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Recent progress in the chemistry of non-monoterpenoid indole alkaloids

Masahiro Toyota and Masataka Ihara

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980-8578, Japan

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Covering: July 1996 to June 1997
Previous review: 1996, 14

1 Introduction

This section covers the literature on non-monoterpenoid indole alkaloids and their analogs since the last review in this journal, which included the literature from July 1995 to June 1996.

2 Simple alkaloids

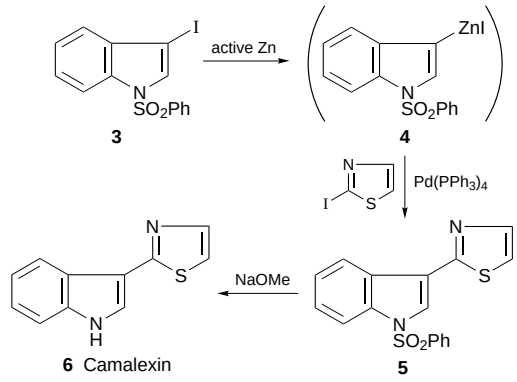
2.1 Non-tryptamines

The simple disubstituted indole, 5,6-dihydroxyindole, **1a**, has been isolated from *Rhaphidophora korthalsii*. In spite of its simple structure, the ED_{50} of **1a** against p 388 cells was 3.5 μg ml^{-1}, and its structure was elucidated spectroscopically after transformation of **1a** into the corresponding stable diacetate **1b**. The structure was further confirmed by total synthesis.[1] (±)-Convolutamydine A **2**, a metabolite isolated from the marine Bryozoan *Amathia convoluta*, has been prepared by a concise synthesis from 3,5-dibromoaniline using modified Sandmeyer methodology.[2] Phytoalexins are anti-microbial low-molecular weight secondary metabolites, and produced by plants after exposure to biological, chemical or physical stress.

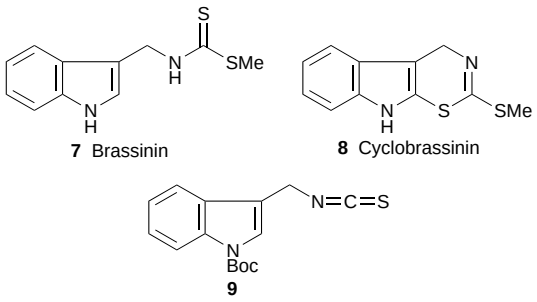
Camalexin **6**, a phytoalexin produced in the leaves of *Camelina sative* in response to infection by the fungus *Alternara brassicae*, was synthesised from **3** employing palladium-catalysed arylation (**4**→**5**) as the key step (Scheme 1).[3] Cancer chemopreventive phytoalexins, brassinin **7** and cyclobrassinin **8**, have been biomimetically prepared by way of the isothiocyanate **9** as a common synthetic intermediate.[4] Biosynthetic studies on the sulfur-containing indole phytoalexins have been examined by a trapping experiment with aniline for a biosynthetic intermediate.[5]

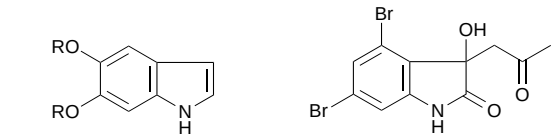
Three new indoline alkaloids with neuronal cell protecting activity, benzastatins E **10a**, F **10b** and G **10c**, were isolated from *Streptomyces nitrosporeus* 30643.[6] Their structures were established on the basis of spectral data. Spider toxin was the first blocker found from natural sources and it has recently attracted great interest because the glutamate receptors play the most important role in brain function. In order to confirm the aromatic subunit of nephilatoxins (NPTX-1–6), the hydrolysis product of **11**, both 4- and 6-hydroxyindole-3-acetic acid were prepared. As a result, the substitution pattern of the oxygen function of NPTX-1–6 has been revised as shown in **12** through ^1H NMR studies of the authentic 4- and 6-hydroxyindole-3-acetic acids.[7]

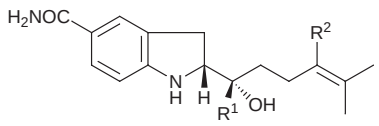
Chuangxinmycin **16**, isolated from *Actinoplanes tsinanensis*, exhibits an antibacterial spectrum (*in vitro*) that includes a number of Gram-positive and Gram-negative bacteria.

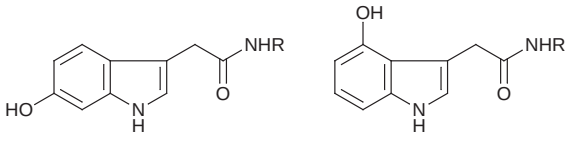


Scheme 1









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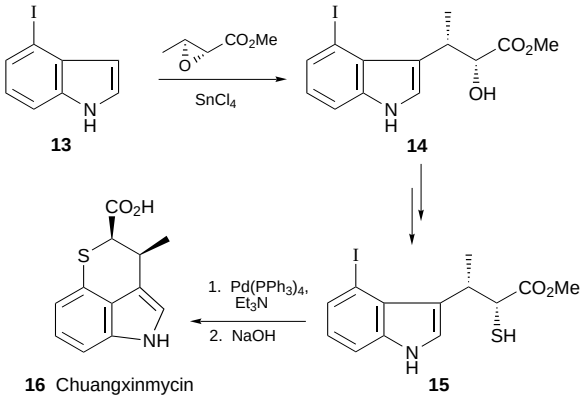
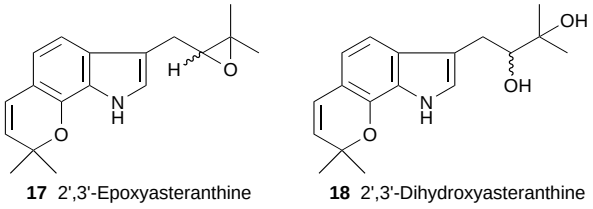


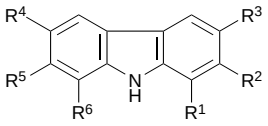
Scheme 2

Regio-selective alkylation of the indole **13** with (±)-*trans*-2,3-epoxy butanoate in the presence of $SnCl_4$ afforded (±)-4′-iodoindolmycenate **14**, which was stereoselectively converted to the thiol **15** *via* a double S_N2 reaction. Palladium-catalysed cyclisation of **15** provided (±)-chuangxinmycin **16** after hydrolysis (Scheme 2).[8]

Two new diprenylated indoles, 2′,3′-epoxyasteranthine **17** and 2′,3′-dihydroxyasteranthine **18**, were isolated from the



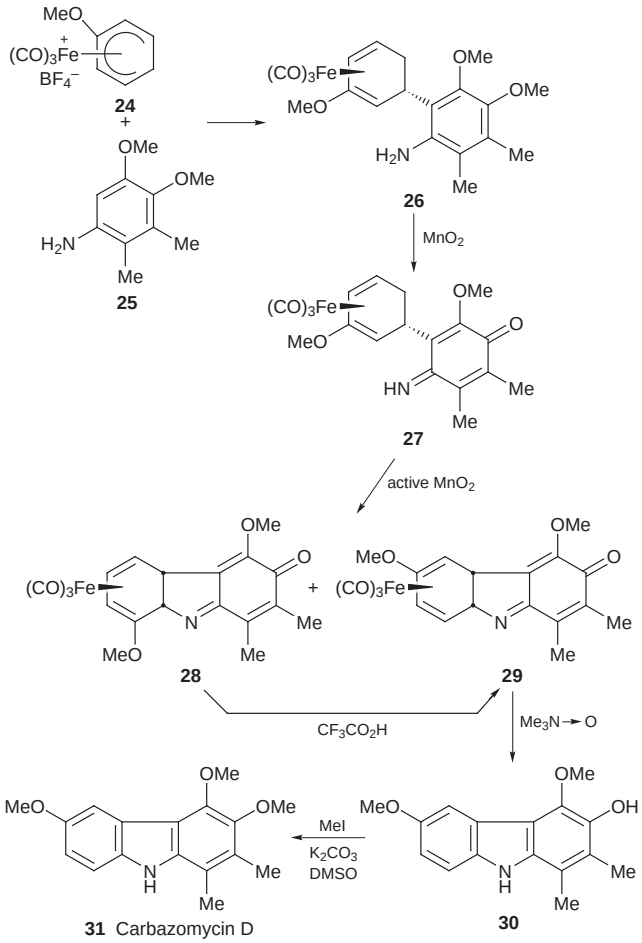
stem bark and the root bark of *Asteranthe asterias*. Their structures were elucidated by spectroscopic methods. Each of the two compounds was obtained in an enantiomeric ratio of 3:1 and showed antimycotic activity against *Saprolegnia* and *Rhizoctonia* species.[9] Five new carbazole alkaloids, clausines B **19**, E **20**, H **21**, I **22** and K **23** were isolated from the stem



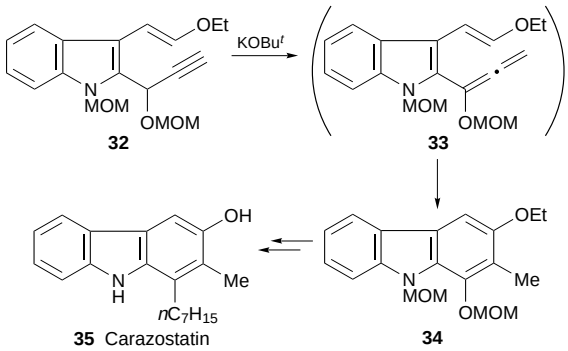
		R^1	R^2	R^3	R^4	R^5	R^6
19	Clausine B	H	OH	CHO	OMe	H	OMe
20	Clausine E	OH	H	CO_2Me	H	H	H
21	Clausine H	H	OMe	CO_2Me	H	OMe	H
22	Clausine I	OH	H	CHO	OMe	H	H
23	Clausine K	H	OMe	CO_2H	H	OMe	H

bark of *Clausena excavata*. The structures were established from spectral data and chemical transformation, and these carbazoles exhibited significant inhibition of rabbit platelet aggregation and caused vasocontraction.[10]

Carbazomycin D **31**, isolated from *Streptoverticillium ehimense*, was synthesised by means of iron-mediated consecutive C–C and C–N bond formation (Scheme 3).[11a] This transition metal promoted cyclisation method for the construction of the carbazole framework (**24**→**30**) was further applied to more functionalised carbazole syntheses by the same group.[11]



Scheme 3



Scheme 4

Carazostatin **35**, a free radical scavenger, has been isolated from *Streptomyces chromofuscus*. Total synthesis of **35** was achieved employing an allene-mediated electrocyclic reaction (**32**→**33**→**34**) as the pivotal step (Scheme 4).[12a] Hyellazole,[12a] carbazoquinocins B–F,[12a] antiostatins A_1–A_4,[12b] antiostatins B_2–B_5[12b] and carbazoquinocin A[12b] were prepared by the same protocol.

Four new carbazole alkaloids, clausines A **36**, C **37**, G **38** and J **39** have also been found in *C. excavata*.[13] Two pyranocarbazole alkaloids, clausine-W **40** and -T **41**, furoclausine-A **42** and -B **43**, clausenamine-A **44** (binary carbazole dimer) and carbazomarin-A **45** (carbazole-pyranocoumarin dimer) were also isolated from *C. excavata* by the same authors and their structures were elucidated using spectroscopic analses.[14] The extracts of the leaves and bark of the plant further gave seven new carbazole alkaloids, named clauszoline-A **46**, -B **47**, -C **48**,

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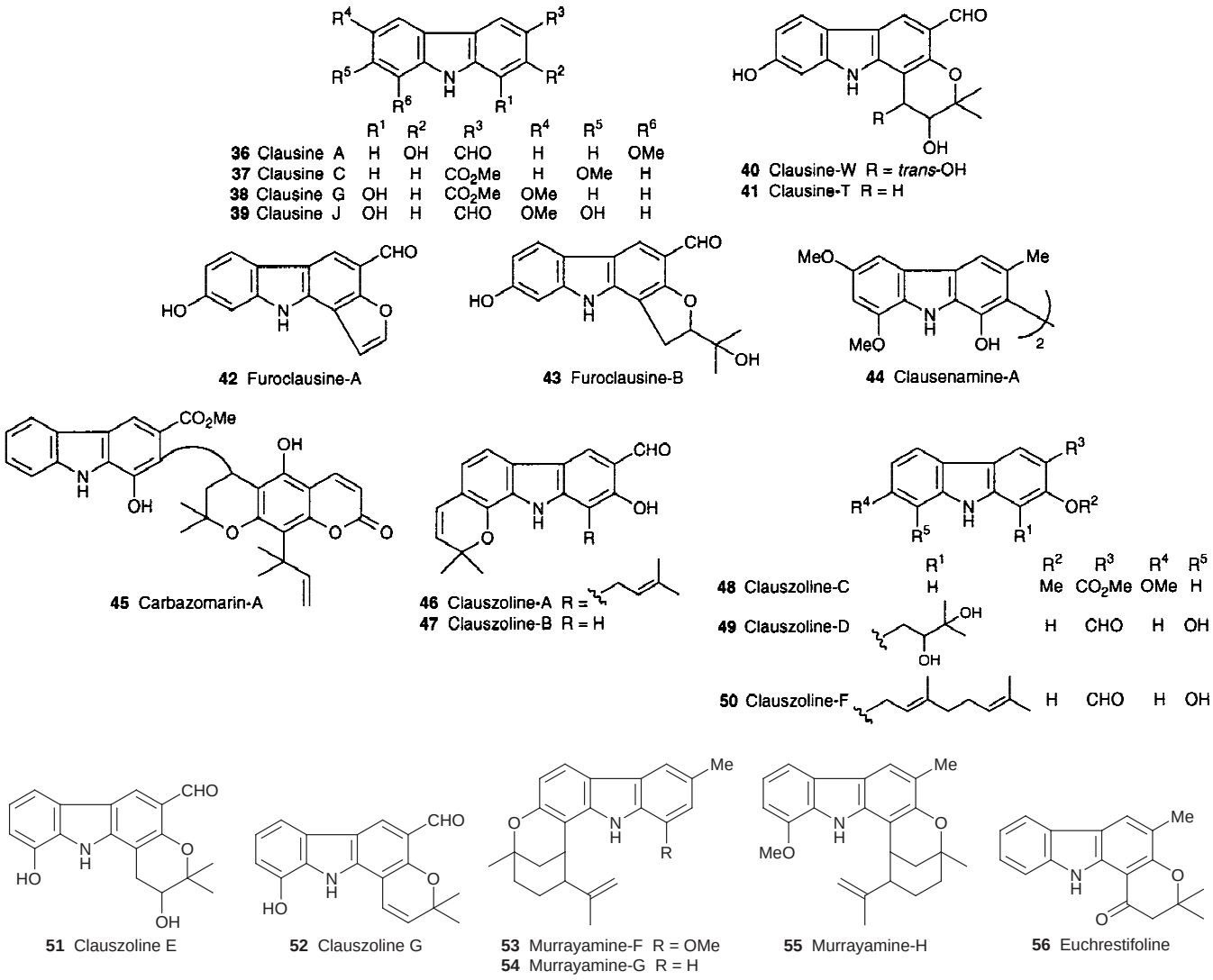
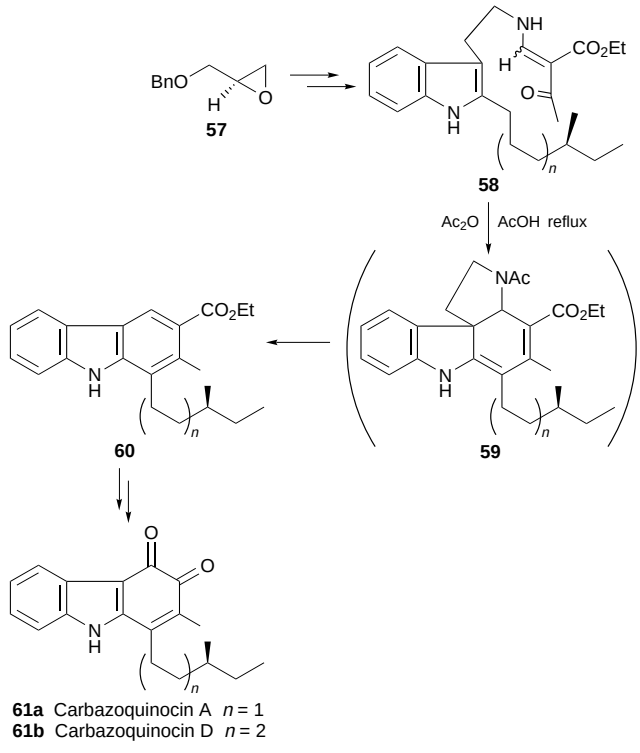


-D **49**, -F **50**, -E **51** and -G **52**.[15] Four new carbazoles, murrayamine-F **53**, -G **54**, -H **55** and euchrestifoline **56** have been isolated from the leaves of *Murraya euchrestifolia*. In addition, the variation of 26 carbazole alkaloids in the leaves with the seasons was also examined.[16]

Carbazoquinocins A **61a** and D **61b**, potent lipid peroxidation inhibitors isolated from *Streptomyces violaceus*, have been prepared for the first time chirally. Thermal condensation (**58**→**59**→**60**) of the enamines **58**, synthesised from the (*R*)-glycidol **57**, yielded the carbazoles **60**, which were converted to carbazoquinocins A **61a** and D **61b** (Scheme 5).[17]

Indolmycin **65**, produced by *Streptomyces griseus*, exhibits an antibacterial spectrum that includes the pathogenic species *Pasteurella*, *Haemophilus* and *Mycoplasma*, which are responsible for many of the respiratory diseases in farm animals. A practical and short synthesis of (±)-**65** has been achieved. Alkylation of 3-[1-(*N*,*N*-dimethylamino)ethyl]indole **62** with 5-benzyloxycarbonyl oxazolinone **63** proceeded smoothly to give rise to the coupled products **64**, which were transformed into (±)-indolmycin **65** and (±)-isoindolmycin (Scheme 6).[18]

Alboinon **66**, an oxadiazinone alkaloid from the ascidian *Dendrodoa grossularia*, was isolated and its structure was confirmed by synthesis.[19] In the course of screening for inhibitors of protein farnesyltransferase, kurasoin B **67** has been isolated from a fermentation broth of *Paecilomyces* species. The IC_{50} value of **67** against protein farnesyltransferase is 58.0 μM.[20] The absolute configuration of **67** was decided *via* its enantioselective synthesis.[20] The structures of novel tumor cell



Scheme 5

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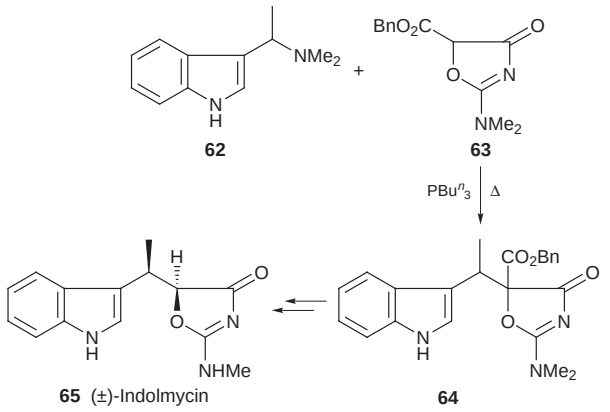
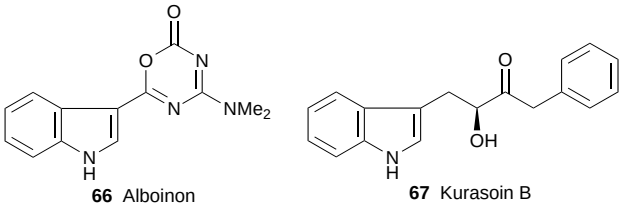


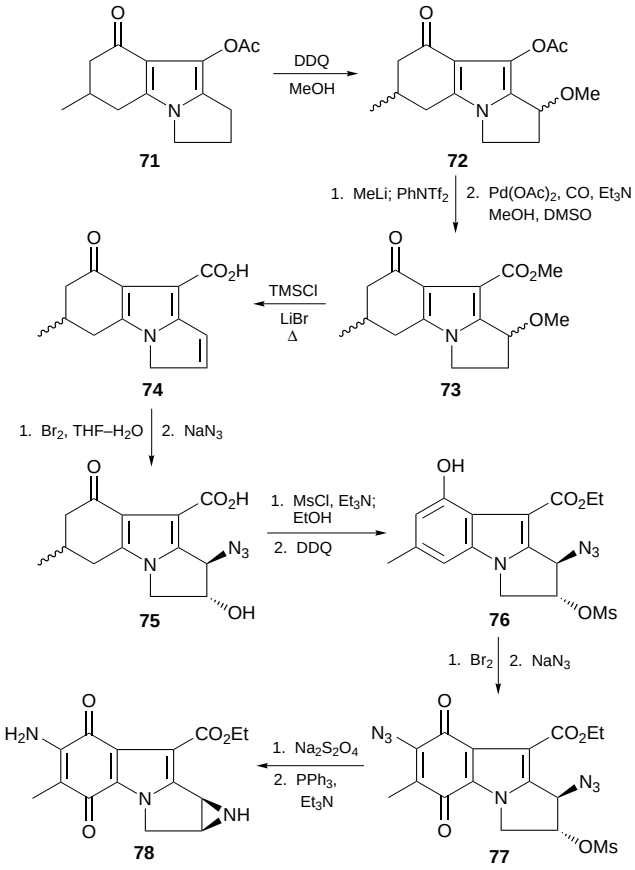
Scheme 6



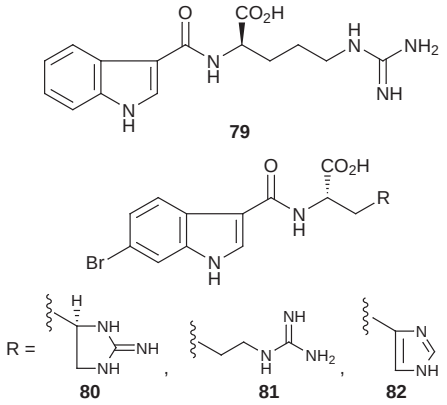
growth inhibitory glycosides, secalosides A **68** and B **69**, have been elucidated through NMR spectroscopy.[21]

Mescengricin **70**, an α-carboline structure substituted by glycerol-ester and dihydropyrone residues, was isolated from *Streptomyces griseoflavus* as a neuronal cell protecting substance.[22]

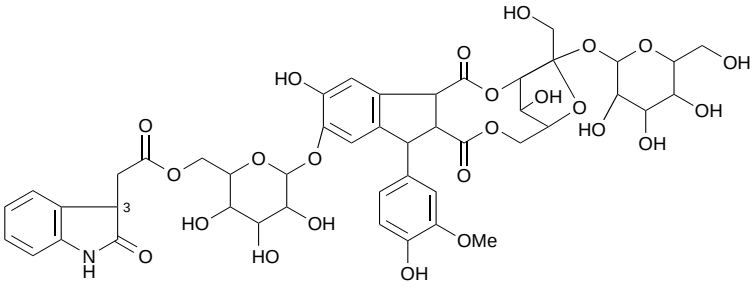
The clinical significance and unique structures of mitomycins have prompted a number of model studies directed toward their synthesis, however, there still remains major interest in the synthesis and biological evaluation of structural analogs which possess strong activity against tumor cells and reveal lower associated toxicity towards healthy cells. Commencing from the easily obtainable 2,3,5,6,7,8-hexahydro-8-oxo-1*H*-pyrrolo[1,2-*a*]indole **71**, an efficient 12-step route to the fully functionalised aziridinomitosene analog **81** has been developed. After DDQ oxidation, the resulting vinyl acetate **72** was subjected to palladium-catalysed methoxycarbonylation to afford the unsaturated ester **73**, which was converted to the carboxylic acid **74**. When **74** was treated with aqueous bromine, the corresponding bromohydrin was produced in good yield. This compound was treated with sodium azide to furnish the azido alcohol **75** as the major isomer. After mesylation of **75**, DDQ-mediated dehydrogenation was conducted to give the 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole **76**. Solvolytic bromination followed by reaction with sodium azide provided the 1,7-diazidoquinone **77**. Finally, exposure of **77** to

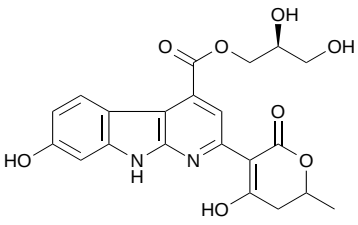


Scheme 7



sodium dithionite gave rise to the corresponding azidohydroquinone intermediate, which was subjected to subsequent thermal reaction to produce **78** (Scheme 7).[23] In addition to the





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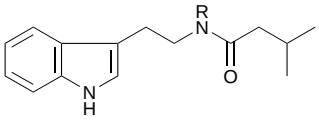
above synthetic study, a cellular resistance mechanism to mytomycin is also reported.[24]

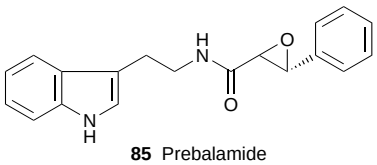
Simple peptides **79**–**82** were isolated from *Leptoclinides dubius* and their structures were elucidated by spectroscopic analyses and degradation experiments.[25]

2.2 Non-isoprenoid tryptamines

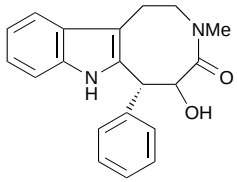
An historical development of the chemistry of the cyclic tautomer of tryptophan has been reviewed.[26] Leaf extracts, from Sri Lankan *Clausena indica* of different provenances gave



83 Madugin R = H
84 Methylmadugin R = Me

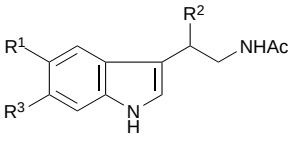


85 Prebalamide

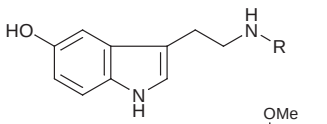


86 Balasubramide

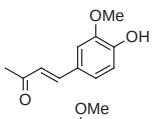
four new tryptamine derived amides, madugin **83**, methylmadugin **84**, prebalamide **85** and balasubramide **86**.[27] Five new alkaloids **87**–**91** were obtained from biotransformations using *Streptomyces staurosporeus*.[28] Four novel indole



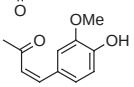
	R^1	R^2	R^3
87	H	OH	H
88	F	OH	H
89	H	OH	F
90	*O*-β-D-quinovose	H	H
91	*O*-α-L-rhamnose	H	H

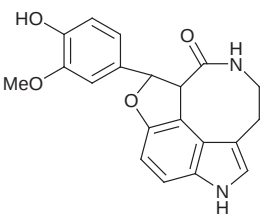


92 Moschamine R =

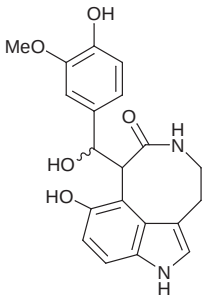


93 *cis*-Moschamine R =



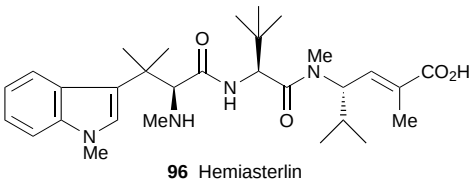


94 Moschamindole

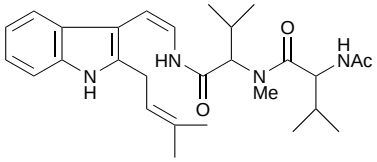


95 Moschamindolol

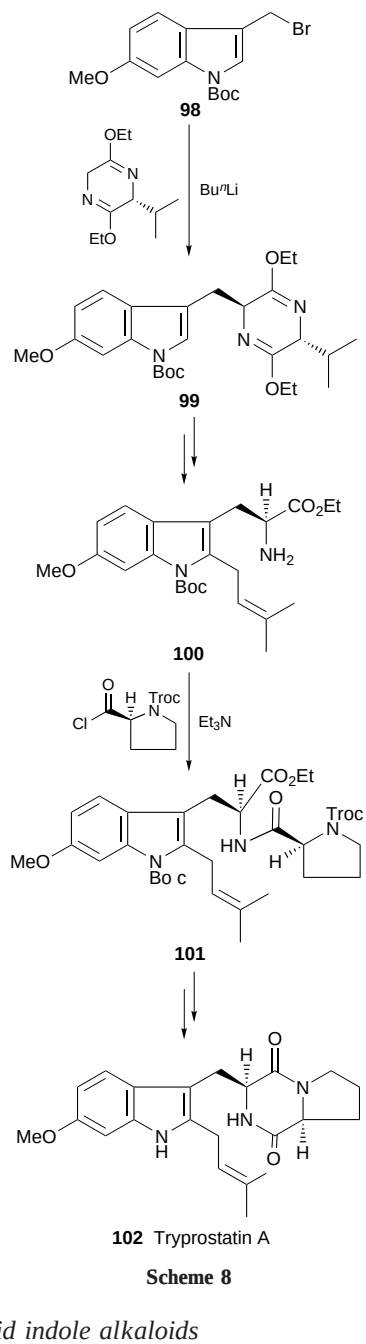
alkaloids, moschamine **92**, *cis*-moschamine **93**, moschamindole **94** and moschamindolol **95**, have been isolated from the seeds of *Centaurea moschata*. The structures of these compounds were determined primarily on the basis of NMR



96 Hemiasterlin



97 Terpeptin



98

99

100

101

102 Tryprostatin A

Scheme 8

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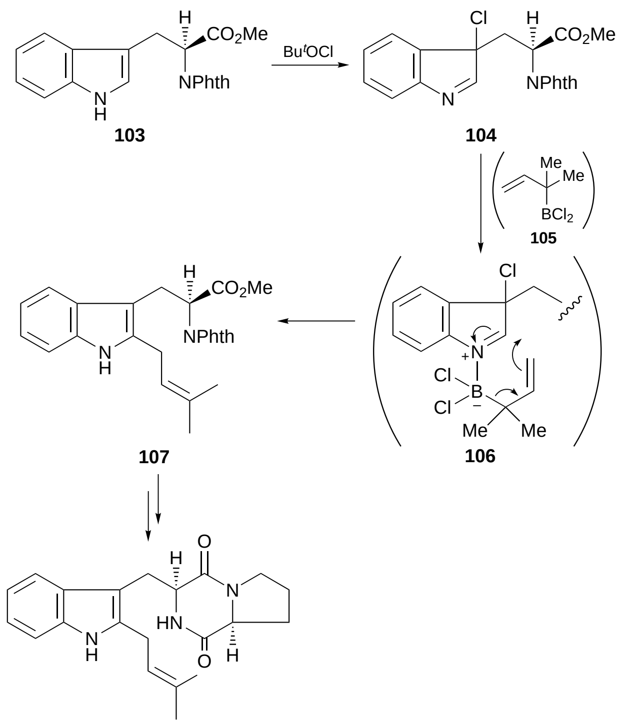
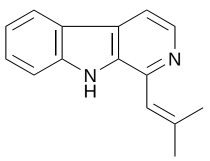
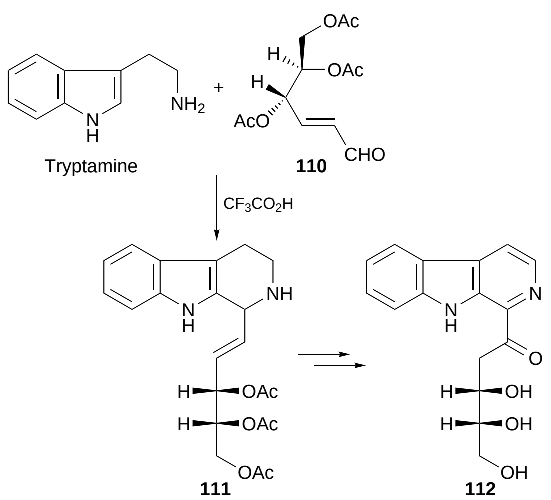


108 Tryprostatin B

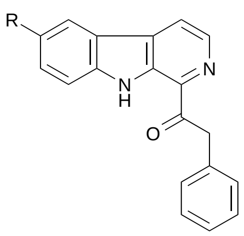
Scheme 9

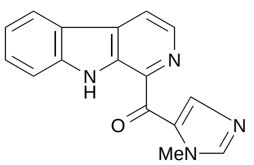


109 Vulcanine



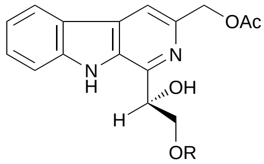
Scheme 10

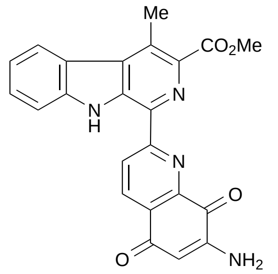




113 Eudistomin S R = Br
114 Eudistomin T R = H

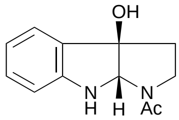
115 Xestomanzamine A





116 Pyridiondolol K1 R = Ac
117 Pyridiondolol K2 R = H

118 Lavendamycin methyl ester



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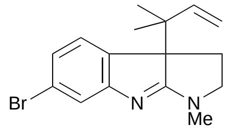
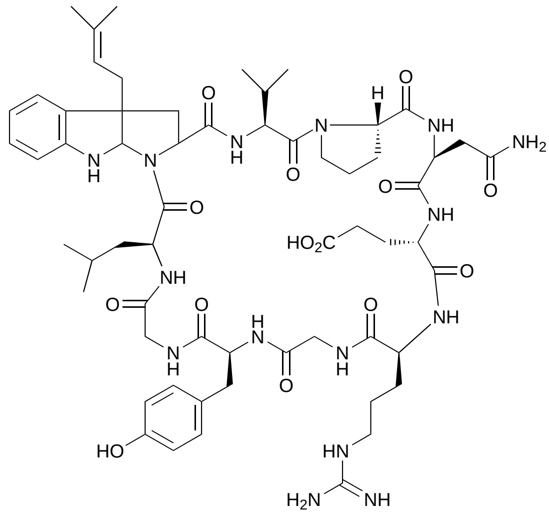
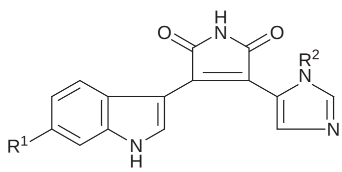


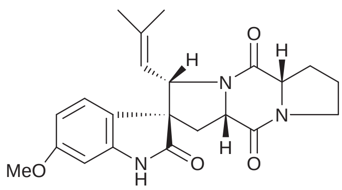
120 Flustramine C



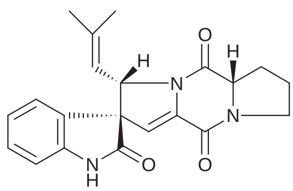
121 Oscillatorin



	R^1	R^2
122a Didemnimide A	H	H
122b Didemnimide B	Br	H
122c Didemnimide C	H	Me
122d Didemnimide D	Br	Me



123 Spirotryprostatin A



124 Spirotryprostatin B

experiments.[29] An improved degradation procedure for determination of the absolute configuration in chiral β-carboline derivatives has been reported.[30] Hemiasterlin **96** is an antibiotic agent which inhibits tubulin polymerisation by binding

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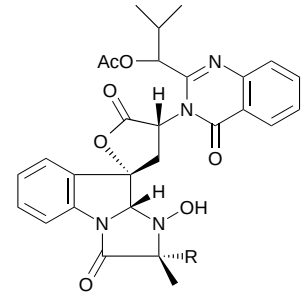
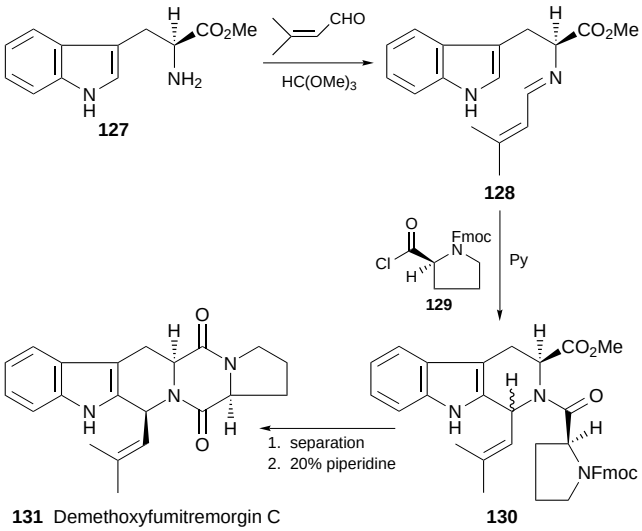
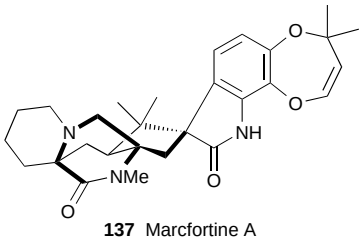


125 27-*epi*-Nortryptoquivaline R = H
126 27-*epi*-Tryptoquivaline R = Me



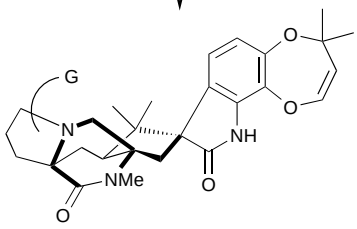
127 **128** **129** **130** **131** Demethoxyfumitremorgin C

Scheme 11



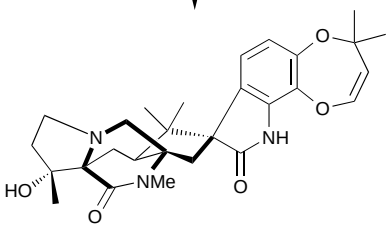
137 Marcfortine A

6 steps



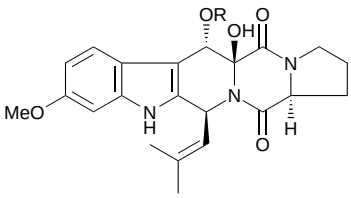
138 Paraherquamide B

7 steps

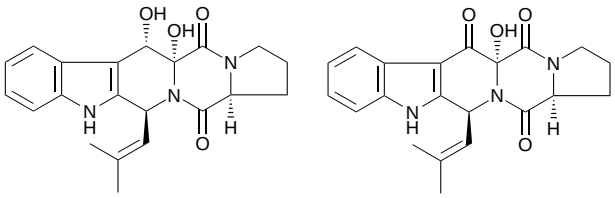


139 Paraherquamide A

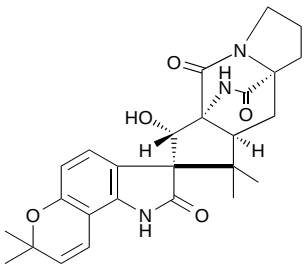
Scheme 12



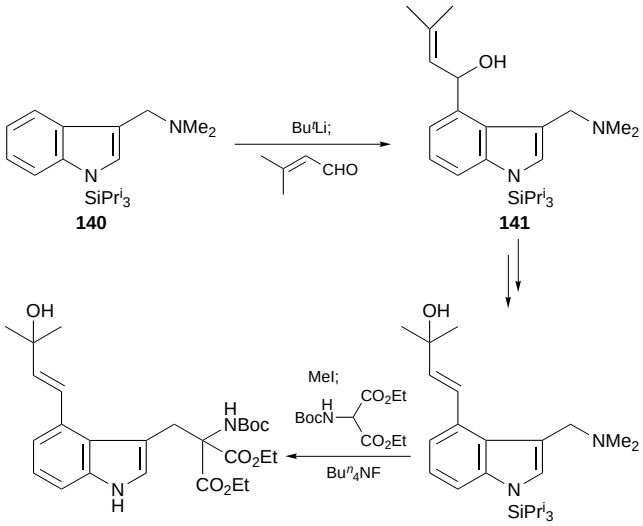
132 Cyclotryprostatin A R = H
133 Cyclotryprostatin B R = Me



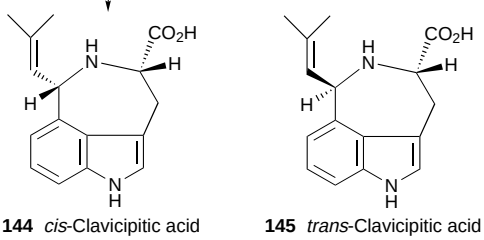
134 Cyclotryprostatin C **135** Cyclotryprostatin D



136 Sclerotiamide



140 **141** **142** **143**



144 *cis*-Clavicipitic acid **145** *trans*-Clavicipitic acid

Scheme 13

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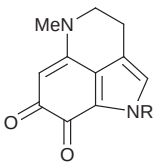
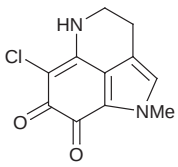
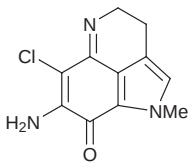


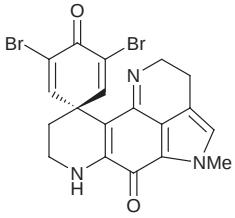
146 Damirone A R = Me
147 Damirone B R = H



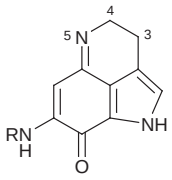
148 Batzelline C



149 Isobatzelline C



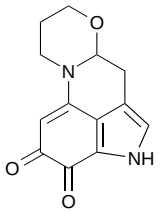
150 Discorhabdin C



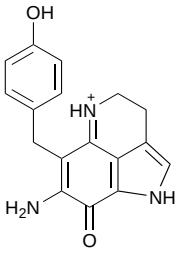
151a Makuluvamine A R = H
151b Makuluvamine B 3,4-dihydro-
151c Makuluvamine C N^{+}5-Me
151d Makuluvamine D R = 4-$HOC_6H_4(CH_2)_2$

to the Vinca alkaloid site. A general synthetic route to this family of peptides has been accomplished.[31] A novel mammalian cell cycle inhibitor, terpeptin **97**, has been isolated from the cultured broth of *Aspergillus terreus* and its structure was elucidated by spectral analyses.[32]

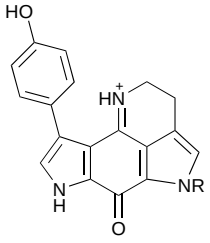
Tryprostatins A **102** and B **108** are cell cycle progression inhibitors of tsFT210 cells in the G2/M phase: **102** and **108** have been prepared independently by two different groups. When the bromide **98** was alkylated with the Schöllkopf chiral auxiliary, only one diastereomer **99** was obtained. A series of functional group modifications in **99** led to the tryptophan ethyl ester **100**. After amidation, the proline substituted intermediate **101** was converted to **102** (Scheme 8).[33] 3-Chloroindolenine **104**, synthesised from *N*-phthaloyl-L-tryptophan methyl ester **103** with *tert*-butyl hypochlorite, was treated with the allyl borane derivative **105** to afford the desired prenylated **107** by way of the 'ate'-like intermediate **106**. Functional group manipulations of **107** led to (−)-tryprostatin B **108** (Scheme 9).[34]



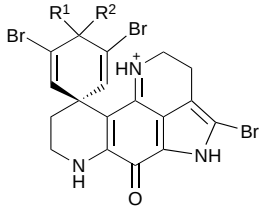
152 Haematopodin



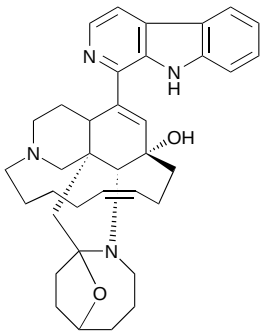
153 Veiutamine



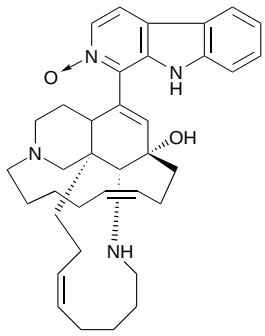
154a Tsitsikammarine A R = H
154b Tsitsikammarine B R = Me



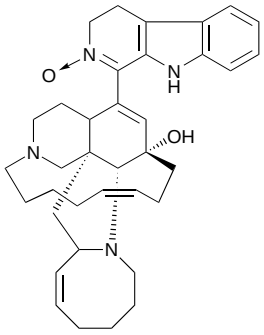
155 14-Bromodiscorhabdin C
$R^1 + R^2 = O$
156 14-bromodihydrodiscorhabdin C
R^1 = OH, R^2 = H



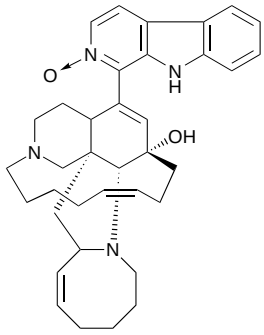
157 6-Deoxymanzamine X



158 Manzamine J *N*-oxide



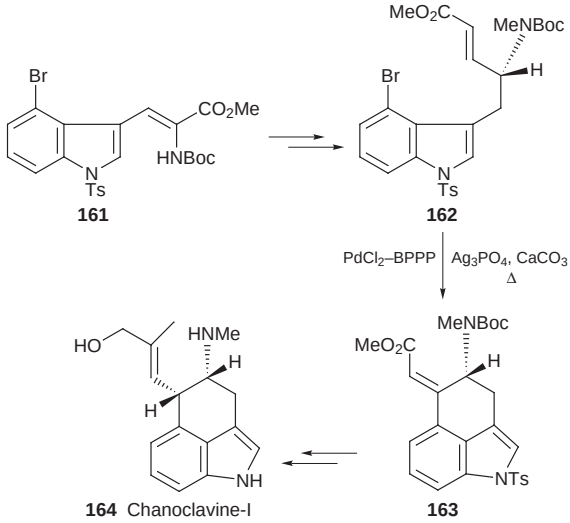
159 3,4-Dihydromanzamine A *N*-oxide



160 Manzamine A *N*-oxide

Simple β-carboline alkaloid, vulcanine **109**, has been isolated from *Haplophyllum vulcanicum* and its structure was established by X-ray analysis.[35] The structure of new β-carboline triol **112**, isolated from cultured hybrid cells of two Apocynaceae plants *Rauwolfia serpentina* and *Rhazya stricta*, was confirmed by its total synthesis. The aldehyde **110**, prepared from D-glucose, was condensed with tryptamine in the presence of CF_3CO_2H to yield the tetrahydro-β-carboline **111**, which was transformed into **112** by several steps (Scheme 10).[36] Antimicrobial active eudistomins S **113**, T **114** and xestomanzamine A **115**, which display cytotoxic activity, have been synthesised employing a tandem aza Wittig–electrocyclic ring closure process.[37]

Pyridiondolols K1 **116** and K2 **117** were isolated from the culture broth of *Streptomyces* species. In particular, **117** inhibits the adhesion of HL-60 cells to LPS-activated HUVEC



161 **162** **163** **164** Chanoclavine-I

Scheme 14

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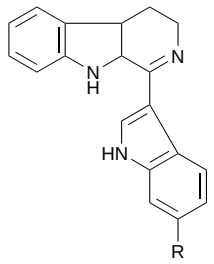
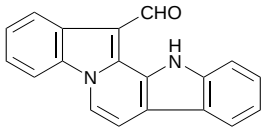
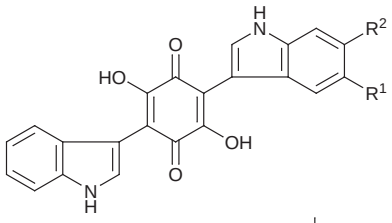
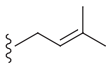


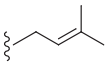
165a 19-Bromoisoeudistomin U R = Br
165b Isoeudistomin U R = H

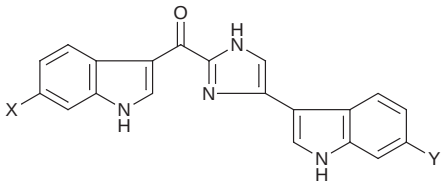


166 Homofascaplysin C

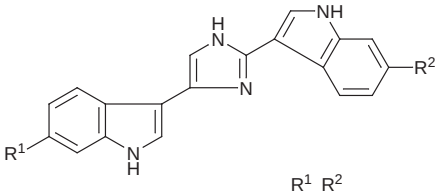


167a Semicochliodinol A R^1 =  ; R^2 = H

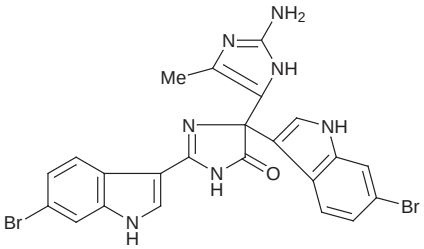
167b Semicochliodinol B R^1 = H; R^2 = 



		X	Y
169a	Deoxytopsentin	H	H
169b	Topsentin	OH	H
169c	Bromotopsentin	OH	Br



		R^1	R^2
170a	Nortopsentin A	Br	Br
170b	Nortopsentin B	Br	H
170c	Nortopsentin C	H	Br

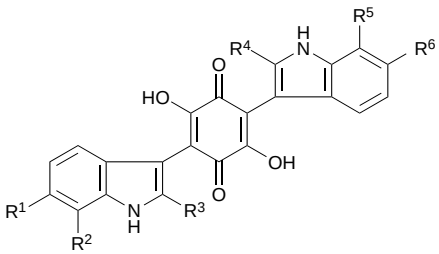


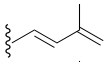
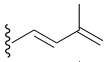
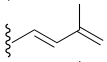
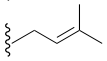
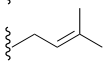
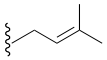
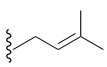
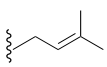
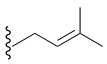
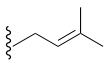
171 Nortopsentin D

monolayer (IC_{50} = 75 μg ml^{-1}).[38] A practical preparation of the potent antitumor agent lavendamycin methyl ester **118** has been achieved.[39]

A new tryptamine metabolite, **119**, was isolated from *Streptomyces staurosporeus*.[40] The first total synthesis of flustramine C **120** was accomplished employing a tandem olefination-Claisen rearrangement process as the key step.[41] Oscillatorin **121**, a chymotrypsin inhibitor, was isolated from freshwater toxic cyanobacterium *Oscillatoria agardii*, and its structure was elucidated by chemical degradation and NMR analyses.[42]

Four new alkaloids, didemnimides A–D (**122a–d**), possessing a unique indole–maleimide–imidazole carbon skeleton, have been obtained from the Caribbean mangrove ascidian *Didemnum conchyliatum*.[43] Two novel diketopiperazine alkaloids, spirotryprostatin A **123** and B **124**, were isolated as new inhibitors of the mammalian cell cycle from the secondary metabolites of *Aspergillus fumigatus* through a separation procedure guided by cell cycle inhibitory activity.[44] From



		R^1	R^2	R^3	R^4	R^5	R^6
168a	Asterriquinone CT1		H	H	H	H	
168b	Asterriquinone CT2		H	H	H	H	
168c	Asterriquinone CT3		H	H	H	H	
168d	Asterriquinone CT4	H		H	H		H
168e	Asterriquinone CT5	H	H			H	H

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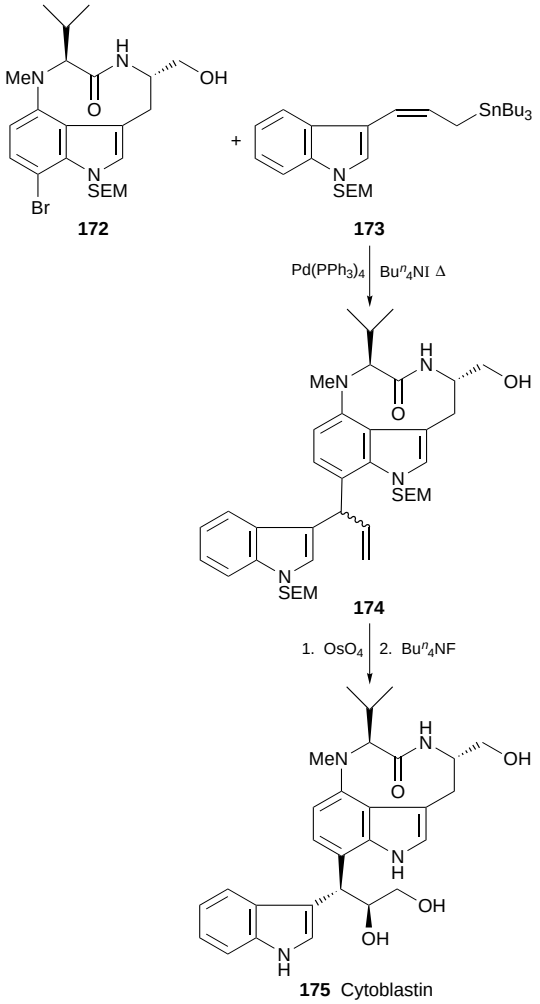
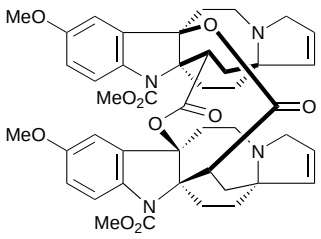
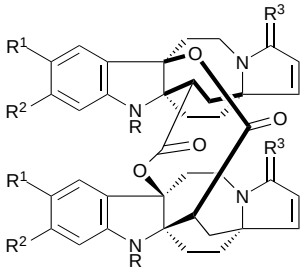


Scheme 15





		R	R^1	R^2	R^3
177a	Tenuisine B	CO_2Me	OMe	OMe	H_2
177b	Tenuisine C	CO_2Me	OMe	H	O

Corynascus setosus, two new 27-*epi*-isomers of tryptoquivalines **125** and **126** have been obtained.[45]

Cell cycle inhibitor, demethoxyfumitremorgin C **131**, was synthesised *via* acyliminium Pictet–Spengler condensation. After conversion of L-tryptophan methyl ester **127** to the imine **128**, the pivotal acyliminium Pictet–Spengler condensation of **128** was performed by treatment with the acid chloride **129** to furnish the tetrahydro-β-carboline **130**. Separation followed by deprotection gave rise to **131** (Scheme 11).[46]

Four new natural diketopiperazine derivatives, cyclotryprostatins A **132**, B **133**, C **134** and D **135**, were isolated as new inhibitors of the mammaliam cell cycle from the secondary metabolites of *Aspergllus fumigatus*. The structures of these natural products were determined by detailed analyses of their ^{1}H and ^{13}C NMR spectra.[47] A new member of the paraherquamide class with potent insecticide activity, sclerotiamide **136**, has been isolated from the sclerotia of *Aspergillus sclerotiorum*.[48] The paraherquamides and marcfortines are a novel class of anthelmintics. Only one structural difference between paraherquamide A **139** and marcfortine A **137** occurs in ring G. Beginning with marcfortine A **137**, the first formal synthesis of paraherquamide A **139** has been achieved *via* paraherquamide B **138** in 13 steps (Scheme 12).[49]

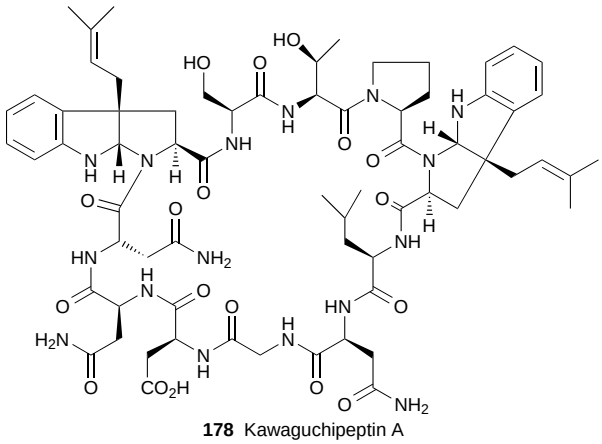
A concise total synthesis of (±)-clavicipitic acids **144** and **145** was accomplished by combinational use of 4-selective lithiation of **140** and a fluoride ion-induced elimination–addition reaction of **142** with an aminomalonate derivative as the key step (Scheme 13).[50]

Several marine alkaloids such as damirone A **146** and B **147**, batzelline C **148**, isobatzelline C **149**, discorhabdin C **150** and makuluvamine A **151a**, B **151b**, C **151c** and D **151d** were synthesised utilising quinoline derivatives as the synthetic intermediate.[51] A mushroom pigment, haematopodin **152**, has been prepared from 6,7-bis(benzyloxy)indole.[52] Veiutamine **153**, a new pyrroloiminoquinone derivative, was isolated from the Fijian sponge *Zyzzya fuliginosa*: **153** is the first pyrroloiminoquinone alkaloid bearing a C-6 *p*-benzyloxy substituent.[53] New bis-pyrroloiminoquinone alkaloids, tsitsikammarine A **154a** and B **154b**, and novel pyrroloiminoquinones, 14-bromodiscorhabdin C **155** and 14-bromodihydrodiscorhabdin C **156**, have been isolated from a South African latrunculid sponge, and all these natural products show antimicrobial activity.[54]

Analysis of the Phillippine marine sponge *Xestospongia ashmorica* afforded four novel manzamine congeners **157**–**160**. These structures were unambiguously established on the basis of spectroscopic data. 3,4-Dihydromanzamine A *N*-oxide **159** and manzamine A *N*-oxide **160** exhibit cytotoxicity against L1578y mouse lymphoma cells.[55] Several synthetic studies toward the unusual skeleton have been reported.[56,57]

3 Ergot alkaloids

A diastereoselective total synthesis of (–)-chanoclavine-I **164**, an ergot alkaloid, has been accomplished. Intramolecular



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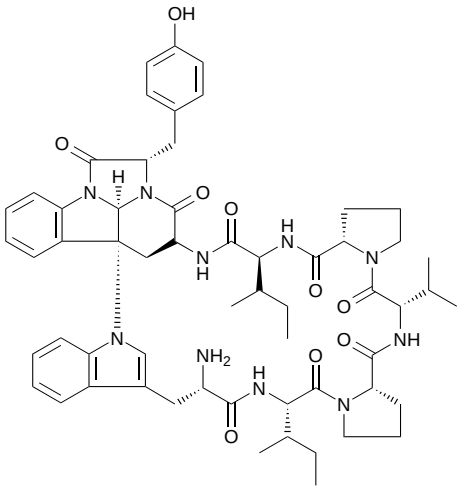
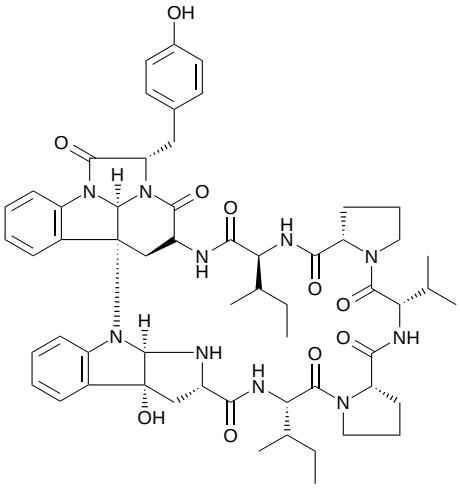
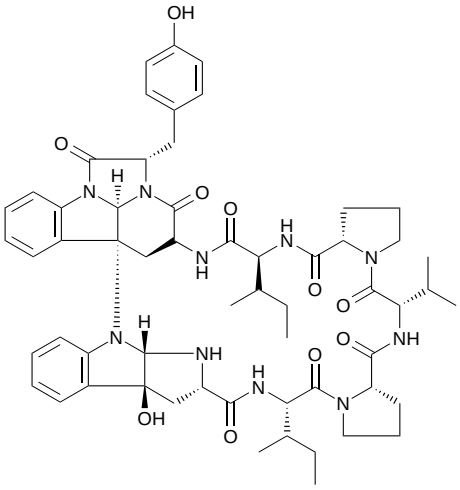


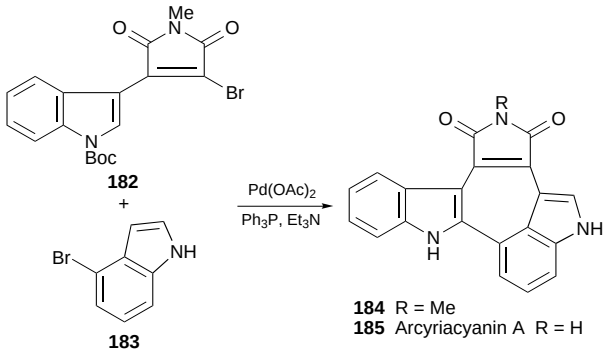
179 Kapakahine A



180 Kapakahine C



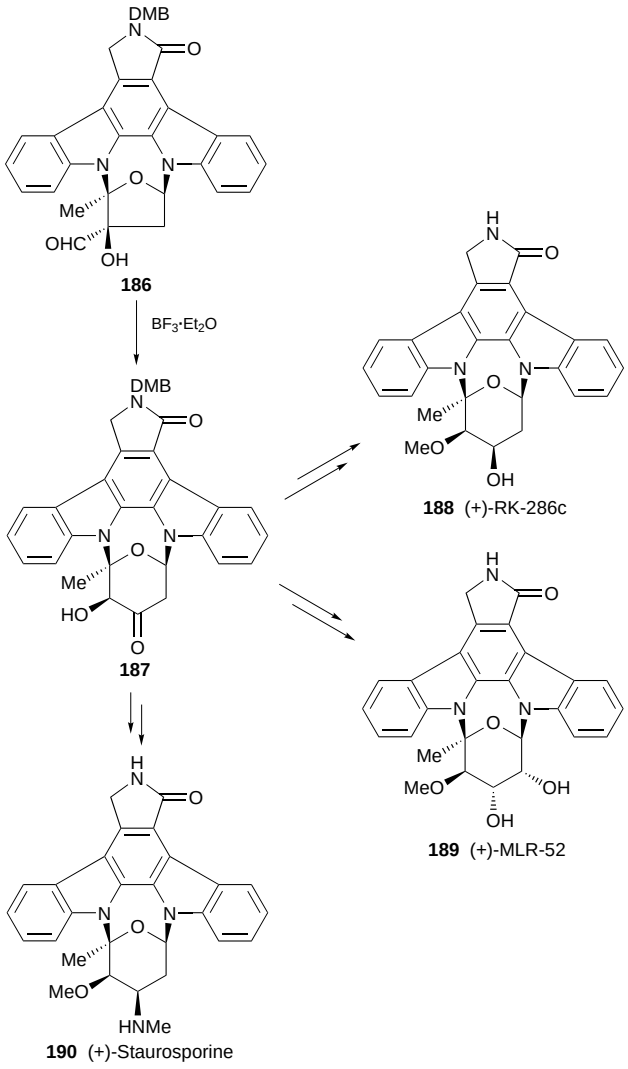
181 Kapakahine D



182 + **183**

184 R = Me
185 Arcyriacyanin A R = H

Scheme 16



186 **187** **188** (+)-RK-286c **189** (+)-MLR-52 **190** (+)-Staurosporine

Scheme 17

Heck reaction of the conjugate ester **162** yielded the expected tricyclic ester **163**, which was transformed into (−)-**164** by several steps (Scheme 14).[58]

4 Bisindole alkaloids

19-Bromoisoeudistomin U **165a** and isoeudistomin U **165b**, two new dihydro-β-carbolines, have been isolated from an undescribed Western Australian ascidian of the genus *Eudistoma*.[59] A short and efficient synthesis of homofascaplysin C **166**, the first natural 12*H*-pyrido[1,2-*a*:3,4-*b*′]diindole, was achieved.[60] Semicochliodinols A **167a** and B **167b** have been isolated as inhibitors of HIV-1 protease from the culture broth of the fungus *Chrysosporium merdarium* P-5656. The structures were elucidated by spectroscopic methods. The metabolites inhibit HIV-1 protease with an IC_{50} value as low as 0.17 μM and epidermal growth factor receptor protein tyrosine kinase at 15–60 μM.[61] Five new quinone pigments asterriquinones CT 1–5 **168a–e** have been discovered from the fermentation broth of *Aspergillus*, *Humicola* and *Botryotrichum* species isolated

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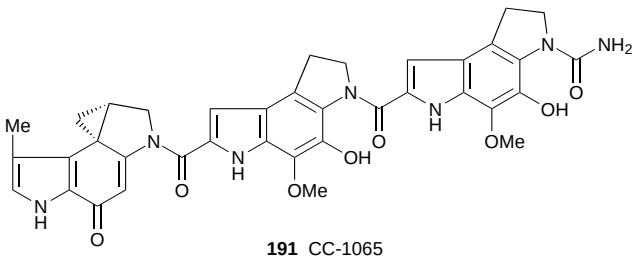
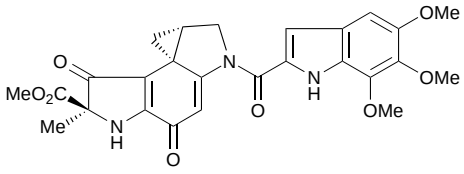


191 CC-1065

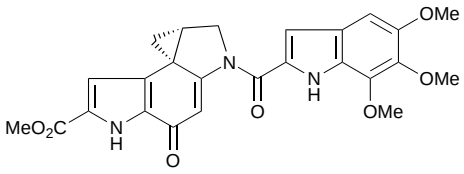
from different soil samples. These natural products show serine proteases of the coagulation pathway.[62]

Total syntheses of three marine bisindole alkaloids, deoxytopsentin **169a**, topsentin **169b** and bromotopsentin **169c**, have been reported.[63] Cytotoxic and antifungal constituents of a marine sponge, *Spongosorites ruetzleri*, nortopsentins A **170a**, B **170b** and C **170c** have been prepared through a palladium-catalysed cross-coupling reaction as the key step.[64] Nortopsentin D **171**, a bisindole alkaloid, was isolated from the deep-water axinellid sponge *Dragmacidon* species: **171** possesses a 2-amino-5-methylimidazole appendage at the central 4,5-dihydro-1*H*-imidazol-5-one nucleus.[65]

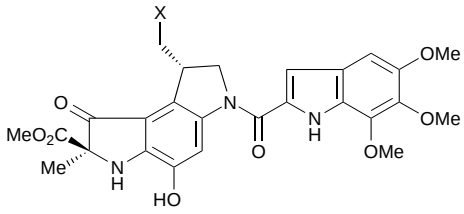
The first total synthesis and stereochemical elucidation of cytoblastin **175**, a low molecular weight immunomodulator produced by *Streptoverticillium eurocidium*, has been reported. Palladium-mediated coupling reaction of 7-bromoindolactam V **172** with the allylstannane **173** provided **174**, which was subjected to osmylation to afford the desired triol as the major product. After removal of the protecting groups, cytoblastin **175** was obtained. The success of the above total synthesis rests



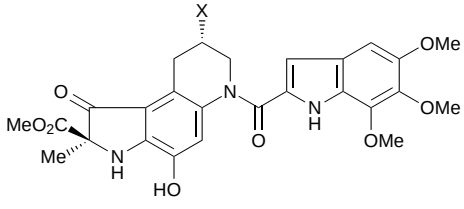
192a Duocarmycin A



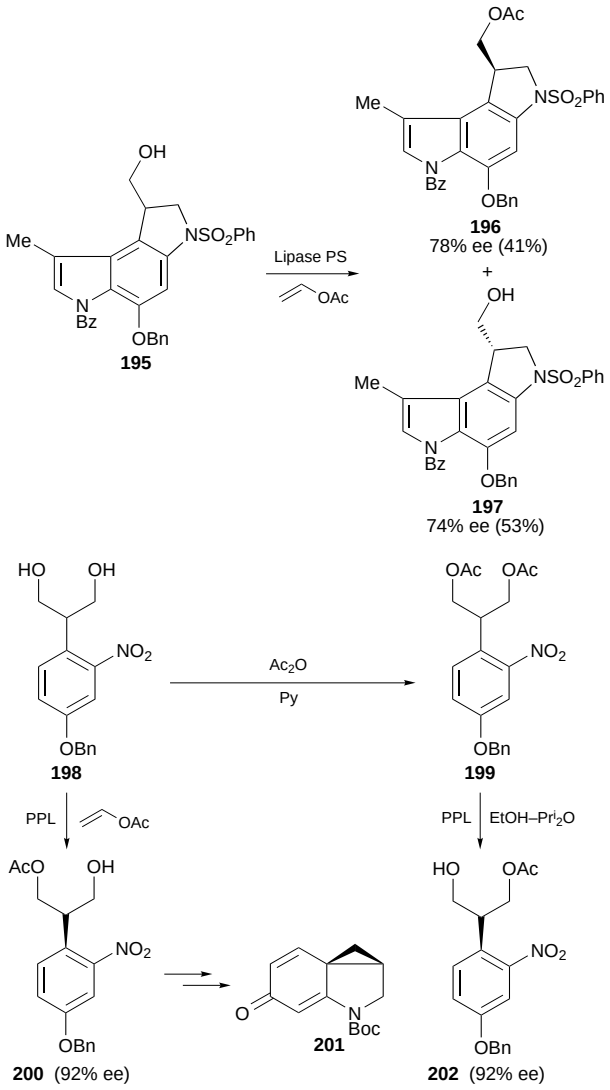
192b Duocarmycin SA



193a Duocarmycin B_2 X = Br
193b Duocarmycin C_2 X = Cl



194a Duocarmycin B_1 X = Br
194b Duocarmycin C_1 X = Cl



Scheme 18

on high regio- and stereo-selectivities observed through the overall sequence (Scheme 15). Synthetic **175** matched the naturally occurring cytoblastin in all analyses performed. After re-investigation on the biological activity of **175**, it was found that cytoblastin **175** exhibited an activity toward PKC that is roughly equivalent to that of (−)-indolactam V.[66]

Three novel dimeric indoles, tenuisines A **176**, B **177a** and C **177b**, were isolated from *Kopsia tenuis*. These natural products possess a unique carbon framework with a C_2 axis and their structures were elucidated by spectral analysis.[67] Kawaguchipeptin A **178**, a novel cyclic undecapeptide, has been obtained from cyanobacterium *Microcystis aeruginosa*. The absolute stereochemistry of **178** was deduced by a combination of spectral and chemical studies.[68] The marine sponge *Cribrochalina olemda* gave three cyclic peptides, kapakahines A **179**, C **180** and D **181**, and their structures including complete stereochemistry were elucidated by spectral analysis and chemical elucidation. The three octapeptides have identical eastern amino acid patterns.[69]

Arcyriacyanin A **185**, a modified bisindolylmaleimide alkaloid isolated from yellowish sporangia of the slime mold *Arcyria obvelata*, has been prepared by three different methods. The most sophisticated route is shown in Scheme 16. Namely, a domino Heck reaction between bromo(indolyl)-maleimide **182** and 4-bromoindole **183** was conducted to give rise to the hexacyclic compound **184**, which was converted to **185**.[70]

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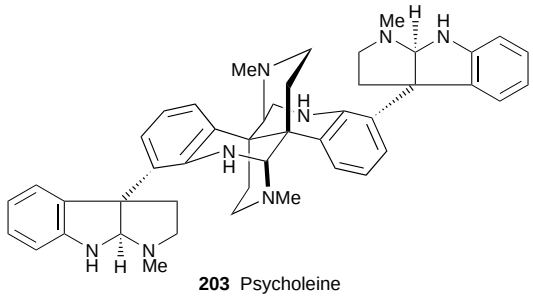
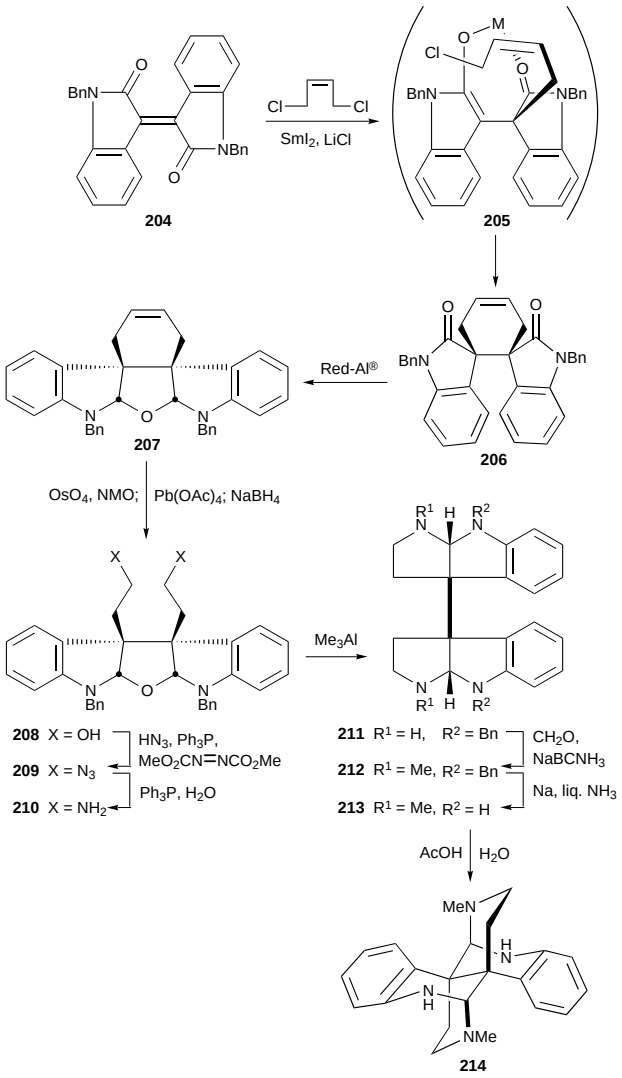


203 Psycholeine

Many compounds containing an indolopyrrolocarbazole ring system have recently been reported to inhibit protein kinase C or topoisomerases. In order to develop an effective synthetic route to the target molecules, a unified strategy *via* the common intermediate has recently been reported.[71] Interestingly, ring expansion of the hydroxy aldehyde **186** proceeded stereo- and regio-selectively to **187**, which was in turn transformed into (+)-RK-286c **188**, (+)-MLR-52 **189** and (+)-staurosporine **190** (Scheme 17).

Reviews about CC-1065 **191** and duocarmycins **192**–**194**, which show strong cytotoxic activity, have been published.[72] Enzymatic preparations of optically active precursors (**196**, **197**, **200** and **202**) of CPI unit and the common pharmacophore of CC-1065 and duocarmycins have been reported independently by two groups (Scheme 18).[73] Details concerning the syntheses, chemical properties and evaluation of CC-1065 **191** and duocarmycins **192**–**194** have been published.[74]



Scheme 19

Following the isolation of the dodecacyclic polyindole alkaloid, psycholeine **203**, and the demonstration of its potential pharmacological uses, a number of chemists pursued its total synthesis. Recently, a stereocontrolled total synthesis of *meso*-chimonanthine **213** and *meso*-calycanthine **214** has been published as the initial step in the development of a strategy for the total synthesis of psycholeine **203**.[75] The key conversion of **204** to **206** was accomplished by a samarium-promoted reductive dialkylation *via* the chelation transition state **205**. After Red-Al® reduction of **206**, the structure of the resulting hexacyclic compound **207** was elucidated by X-ray analysis. Further transformation led to the exclusive formation of the *meso*-chimonanthine **213**, whose structure was also confirmed by X-ray crystallography. Finally, **213** was converted to the *meso*-calycanthine **214** (Scheme 19).

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