MARINE, NITROGEN-CONTAINING HETEROCYCLIC NATURAL PRODUCTS - STRUCTURES AND SYNTHESES OF COMPOUNDS CONTAINING INDOLE UNITS

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Abstract - The structures, biological activities, and syntheses of marine natural products containing indole and dihydroindole nuclei are reviewed.

The natural product chemistry of sea-dwelling organisms has been developed only over the last twenty years or so;[1] a fascinating variety of heterocyclic natural products,[2,3] many structurally novel, and many with significant biological acitivity, have been described. Because of the obvious relevance to medicinal chemistry we have reviewed the structures, biological activities, and syntheses of marine alkaloids containing quinoline and/or isoquinoline nuclei,[4] and here deal in the same way with indole- (and dihydroindole-) -containing compounds.[5]

Most marine alkaloids are probably derived by elaboration of amino acid precursors, but necessarily in ways which are different from the relatively familiar biosynthetic pathways established for the plant alkaloids.[6] Experimental study of the biosynthetic pathways leading to sea alkaloids is virgin territory.[7]

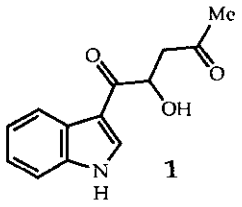
This Review covers the literature to the end of 1990, deals only with structure and synthesis, and arbitrarily excludes compounds which contain an indole nucleus simply as a tryptophan side-chain in a peptide. Reported biological activity is also mentioned.

(a) Simple Indoles (non-tryptamines)

Structures

The compound produced by an *Alteromonas* sp. bacterial strain inhabiting the surface of embryos of the caridean shrimp *Palaemon macrodectylus*, which protects them

from the otherwise lethal effects of infection by the pathogenic fungus *Lagenidium callinectes*, was shown to be simply isatin.[8] 3-Formylindole was isolated from the sponge *Dysidea etheria*[9] and in low yield from the alga *Botrocladia leptopoda*[10] and from an unidentified marine *Pseudomonas*,[11] in this last case along with its 6-bromo-derivative, indeed a large number of halogenated, simple indoles have been isolated from marine sources, many of them having antifungal activity (see below). Also isolated from *D. etheria*[9] were indol-3-ylacetamide and diketo alcohol (**1**), which is a plant growth regulator. Indolyl ketone (**2**) was obtained from an algae-infested



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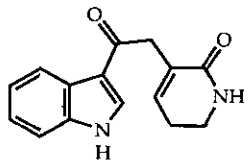
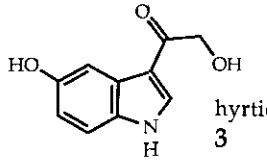
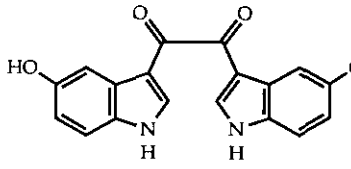


2

sample of the sponge *Halichondria melanodocia*; it was pointed out that it is often difficult to be sure, in marine natural product chemistry, whether the isolated metabolite is produced by the animal under study, or by an algal infestation, or indeed has simply been ingested.[12] As well as 5-hydroxyindol-3-aldehyde, hyrtiosines A and B, (**3**) and (**4**), also indolyl ketones, were obtained from the Okinawan sponge *Hyrtios erecta*.[13]



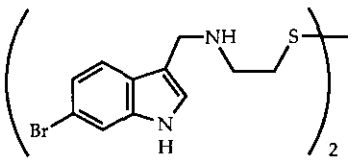
hyrtiosine A
3



hyrtiosine B
4

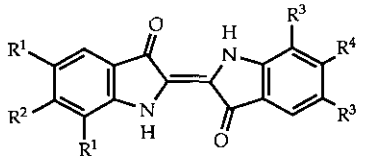
The Caribbean alga *Laurencia brogniartii* produces 'copious' amounts of brominated indoles having antibacterial and antifungal activity; after separation into four components, 2,3,6-tribromo-1-methyl-, 2,3,5-tribromo-1-methyl-, 2,3,5,6-tetrabromo-1-methyl- and 2,3,5,6-tetrabromoindoles, only the latter had antimicrobial activity.[14] Antifungal activity was also noted in the mixture of halogenated indoles obtained from the red, New Zealand waters alga, *Rhodophyllis membranacea*, separation giving trihalogenated: 2,3,7-tribromo-, 2,3,7-trichloro-, 7-bromo-2,3-dichloro-, 2,7-dibromo-3-chloro-, and 2,3,4-trichloro-, and tetrahalogenated: 2,3,4,7-tetrabromo-, 2,3,4,7-tetrachloro-, 4,7-dibromo-2,3-dichloro-, 2,3-dibromo-4-bromo(chloro)-7-chloro(bromo)-, and 2,3-dichloro-4-bromo(chloro)-7-chloro(bromo)indoles.[15] Acorn worms of the genera *Ptychodera* and *Glossobalanus* also produce simple halogenated indoles which are responsible for the haloform-like odour of the *Ptychodera*; monohalogenated: 3-bromo-, 3-chloro-, dihalogenated: 3,6-dibromo-, 6-bromo-3-chloro-, 5,7-dibromo-6-methoxy-, 4,5-dibromo-, and 4,5-dibromo-2-methyl- and trihalogenated: 3,4,6-tribromo-, 3,5,7-

tribromo- and 3,5,7-tribromo-6-methoxyindoles were identified.[16] Methyl 3-(6-bromoindol-3-yl)-acrylate was isolated from an Australian sponge of the genus *Iotrochota*,[17a] and the corresponding acid, which has potent Ca-releasing activity in sarcoplasmic reticulum, from an Okinawan sponge of the genus *Penares*.[17b]



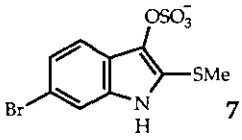
citorellamine
5

The structure of citorellamine, which is cytotoxic, insecticidal, and antimicrobial and isolated from a Fijian tunicate *Polycitorella mariae*, was revised from an earlier assignment[18] to **5**.[19] 2,5,6-Tribromo-1-methylgramine and its *N*-oxide were obtained from a bryazoan, *Zoobotryon verticillatum*, living in Pacific waters near San Diego.[20]



6	R^1	R^2	R^3	R^4
a	H	Br	H	Br
b	Br	OMe	Br	OMe
c	Br	OMe	H	Br

The ancient dye, Tyrian purple (**6a**)[21,22] can be obtained from extracts of the hypobronchial glands of numerous mollusks of the genera *Murex*, *Purpura*, and *Dicathais*. The dye is not itself a natural product being produced from a primary precursor, known as tyrindolyl sulphate (**7**) which has been isolated with, as



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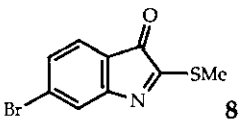

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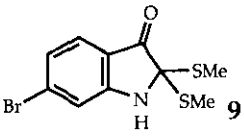

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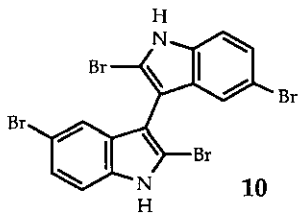
counterion, choline and choline 3-methylbutenoate from *Dicathis orbita* and *Marcinella beineri* respectively,[23] or sodium, from *Ptychodera flava laysanica*.[24]



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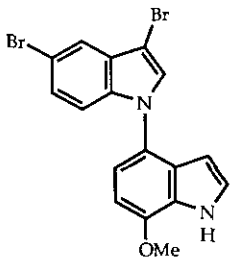

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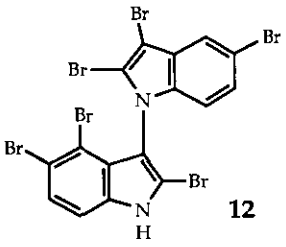
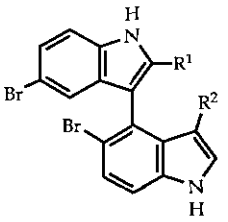


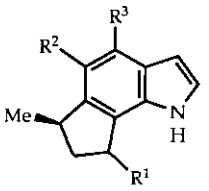
12

Related materials (**8**) and (**9**) were isolated from *Dicanthus orbita*, though it is not clear whether these are artefacts.[25] Other coloured 'dimers' (**6b**) and (**6c**) were obtained from *Ptychodera flava laysanica*.[16] Non-coloured dimers (**10-12**) and (**13a-c**), linked in a different manner, were obtained from the blue-green alga *Rivularia firma*.[26]



13	R^1	R^2
a	Br	Br
b	H	Br
c	Br	H

The five trikentrines (**14a-e**) and the three herbindoles (**14f-h**) probably derive from a different biosynthetic route, the absence of substitution on the pyrrole ring and the alkyl substitution on the benzene ring giving them their structural individuality. The trikentrines were isolated from a sponge, *Trikentrion flabelliforme*, obtained from the coastal waters off Northern Australia; they have antimicrobial activity.[27a] The herbindoles were obtained from an orange sponge *Axinella* sp. from the waters off Western Australia; they are cytotoxic against KB cells. [27b]



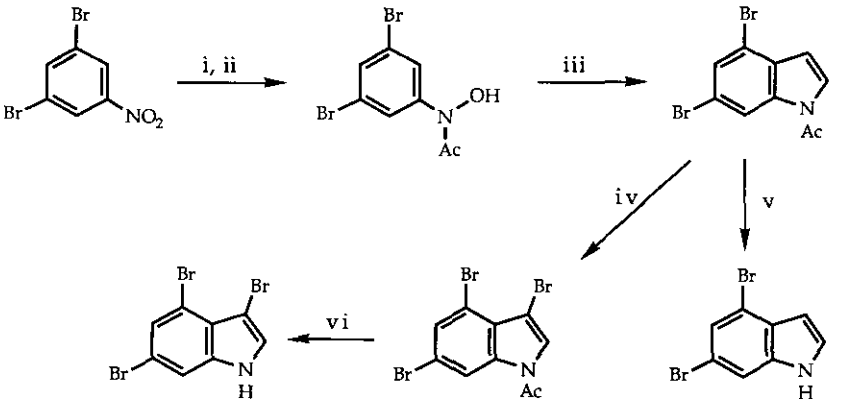
trikentrines: *cis* A, *trans* A,
iso-*trans* B, *cis* B, *trans* B;
herbindoles A, B, C

14	R^1	R^2	R^3
a	β-Me	H	Et
b	α-Me	H	Et
c	α-Me	H	$CH_2CH\overset{E}{=}CHEt$
d	β-Me	$CH\overset{E}{=}CHEt$	H
e	α-Me	$CH\overset{E}{=}CHEt$	H
f	β-Me	Me	Me
g	β-Me	Me	Et
h	β-Me	Me	$CH\overset{E}{=}CHEt$

Syntheses

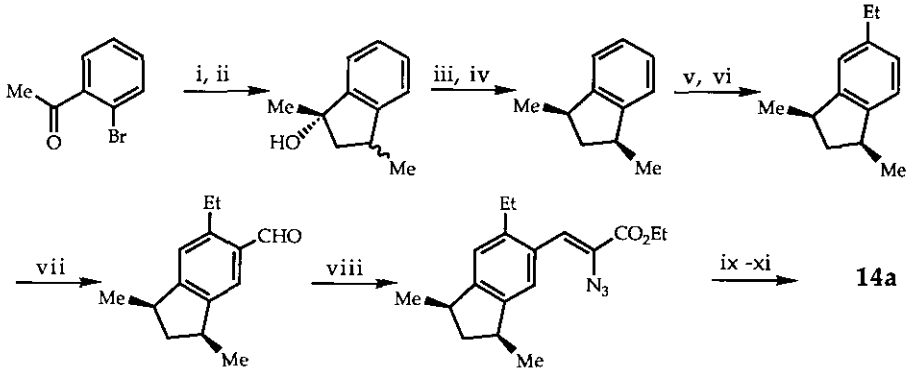
2,3,5,6-Tetrabromoindole[28] and its 1-methyl homologue[29] were obtained by bromination of 1-methylindole and 3-formylindole respectively with bromine in acetic acid. 4,6-Dibromoindole and 3,4,6-tribromoindole were produced *via* a ring synthesis, involving the generation of a hydroxylamine vinyl ether and its hetero-Cope rearrangement,[30] as shown in Scheme 1.[31] The Leimgruber-Batcho procedure was used to provide 6-bromoindole, Vilsmeier formylation then condensation of the aldehyde with methyl malonate affording methyl 3-(6-bromoindol-3-yl)acrylate.[17] Condensation of this same aldehyde with 2-(2-aminoethylthio)ethylamine followed

by borohydride reduction of the imine double bonds provided citorellamine (5).[19] Using sodium hydride as base, gramine was indole-*N*-methylated, halogen introduced by reaction with bromine[32] to provide 2,5,6-tribromo-1-methylgramine which could then be N_b-oxidised using hydrogen peroxide to afford the natural product.[31]



Scheme 1 Reagents : i, H_2, Pt, THF, DMSO, aq. NH_3, room temperature; ii, AcCl, Na_2CO_3, H_2O, Et_2O, 0°C, (76% overall i, ii); iii, $MeCO_2CH{=}CH_2$, Li_2PdCl_4, 55°C (55%); iv, Br_2, CH_2Cl_2, 5-10°C (72%); v, NaOH, MeOH, 10°C (76%); vi, NaOH, MeOH, 10°C (96%).

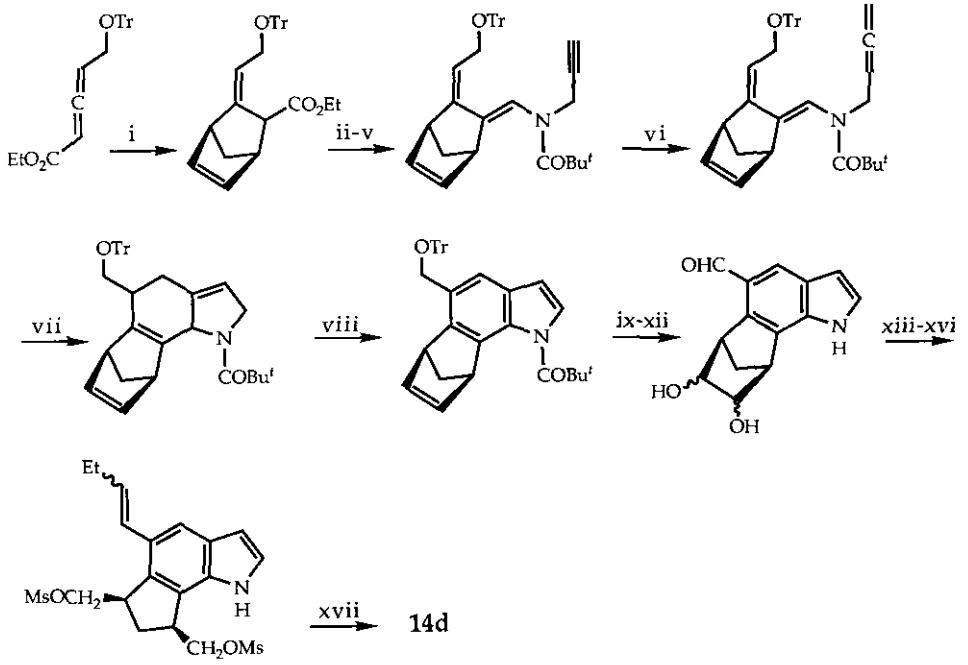
The first trikentrine synthesis[33] employed radical cyclisation to produce a dimethyl-substituted indane, then introducing two further carbon substituents *via* Friedel-Crafts processes, building up the indole using ethyl azidoacetate and a nitrene insertion produced (±)-**14a** (Scheme 2).



Scheme 2 Reagents : i, $CH_2{=}CHCH_2MgBr$, Et_2O (75%); ii, Bu_3SnH, AIBN, PhH, then KF; iii, silica, $CHCl_3$ (-H_2O); iv, H_2, Pd/C, $CHCl_3$ (88%, overall ii-iv); v, AcCl, $AlCl_3$, CH_2Cl_2 (85%); vi, $NaBH_4$, MeOH then H_2, Pd/C, $CHCl_3$ (79%); vii, Cl_2CHOMe, $TiCl_4$, CH_2Cl_2 (74%); viii,

$EtO_2CCH_2N_3$, NaOEt, EtOH; ix, PhMe, heat (95% overall viii,ix); x, KOH, aq. dioxan (74%); xi, FVP (600°C, 0.003 mm Hg) (-CO_2) (89%).

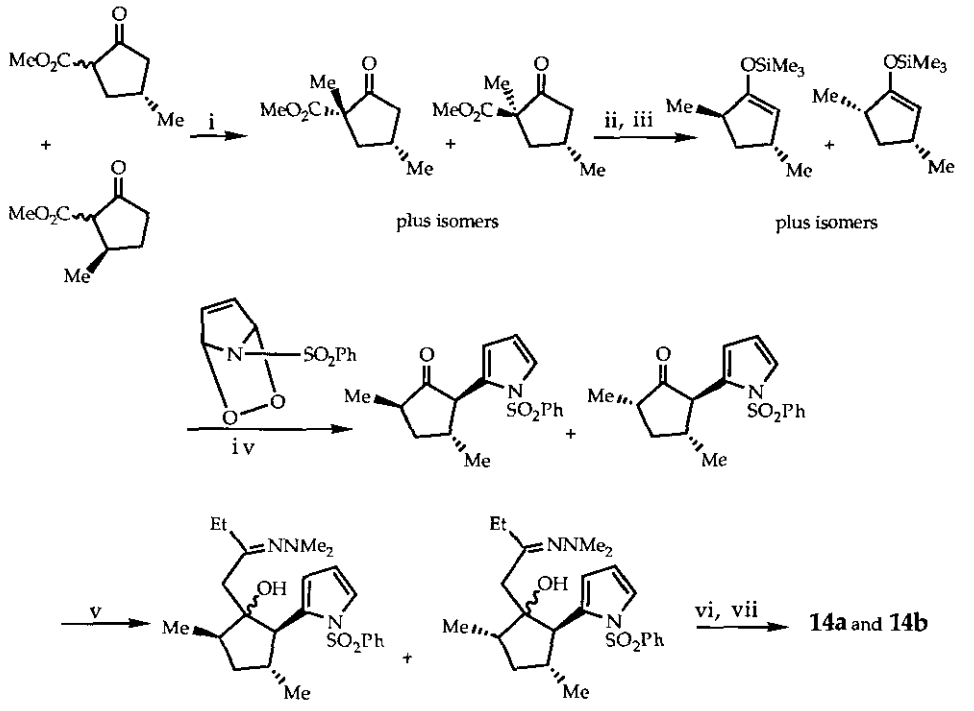
A synthesis[34] of (±)-*cis*-trikentrine B adopted a totally different strategy: an allene cycloaddition with cyclopentadiene was the means for generating the *cis*-substituted five membered ring, albeit requiring a later cleavage of the fused cyclopentene. The indole system, with a necessary 5-carbon substitutent was achieved *via* a second, this time intramolecular, allene cycloaddition, considerable further functional group manipulation completing the synthesis.



Scheme 3 Reagents : i, cyclopentadiene, PhH, 80°C, 3 h (93%); ii, $LiAlH_4$, THF, 0°C, 1 h; iii, PCC, CH_2Cl_2, room temperature, 30 min (78% overall ii, iii); iv, $HC{\equiv}CCH_2NH_2$, 4A sieves, Et_2O, 3 h; v, NaH, DME, -18°C then *t*-BuCOCl, -18°C→room temperature (45% overall iv, v); vi, aq. CH_2O, *i*-Pr_2NH, CuBr cat., dioxan, 100°C (74%); vii, PhMe, 160°C, 2 h (74%); viii, chloranil, PhMe, 110°C (54%); ix, CSA, MeOH, THF, room temperature, 10 h (90%); x, PCC, CH_2Cl_2, room temperature; xi, OsO_4, NMO, aq. dioxan, room temperature; xii, aq. NaOH, MeOH, room temperature, 10 min (60% overall x-xii); xiii, $Ph_3P{=}CHEt$, THF, 0°C→room temperature (60% mixture, E:Z, 2:1); xiv, $NaIO_4$, aq. THF, room temperature, 5 h; xv, DIBAH, PhMe, -78°C, 30 min; xvi, MsCl, NEt_3, CH_2Cl_2, 0°C, 30 min (58% overall xiv-xvi); xvii, Zn, NaI, DME, 85°C (85%).

The absolute configurations of *cis*-trikentrine A and *trans*-trikentrine A were established by a synthesis of their enantiomers (Scheme 4).[35] Deriving from the

degradation of pulegone, (*R*)-3-methyladipic acid was converted into a mixture of dimethylcyclopentanones, the silyl enol ethers from which were reacted with the 1-phenylsulphonylpyrrole/singlet oxygen adduct affording a mixture of cyclopentanone-substituted pyrroles, completion of the carbocyclic ring producing finally a mixture of *cis*- and *trans*-trikentrins A, but enantiomeric with the natural compounds.



Scheme 4 Reagents : i, NaOMe, MeOH, -8°C, 1 h then MeI, -18→20°C, 14.5 h; ii, 47% aq. HBr, 110°C, 6 h (71% mixture of 4 ketones); iii, LDA, THF, Me_3SiCl, -80°C, 15 min (90%); iv, $SnCl_2$, EtOH, -40→0°C (56%); v, $EtC(=NNMe_2)CH_2Li$, PhMe, Et_2O, -75→-65°C, 1 h (61% mixture); vi, H_2SO_4, *i*-PrOH, heat (73% mixture); vii, 20% aq. KOH, DME, MeOH, 90°C, 6.5 h (89%, 52:37, *cis*:*trans*).

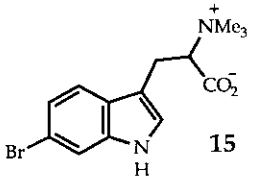
(b) Simple Indoles (tryptamine/tryptophan derivatives)

Structures

This group of substances differs from those in Section (a) in having an intact tryptamine ethanamine side-chain; this is to imply that they are derived biosynthetically from tryptophan/tryptamine but of course many of the compounds

described in the previous section may also have been so derived. Compounds included in this Section do not have any other rings fused to the indole nucleus.

5,6-Dibromotryptamine and 5,6-dibromo-N_b-methyltryptamine, isolated from the Caribbean sponge *Polyfibrospongia maynardii*, are antibacterial;[36] 5-bromo- and 5,6-dibromo-N_b,N_b-dimethyltryptamines were obtained from *Smenospongia aurea* and *S. edine* respectively,[37,38] and 6-bromo-N_b-formyl-N_b-methyltryptamine from *Flustra foliacea*.[39] Tryptophan itself and 6-bromohypaphorine (**15**) were isolated from a British sponge, *Pachymatsima johnstoni*,[40] and the bromotryptophan amide (**16**) as its tetraacetyl derivative, from the British Columbian sponge *Cliona celata*.[41]



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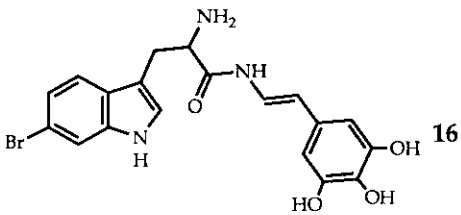

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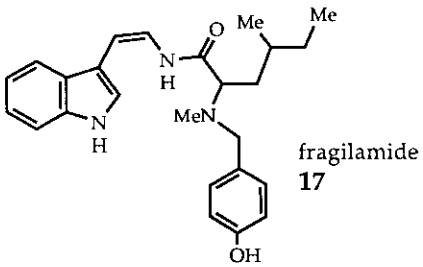
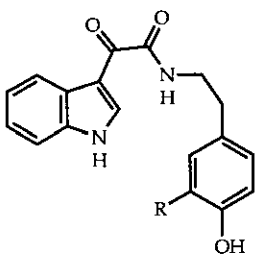
Fragilamide (**17**)[42] from the red alga *Martensia fragilis*, and the polyandrocarpamides A-C[43] (**18a-c**) isolated from a colonial ascidian *Polyandrocarpa* sp. from the Philippines, are also amides clearly derived from tryptamine.



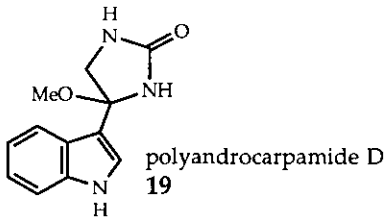
fragilamide
17



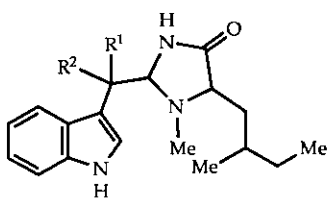
polyandrocarpamides A-C

18	R
a	Br
b	I
c	H

A fourth polyandrocarpamide, D (**19**) incorporates a third nitrogen into a ring thus being both a tryptamine and a gramine.[43] The antibacterial martensines A and B (**20a, b**) isolated from *M. fragilis*, each also have the unusual side-chain seen in co-occurring fragilamide.[42]



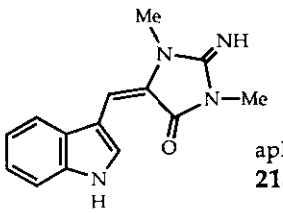
polyandrocarpamide D
19



martensines A and B

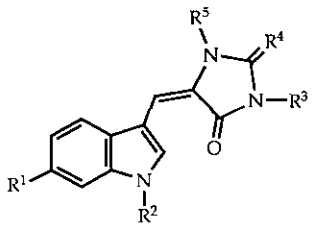
20	R^1	R^2
a	H	OH
b	—O—	

There has been considerable interest in aplysinopsine (**21a**) which has significant antineoplastic activity; this dehydrotryptophan derivative has been obtained from the Great Barrier Reef sponge *Thorecta aplysinopsis*, from *Fascaplysinopsis reticulata*,[44] from the Caribbean sponge *Verongia spengelii*,[45] a *Dendrophylla* sp.,[46] a Mediterranean anthozoan *Astroides calycularis*,[47] and a Japanese coral *Tubastrea aurea*.[48] The E form of aplysinopsine (shown) predominates though this is not true of all analogues; the E/Z ratio in these systems can be influenced by light and heat.[46]



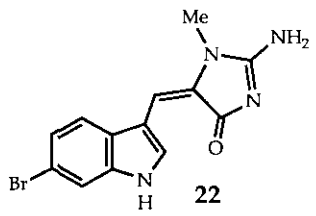
aplysinopsine
21a

The Philippine coral *Dendrophyllia* sp. gave aplysinopsine analogues (**21b**) and (**21c**).[46] *A. calycularis* contained **21d-f**, **21g**, and **21h** came from a *Dercitus* sp.,[49] **21i** from *Smenospongia aurea*,[37] and **21b**, **c**, **i**, and **j** from the coral *Tubastraea* sp.[50]

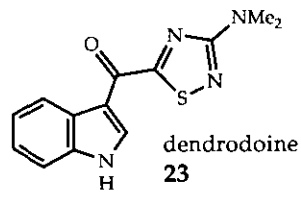


21	R^1	R^2	R^3	R^4	R^5
b	H	H	Me	O	Me
c	H	H	H	O	H
d	Br	H	Me	NH	Me
e	H	COEt	Me	NH	Me
f	Br	COEt	Me	NH	Me
g	H	H	Me	NH	H
h	Br	H	Me	NH	H
i	Br	H	H	O	H
j	Br	H	Me	O	Me

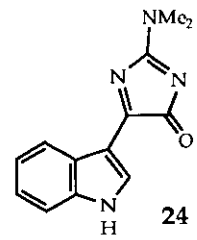
Variant (**22**) is produced by the sponge *S. aurea*[38] and from *Dendrodoa grossularia*[51] sulphur-containing **23** was obtained. The first natural 4*H*-imidazol-4-one, (**24**) was isolated from this same Northern Brittany tunicate.[52]



22

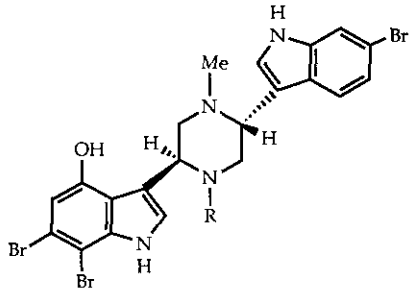


dendrodoine
23



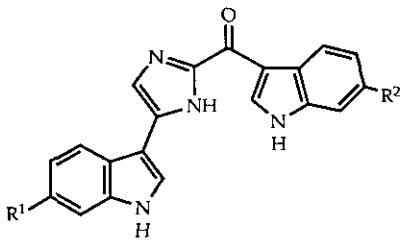
24

In dragmacidon A (**25a**), which inhibits *in vitro* growth of P388 murine leukemia cells and was isolated from the sponge *Dragmacidon* sp.[53] and a sponge, *Hexadella* sp.,[54] and in dragmacidon B (**25b**) from the latter source, evidently two tryptamine units have been combined. One may also discern two tryptamine moieties in the bright yellow topsentines A and B1 (= topsentine) (**26a**) and (**26b**), from the Mediterranean sponge *Topsentia genitrix*,[54,55] B2 (= bromotopsentine) (**26c**) from *T. genetrix* and *Hexadella* sp.,[56,57] and **26b** and **c** together with isotopsentine, hydroxytopsentine (**26d**) and (**26e**), and topsentine C, **27**, a dihydro version from *Hexadella* sp.[54] Bromotopsentine (**26c**) was converted by catalytic hydrogenolysis into topsentine (**26b**).[57] All the topsentines and their analogues are active as antiviral and antitumour agents.



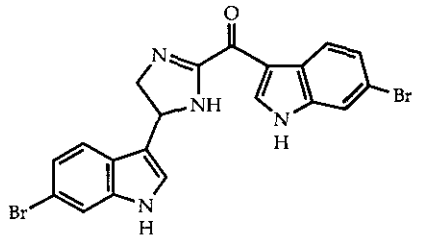
dragmacidons A and B

25	R
a	H
b	Me



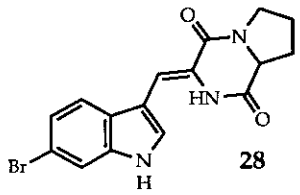
topsentines A, B1, B2, isotopsentine, and hydroxytopsentine

26	R^1	R^2
a	H	H
b	H	OH
c	Br	OH
d	OH	H
e	OH	OH



topsentine C
27

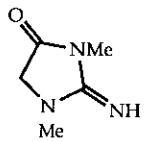
The structure (**28**) originally proposed for barettine,[58] from the sponge *Geodia baretti*, was abandoned after a synthesis[59] of **28** produced material different from the natural amide. A 12-membered cyclic peptide structure, involving two dehydrotryptophans and two prolines was then proposed.



28

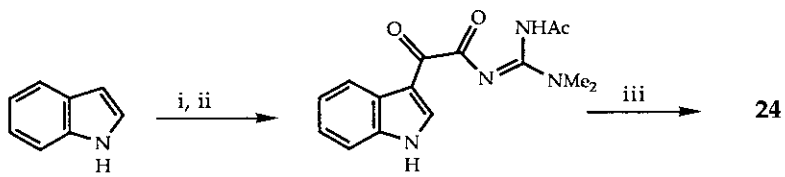
Syntheses

The aplysinopsine type structure and variants, can be readily synthesised[44,46,49-50] by base-catalysed condensation of the appropriate 3-formylindole with a five-ring α-methylene carbonyl compound, *e.g.*, for aplysinopsine itself, **29**, available from creatinine by methylation.[60] The geometry of the double bond formed is that of the stabler isomer.[46]



29

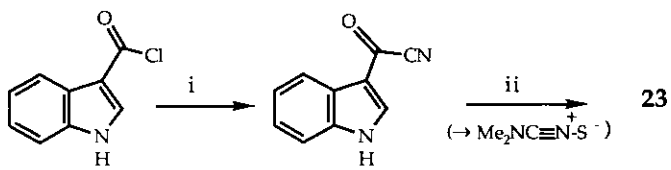
The 4*H*-imidazol-4-one (**24**) was synthesised from indole as shown in Scheme 5.[51]



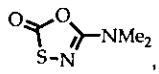
24

Scheme 5 Reagents : i, $(COCl)_2$; ii, $AcHNC(=NH)NMe_2$; iii, H_2O (no yields given).

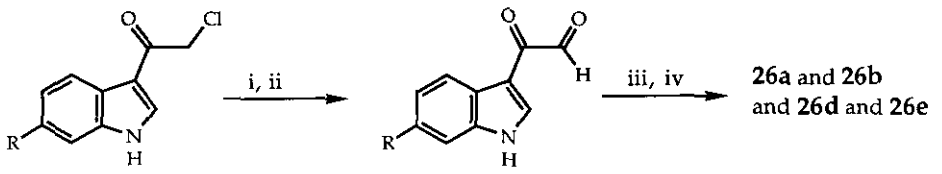
Dendrodoine was produced by the dipolar cycloaddition shown in Scheme 6[61] using *N,N*-dimethylaminonitrile sulfide generated *in situ* by thermolysis of 5-(*N,N*-dimethylamino)-1,3,4-oxathiazol-2-one.



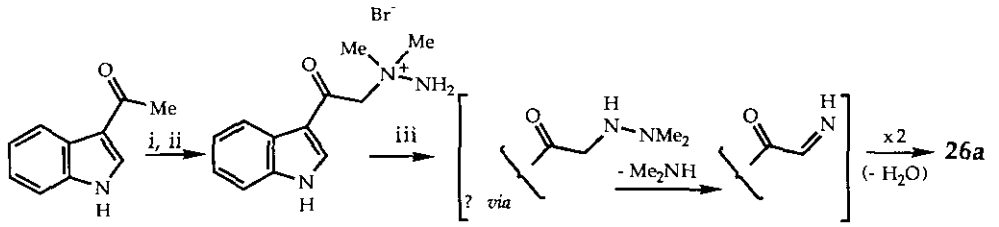
23

Scheme 6 Reagents : i, CuCN, MeCN, PhMe, 110°C, 6 h (53%); ii,  , 145°C, DMF (17%).

A route which inevitably produces mixtures and allowed synthesis of the topsentines (**26a, b, d** and **e**) is shown in Scheme 7.[57] Another route (Scheme 8) allowed synthesis of topsentine A (**26a**), proceeding, it is believed, *via* the dehydrative self condensation of an assumed α-ketoimine intermediate.[62]



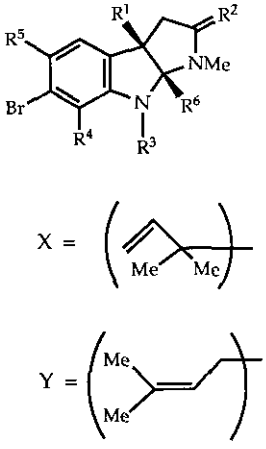
Scheme 7 Reagents : i, H_2O, formamide, heat (97%, R=H; 82%, R=OBn); ii, $Cu(OAc)_2$, aq. AcOH, EtOH, heat (99%, R=H and BnO); iii, NH_3(gas), EtOH (53% of four compounds); iv, (where necessary) H_2, Pd/C (100%).



Scheme 8 Reagents : i, $CuBr_2$, $CHCl_3$, EtOAc, reflux, 48 h (37%); ii, Me_2NNH_2, EtOH, cold, 48 h (82%); iii, *n*-PrOH, reflux, 34 h, dark, N_2 (27%).

(c) Tryptamines (N_b cyclised onto indole C-2)

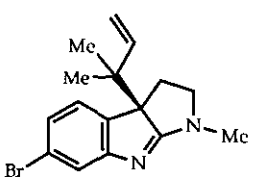
Structures



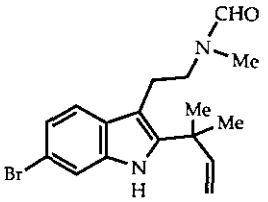
flustramines A, B, D, isoflustramine D, dihydroflustramine C, flustraminols A, B, and flustramides A, B

30	R^1	R^2	R^3	R^4	R^5	R^6
a	X	H_2	Y	H	H	H
b	Y	H_2	Y	H	H	H
c	X	H_2	H	H	Y	H
d	X	H_2	H	Y	H	H
e	X	H_2	H	H	H	H
f	OH	H_2	H	H	H	X
g	OH	H_2	Y	H	H	H
h	X	O	Y	H	H	H
i	Y	O	Y	H	H	H

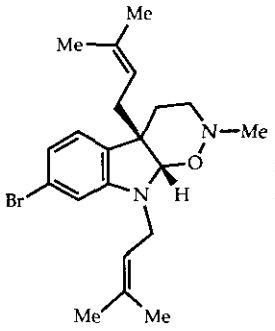
The marine bryazoan *Flustra foliacea* has provided a group of tryptamine derivatives,[63] carrying one or two added isoprene units, and with the side-chain nitrogen cyclised onto the indole 2-position, as in the terrestrial Calebar bean alkaloids.[64] Flustramines A, B,[65] D (and its *N*-oxide) and isoflustramine D (**30a-d**)[66] and flustramides A and B[67] (**30h**) and (**30i**), have two isoprene units where flustramine C (**31**),[68] dihydroflustramine C (**30e**) (and its *N*-oxide),[69] the flustraminols,[68] (**30f**) and (**30g**), and flustrabromine (**32**)[70] have only one; the last may be biosynthetically derived from **30f**. Flustramines A and B were shown to be muscle relaxants.[71] Flustramide B is isomeric with the cyclic hydroxylamine derivative flustrarine B (**33**); the latter could be produced by oxidising flustramine B with hydrogen peroxide.[67b]



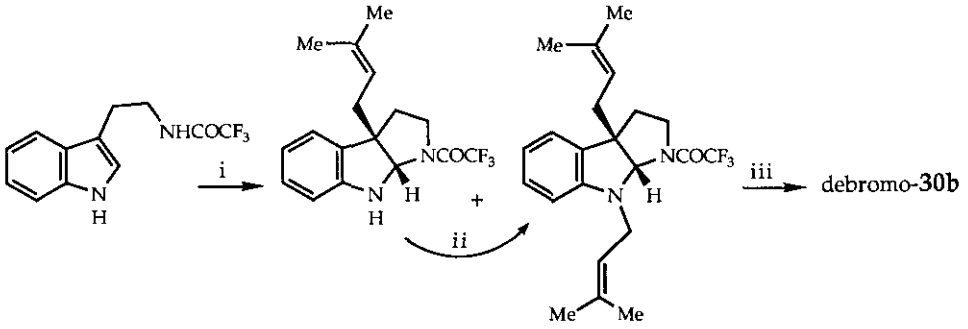
flustramine C
31



flustrabromine
32



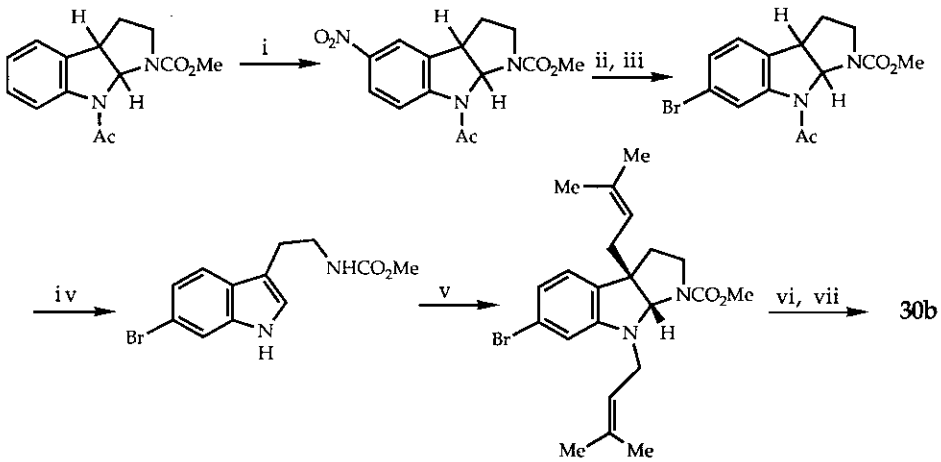
flustrarine B
33



Scheme 9 Reagents : i, $Me_2C{=}CHCH_2Br$, aq. AcOH, NaOAc, 3 h (6%, plus 5% doubly alkylated product); ii, $Me_2C{=}CHCH_2Br$, K_2CO_3, Me_2CO (69%); iii, HCHO, $NaB(CN)H_3$, MeCN, 15 min (57%).

Syntheses

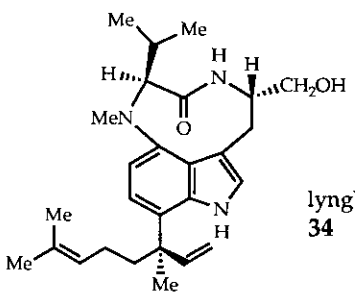
Syntheses of (±)-debromoflustramine B[72] and of (±)-flustramine B[73] have been described and are summarised in Schemes 9 and 10. Each route depends upon the intramolecular trapping, by side-chain-nitrogen, of a 3-dimethylallylated 3*H*-indolium cation intermediate, almost certainly mirroring the biosynthesis.



Scheme 10 Reagents : i, nitration ; ii, catalytic reduction then NBS, DMF (27%); iii, *i*-AmONO (excess), THF (60%); iv, 10% aq. H_2SO_4, MeOH, room temperature ('excellent'%); v, $Me_2C{=}CHCH_2Br$, aq. AcOH, NaOAc, room temperature (71%); vi, aq. NaOH, EtOH, 100 h, reflux (39%); vii, MeI, K_2CO_3, Me_2CO, room temperature (18%).

(d) Tryptophanol Derivatives (cyclised onto C-4)

Structures



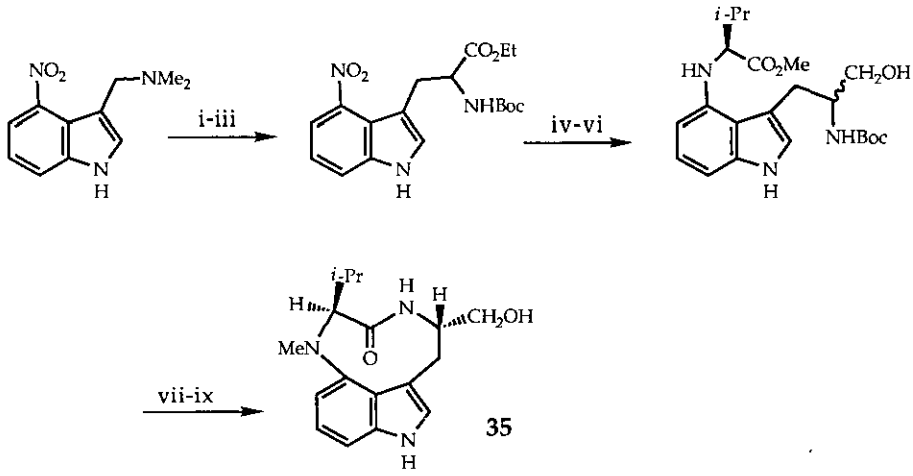
lyngbyatoxine A
34

Lyngbyatoxine A[74,75] (**34**) is a highly inflammatory and vesicatory substance obtained from an Hawaiian blue-green alga *Lyngbya majuscula*; the alga is responsible for 'swimmers itch' in Hawaii. Lyngbyatoxine A is a potent tumor promoter.[76] The structure is reminiscent of the *Streptomyces* substances the teleocidins, indeed teleocidin A-1 is identical with lyngbyatoxine A.

Syntheses

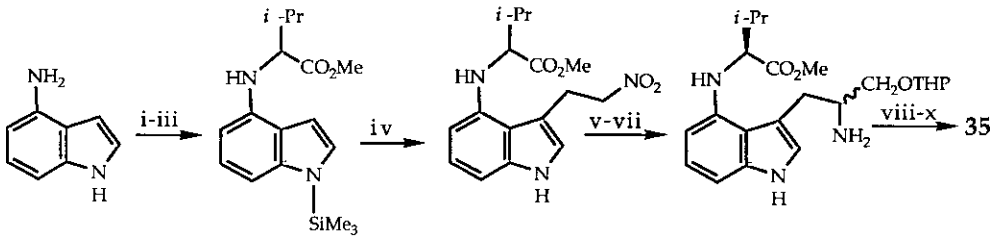
Considerable ingenuity has been exercised in the development of methods for the construction of the 4,7-disubstituted indole and the medium sized ring in the teleocidins and latterly lyngbyatoxine A. A selection of the work geared to the teleocidins is given here because of its relevance to lyngbyatoxine A. Indolic starting materials have been used for syntheses[77,78,79,80] of the *Streptomyces* natural product indololactam V (**35**) the key features of these four routes are summarised in Schemes 11-14. Synthesis of the tricycle (**35**) is relevant to lyngbyatoxine A in that the introduction of electrophiles (*e.g.* electrophilic alkylation) of 4-aminoindoles at C-7 has been demonstrated.[81]

Gramine chemistry on its 4-nitro derivative was used to build up the tryptophanol side-chain, elaboration of the 4-substituent then being followed by amide-forming medium-sized ring cyclisation (Scheme 11).[77] Scheme 12 shows how indole-β-alkylation with nitroethene allowed the same effect to be achieved, in this case after elaboration of the 4-amino-substituent, diphenylphosphoryl azide being the cyclic-amide forming reagent in this work.[78]



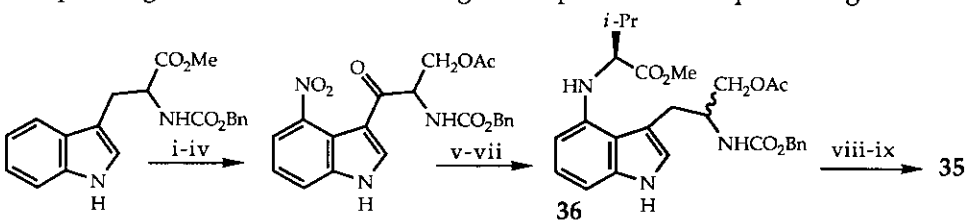
Scheme 11 Reagents : i, $CH(NHAc)(CO_2Et)_2$, NaOEt, EtOH, 0°C, then Me_2SO_4, 4 h, room temperature (76%); ii, aq. NaOH, reflux, then H_2O, reflux, then $SOCl_2$, EtOH, 0°C (68%); iii, HCl, EtOH, reflux, 48 h, then Me_3CON_3, $NaHCO_3$, aq. dioxan, 45°C, 40 h (90%); iv, $LiBH_4$, THF, room temperature, 3 h (89%); v, H_2 (1 atm), Pd/C, EtOAc, room temperature, 1 h (89%); vi, $Me_2CHCOCO_2Me$, $CHCl_3$, reflux then $NaB(CN)H_3$, THF, room temperature (58%, mixture of

diastereoisomers); vii, aq. KOH, MeOH, room temperature, 24 h then *N*-hydroxysuccinimide, DCC, MeCN, room temperature, 1 h (57%); viii, CF_3CO_2H, CH_2Cl_2, 0°C, 1 h then aq. $NaHCO_3$, reflux, 1 h (67%); ix, MeI, $NaHCO_3$, MeOH, reflux, 60 h (62% plus diastereoisomer).



Scheme 12 Reagents : i, $Me_2CHCOCO_2Me$, *p*-TsOH, $CHCl_3$, reflux (57%); ii, 10xMg, MeOH, ultrasound (100%); iii, $Me_3SiOSO_2CF_3$, CH_2Cl_2, 0°C (86%); iv, $CH_2{=}CHNO_2$, $SnCl_4$, CH_2Cl_2, -78°C then n-$Bu_4N^+F^-$ (47%); v, $(CH_2O)_n$, DMF, 0°C, cat NaOMe (57%); vi, dihydropyran, pyridinium tosylate, CH_2Cl_2 (61%); vii, $NaBH_4$, $CoCl_2.6H_2O$, MeOH, 0°C (73%); viii, NaOH, EtOH, H_2O (100%); ix, $(PhO)_2PON_3$, Et_3N, DMF (60%, 1:1 mixture of diastereoisomers); x, H^+, MeOH, reflux then MeI, $NaHCO_3$, EtOH, reflux (80%).

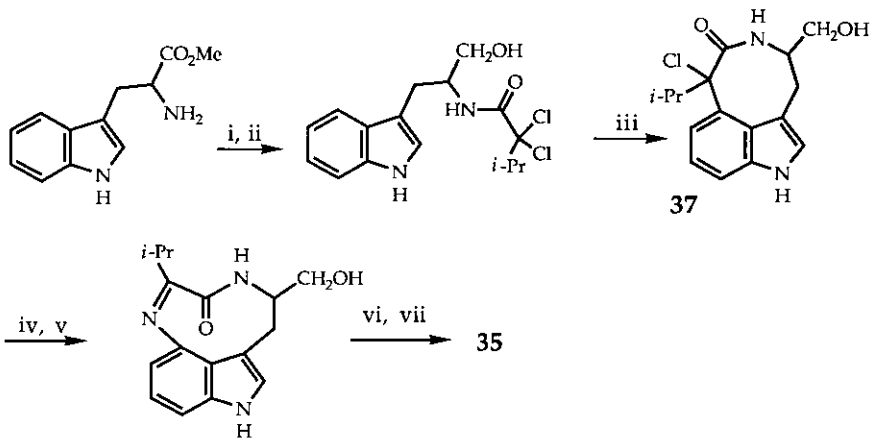
Methyl tryptophanate was converted (Scheme 13)[79] into a 3-ketone (later removable by borohydride reduction) which directed nitration to C-4 thus allowing elaboration to **36**, for the subsequent reaction of a 4-amino group with 3-methyl-2-oxobutanoic acid, as in both previous Schemes. A quite different approach to the introduction of the 4-substituent is shown in Scheme 14,[80] where intramolecular photo-catalysed alkylation produced **37** for a subsequent nitrene-mediated ring expansion on the coresponding azide to insert the 4-nitrogen and produce the requisite ring in one step.



Scheme 13 Reagents : i, $LiBH_4$, 25°C, 4.5 h; ii, Ac_2O, pyridine (97%); iii, 2xDDQ, aq. THF, 25°C, 1 h (74%); iv, c. HNO_3 (40%); v, H_2, Pt, MeOH, 1 h (60%); vi, $NaBH_4$, aq. DMF, room temperature, 2.5 h (90%); vii, $Me_2CHCOCO_2H$, DMF, room temperature, 10 min then $NaB(CN)H_3$, room temperature, 15 min; viii, *N*-hydroxysuccinic acid, DCC, MeCN, room temperature, 20 min (76% overall vii, viii); ix, H_2, Pd/C (60%, plus stereoisomer).

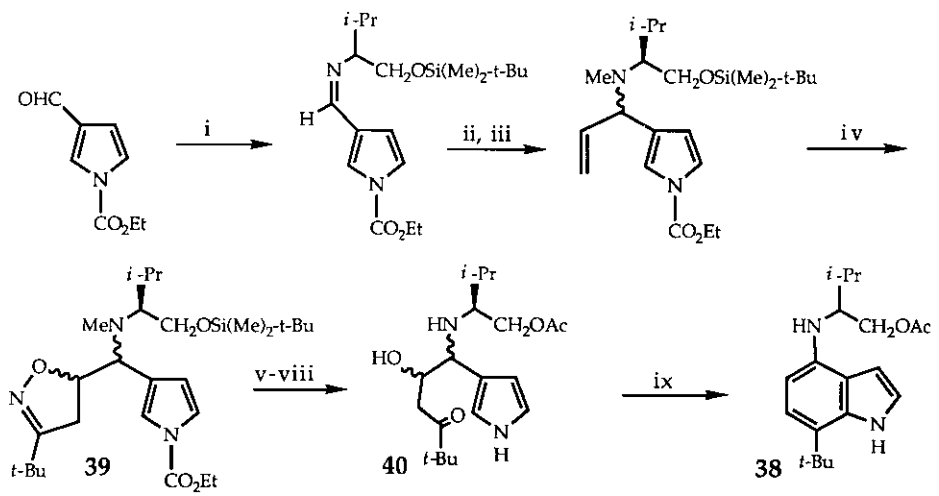
The disubstitution of the benzene ring in lyngbyatoxine A has encouraged synthetic approaches from pyrroles, to facilitate the controlled introduction of 4- and 7-substitutuents. The synthesis (Scheme 15) of model indole (**38**), carrying a quaternary

substituent at C-7, was achieved *via* a nitrile oxide cycloaddition (→**39**) which then gave rise to ketone (**40**) for intramolecular pyrrole-α-alkylation (with loss of water) to generate indole (**38**).[82] A variant (Scheme 16) on this approach was used to



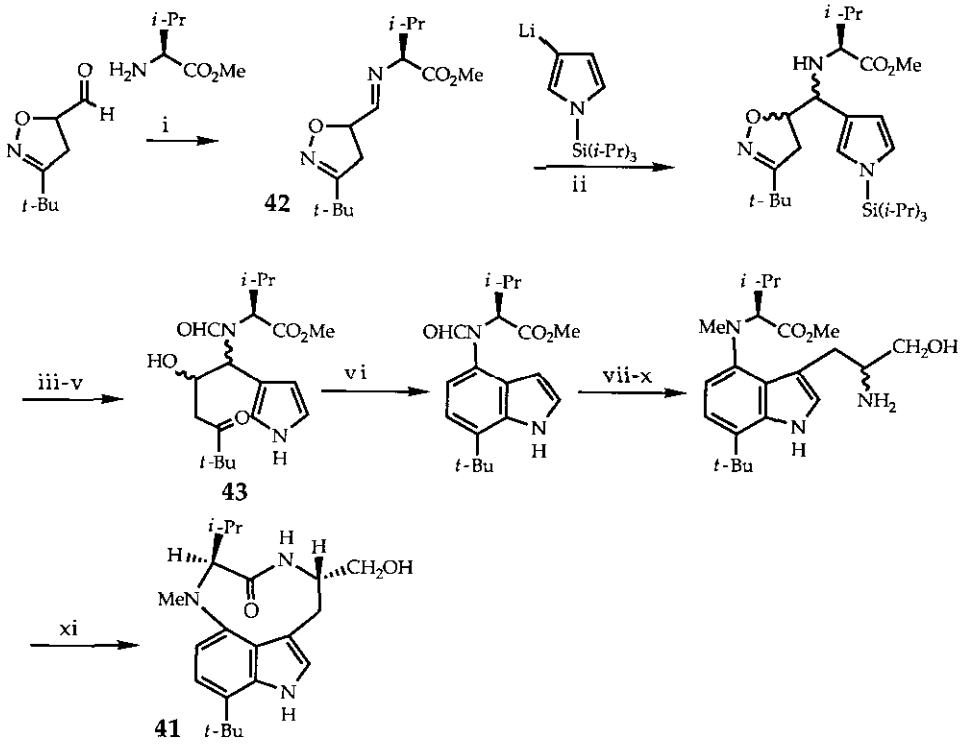
Scheme 14 Reagents : i, Me_2CHCCl_2COCl, aq. $NaHCO_3$, CH_2Cl_2 (97%); ii, $NaBH_4$, EtOH, room temperature (83%); iii, hv, aq. MeCN (60%); iv, NaN_3, CF_3CO_2H, $CHCl_3$, room temperature (35%); v, hv, MeCN (23%, plus isomer); vi, $NaB(CN)H_3$, MeOH (69%); vii, MeI, $NaHCO_3$, MeOH.

construct tricyclic model (**41**),[83] thus 3-lithio-1-triisopropylsilylpyrrole was added to imine (**42**) leading in three subsequent steps to ketone (**43**) for a comparable intramolecular cyclialkylation/dehydration. Indole-β-alkylation with the oxime of ethyl 3-bromopyruvate was the means used for the introduction of an appropriate



Scheme 15 Reagents : i, $H_2NCH(i\text{-Pr})CH_2OSi(Me)_2\text{-}t\text{-Bu}$, PhH, reflux; ii, $MeOSO_2CF_3$, CH_2Cl_2, room temperature; iii, CH_2=CHMgBr, THF, -23°C ; iv, t-BuC≡N^+O^-, PhH, reflux; v, aq. KOH, MeOH, room temperature , 10 min; vi, n-$Bu_4N^+F^-$, THF; vii, Ac_2O, pyridine; viii, H_2, Raney-Ni, aq. MeOH, AcOH; ix, $Zn(OSO_2CF_3)_2$, CH_2Cl_2 (51%).

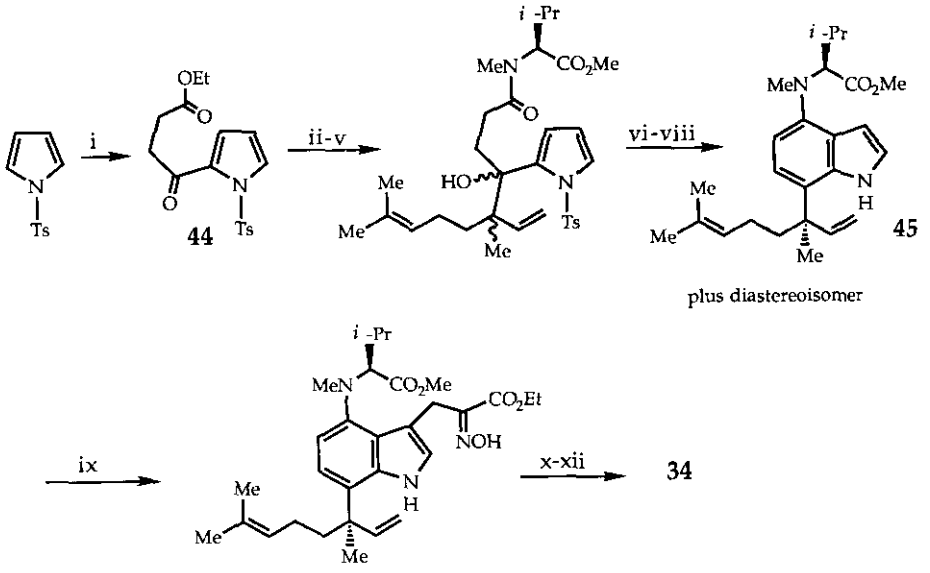
side-chain (indeed this device was also used in the elegant total synthesis of lyngbyatoxin A itself, shown below in Scheme 17) with the final amide forming closure being effected with triethylaluminium.



Scheme 16 Reagents : i, $MgSO_4$, PhH, room temperature; ii, THF, HMPA, -78°C (50% overall i, ii); iii, AcOCHO, room temperature (88%); iv, n-$Bu_4N^+F^-$, THF (82%); v, H_2, Raney Ni (W-2), aq. MeOH, AcOH (87%); vi, t-$Bu(Me)_2SiOSO_2CF_3$, CH_2Cl_2 (54%); vii, $BH_3.Me_2S$, THF, 60°C (65%); viii, $BrCH_2C(=NOH)CO_2Et$, Na_2CO_3, CH_2Cl_2, room temperature, 24 h (82%); ix, Al-Hg, aq. THF, room temperature, 3 h (89%); x, $NaBH_4$, LiCl, EtOH, room temperature (80%); xi, Et_3Al, PhMe, reflux, 12 h (49%, plus diastereoisomer).

In a total synthesis of lyngbiatoxine A (Scheme 17), 1-tosylpyrrole was acylated with the half-ester half-acid chloride of succinic acid and the ketone carbonyl in product (44) utilised for the introduction of the terpenoid 7-substituent. The 4-amino-substituent was introduced making use of the ester, before Bischler-Napieralski type

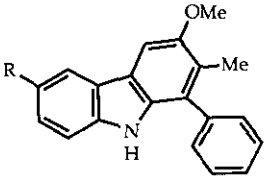
cyclisation to indole (45), which was achieved by conversion of amide to thioamide then *S*-methylation.[84]



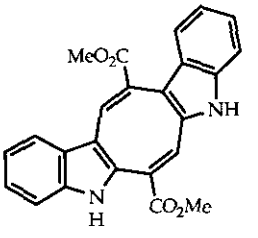
Scheme 17 Reagents : i, $EtO_2C(CH_2)_2COCl$, $BF_3.Et_2O$, $(CH_2Cl)_2$, room temperature (80%); ii, aq. KOH, THF, room temperature (95%); iii, $ClCO_2Et$, Et_3N, THF, -20°C; iv, methyl *N*-methyl-L-valinate hydrobromide, -20°C→room temperature (87%, overall iii, iv); v, geranyl bromide, Mg, THF, 0°C (80%); vi, *p*-TsOH, PhH, reflux (88% overall v, vi); vii, Lawesson's reagent, THF, reflux (65%); viii, MeI, DMF, room temperature (61%, *mixture of distereoisomers*); ix, $BrCH_2C(=NOH)CO_2Et$, Na_2CO_3, CH_2Cl_2, room temperature (59%); x, Al-Hg, aq. THF, room temperature (92%); xi, $NaBH_4$, EtOH, reflux (51%); xii, KOH, aq. MeOH, reflux, then $Et_3N.HCl$, then $(PhO)_2PON_3$, Et_3N, THF, 0°C→room temperature (23%, plus diastereoisomer).

(e) Carbazoles and Related Compounds (no tryptamine side-chain N)

Structures

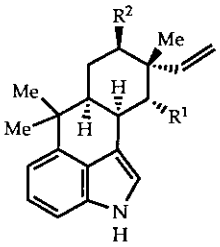


hyellazole and chlorohyellazole
46 R
a H
b Cl



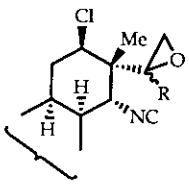
caulerpine
47

Hyellazole and its chloro derivative, (**46a**) and (**46b**), were obtained from a blue-green alga *Hyella caespitosa*.[85] The ester groups in caulerpine (**47**) may bear witness to two tryptophans as biosynthetic precursors; the orange pigment was obtained from a tropical green alga *Caulerpa racellosa*,[86] and from Australian *C. pelata*, and *C. racemosa*.[87]



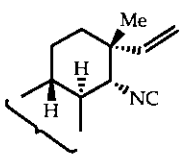
hapalindoles
A, B, J, M, and O

48	R^1	R^2
a	NC	Cl
b	NCS	Cl
c	NC	H
d	NCS	H
e	NCS	OH

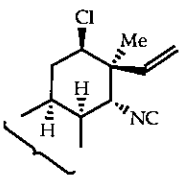


hapalindoles
N and P

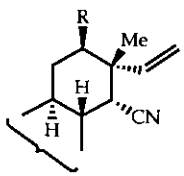
48	R
f	α/β-H
g	β/α-H



hapalindole H
48h

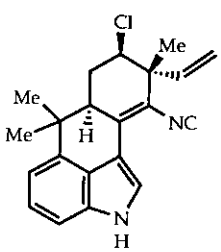


hapalindole L
48i

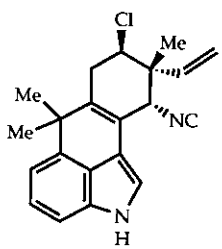


hapalindoles
G and U

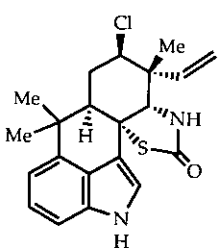
48	R
j	Cl
k	H



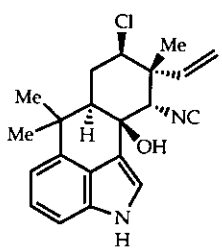
hapalindole I
49



hapalindole K
50

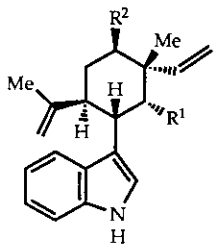


hapalindole T
51



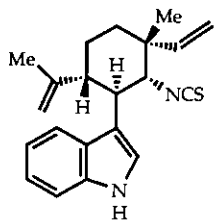
hapalindole V
52

With a plainly monoterpenoid/tryptamine origin, the twenty hapalindoles (**48a-k**, **49-52**, **53a-d**, and **54**) and hapalindolinone (**55**),[96a] an oxindole, were obtained from a detailed study of the blue-green alga *Haposiphon fontinalis*;[88] hapalindoles A and B are the major metabolites.[89] The hapalindoles have antibacterial and antimycotic activity.

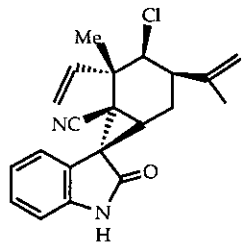


hapalindoles C, D, E, and F

53	R^1	R^2
a	NC	H
b	NCS	H
c	NC	Cl
d	NCS	Cl



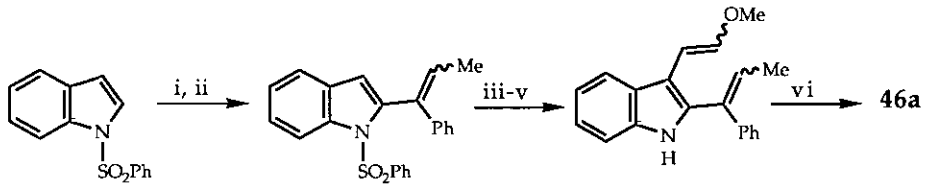
hapalindole Q
54



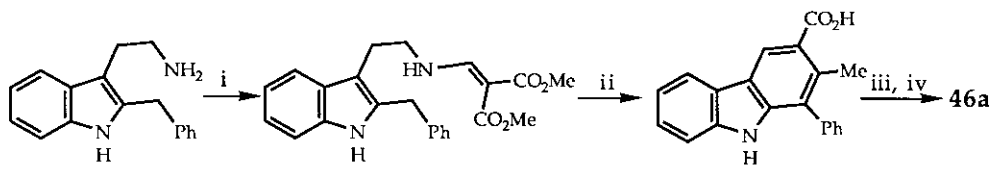
hapalindolinone A
55

Syntheses

There have been five total syntheses[90,91,92,93,94] of hyellazole, one[90] of them also affording chlorohyellazole. The novel chemistry involved shows the stimulus to the evolvement of new carbazole forming processes[95] which the isolation of hyellazole and other, terrestrial carbazole alkaloids provided. Scheme 18[90] shows how a 2,3-divinylindole was assembled, electrocyclic ring closure of which in the presence of a dehydrogenating agent afforded the carbazole. A quite different ring-forming step was used in a second route (Scheme 19), which may be biomimetic in that it starts from a tryptamine,[91] conversion of a carboxyl into a methoxyl group in the latter stages being achieved *via* isocyanate → amine then diazotisation in methanol. This route is notable for the high-yielding cyclisation step in which the ethanamine unit is lost.

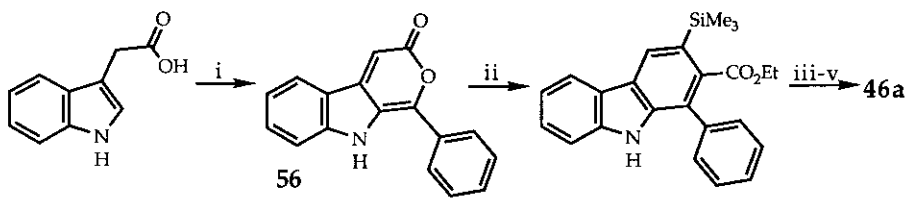


Scheme 18 Reagents : i, LDA, THF, 0°C, 0.5 h then $(PhCO)_2O$, -78°C→room temperature, 4 h (72%); ii, Ph_3P=CHMe, -30°C→room temperature, THF (73%, 1:1, E:Z); iii, NaOH, aq. EtOH, dioxan, 48 h (80%); iv, $POCl_3$, DMF, 45°C, 1 h (85%); v, Ph_3P=CHOMe, THF, 0°C, 0.5 h; vi, xylene, Pd/C, reflux, 40 h (21% overall v, vi).



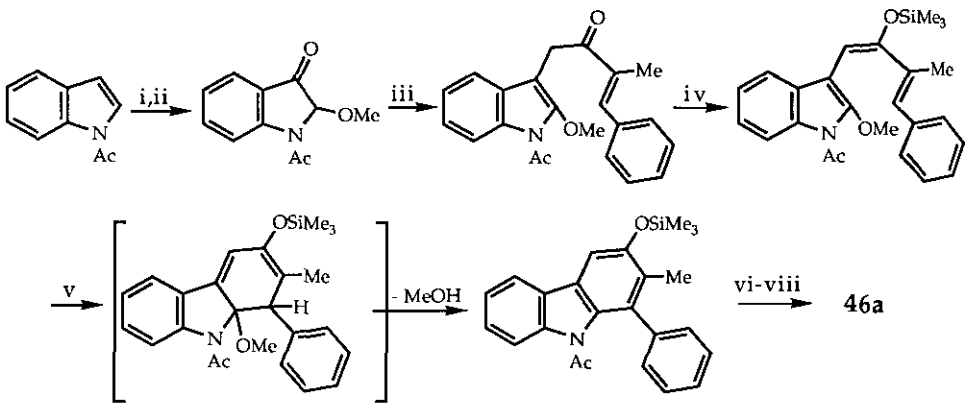
Scheme 19 Reagents : i, $MeOCH=C(CO_2Me)_2$ (100%); ii, Ac_2O, AcOH, reflux, then aq. NaOH, reflux (76%); iii, $(PhO)_2PON_3$, MeCN, reflux, then H_2O then NaOH, $(CH_2OH)_2$, reflux (78%); iv, $NaNO_2$, H_2SO_4, MeOH, -15°C→reflux (10%).

The diene character of pyrano[3,4-*b*]indole (**56**) provided yet another route (Scheme 20) for the construction of a carbazole system.[92]



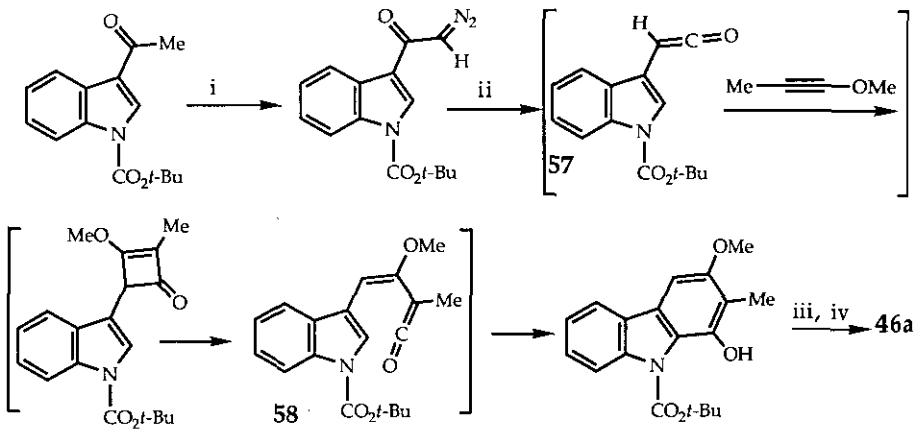
Scheme 20 Reagents : i, $PhCO_2H$, P_4O_{10}, H_3PO_4, 90°C (17%); ii, $Me_3SiC{\equiv}CCO_2Me$, PhBr, reflux (40-62%); iii, $LiAlH_4$, dioxane, reflux (92%); iv, $Hg(OAc)_2$, AcOH, room temperature, then BH_3.THF, room temperature, then H_2O_2, aq. NaOH, room temperature (41%); v, MeI, K_2CO_3, Me_2CO, reflux (92%).

A 2-methoxy-3-(buta-1,3-dien-1-yl)indole was constructed to form the basis for the fourth synthesis[93] of hyellazole. An intramolecular Diels-Alder process, with loss of the methoxyl as methanol providing an irreversible aromatisation step, produced a carbazole suitable for elaboration (Scheme 21).



Scheme 21 Reagents : i, MoO_5.HMPA, room temperature, 7 days (56%); ii, CrO_3, aq. pyridine (81%); iii, Ph_3P=CHCOC(Me)=CHPh, dioxan, reflux (74%); iv, Me_3SiI, HMDS, -20°C→room temperature, CH_2Cl_2 (80%); v, decalin, reflux (53%); vi, Bu_4N^+ F^-, aq. THF, 0°C (81%); vii, Me_2SO_4, aq. 50% NaOH, Bu_4N^+ HSO_4^-, room temperature; vii, aq. 50% NaOH, Bu_4N^+ HSO_4^-, PhH, reflux (72% overall vi, vii).

In the fifth route (Scheme 22) introduction of the phenyl substituent was left to a final, palladium-catalysed coupling step;[94] this route employed a very elegant sequence for the construction of the carbazole nucleus in which the ketene (57) formed by a Wolff rearrangement of precursor diazo-ketone, was trapped by cycloaddition to an alkyne, the cyclobutane then opening in the alternative sense to generate 58 for the 6π ring closure.

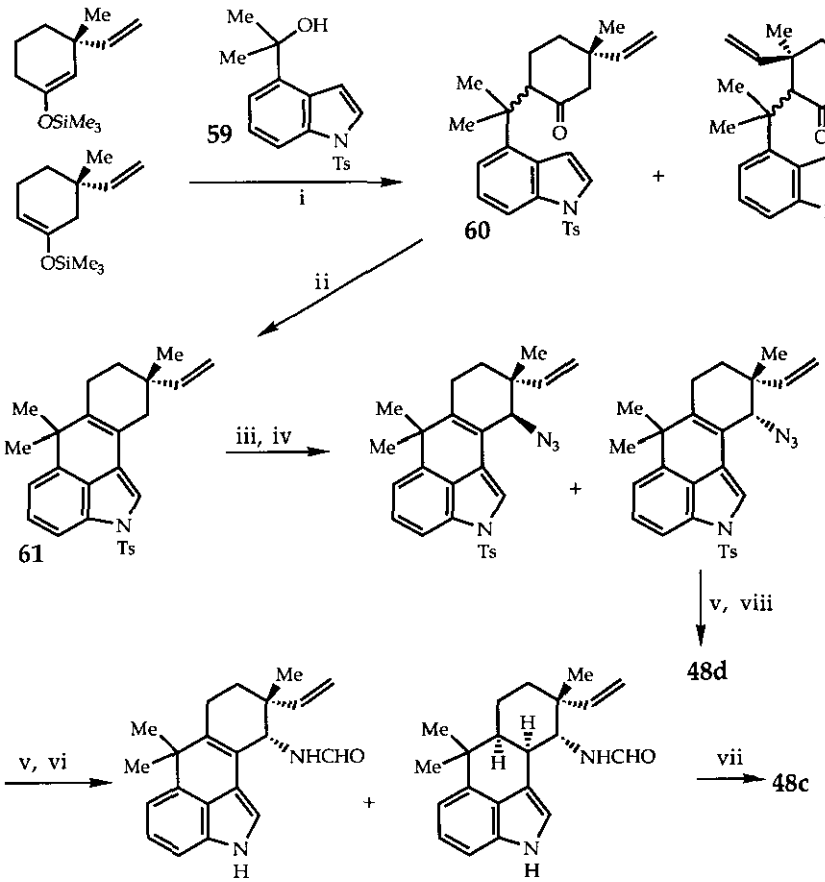


Scheme 22 Reagents : i, LiHMDS, THF, -78°C, then $CF_3CO_2CH_2CF_3$ then $MeSO_2N_3$, Et_3N, aq. MeCN (86%); ii, MeC≡COMe, $(CH_2Cl)_2$, hν, 19.5 h, reflux, 5 h (56%); iii, $(CF_3SO_2)_2O$, DMAP,

pyridine, 0°C→room temperature (78%); iv, Me_3SnPh, 10 mol% $PdPh_4$, LiCl, dioxan, 94→150°C (63%).

Caulerpine (**47**) was synthesised straightforwardly by the double aldol condensation between two molecules of methyl 3-formylindol-2-ylacetate.[96]

(±)-Hapalindoles H, J, M, and U have been synthesised.[97] To illustrate the approach, Scheme 23 summarises the routes to **48c** and **48d**. Alkylation of the mixture of silyl enol ethers obtained from 3-methyl-3-vinylcyclohexanone with indole alcohol (**59**) gave **60** (and its isomer) ring closure of which afforded **61**. After allylic bromination, fortuitously in the desired regio-sense, and azide displacement, lithium aluminium hydride treatment effected both azide reduction and (some) *cis*-reduction (as desired) of the carbon-carbon double bond.



Scheme 23 Reagents : i, $SnCl_4$, CH_2Cl_2, -78°C, 10 min; ii, $BF_3.Et_2O$, CH_2Cl_2, room temperature, 1.5 h (57%); iii, NBS, $(PhCO_2)_2$, CCl_4, reflux, 30 min; iv, NaN_3, DMF, room temperature, 16 h

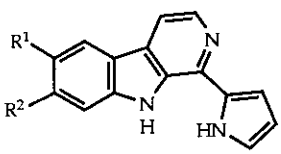
(63%, *ca.* 1:1 mixture); v, $LiAlH_4$, THF, room temperature, 15 h; vi, HCO.OCO.Me, pyridine, CH_2Cl_2, -20→-16°C 4.5 h (64% overall v and vi *ca.* 1:2 mixture); vii, $POCl_3$, pyridine -20°C, 40 min (76%); viii, 1,1'-thiocarbonyldiimidazole, CH_2Cl_2, 0→18°C, 2.5 h (35%).

(f) β-Carbolines (9*H*-pyrido[3,4-*b*]indoles) and Related Compounds

Structures

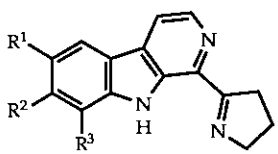
A series of β-carbolines, ranging from very simple to polycyclic, have been isolated from marine organisms. Harman (1-methyl-β-carboline) and norharman (β-carboline itself) are present in the marine dinoflaggelate *Noctiluca miliaris*,[98] in the bryazoan *Costaticella hastata* and in *Amathia wilsoni*,[99] *C. hastata* also having 1-ethyl-, 1-vinyl-, and 1-(1-hydroxyethyl)-β-carbolines.

More than twenty alkaloids have been isolated from *Eudistoma* species. Some of the compounds obtained[100,101,102,103] from the tunicate *Eudistoma olivaceum*, and related species, were simple β-carbolines: 5-bromo-6-hydroxy-, 7-bromo-6-hydroxy-, 6-bromo-, and 7-bromo-β-carbolines, others carry a pyrrole, **62a** and **b** or pyrroline, **63a-f**, at the 1-position and others, (**64a-e**) include a fused [1,6,2]oxathiazepine. Debromoeudistomin K (**64f**) along with eudistomins C and O, β-carboline itself, and eudistomin K sulphoxide were obtained from a New Zealand ascidian *Ritterella sigillinoides*.[104,105] The sulphoxide could be produced by oxidation of *N*-Boc-protected eudistomin K.[103] Eudistomins C, E, K, and L have potent antiviral activity, for example against *Herpes simplex*.[106,107] Eudistomidin A (**63f**) is an antagonist of the calcium-ion-binding protein calmodulin.[108] The eudistomidins B and C (**65**) and (**66**) and 5-bromo-6-hydroxy-9-methyl-β-carboline (eudistomin D), are antileukemic substances isolated from a green Okinawan tunicate *Eudistoma glaucus*,[109] along with the eudistomins D, E, H, and I. Eudistomins R, S, and T were shown to have the structures (**67a-c**).[110]



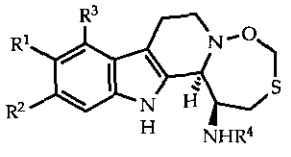
eudistomins A and M

62	R
a	Br
b	H



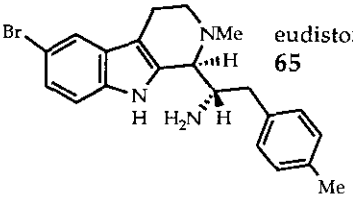
eudistomins G, H, I, P, and Q, and eudistomidin A

63	R^1	R^2	R^3
a	H	Br	H
b	Br	H	H
c	H	H	H
d	HO	Br	H
e	HO	H	H
f	Br	H	HO

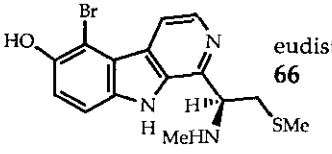


eudistomins
C, E, F, K, and L

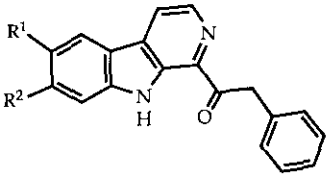
64	R^1	R^2	R^3	R^4
a	HO	Br	H	H
b	HO	H	Br	H
c	HO	Br	H	Ac
d	H	Br	H	H
e	Br	H	H	H



eudistomidin B
65



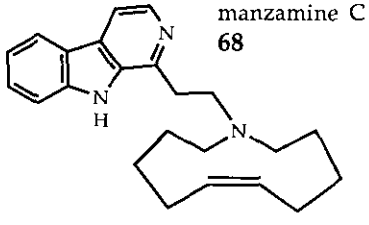
eudistomidin C
66



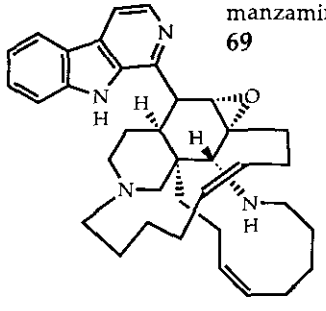
eudistomins
R, S, and T

67	R^1	R^2
a	H	Br
b	Br	H
c	H	H

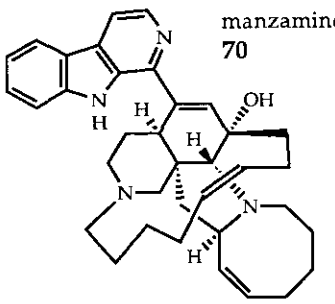
Of the five manzamines described from an Okinawan sponge *Haliclona* sp., manzamine C (**68**)[111] is the simplest. Manzamine B (**69**)[111] has a much more complex, tetracyclic β-carboline 1-substituent, and the remaining three manzamines, A (**70**)[112] which is identical with keramamine A from a *Pellina* sp. sponge,[113] E and F, (**71a**) and (**71b**),[114] contain a corresponding carbon skeleton at C-1, but now pentacyclic with an additional C-N bond. Another β-carboline from the *Pellina* sp. sponge from the Okinawan Kerama islands, keramamine B for which structure (**72**) has been proposed, has elements in common with the manzamines; the three contiguous nitrogen atoms are probably unique in a natural product.[113]



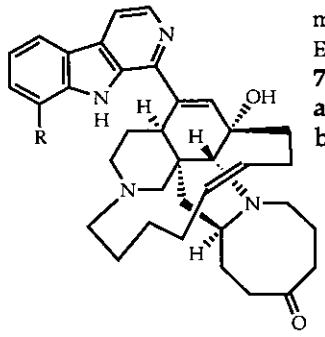
manzamine C
68



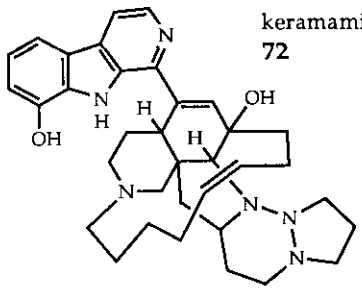
manzamine B
69



manzamine A
70

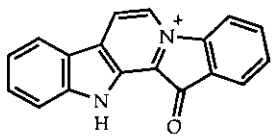


manzamines
E and F
71 R
a H
b OH



keramamine B
72

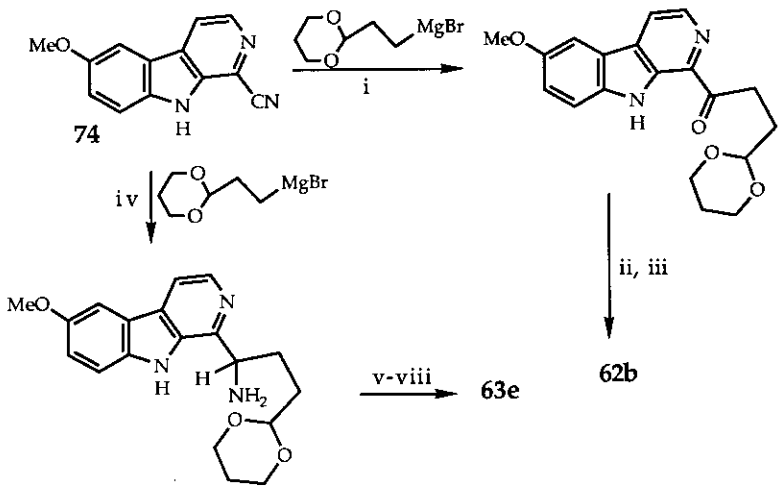
Fascaplysine (**73**)[115] an antimicrobial pigment from a marine sponge, *Fascaplysinopsis* sp., has two indole nuclei, though clearly only one tryptamine moiety is involved.



fascaplysine
73

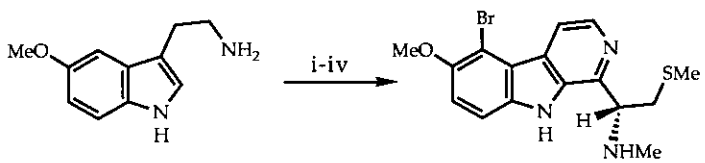
Syntheses

Bromination of β-carboline gave the 6-bromo-derivative, eudistomin N, and bromination of 6-methoxy-β-carboline produced 5-bromo-6-methoxy-β-carboline, demethylation of which afforded eudistomin D.[101] 6-Bromoindole was converted into the corresponding tryptamine and thence into 7-bromo-1,2,3,4-tetrahydro-β-carboline, dehydrogenation of which produced 7-bromo-β-carboline, eudistomin O.[101] 6-Methoxy-1,2,3,4-tetrahydro-β-carboline-1-carboxylic acid was converted into the corresponding fully aromatic nitrile (**74**) the functional group then being developed by alternative means to produce eudistomins M (**62b**) and Q (**63e**) respectively (Scheme 24).[101]



Scheme 24 Reagents : i, THF, 0°C then H_3O^+ (75%); ii, NH_4OAc, AcOH, reflux (67%); iii, BBr_3, CH_2Cl_2 (67%); iv, THF, 0°C then $NaBH_4$, MeOH (68%); v, aq. $HClO_4$, THF (68%); vi, $BH_3.NMe_3$, AcOH, THF, 0°C (77%); vii, NaOCl then Na_2CO_3 (74%); viii, BBr_3, CH_2Cl_2 (23%).

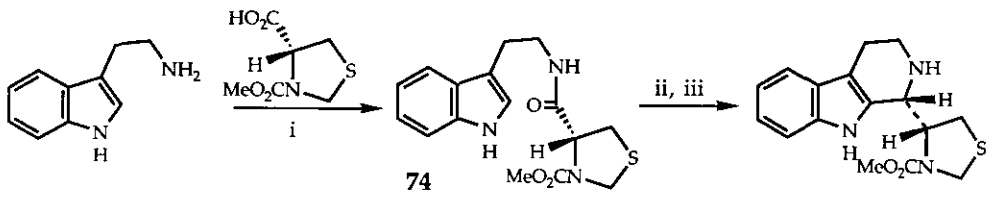
The methyl ether of the C-10 entantiomer of eudistomidin C was synthesised, for optical comparison, as shown in Scheme 25.[109]



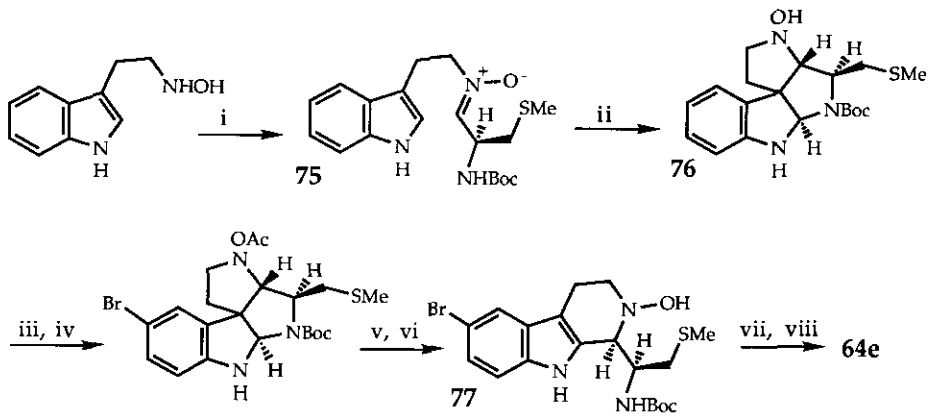
Scheme 25 Reagents : i, L-$MeSCH_2CH(NHCOOBn)CHO$, TFA, -78°C, 2 h (84%); ii, DDQ, PhH, room temperature (45%); iii, $LiAlH_4$, THF, reflux (82%); iv, Br_2, AcOH, 0°→room temperature.

The Pictet-Spengler type ring closure of *N*-hydroxytryptamine was demonstrated in a model study, producing a variety of 1-alkyl-2-hydroxy-1,2,3,4-tetrahydro-β-carbolines.[116] Another model study demonstrated that with an *N*-hydroxy-tryptophanate, the chirality at the newly formed centre, C-1, could be controlled.[117] Other model studies showed the Bischler-Napieralski closure of amide (**74**) to a tetrahydro-β-carboline[118] (Scheme 26), and this work was later extended to a synthesis (Scheme 27) of (-)-eudistomin L (shown) and (-)-debromoeudistomin L.[119] The careful, acid-promoted closure of **75** generated **76**, in which the presumed intermediate from indole-β-attack has been trapped by the apposite side-chain nitrogen. The aniline reactivity of **76** was then used to introduce the aromatic halogen before rearrangement to give **77**, Pummerer reaction in the side-chain of

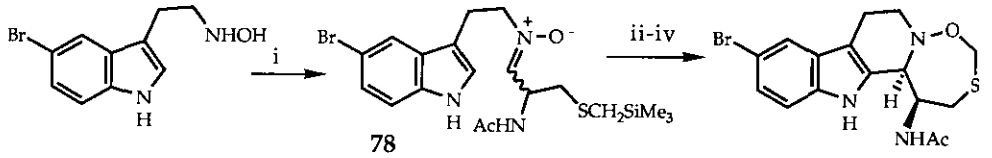
which, and cyclisation, produced the natural product. A variant, for the achievement of a mild Pummerer, involved trimethylsilylmethyl sulphide (78) (Scheme 28).[120]



Scheme 26 Reagents : i, DCC, CH_2Cl_2 (98%); ii, $POCl_3$, PhH, reflux; iii, $NaBH_4$ (63% overall ii, iii, plus diastereoisomer (20%)).

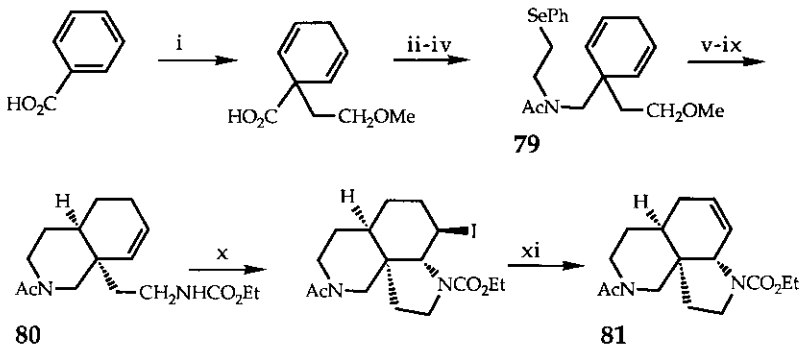


Scheme 27 Reagents : i, (*S*)-$MeSCH_2CH(NHBoc)CHO$, CH_2Cl_2, room temperature, 2 h (96%); ii, TFA, room temperature (69%); iii, Ac_2O; iv, NBS, room temperature, 20 min; v, deacetylation (75% overall iii-v); vi, 3xTFA, room temperature, 40 h (33%); vii, NCS, CH_2Cl_2, -78°C, 2 h (4%); viii, deprotection (76%).



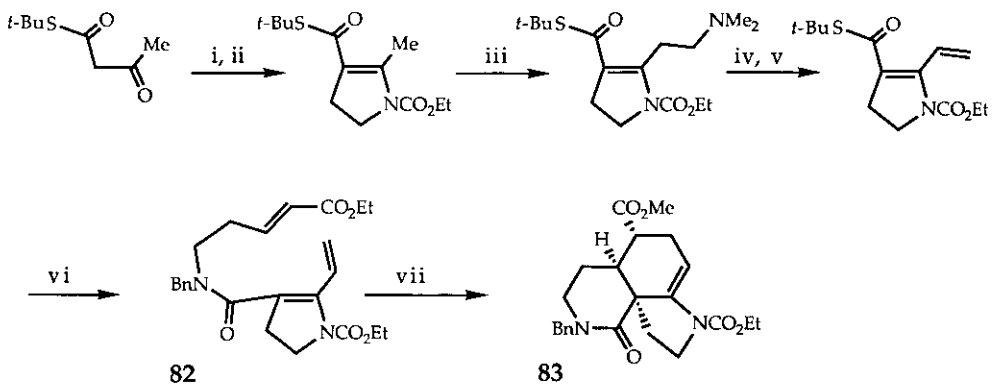
Scheme 28 Reagents : i, $Me_3SiCH_2SCH_2CH(NHAc)CHO$, $MgSO_4$, 7 h (28%); ii, TFA, CH_2Cl_2, room temperature, 16 h (24%); iii, MCPBA, $NaHCO_3$ (70%); iv, 23→80°C (17-21%).

The complex pentacyclic ring system of the β-carboline 1-substituent in manzamine A has provoked some ingenious synthetic chemistry, but this activity has not so far produced a total synthesis. In one approach (Scheme 29)[121] benzoic acid was elaborated into intermediate (**79**), in which the two double bonds were to be used to construct the two additional rings. Free radical cyclisation of **79** gave a perhydroisoquinoline and iodoamination led through to **81**.



Scheme 29 Reagents : i, $Br(CH_2)_2OMe$, reductive alkylation (95%); ii, $(PhO)_2PON_3$, $PhSe(CH_2)_2NH_2$, *i*-Pr_2NEt (87%), iii, $LiAlH_4$, THF, reflux (49%); iv, AcCl, Et_3N (84%); v, *n*-Bu_3SnH, AIBN, PhH, reflux (67%); vi, BBr_3, CH_2Cl_2, -78°C→room temperature (74%); vii, TsCl, pyridine, 0°C (64%); vii, NaN_3, DMF, room temperature→40°C (60%); viii, Ph_3P, aq. THF; ix, $ClCO_2Et$, Et_3N (70% overall viii and ix); x, I_2, K_2CO_3 (76%); xi, DBU, PhMe, reflux (62%).

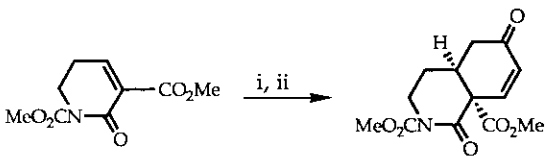
A totally different sequence (Scheme 30) centering on an intramolecular Diels-Alder cycloaddition, **82** → **83**, also allowed the assembly of a tricycle.[122]



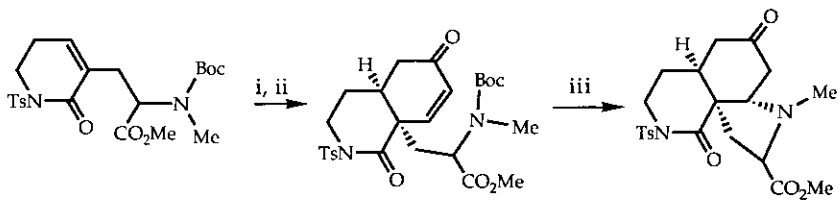
Scheme 30 Reagents : i, NaH, $I(CH_2)_2NHCO_2Et$, DME, room temperature, 4 days ; ii, *p*-TsOH, quinoline, reflux, 30 min (58% overall i, ii); iii, LDA, THF, $CH_2{=}NMe_2^+\ I^-$ (49%); iv, MeI, MeCN, room temperature, 16 h; v, DBU, CH_2Cl_2, room temperature, 1 h (76% overall iv, v); vi,

$AgOSO_2CF_3$, $BnNH(CH_2)_2CH{=}CHCO_2Me$, room temperature, 16 h (77%); vii, PhMe, reflux, 6 h (96%).

Intermolecular Diels-Alder strategies with 5,6-dihydropyridin-2-ones as dienophile were at the heart of other routes (Schemes 31 and 32).[123,124]

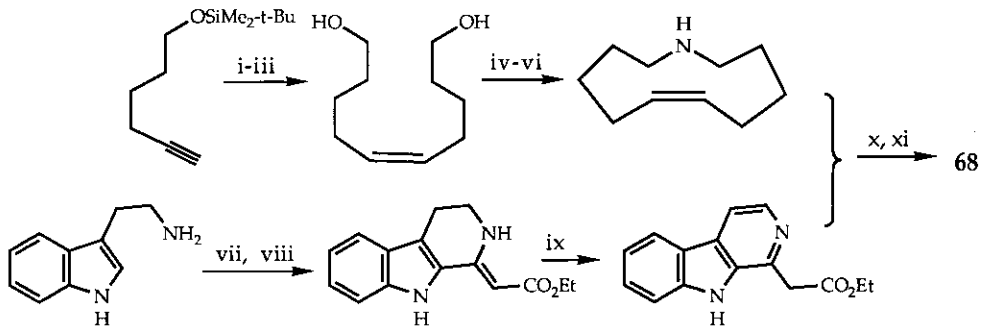


Scheme 31 Reagents : i, $CH_2{=}C(OSiMe_3)CH{=}CHOMe$, PhH, reflux; ii, CSA, THF (quantitative yield).



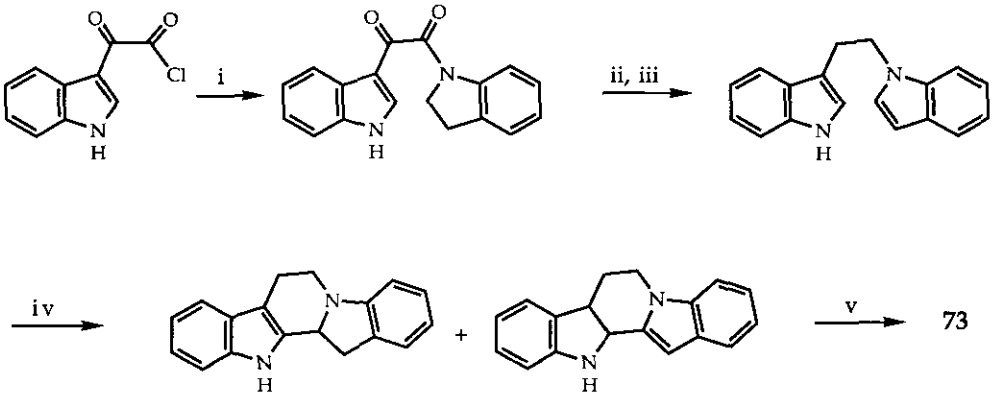
Scheme 32 Reagents : i, $CH_2{=}C(OSiMe_3)CH{=}CHOMe$, *p*-cymene, reflux; ii, CSA, THF (30% overall i, ii); iii, TFA, CH_2Cl_2, room temperature (40%).

A total synthesis of manzamine C, the simplest of the manzamines, has been described (Scheme 33).[125] An eleven-membered cyclic unsaturated amine was elaborated *via* alkyne alkylations then coupled with a β-carboline ester.



Scheme 33 Reagents : i, lithium salt of the acetylene, t-$BuMe_2SiO(CH_2)_4I$; ii, H_2, Lindlar catalyst; iii, desilylation (64% overall i-iii); iv, formation of ditosylate; v, $TsNH_2$, NaOH, PhH, reflux, 4 h (73%); vi, Red-Al (60%); vii, $ClCOCH_2CO_2Et$ (98%); viii, $POCl_3$ (70%); ix, Pd/C, *p*-cymene (70%); x, PhMe, reflux (52%); xi, $LiAlH_4$ (65%).

A synthesis (Scheme 34) of fascaplysine from indole in six steps played nicely on typical indolic reactivity.[126]

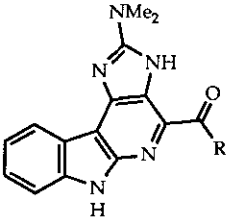


Scheme 34 Reagents : i, 2,3-dihydroindole, K_2CO_3, THF, room temperature (93%); ii, AlH_3, THF (97%); iii, MnO_2, $CHCl_3$, reflux (99%); iv, TFA, room temperature; v, Pd/C, $(EtOCH_2CH_2)_2O$, reflux, 6 h (93%).

(g) α-Carbolines (9*H*-pyrido[2,3-*b*]indoles)

Structures

The original structure proposed for grossularine-1[127] was later revised[128] to **84a**, in line with grossularine-2 (**84b**). These yellow substances were obtained from the tunicate *Dendrobia grossularia*, and have cytotoxic activity.



grossularines-1 and -2

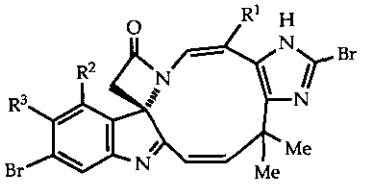
84	R
a	indol-3-yl
b	4-hydroxyphenyl

(h) Polycyclic Tryptamine Derivatives

Structures

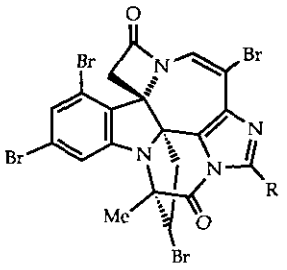
Chartelline A (**85**)[129] was the first a set of five extraordinary β-lactam-containing alkaloids from the bryazoan *Chartella papyracea* which have no precedent in all the many terrestrial tryptamine-derived alkaloids. Later, chartellines B, C (**85b**) and (**85c**) and methoxydechlorochartelline A (**85d**) which may be an artefact of isolation

procedure, were described.[130,131] Chartellamides A and B (**86a**) and (**86b**) are yet more complex compounds in which a further cyclisation onto the original indolic nitrogen has occurred.[132]



chartellines A, B, C, and methoxydechlorochartelline A

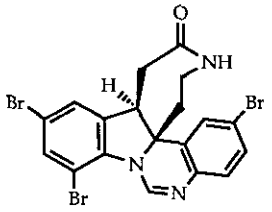
85	R^1	R^2	R^3
a	Cl	Br	Br
b	Cl	Br	H
c	Cl	H	H
d	OMe	Br	Br



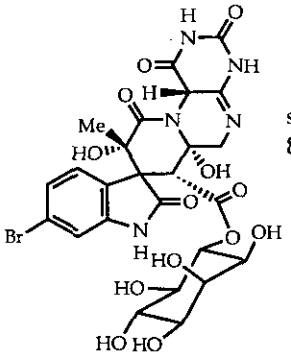
chartellamides A and B

86	R
a	H
b	Br

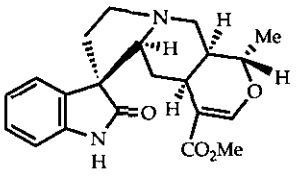
Hinckdentine A, from the marine bryazoan *Hincksinoflustra denticulata*, gathered off the East coast of Tasmania, has a unique structure (**87**)[133] in which, in biosynthetic terms, one may possibly discern the remnants of two halogenated tryptamines.



hinckdentine
87



surugatoxin
88



isopteropodine
89

(i) Oxindoles

Structures

Surugatoxin[134] a toxin from the carnivorous gastropod, *Babylonia japonica* gathered in Suruga Bay near Mount Fuji, has the extraordinary structure (**88**).

The isolation of the typical terrestrial oxindole alkaloid isopteropodine (**89**)[135] from a marine mollusc *Nerita albicilla* has been claimed.[136]

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