Simple indole alkaloids and those with a nonrearranged monoterpenoid unit

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Covering: 2006 to 2007

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

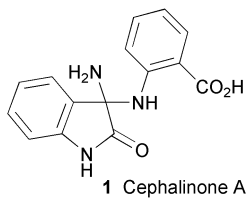
1 Introduction

This review covers the literature on simple indole alkaloids and those with a nonrearranged monoterpenoid unit from the beginning of 2006 to the end of 2007. In this series, marine natural products and peptide alkaloids have been also surveyed. As a result, these will be some overlap with marine alkaloids and peptide alkaloids containing an indole ring. Reviews on pyrrolidinyl-spirooxindoles,[1] strategies for the synthesis of manzamine alkaloids,[2] total synthesis of complex cyclotryptamine alkaloids,[3] and recent advances in the chemistry of macroline, sarpagine and ajmaline-related indole alkaloid[4] have appeared.

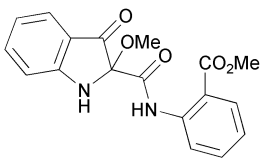
2 Simple indole alkaloids

2.1 Non-tryptamines

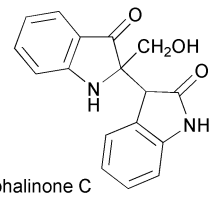
Seven new indole alkaloids, cephalinones A (**1**), B (**2**), C (**3**), D (**4**) and cephalandoles A (**5**), B (**6**), C (**7**), were isolated from the MeOH extract of *Cephalanceropsis gracilis*, a native orchid of Taiwan.[5] The absolute configuration of **1–4** could not be determined due to insufficient amounts of these compounds. All seven alkaloids were evaluated for their cytotoxic effects, and **4** showed significant cytotoxicity against MCF-7, NCI-H460 and SF-268 cell lines.



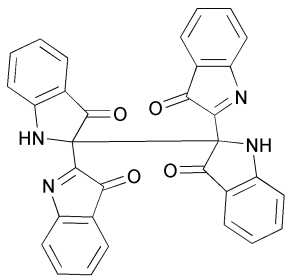
1 Cephalinone A



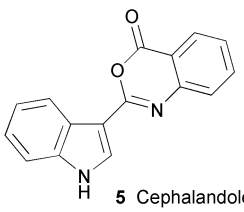
2 Cephalinone B



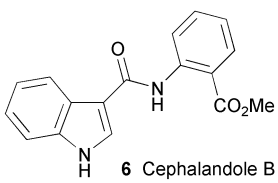
3 Cephalinone C



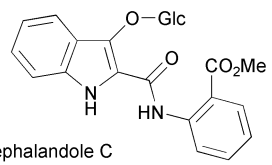
4 Cephalinone D



5 Cephalandole A



6 Cephalandole B



7 Cephalandole C

Two novel indole alkaloids, flabelliformides A (**8**) and B (**9**), were isolated from the stem of *Ervatamia flabelliformis*, commonly cultivated in the Yunnan and Guanxi provinces in China.[6] The structures of **8** and **9** were elucidated on the basis of spectral analysis and X-ray crystallography. The dried unripe fruits of *Evodia rutaecarpa* (juss.) Benth (Rutaceae) provided two new indoloquinazoline alkaloids, wuzhuyurutines A (**10**) and B (**11**).[7] Indole acetic acid polyacetylenic ester **12** was isolated from Japanese ivy (*Hedera rhombea* Bean) flower buds and the absolute configuration was determined by chemical means and the modified Mosher's method.[8] Compound **12** selectively showed growth inhibitory activity against dicotyledons. A new bis-oxygenated pyrroloacridine alkaloid, plakinidine E (**13**), was isolated from the sponge

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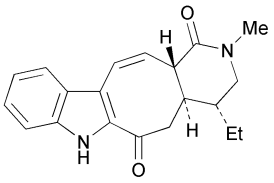
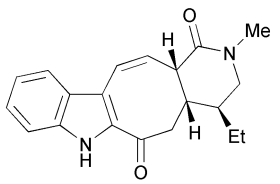
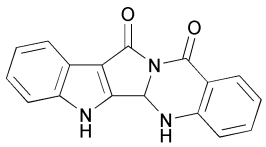


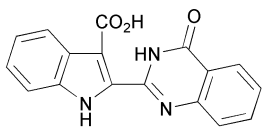
8 Flabelliformide A



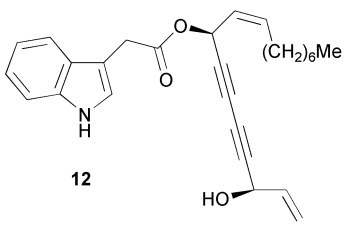
9 Flabelliformide B



10 Wuzhuyurutine A



11 Wuzhuyurutine B



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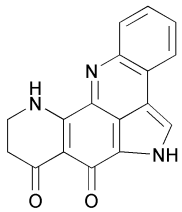
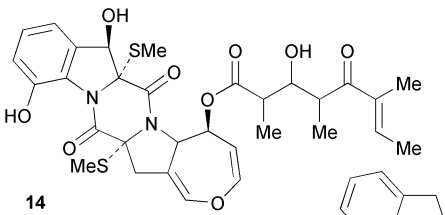


13 Plakinidine E



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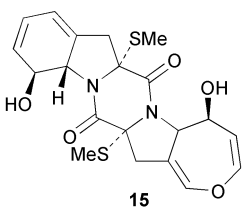

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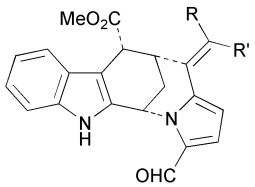
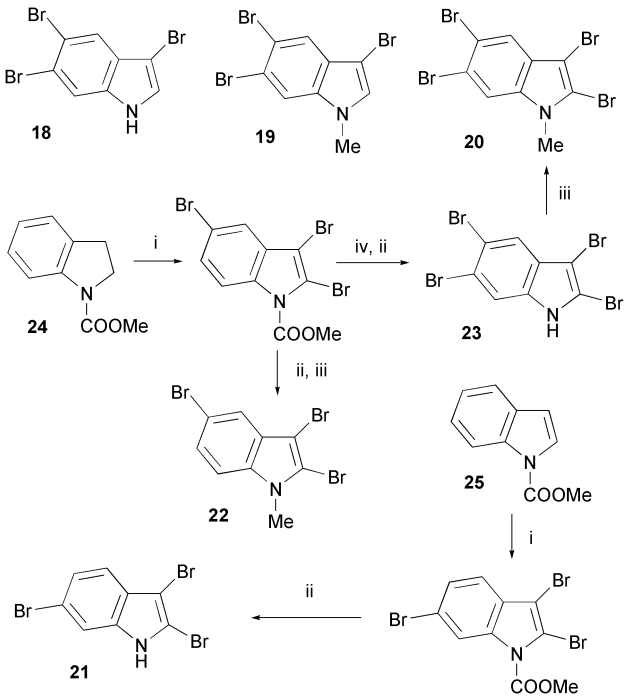


16 (19,20) *E*-Alstoscholarine (R = Me R' = H)

17 (19,20) *Z*-Alstoscholarine (R = H R' = Me)

Plakortis quasiamphiaster.[9] The seed fungus *Menisporopsis theobromae* BCC 3975 produced two new indole alkaloids **14** and **15**. Compound **14** showed cytotoxicity against NCI-H187 cell line and antimalarial activity.[10] A pair of geometrically isomeric indole alkaloids, (19,20) *E*-alstoscholarine (**16**) and (19,20) *Z*-alstoscholarine (**17**), were isolated from the leaf extract of *Alstonia scholaris*.[11] Their structures were elucidated on the basis of spectroscopic analyses and confirmed by X-ray crystal diffraction.

Polybrominated indoles **18–21** were isolated from the marine red alga *Laurencia similis* and *Laurencia decumbens*, and their structures were elucidated on the basis of detailed spectroscopic



Scheme 1 *Reagents and conditions*: i, Br_2 (8 eq.), CCl_4; ii, NaH, MeOH; iii, NaH, MeI, THF; iv, Br_2 (8 eq.), AcOH.

Minoru Ishikura

Minoru Ishikura was born in 1955 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 worked as a postdoctoral fellow with Ernest Wenkert at University of California, San Diego (1985–1986). His main research interests are the development of synthetic methods using organometallic reagents and the syntheses of bioactive natural products.

Koji Yamada

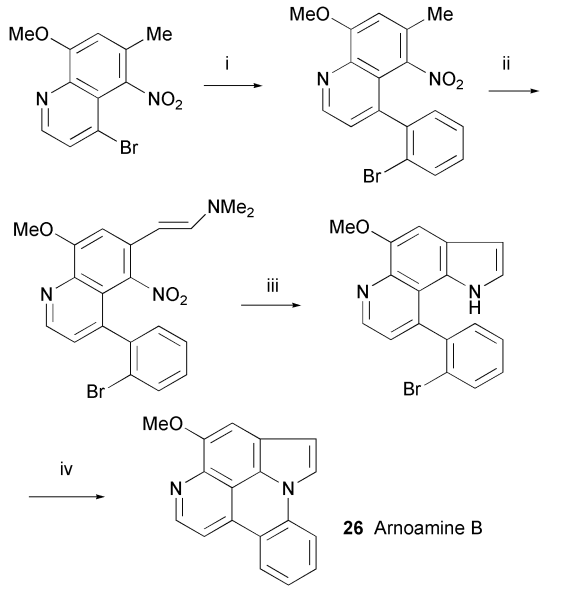
Koji Yamada was born in 1971 in Niigata, Japan. He graduated in 1995 from Toyama Medical and Pharmaceutical University, and worked at Faculty of Pharmaceutical Sciences, Kanazawa University (1995–2006). He received his Ph. D. degree from Kanazawa University under the supervision of Professor Masanori Somei in 2003, and worked as a research fellow with Professor Kuo-Hsiung Lee at University of North Carolina (2005). Then, he has been an Associate Professor at Faculty of Pharmaceutical Sciences, Health Sciences University of Hokkaido. His current research is the synthesis of biologically active natural products and the related compounds.

analyses, as well as by comparison with literature data.[12] Syntheses of **20–23** have been achieved from **24** and **25** *via* a sequential one-pot bromination/aromatization/bromination (Scheme 1).[13]

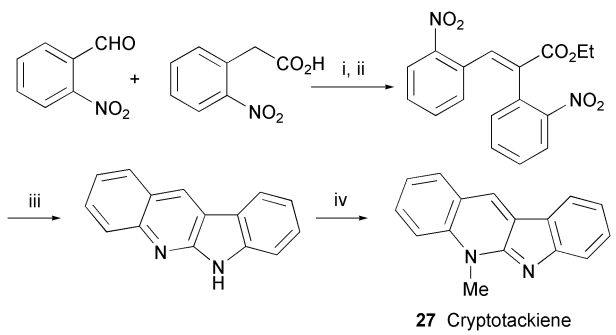
A four-step synthesis of arnoamine B (**26**), obtained from the brownish-purple ascidian *Cystodytes* sp., has been reported and the antimicrobial activity of **26** was evaluated (Scheme 2).[14]

Indoloquinoline alkaloid, cryptotackiene (**27**), isolated from the ethanolic extract of *Cryptolepis sanguinolenta* a shrub indigenous to West Africa, was synthesized from *o*-nitrobenzaldehyde and *o*-nitrophenylacetic acid through a tandem double reduction-double cyclization (Scheme 3).[15] Compound **27** exhibited strong antiplasmodial activity against chloroquine-resistant *Plasmodium falciparum* strains.

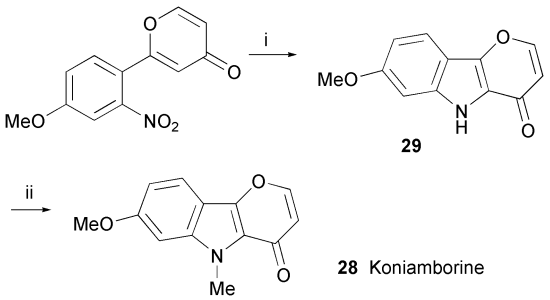
Pyrano[3,2-*b*]indole, koniamborine (**28**), isolated from *Boronella koniambiensis*, was synthesized through a palladium-catalyzed reductive *N*-heteroannulation in **29** as the key pyranoindole forming step (Scheme 4).[16]



Scheme 2 *Reagents and conditions*: i, 2-bromophenylboronic acid, $Pd(PPh_3)_4$, K_2CO_3, H_2O, toluene, EtOH, reflux; ii, DMFDMA, 145 °C; iii, Zn, AcOH, H_2O, 75 °C; iv, $Pd(OAc)_2$, *t*-Bu_3P, K_2CO_3, xylene, 110 °C.



Scheme 3 *Reagents and conditions*: i, Ac_2O, Et_3N, reflux; ii, EtOH, H_2SO_4, reflux; iii, Fe, AcOH, HCl, EtOH, H_2O, 120 °C; iv, Me_2SO_4, DMF, microwave, 140 °C.

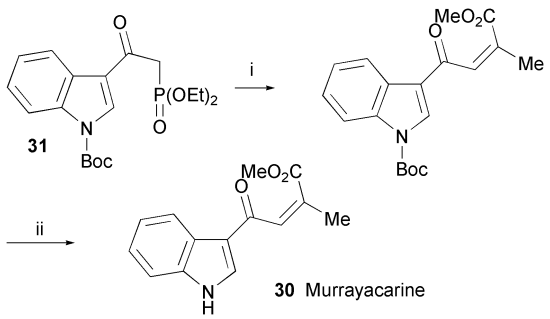


Scheme 4 *Reagents and conditions*: i, dppp, HCl, $Pd(dba)_2$(1,10-phenanthroline), CO (6 atm), DMF, 120 °C; ii, MeI, NaH, DMF.

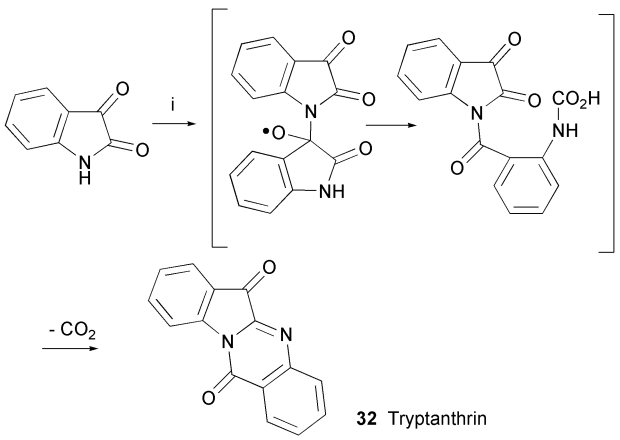
A short and stereoselective synthesis of murrayacarine (**30**), isolated from the root bark of *Murraya paniculata* var. *omphalocarpa* Hayata (Rutaceae), and phosphonate ester (**31**) was reported (Scheme 5).[17]

Tryptanthrin (**32**) is the active principle of a traditional Japanese herbal remedy for fungal infection, and was synthesized by cathodic reduction of isatin *via* a low energy consumption process involving an electron transfer to the oxygen in air (Scheme 6).[18]

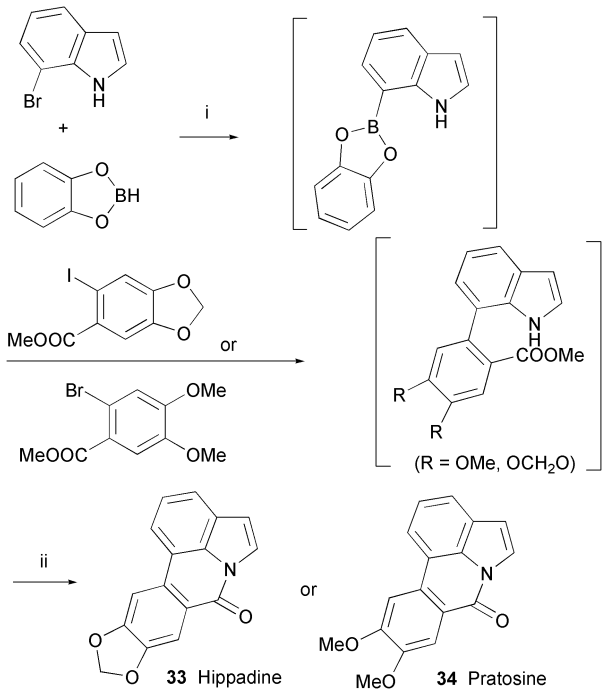
Hippadine (**33**) and pratosine (**34**) were synthesized through a one-pot borylation/Suzuki cross-coupling reaction/lactamization strategy starting from either 7-bromoindole or 6-halogenated methyl piperonate (Scheme 7).[19]



Scheme 5 *Reagents and conditions*: i, NaH, toluene, methyl pyruvate, reflux; ii, TFA, CH_2Cl_2.



Scheme 6 *Reagents and conditions*: i, Pt or Hg cathode, Et_4NCl, CH_2Cl_2.

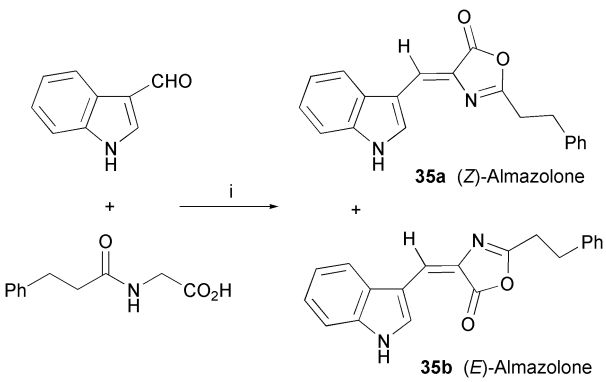


Scheme 7 *Reagents and conditions*: i, $Pd(OAc)_2$, Et_3N, 2-(dicyclohexylphosphino)biphenyl, dioxane, 80 °C; ii, CsF, H_2O, dioxane, 80 °C.

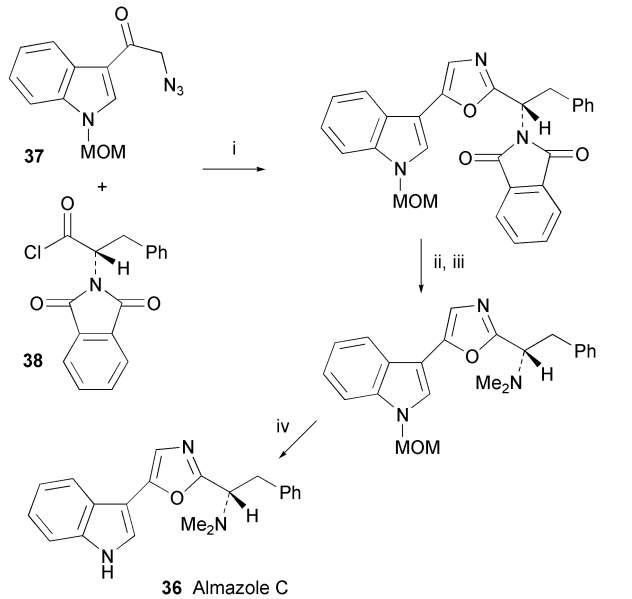
A new indole alkaloid, almazolone (**35**), was isolated as an 88:12 mixture of *Z*/*E* isomers from *Haraldiophyllum* sp. collected at low tide at Almadies north of Dakar. Condensation of indole-3-carboxaldehyde with (3-phenylpropionylamino)acetic acid produced a mixture of **35a** and **35b** (Scheme 8).[20]

Almazole C (**36**), isolated from a red seaweed of family Delesseriaceae of genus *Haraldiophylum* sp. on the north of Dakar, was synthesized, in which the 2,5-disubstituted oxazole ring was assembled through the aza-Wittig reaction of the iminophosphorane generated from azide **37** and *N*-phthaloylphenylalanyl chloride (**38**) (Scheme 9).[21]

Oxindole alkaloids, costinones A (**39**) and B (**40**), were newly isolated from *Isatis costata*, an annual or biennial herb found in the northern part of Pakistan. Both compounds inhibited lopoxygenase and butyrylcholinesterase.[22] A novel indole alkaloid, 4,5-dihydroxy-1-methyl-3-oxo-2-(trichloromethyl)-3*H*-

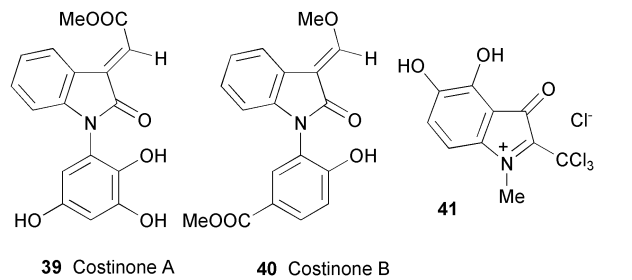


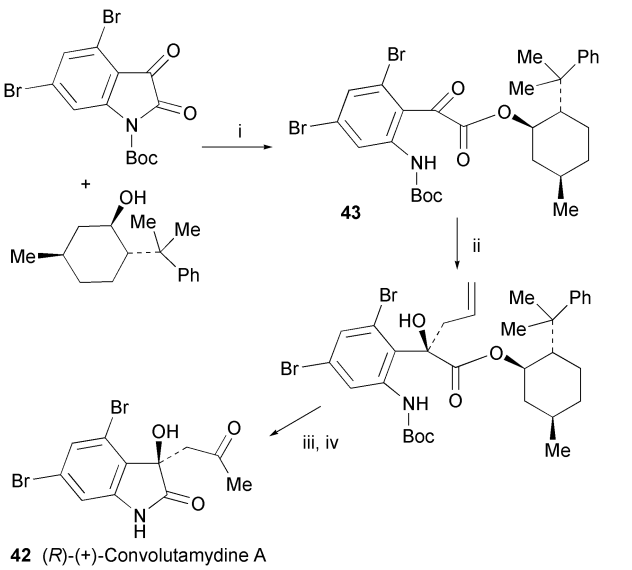
Scheme 8 *Reagents and conditions*: i, Ac_2O, $Ca(OAc)_2$, 50 °C, 3 h.



Scheme 9 *Reagents and conditions*: i, *n*-Bu_3P, Et_3N, THF; ii, N_2H_4, EtOH, rt; iii, HCHO, Pd/C, H_2, EtOH; iv, HCOOH, THF/H_2O, reflux.

indolium chloride (**41**) was obtained from the extract of the root of *Zanthoxylum nitidum*, a traditional Chinese medicine.[23]

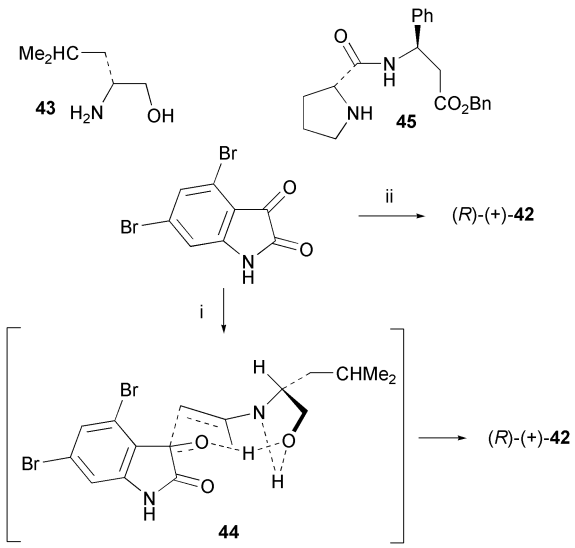




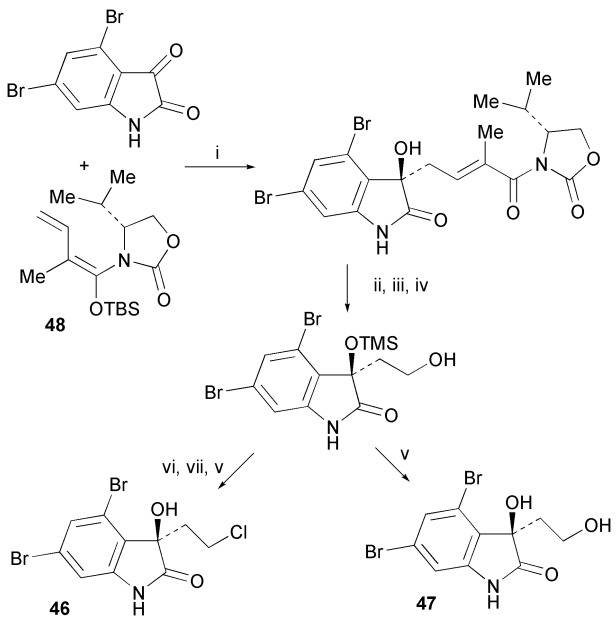
Scheme 10 *Reagents and conditions*: i, KH, 18-crown-6, THF, rt; ii, In, KI, DMF, allyl bromide, rt; iii, TFA, CH_2Cl_2, rt; iv, $PdCl_2$, $CuCl_2$, O_2, MeCN, H_2O, 40 °C.

Three asymmetric approaches to convolutamydine A (**42**), isolated from the marine bryozoans species *Amathia convolute* and identified as an anti-leukemia agent, have been reported. The absolute configuration of **42** was established as (*R*) by enantioselective synthesis through chiral auxiliary-directed π-face discrimination in an addition of $(allyl)_3InBr_3$, generated *in situ* from In (2 equiv) and allyl bromide (3 equiv), to **43** (Scheme 10).[24]

Asymmetric cross-aldol reaction of 4,6-dibromoisatine with acetone in the presence of D-leucinol **43**[25] or dipeptide **45**[26] was applied for a total synthesis of **42**. Transition state **44** was proposed to account for the D-leucinol-catalyzed process (Scheme 11).



Scheme 11 *Reagents and conditions*: i, **43** (20 mol%), acetone, CH_2Cl_2, rt, 94% ee; ii, **45** (10 mol%), acetone, CH_2Cl_2, −15 °C, 97% ee.



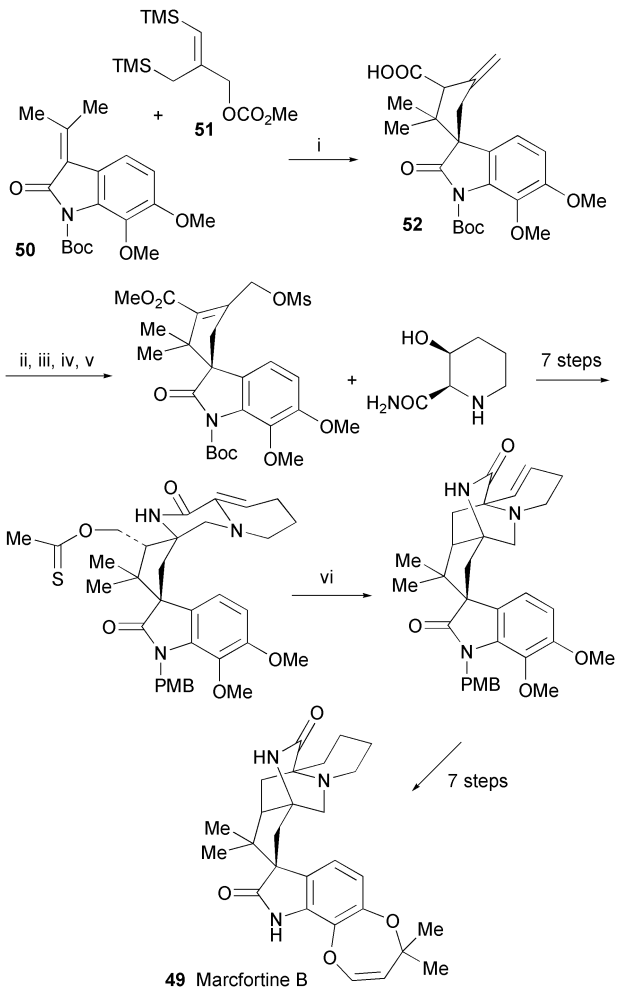
Scheme 12 *Reagents and conditions*: i, $TiCl_4$, CH_2Cl_2, −78 °C; ii, TMSOTf; iii, O_3, then Me_2S; iv, $NaBH_4$; v, TBAF, THF; vi, TsCl, pyridine; vii, LiCl, DMF.

Oxindole alkaloids, convolutamydines B (**46**) and E (**47**), isolated from the Floridian marine bryozoans *Amathia convoluta*, were enantioselectively synthesized through vinylogous Mukaiyama aldol reaction of 2,6-dibromoisatine with **48** (Scheme 12).[27]

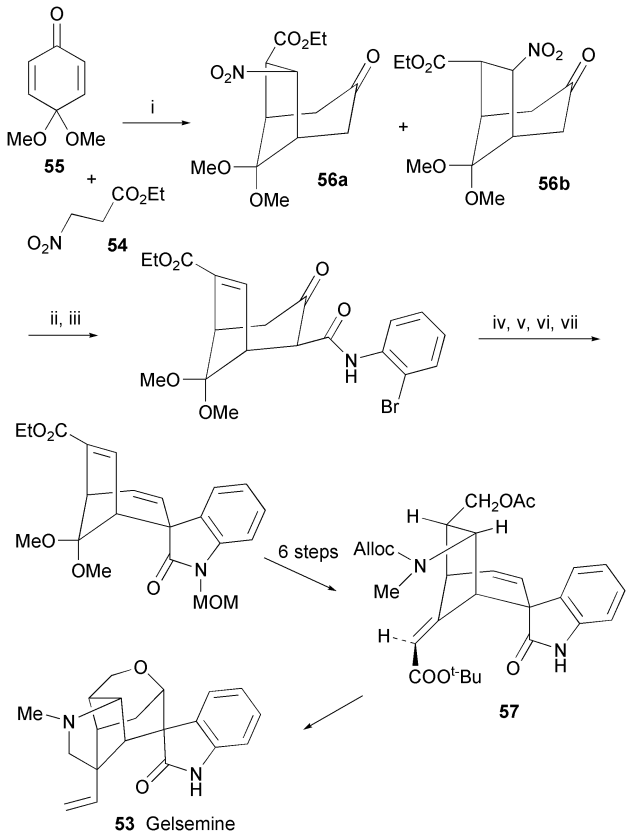
The first total synthesis of racemic marcfortine B (**49**), isolated from *Penicillium* sp., has been achieved through palladium-catalyzed [3 + 2] cycloaddition of trimethylenemethane (TMM)-donor **51** with **50** producing spirocyclic acid **52**. The synthesis has completed *via* the intramolecular Michael addition followed by free radical cyclization (Scheme 13).[28]

A formal synthesis of gelsemine (**53**), the principle component of *Gelsemium sempervirens*, has been achieved.[29] A double conjugate addition between the lithium dianion of **54** and **55** provided a mixture of diastereomers **56**, which was converted to Fukuyama's gelsemine intermediate **57** (Scheme 14).

Two total syntheses of (+)-madindolines A (**58**) and B (**59**), isolated from a culture broth of *Streptomyces nitrosporeus*

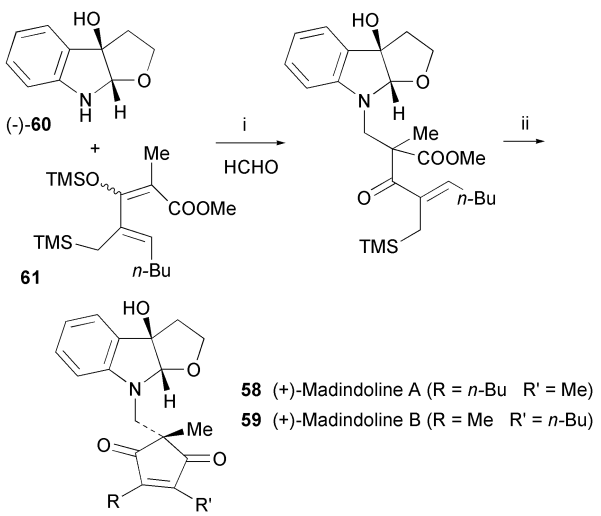


Scheme 13 *Reagents and conditions*: i, $Pd(OAc)_2$, $(O\text{-}i\text{-}Pr)_3P$, toluene, reflux; ii, Me_2SO_4, K_2CO_3, acetone, reflux; iii, *m*-CPBA, CH_2Cl_2, 0 °C; iv, DBU, THF, 0 °C to rt; v, MsCl, Et_3N, CH_2Cl_2; vi, 170% AIBN, 20% $n\text{-}Bu_3SnH$, benzene, reflux.

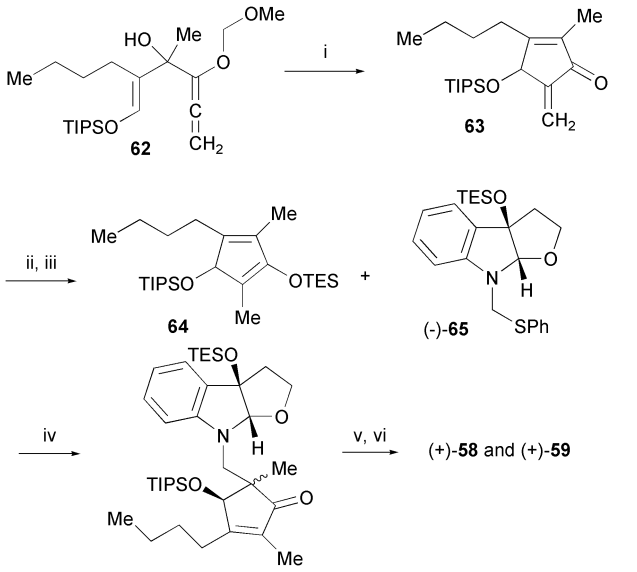


Scheme 14 *Reagents and conditions*: i, LDA, HMPA, TMEDA, THF; ii, DBU, THF; iii, LHMDS, THF, HMPA, −78 °C, then 2-bromophenylisocyanate; iv, Tf_2O, −78 °C, Et_3N; v, $Pd(PPh_3)_4$, *n*-Bu_3SnH, LiCl, THF; vi, NaH, MOMCl; vii, $Pd(PPh_3)_4$, MeCN, microwave.

K93-0711, have been reported. Omura's strategy involved a three-component Mannich reaction of (−)-hydroxyfuroindole **60**, ketoester **61** and formaldehyde (Scheme 15).[30]

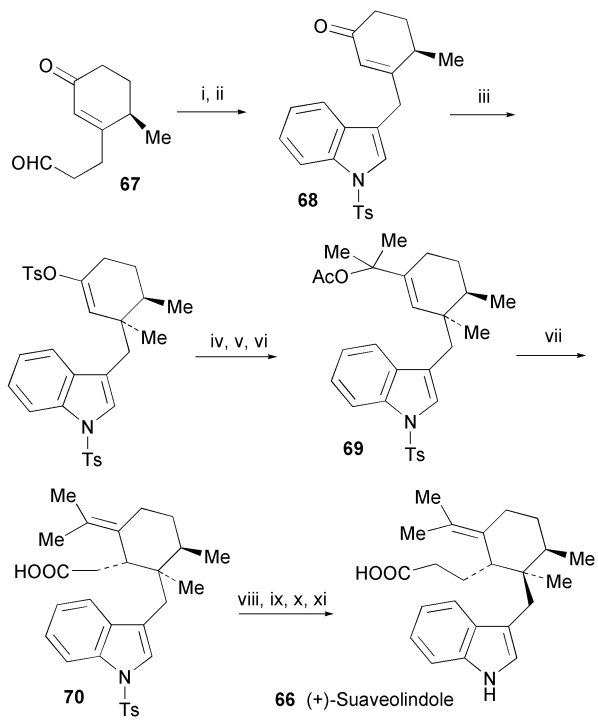


Scheme 15 *Reagents and conditions*: i, $Sc(OTf)_3$, $Sc(Ds)_3$, H_2O, rt; ii, TAS-F, DMF, rt.



Scheme 16 *Reagents and conditions*: i, TFAA, 2,6-lutidine, CH_2Cl_2, −20 °C; ii, Pd/C, H_2, EtOH; iii, LDA, THF, TESCl, −50 °C; iv, $ZnBr_2$, CH_2Cl_2, −30 °C; v, TBAF, THF; vi, PDC, DMF.

Tius's approach applied the allene ether version of the Nazarov cyclization in **62** leading to the cyclopentane portion **63** of (+)-**58** and (+)-**59** and Mannich reaction of (−)-**65** with **64** as the key steps. (Scheme 16).[31]



Scheme 17 *Reagents and conditions*: i, 2-iodoaniline, $Pd(OAc)_2$, DABCO, DMF; ii, TsCl, *n*-Bu_4NBr, aq. NaOH, benzene; iii, CuI, MeLi, Et_2O, THF, then $PhNTf_2$; iv, CO, $Pd(PPh_3)_4$, *i*-Pr_2NEt, MeOH, DMF; v, MeLi, Et_2O; vi, Ac_2O, DMAP, *i*-Pr_2NEt, CH_2Cl_2; vii, LHMDS, TMSCl, THF, −78 °C; viii, $(COCl)_2$, DMF, CH_2Cl_2; ix, CH_2N_2, *i*-Pr_2NEt, THF; x, CF_3COOAg, Et_3N, THF, H_2O; xi, naphthalene, Na, DME.

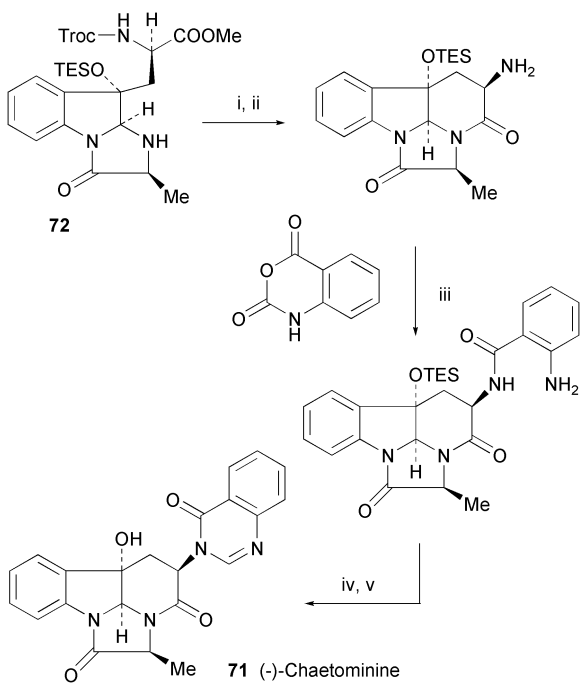
The first total synthesis of (+)-suaveolindole (**66**), isolated from the fruit of *Greenwayodendron suaveolens*, has been completed, and the absolute configuration was established.[32] Annulation of **67** with 2-iodoaniline produced indole **68**, and the Ireland-Claisen reaction in **69** provided **70** as a single stereoisomer (Scheme 17).

Chaetominine (**71**), a cytotoxic alkaloid, was isolated from the solid-substrate culture of *Chaetomium* sp. IFB-E015, an endophytic fungus, and the absolute configuration was elucidated by Marfey's method.[33] Synthesis of (−)-**71** was achieved *via* the assemble of the δ-lactam ring by heating **72** with a catalytic amount of DMAP as the key step (Scheme 18).[34]

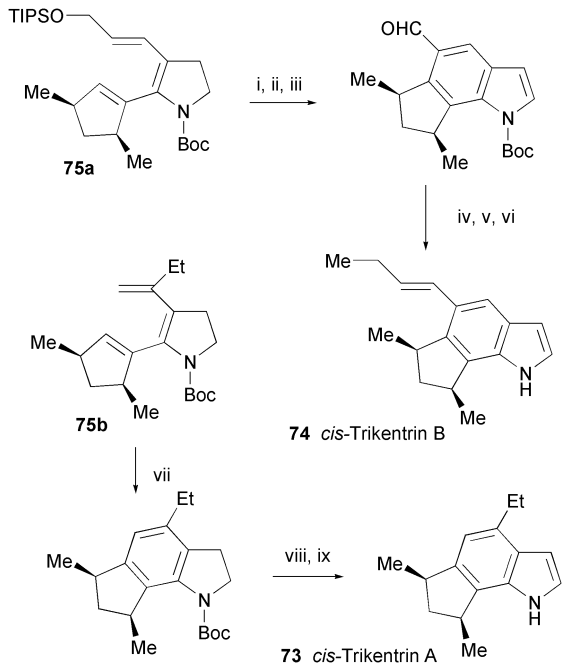
A convergent strategy for the diastereoselective synthesis of *cis*-trikentrins A (**73**) and B (**74**), isolated from the marine sponge *Trikentrion flabelliforme*, was reported, which involved the construction of the central benzene ring *via* a facile 6-electrocyclic cyclization of 2,3-vinylpyrrolines **75** (Scheme 19). These compounds showed antimicrobial activity against the gram positive *Bacillus subtillus*.[35]

A full account of the previous studies[36] toward to a divergent synthesis of **73**, herbindole A (**76**) and herbindole B (**77**) was reported, in which tricyclic indole **80**, derived from Diels–Alder reactions of monoamine quinoids **78** with cyclopentadiene followed by cyclization in **79**, was used as the key intermediate (Scheme 20).[37]

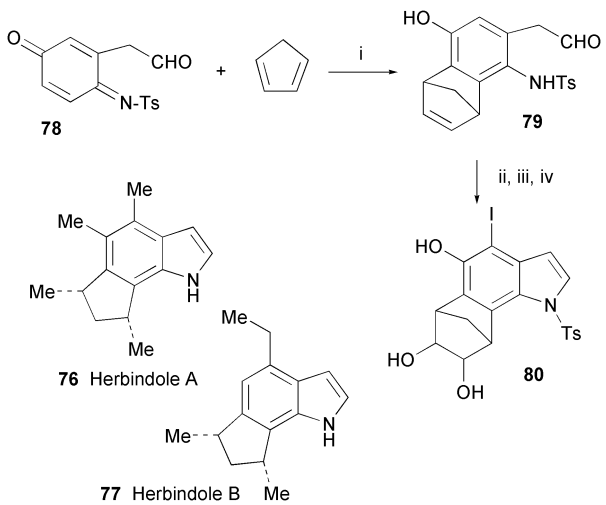
Chemical examination of the endophytic fungus *Penicillium* sp. isolated from the mangrove plant *Aegiceras corniculatum* resulted in the isolation of five indole triterpenoids, shearinines D (**81**), E (**82**), F (**83**), G (**84**) and K (**85**).[38] The marine-derived strain of the fungus *Penicillium janthinellum* Biourge also produced **81**, **82** and **83**.[39] Significant *in vitro* blocking activity on large-conductance calcium-activated potassium channel and



Scheme 18 *Reagents and conditions*: i, DMAP, toluene, 115 °C; ii, Zn, MeOH, AcOH; iii, benzene, reflux; iv, $HC(OEt)_3$, TsOH, benzene, reflux; v, aq, HF/MeCN.



Scheme 19 *Reagents and conditions*: i, xylene, reflux; ii, DDQ; iii, MnO_2, CH_2Cl_2; iv, *n*-PrMgCl; v, *p*-TsOH; vi, 2,6-lutidine, TMSOTf; vii, toluene, 80 °C, then MnO_2; viii, 2,6-lutidine, TMSOTf; ix, Co(salen), O_2, MeOH.

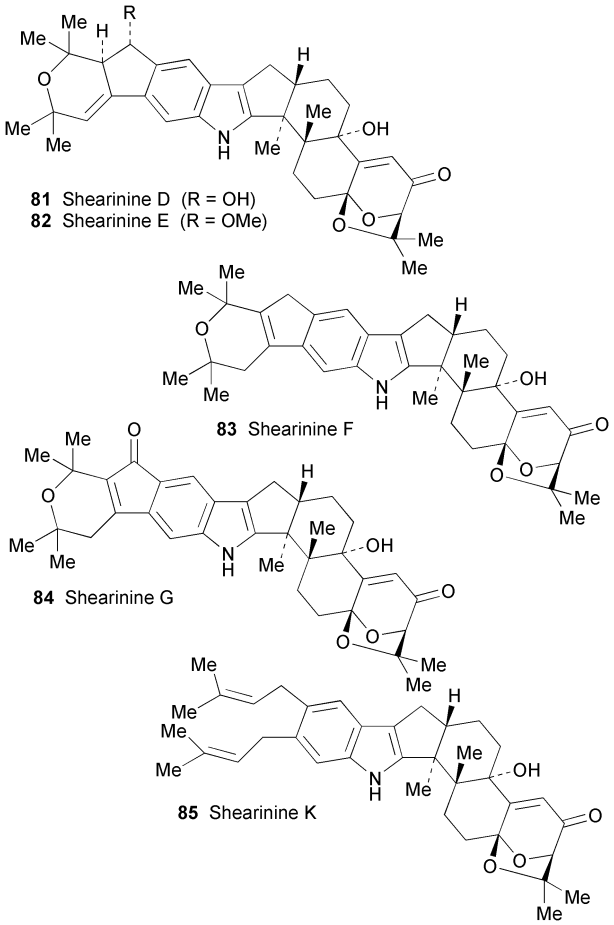


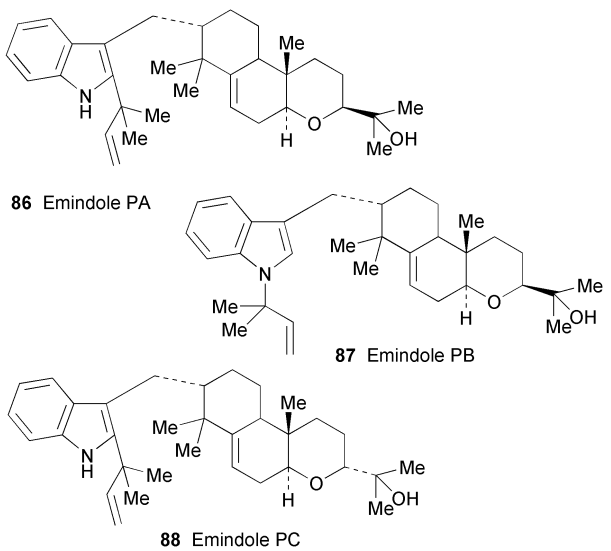
Scheme 20 *Reagents and conditions*: i, CH_2Cl_2, 0 °C; ii, HCl, THF; iii, OsO_4, NMO, THF, H_2O; iv, NIS, THF, 0 °C.

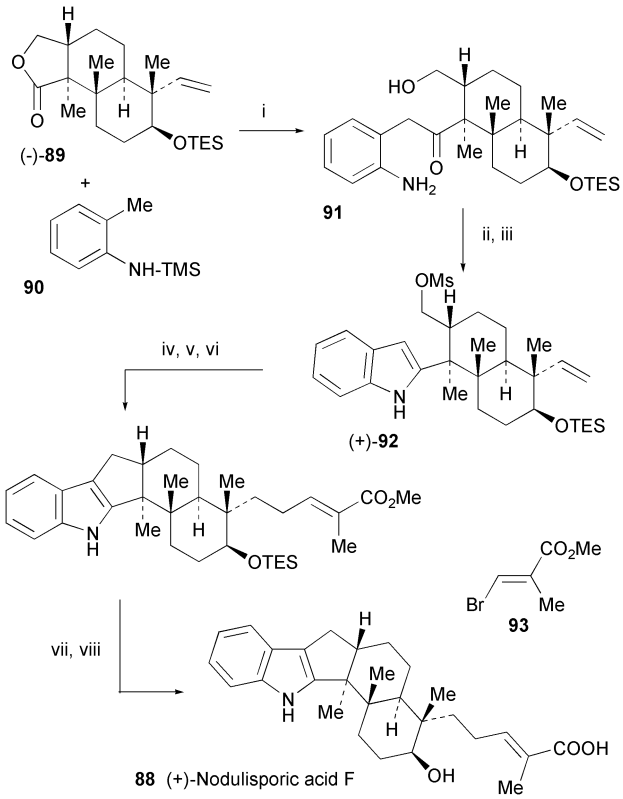
apoptosis in human leukemia HL-60 cells were observed in **81** and **82**, and **83** inhibited EGF-induced malignant transformation of JB6 P^+ Cl 41 cells in a soft agar.

Three new indolediterpenes, emindoles PA (**86**), PB (**87**) and PC (**88**), were isolated from the mycelium of *Emericella purpurea*, and the structure of **86** was revised.[40]

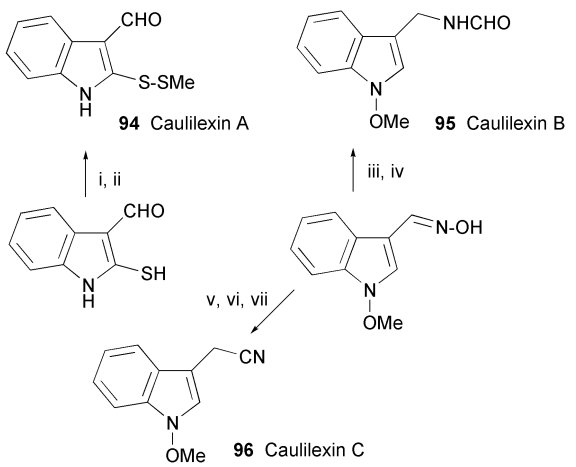
A stereocontrolled total synthesis of (+)-nodulisporic acid F (**89**), isolated from the endophytic fungus *Nodulisporium* sp. (MF5954), has been achieved. Treatment of the *N*-silylated dianion derived *in situ* from **91** with (−)-**90** provided **92**, followed by acid-catalyzed cyclodehydration furnished indole (+)-**93**.







Scheme 21 *Reagents and conditions*: i, *s*-BuLi, Et_2O, −30 °C; ii, PTSA, benzene, 80 °C; iii, MsCl, DMAP, CH_2Cl_2, 0 °C; iv, *t*-BuMgCl, $Zn(OTf)_2$, toluene, 110 °C; v, 9-BBN, toluene, 80 °C; vi, $Pd(dppf)_2Cl_2$, **94**, K_3PO_4, DMF, 65 °C; vii, LiOH, MeOH, THF; viii, *p*-TsOH, MeOH.

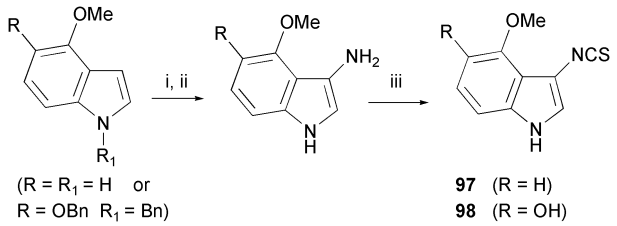


Scheme 22 *Reagents and conditions*: i, I_2, pyridine; ii, MeSNa; iii, $NaBH_3CN$, $TiCl_3$, $AcONH_4$, MeOH, H_2O; iv, HCO_2Et; v, $NaBH_3CN$, AcOH; vi, H_2O_2, Na_2WO_4; vii, Me_2SO_4, K_2CO_3, MeOH, H_2O.

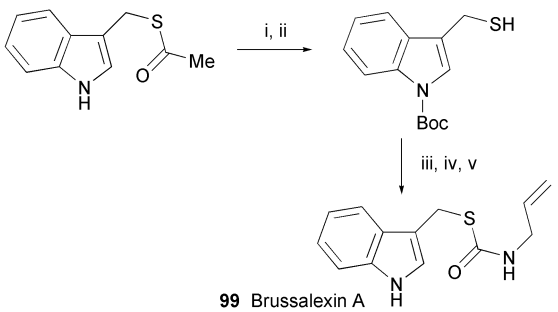
Indole (+)-**93** was converted to (+)-**89** *via* Suzuki-Miyaura cross-coupling reaction (Scheme 21).[41]

2.1.1 Indole phytoalexins. Florets of cauliflower (*Brassica oleracea* var. *botrytis*) under abiotic elicitation produced three new phytoalexins, cauliexins A (**94**), B (**95**) and C (**96**). The synthesis and antifungal activity of **94–96** were also reported (Scheme 22).[42]

Indole-3-isothiocyanate phytoalexins, rapalexins A (**97**) and B (**98**), were obtained from infested leaf of canola.[43] The first synthesis and the investigation of the antimicrobial activity of **97** and **98** were performed (Scheme 23).



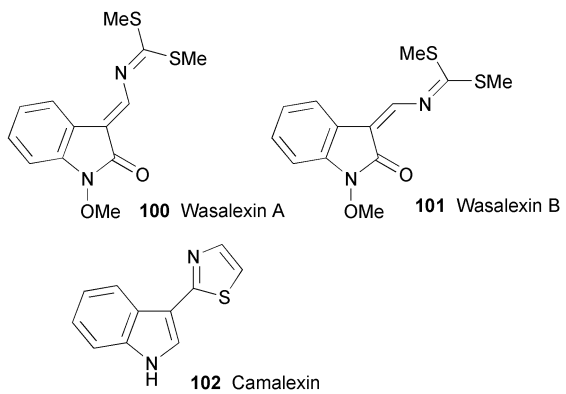
Scheme 23 *Reagents and conditions*: i, $AgNO_3$, PhCOCl, MeCN; ii, Pd/C, H_2, AcOH; iii, $CSCl_2$, $CaCO_3$, CH_2Cl_2.



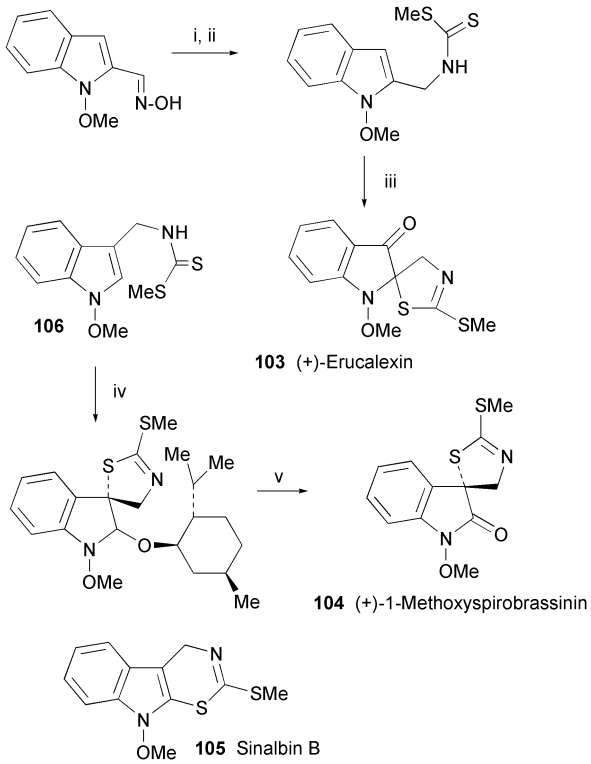
Scheme 24 *Reagents and conditions*: i, Boc_2O, DMAP, THF; ii, KOH, THF, Ar; iii, allylisocyanate, KOH, 70 °C; iv, TFA, rt; v, 50 °C.

Brussels sprouts under stress were shown to produce thiolcarbamate phytoalexin, brussalexin A (**99**) (Scheme 24).[44] The structure of **99** was confirmed by synthesis, and its antifungal activity was investigated.

Metabolism of crucifer phytoalexin, wasalexins A (**100**) and B (**101**), in the plant pathogenic fungus *Leptospheria maculans* was investigated.[45] A mini review of camelexin (3-thiazol-2′-ylindole) (**102**), characteristic phytoalexin of *Arabidopsis thaliana*, has appeared.[46]



A new phytoalexin, (+)-erucalexin (**103**), was isolated from the leaves of wild crucifer dog mustard, and synthesized from 1-methoxyindole.[47] The biosynthetic relations between (+)-**103**, (+)-1-methoxyspirobrassinin (**104**), sinalbin B (**105**) and 1-methoxybrassinin (**106**),[48] and detoxification pathway of **104** were revealed.[49] Stereoselective synthesis of (+)-**104** was achieved from **106** *via* the spirocyclization in the presence of (−)-menthol (Scheme 25).[50]

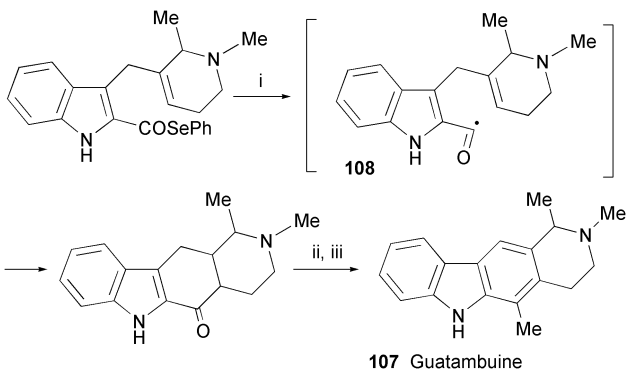


Scheme 25 *Reagents and conditions*: i, $NaBH_3CN$, $TiCl_3$, $AcONH_4$, $MeOH/H_2O$; ii, CS_2, Et_3N, MeI, pyridine; iii, CrO_3, $AcOH/H_2O$; iv, Br_2, (−)-menthol, Et_3N, MS, CH_2Cl_2; v, PCC, CH_2Cl_2.

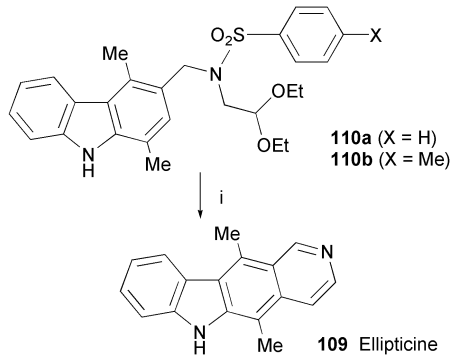
2.1.2 Carbazoles and related compounds. A total synthesis of pyrido[4,3-*b*]carbazole alkaloid guatambuine (**107**) has been reported. The key step of a straightforward approach is a regioselective 6-*endo* reductive cyclization in 2-indolylacyl radical **108** (Scheme 26).[51]

Simple modification of the previously reported ellipticine (**109**) synthesis[52] was reported. Replacement of *p*-toluenesulfonamide **110b** with benzenesulfonylamide **110a** accelerated the acid-catalyzed cyclization reaction, producing **109** in high yield and high purity. (Scheme 27).[53]

An efficient method for the preparation of polyfunctional aryl azides from the corresponding aryl triazines was developed.



Scheme 26 *Reagents and conditions*: i, AIBN, *n*-Bu_3SnH, benzene, reflux; ii, MeLi, −10 °C, THF; iii, 10% Pd/C, TFA, rt.

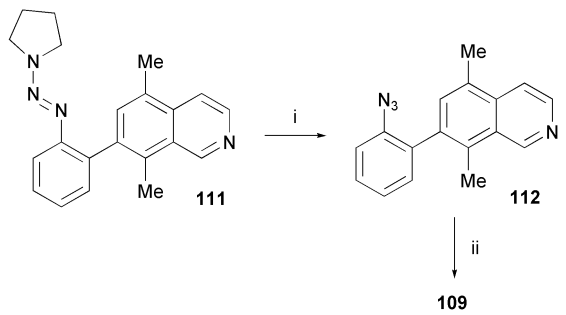


Scheme 27 *Reagents and conditions*: i, HCl, dioxane, reflux.

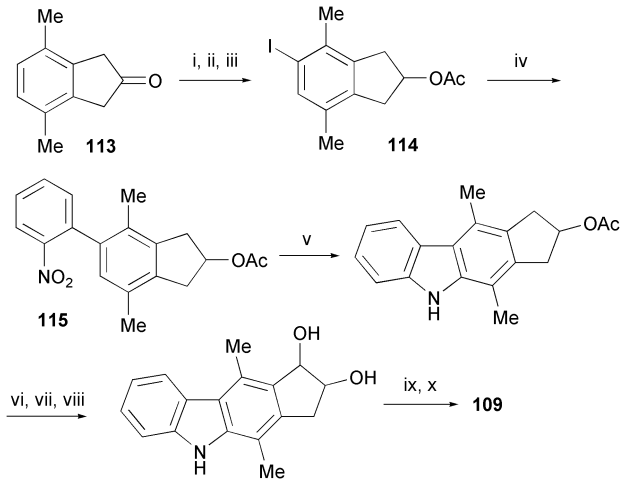
Azide **112**, derived from triazine **111**, was applied to a new synthesis of ellipticine (**109**) (Scheme 28).[54]

An eight-step synthesis of ellipticine (**109**) from 1*H*-indenone **113** was performed, in which Suzuki-Miyaura coupling of **114** and heterocyclization in **115** were the key steps (Scheme 29).[55]

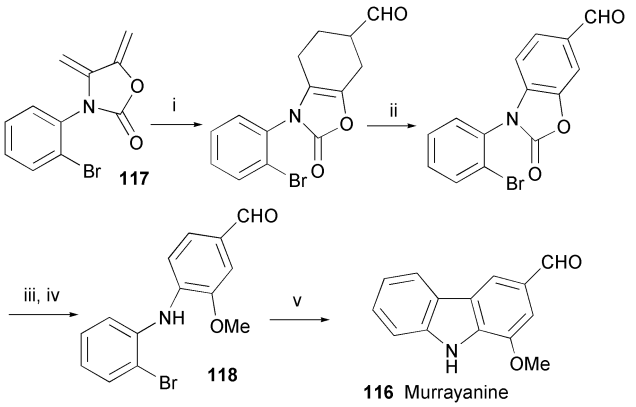
A total synthesis of murrayanine (**116**), isolated from *Murraya koenigii* (Rutaceae), was developed through Diels–Alder reaction of **117** with acrolein followed by Pd-catalyzed intramolecular diaryl coupling of **118** (Scheme 30).[56]



Scheme 28 *Reagents and conditions*: i; NaN_3, BF_3OEt_2, TFA, CH_2Cl_2, rt; ii, mesitylene, reflux.

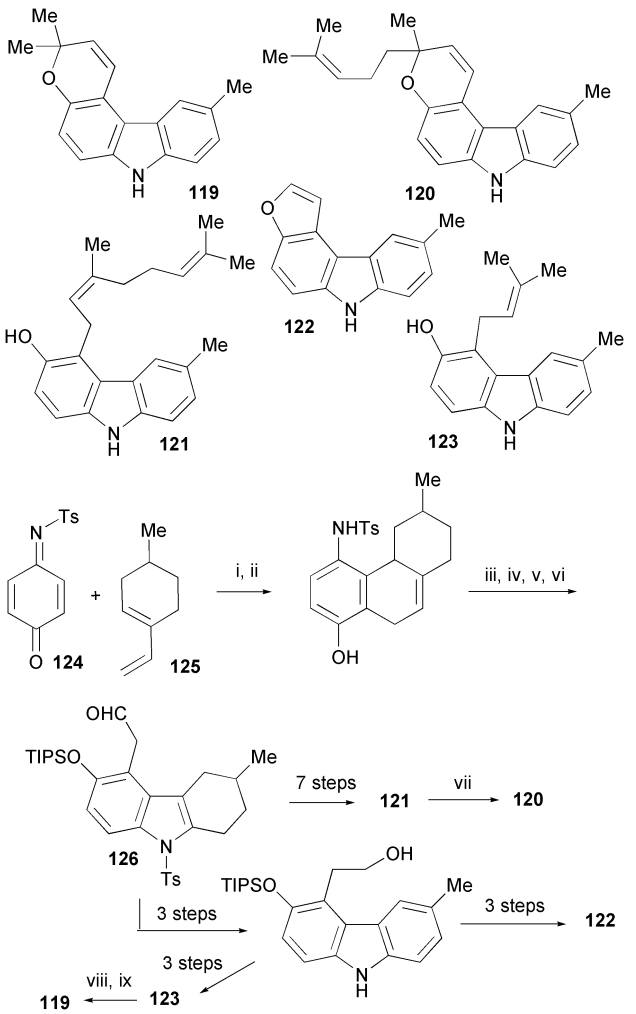


Scheme 29 *Reagents and conditions*: i, $NaBH_4$, $MeOH/CH_2Cl_2$; ii, I_2, $Fe(NO_3)_3$, CH_2Cl_2; iii, Ac_2O, pyridine, DMAP, rt; iv, (2-nitrophenyl)boronic acid, $PdCl_2(PPh_3)_2$, $NaHCO_3$, DME, H_2O, 80 °C; v, $P(OEt)_3$, 150 °C; vi, DDQ, THF/H_2O; vii, aq. K_2CO_3; viii, $LiAlH_4$, THF; ix, $NaIO_4$, *t*-BuOH, H_2O; x, aq. NH_4OAc.

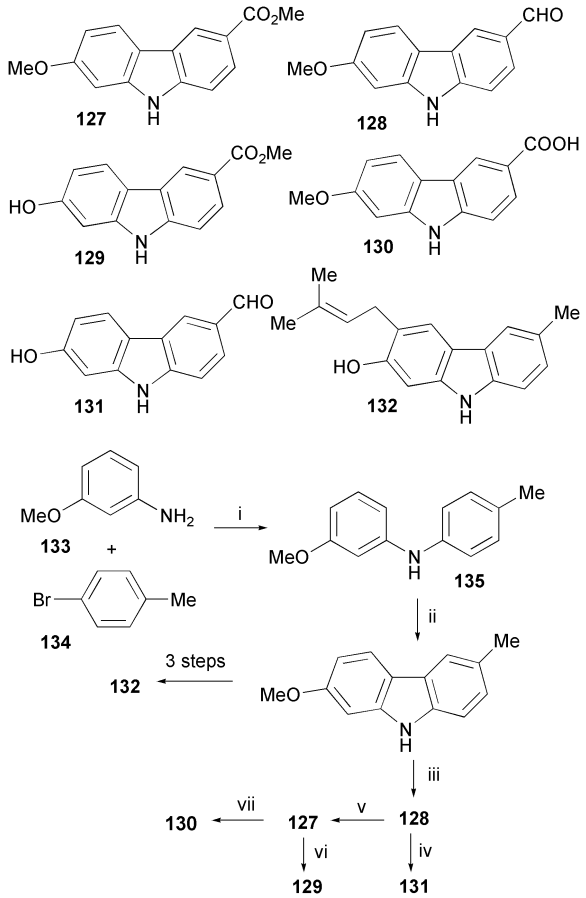


Scheme 30 *Reagents and conditions*: i, acrolein, BF_3OEt_2, CH_2Cl_2, −78 °C; ii, DDQ, benzene, reflux; iii, aq. KOH, rt; iv, MeI, K_2CO_3, acetone, reflux; v, $Pd(PPh_3)_4$, Li_2CO_3, LiCl, MeCN, reflux.

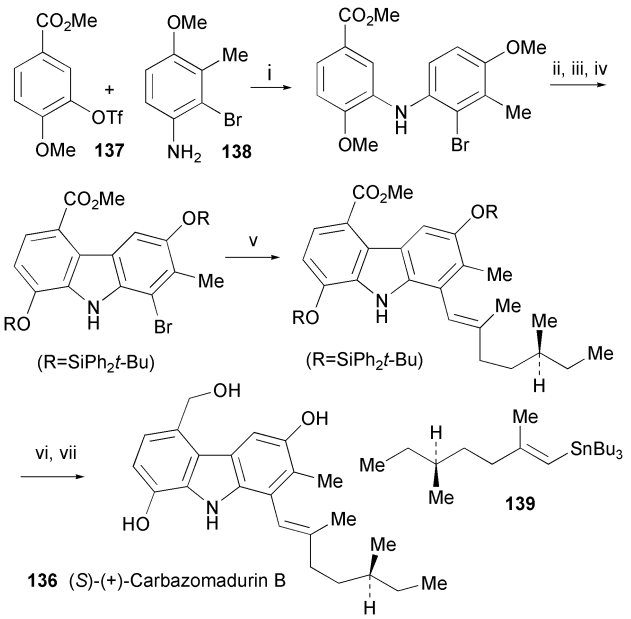
A divergent synthetic strategy for eustifoline A (**119**) and glycomaurrol (**123**), isolated from the stem bark of *Glycosmis mauritiana*, and eustifolines B (**120**), C (**121**) and D (**122**),



Scheme 31 *Reagents and conditions*: i, CH_2Cl_2, reflux; ii, DBU; iii, NaH, TIPSCl, THF, 0 °C; iv, NMO, OsO_4, THF, *t*-BuOH, H_2O; v, $NaIO_4$, CH_2Cl_2; vi, H_2SO_4, THF; vii, $Pd(OAc)_2$, THF, 65 °C; viii, PhSeCl, −40 °C, CH_2Cl_2; ix, H_2O_2, CH_2Cl_2.



Scheme 32 *Reagents and conditions*: i, $Pd(OAc)_2$, BINAP, Cs_2CO_3, toluene, reflux; ii, $Pd(OAc)_2$, $Cu(OAc)_2$, AcOH, reflux; iii, DDQ, MeOH/H_2O, rt; iv, BBr_3, −78 °C, CH_2Cl_2; v, MnO_2, KCN, MeOH, rt; vi, BBr_3, CH_2Cl_2, −78 °C; vii, KOH, EtOH/H_2O, reflux.



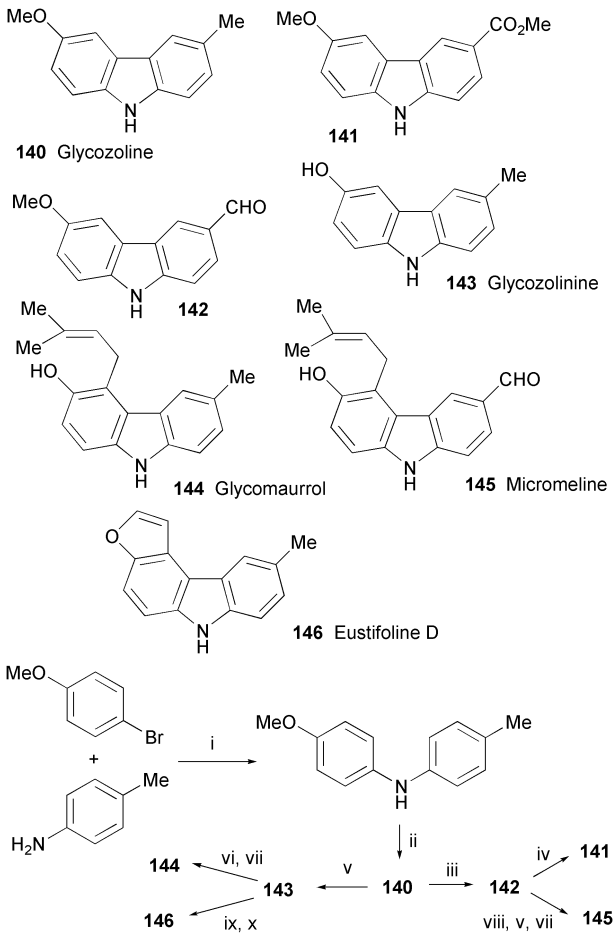
Scheme 33 *Reagents and conditions*: i, $Pd(OAc)_2$, BINAP, Cs_2CO_3, toluene, 100 °C; ii, $Pd(OAc)_2$, AcOH, dioxane, 100 °C; iii, BBr_3, CH_2Cl_2, −78 °C; iv, *t*-$BuPh_2SiCl$, imidazole, DMF, 70 °C; v, **139**, $Pd(PPh_3)_4$, toluene, 110 °C; vi, DIBAL, toluene 0 °C; vii, TBAF, THF, rt.

isolated from the root bark of *Murraya euchrestifolia*, was developed. Carbazole **126**, derived from a regioselective Diels–Alder reaction of quinone monoimine **124** with **125**, was utilized as the key intermediate in the synthesis of natural products **119–123** (Scheme 31).[57]

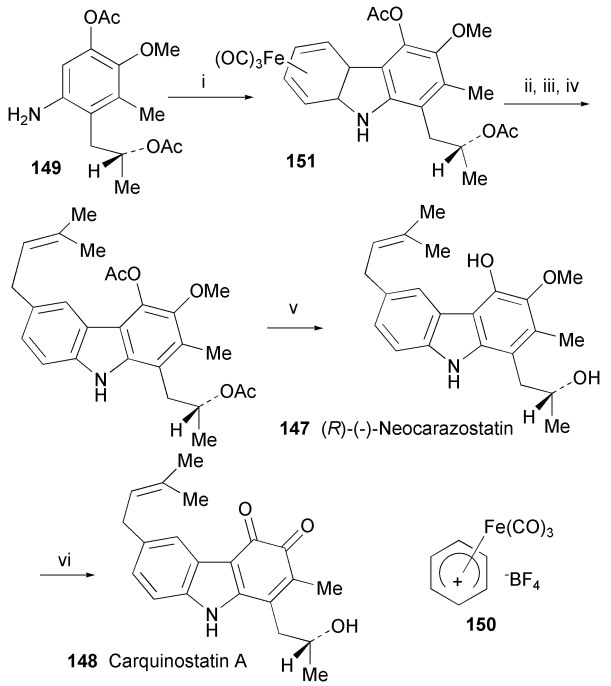
A convergent palladium-catalyzed approach to 7-oxygenated carbazole alkaloids, clauszolines C (**127**), K (**128**), M (**129**), N (**130**), 3-formyl-7-hydroxycarbazole (**131**) and siamenol (**132**) has been developed, which involved palladium-catalyzed amination of **134** with **133** and palladium-mediated intramolecular coupling in **135** as the key steps (Scheme 32).[58]

A first synthesis of carbazomadurin B (**136**), isolated from the microorganism *Actinomadura madurae* 2808-SV1, has been achieved based on sequential Pd-catalyzed Buchwart-Hartwig amination of **137** with **138** and intramolecular cyclization. The absolute configuration was confirmed to be (*S*)-(+)-**136** (Scheme 33).[59]

The palladium-catalyzed amination/cyclization protocol was further applied to syntheses of 6-oxygenated carbazoles, glycozoline (**140**), methyl 6-methoxycarbazole-3-caboxylate (**141**),



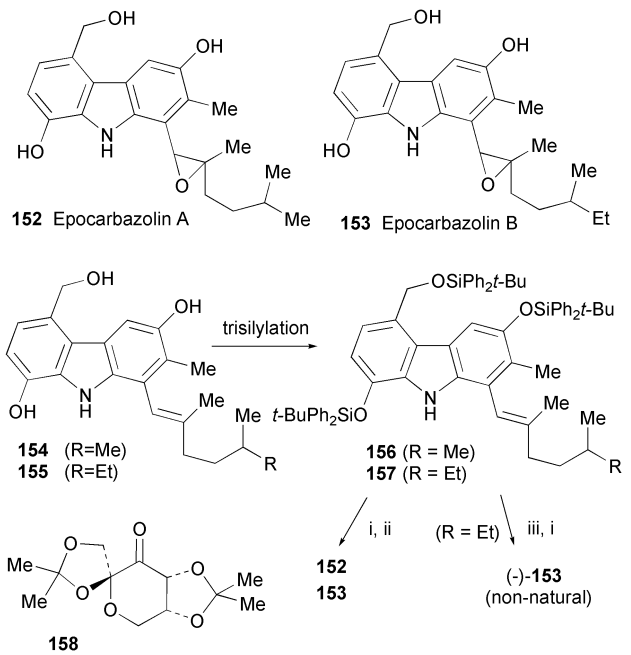
Scheme 34 *Reagents and conditions*: i, $Pd(OAc)_2$, BINAP, Cs_2CO_3, toluene, 110 °C; ii, $Pd(OAc)_2$, $Cu(OAc)_2$, AcOH, 117 °C; iii, DDQ, MeOH/H_2O, rt; iv, MnO_2, KCN, MeOH, rt; v, BBr_3, CH_2Cl_2, −78 °C; vi, NBS, CH_2Cl_2, rt; vii, prenyl bromide, $Ni(COD)_2$, DMF, rt; viii, NBS, HBr, MeCN, rt; ix, K_2CO_3, 2-bromo-1,1-diethoxyethane, DMF, 152 °C; x, amberlyst, chlorobenzene, 120 °C.



Scheme 35 *Reagents and conditions*: i, **150**, MeCN, rt; ii, NBS, MeCN; iii, NBS, HBr, MeCN; iv, prenyl bromide, $Ni(CO)_4$, DMF, 60 °C; v, $LiAlH_4$, Et_2O; vi, CAN, $MeCN/H_2O$.

3-formyl-6-methoxycarbazole (**142**), glycozolinine (**143**), glycomaurrol (**144**), micromeline (**145**) and eustifoline D (**146**) (Scheme 34).[60]

The first enantioselective synthesis of (*R*)-(−)-neocarazostatin (**147**), isolated from the culture of *Streptomyces* sp. Stran GP 38, has been achieved, which elucidated the absolute configuration.

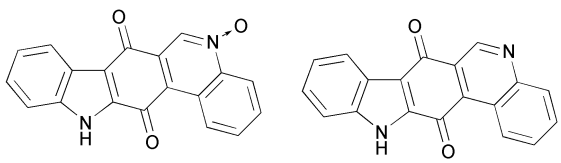


Scheme 36 *Reagents and conditions*: i, dimethyldioxirane, acetone, CH_2Cl_2, −20 °C; ii, TBAF, THF; iii, **158**, oxone, K_2CO_3, *n*-Bu_4NHSO_4, H_2O/DME/hexane, rt.

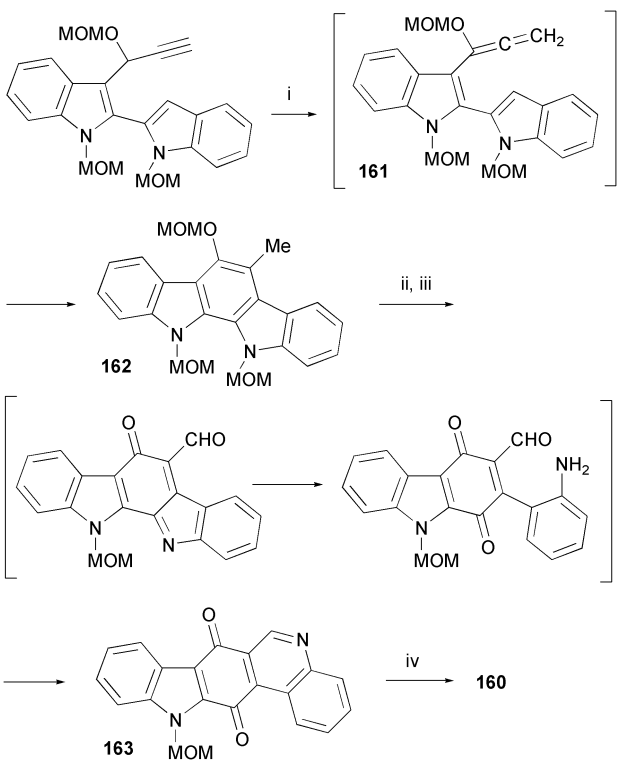
The key step of the construction of carbazole **151** was achieved *via* the reaction of arylamine **149** with iron complex **150**. A clean conversion of **147** to carquinostatin A (**148**), isolated from *Streptmyces exfoliates* 2419-SVT2, was achieved by CAN oxidation (Scheme 35).[61]

Epocarbazolins A (**152**) and B (**153**) were isolated from the actinomycete strain *Streptomyces anulatus* T688-8, and exhibit a potent inhibition of 5-lipoxygenase. Epoxidation of **156** and **157**, available from trisilylation of carbazomadurin A (**154**) and B (**155**), with dimethyldioxirane provided racemic **152** and **153**, respectively. The modified Shi epoxidation of **157** in the presence of catalyst **158** produced non-natural (−)-**153**. However, the absolute configuration was not assigned (Scheme 36).[62]

Indolo[3,2-*j*]phenanthridine alkaloids, calothrixins A (**159**) and B (**160**), were isolated from cell extracts of cyanobacterial *Calothrix* sp., and these compounds exert *in vitro* growth inhibitory in human malarial parasite and human cancer cells. Syntheses of calothrixins have been accomplished by the groups of Hibino, Moody, Bennasar, Guingant and Chai.



Hibino's approach to **160** used an allene-mediated electrocyclization in **161** to construct indolo[2,3-*a*]carbazole **162** and



Scheme 37 *Reagents and conditions*: i, *t*-BuOK, *t*-BuOH, 90 °C; ii, DDQ, DMF, rt; iii, CAN, $MeOH/H_2O$, 0 °C; iv, HCl, THF, 55 °C.

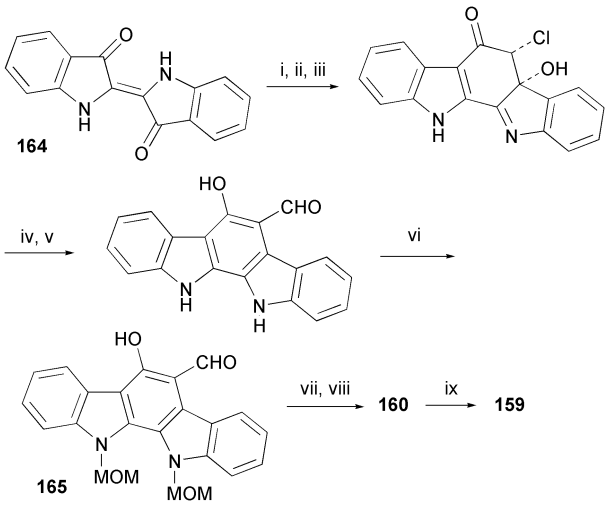
a biomimetic oxidative transformation of **162** to indolophenanthridine **163** (Scheme 37).[63]

Moody's group has synthesized **159** and **160** through the construction of the key carbazole **165** from indigo (**164**), followed by a biomimetic transformation of **165** to **160**. Oxidation of **160** with peracetic acid cleanly produced **159** (Scheme 38).[64]

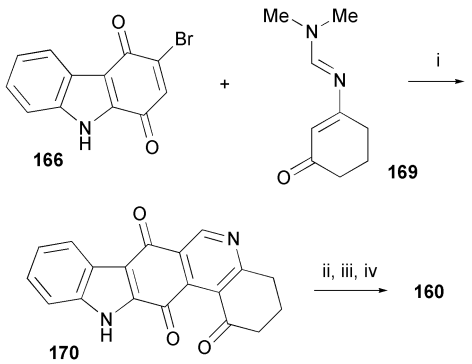
Guingant's approach to **160** is based on a regioselective hetero-Diels–Alder reaction between 2-azadiene **167** and carbazole-1,4-dione **166**, leading to **168** (Scheme 39).[65]

Bennasar's formal synthesis of **160** involved a regioselective intramolecular cyclization in 3-(3-quinolyl)methyl-2-indolyl radical **169** leading to indolophenanthridine **170** as the key step. Oxidation of **170** produced a known precursor **171** (Scheme 40).[66]

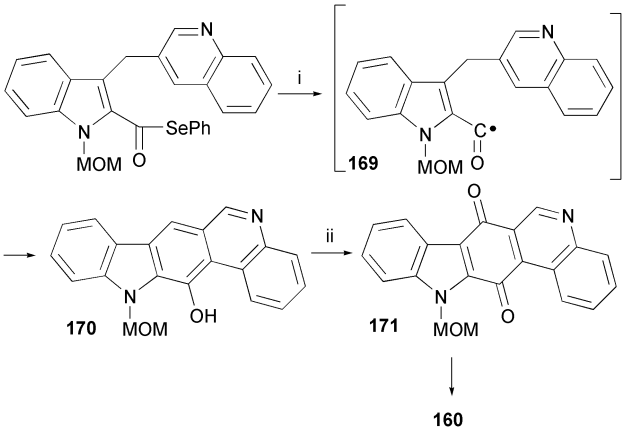
Chai's total synthesis of **160** involved Pd-catalyzed Heck cyclization in **172**, Suzuki coupling of **173** with **174**, and Cadogan reaction of **175** under microwave irradiation leading to phenanthridine **176** as the key steps (Scheme 41).[67]



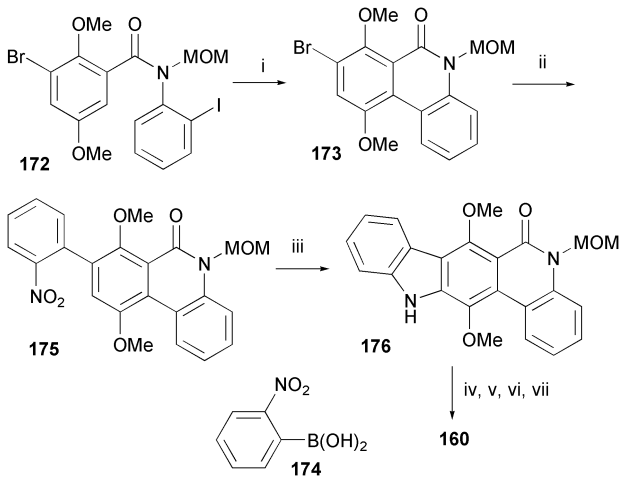
Scheme 38 *Reagents and conditions*: i, Sn, AcOH, Ac_2O, 64–66 °C; ii, $Cl_2CHCOCl$, AcOEt, reflux; iii, aq. NH_3, DMF, MeOH; iv, Zn, NH_4Cl, THF, MeOH; v, $POCl_3$, DMF; vi, MOMCl, NaH, DMF; vii, CAN, aq. MeCN; viii, HCl, THF, 55 °C; ix, $MeCO_3H$, CH_2Cl_2.



Scheme 39 *Reagents and conditions*: i, MeCN, 40 °C; ii, LHMDS, THF, HMPA, −78 °C, then $PhNTf_2$; iii, DDQ, dioxane, reflux; iv, $Pd(PPh_3)_4$, Et_3N, HCOOH, dioxane, reflux.



Scheme 40 *Reagents and conditions*: i, TTMss, AIBN; ii, acetone, O_2, NaOH.

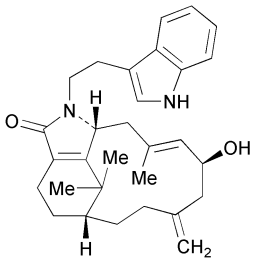


Scheme 41 *Reagents and conditions*: i, $Pd(OAc)_2$, PPh_3, K_2CO_3, DMF, 100 °C; ii, **174**, $Pd(OAc)_2$, PPh_3, K_2CO_3, DMF, 150 °C; iii, $P(OEt)_3$, microwave, sealed tube, 174 °C; iv, $LiAlH_4$, THF, rt; v; 6 N HCl, rt; vi, BBr_3, CH_2Cl_2, rt; vii, air, MeOH.

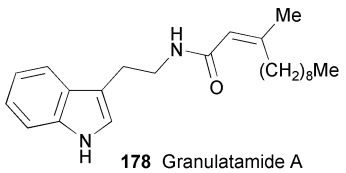
2.2 Non-isoprenoid tryptamines

The ethanolic extract of the soft coral *Cespitularia taeniata* collected in Taiwan produced a new indole alkaloid, cespitulactam J (**177**) which showed significant antimicrobial activity against *M. luteus* (IFM2066) and *C. neoformans* (IFM46914).[68] Two new tryptamine derivatives, granulatamides A (**178**) and B (**179**), were isolated from the 2-propanol extract of the soft coral *Eunicella granulate*. These showed moderate cytotoxicity in vitro against a panel of 16 human tumor cell lines.[69]

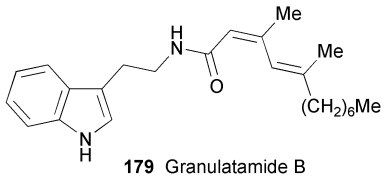
Three new indole alkaloids, bufoserotonins A (**180**), B (**181**) and C (**182**), were isolated from the traditional Chinese medicine ChanSu prepared from the skin secretions of giant toads, *Bufo bufo gargarizans*.[70] Ethyl acetate extract of the fungus *Malbranchea aurantiaca* provided the novel phytotoxic alkaloid, malbrancheamide (**183**), which showed moderate inhibition of radical growth of *Amaranthus hypochondriacus*, and inhibited the



177 Cespitulactam J

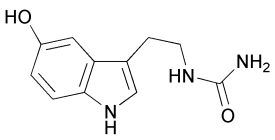


178 Granulatamide A

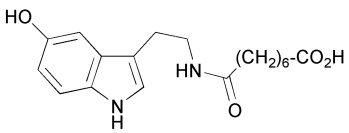


179 Granulatamide B

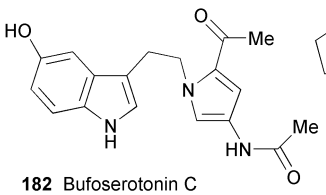
activation of the calmodulin-dependent enzyme PDE1.[71] A new cytotoxic cytochalasin alkaloid, chaetoglobosin U (**184**), was obtained from the AcOEt extract of a solid culture of *Chaetomium globosum* IFB-E019, an endophytic fungus residing inside the stem of healthy *Imperata cylindrical*.[72] Bioassay-guided investigation of isolate SP31, a *Bacillus endophyticus*, led to the isolation of two new alkaloids, bacillamides B (**185**) and C (**186**) along with the known bacillamide A.[73]



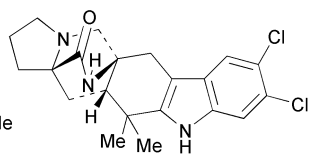
180 Bufoserotonin A



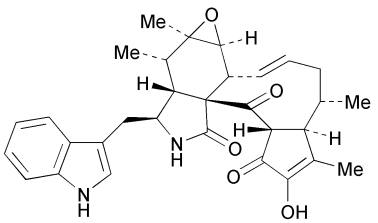
181 Bufoserotonin B



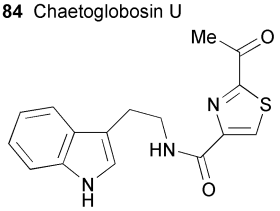
182 Bufoserotonin C



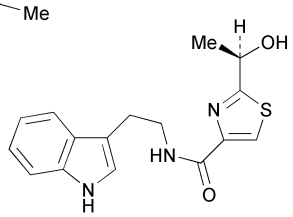
183 Malbrancheamide



184 Chaetoglobosin U

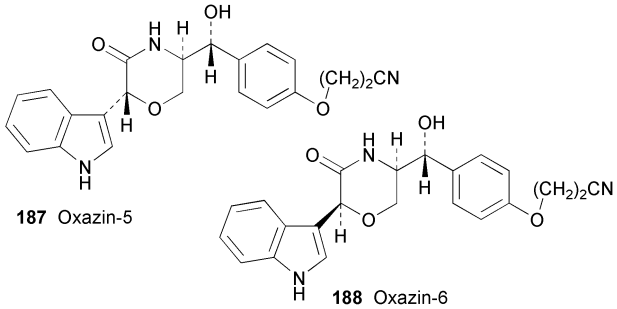


185 Bacillamide B



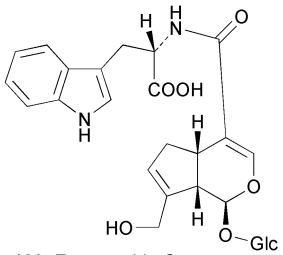
186 Bacillamide C

Two oxazins, oxazin-5 (**187**) and oxazin-6 (**188**), were isolated from toxic mussels *M. galloprovincialis* collected along the Northern Adriatic coast.[74] A novel azepino-indole alkaloid, hyrtiazepine (**189**), was isolated from the methanolic extract of the marine sponge *Hyrtio ereus* collected in the Red sea. This showed a significant antiphospholipase A_2 activity.[75] From the green leaves of *Eucommia ulmoides*, a new iridoid alkaloid, eucomoside C (**190**), was isolated.[76]

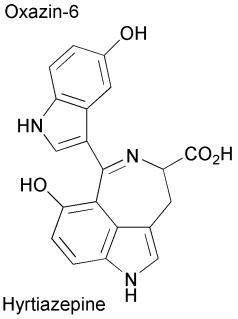


187 Oxazin-5

188 Oxazin-6

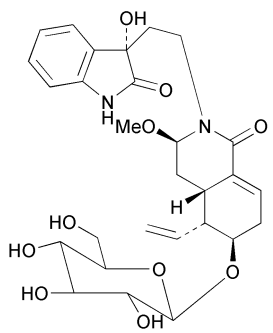


190 Eucomoside C

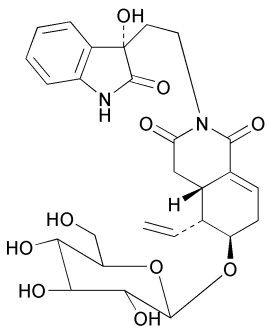


189 Hyrtiazepine

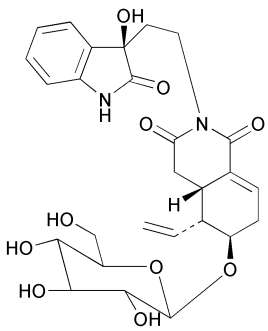
Four new oxindole alkaloids, paratunamides A (**191**), B (**192**), C (**193**) and D (**194**), were isolated from the bark of *Cinnamodendron axillare*. The structures and relative configurations were elucidated by spectroscopic data, and the absolute configuration was assigned on the basis of the CD spectra.[77]



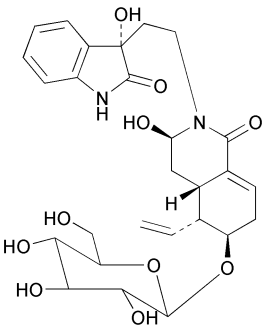
191 Paratunamide A



192 Paratunamide B



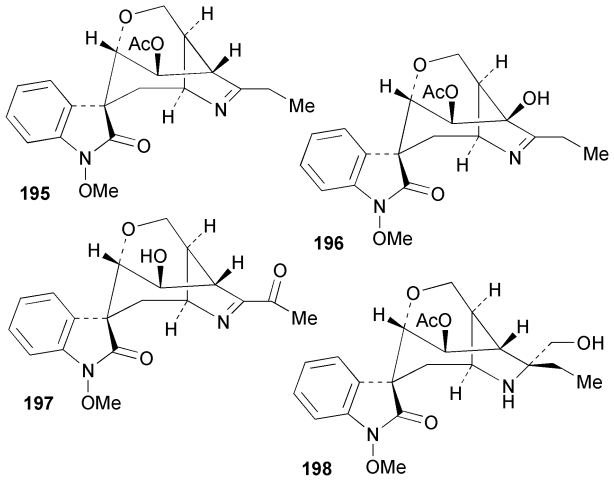
193 Paratunamide C



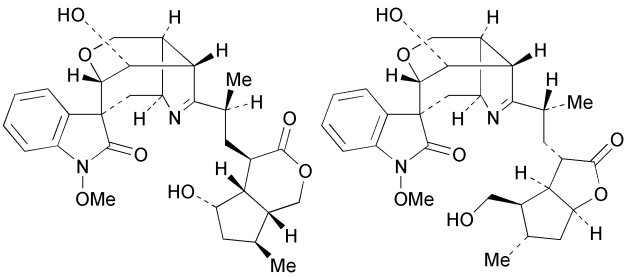
194 Paratunamide D

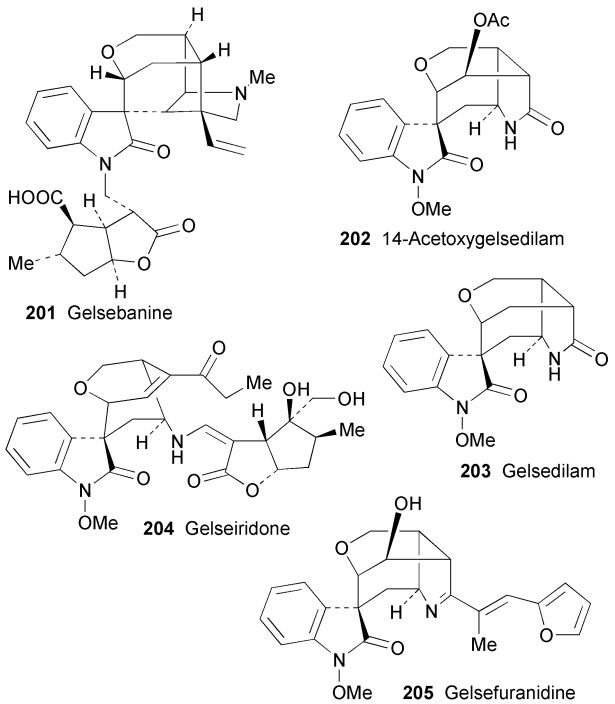
Four new gelsemine-type alkaloids, 14-acetoxygelsenicine (**195**), 14-acetoxy-15-hydroxygelsenicine (**196**), 14-hydroxy-19-oxogelsenicine (**197**) and 14-acetoxygelselegine (**198**), were

isolated from the leaves of *Gelsemium elegans*, and cytotoxic activity against the A431 human epidermoid carcinoma cell line was evaluated.[78]



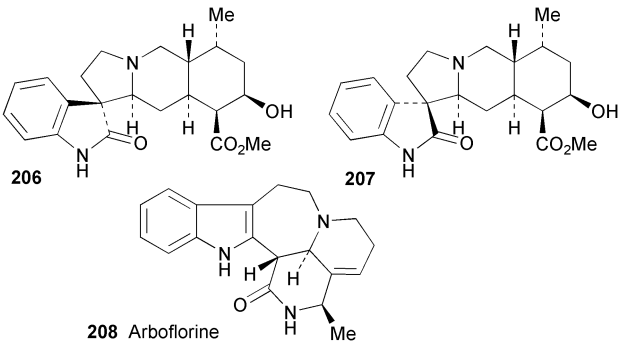
Three new alkaloids, gelsebanine (**201**), 14α-hydroxyelegansamine (**199**) and 14α-hydroxygelsamydine (**200**), were isolated from the stems and leaves of *Gelsemium elegans*.[79] New



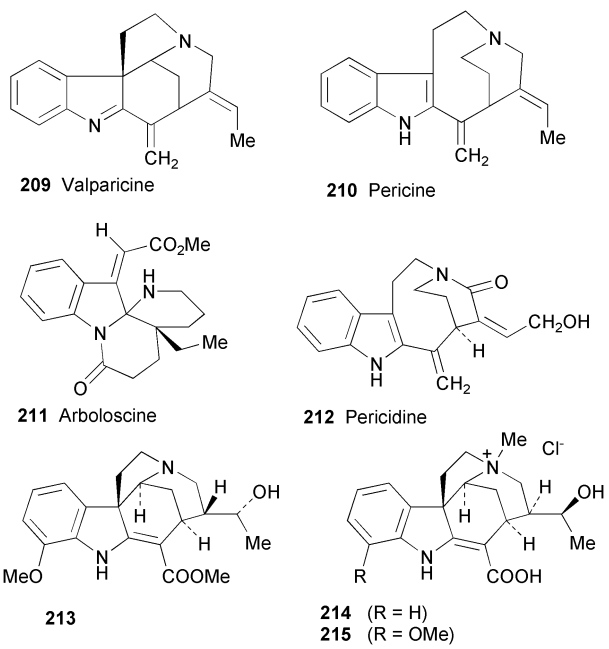


type of four gelsenicine oxindole alkaloids, gelsedilam (**203**), 14-acetoxygelsedilam (**202**), gelsefuranidine (**205**) and gelseiridone (**204**), were isolated from the leaves of *Gelsemium elegans* Beth.[80]

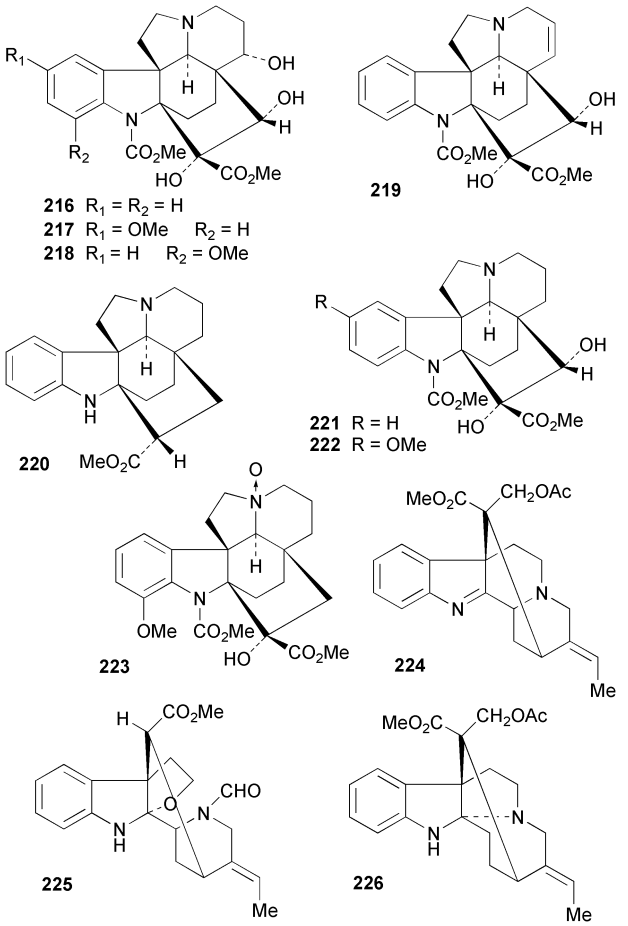
The leaves of the plant *Mitragyna parvifolia* afforded two new indole alkaloids, 16,17-dihydro-17β-hydroxyisomitraphylline (**206**) and 16,17-dihydro-17β-hydroxymitraphylline (**207**).[81] Arboflorine (**208**), a new indole alkaloid possessing a novel pentacyclic carbon skeleton, was obtained from the Malayan *Kopsia arborea*.[82]



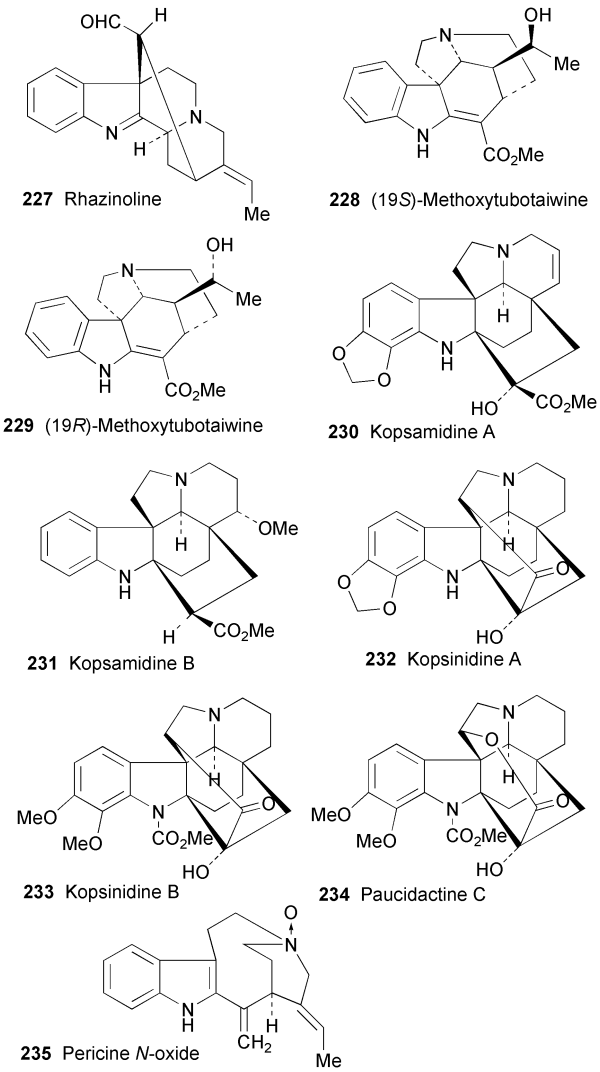
A new pentacyclic indole alkaloid of the pericine-type, valparicine (**209**), was isolated from the stem-bark extract of Malayan *Kopsia arborea*, and the structure was established by spectroscopic analysis and **209** was derived from pericine (**210**) *via* Potier-Polovski reaction.[83] Two new indole alkaloids, arboloscine (**211**) and pericidine (**212**), were obtained from the stem-bark of the Malayan *Kopsia arborea*.[84] Three new indole alkaloids, *N*(4)-demethyl-12-methoxyalstogustine (**213**), 17-carboxy-*N*(4)-methyl-echitamidine chloride (**214**) and 17-carboxy-12-methoxy-*N*(4)-methylechitamidine chloride (**215**), were isolated from the ethanolic extract of the stem bark of *Winchia calophylla*.[85]



Eleven new alkaloids, kopsiloscines C (**216**), E (**217**), F (**218**), A (**219**), 16-epikopsinine (**220**), kopsiloscines B (**221**), D (**222**), kopsilongine-*N*-oxide (**223**), 16-epiakuammiline (**224**), aspiophylline A (**225**) and vincophylline (**226**), were obtained from the Malayan *Kopsia singapurensis*.[86]



Nine new indole alkaloids, rhazinoline (**227**), 19(*S*)-methoxytubotaiwine (**228**), 19(*R*)-methoxytubotaiwine (**229**), kopsamidines A (**230**) and B (**231**), kopsinidines A (**232**), B (**233**), paucidactine C (**234**) and pericine *N*-oxide (**235**), were isolated from the stem-bark of the Malayan *Kopsia arborea*.[87]



The leaf extract of *Kopsia griffithii* produced 6-oxoleuconoxine (**236**), and kopsinitarine E (**237**), kopsijasminine (**238**) and kopsonoline (**239**) were isolated from the stem-bark extract of *Kopsia teoi*.[88] Three new alkaloids, 11,12-de(methylenedioxy)danuphylline (**240**), methyl (2,11,12,19)-6,7-didehydro-8,21-dioxo-11,21-cycloaspidospermidine-2-carboxylate (**241**) and (2,5)-aspidofractinin-16-ol (**242**), were isolated from the leaves of *Kopsia officinalis*.[89]

Four new doubly prenylated indole alkaloids, notoamides A (**243**), B (**244**), C (**245**) and D (**246**), were obtained from a culture of marine-derived fungus *Aspergillus* sp., which was separated from the common mussel *Mytilus edulis*. The structure elucidation with the absolute configuration and the biological activity were reported. Notoamides A–C (**243–245**) showed moderate cytotoxicity against HeLa and L1210 cells.[90]

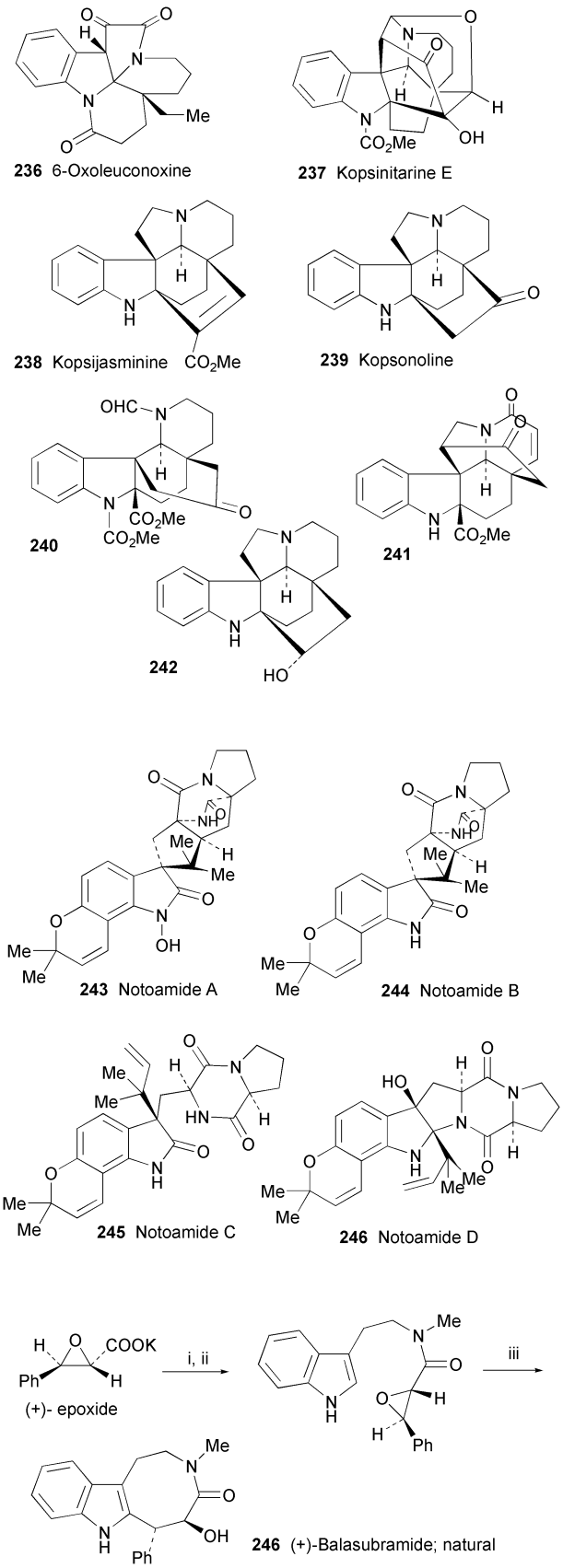
A two-step protecting-group-free biomimetic synthesis of (+)-balasubramide (**246**), isolated from Rutaceae *Clausena indica*, was achieved by using an $Yb(OTf)_3$-catalyzed intramolecular epoxide opening as the key step (Scheme 42).[91]

Unnatural (−)-**246** was obtained through CuI/*N*,*N*-dimethylglycine-catalyzed *N*-vinylation of oxiranecarboxamide, followed by the unprecedented intramolecular 8-*endo*-epoxy-arene cyclization (Scheme 43).[92]

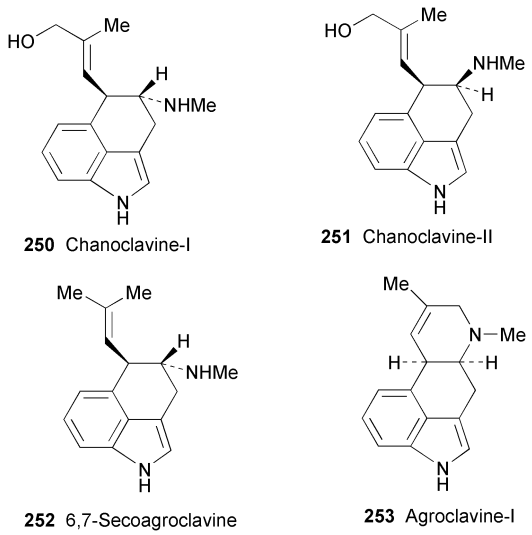
The first synthesis of decursivine (**247**), isolated from *Rhaphidophora decursivine*, has been completed. Indole intermediate **249**, obtained through a Diels–Alder/Plienger indolization sequences from quinone imide **248** and butadiene, followed by aldol condensation with piperonal, was converted to **247** (Scheme 44).[93]

Full details of the previous syntheses of 6,7-secoagroclavine (**252**), chanoclavine-I (**250**), chanoclavine-II (**251**) and agroclavine-I (**253**), have been reported.[94]

(*S*)-Cypridina luciferin (**254**), first isolated from a luminous ostracod *Cypridia hilgendorfi*, is the substrate in the bioluminescence, and was synthesized by the condensation of (*S*)- **256** with ethioluciferin (**255**) (Scheme 45).[95]

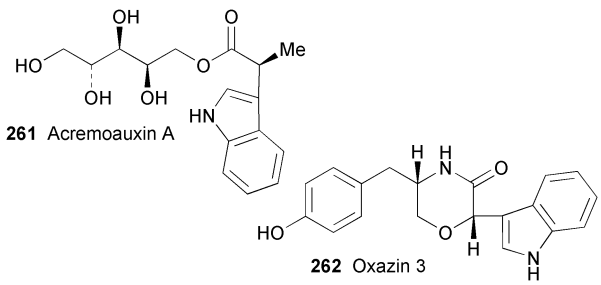


Scheme 42 *Reagents and conditions*: i, HCl, Et_2O; ii, Piv-Cl, Et_3N, CH_2Cl_2, then *N*-methyltryptamine; iii, $Yb(OTf)_3$, CH_2Cl_2, microwave, 80 °C.



A total synthesis of marine-derived alkaloid, chartelline C (**257**), isolated from the bryozoans *Chartella papyracea*, has been achieved (Scheme 46).[96] The key macrocycle **259** was derived from **258** in six steps. The synthesis was completed through thermolysis of **259** leading to **260**.

Full details of the recently invented method of metal-catalyzed direct coupling of indole with carbonyl compounds and its application to a total synthesis of acremoauxin A (**261**) and oxazin 3 (**262**) have been reported.[97]

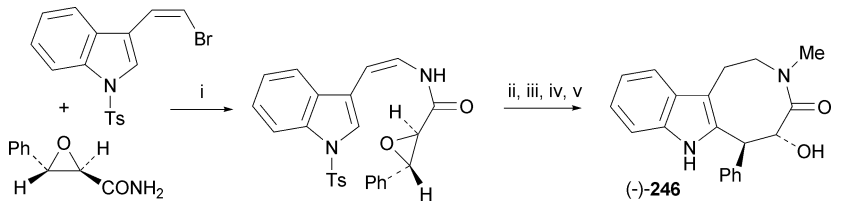


A convergent strategy to ibophylline alkaloids, deethylibophyllidine (**263**) and 14-epideethylibophyllidine (**264**), isolated from the bark of *Tabernaemontana albiflora*, has been developed through a [4 + 2] cycloaddition in **267** generated *in situ* from **266** and tryptamine **265** in the presence of TsOH in boiling toluene (Scheme 47).[98]

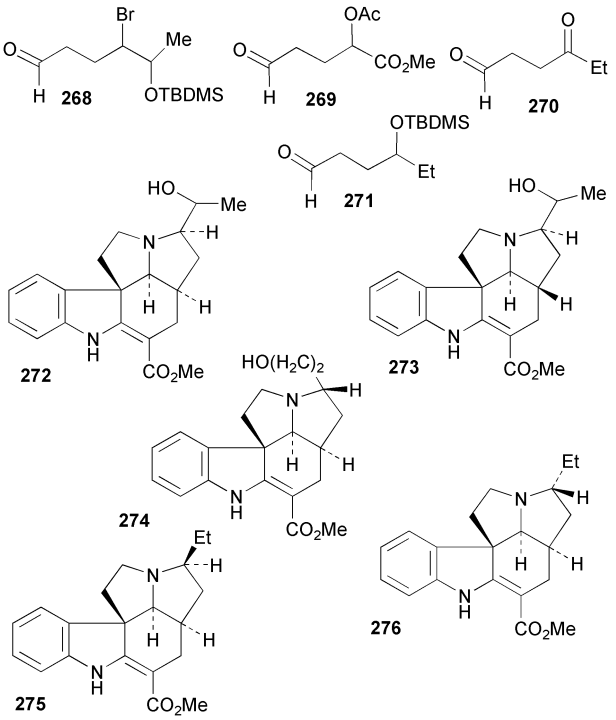
The cycloaddition protocol using **265** was further developed for the synthesis of 19-hydroxyibophyllidine (**272**) and 19-hydroxy-20-epiibophyllidine (**273**) from aldehyde **268**,[99] 18-hydroxy-20-epiibophyllidine (**274**) from aldehyde **269**,[100] ibophyllidine (**275**) from aldehyde **270**[101] and epiibophyllidine (**276**) from aldehyde **271**.[101]

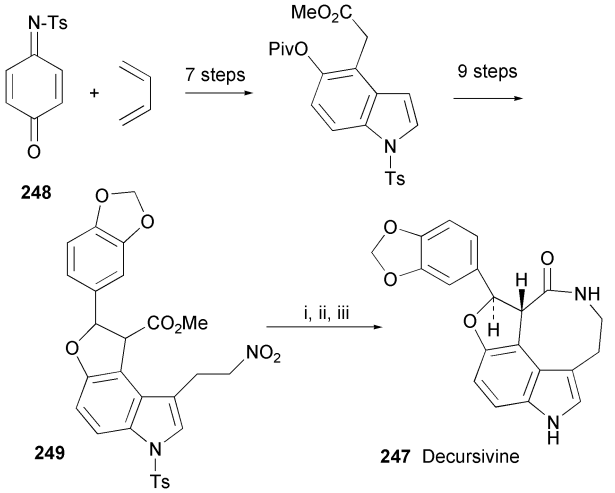
A formal synthesis of epideethylibophyllidine (**264**) was achieved through an intramolecular dipolar cycloaddition reaction in **277** as the key step to assemble the known precursor **278** (Scheme 48).[102]

The asymmetric synthesis of the oxindole alkaloid (−)-horsfiline (**280**) was achieved through a palladium-catalyzed

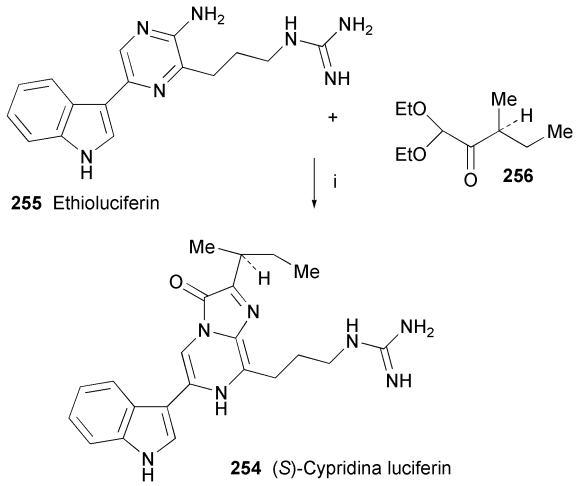


Scheme 43 *Reagents and conditions*: i, CuI, *N*, *N*′-dimethylglycine, Cs_2CO_3, dioxane, reflux; ii, MeI, NaH, DMF; iii, TsOH, MeCN; iv, Mg, MeOH; v, Pd/C, H_2, MeOH.

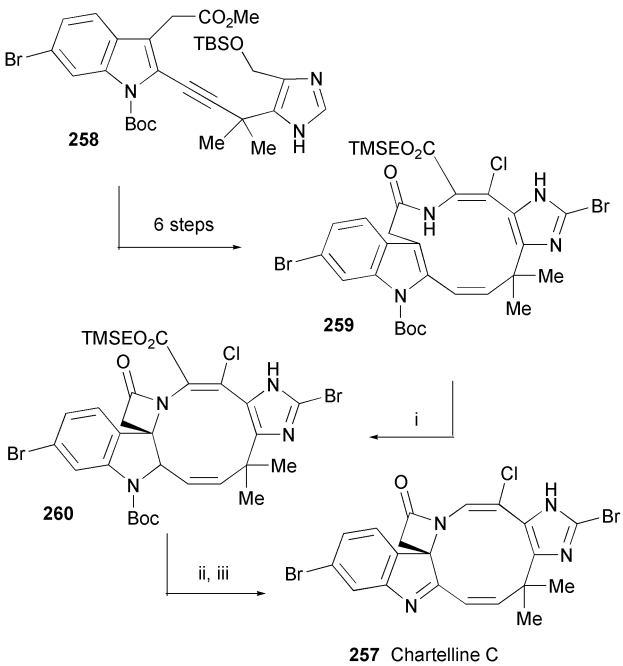




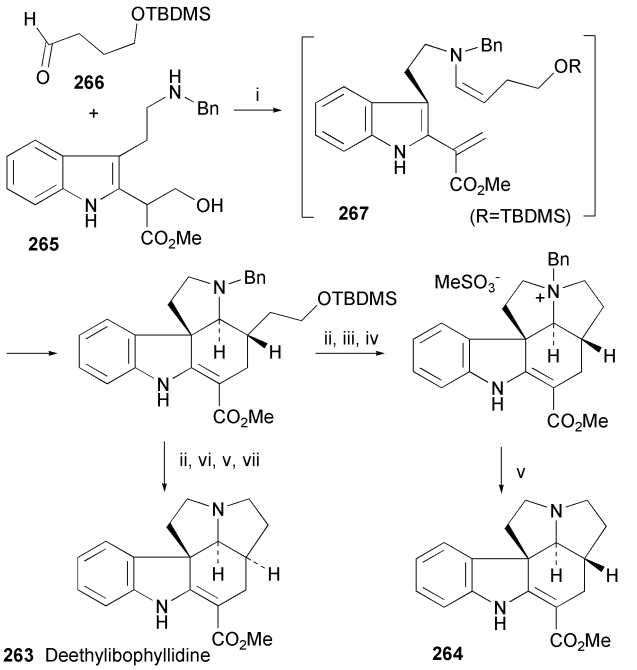
Scheme 44 *Reagents and conditions*: i, Zn, HCl, THF; ii, pyridine, microwave; iii, Mg, NH_4Cl, MeOH, THF.



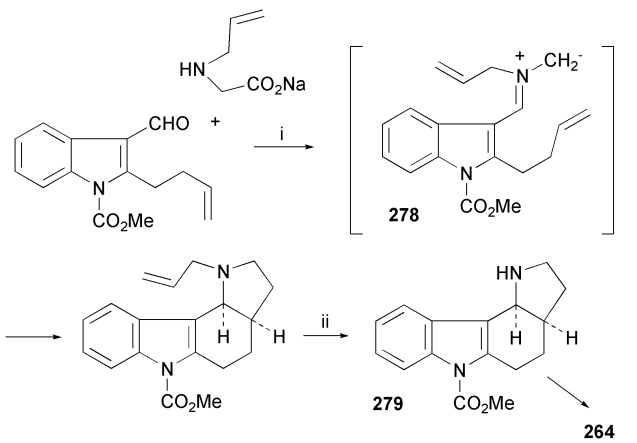
Scheme 45 *Reagents and conditions*: i, aq. 47% HBr, EtOH, H_2O, reflux.



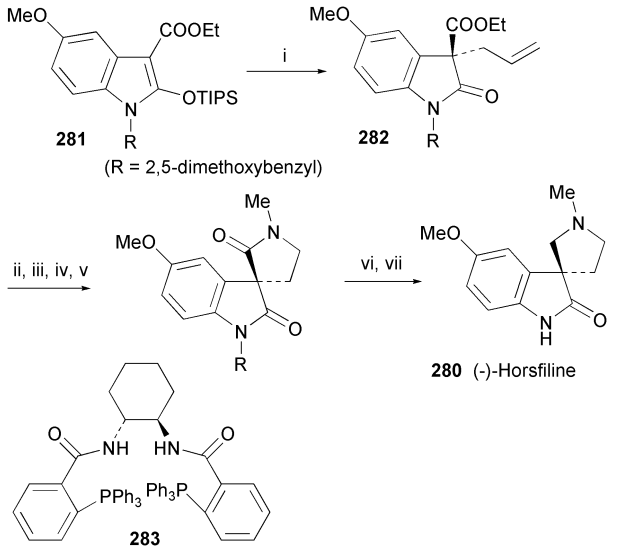
Scheme 46 *Reagents and conditions*: i, 185 °C, then MeCN, 3 Å MS, NBS, rt, then 18-crown-6, K_2CO_3, then aq. $NaHCO_3$, then brine; ii, TFA, DCE, rt; iii, *o*-dichlorobenzene, 200 °C.



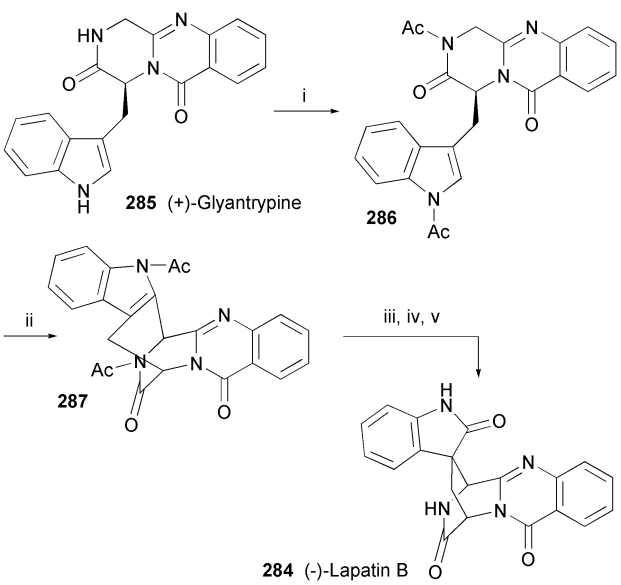
Scheme 47 *Reagents and conditions*: i, *p*-TsOH, toluene, reflux; ii, 5 M HCl, THF; iii, MsCl, Et_3N, CH_2Cl_2, 0 °C; iv, THF, reflux; v, Pd/C, H_2, AcOH; vi, PhCOOH, DCC, DMAP, CH_2Cl_2, 0 °C; vii, toluene, reflux.



Scheme 48 *Reagents and conditions*: i, CSA, toluene, reflux; ii, $Pd(dba)_2$, THF, thiosalicylic acid.



Scheme 49 *Reagents and conditions*: i, $[Pd(C_2H_5)Cl]_2$, toluene, allyl acetate, TBAF, **283**, rt; ii, OsO_4, NMO, CH_2Cl_2; iii, $Pb(OAc)_4$, CH_2Cl_2; iv, $MeNH_2$, $MgSO_4$, THF; v, $NaBH_4$, EtOH; vi, DDQ, TFA, CH_2Cl_2, H_2O, 45 °C; vii, Ph_3CLi, DME, then $LiAlH_4$, rt.



Scheme 50 *Reagents and conditions*: i, Ac_2O, BF_3OEt_2, rt; ii, PhI(O-H)OTs, MeCN, 85 °C; iii, NaOMe, MeOH; iv, NBS, TFA/THF/H_2O (1:2:1); v, Pt/C, MeOH, AcOH, NaOAc.

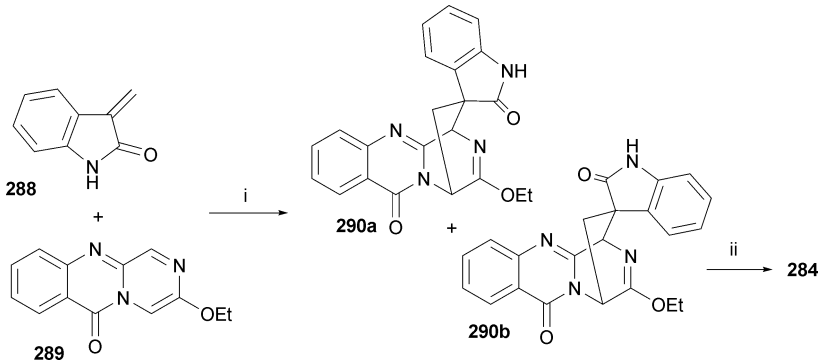
asymmetric allyl alkylation (AAA) of **281** with allyl acetate to set the spiro(pyrrolidine-oxindole)stereogenic center. Through ring-closure and chemoselective reduction sequences, **282** was transformed to (−)-**280** (Scheme 49).[103]

Spirooxindole alkaloid, lapatin B (**284**), was synthesized by two groups of Hart's and Loiseleur's. Hart's approach to (−)-**284** used (+)-glyantrypine (**285**), available from L-tryptophan, as a point of departure. The key step involved an oxidative cyclization of **286** to bridged indole **287** (Scheme 50).[104]

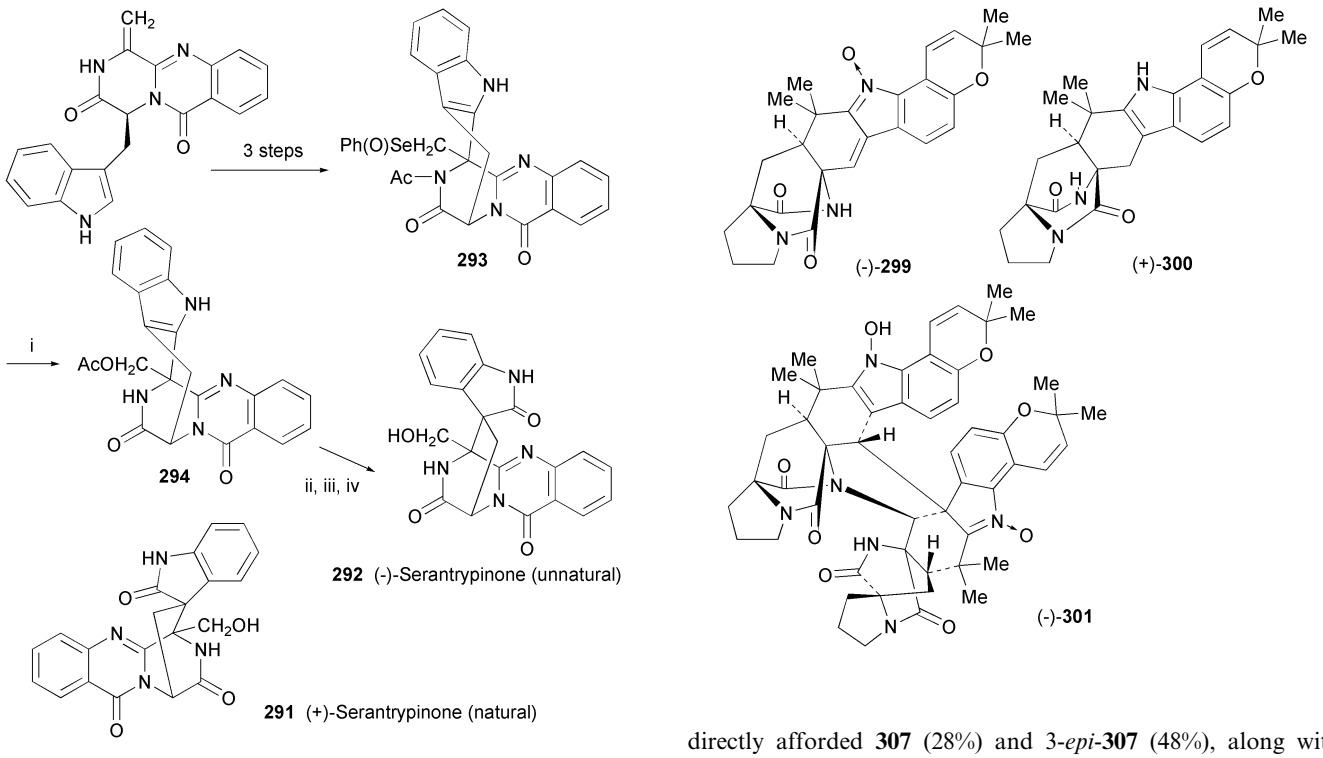
Total synthesis of racemic **284** has been achieved by Loiseleur through aza-Diels–Alder reaction as the key step. Azadiene **289** reacted with oxindole **288** in the presence of TfOH to provide *exo* **290b** and *endo* **290a** cycloadducts in a 1:1 ratio. The *exo* adduct **290b** was transformed to **284** (Scheme 51).[105]

A total synthesis of unnatural (−)-serantrypinone (**292**) from L-tryptophan has been reported. The key step involved the transformation of selenoxide **293** to acetate **294** *via* trapping of a presumed intermediate in a seleno-Pummerer reaction. The absolute configuration of natural (+)-serantrypinone (**291**), isolated from the fungus *Penicillium thymicola*, was established based on the synthesis of (−)-**292** (Scheme 52).[106]

The total synthesis of racemic phalarine (**295**) has been achieved through a novel rearrangement in azaspiroindolenine



Scheme 51 *Reagents and conditions*: i, TfOH, CH_2Cl_2, −20 °C, *endo*/*exo* = 1/1; ii, 2 N HCl, AcOEt, rt.



Scheme 52 *Reagents and conditions*: i, Ac_2O, 75 °C; ii, NBS, TFA, THF/H_2O; iii, Pt/C, H_2; iv, NaOMe, DMSO.

297, generated from **296**, to the key precursor **298** (Scheme 53).[107]

Full details of the previously reported enantioselective total synthesis of arrainvillamide (**299**) and stephacidins A (**300**), B (**301**)[108] by Baran's group have appeared.[109]

Improvement of biomimetic total synthesis of racemic **300** was reported, which involved the Mitsunobu-based intramolecular Diels–Alder cycloaddition. Treatment of **302** with DEAD and Bu_3P directly afforded **300** in 64% yield (Scheme 54).[110]

A biomimetic total synthesis of **300** and notoamide B (**303**) was achieved through the intramolecular Diels–Alder cycloaddition of **305** generated from precursor **304** (Scheme 55).[111]

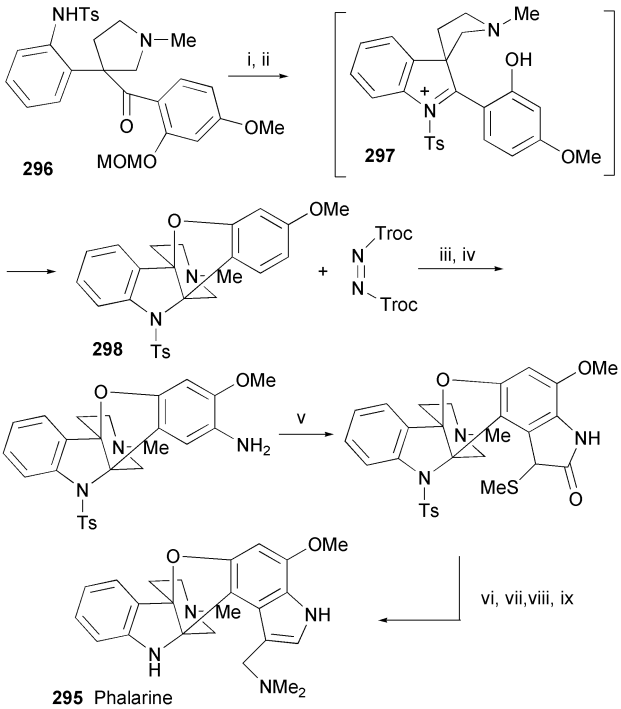
Total syntheses of notoamides C (**307**) and D (**308**) have been developed (Scheme 56). Oxidation of **309** with oxaziridine **306** directly afforded **307** (28%) and 3-*epi*-**307** (48%), along with a minor amount of **308** and 2,3-*epi*-**308**.[112]

A biomimetic total synthesis of racemic macrofortine C (**310**), isolated from *Penicillium roqueforti*, was achieved by the use of an intramolecular Diels–Alder reaction as the key step (Scheme 57).[113]

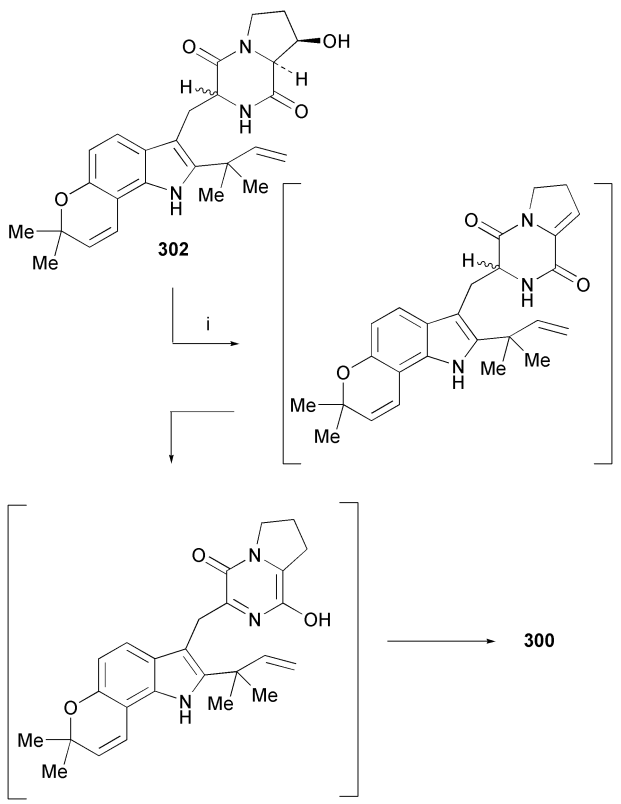
The first enantioselective synthesis of (−)-(19*R*)-ibogamin-19-ol (**311**), isolated from *Tabernaemontana quadrangularis*, was achieved (Scheme 58). The key step involved an intramolecular nitrone-olefin 1,3-dipolar cycloaddition reaction to form isoquinuclidine (+)-**313** from (−)-**312**.[114]

A total synthesis of racemic strychnine (**314**) has been developed *via* an intramolecular [4 + 2]-cycloaddition/rearrangement cascade of an indolyl-amidofuran **315** leading to **316**. The critical D-ring was assembled by a palladium-catalyzed intramolecular enolate-driven cross-coupling of vinyl iodide **317** (Scheme 59).[115]

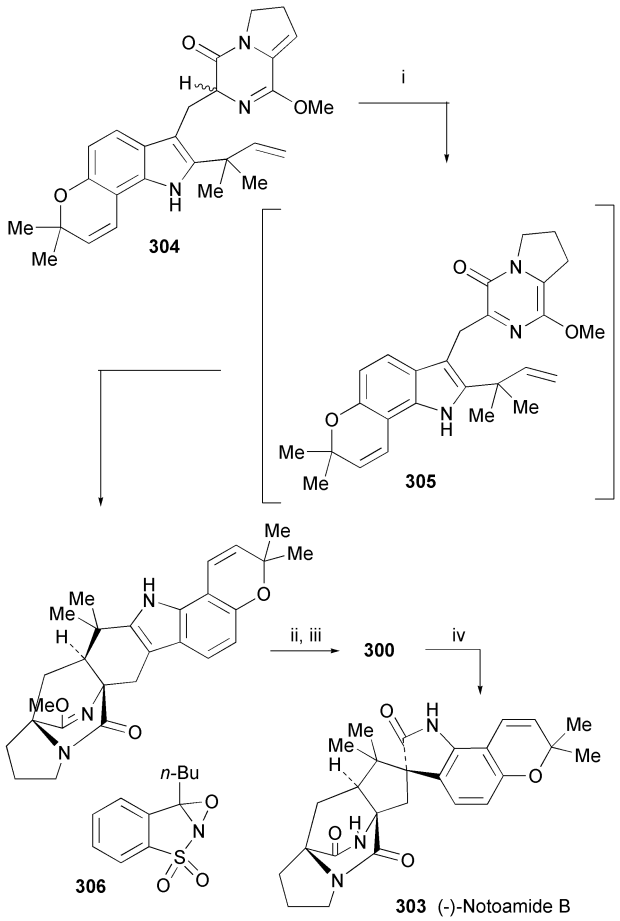
Stereoselective generation of the quaternary carbon center of the key intermediate **320** *via* the sequential dialkylation of the enolate of lactam **319** was applied to a total synthesis of (−)-quebrachamine (**318**) (Scheme 60).[116]



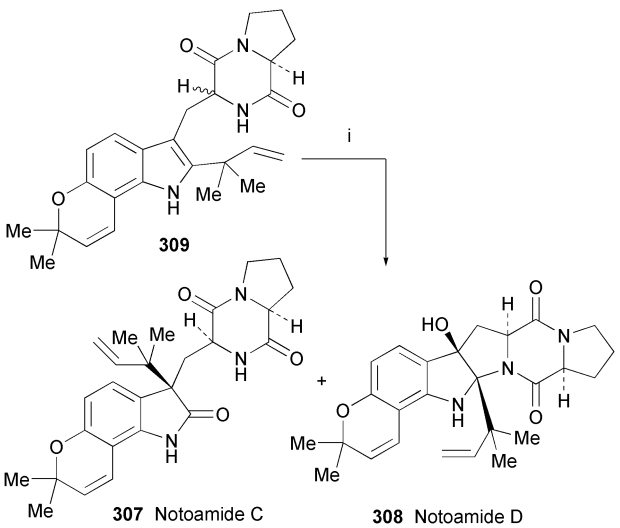
Scheme 53 *Reagents and conditions*: i, TFA, CH_2Cl_2, 0 °C; ii, CSA, toluene, 130 °C; iii, TFA; iv, Zn dust, AcOH; v, $MeSCH_2COOEt$, SO_2Cl_2, CH_2Cl_2, −78 °C, proton sponge, then Et_3N, −78 °C to rt; vi, BH_3, THF, 0 °C; vii, Raney Ni, EtOH; viii, $[CH_2{=}NMe_2]Cl$, AcOH; ix, Na(Hg), Na_2HPO_4, MeOH, 0 °C to rt.



Scheme 54 *Reagents and conditions*: i, Bu_3P, DEAD, CH_2Cl_2, 40 °C.

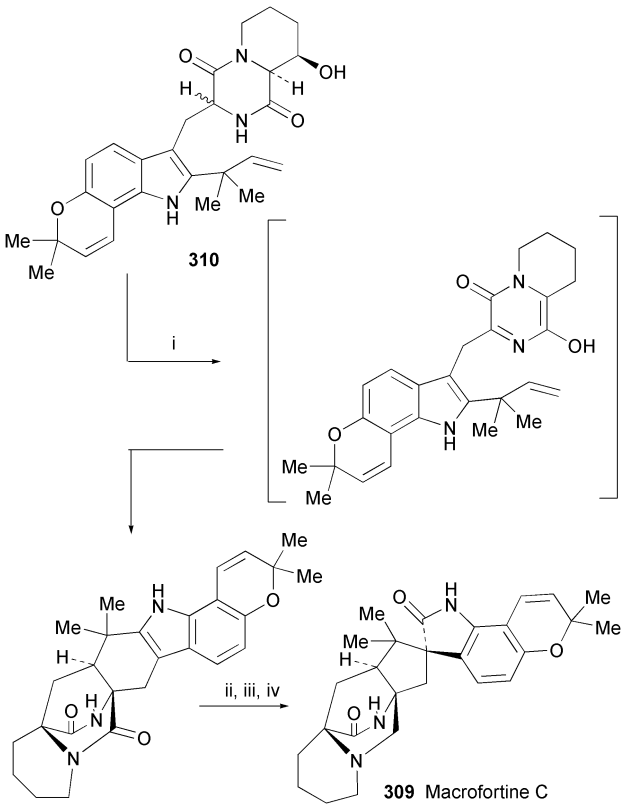


Scheme 55 *Reagents and conditions*: i, 20% KOH, MeOH, 0 °C to rt; ii, 0.1 M HCl, THF, 0 °C; iii, $NaHCO_3$; iv, **306**, CH_2Cl_2.

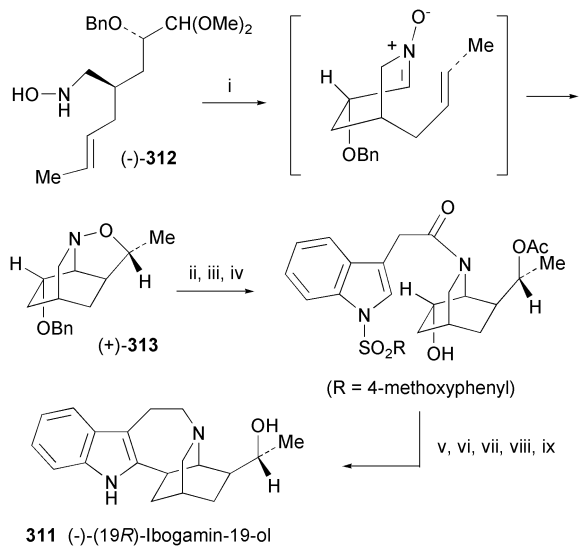


Scheme 56 *Reagents and conditions*: i, **306**, CH_2Cl_2.

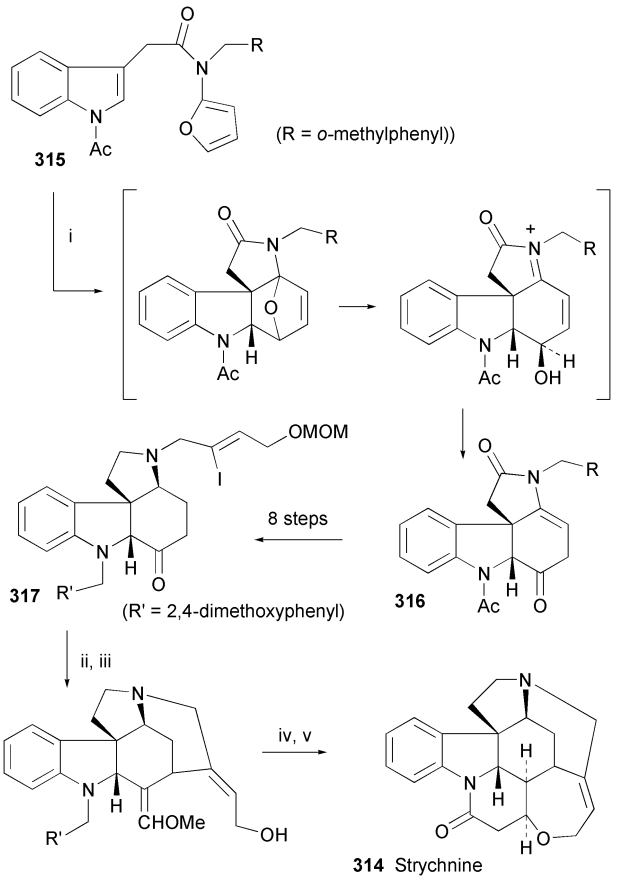
A cascade radical cyclization starting from an amidyl radical has been applied for a total synthesis of racemic aspidospermidine (**322**) (Scheme 61). Amidyl radical **324**, generated by treating **323** with Bu_3SnH and ACCN, underwent 5-*exo* cyclization to



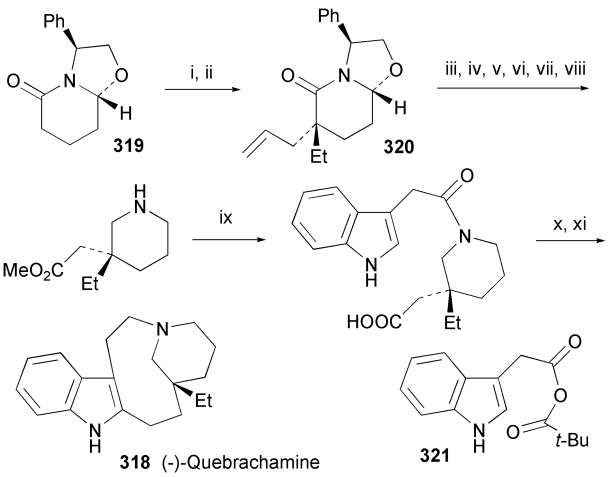
Scheme 57 *Reagents and conditions*: i, Bu_3P, DEAD, CH_2Cl_2, 40 °C; ii, DIBAH, toluene, rt; iii, PPTS, CH_2Cl_2; iv, **306**, CH_2Cl_2.



Scheme 58 *Reagents and conditions*: i, 1.5 M H_2SO_4, 47 °C; ii, Zn, AcOH, MeOH, rt; iii, [1-(4-methoxyphenylsulfonyl)indol-3-yl]acetic acid, DCC, CH_2Cl_2, 0 °C, then Ac_2O, pyridine, DMAP, CH_2Cl_2, rt; iv, Pd/C, H_2, EtOH, AcOH; v, DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2; vi, $HC(OMe)_3$, TsOH, rt; vii, Na/Hg, KH_2PO_4, THF/MeOH, −20 °C; viii, AcCl, MeOH, 45 °C; ix, $LiAlH_4$, $AlCl_3$, THF, rt.



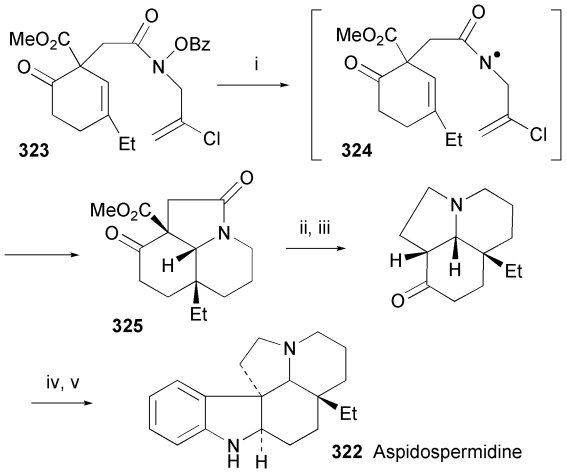
Scheme 59 *Reagents and conditions*: i, MgI_2, toluene, 150 °C, microwave; ii, $Pd(PPh_3)_4$, PhOK; iii, LDA, $Ph_2P(O)CH_2OMe$; iv, 3 N HCl, 55 °C; v, $CH_2(COOH)_2$, Ac_2O, NaOAc, AcOH.



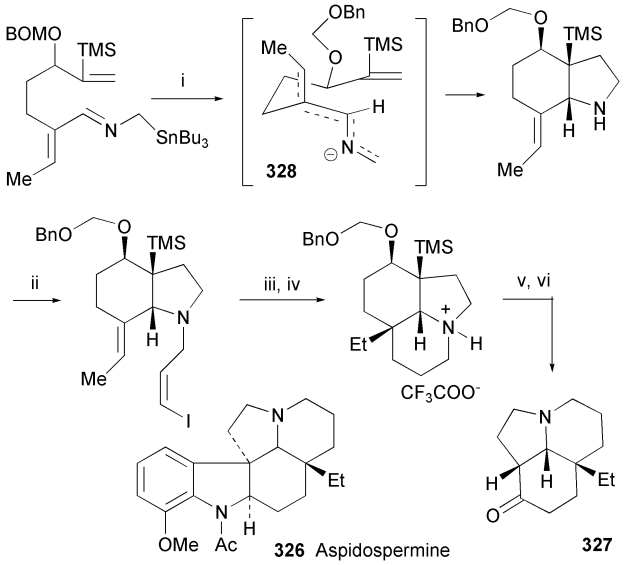
Scheme 60 *Reagents and conditions*: i, allyl bromide, LHMDS, THF, −78 °C; ii, EtI, KHMDS, toluene, −78 °C; iii, $RuCl_3$, $NaIO_4$; iv, $LiAlH_4$; v, $Pd(OH)_2$, H_2; vi, Boc_2O, vii, PDC, DMF; viii, TMSCl, MeOH; ix, **321**, aq. NaOH; x, PPA; xi, $LiAlH_4$, NMM, reflux.

afford tricycle **325**. Conversion of **325** to **322** was performed *via* reduction and decarboxylation followed by Fischer indolization.[117]

Formal synthesis of **322**, aspidospermine (**326**) and **318** was reported. Stork's penultimate intermediate **327** was prepared *via* an intramolecular [3 + 2] cycloaddition of the



Scheme 61 *Reagents and conditions*: i, Bu_3SnH, ACCN, $PhCF_3$, reflux; ii, 9-BBN, THF, reflux; iii, LiCl, DMF, reflux; iv, $PhNHNH_2$, AcOH; v, $NaBH_4$, MeOH.

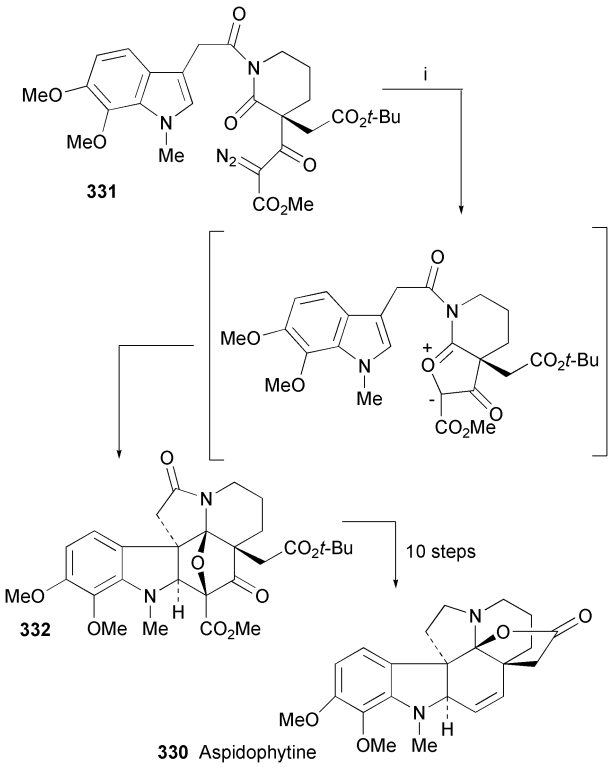


Scheme 62 *Reagents and conditions*: i, *n*-BuLi, THF, −78 °C; ii, (*Z*)-3-bromo-1-iodopropene, THF, K_2CO_3; iii, $Pd(OAc)_2$, *n*-Bu_4NCl, K_2CO_3, DMF; iv, Pd/C, H_2, MeOH, TFA; v, Li, NH_3, THF, then HCl, MeOH, H_2O, THF; vi, Dess–Martin reagent, HCl, H_2O, Et_2O.

azapentadienyllithium **328** and an intramolecular Heck reaction to assemble tricycle **329** as the key steps (Scheme 62).[118]

Two total syntheses of aspidophytine (**330**) have been reported by two groups of Padwa's and Marino's. Padwa's approach involved the successful application of a Rh(II)-catalyzed cyclization/dipolar cycloaddition cascade methodology to construct the key pentacyclic intermediate **332** by the reaction of **331** with $Rh_2(OAc)_4$. The intermediate **332** was explored in the further steps, leading to the completion of the synthesis of **330** (Scheme 63).[119]

Marino's synthesis involved a ketene-lactonization reaction in chiral vinyl sulfoxide **333** (Marino annulation reaction) to set up the chiral quaternary carbon center, and a tandem Michael

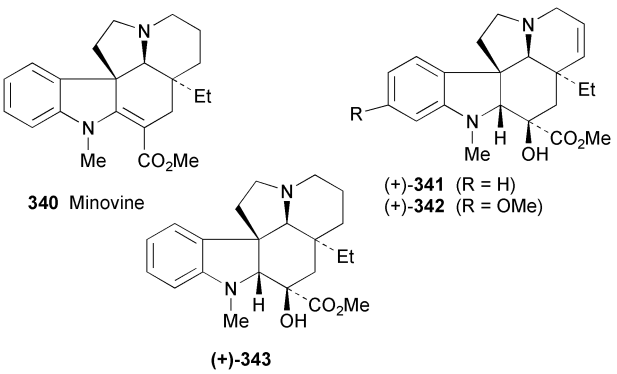


Scheme 63 *Reagents and conditions*: i, $Rh_2(OAc)_4$.

addition-alkylation reaction sequence triggered from **334** leading to pentacyclic intermediate **335** (Scheme 64).[120]

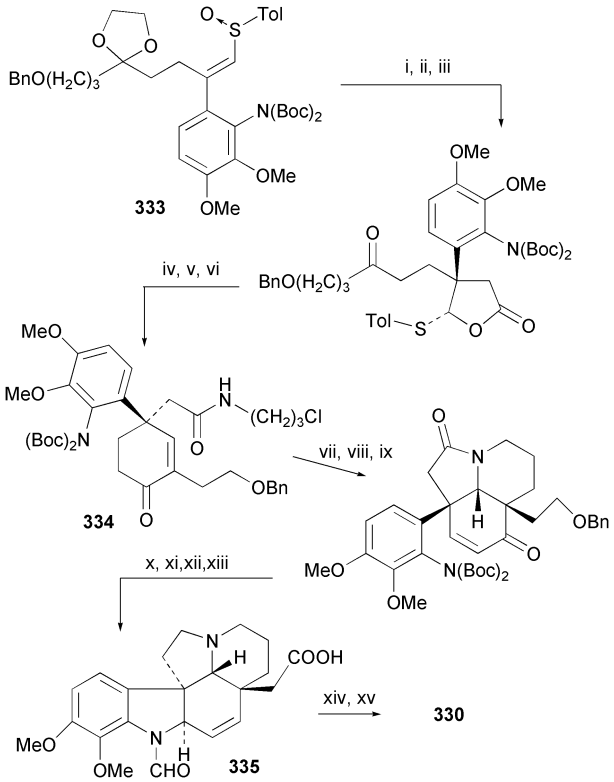
Boger reported a total synthesis of (−)-vindorosine (**336**) and (−)-vindoline (**337**) through a tandem intramolecular Diels–Alder/1,3-dipolar cycloaddition cascade of 1,3,4-oxadiazoles (**338**) (Scheme 65).

The cascade methodology using oxadiazoles **339** was further developed to synthesize minovine (**340**), (+)-4-desacetoxyvindorosine (**341**), (+)-4-desacetoxyvindoline (**342**) and (+)-4-desacetoxy-6,7-dihydrovindorosine (**343**).[121]



15β-Hydroxyvincadifformine (**344**) was synthesized through an acid-catalyzed intramolecular [4 + 2] cycloaddition from **345** (Scheme 66).[122]

A formal synthesis of vallesamidine (**346**), isolated from *Vallesia dichotoma*, was achieved through conversion of



Scheme 64 *Reagents and conditions*: i, Zn(Cu), Cl_3CCOCl, THF; ii, *n*-Bu_3SnH, Et_3B, benzene, reflux; iii, acetone, TsOH, rt; iv, pyrrolidine, benzene; v, pyrrolidine, *i*-PrOH, AcOH; vi, *i*-BuOCOCl, Et_3N, $Cl(CH_2)_3NH_2$, THF; vii, NaH, DMF, 0 °C; viii, KHDMS, TMSCl, THF; ix, $Pd(OAc)_2$, O_2, 60 °C, DMSO; x, HCOOH, rt; xi, KHMDS, $PhNTf_2$, THF, −78 °C, then $Pd(PPh_3)_4$, *n*-Bu_3SnH; xii, Pd/C, H_2, MeOH; xiii, PDC, DMF; xiv, Et_3OBF_4, CH_2Cl_2, then $NaBH_4$, EtOH; xv, $K_3Fe(CN)_6$, *t*-BuOH, H_2O, then $NaHCO_3$.

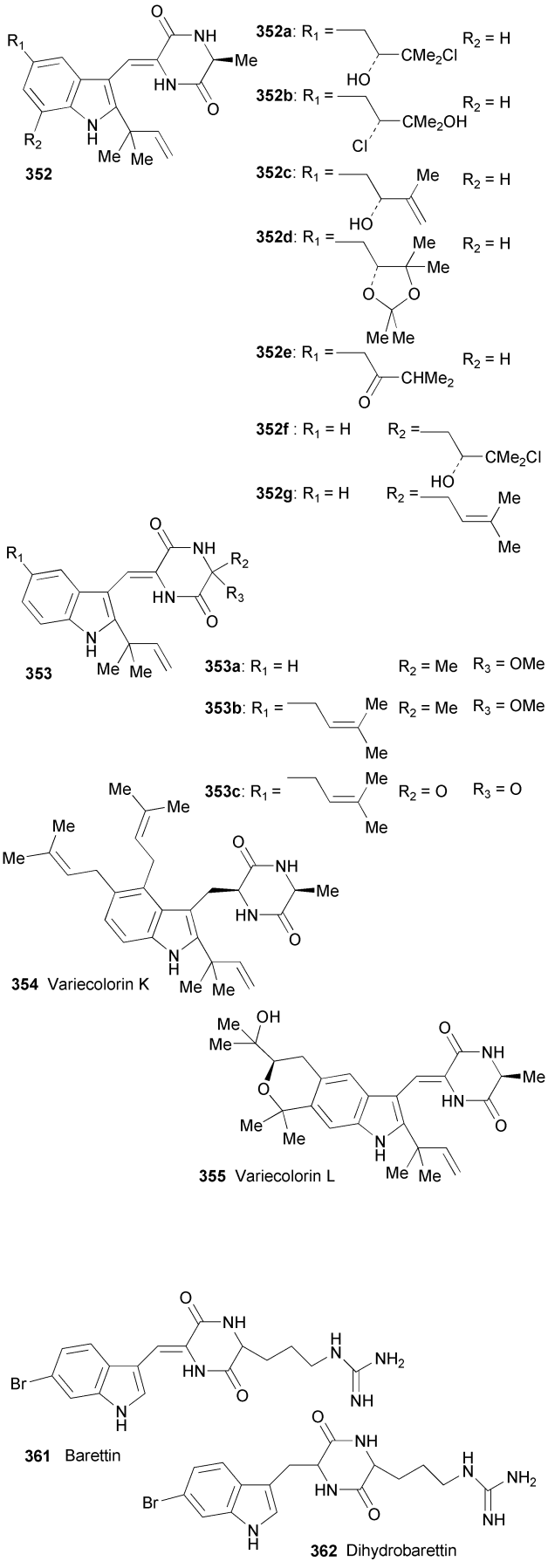
cycloheptenyl derivative **347** to the known precursor **348** (Scheme 67).[123]

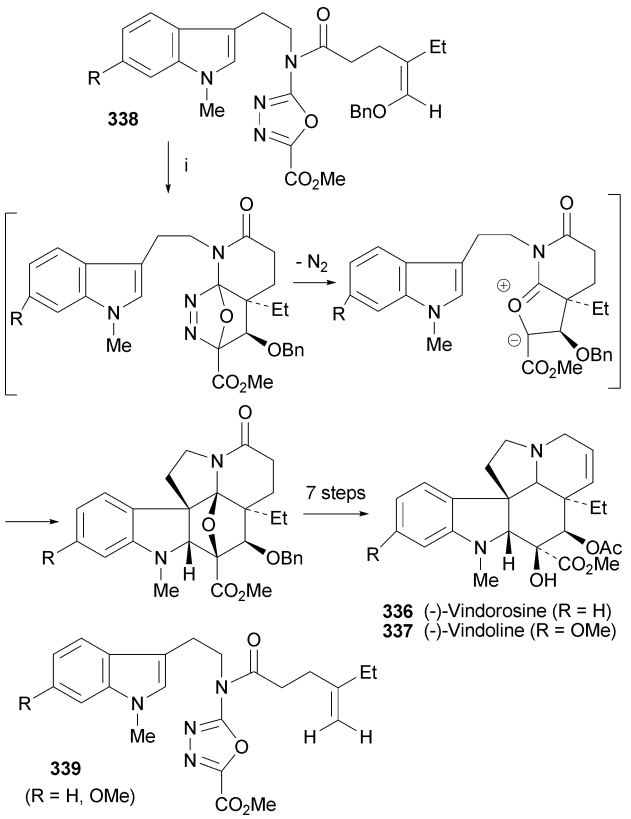
2.2.1 Piperazinediones. A formal synthesis of (−)-tryprostatin B (**349**) was reported. The known advanced precursor **351**[124] was obtained through a sigmatropic rearrangement on **350** derived from (−)-tryptophan in 3 steps (Scheme 68).[125]

Twelve new isoechinulin-type alkaloids, variecolorins A (**352a**), B (**352b**), C (**352c**), D (**352d**), E (**352e**), F (**352f**), G (**352g**), H (**353a**), I (**353b**), J (**353c**), K (**354**) and L (**355**), were isolated from the broth of a halotolerant fungus, *Aspergillus variecolor*. Eleven compounds **352–354** exhibited weak radical scavenger activity against DPPH.[126]

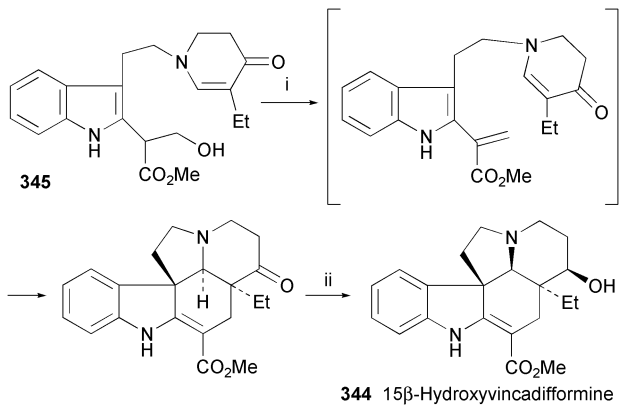
A total synthesis of (−)-neoechinulin A (**356**), isolated from *Aspergillus* sp., has been accomplished, which established the absolute configuration. Treatment of **358** derived from condensation of a diastereomeric mixture of **357** with **360** produced (*Z*)-**359**, and the subsequent thermal cyclization led to **356** with high enantiomeric excess (Scheme 69).[127]

Brominated marine cyclopeptide, barettin (**361**) and 8,9-dihydrobarettin (**362**), isolated from the marine sponge *Geodia barrette*, were identified as selective serotonin receptor ligands.[128]





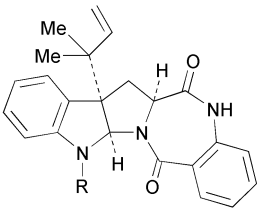
Scheme 65 *Reagents and conditions*: i, 1,1-carbonyldiimidazole, THF, CH_2Cl_2, rt.



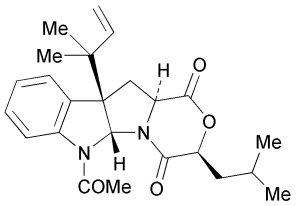
Scheme 66 *Reagents and conditions*: i, TsOH, toluene, reflux; ii, L-selectride, THF, 0 °C.

2.2.2 Physostigmine and related alkaloids. Three new benzodiazepines, *epi*-aszonalenins A (**363a**), B (**363b**) and C (**363c**) were isolated from an unusual chemotype of *Aspergillus novofumigatus*.[129] The organic extract of *Eupenicillium javanicum* IFM 54704 provided two new alkaloid, javanicunines A (**364**) and B (**365**).[130]

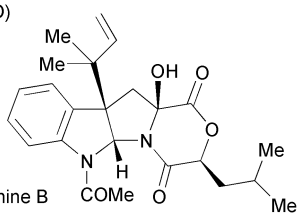
Nine new depsipeptides, kutznerides 1–9 (**366**), were isolated from the actinomycete *Kutzneria* sp. 744. These compounds were tested against several bacterial and fungal human and agricultural pathogens.[131]



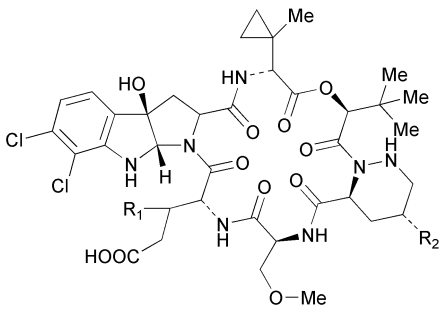
363a *epi*-Aszonalenin A (R = COMe)
363b *epi*-Aszonalenin B (R = CHO)
363c *epi*-Aszonalenin C (R = H)



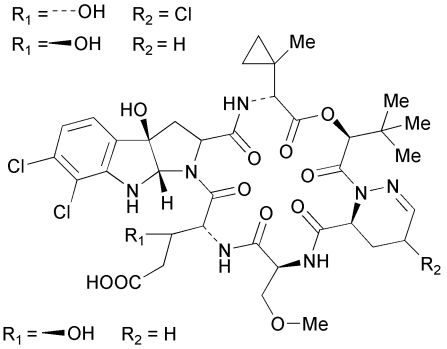
364 Javanicunine A



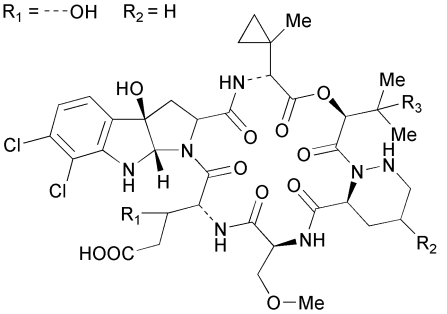
365 Javanicunine B



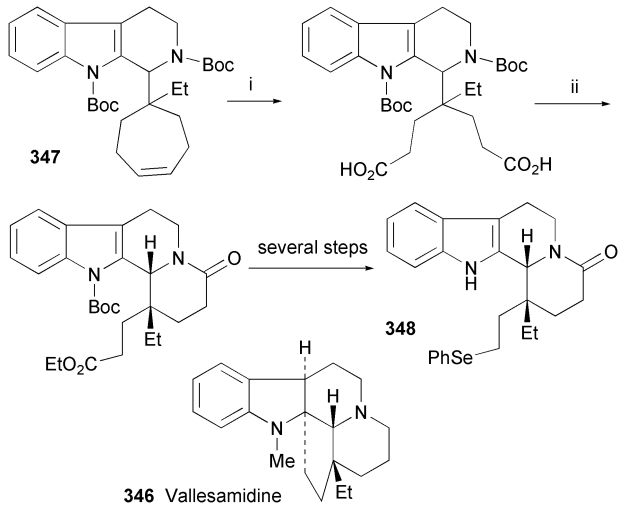
366a Kutzneride 1 R_1 = ---OH R_2 = H
366b Kutzneride 2 R_1 = ---OH R_2 = Cl
366c Kutzneride 3 R_1 = —OH R_2 = H



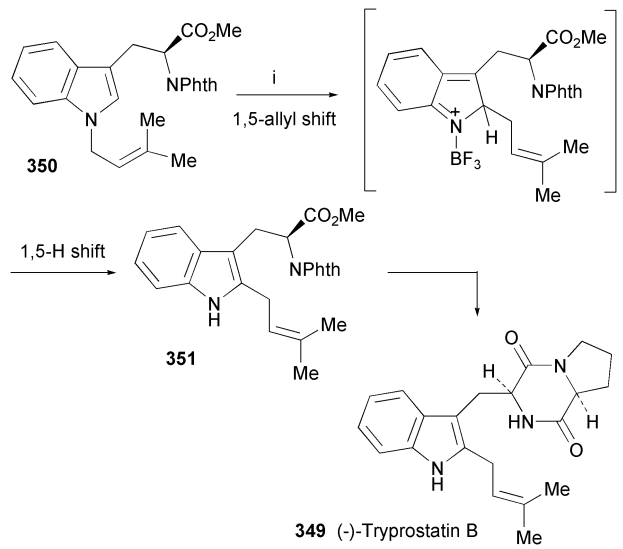
366d Kutzneride 4 R_1 = —OH R_2 = H
366e Kutzneride 6 R_1 = —OH R_2 = OH
366f Kutzneride 9 R_1 = ---OH R_2 = H



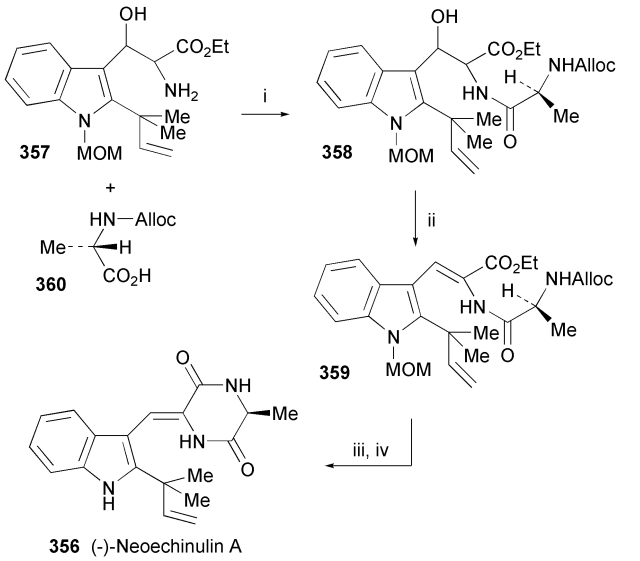
366g Kutzneride 5 R_1 = —OH R_2 = H R_3 = H
366h Kutzneride 7 R_1 = —OH R_2 = OH R_3 = H
366i Kutzneride 8 R_1 = —OH R_2 = H R_3 = Me



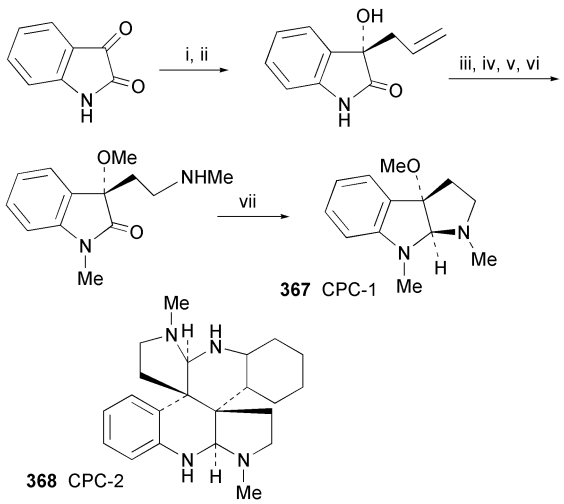
Scheme 67 *Reagents and conditions*: i, $KMnO_4$, *n*-Bu_4NBr, THF, H_2O, 0 °C; ii, TsOH, EtOH, $CHCl_3$, reflux.



Scheme 68 *Reagents and conditions*: i, BF_3OEt_2, CH_2Cl_2, −4 °C.



Scheme 69 *Reagents and conditions*: i, EDC, 1-hydroxy-7-azabenzotriazole, CH_2Cl_2, −15 °C; ii, 1 M HCl, EtOH; iii, $NaBH_4$, $Pd(PPh_3)_4$, THF; iv, toluene, 80 °C.



Scheme 70 *Reagents and conditions*: i, $Sn(CH_2CH{=}CH_2)_4$, $Ti(O\text{-}i\text{-}Pr)_4$, 2-propanol, (*R*)-(+)-binol, 0 °C to rt, 42% ee; ii, recrystallization; iii, MeI, NaH, DMF; iv, OsO_4, NMO, MeCN, H_2O; v, $NaIO_4$, 1,4-dioxane, dioxane, H_2O; vi, $MeNH_2$, $MgSO_4$, MeOH, rt; vii, $LiAlH_4$, THF, 0 °C to rt.

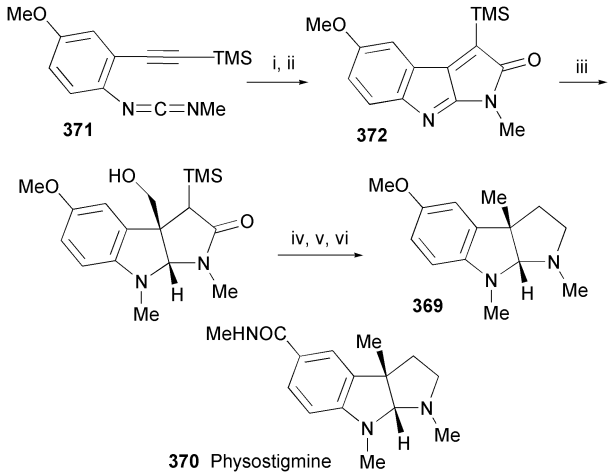
New pyrrolidinoindole alkaloid, CPC-1 (**367**) and tryptamine-derived dimeric alkaloid, CPC-2 (**368**) were isolated from the seeds and rinds of *Chimonanthus praecox* (L.) f. concolor Makino. The absolute configuration of **367** was determined by a chiral total synthesis (Scheme 70).[132]

Synthesis of racemic physostigmine (**370**) has been reported, which involved a one-step construction of pyrrolo[2,3-*b*]indole **372** based on $Co_2(CO)_8$-catalyzed intramolecular hetero-Pauson-Khan reaction of alkynecarbodiimide **371** as the key reaction. Conversion of **372** to racemic esermethole (**369**) was achieved through the conventional procedures, and **370** has been already transformed from **369** in two steps (Scheme 71).[133]

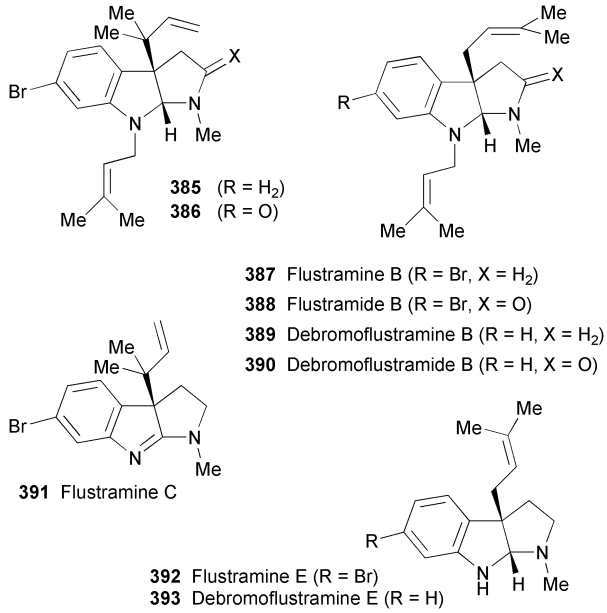
Mo-Catalyzed asymmetric allylation of 3-alkyl oxindole **373** in the presence of ligand **375** was successfully used for the generation of the quaternary stereocenter at the 3 position to afford **374** (Scheme 72). Conversion of **374** *via* oxidation followed by reductive cyclization produced (−)-**369**, which was transformed to (−)-**370**.[134]

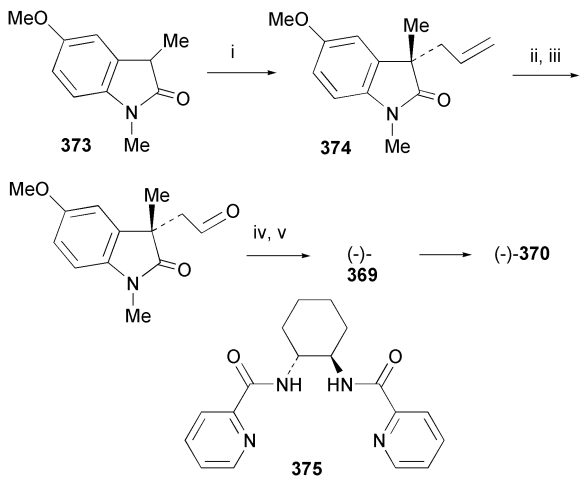
Enantioselective synthesis of (+)-alline (**376**), isolated from *Allium odora*, has been reported, which involved silyl-enolization-asymmetric Claisen rearrangement of 2-allyloxyindolin-3-one **377**, as the key feature, leading to 2-oxyindole (+)-**378** (Scheme 73). The key intermediate **378** was transformed to (+)-**376**, and the absolute configuration was assigned by the synthesis.[135]

A general protocol for the preparation of 3-hydroxyoxindoles by DMD oxidation of indoles and oxindoles has been developed.

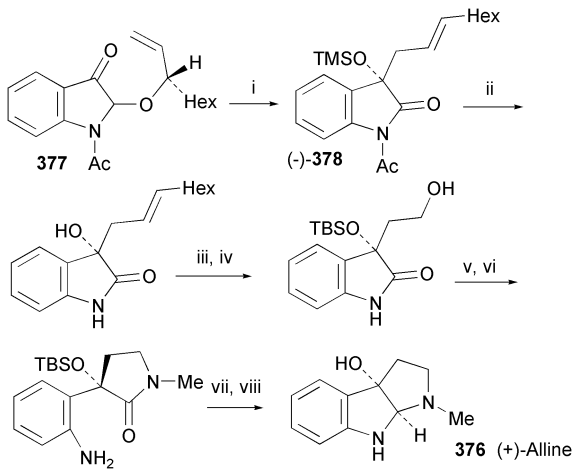


Scheme 71 *Reagents and conditions*: i, CBr_4, PPh_3, Et_3N, CH_2Cl_2, 0 °C to rt; ii, $Co(CO)_8$, TMTU, benzene, CO, 70 °C; iii, $NaBH_3CN$, aq. HCHO, AcOH, MeCN, 0 °C; iv, TBAF, THF; v, I_2, PPh_3, imidazole, $CHCl_3$; vi, $LiAlH_4$, THF.





Scheme 72 *Reagents and conditions*: i, LiO*t*-Bu, $Mo(C_7H_8)(CO)_3$, **375** (15% mol), allyl *t*-butyl carbonate, THF, 4 °C, 82% ee; ii, OsO_4, NMO; iii, $NaIO_4$; iv, $MeNH_2$, Et_3N; v, $LiAlH_4$, THF, reflux.



Scheme 73 *Reagents and conditions*: i, TMSCl, DBU, CH_2Cl_2, −30 °C; ii, 10% LiOH, MeOH, 0 °C; iii, TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, then AcOH, MeOH, reflux; iv, O_3, CH_2Cl_2/MeOH, −78 °C; v, TsCl, pyridine, 0 °C; vi, $MeNH_2$, MeOH, 85 °C, then $NaBH_4$, rt; vii, TBAF, THF, 0 °C; viii, AlH_3-Et_2NH_2, THF, 0 °C.

This strategy was used to construct natural products, **379**, **380** and donaxaridine (**382**). The first synthesis of flustraminol B (**383**), isolated from the bryozoans *Flustra foliacea*, has been achieved from 2,6-dibromoindole **384** as the key compound (Scheme 74).[136]

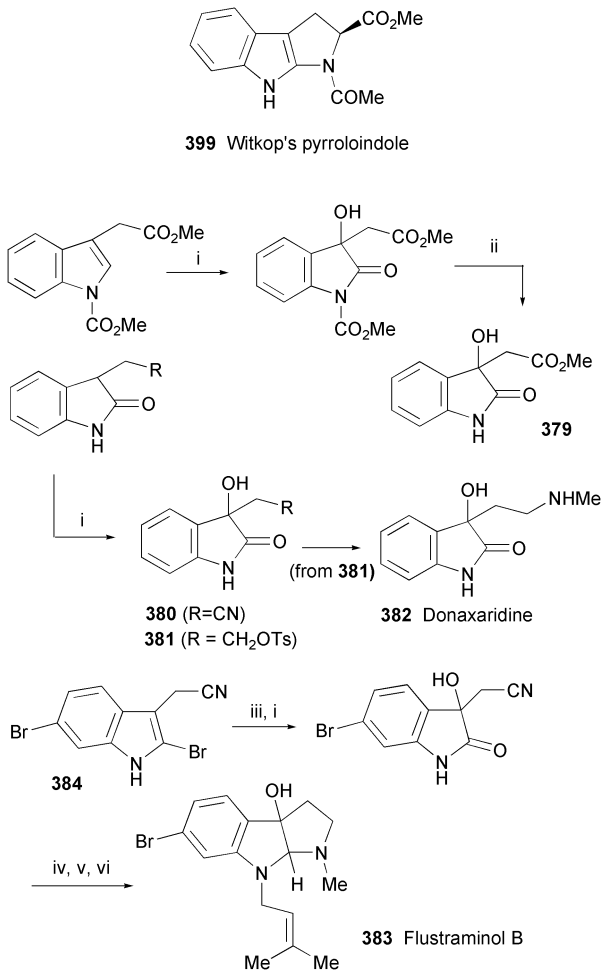
Hexahydropyrroloindole alkaloids, flustramines A (**385**), B (**387**), C (**391**), E (**392**), flustramides A (**386**), B (**388**), debromoflustramine B (**389**), debromoflustramide B (**390**), were isolated from the marine bryozoans *Flustra foliaceae*, exhibiting a broad range of biological activities. Debromoflustramine E (**393**) was obtained from the skin of the Australian frog *Pseudophyrne semimarmorata*, having antibacterial agent active against vancomycin-resistant *Enterococci* and methicillin resistant *Staphylococcus aureus*.

A total synthesis of **389**, **390** and **393** has been accomplished. The key intermediate **395** was concisely obtained from **394** *via* a one-pot intramolecular Ullmann coupling and Claisen rearrangement (Scheme 75).[137]

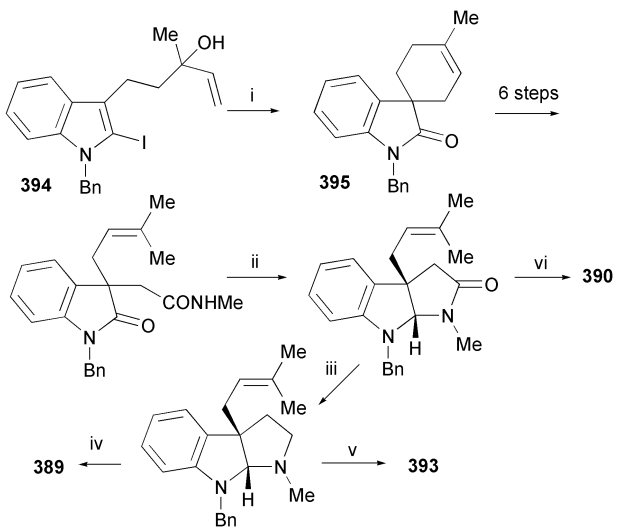
A formal total synthesis of **389** has been achieved through a one-pot procedure involving a new anionic domino process (Scheme 76). Treatment of **396** with ICH_2TMS and Et_3N followed by addition of LHMDS and prenyl bromide produced the known precursor **397** in high yield.[138]

Flustramine C (**391**) was synthesized through a biomimetic oxidation of deformylflustrabromine (**398**) with NBS causing 1,2-rearrangement of the prenyl group as the key step (Scheme 77).[139]

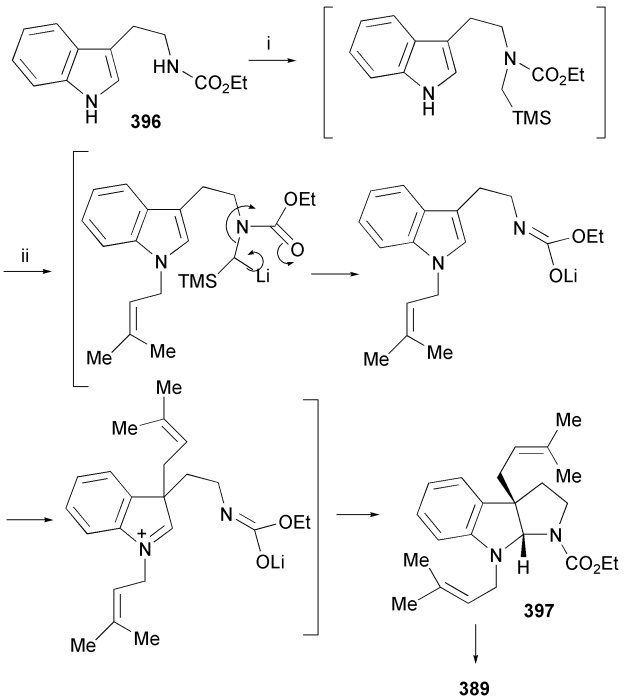
Full details of a synthesis of (−)-**389**, (+)-*ent*-**389** and (+)-*ent*-**390** has appeared, which involved the use of Witkop's pyrroloindole **399** as the key intermediate.[140]



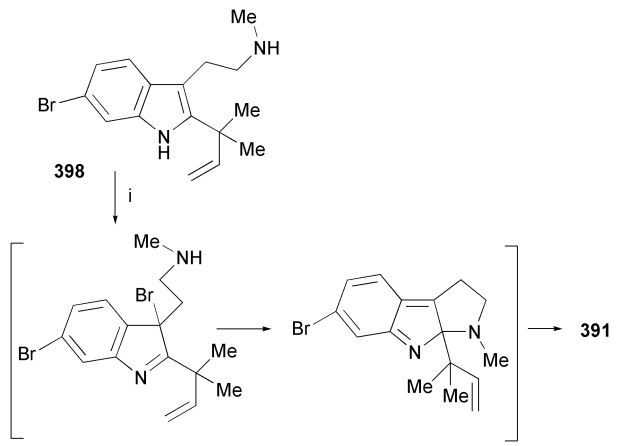
Scheme 74 *Reagents and conditions*: i, DMD, acetone; ii, NaOMe, MeOH, reflux; iii, TFA, CH_2Cl_2; iv, prenyl bromide, K_2CO_3, acetone; v, Red-Al, toluene; vi, HCHO, MeOH, $NaBH_4$.



Scheme 75 *Reagents and conditions*: i, CuCl, 2-aminopyridine, NaOMe/MeOH, diglyme, 130 °C; ii, AlH_3-$EtNMe_2$, THF, −15 °C; iii, AlH_3-$EtNMe_2$, THF, rt; iv, Na, liq. NH_3/THF, −78 °C to rt, then prenyl bromide, −78 °C to rt; v, Na, liq. NH_3/THF, −78 °C, then Ph_2O, −78 °C to rt; vi, prenyl bromide, Na, liq. NH_3/THF, −78 °C, then Ph_2O, −78 °C to rt.



Scheme 76 *Reagents and conditions*: i, ICH_2TMS, Et_3N, CH_2Cl_2, 60 °C; ii, LHMDS (1.5 equiv), prenyl bromide (2.5 equiv), THF, −78 °C to rt, 15 h.

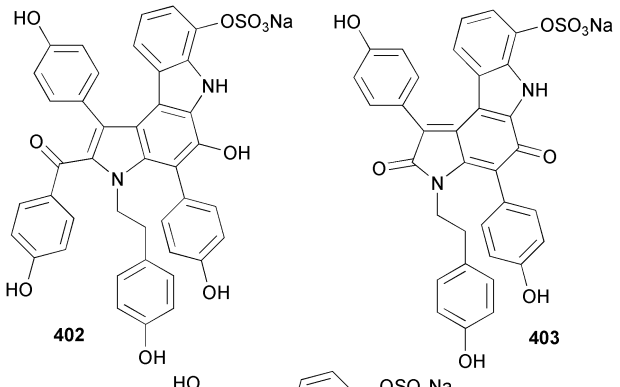


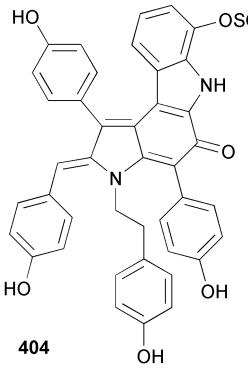
Scheme 77 *Reagents and conditions*: i, NBS, THF, rt.

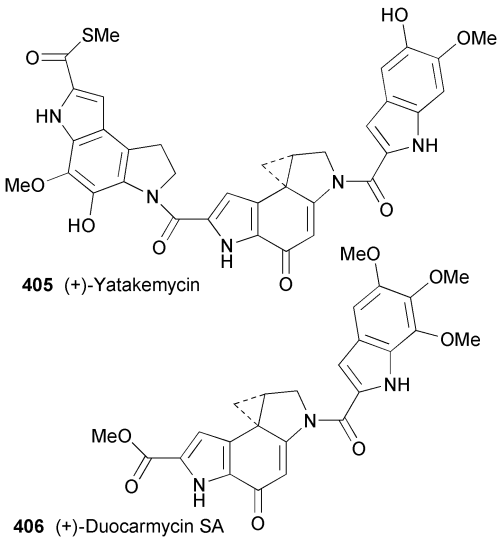
A total synthesis of (−)-**385**, (−)-**387**, (−)-**386** and (−)-**388** has been achieved through domino olefination-isomerization-Claisen rearrangement from **400** leading to **401** with highly enantiomeric excess, followed by reductive cyclization (Scheme 78).[141]

2.2.3 Pyrrolopyrroloindole. Detailed accounts of total syntheses of dictyodendrins B (**402**), C (**403**) and E (**404**), isolated from the sponge *Dictyodendrilla verongiformis* collected off the South Japanese coast, have appeared.[142]

Highly convergent total syntheses of (+)-yatakemycin (**405**) and duocarmycin SA (**406**) have been reported.



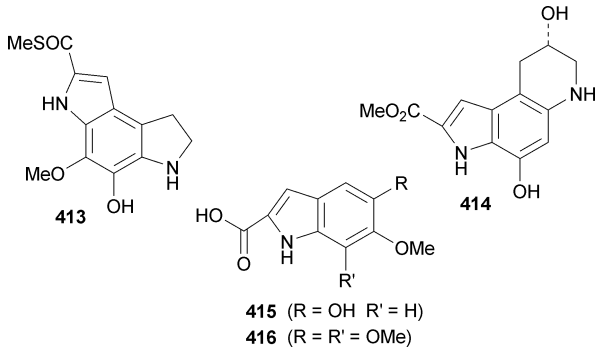




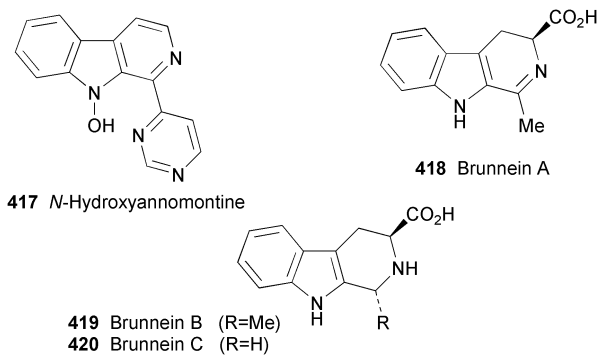
Two highly functionalized segments **409** and **410** were prepared from **407** and **408**, respectively, by the mild copper-mediated aryl amination reaction. After the coupling of **410** with **411**, the subsequent condensation of **412** with **409** brought the synthesis to completion (Scheme 79).[143]

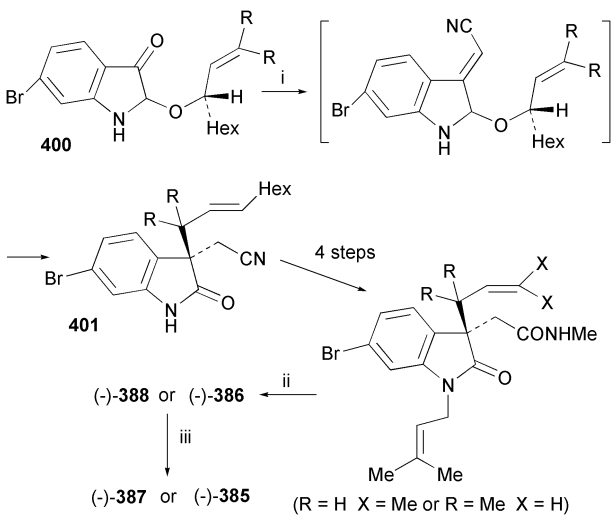
Full details of a second-generation, asymmetric total synthesis of (+)-**405** and (+)-duocarmycin SA (**406**) have been reported by Boger's group, which involved the coupling of three segments **413**, **415** and **415** or **416** as the key features.[144]

2.2.4 β-Carbolines. The bark of *Annona foetida* produced a new pyrimidine-β-carboline alkaloid, *N*-hydroxyannomontine



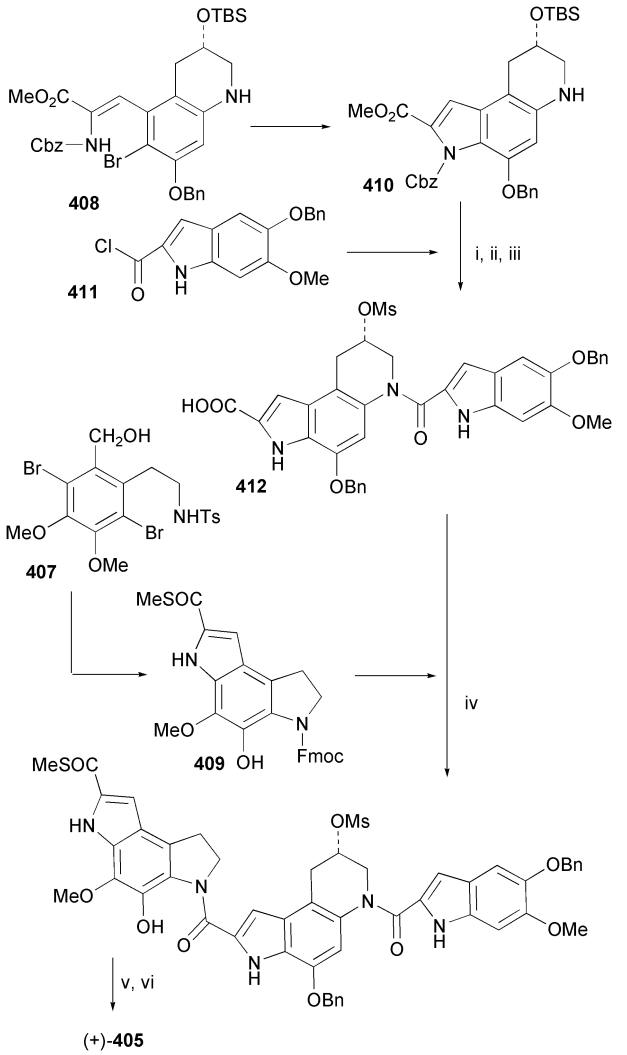
(**417**), exhibiting anti-leishmanial activity.[145] Three new β-carboline alkaloids, brunnein A (**418**), B (**419**) and C (**420**), were isolated from fruiting bodies of the agaricoid fungus *Cortinarius brunneus*.[146]





Scheme 78 *Reagents and conditions*: i, $(EtO)_2P(O)CH_2CN$, *t*-BuOK, DMF, −78 °C to rt; ii, $AlH_3/EtNMe_2$, THF, −15 °C; iii, $AlH_3/EtNMe_2$, THF, rt.

Bauerine A (**421**), B (**422**) and C (**423**), new chloro-containing alkaloids, were isolated from the terrestrial blue-green alga *Dichothrix baueriana*. Bauerine C (**423**), acting against herpes simplex virus type 2, was synthesized through Japp-Klingmann reaction between **424** and **425** (Scheme 80).[147]



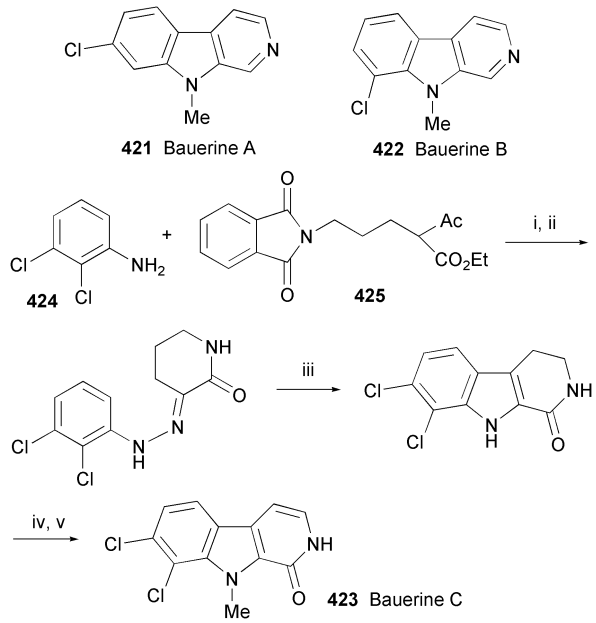
Scheme 79 *Reagents and conditions*: i, pyridine, CH_2Cl_2, 0 °C; ii, TBAF, THF, then MsCl, pyridine, CH_2Cl_2, rt; iii, LiOH, THF/H_2O; iv, TBAF, THF, rt, then WSCDHCl, then HOBt, THF, rt; v, BCl_3, pentamethylbenzene, CH_2Cl_2, −78 °C; vi, $NaHCO_3$, DMF/H_2O, rt.

Nostocarboline (**426**), carbolinium alkaloid, was isolated from the cyanobacterium *Nostoc* 78-12A, and synthesized from norharmane (**427**) in a straightforward manner. Its inhibition of the growth of phytoplanktal organisms and potent anti-fouling activities were reported (Scheme 81).[148]

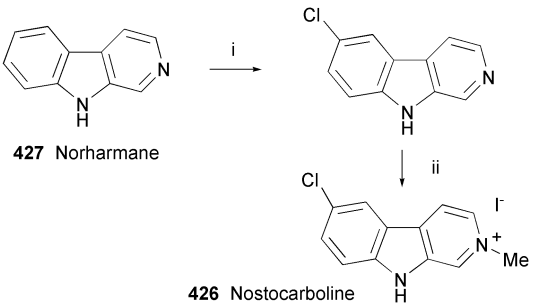
(*S*)-Brevicolline (**428**), isolated from *Carex brevicollins* D. C. (Cyperacee), was derived from (*S*)-nicotine (**429**) in six steps through a regioselective lithiation-halogenation of the pyridine ring, Suzuki coupling and Buchwalt amination reactions (Scheme 82).[149]

The first synthesis of three bromo substituted marine alkaloids, 3-bromofascaplysin (**430**), 10-bromofascaplysin (**431**) and 3,10-dibromofascaplysin (**432**), isolated from the sponge *Fascaplysinopsis reticulata*, was performed by applying previously elaborated method of the synthesis of fascaplysin (Scheme 83).[150]

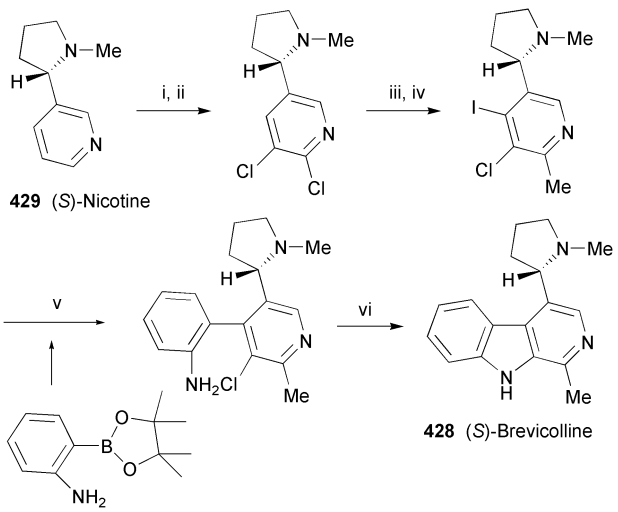
A practical synthesis of rutaecarpine (**433**) and euxylophoricine A (**434**), isolated from the dried fruit of *Evodia rutaecarpa*, has been developed based on an intramolecular aza-displacement



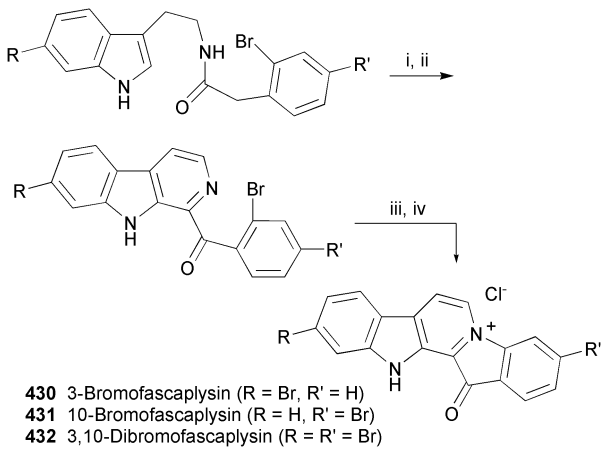
Scheme 80 *Reagents and conditions*: i, NaOAc, EtOH, then $NaNO_2$, HCl; ii, NH_2NH_2, EtOH; iii, HCOOH, toluene; iv, Me_2SO_4, acetone; v, DDQ, dioxane.



Scheme 81 *Reagents and conditions*: i, NaOCl; ii, MeI.



Scheme 82 *Reagents and conditions*: i, *n*-BuLi, $Me_2N(CH_2)_2OLi$, hexane, −20 °C; then C_2Cl_6, −78 °C; ii, LiTHP, THF, −78 °C; iii, trimethylboroxine, $Pd(PPh_3)_4$, K_2CO_3, dioxane, 110 °C; iv, *n*-BuLi, I_2, THF, −78 °C; v, Pd_2dba_3, Xantphos, Cs_2CO_3, dioxane; vi, Pd_2dba_3, PCy_2(*o*-biph), Cs_2CO_3, 110 °C.



Scheme 83 *Reagents and conditions*: i, $POCl_3$, MeCN, reflux; ii, MnO_2, benzene, reflux; iii, 220 °C; iv, HCl (dry), MeOH.

of a methylthio group followed by spontaneous cyclodehydration (Scheme 84).[151]

The first enantioselective total synthesis of (−)-isocyclocapitelline (**435**) and (−)-isochrysotricine (**436**) has been achieved, and the absolute configuration was confirmed. The key step involved homogeneous gold-catalyzed cycloisomerization in allene **437** leading to **438** (Scheme 85).[152]

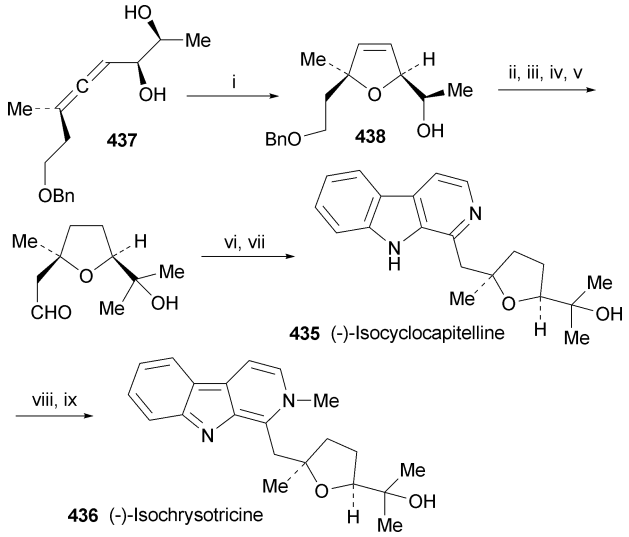
Two asymmetric syntheses of (+)-harmicine (**439**), isolated from the leaf extract of the Malaysian plant *Kopsia griffithii*, were performed by Allin's and Jacobsen's groups.

Allin's strategy involved a diastereoselective *N*-acyliminium cyclization as the key step. Reduction of enantiomerically pure imide **440** resulted in a highly stereoselective cyclization to give **442** *via* iminium **441**. The subsequent removal of the hydroxymethyl auxiliary and the *N*-Boc group produced (+)-**439** (Scheme 86).[153]

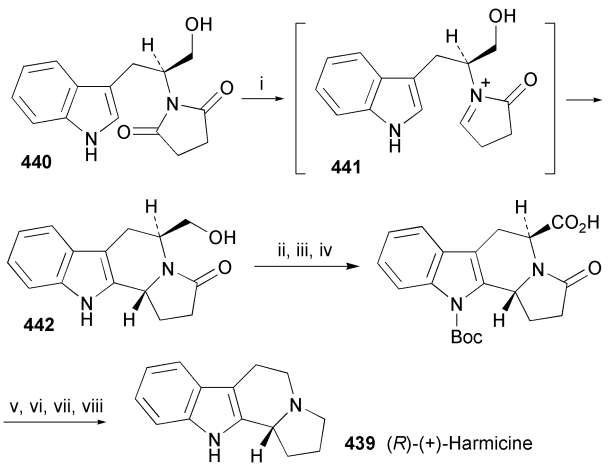
Enantioselective hydroxylactam cyclization promoted by chiral thiourea **443** was applied for the synthesis of (+)-**439** by Jacobsen's group, in which a chiral *N*-acyliminium chloride-thiourea complex **444** was supposed to be involved as the key step (Scheme 87).[154]

Racemic **439** was derived from 4,4-diethoxybutan-1-amide (**445**) through an acid-mediated acyl iminium ion cyclization in two steps (Scheme 88).[155]

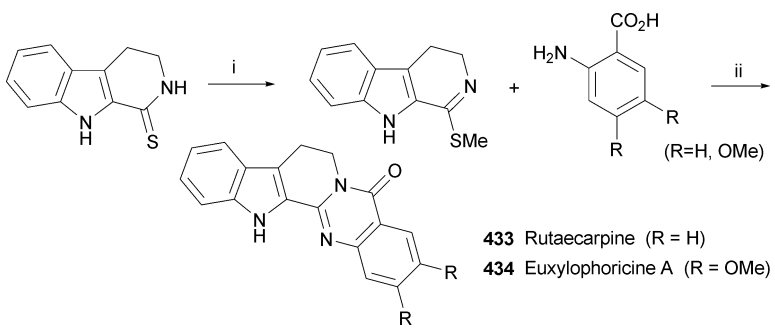
Three new manzamine-type alkaloids, 12,28-oxamanzamine E (**446**), 12,34-oxa-6-hydroxymanzamine E (**447**) and 8-hydroxymanzamine B (**448**) together with 13 known manzamine



Scheme 85 *Reagents and conditions*: i, $AuCl_3$, THF; ii, Dess–Martin reagent; iii, MeMgCl; iv, Pd/C, H_2; v; Dess–Martin reagent, DMSO; vi, tryptamine, TFA; vii, Pd/C, xylene, reflux; viii, MeI, acetone, reflux; ix, aq. NaOH.

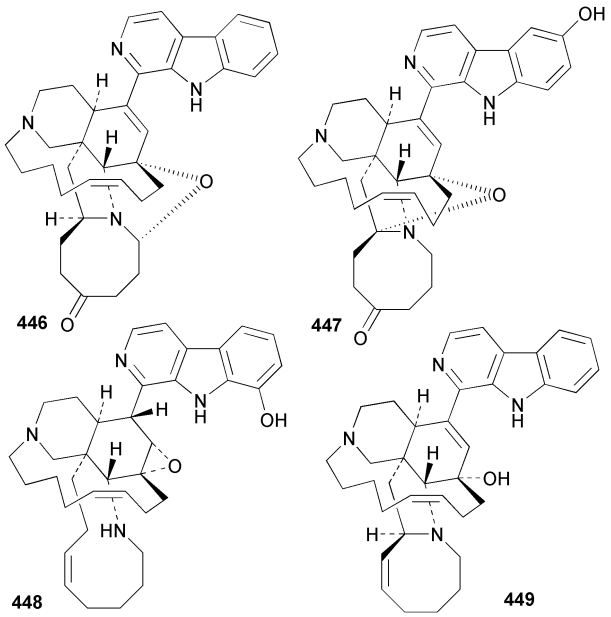


Scheme 86 *Reagents and conditions*: i, $NaBH_4$, EtOH, 2 M HCl; ii, IBX, DMSO, rt; iii, Et_3N, DMAP, Boc_2O, THF, rt; iv, $NaClO_2$, NaH_2PO_4, MeCN, *t*-BuOH, Cyclohexene, 0 °C to rt; v, $(PhSe)_2$, PBu_3, CH_2Cl_2, 0 °C to rt; vi, *n*-Bu_3SnH, AIBN, toluene, reflux; vii, TBAF, THF, reflux, 2 h, then to rt; viii, $LiAlH_4$, THF, reflux.

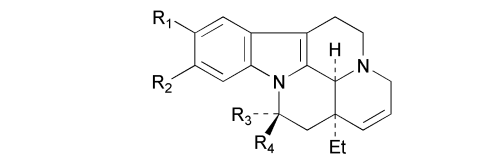


Scheme 84 *Reagents and conditions*: i, MeI, EtOH, aq. NaOH, rt; ii, AcOH, reflux.

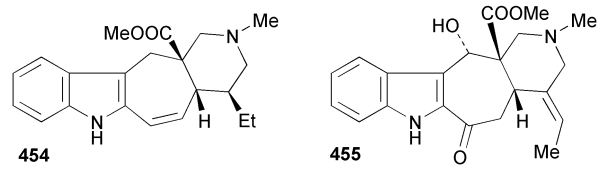
alkaloids, were isolated from an Indonesian sponge of the genus *Acanthostrongylophora* sp., and the bioactivity and SRA for these compounds against malaria, leishmania, tuberculosis and HIV were reported.[156] Manzamine A (**449**) represents an important lead structure for the development of antimalarial,[157] GSK-3 inhibitory,[158] antibacterial[159] and antiprotozoal[159] properties. Synthesis and biological evaluation of analogues of **449** were reported.



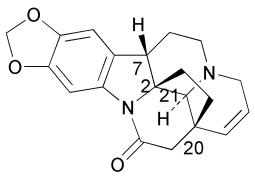
Three species, *Ervatamia officinalis*, *Ervatamia divaricata* and *Ervatamia divaricata* Gouyahua, produced six new indole alkaloids, 14,15-didehydro-10,11-dimethoxy-16-epivincamine (**450**), 14,15-didehydro-10-hydroxy-11-methoxy-16-epivincamine (**451**), 14,15-didehydro-10,11-dimethoxyvincamine (**452**), 14,15-didehydro-10-hydroxy-11-methoxyvincamine (**453**), 19,20,-didehydro-6α-hydroxyervatamine (**455**), and dehydroxyervatamine (**454**) along with 36 known indole alkaloids. The *in vitro* cytotoxic activities of these compounds against the tumor cell line P-388 murine leukemia and A-549 human lung carcinoma were evaluated.[160]



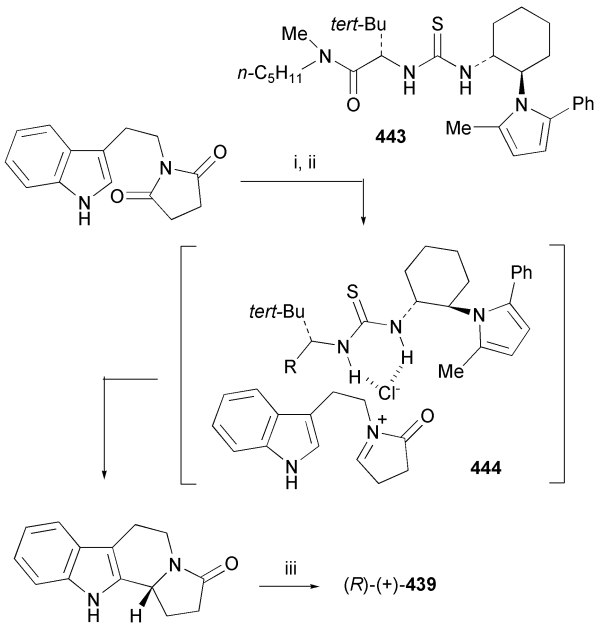
450 (R_1 = R_2 = OMe R_3 = OH R_4 = COOMe)
451 (R_1 = R_3 = OH R_2 = OMe R_4 = COOMe)
452 (R_1 = R_2 = OMe R_3 = COOMe R_4 = OH)
453 (R_1 = OH R_2 = OMe R_3 = COOMe R_4 =OH)



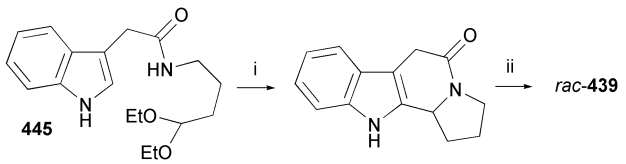
The absolute configuration of naturally occurring (+)-schizozygine (**456**) was determined to be (2*R*,7*S*,20*S*,21*S*) by the first concerted use of density functional theory (DFT) calculations of vibrational dichroism (VCD), electronic circular dichroism (ECD) and transparent spectral region optical rotation (OR).[161]



456 (+)-Schizozygine



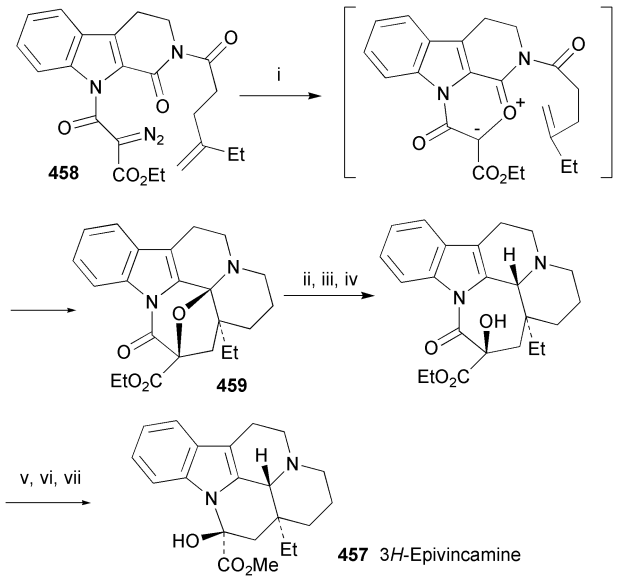
Scheme 87 *Reagents and conditions*: i, $NaBH_4$, MeOH, 0 °C; ii, **443** (10% mol), TMSCl, TBME, −55 °C, 48 h; iii, $LiAlH_4$, THF, rt.



Scheme 88 *Reagents and conditions*: i, BF_3OEt_2, CH_2Cl_2, rt; ii, AlH_3, THF.

Vinca alkaloid, 3*H*-epivincamine (**457**), was synthesized through Rh(II)-catalyzed intramolecular [3 + 2]-cycloaddition of α-diazoindolo amide **458** as the key step producing **459**, followed by reductive ring opening, decarboethoxylation and base-induced keto-amide ring contraction (Scheme 89).[162]

The first synthesis of vincapusine (**461**), isolated from *Voacanga africana.*, was performed in three steps from vincamine



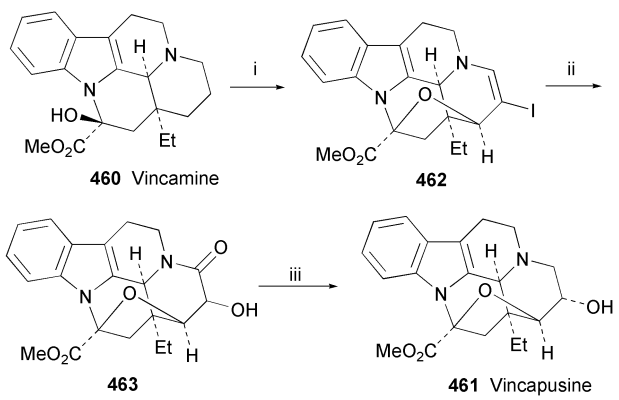
Scheme 89 *Reagents and conditions*: i, $Rh_2(OAc)_4$, benzene, reflux; ii, Lawesson's reagent; iii, Raney-Ni; iv, Zn/AcOH; v, MgI_2, MeCN, reflux; vi, Dess–Martin reagent; vii, Na_2CO_3, MeOH.

(**460**), involving β-iodo-enamine **462** formation, hydroxyl lactam **463** formation and selective reduction sequences (Scheme 90).[163]

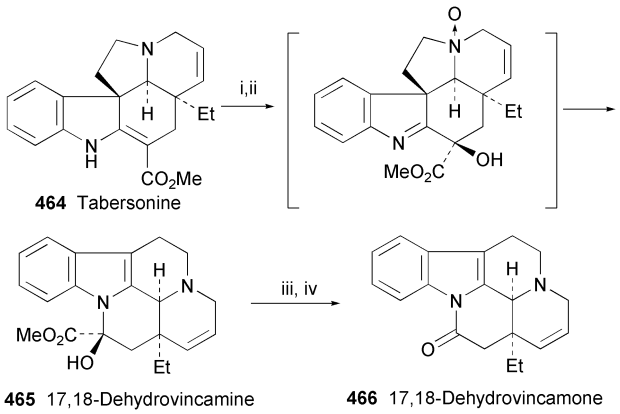
Tabersonine (**464**) was transformed to 17,18-dehydrovincamine (**465**) by a one-pot oxidative ring conversion with permaleic acid in methanol. Hydroboration-oxidation of **465** produced 17,18-dehydrovincamone (**466**) (Scheme 91).[164]

The first total synthesis of racemic subincanadine F (**467**), isolated from the bark of the Brazilian medicinal plant *Aspidosperma subincanum* Mart., was performed from N_a-(*p*-methoxybenzyl)tryptamine in six steps. The key steps were a SmI_2-mediated ring opening of **468**, followed by an acid-mediated Mannich reaction in **469** (Scheme 92).[165]

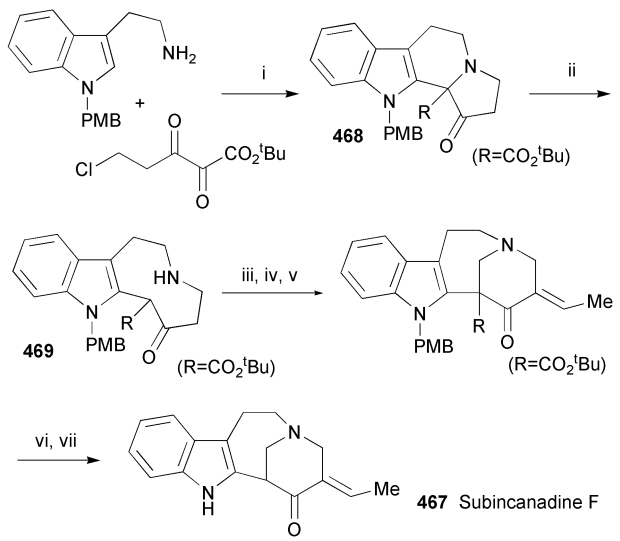
The first asymmetric synthesis of (−)-subincanadines A (**470**) and B (**471**) was performed. The key steps consisted of intramolecular diastereoselective Pictet–Spengler cyclization of tryptamine with ketone **472** followed by intramolecular Nozaki-Hiyama-Kishi reaction of **473** (Scheme 93).[166]



Scheme 90 *Reagents and conditions*: i, I_2, $CHCl_3$, sat. aq. $NaHCO_3$, rt; ii, $CuSO_4$, DMF, H_2O; iii, BH_3SMe_2, THF, rt.

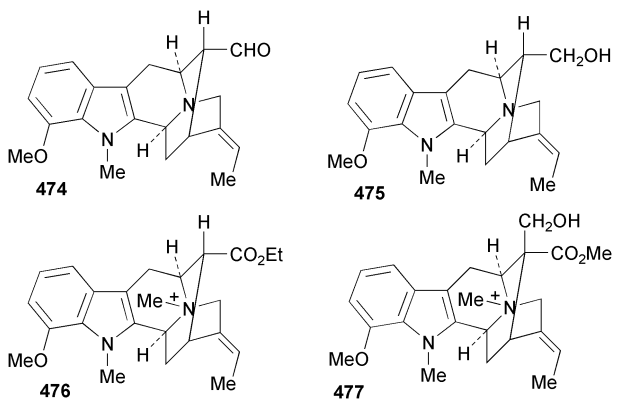


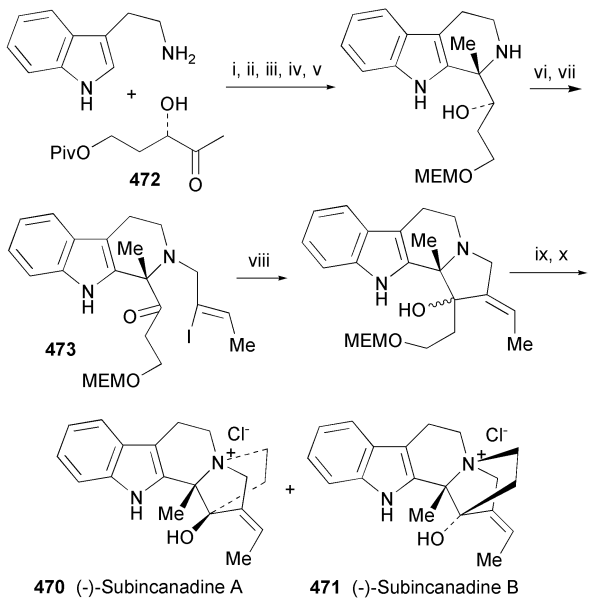
Scheme 91 *Reagents and conditions*: i, permaleic acid, MeOH, 5 °C; ii, *t*-BuOK, MeOH, reflux; iii, $NaBH_4$, BF_3OEt_2, THF, 0 °C; iv, NaOH, H_2O_2, 60 °C.



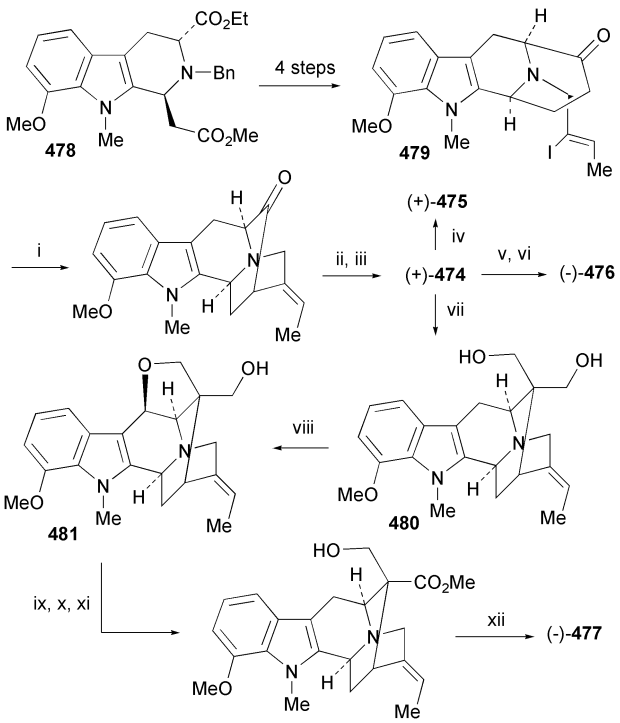
Scheme 92 *Reagents and conditions*: i, MeCN, rt; ii, Sm, I_2, THF, rt; iii, HCl, HCHO, EtOH, rt; iv, LDA, MeCHO, THF, −78 °C; v, TFAA, DBU; vi, $AlCl_3$; vii, HCl, reflux.

Sarpagine alkaloids, (+)-12-methoxy-N_a-methylvellosimine (**474**), (+)-12-methoxy-affisine (**475**), (−)-fuchsiaefoline (**476**) and (−)-12-methoxy-N_b-methylvoachalotine (**477**) have been isolated from *Rauwolfia* sp., and biogenetically related to ajmaline alkaloids.





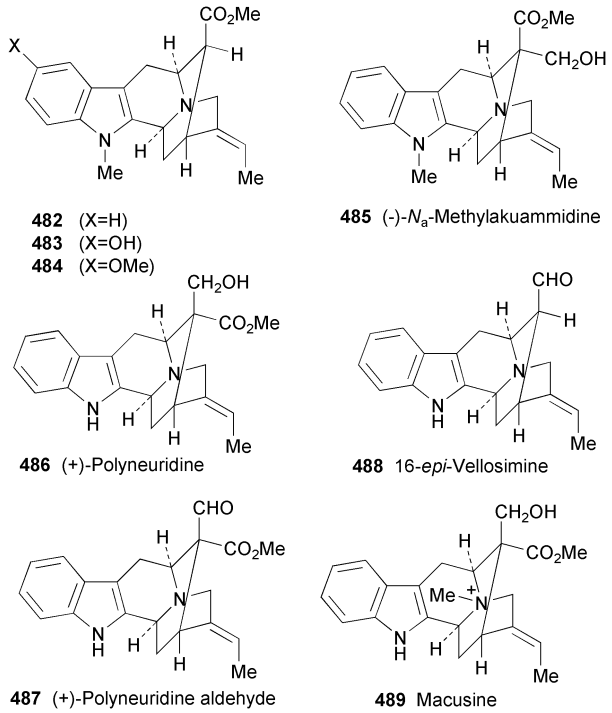
Scheme 93 *Reagents and conditions*: i, 1,1′-carbonyldiimidazole, CH_2Cl_2, rt; ii, TMSCl, CH_2Cl_2, −78 °C; iii, NaOMe, MeOH, rt; iv, MEMCl, *i*-Pr_2NEt, CH_2Cl_2, rt; v, 8 N KOH, DMSO, MeOH, reflux; vi, (2*Z*)-1-bromo-2-iodobut-2-ene, Cs_2CO_3, MeCN, reflux; vii, IBX, AcOEt, reflux; viii, $NiCl_2$, $CrCl_2$, DMSO, rt; ix, TMSCl, NaI, MeCN, −30 °C; x, MsCl, aq. $NaHCO_3$, CH_2Cl_2, rt.



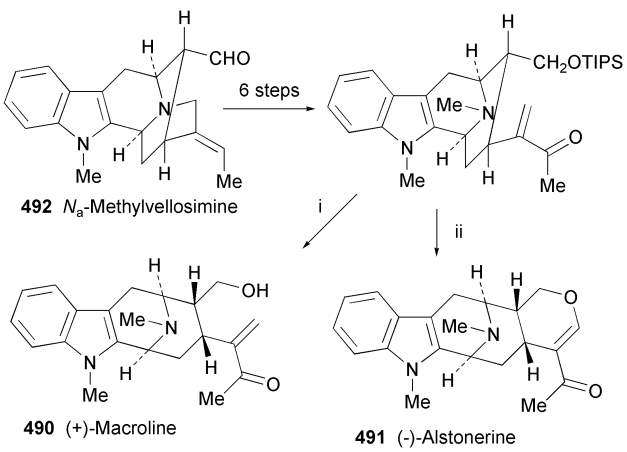
Scheme 94 *Reagents and conditions*: i, $Pd(OAc)_2$, PPh_3, *n*-Bu_4NBr, K_2CO_3, DMF, H_2O, 65 °C, ii, $[MeOCH_2PPh_3]^+Cl^-$, KO*t*-Bu, benzene, rt, iii, 2 N HCl, THF; iv, $NaBH_4$, EtOH; v, KOH, I_2, EtOH; vi, MeI, THF, then AgCl, EtOH; vii, HCHO, KOH, MeOH; viii, DDQ, THF, reflux; ix, $(PhSeO)_2O$, chlorobenzene, 115 °C; x, KOH, I_2, MeOH; xi, TFA, Et_3SiH, CH_2Cl_2, rt; xii, MeI, THF, then AgCl, MeOH, rt.

The first region- and stereospecific total syntheses of (+)-**474**, (+)-**475**, (−)-**476** and (−)-**477** have been completed (Scheme 94).[167] Enolate-driven palladium-catalyzed cross-coupling of **479**, derived from β-carboline **478**, served as the key step. The two prochiral primary alcohols in **480** were differentiated by the oxidative cyclization with DDQ to form **481**.

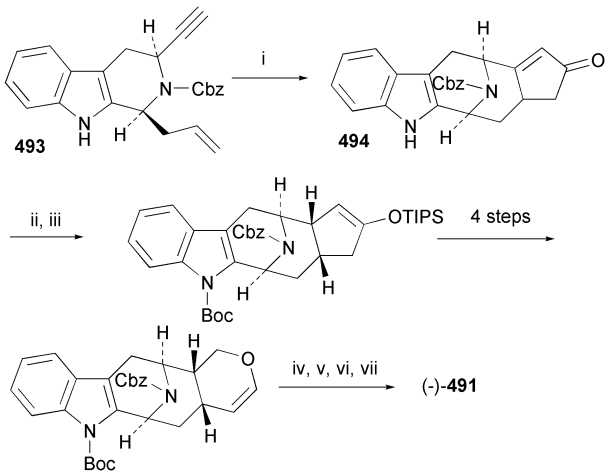
The same strategy was developed for enantiospecific total syntheses of (+)-N_a-methylpericyclivine (**482**), 10-hydroxy-N_a-methylpericyclivine (**483**), (+)-10-methoxy-$N_a$methylpericyclivine (**484**), (−)-N_a-methylakuammidine (**485**), (+)-polyneuridine (**486**), (+)-polyneudine aldehyde (**487**), 16-*epi*-vellosimine (**488**), and macusine A (**489**).[168]



Macroline/sarpagine class of alkaloid, (+)-macroline (**490**) and (−)-alstonerine (**491**), were synthesized from N_a-methylvellosimine (**492**) (Scheme 95).[169]



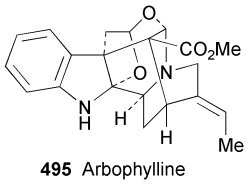
Scheme 95 *Reagents and conditions*: i, TBAF, THF; ii, Na_2PdCl_4, *t*-BuOOH, AcOH, then H_2O, *t*-BuOH, 80 °C.



Scheme 96 *Reagents and conditions*: i, $Co(CO)_8$, DMSO, THF, 65 °C; ii, Boc_2O, DMAP, MeCN; iii, Karstedt's catalyst, *i*-Pr_3SiH, toluene, 80 °C; iv, Cl_3CCOCl, pyridine; v, Zn, AcOH; vi, TMSI, MeCN; vii, NaH, THF, then MeI, NaH.

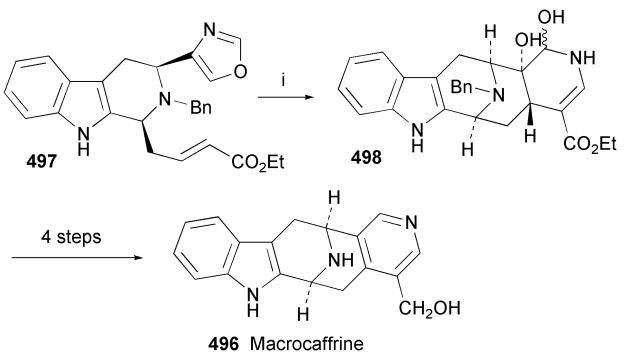
Enantioselective total synthesis of (−)-**491** has been completed using Pauson–Khand reaction of **493** as the key step to assemble azabridged bicycle **494** (Scheme 96).[170]

A new indole alkaloid, arbophylline (**495**), possessing an unprecedented heptacyclic system and incorporating an acetal unit, was isolated from the stem-bark extract of *Kopsia arborea*, and the structure was established by spectroscopic analysis.[171]

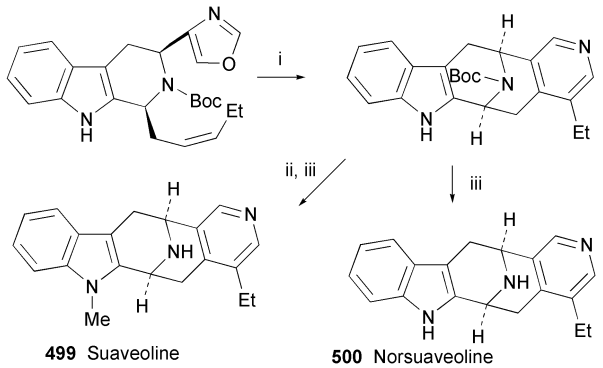


A full account of the total synthesis of macrocaffrine (**496**) was presented, in which the key step was an intramolecular cycloaddition of the oxazole-olefin in **497** giving **498**. However, its spectral data and specific rotation were not in agreement with those of natural product (Scheme 97).[172]

Furthermore, the strategy has been developed for a synthesis of suaveoline (**499**) and norsuaveoline (**500**) (Scheme 98).[173]



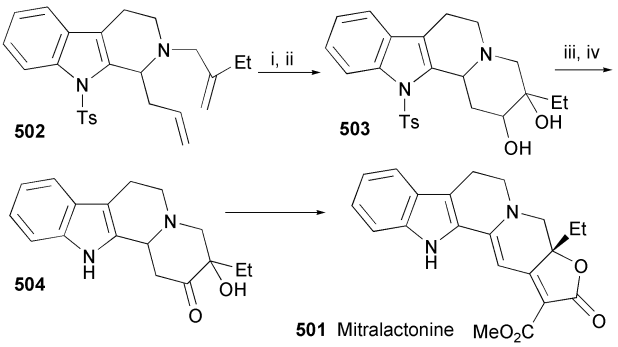
Scheme 97 *Reagents and conditions*: i, THF/H_2O, reflux.



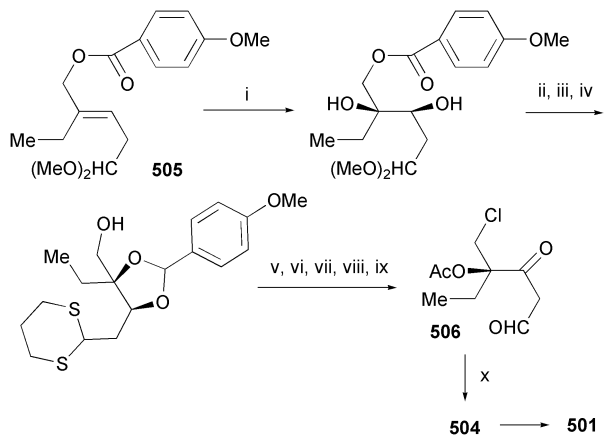
Scheme 98 *Reagents and conditions*: i, DBN, xylene, reflux; ii, MeI, NaH, DMF; iii, TFA, CH_2Cl_2, 0 °C.

A formal synthesis of mitralactonine (**501**), isolated from the young leaves of *M. speciosa*, has been reported, in which ring-closing metathesis was performed on **502** to assemble tetracycle **503** as the key step (Scheme 99).[174] Tetracycle **503** was easily converted to the known precursor **504**.

A practical approach to (−)-**501** was reported (Scheme 100).[175] Chiral aldehyde **506** was obtained by Sharpless asymmetric



Scheme 99 *Reagents and conditions*: i, Grubbs' catalyst, toluene, 80 °C; ii, OsO_4, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH, H_2O, rt; iii, oxalyl chloride, DMSO, CH_2Cl_2, Et_3N, −60 °C; iv, TBAF, THF, reflux.

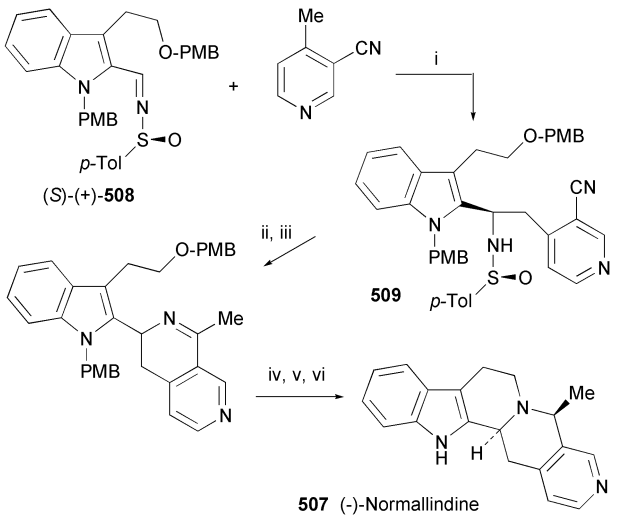


Scheme 100 *Reagents and conditions*: i, $(DHQ)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH, H_2O, 0 °C; ii, $HS(CH_2)_3SH$, BF_3OEt_2, CH_2Cl_2, rt; iii, *p*-anisaldehyde dimethylacetal, PTSA, CH_2Cl_2, rt; iv, K_2CO_3, MeOH, rt; v, Ph_3P, CCl_4, imidazole, reflux; vi, PTSA, MeOH, rt; vii, DMP, CH_2Cl_2, rt; viii, Ac_2O, DMAP, rt; ix, MeI, $MeCN/H_2O$, reflux.

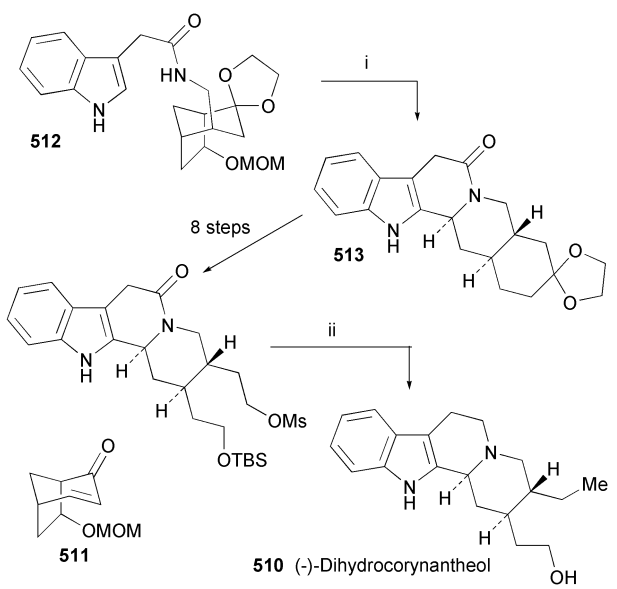
dihydroxylation on olefin **505** as the key step. Pictet–Spengler reaction of **506** with tryptamine afforded the known precursor **504** as a mixture of diastereomers.

Asymmetric total synthesis of (−)-normallindine (**507**), isolated from the root bark of *Strychnos johnsonii* has been developed through the addition of laterally metalated 4-methyl-3-cyanopyridine to enantiopure sulfimine **508** leading to **509** in better than 80% ee (Scheme 101).[176]

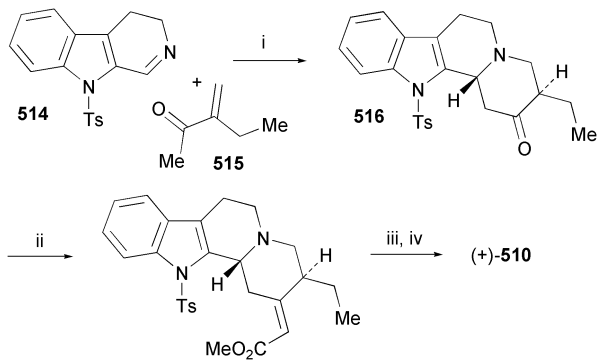
The diastereocontrolled total synthesis of (−)-dihydrocorynantheol (**510**) has been achieved (Scheme 102). Amide **512**, prepared from chiral building block **511**, was subjected to



Scheme 101 *Reagents and conditions*: i, NaHMDS, THF, −78 °C; ii, MeLi, Et_2O, −18 °C; iii, HCl; iv, $NaBH_4$, MeOH; v, TFA, anisole; vi, MsCl, DMAP, *i*-Pr_2NEt, CH_2Cl_2/THF.



Scheme 102 *Reagents and conditions*: i, $MeSO_3H$, $(CH_2OH)_2$, dioxane, reflux; ii, $LiAlH_4$, dioxane, reflux.



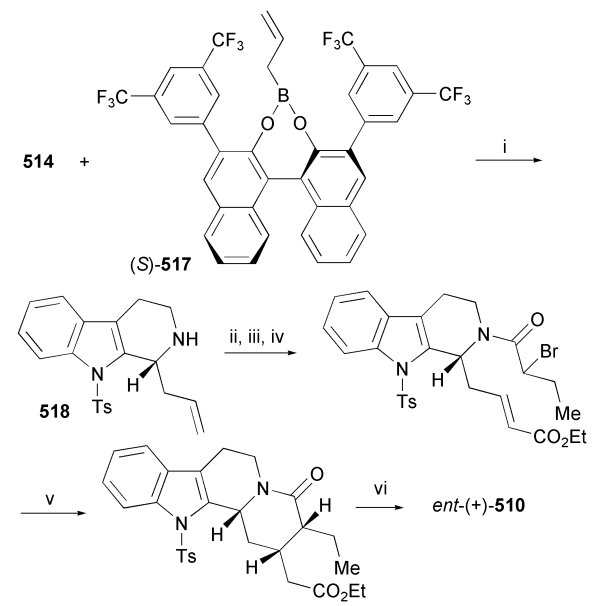
Scheme 103 *Reagents and conditions*: i, (*S*)-proline (50 mol%), DMSO, rt, 96% ee; ii, methyl (dimethoxyphosphoryl)acetate, NaH, THF; iii, Red-Al, toluene, reflux; iv, Pd/C, H_2, MeOH, rt.

a tandem Pictet–Spengler reaction/C-3 epimerization to give **513** as the key step.[177]

Total synthesis of *ent*-(+)-**510** was performed through proline-catalyzed asymmetric reaction of **514** with **515** (30 equiv) in the presence of (*S*)-proline (30 mol%) in DMSO, producing **516** with 99% ee (Scheme 103).[178]

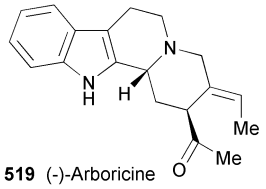
The enantioselective allylboration of cyclic imine **514** with (*S*)-allylboronate **517** gave allylation product **518** with 99% ee, which was in turn converted to (+)-**510** (Scheme 104).[179]

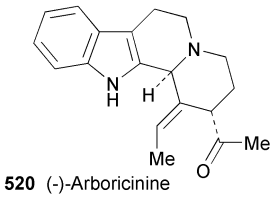
New deplancheine-type indole alkaloids, arboricine (**519**) and arboricinine (**520**), were isolated from the leaf extract of *Kopsia arborea*, and the structures were elucidated by spectroscopic analysis.[180] From the root of *Rauvolfia yunnanensis*, three new indole alkaloids, (16*S*,19*E*)-N^1-(hydroxylmethyl)isositsirikine (**521**), 5β-17-*O*-deacetyl-5,11-dimethoxyakuammilline (**522**) and

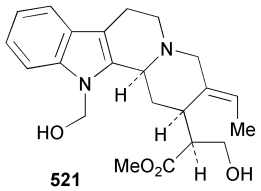


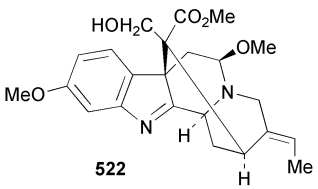
Scheme 104 *Reagents and conditions*: i, toluene, −78 °C, 99% ee; ii, DCC, HOOCCH(Br)Et, CH_2Cl_2; iii, OsO_4, $NaIO_4$, 2,6-lutidine, dioxane, H_2O; iv, $Ph_3P{=}CHCOOEt$, CH_2Cl_2; v, *n*-BuLi, THF; vi, $LiAlH_4$, THF.

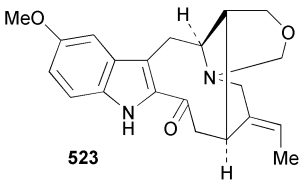
10-methoxy-16-de(methoxycarbonyl)pagicerine (**523**) were isolated.[181]







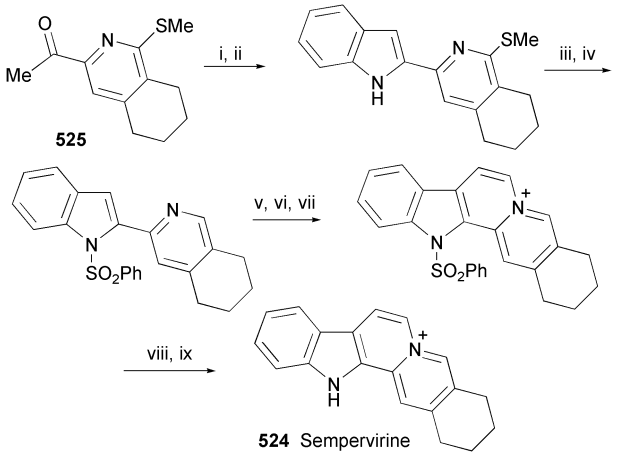




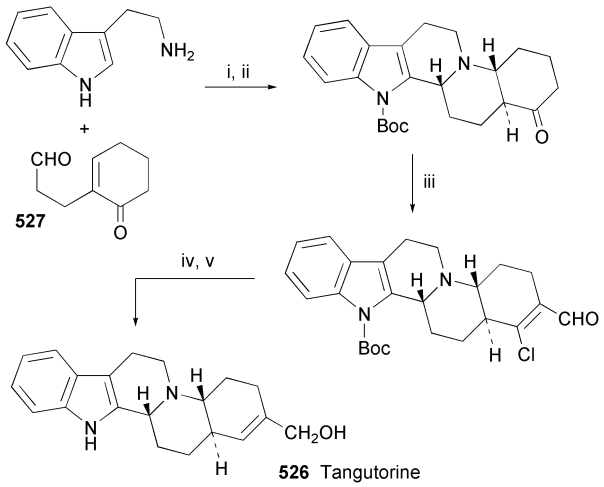
A new indoloquinolizine alkaloid, sempervirine (**524**), isolated from the rhizome and roots of *Gelsemium sempervirens*, has been concisely elaborated from 3-acetyl-1-methylthiocyclohexapyridine (**525**). Sempervirine (**524**) was known as cardiac species, but recently its anticancer, immunostimulative and anti-HIV, sedative and anti-psychotic activities have been shown (Scheme 105).[182]

Benz[*f*]indolo[2,3-*a*]quinolizidine, tangutorine (**526**) isolated from the leaves of the Chinese medicinal plant *Nitraria tangutorum* L., has been assembled from tryptamine and aldehyde **527** in 5 steps (Scheme 106).[183]

A formal synthesis of racemic alloyohimbane (**528**) has been reported. The key step was [3 + 3] annulations between



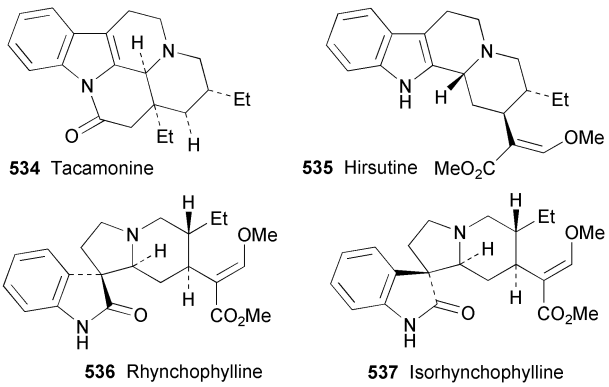
Scheme 105 *Reagents and conditions*: i, $PhNHNH_2$, EtOH, AcOH; ii, $ZnCl_2$, TEG, microwave, 190 °C; iii, Raney-Ni, EtOH; iv, $PhSO_2Cl$, NaH, THF, 0 °C; v, *n*-BuLi, THF, −75 °C; vi, $BrCH_2CHO$, then aq. NH_4Cl; vii, $CHCl_3$, reflux; viii, aq. 20% NaOH, MeOH, reflux; ix, aq. 20% NaOH, $CHCl_3$.



Scheme 106 *Reagents and conditions*: i, TFA, CH_2Cl_2, rt; ii, Boc_2O, DMAP, CH_2Cl_2; iii, $POCl_3$, DMF, $CHCl_3$, rt; iv, $NaBH_4$, EtOH; v, Na/naphthalenide, THF, 0 °C.

α-sulfonyl acetamide **529** and **530** leading to glutarimide **531**. Regioselective reduction of **531** followed by reduction gave the known precursor **533** (Scheme 107).[184]

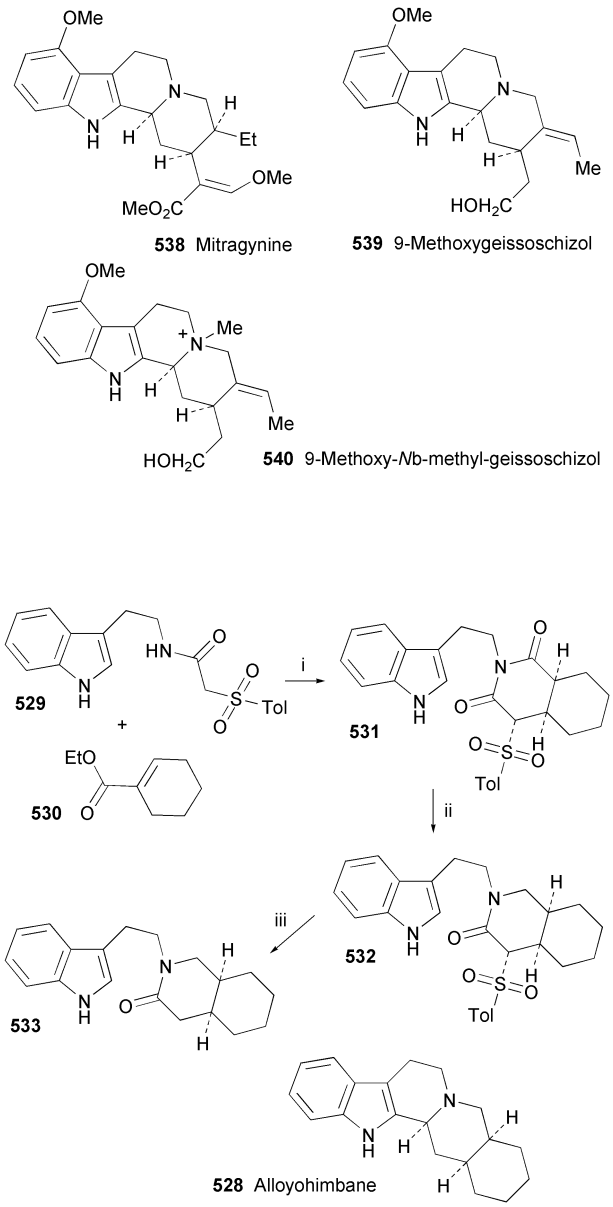
Full accounts of general strategy for the syntheses of dihydrocorynantheol (**510**), tacamonine (**534**), hirsutine (**535**), rhynchophylline (**536**) and isorhynchophylline (**537**) have been reported.[185]



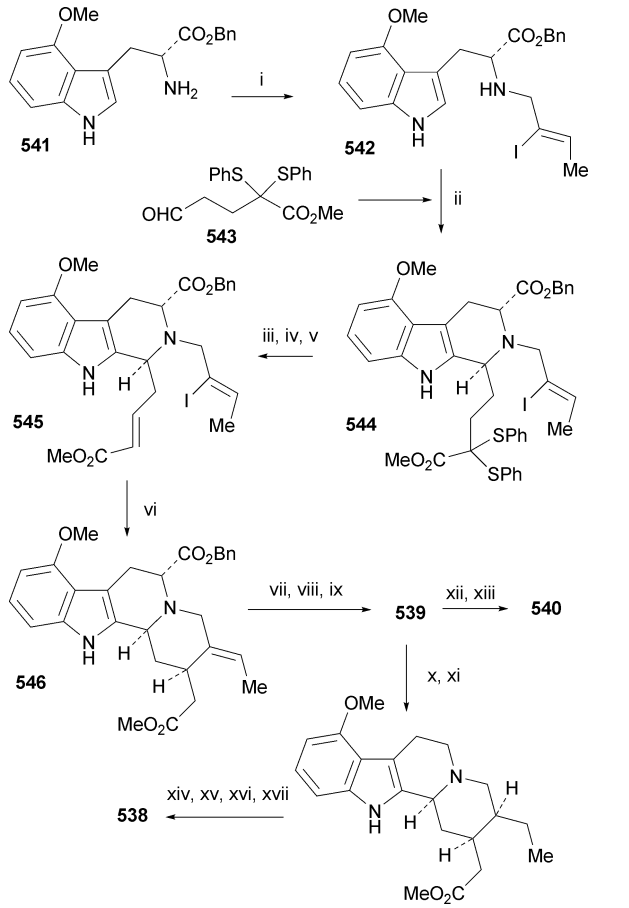
Mitragynine (**538**) was isolated from *Mitragyna speciosa* Korth and acts as a full opioid agonist on μ- and δ-opioid receptors. 9-Methoxygeissoschizol (**539**) and 9-methoxy-N_b-methylgeissoschizol (**540**) were isolated from the bark of *Strychnos guianesis*.

Total syntheses of **538–540** have been achieved from 4-methoxy-D-tryptophan (**541**) prepared on a large scale *via* Larock heteroannulation. The asymmetric Pictet–Spengler reaction between **542** and aldehyde **543** producing **544**, and $Ni(COD)_2$-mediated cyclization on **545** leading to **546** served as key steps to set up the stereochemistry (Scheme 108).[186]

Asymmetric synthesis of (+)-12*b*-epidevinylantirhine (**547**) has been developed using ketone **550** as key building block.[187] Tetracycle **549** was obtained from **548** *via* stereoselective cyclization



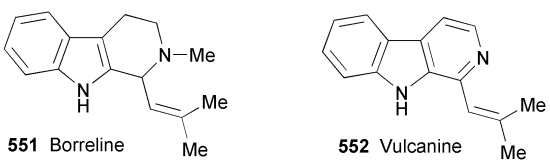
Scheme 107 *Reagents and conditions*: i, Et_3N, THF; ii, $LiAlH_4$, THF, reflux; iii, Na/Hg, MeOH.



Scheme 108 *Reagents and conditions*: i, (*Z*)-1-bromo-2-iodo-2-butene, Cs_2CO_3, THF, DMF, rt; ii, AcOH, CH_2Cl_2, then TFA, CH_2Cl_2; iii, PhSH, NaH, DME; iv, *m*-CPBA, CH_2Cl_2, −78 °C; v, Na_2CO_3, toluene, reflux; vi, $Ni(COD)_2$, $E_{t3}N$, MeCN; vii, $PdCl_2$, Et_3SiH, Et_3N, toluene; viii, ClCOO*i*-Bu, NMM, THF, then PhSeLi; ix, *n*-Bu_3SnH, AIBN, benzene; x, $LiAlH_4$, THF; xi, MeI, MeOH, then AgCl, MeOH; xii, Crabtree's catalyst; xiii, Boc_2O, DMAP, THF; xiv, LDA, THF, −78 °C, then HCOOMe; xv, HCl, AcOEt; xvi, $CH(OMe)_3$, MeOH, HCl; xvii, *t*-BuOK, DMF.

of the indole ring onto an *N*-acyliminium ion, as previously reported, and converted to enantiomerically pure key intermediate **550** (Scheme 109).

A full account of the syntheses of borreline (**551**) and vulcanine (**552**) has appeared.[188]



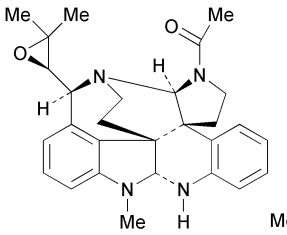
3 Isoprenoid tryptamines

A biosynthetic study was undertaken to seek the role of tryptophan, acetate, mevalonate and methionine in the biosynthesis of communesins A (**553**) and B (**554**), potent cytotoxic fungal alkaloids isolated from a marine fungal strain of *Penicillium* sp. based on isotopic labeling techniques.[189]

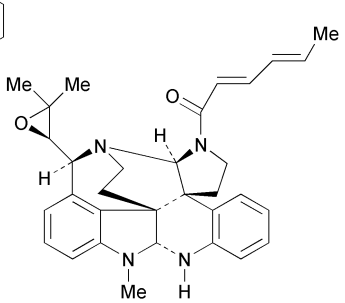
The first total synthesis of racemic communesin F (**555**) has been accomplished from 4-bromotryptophol. The key steps relied on the assembly of pentacyclic structure **557** from diazo ketone **556** using an intramolecular cyclopropanation, ring opening, and ring closing sequences (Scheme 110).[190]

4 Bisindole alkaloids

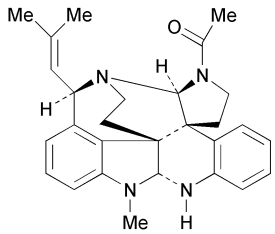
Reversed-phase preparative HPLC analysis of the MeOH extract of the seed of *Centaurea montana* afforded a novel dimeric indole



553 Communesin A

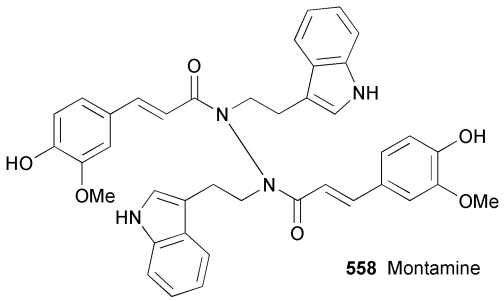


554 Communesin B

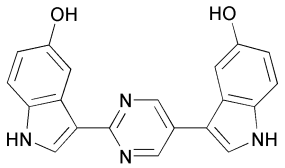


555 Communesin F

alkaloid, montamine (**558**), showing significant in vitro anticolon cancer activity.[191] A new cytotoxic bis-indole alkaloid, hyrtiadine (**559**), was isolated from the extract of an Okinawan marine sponge *Hyrtia* sp.[192]

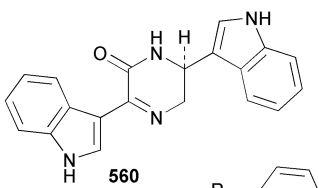


558 Montamine

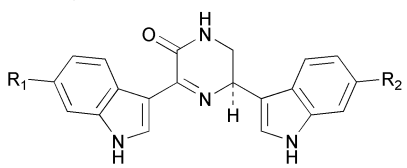


559 Hyrtiadine

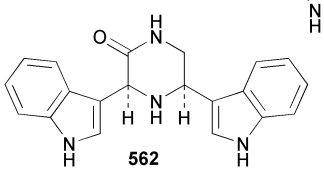
Seven new bis-indole alkaloids, (*S*)-6′,6″-didebromohamacanthin A (**560**), (*R*)-6′,6″-didebromohamacanthin B (**561a**), (*R*)-6″-debromohamacanthin B (**561b**), (3*S*,5*R*)-6′,6″-didebromo-3,4-dihydrohamacanthin B (**562**), and spongotines A (**563a**), B (**563b**), C (**563c**), were isolated from the MeOH extract of a marine sponge *Spongosorites* sp. Some of them showed marginal cytotoxicity against five human solid tumor cell lines.[193]



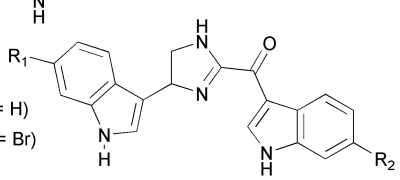
560



561a (R_1 = R_2 = H)
561b (R_1 = Br, R_2 = H)



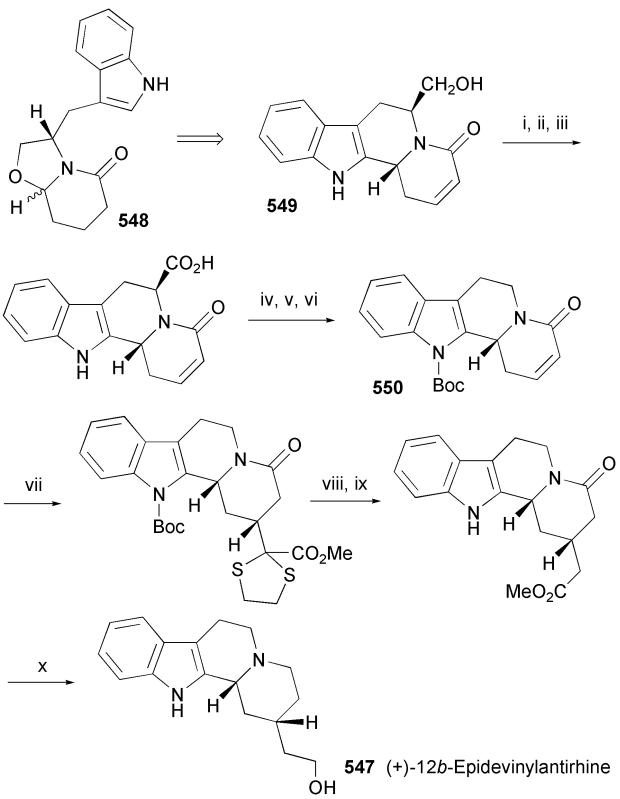
562



563a (R_1 = Br, R_2 = H)
563b (R_1 = H, R_2 = Br)
563c (R_1 = R_2 = Br)

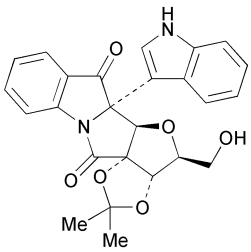
Isatis indigotica Fort. (Cruciferae) is a biennial herbaceous plant widely distributed in China, whose root and leaves have been used as a traditional Chinese medicine. From the leaves of this plant, 9α,13α-dihydroxyisopropylidenylisatisine A (**564**) was isolated, and this compound showed moderate anti-HIV activity. Compound **564** was an artifact and isatisine A (**565**) was shown to be a genuine natural product in this plant.[194]

New bis-indole alkaloids, **566** and arcyroxocin B (**567**) were isolated from wild fruiting bodies of *Arcyria denudate*, and

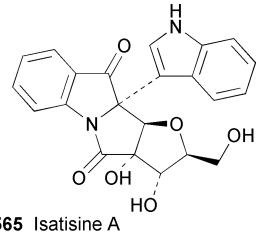


548 549 550 547 (+)-12*b*-Epidevinylantirhine

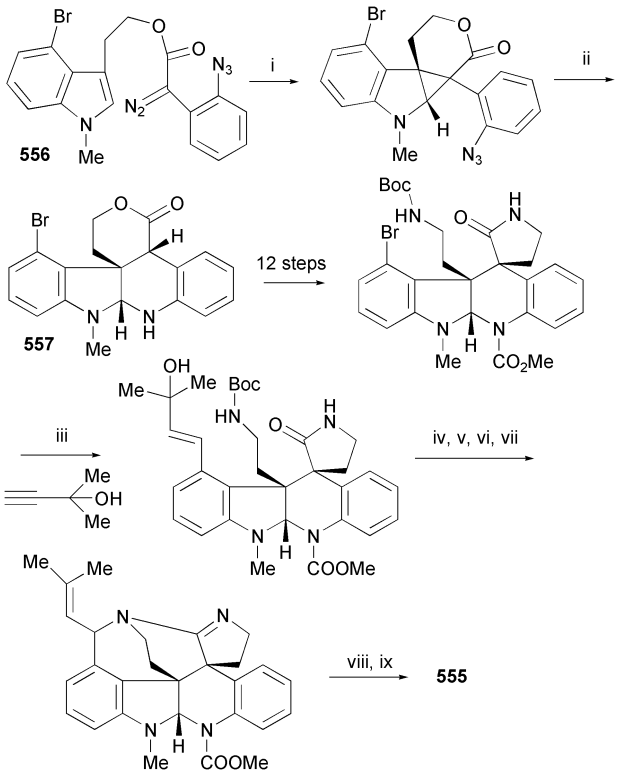
Scheme 109 *Reagents and conditions*: i, IBX, DMSO, rt; ii, Boc_2O, Et_3N, DMAP, THF, rt; iii, $NaClO_2$, NaH_2PO_4, 1-methyl-1-cyclohexene, MeCN, *t*-BuOH, H_2O, 0 °C to rt; iv, $(PhSe)_2$, PBu_3, CH_2Cl_2, 0 °C to rt; v, *n*-Bu_3SnH, AIBN, toluene, 80 °C; vi, LDA, PhSeBr, THF, −78 °C to rt, then $NaIO_4$, $NaHCO_3$, MeOH/HO, rt; vii, methyl 1,3-dithiolane-2-carboxylate, *n*-BuLi, THF, −78 °C to rt; viii, $NiCl_2$, $NaBH_4$, THF/MeOH, 0 °C to rt; ix, HCOOH, rt; x, $LiAlH_4$, THF, reflux, then rt.



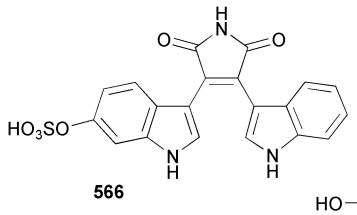
564 9α,13α-Dihydroxyisopropenylidenylisatisine A



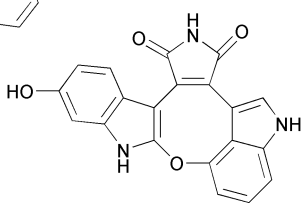
565 Isatisine A



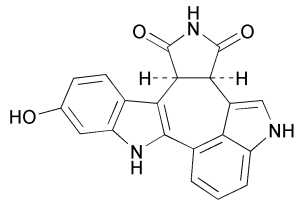
Scheme 110 *Reagents and conditions*: i, CuOTf, CH_2Cl_2, rt; ii, PBu_3, THF/H_2O; iii, $Pd(OAc)_2$, P(*o*-Tol)$_3$, Et_3N, microwave, neat; iv, PPTS, $CHCl_3$; v, BF_3OEt_2, *i*-Pr_2NEt, CH_2Cl_2, rt; vi, TFA, CH_2Cl_2, rt; vii, SiO_2, $MeOH/CH_2Cl_2$, 50 °C; viii, aq. KOH, MeOH; ix, $NaBH_4$, $AcOH/Ac_2O$.



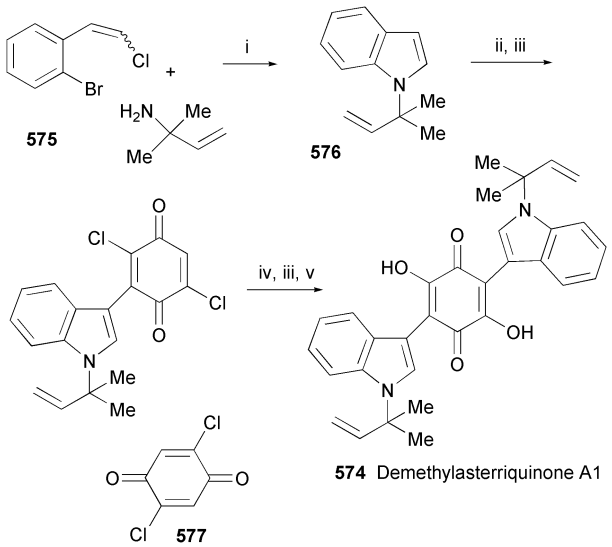
566



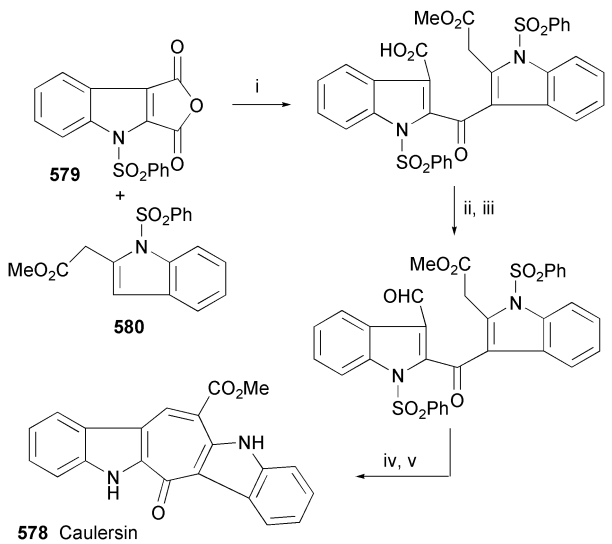
567 Arcyroxocin B



568 Dihydroarcyriacyanin A



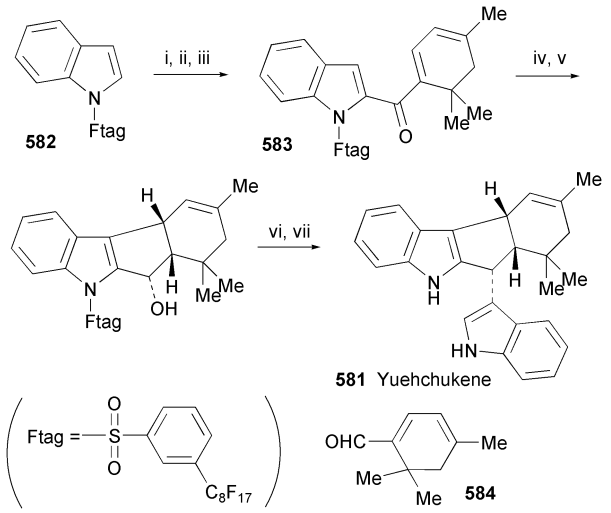
Scheme 111 *Reagents and conditions*: i, $Pd(OAc)_2$, HBF_4, *t*-Bu_3P, NaO*t*-Bu, toluene 130 °C; ii, **577**, HCl, THF, rt; iii, DDQ; iv, **576**, $Zn(OTf)_2$, THF, reflux; v; aq. NaOH, MeOH, reflux.



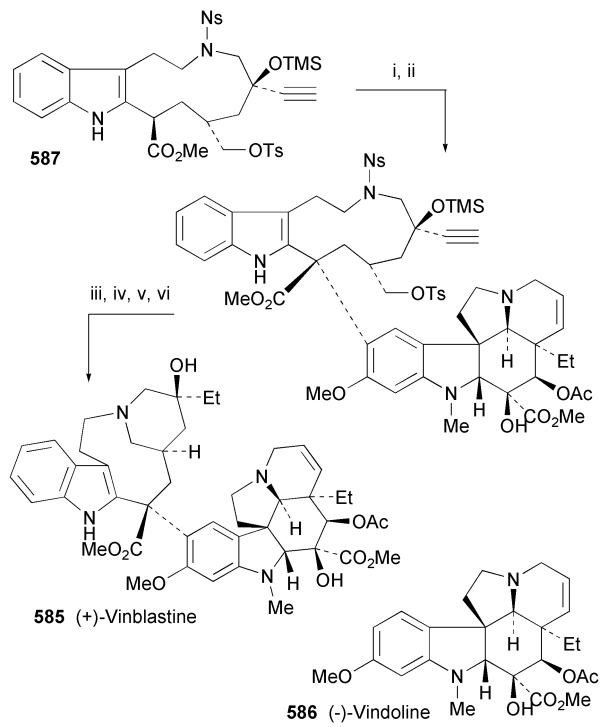
Scheme 112 *Reagents and conditions*: i, $TiCl_4$, CH_2Cl_2; ii, $(COCl)_2$; iii, *n*-Bu_3SnH, $Pd(PPh_3)_4$, toluene; iv, NaH, THF; v, TBAF, THF.

dihydroarcyriacyanin A (**568**) was obtained from wild fruiting bodies of *Arcyria obvelata*. Compounds **567** and **568** showed cytotoxicity against Jurkat cells.[195]

Three new epidithiodioxopiperazines, bionectins A (**569a**), B (**569b**) and C (**570**), were isolated from the mycelium of liquid fermentation cultures of the fungus *Bionectra byssicola* F120. Compounds **569** exhibited antibacterial activity against *Staphylococcus aureus*.[196] Three new epipolythiodioxo piperazines, chaetocochins A (**571**), B (**572**) and C (**573**), were isolated from the AcOEt extract of the solid-state fermented rice culture of the fungus *Chaetomium cochliodes*. Compounds **571** and **573**



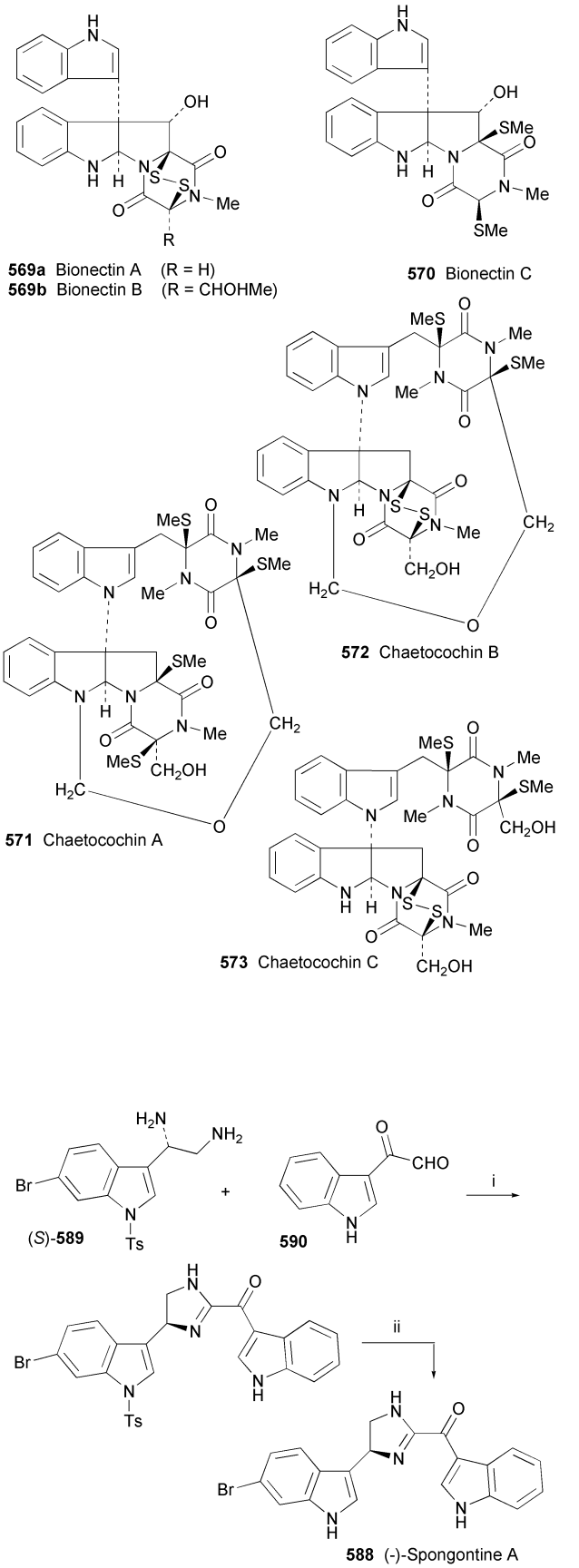
Scheme 113 *Reagents and conditions*: i, MesLi, Et_2O, −40 °C; ii, **584**, −78 °C to 0 °C; iii, IBX, DMSO, rt; iv, BF_3OEt_2, benzene, 80 °C; v, DIBAH, THF, 0 °C; vi, indole, BF_3OEt_2, Et_2O; vii, TBAF, dioxane, 80 °C.



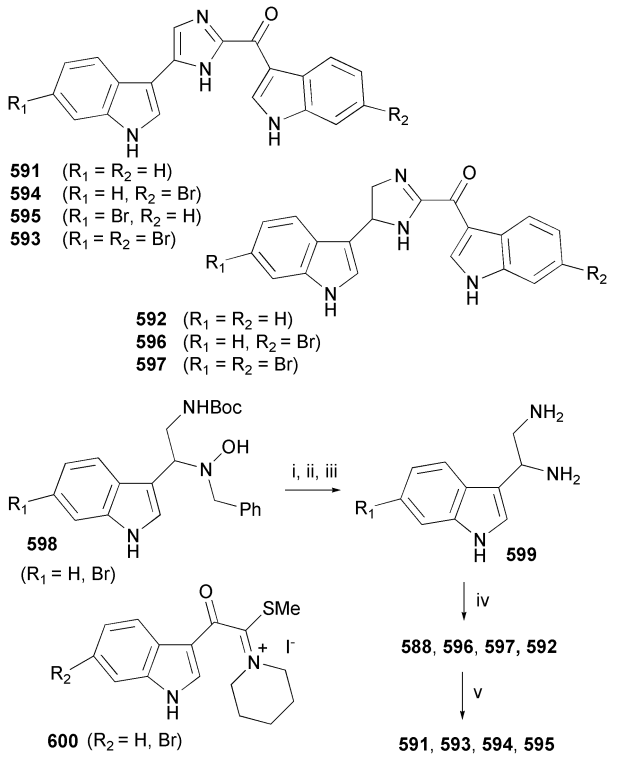
Scheme 114 *Reagents and conditions*: i, *t*-BuOCl, CH_2Cl_2, 0 °C; ii, (−)-**586**, TFA, CH_2Cl_2, 0 °C; iii, DBU, $HSCH_2COOH$, MeCN; iv, $NaHCO_3$, *i*-PrOH, MeCN/H_2O, 60 °C; v, TBAF, THF; vi, Pd/C, H_2, EtOH.

exhibited significant cytotoxicity in vitro against cancer cell lines Bre-04, Lu-04 and N-04.[197]

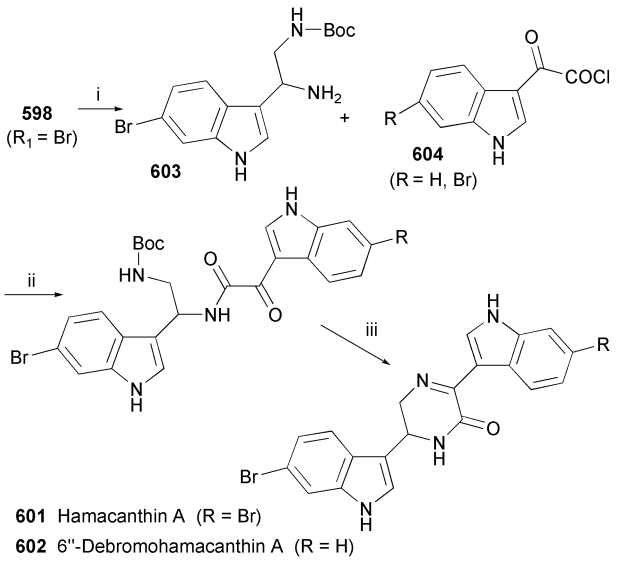
A total synthesis of demethylasterriquinone A1 (**574**) has been achieved through *N*-prenyl indole **576** formation *via* the tandem Pd-catalyzed aryl/alkenyl C–N bond formation from **575** and the direct nucleophilic addition of two molecule of **576** onto activated quinone **577** as the key steps (Scheme 111).[198]



Scheme 115 *Reagents and conditions*: i, NCS; ii, aq. NaOH, MeOH, reflux.

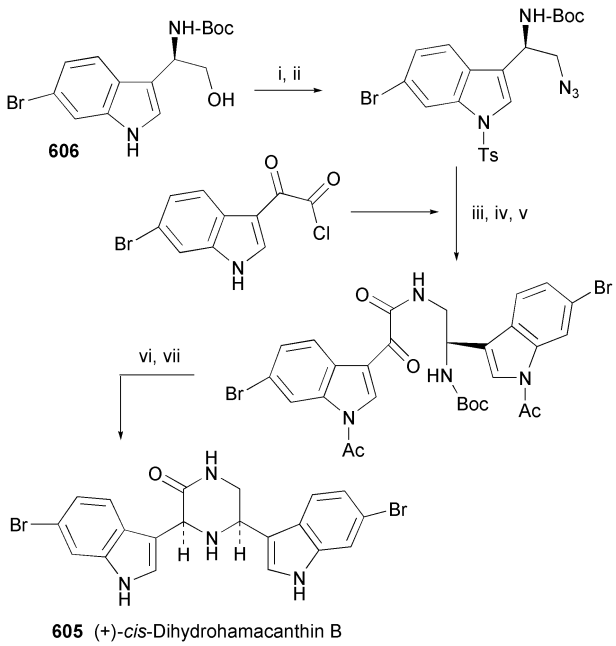


Scheme 116 *Reagents and conditions*: i, $Pd(OH)_2$, H_2, MeOH, AcOH, rt; ii, HCOOH, rt; iii, aq. NaOH; iv, **600**, Amberlist A21, MeOH, rt; v, IBX, DMSO, rt.

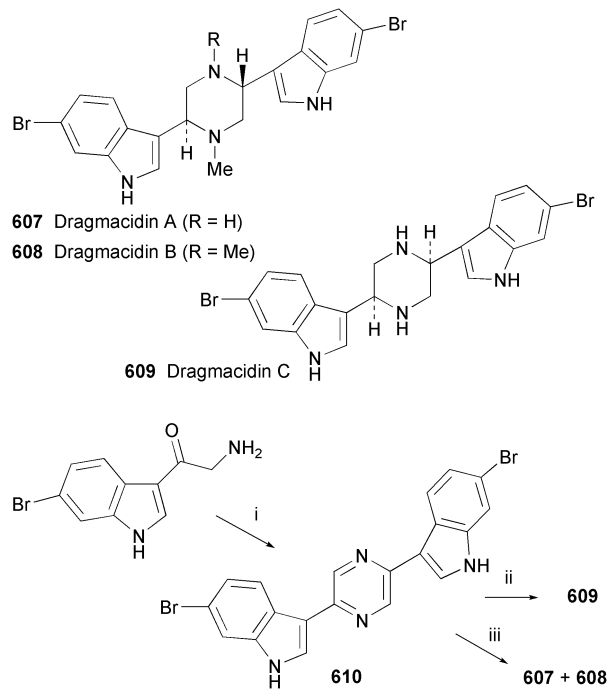


Scheme 117 *Reagents and conditions*: i, $Pd(OH)_2$, H_2, MeOH, AcOH, rt; ii, **604**, Et_3N, THF, 0 °C to rt; iii, HCOOH, $ClCH_2CH_2Cl$, reflux.

Caulersin (**578**), isolated from *Caulerpa serrulata*, has been synthesized by treating indole-2,3-dicarboxylic anhydride **579** with methyl indoleacetate **580**, followed by an intramolecular cyclization. The real structure of **578** was confirmed based on the synthesis (Scheme 112).[199]

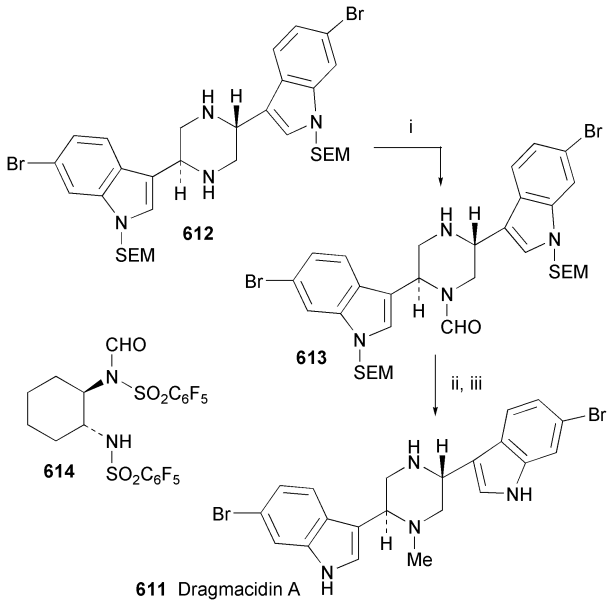


Scheme 118 *Reagents and conditions*: i, TsCl, DMAP, Et_3N, CH_2Cl_2, −20 °C; ii, NaN_3, DMF, 80 °C; iii, PPh_3, H_2O, THF, reflux, then Et_3N, THF, 0 °C; iv, 10% KOH, EtOH, reflux; v, Ac_2O, DMAP, THF, rt; vi, HCOOH, CH_2Cl_2, rt, then EtOH, reflux; vii, $NaBH_3CN$, MeOH, rt.



Scheme 119 *Reagents and conditions*: i, EtOH, xylene, sealed tube, 130 °C; ii, $NaBH_3CN$, AcOH, 0 °C; iii, $NaBH_3CN$, HCOOH, 0 °C.

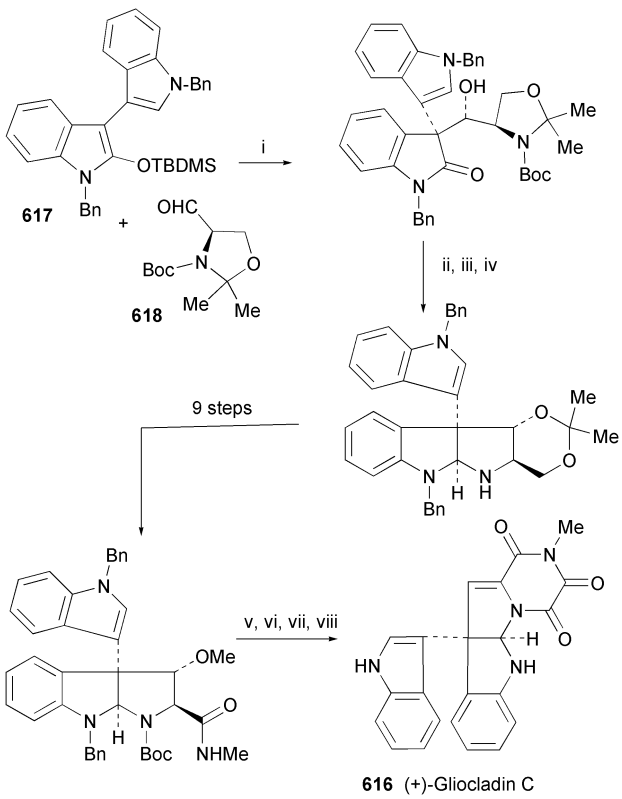
A fluorous synthesis of yuehchukene (**581**) was achieved from perfluoroalkyl-tagged 1-arylsufonylindole **582**. Lithiation at the 2-position of **582** by treating with MesLi followed by



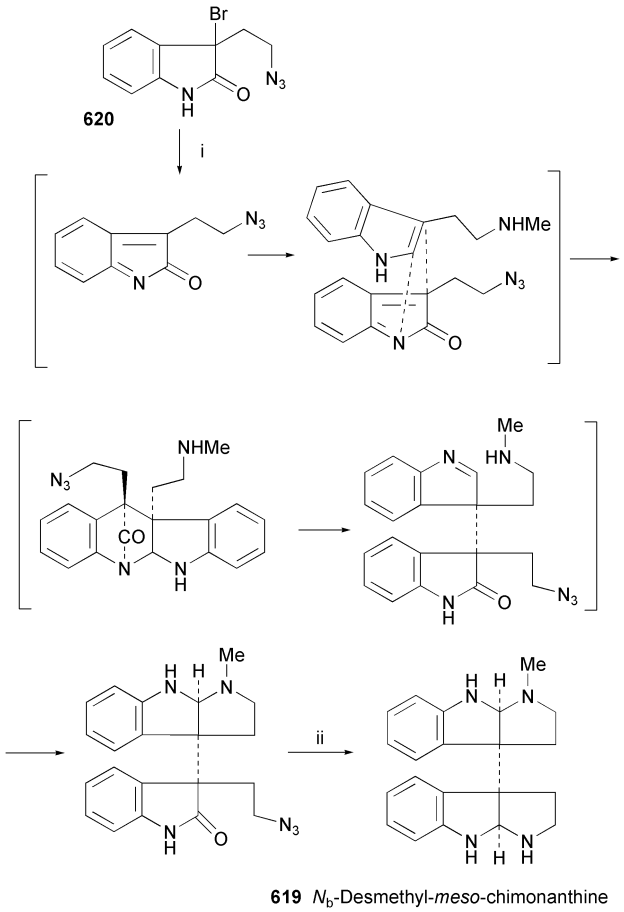
Scheme 120 *Reagents and conditions*: i, **614**, dioxane, rt, 48% ee; ii, TBAF, THF; iii, BH_3, THF.

electrophilic trap and oxidation produced **583**, which was converted to **581** (Scheme 113).[200]

A total synthesis of (+)-vinblastine (**585**) has been accomplished through a stereoselective coupling of an optically active



Scheme 121 *Reagents and conditions*: i, BF_3OEt_2, DTBMP, CH_2Cl_2, −78 °C; ii, 3 M HCl, MeOH, rt; iii, 2,2-dimethoxypropane, CSA, benzene, 60 °C; iv, $LiAlH_4$, THF, rt, then SiO_2, MeOH, rt; v, TMSI, MeCN, rt; vi, Na, NH_3, *t*-BuOH, THF, −78 °C; vii, ClCOCOOEt, Et_3N, CH_2Cl_2, rt; viii, $(TMS)_2NH$, 140 °C, sealed tube.



Scheme 122 *Reagents and conditions*: i, N_b-methyltryptamine, Cs_2CO_3, CH_2Cl_2, rt; ii, Red-Al, toluene, reflux.

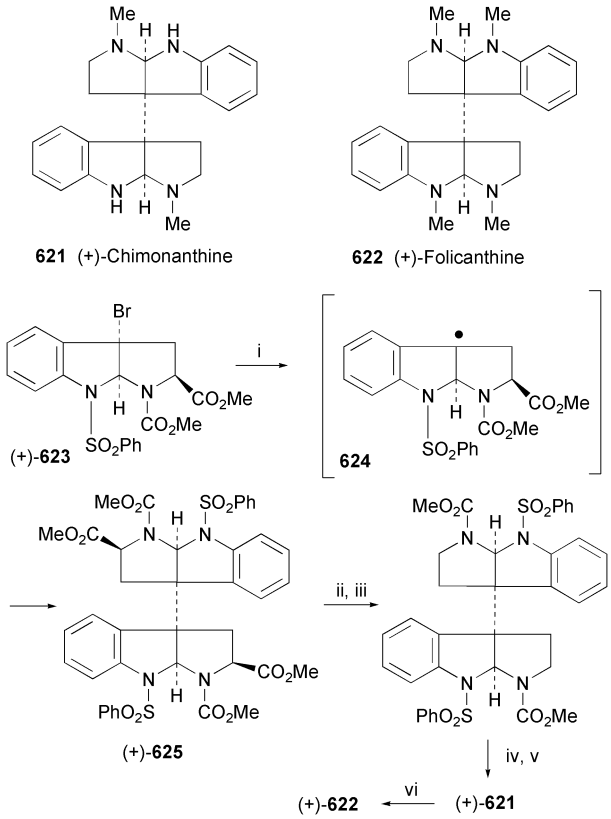
11-membered intermediate **587** with (−)-vindoline (**586**) as the key reaction (Scheme 114).[201]

The first asymmetric synthesis of (−)-spongontine A (**588**), isolated from the marine sponge *Spongosorites* sp., has been performed through the oxidative synthesis of the imidazoline/ketone unit from keto aldehyde (**590**) and (*S*)-diamine (**589**) as a key step. The absolute configuration of **588** was elucidated to be the (*S*)-configuration based on the synthesis (Scheme 115).[202]

A convergent approach to marine sponge alkaloids, topsentin A (deoxytopsentin) (**591**), topsentin D (**592**), dibromodeoxytopsentin (**593**), isobromodeoxytopsentin (**594**), bromodeoxytopsentin (**595**), spongontines A (**588**), B (**596**) and C (**597**) was developed using the condensation between α-ketothioimidate **600** and diamine **599** derived from *N*-hydroxylamine (**598**) as the key step (Scheme 116).[203]

The same strategy was applied to a total syntheses of hamacanthin A (**601**) and 6″-debromohamacanthin A (**602**) using diamine **603** as the key starting building block (Scheme 117).[204]

A total synthesis of (+)-*cis*-dihydrohamacanthin B (**605**), isolated from the marine sponges *Rhaphisia lacazei* and *Spongosorites* sp., have been achieved from optically pure (*R*)-indolylglycinol (**606**) (Scheme 118).[205]

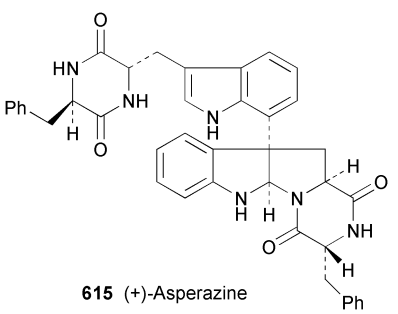


Scheme 123 *Reagents and conditions*: i, $[CoCl(PPh_3)_3]$, acetone, rt; ii, aq. KOH, MeOH, rt; iii, oxalyl chloride, DMF, CH_2Cl_2, rt, then TMS_2NH, AIBN, toluene, 80 °C; iv, Na(Hg), Na_2HPO_4, MeOH, rt; v, NaAlH$(OCH_2CH_2OMe)_2$, toluene, reflux; vi, aq. HCHO, $NaBH_3CN$, MeCN, rt.

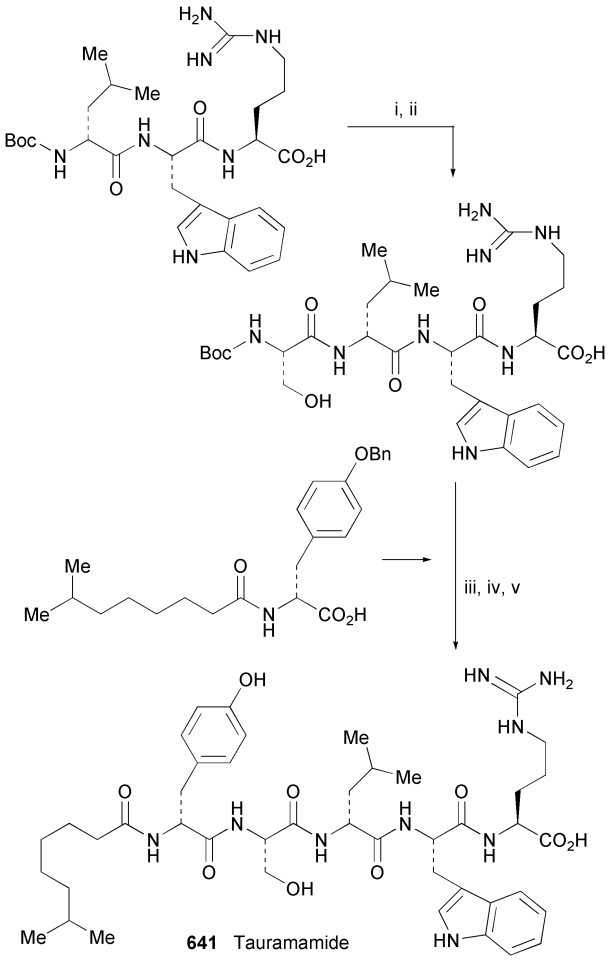
A concise total synthesis of dragmacidin A (**607**), B (**608**) and C (**609**), isolated from the marine sponge *Hexadella* sp., was reported. The key feature was the reduction of the pyrazine ring of **610** to the piperazine ring (Scheme 119).[206]

Total synthesis of dragmacidin A (**611**) was performed based on the deasymmetrization of piperazine of **612** by enantioselective acylation (Scheme 120). Treatment of **612** with chiral acylating agent **614** in dioxane produced **613** in 48% ee, which was converted to **611** in two steps.[207]

The full detail of the first total synthesis of cyclotryptophan alkaloid, asperazine (**615**) isolated from a saltwater culture of the fungus *Aspergillus niger* obtained from a Caribbean *Hyrtios* sponge, has appeared.[208]



The first total synthesis of (+)-gliocladin C (**616**), isolated from a strain of *Gliocladium roseum* originally obtained from the



Scheme 124 *Reagents and conditions*: i, TFA, CH_2Cl_2; ii, Boc-L-Ser(Bn), PyBOP, CH_2Cl_2; iii, TFA, CH_2Cl_2; iv, PyBOP, CH_2Cl_2; v, Pd/C, H_2, EtOH.

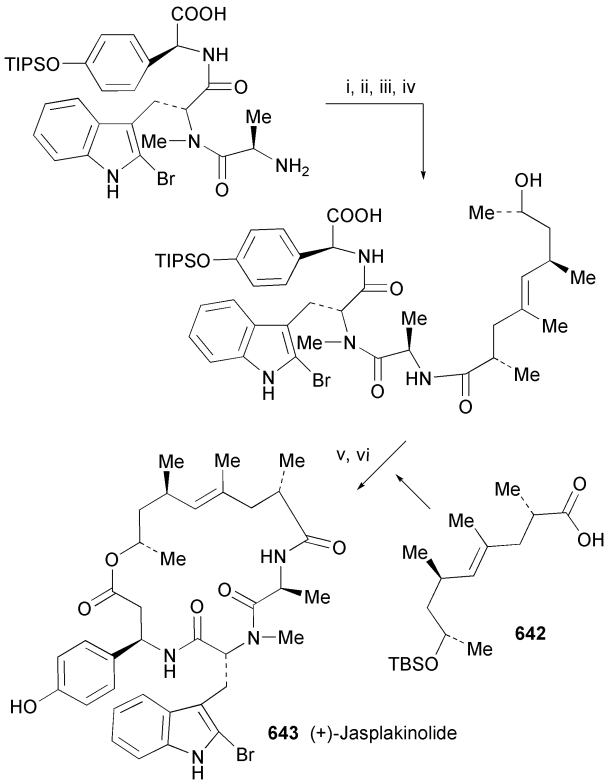
sea hare *Aplysia kurodai*, has completed, and the absolute configuration was established by the asymmetric synthesis (Scheme 121).[209] The key step was asymmetric construction of the quaternary carbon center through Mukaiyama aldol reaction of **617** with enantiopure **618**.

The first total synthesis of bis-pyrrolidinoindoline alkaloid, N_b-desmethyl-*meso*-chimonanthine (**619**) isolated from *Psychotria lyciiflora*, has been reported (Scheme 122). The key step was a diastereoselective tandem [4 + 2] cycloaddition/cyclization of bromooxindole **620** with N_b-methyltryptamine.[210]

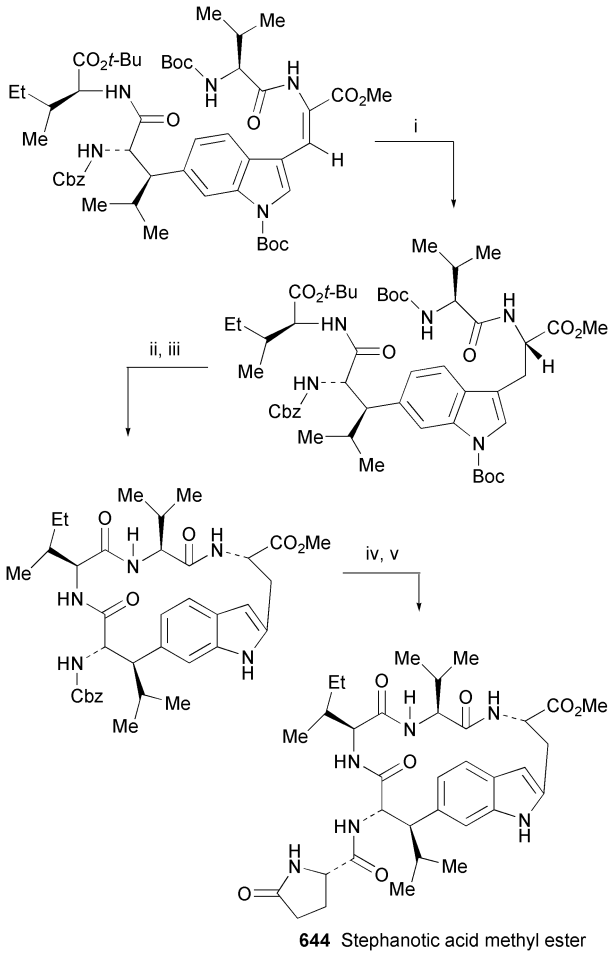
Enantioselective synthesis of (+)-chimonanthine (**621**) and (+)-folicanthine (**622**), hexahydropyrroloindole alkaloids, has been performed through a convergent reductive dimerization strategy as the key step (Scheme 123). Irradiation of a mixture of bromide (+)-**623** with a Mn catalyst (0.5 equiv) in CH_2Cl_2 by visible light led to dimer (+)-**625** *via* radical intermediate **624**.[211]

5 Peptide alkaloids containing a tryptophan residue

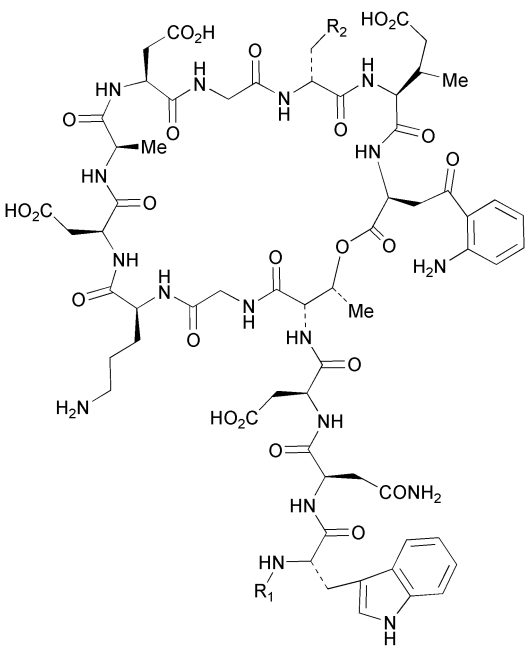
Deptomycin (**626**) is a member of the A21978C family of antibiotics, and three deptomycin-related lipopeptides A21978C_1



Scheme 125 *Reagents and conditions*: i, **642**, DCC, HOBT, THF, −20 °C to 0 °C; ii, aq. LiOH; iii, TIPSOTf, 2,6-lutidine; iv, aq. K_2CO_3; v, 2,4,6-trichlorobenzoyl chloride, *i*-Pr_2NEt, then DMAP; vi, TBAF, THF.



Scheme 126 *Reagents and conditions*: i, [(COD)Rh(*S*,*S*)-Et-DuPHOS]OTf, MeOH, H_2; ii, TFA, $CHCl_3$; iii, HATU, HOAt, *i*-Pr_2NEt, DMF; iv, $Pd(OH)_2$, H_2, MeOH; v, (*S*)-pyroGlu-OH, HOAt, *i*-Pr_2NEt, DMF.



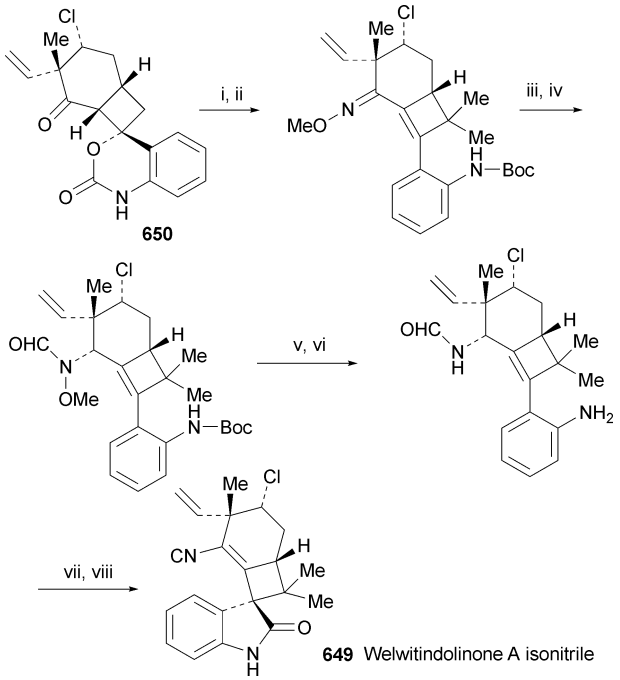
626 Deptomycin (R_1 = $CO(CH_2)_8CH_3$, R_2 = OH)
627 A21978C1 (R_1 = $CO(CH_2)_6CH(CH_3)_2$, R_2 = $CONH_2$)
628 A21978C2 (R_1 = $CO(CH_2)_8CH(CH_3)_2$, R_2 = $CONH_2$)
629 A21978C3 (R_1 = $CO(CH_2)_8CH(CH_3)CH_2CH_3$, R_2 = $CONH_2$)

(**627**), A21978C_2 (**628**) and A21978C_3 (**629**) were purified from the fermentation broth of a recombinant *Streptomyces roseosporus* strain.[212]

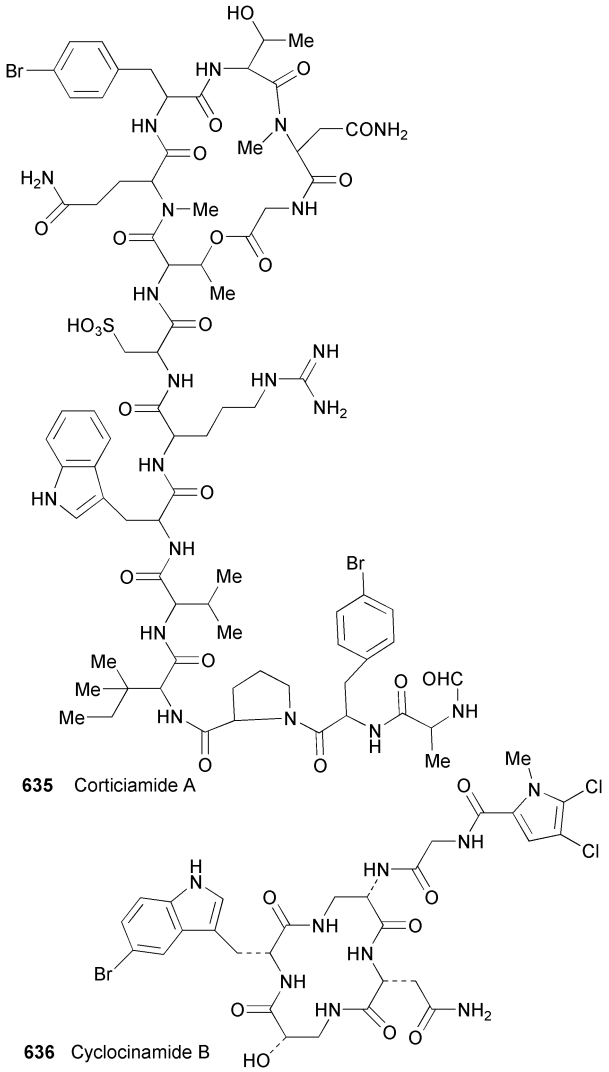
Jaspamide (**630**) has remarkable biological properties including anthelminthic, catatonic, insecticidal and ichthyotoxic activities. The sponge *Jaspis splendas*, collected at the Vanuatu island, contains large amounts of **630** together with minor analogues. Re-examination of the extract of the sponge produced four new jaspamides D (**631**), E (**632**), F (**633**) and G (**634**).[213]

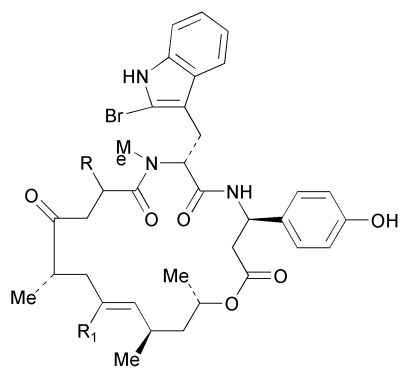
Corticiamide A (**635**) and cyclocinamide B (**636**) were the first halogenated cyclic peptide isolated from the sponge *Corticium* sp. collected from Fiji. The structures were elucidated by spectroscopic analyses and the absolute configuration of **636** was determined by acid hydrolysis and Marfey's analysis.[214]

Cyclic peptide alkaloid, chamaedrine (**637**), was isolated from the roots of *Melochia chamaedris* along with four known cyclic peptides.[215] The latex of *Jatropha integerrima* produced two new cyclic heptapeptides, integerrimides A (**638**) and B (**639**), which inhibited neurite outgrowth in neuronal cell culture.[216] Two new tryptophan derivatives, *cis*- (**640a**) and *trans*-tryptophan-4-aminocinnamamides (**640b**), were isolated from field collected fruit bodies of a myxomycete *Fuligo aurea*.[217]

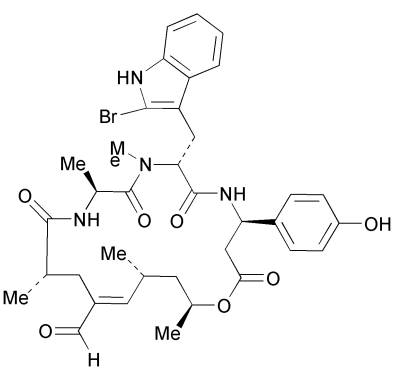


Scheme 127 *Reagents and conditions*: i, Boc_2O, DMAP, DBU, CH_2Cl_2; ii, $MeONH_2$, pyridine; iii, $NaBH_3CN$, AcOH; iv, $CH_3COOCHO$; v, SmI_2, THF; vi, HCOOH, THF; vii, $COCl_2$, Et_3N; viii, LHMDS, THF, THF, −78 °C.





630 Jaspamide R = Me R_1 = Me
631 Jaspamide D R = Et R_1 = Me
632 Jaspamide E R = CH_2OH R_1 = Me
633 Jaspamide F R = Me R_1 = H



634 Jaspamide G

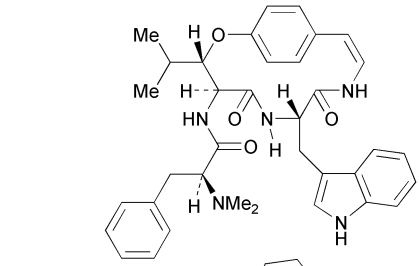
A new lipopeptide antibiotics, tauramamide (**641**), was isolated from *Brevibacillus laterosporus* PNG276 obtained from Papua New Guinea, and a total synthesis of **641** confirmed the structure (Scheme 124).[218]

An enantioselective total synthesis of (+)-jasplakinolide (**643**), isolated from the marine sponge *Japis splendens*, has been performed (Scheme 125).[219]

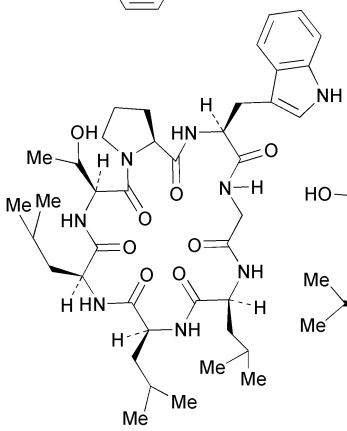
The methyl ester of the naturally occurring macrocyclic pentapeptide, stephanotic acid (**644**) isolated from *Stephanotis floribunda*, was synthesized (Scheme 126).[220]

6 Indole alkaloids with a nonrearranged monoterpenoid unit

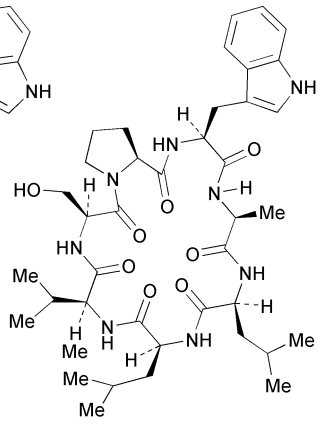
A new hapalindole, 12-*epi*-hapalindole J isonitrile (**645**), and three known hapalindoles were isolated from the biofilm-forming freshwater cyanobacterium *Fischerella* ATCC 43239, and the insecticidal activity was observed for these compounds.[221] Bioassay-guided fractionation of the MeOH/water extract of a cultured cyanobaterium strain *Fischerella* sp. yielded three new



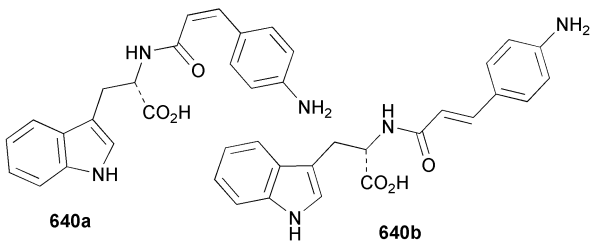
637 Chamaedrine



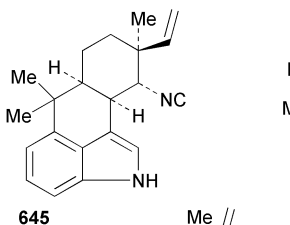
638 Integerrimide A



639 Integerrimide B



640a 640b



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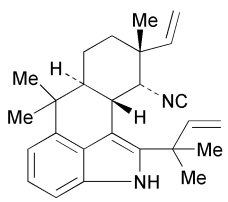

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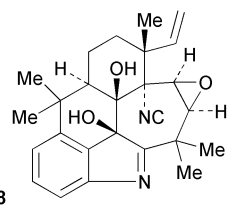

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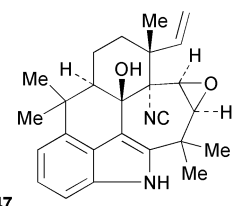

647

alkaloids, ambiguine H isonitrile (**646**), ambiguine I isonitrile (**647**) and ambiguine J isonitrile (**648**). Compounds **646** and **647** exhibited antibacterial and antimycotic activities.[222]

Total synthesis of racemic welwitindolinone A isonitrile (**649**), isolated from blue-green algae, has been developed from urethane intermediate **650** (Scheme 127).[223]

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