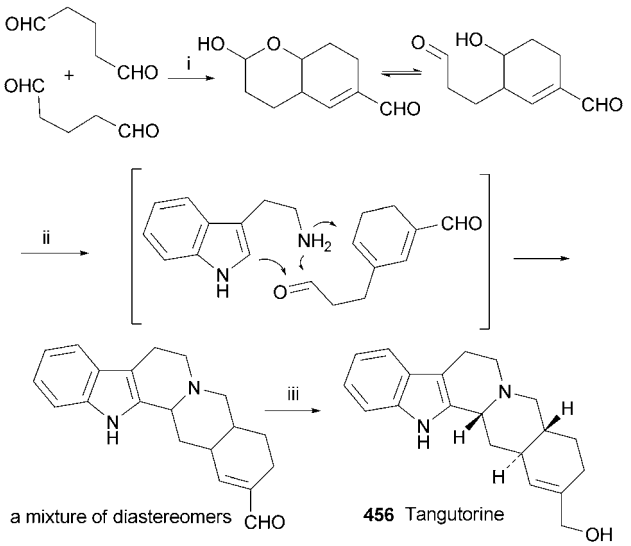
A concise asymmetric synthesis of (+)-evodiamine (**464**), obtained from *Evodia fructus*, has been achieved. Rhetsinine (**465**), one of the constituents of *Evodia fructus*, is known to exist in the cyclic iminium form (**466**) in acidic medium. Ruthenium-catalyzed asymmetric transfer hydrogenation of **466** produced (+)-**464** with 99% ee (Scheme 86).[190]



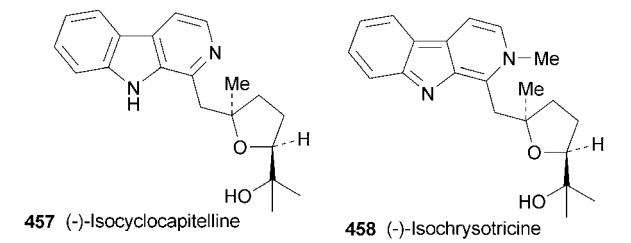
Scheme 80 *Reagents and conditions*: i, **452**, 4 Å MS, toluene, rt, 18 h, 89% ee; ii, Boc_2O, DMAP, CH_2Cl_2; iii, HCl, H_2O, acetone; iv, $Pd(Ph_3P)_4$, PhOH, *t*-BuOK, THF, reflux, 0.5 h; v, TFA, CH_2Cl_2, rt, 2 h.

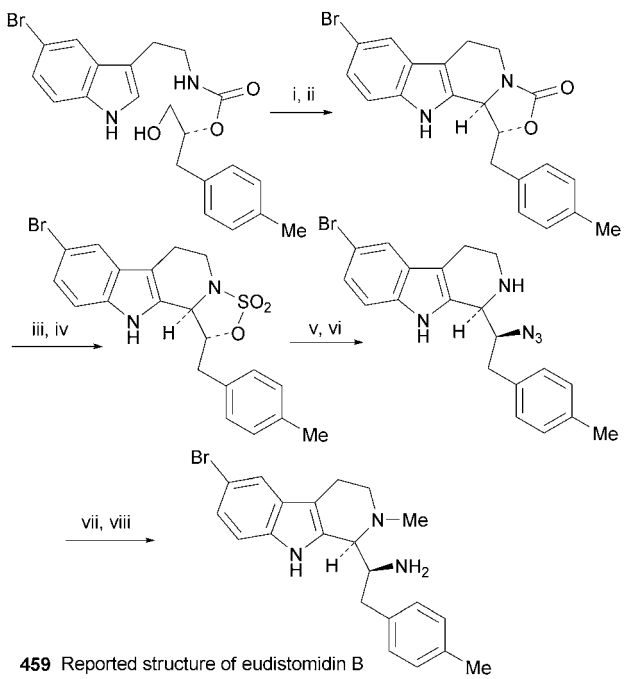


Scheme 81 *Reagents and conditions*: i, Na_2SO_4, CH_2Cl_2, Et_2O, 23 °C, 2 h; ii, **454**, AcCl, 2,6-lutidine, Et_2O, −78 °C to −60 °C, 23 h, 94% ee; iii, $BH_3{\cdot}NH_3$, *i*-Pr_2NH, *n*-BuLi, THF; iv, **455**, $PhCO_2H$, $NaBH_3CN$, benzene, 23 °C, 6 h; v, CbzCl, KHMDS, THF, 0 °C, 40 min; vi, TBAF, CF_3CH_2OH, 0 °C to 23 °C, 2 h; vii, $SO_3{\cdot}$pyridine, DMSO, *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 25 min; viii, Ph_3P=$CHCO_2Me$, CH_2Cl_2, 23 °C, 14 h; ix, $Sc(OTf)_3$, MeCN, 23 °C, 67 h; x, Cs_2CO_3, THF, MeOH, 23 °C, 2 h; xi, Pd/C, H_2, EtOAc, 23 °C.

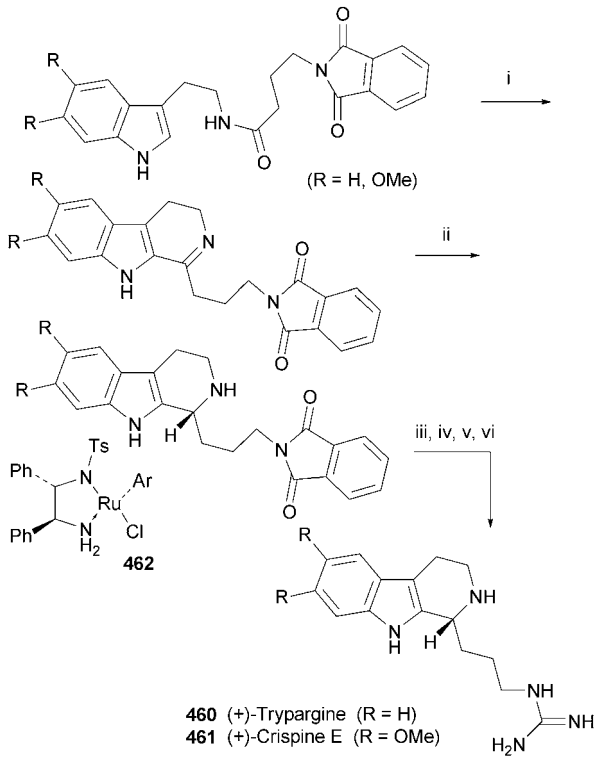


Scheme 82 *Reagents and conditions*: i, $NaHCO_3$, H_2O, 60 °C, 2 h; ii, tryptamine, AcOH, CH_2Cl_2, rt, 48 h; iii, $NaBH_4$, $CeCl_3$, MeOH.

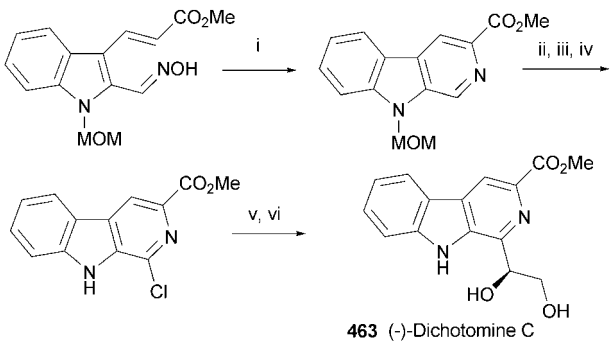




Scheme 83 *Reagents and conditions*: i, IBX, DMSO; ii, TFA, CH_2Cl_2, 0 °C; iii, 2 N NaOH, EtOH; iv, SO_2Cl_2, Et_3N, CH_2Cl_2; v, NaN_3, DMF; vi, 10% H_2SO_4, $CHCl_3$; vii, HCHO, MeOH, then $NaCNBH_3$; viii, Red-Al, toluene.



Scheme 84 *Reagents and conditions*: i, $POCl_3$, MeCN; ii, **462**, Et_3N, HCO_2H,; iii, NH_2NH_2, EtOH, 1 h; iv, *N*,*N*′-bis(Boc)-*S*-methyl-isothiourea, DMF, rt; v, TFA, CH_2Cl_2; vi, HCl, MeOH.

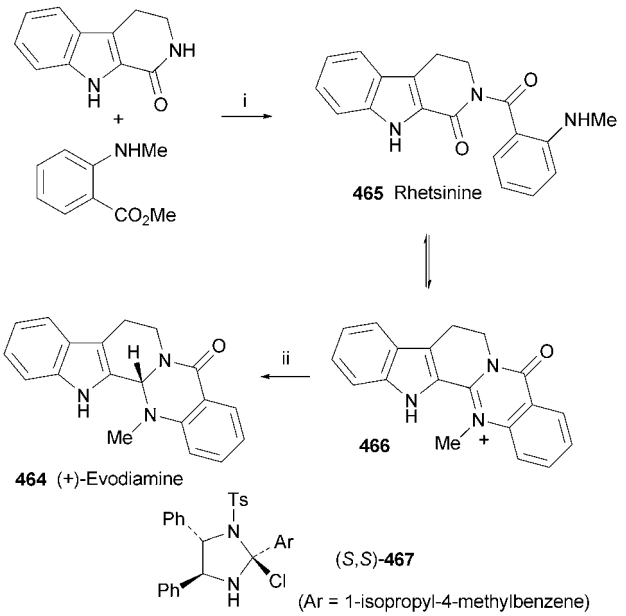


Scheme 85 *Reagents and conditions*: i, 1,2-dichlorobenzene, MW, 180 °C, 1.5 h; ii, MCPBA, CH_2Cl_2; iii, $(COCl)_2$, DMF, CH_2Cl_2; iv, CF_3SO_3H, $CH(OMe)_3$, MeOH, $MeNO_2$, 100 °C, 3 h; v, $CH_2{=}CHSnBu_3$, $PdCl_2(PPh_3)_2$, Et_4NCl, DMF, 100 °C, 2 h; vi, AD-mix-β, *t*-BuOH, H_2O.

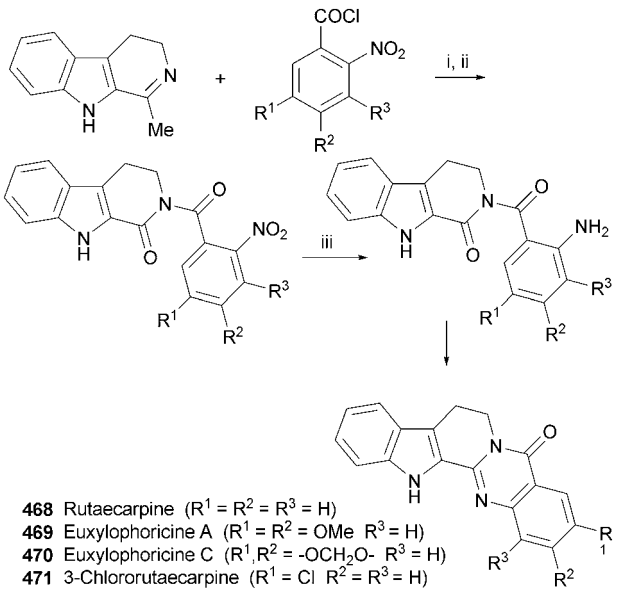
Rutaecarpine (**468**), euxylophoricine A (**469**), euxylophoricine C (**470**) and 3-chlororutaecarpine (**471**) have been isolated from the dried fruits of *Evodia rutaecarpa*, and synthesized from the ring-opened β-carboline by a one-pot reductive cyclization process (Scheme 87).[191]

Full results of the synthesis of 3*H*-epivincamine (**472**) and tacamonine (**473**) *via* Rh-catalyzed intramolecular [3 + 2] cycloaddition reaction of α-diazo indoloamide **474** have been documented.[192]

A stereoselective total synthesis of (±)-**473** has been achieved starting from a symmetrical bridged diketone that contains all the carbon atoms of the non-tryptamine part (Scheme 88).[193]



Scheme 86 *Reagents and conditions*: i, $POCl_3$, THF, reflux, then NH_4OH; ii, (*S*,*S*)-**467**, HCO_2H, Et_3N, DMF.

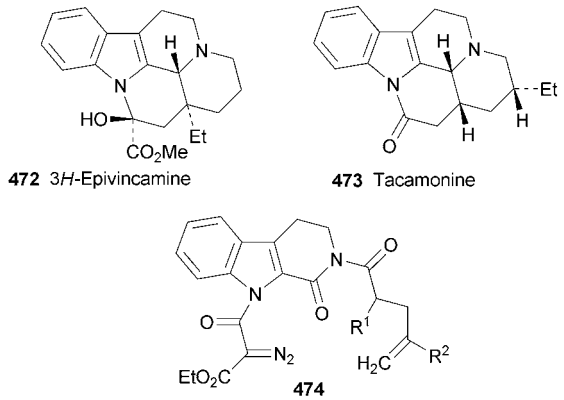


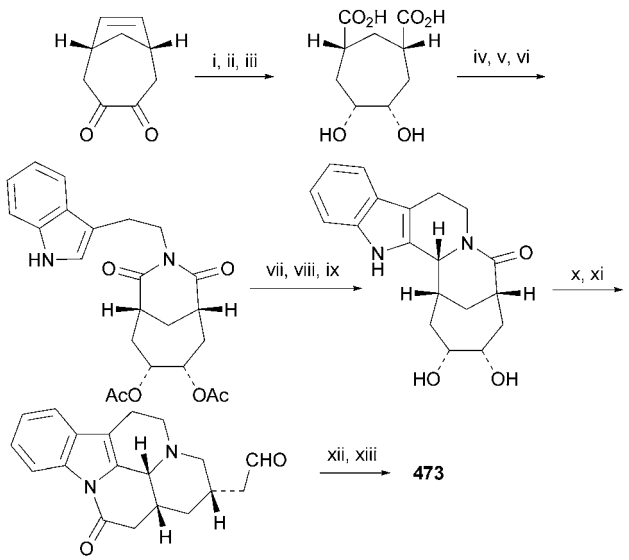
Scheme 87 *Reagents and conditions*: i, CH_2Cl_2, rt, 2 h; ii, $KMnO_4$, acetone, 0 °C; iii, Sn, HCl, MeOH, then NaOH, Et_3N, CH_2Cl_2.

Full accounts of the synthesis of (−)-alstonerine (**475**) using a Pauson–Khand reaction to assemble the azabridged bicycle have been reported (Scheme 89).[194]

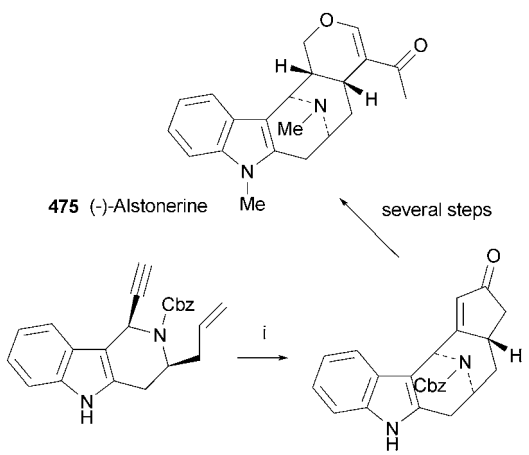
An improved synthesis of eudistomin C (**476**) has been reported, in which a concise route to the indole core of key intermediate **478** was developed using Makosza's indole synthesis. A total synthesis of eudistomin E (**477**) was also achieved *via* key intermediate **479** based on a modification of this improved route (Scheme 90).[195]

The shizozygane alkaloid (±)-strempeliopine (**480**) has been synthesized using an intramolecular 1,4-dipolar cycloaddition of

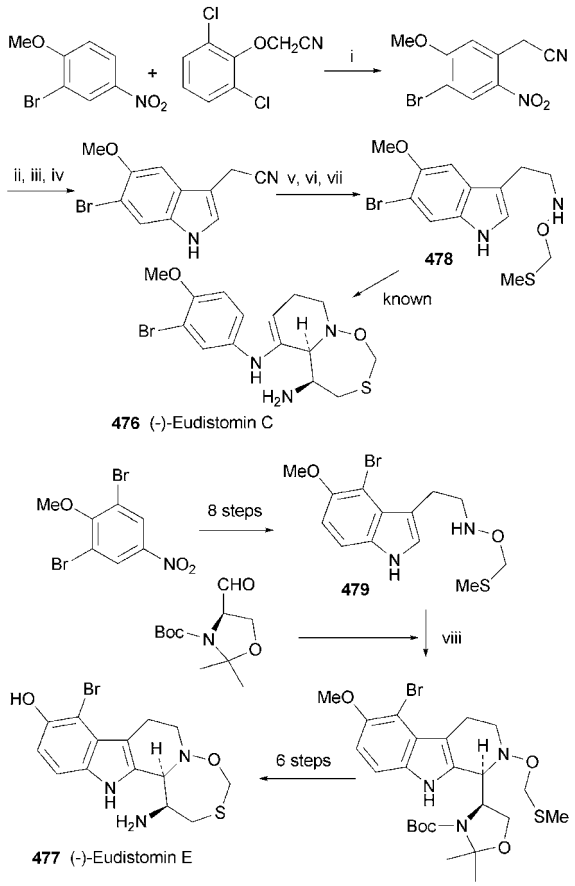




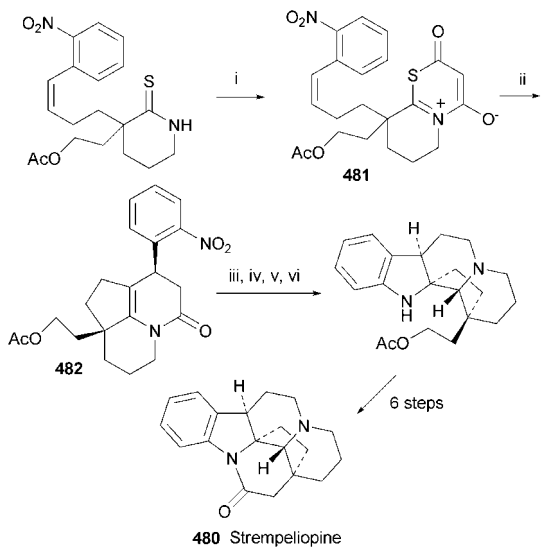
Scheme 88 *Reagents and conditions*: i, $NaBH_4$, MeOH, CH_2Cl_2, 0 °C; ii, Ac_2O, DMAP, pyridine, CH_2Cl_2; iii, $KMnO_4$, Et_2O, H_2O; iv, $ClCO_2Et$, Et_3N, THF, 0 °C, 30 min; v, tryptamine, rt, 16 h; vi, AcCl, THF, reflux; vii, Lawesson's reagent, toluene, reflux, 8 h; viii, Raney® Ni, EtOH, 60 °C, 3 h; ix, $POCl_3$, benzene, reflux, 3 h, then $LiAlH_4$; x, $NaIO_4$, THF, H_2O, rt, 1 h; xi, PCC, 4 Å MS, CH_2Cl_2; xii, $(CH_2SH)_2$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, rt, 2.5 h; xiii, Raney® Ni, EtOH, reflux, 4.5 h.



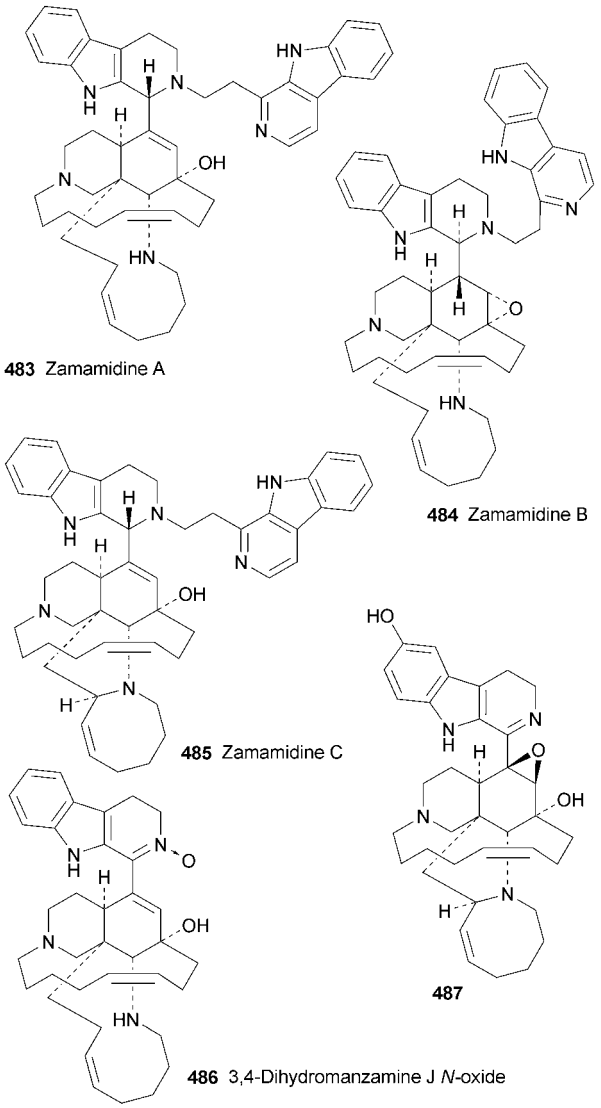
Scheme 89 *Reagents and conditions*: i, $Co_2(CO)_8$, DMSO, THF, 65 °C.



Scheme 90 *Reagents and conditions*: i, *t*-BuOK, DMF, 0 °C; ii, Rh/C, H_2, EtOH; iii, $MeNH_2$, HCHO, AcOH, DMF, then NaOH; iv, NaCN, H_2O, reflux; v, DIBAH, CH_2Cl_2, 0 °C; vi, $MeSCH_2ONH_2$, MeOH, H_2O; vii, $NaBH_3CN$, TFA, MeOH; viii, $BrCH_2COOH$, toluene, 0 °C.



Scheme 91 *Reagents and conditions*: i, carbon suboxide, CH_2Cl_2, −78 °C to rt; ii, toluene, sealed tube, 200 °C, 1 h; iii, 10% Pd/C, H_2, EtOH, THF; iv, NBS, CH_2Cl_2, rt; v, $AgNO_3$, MeOH, H_2O, rt, 1 h; vi, $NaBH_3CN$, AcOH, H_2O, rt, 30 min, then 50 °C, 2 h.



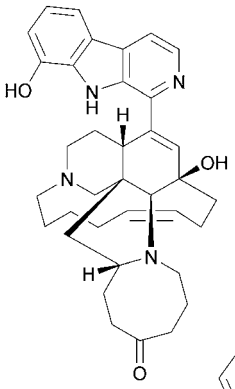
a cross-conjugated heteroaromatic betaine **481**. The resulting cycloadduct **482** was transformed into **480** (Scheme 91).[196]

Five new manzamine alkaloids – zamamidines A (**483**), B (**484**) and C (**485**), 3,4-dihydromanzamine J *N*-oxide (**486**) and 3,4-dihydro-6-hydroxy-10,11-epoxymanzamine A (**487**) – have been isolated from an Okinawan marine sponge *Amphimedon* sp. (SS-975).[197]

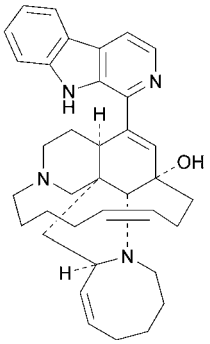
(−)-Manzamine F (**488**), manzamine A (**489**) and 8-hydroxymanzamine A (**490**) have been transformed to 13 new semisynthetic manzamine derivatives, and their potential importance as antituberculosis and anti-inflammatory agents examined.[198]

3 Bisindole alkaloids

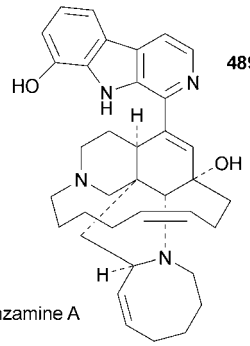
Two new bis-spiroimidazolidinone alkaloids, dictazolines A (**491**) and B (**492**), have been obtained from the marine sponge *Smenospongia cerebriformis*.[199]



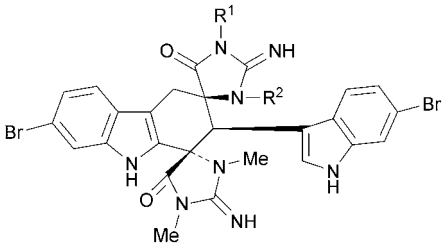
488 Manzamine F



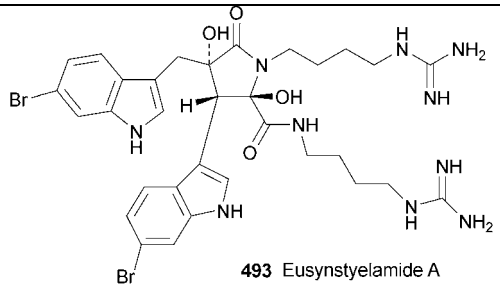
489 Manzamine A



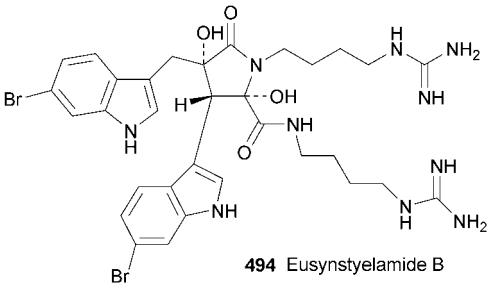
490 8-Hydroxymanzamine A



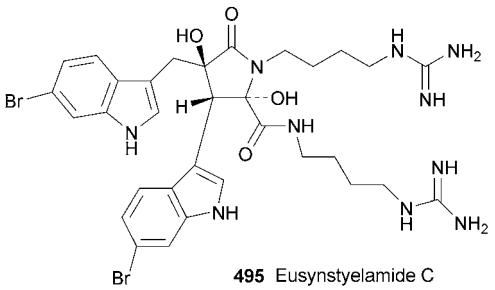
491 Dictazoline A ($R^1 = R^2 = Me$)
492 Dictazoline B ($R^1 = R^2 = H$)



493 Eusynstyelamide A



494 Eusynstyelamide B



495 Eusynstyelamide C

Three new alkaloids, eusynstyelamides A (**493**), B (**494**) and C (**495**), have been isolated from the Great Barrier Reef ascidian *Eusynstyela latericius*. All compounds exhibited inhibitory activity against neuronal nitric oxide synthase (*n*NOS).[200]

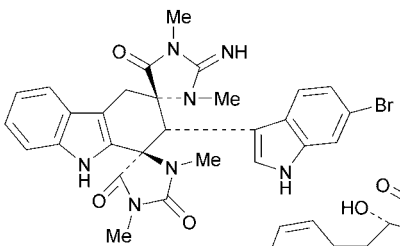
Five new bisindole alkaloids, tubastrindoles D–H (**496–500**), have been obtained from a stony coral, *Tubastraea aurea*.[201]

Three new nonsymmetrical β-carboline dimers **501–503** have been obtained from an ascidian, *Didemnum* sp.[202]

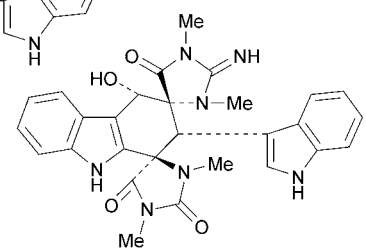
Two new indole alkaloids, kopsiyunnanines A (**504**) and B (**505**), have been isolated from the aerial part of Yunnan *Kopsia arborea*.[203]

A cytotoxic bisindole alkaloid, bipleiophylline (**506**), has been isolated from *Alstonia angustifolia*. This compound has an unprecedented structure in which two indole moieties are bridged by an aromatic spacer.[204]

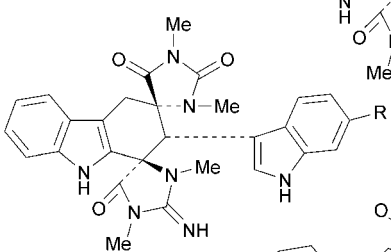
A novel vobasine–vobasine bisindole alkaloid, bisnicalaterine A (**507**), has been obtained from the leaves of *Hunteria zeylanica*, and was found to have moderate cytotoxicity against human cancer cell lines.[205]



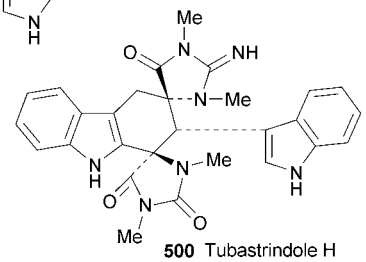
496 Tubastrindole D



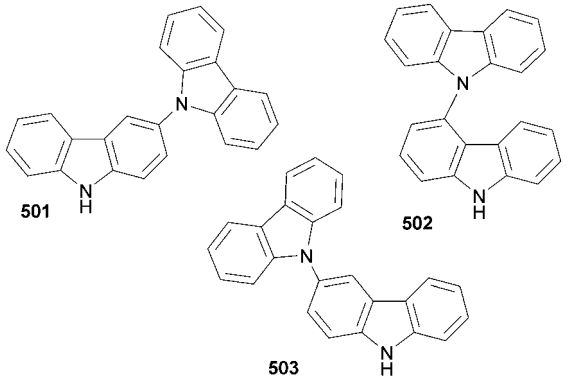
497 Tubastrindole E

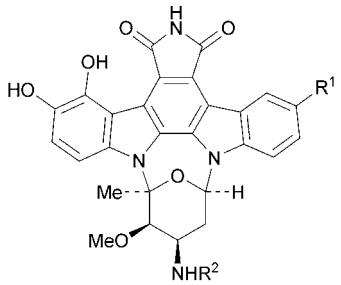


498 Tubastrindole F (R = Br)
499 Tubastrindole G (R = H)

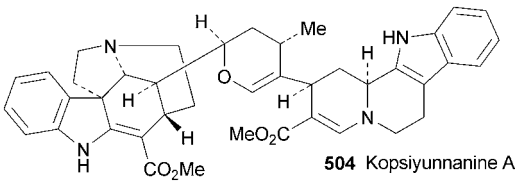


500 Tubastrindole H

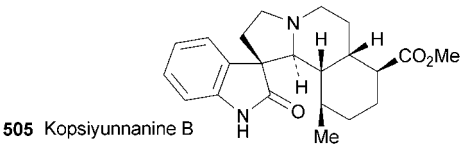




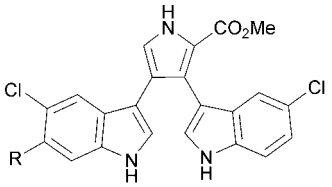
508 7-Oxo-3,8,9-trihydroxystaurosporine (R^1 = OH, R^2 = Me)
509 7-Oxo-8,9-dihydroxy-4′-*N*-demethylstaurosporine (R^1 = R^2 = H)



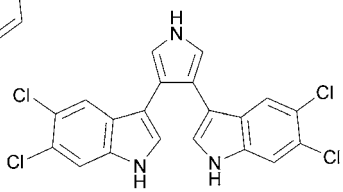
504 Kopsiyunnanine A



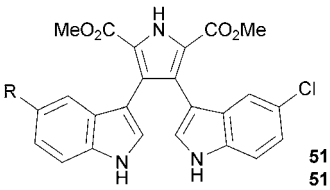
505 Kopsiyunnanine B



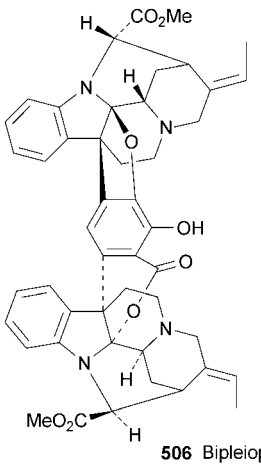
510 Lynamicin A (R = H)
511 Lynamicin B (R = Cl)



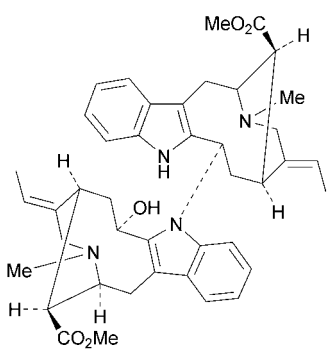
512 Lynamicin C



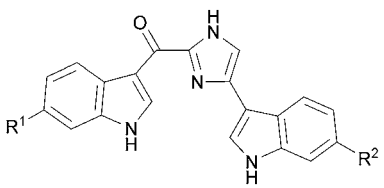
513 Lynamicin D (R = Cl)
514 Lynamicin E (R = H)



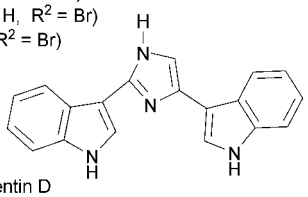
506 Bipleiophylline



507 Bisnicalaterine A



515 Deoxytopsentin (R^1 = R^2 = H)
516 Topsentin (R^1 = OH, R^2 = H)
517 Dibromodeoxytopsentin (R^1 = R^2 = Br)
518 Deoxybromotopsentin (R^1 = H, R^2 = Br)
519 Bromotopsentin (R^1 = OH, R^2 = Br)



520 Nortopsentin D

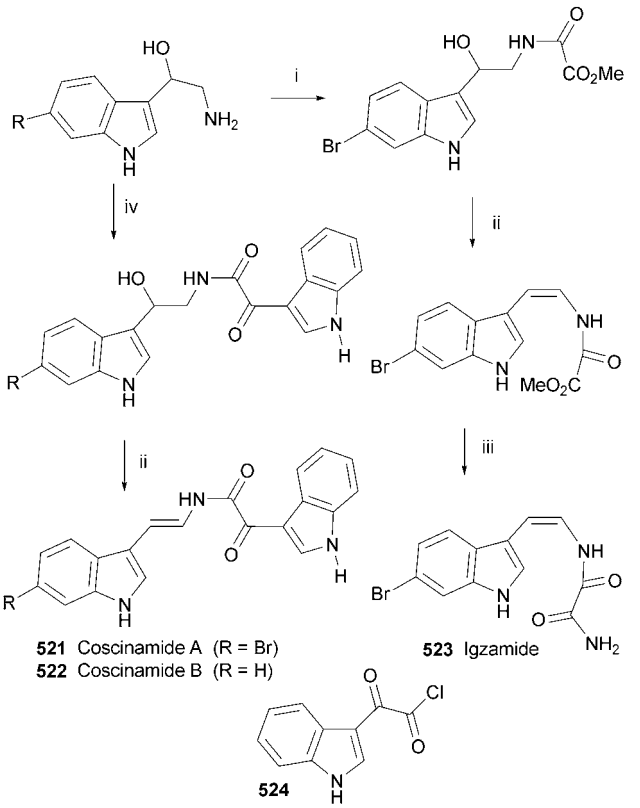
Two new cytotoxic staurosporines, 7-oxo-3,8,9-trihydroxystaurosporine (**508**) and 7-oxo-8,9-dihydroxy-4′-*N*-demethylstaurosporine (**509**), have been isolated from the marine ascidian *Cystodytes solitus*.[206]

Five new chlorinated bisindoles, lynamicins A (**510**), B (**511**), C (**512**), D (**513**) and E (**514**), have been obtained from a novel marine actinomycete, NPS12745, which was isolated from a marine sediment collected off the coast of San Diego, California.[207]

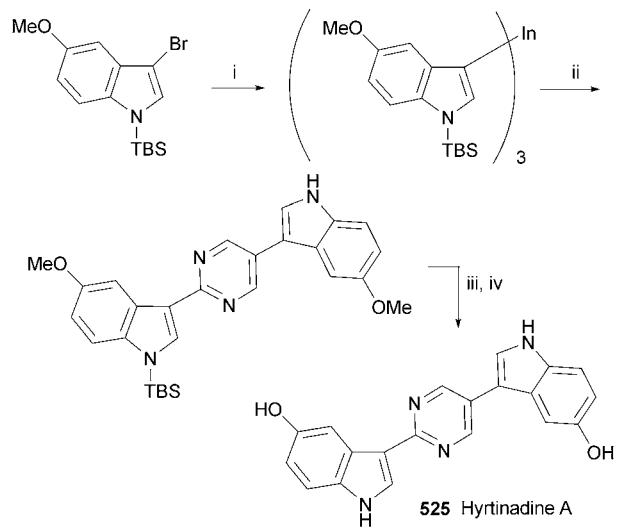
Full experimental details of the previously communicated synthesis of topsentins (**515–520**) have been reported.[208]

Indolic enamides, coscinamides A (**521**) and B (**522**), and igzamide (**523**), have been synthesized through the thermally assisted dehydration of amino alcohols (Scheme 92).[209]

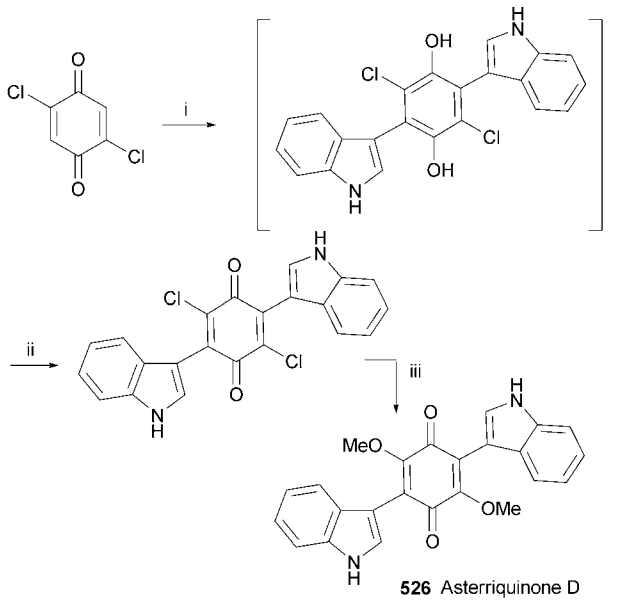
A concise synthesis of hyrtinadine A (**525**) has been achieved using the Pd-catalyzed cross-coupling of tri(3-indolyl)indium with 5-bromo-2-chloropyrimidine (Scheme 93).[210]



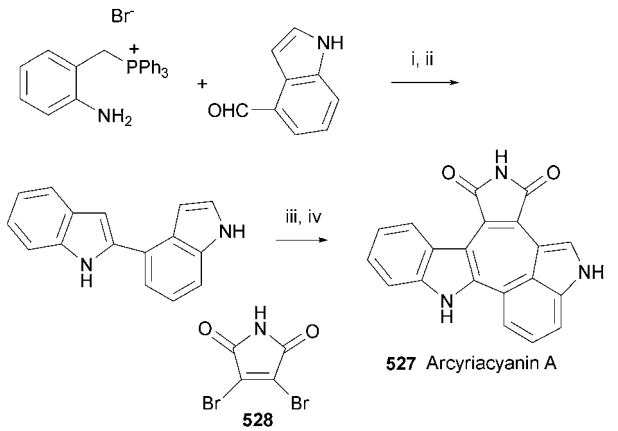
Scheme 92 *Reagents and conditions*: i, $ClCOCO_2Me$, Et_3N; ii, xylene, 130 °C; iii, NH_3, MeOH, 0 °C; iv, **524**, Et_3N.



Scheme 93 *Reagents and conditions*: i, *n*-BuLi, THF, −78 °C, then $InCl_3$; ii, 5-bromo-2-chloropyrimidine, $Pd(PPh_3)_4$, THF, 80 °C; iii, BBr_3, CH_2Cl_2; iv, TBAF, THF.



Scheme 94 *Reagents and conditions*: i, indole, $Pd(OAc)_2$, MeCN, rt, 22 h; ii, CAN, MeCN, rt, 2 h; iii, NaOH, MeOH, 2–4 °C, 1 h.



Scheme 95 *Reagents and conditions*: i, AcOH, microwaves, 80 °C, 10 min; ii, *t*-BuOK, THF, rt, 1 h; iii, MeMgI; iv, **528**, toluene, reflux.

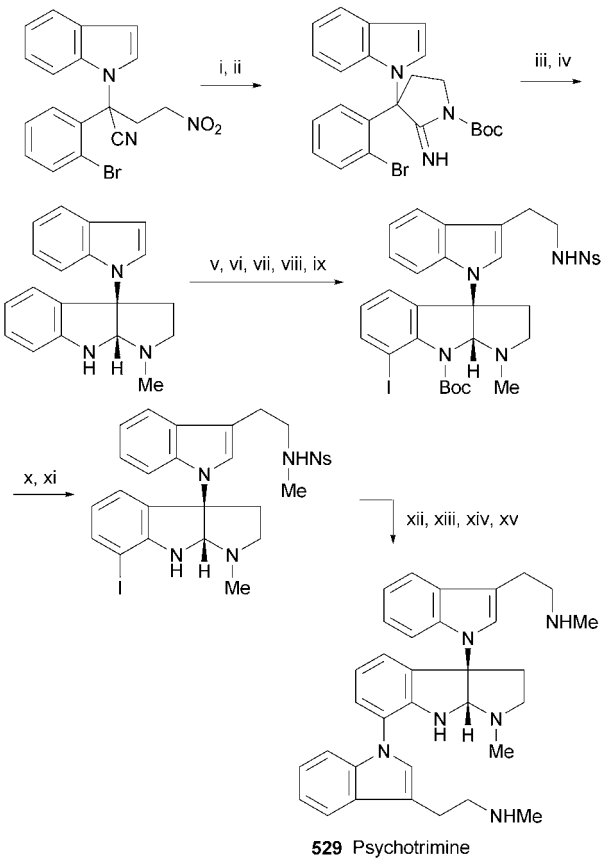
Asterriquinone D (**526**), isolated from *Aspergillus terreus* IFO 6123 as an intracellular metabolic product, has been synthesized in three steps from 2,5-dichloro-1,4-benzoquinone (Scheme 94).[211]

A formal total synthesis of arcyriacyanin A (**527**), a pigment of the slime mold *Arcyria obvelata*, has been achieved through one-pot construction of 2-arylindole from phosphonium salt with aldehyde under microwave irradiation (Scheme 95).[212]

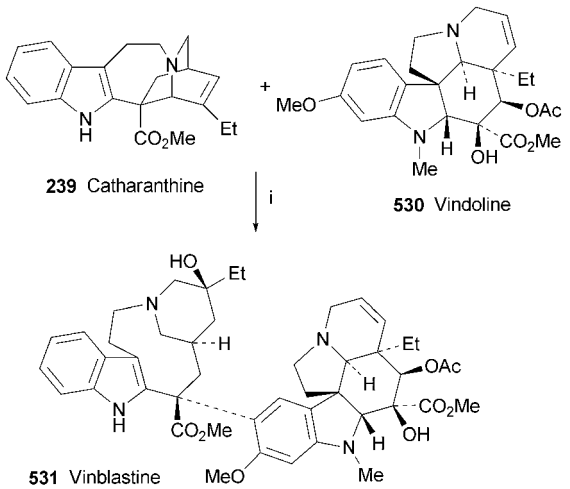
The first total synthesis of the trimeric indole alkaloid psychotrimine (**529**), obtained from a Rubiaceous plant indigenous to Malaysia, *Psychotria rostrata*, has been completed using Cu-mediated amination of halobenzenes (Scheme 96).[213]

A single-step biomimetic coupling of vindoline (**530**) with catharanthine (**239**) has been developed, producing vinblastine (**531**). Full details of the direct coupling were reported, along with mechanistic studies (Scheme 97).[214]

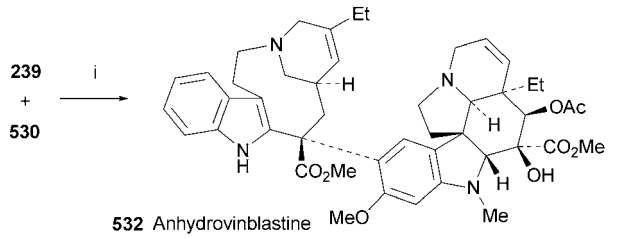
The efficient enzyme-catalyzed coupling of **239** with **530** has been carried out by exploiting laccases and atmospheric oxygen, providing anhydrovinblastine (**532**). Laccases are copper-containing oxido-reductases (blue oxidases) (Scheme 98).[215]



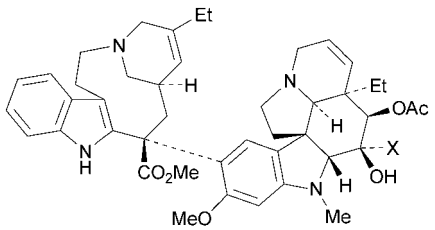
Scheme 96 *Reagents and conditions*: i, Fe, HCl, EtOH, reflux; ii, Boc_2O, *i*-Pr_2NEt, MeCN, rt; iii, CuI, K_3PO_4, DMSO, 80 °C; iv, Red-Al, toluene, 0 °C to 90 °C; v, NHMDS, Boc_2O, THF, −78 °C to 0 °C; vi, *sec*-BuLi, TMEDA, I_2, THF, −78 °C to 0 °C; vii, $InBr_3$, nitroethylene, CH_2Cl_2, rt; viii, Fe, AcOH, EtOH, dioxane, reflux; ix, NsCl, Et_3N, CH_2Cl_2, rt; x, DBU, Me_2SO_4, DMF, 0 °C; xi, TMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt; xii, NsCl, Et_3N, CH_2Cl_2, xiii, Me_2SO_4, DBU, DMF, 0 °C; xiv, N^b-methyl-N^b-Ns-tryptamine, CuI, K_3PO_4, *N*,*N*′-dimethylethylenediamine, dioxane; xv, PhSH, Cs_2CO_3, MeCN, rt.

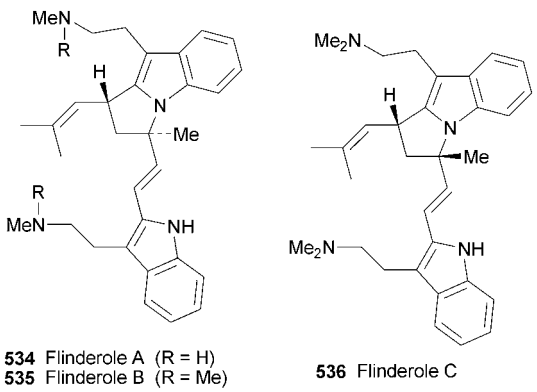


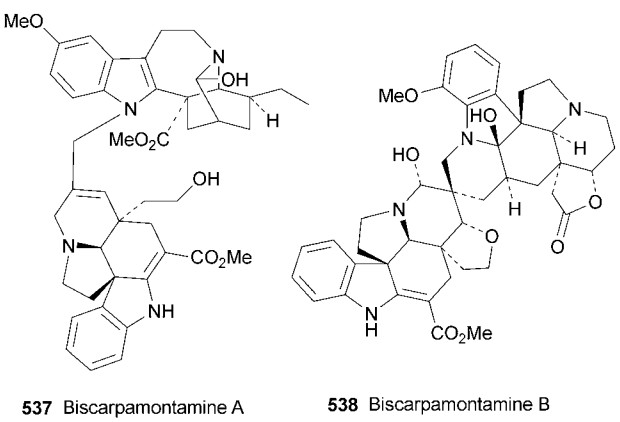
Scheme 97 *Reagents and conditions*: i, $FeCl_3 \cdot 6H_2O$, 0.1 N HCl, CF_3CH_2OH, rt, 2 h, then $FeCl_3 \cdot 6H_2O$, ammonium oxalate, H_2O, air, 0 °C, 30 min, then $NaBH_4$, H_2O, 0 °C.

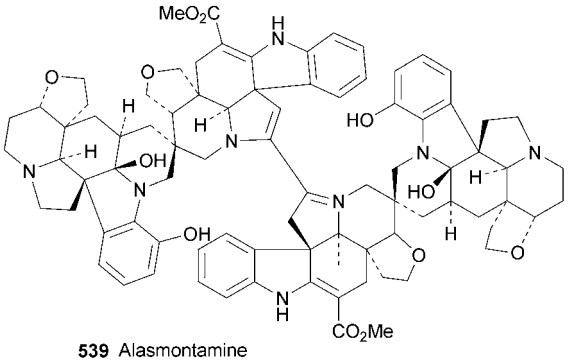


Scheme 98 *Reagents and conditions*: i, laccase, O_2, acetate buffer, 30 °C, then $NaBH_4$, 1 M NaOH.

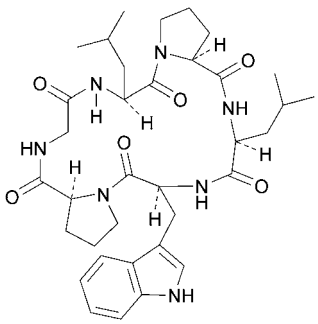




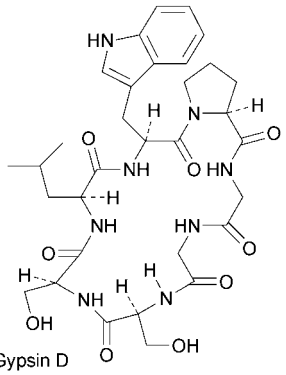




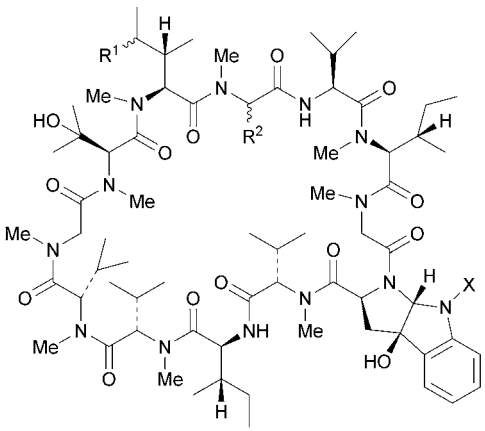
539 Alasmontamine

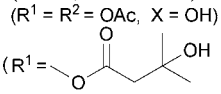


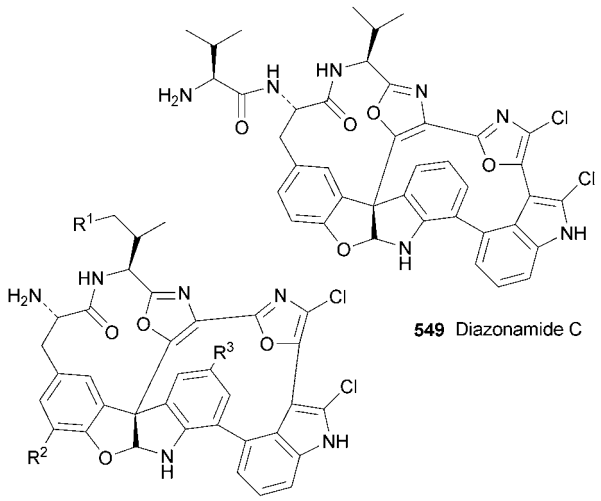
547 Gypsin A



548 Gypsin D

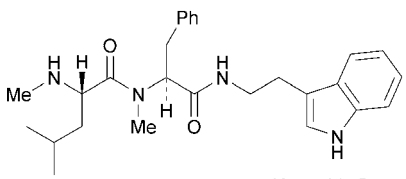


540 Omphalotin E ($R^1 = R^2 = X = H$)
541 Omphalotin F ($R^1 = R^2 = H$, $X = OH$)
542 Omphalotin G ($R^1 = H$, $R^2 = X = OH$)
543 Omphalotin H ($R^1 = R^2 = OAc$, $X = OH$)
544 Omphalotin I ($R^1 =$ 
$R^2 = OAc$, $X = OH$)

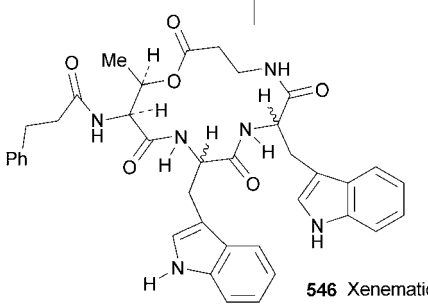


549 Diazonamide C

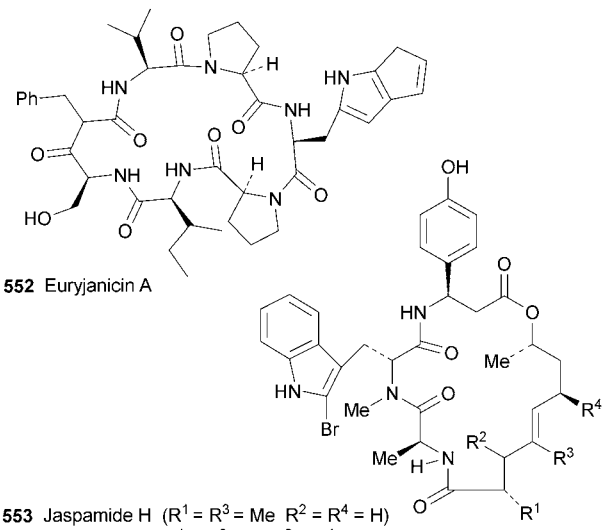
550 Diazonamide D ($R^1 = Me$ $R^2 = H$ $R^3 = Cl$)
551 Diazonamide E ($R^1 = R^3 = H$ $R^2 = Br$)



545 Xenortide B

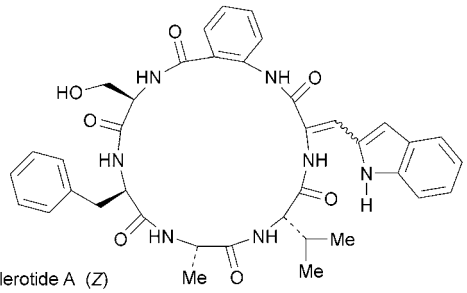


546 Xenematide



552 Euryjanicin A

553 Jaspamide H ($R^1 = R^3 = Me$ $R^2 = R^4 = H$)
554 Jaspamide J ($R^1 = R^2 = H$ $R^3 = R^4 = Me$)
555 Jaspamide K ($R^1 = R^3 = R^4 = Me$ $R^2 = OH$)
556 Jaspamide L ($R^1 = R^4 = Me$ $R^2 = H$ $R^3 = CH_2OH$)



557 Sclerotide A (*Z*)
558 Sclerotide B (*E*)

Two new series of anhydrovinblastine derivatives (**533**) have been prepared and their inhibitory activities against human non-small-cell lung cancer and HeLa cell lines evaluated.[216]

The Australian plant *Flindersia acuminata* produced flinderoles A (**534**), while B (**535**) and C (**536**) have been obtained from the Papua New Guinean plant *Flindersia amboinensis*. All compounds showed antimalarial activities.[217]

Two new bisindole alkaloids, biscarpamontamines A (**537**) and B (**538**), have been isolated from stems of *Tabernaemontana sphaerocarpa*. Compound **538** showed potent cytotoxicity against various human cancer cell lines.[218]

A novel indole alkaloid, alasmontamine A (**539**), containing a bis-vobtusine-type core, has been isolated from the leaves of *Tabernaemontana elegans*. This compound showed moderate cell growth inhibitory activity.[219]

4 Peptide alkaloids

Omphalotins E (**540**), F (**541**), G (**542**), H (**543**) and I (**544**), oxidatively modified cyclic dodecapeptides, have been isolated from mycelial extracts of the basidiomycete *Omphalotus olearius*. All compounds showed strong nematicidal activity against the plant pathogen *Meloidogyne incognita*.[220]

Two new peptides, xenortide B (**545**) and xenematide (**546**), have been isolated from a culture of the nematode-associated entomopathogenic bacterium *Xenorhabdus nematophilus*. Xenematide (**546**) showed moderate antibacterial activity.[221]

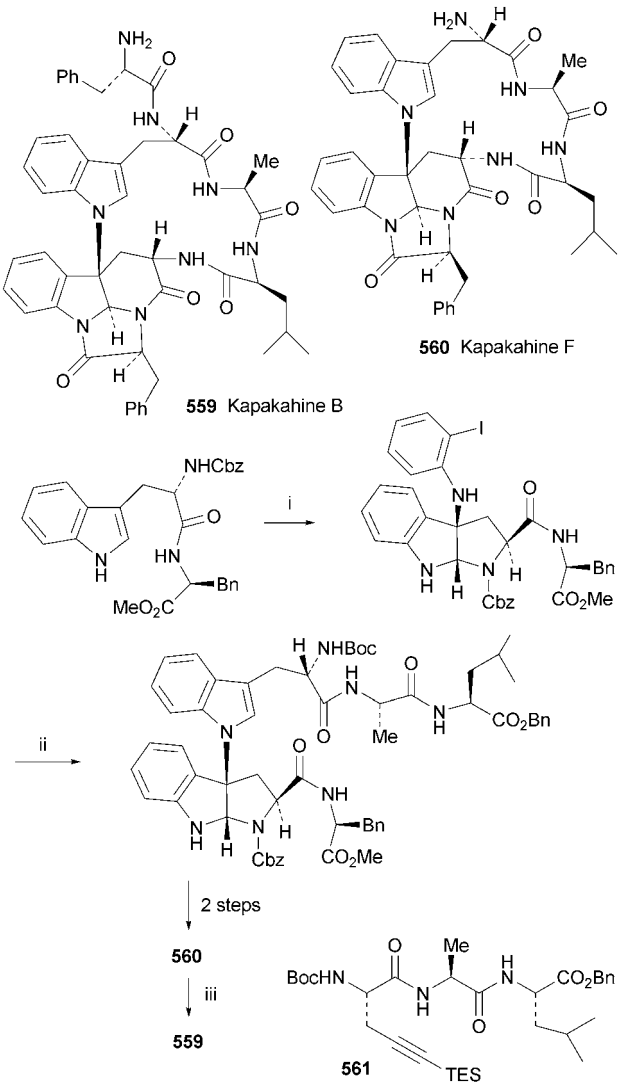
Two new cyclopeptides, gypsins A (**547**) and D (**548**), have been obtained from the roots of *Gypsophila arabica*.[222]

Three new macrocyclic peptides, diazonamides C (**549**), D (**550**) and E (**551**), have been isolated from the marine ascidian *Diazona* sp. collected in Indonesia.[223]

A new proline-containing cycloheptapeptide, euryjanicin A (**552**), has been isolated from the marine sponge *Prosuberites laughlini* indigenous to Puerto Rico.[224]

Jaspamides H (**553**), J (**554**), K (**555**) and L (**556**) have been obtained from the marine sponge *Jaspis splendans*. All compounds exhibited potent cytotoxic activities.[225]

Two new cyclic hexapeptides, sclerotides A (**557**) and B (**558**), have been isolated from the marine-derived halotolerant *Aspergillus sclerotiorum* PT06-1 in a nutrient-limited hypersaline medium. Both compounds (**557**, **558**) are photochemically interconvertible.[226]



Scheme 99 *Reagents and conditions*: i, 2-iodoaniline, NIS, MeCN, −45 °C to −35 °C, 1 h; ii, **561**, $Pd(OAc)_2$, NaOAc, LiCl, DMF, 100 °C, 24 h; iii, Boc-Phe-OH, EDC, HOBt, Et_3N, CH_2Cl_2, then TFA, CH_2Cl_2, 1 h.

Enantiospecific syntheses of kapakahines B (**559**) and F (**560**), isolated from the marine sponge *Cribrochalina olemda*, have been completed (Scheme 99).[227]

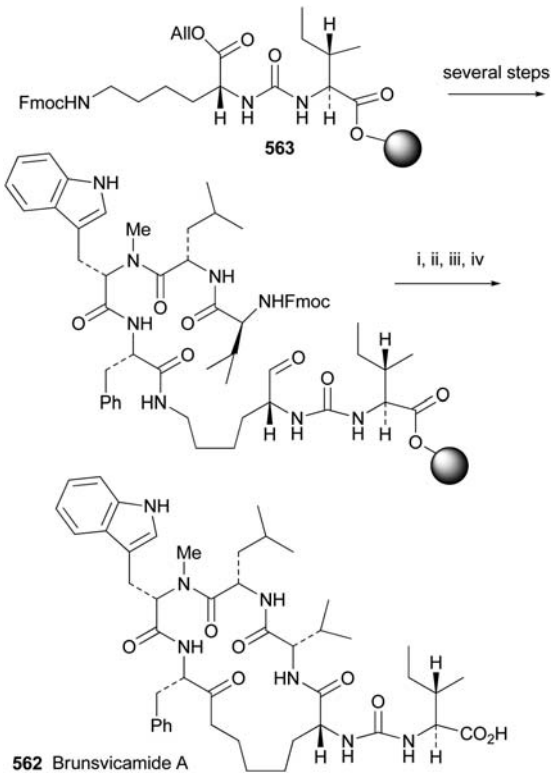
The total synthesis of brunsvicamide A (**562**) has been performed on a solid support from a urea building block **563**. The originally assigned stereochemistry was corrected (Scheme 100).[228]

The total synthesis of chondramide C (**564**) has been accomplished and the absolute configuration determined (Scheme 101).[229]

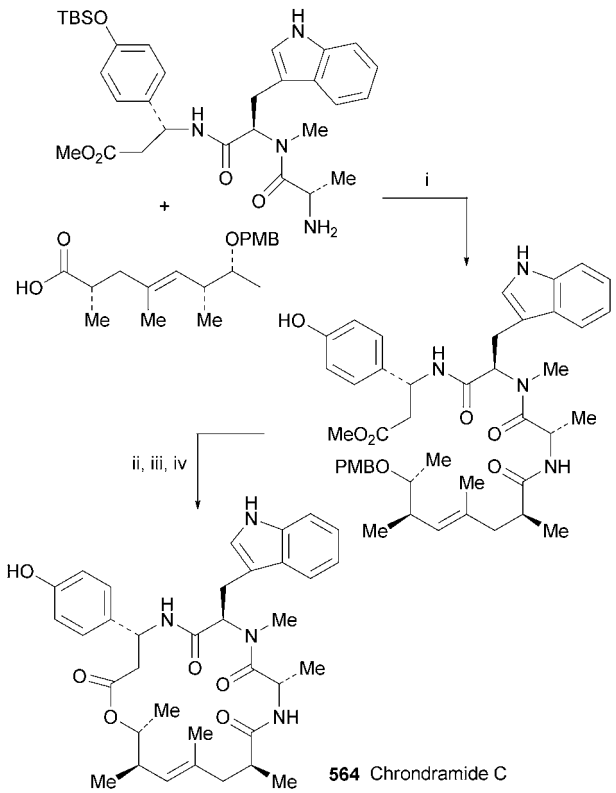
A total synthesis of **564** has been accomplished, featuring an *E*-selective ring-closing metathesis as the key step (Scheme 102).[230]

A bicyclic octapeptide, celogentin C (**565**) isolated from the seeds of *Celosia argentea*, has been synthesized (Scheme 103).[231]

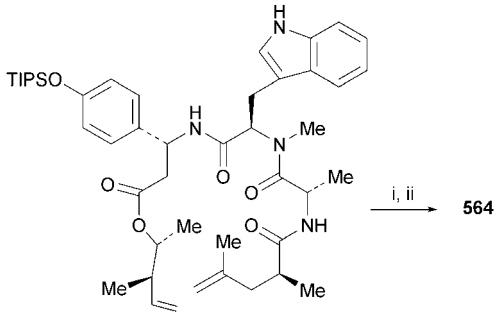
The marine cyclopeptide LL15G256γ (**567**) has been isolated from the marine fungus *Hypoxylon oceanicum*. A total synthesis



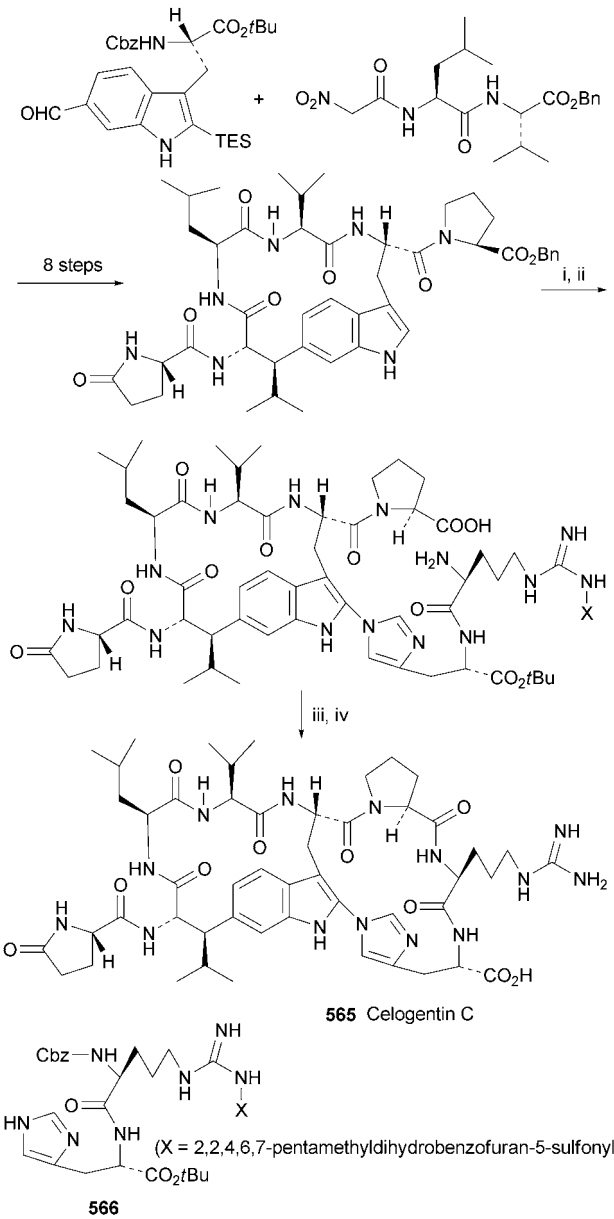
Scheme 100 *Reagents and conditions*: i, $Pd(PPh_3)_4$; ii, DMF, piperidine; iii, DIC, HOBt, DMF; iv, 2% TFA, CH_2Cl_2.



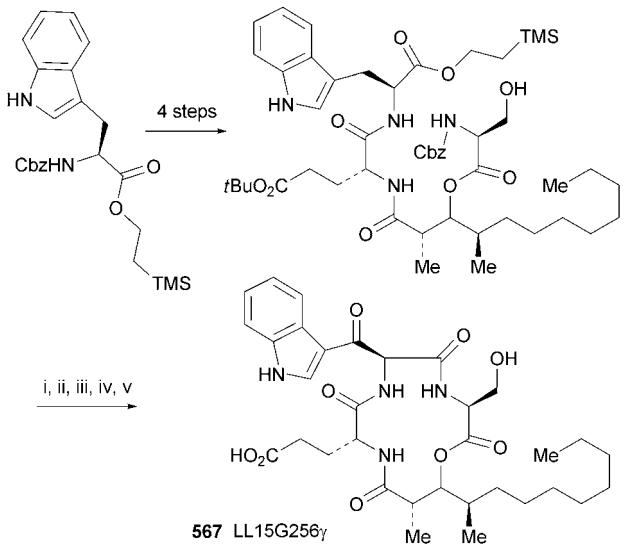
Scheme 101 *Reagents and conditions*: i, DCC, HOBt, CH_2Cl_2; ii, $BCl_3 \cdot SMe_2$, CH_2Cl_2; iii, LiOH, THF, EtOH, 16 h; iv, MNBA, DMAP, CH_2Cl_2, 4 h.



Scheme 102 *Reagents and conditions*: i, Grubbs' 2nd-generation catalyst, toluene, Ar, 110 °C, 2 h; ii, TBAF, THF, 0 °C, 1 h.



Scheme 103 *Reagents and conditions*: i, Pro-OBn, NCS, 1,4-dimethylpiperazine, CH_2Cl_2, then **566**; ii, 10% Pd/C, HCO_2NH_4, MeOH, H_2O; iii, HOBt, HBTU, DMF; iv, TFA, H_2O.



Scheme 104 *Reagents and conditions*: i, TBAF, THF; ii, Pd/C, H_2, MeOH; iii, DEPC, DIPEA, DMF; iv, DDQ, THF, H_2O; v, TFA, CH_2Cl_2.

of **567** with the proposed stereochemistry was performed, but the synthesized material appeared to be different to the marine natural product (Scheme 104).[232]

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