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# Marine natural products

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This review covers the literature published in 2002 for marine natural products, with 579 citations (413 for the period January to December 2002) referring to compounds isolated from marine microorganisms and phytoplankton, green algae, brown algae, red algae, sponges, coelenterates, bryozoans, molluscs, tunicates and echinoderms. The emphasis is on new compounds (677 for 2002), together with their relevant biological activities, source organisms and country of origin. Syntheses that lead to the revision of structures or stereochemistries have been included (114), including any first total syntheses of a marine natural product.

Covering: 2002. Previous review: *Nat. Prod. Rep.*, 2003, **20**, 1.



## 1 Introduction

In the introduction to the previous review[1] in this series, we paid tribute to the late Professor D John Faulkner for his contributions not only to the preparation of all the prior reviews in this series, but also for his enormous contribution to research in marine natural products. We are very pleased to be able to continue this series of reviews, especially for inclusion in this issue dedicated to John Faulkner.

Unfortunately, we now have to pay a further tribute - this time, to the late Professor Paul J Scheuer who died in January 2003. Paul Scheuer has been widely regarded as the 'grandfather' of marine natural products. There are many working in the field today who can track their academic genealogy back to Professor Scheuer. Like John Faulkner, he was a true leader in the field. His vision and personality have marked the last forty plus years of research into marine natural products and his contributions too have been of enormous impact. Scheuer would have been cited over 150 times in the 'Faulkner' review series. The earliest reference describing his interests with marine natural products was his paper in 1960 on "Observations on ciguatera-type toxin in fish".[2]

Despite health problems over the past few years both Paul Scheuer and John Faulkner continued their vital interest in research. An indication of their continued involvement until the times of their death is the inclusion in this review of four publications from Professor Scheuer describing 18 new compounds, and seven publications from Professor Faulkner describing 16 new compounds. Over the next year much will be written about the contributions each has made, but one thing is certain: between them Scheuer and Faulkner set the foundations for 'marine natural products', and then were instrumental in the evolution of the general field into more niche areas such as marine ecology and marine pharmacology.

This review is of the literature for 2002 and describes 677 new compounds from 257 articles. We show structures only for new compounds, or for previously reported compounds where there has been a structural revision or a newly established stereochemistry. Previously reported compounds for which first syntheses or new bioactivities are described, are referenced, but structures are not given.

## 2 Reviews

Several reviews have dealt with particular marine-derived compounds. The microcystins and nodularins are the focus of "Peptide toxins of cyanobacteria".[3] Didemnins are comprehensively

reviewed in "Natural products as probes of cell biology: 20 years of didemnin research".[4] "Okadaic acid: the archetypal serine/threonine protein phosphatase inhibitor"[5] focuses on the role that okadaic acid has played in stimulating a broad spectrum of modern scientific research. Dolastatins and related compounds are reviewed in two articles, "Symbiotic and dietary marine microalgae as a source of bioactive molecules"[6] and "The cyanobacterial origin of potent anticancer agents originally isolated from sea hares".[7] A personal perspective on research programs which have been inspired by palytoxin has been given by Kishi.[8] Callystatins are included in "The chemistry and biology of the leptomycin family".[9] Ecteinascidins feature in two reviews, "Ecteinascidin 743: a novel anticancer drug with a unique mechanism of action"[10] and "Chemistry and biology of the tetrahydroisoquinoline antitumor antibiotics".[11] Bryostatins are reviewed in "The chemistry and biology of the bryostatin antitumour alkaloids"[12] and "The clinical development of the bryostatins".[13]

A series of reviews have dealt with broad compound classes. "Survey of briarane-type diterpenoids of marine origin"[14] contains a compilation of 299 briarane-type metabolites. Marine-derived compounds are included in "Natural guanidine derivatives",[15] "Muscarine, imidazole, oxazole, thiazole, Amararyllidaceae and *Sceletium* alkaloids",[16] "Natural halogenated fatty acids: their analogues and derivatives",[17] "Simple indole alkaloids and those with a nonrearranged monoterpenoid unit",[18] "Indolizidine and quinolizidine alkaloids",[19] "Bromo- and iodo-containing alkaloids from marine microorganisms and sponges",[20] "Natural occurrence of boron-containing compounds in plants, algae and microorganisms",[21] "Sterols in marine invertebrates",[22] and "Structural diversity of marine oxylipins".[23] An unusual approach to looking at possible biosynthetic relationships is presented in "The pyridoacridine family tree: a useful scheme for designing synthesis and predicting undiscovered natural products".[24] Synthesis is the focus of "Ladder-extension in the synthesis of marine polyether toxins".[25]

Reviews of the chemistry of particular types of marine organism include "The oxylipin chemistry of attraction and defense in brown algae and diatoms",[26] "Bioactive compounds from

bryozoans",[27] "Neuropeptides in cnidarians",[28] "Toxins and bioactive compounds from cyanobacteria and their implications on human health",[29] "The heterocyclic natural products of gorgonian corals of genus *Briareum* exclusive of briarane-type diterpenoids",[30] "Secondary metabolites from marine fungi",[31] "Secondary metabolites from marine microorganisms",[32] "Pore-forming proteins from sea anemones and the construction of immunotoxins for selective killing of harmful cells",[33] "A survey of the sterol composition of the marine dinoflagellates *Karenia brevis*, *Karenia mikimotoi* and *Karlodinium micrum*",[34] "The chemistry of lithistid sponge: a spectacular source of new metabolites",[35] and "Chemical defense of early life stages of benthic marine invertebrates".[36]

More general reviews have been "Drugs from the seas – current status and microbiological implications",[37] "Marine pharmacology in 1999: compounds with antibacterial, anticoagulant, antifungal, anthelmintic, anti-inflammatory, antiplatelet, antiprotozoal and antiviral activities affecting the cardiovascular, endocrine, immune and nervous systems, and other miscellaneous mechanisms of action",[38] "Australian biodiversity via its plants and marine organisms. A high-throughput screening approach to drug discovery",[39] and "Secondary metabolites with antinematodal activity".[40] While not specifically focussing on marine natural products, the article on "Application of a new expert system for the structure elucidation of natural products from their 1D and 2D NMR data"[41] should be of significant interest to those investigating new compounds. There has been a further report on the Chinese database "A marine natural product database"[42] while the Marinlit database[43] continues to be updated and has again been used as the basis for the preparation of this present review.

## 3 Marine microorganisms and phytoplankton

Extracts of marine microorganisms, whether obtained from culture or directly from a collected sample, continue to yield an array of novel compounds. A culture of *Bacillus laterosporus*, isolated

from the tissues of an unidentified tube worm from Loloata Island, Papua New Guinea, was the source of the novel antifungal polyketide metabolites basiliskamides A **1** and B **2** and of two new acyldipeptides, tupuseleiamides A **3** and B **4**.[44] The (*S*) configuration of the secondary alcohol at C-7 in basiliskamide A **1** was determined by Ohtani's Mosher ester analysis method,[45] but the configuration at C-10 was not determined and is assumed to be (*S*) as in a known homologue.[46,47] The diagrams here for **1** and **2**, showing (7*S*,8*S*,9*R*,10*S*), are corrections from those given in the original paper.[44] The (*R*) configuration of the tyrosine and serine residues in tupuseleiamides A **3** and B **4** was determined by chiral GC analysis but the configuration at C-18 was not determined. Basiliskamides A **1** and B **2** were both converted to the same diol by DIBAL reduction, indicating identical configurations in both molecules. Basiliskamides A and B showed potent *in vitro* activity against *Candida albicans* while basiliskamide A **1** exhibited activity comparable to amphotericin B, but was at least four-fold less cytotoxic to human fibroblast cells.[44] Cultured *Bacillus pumilus*, isolated from the surface of the ascidian *Halocynthia aurantium* from Troitza Bay in Russian waters, yielded a mixture of surfactin-like cyclic depsipeptides **5**–**9**. These lipopeptides differed from surfactin by substitution of the 4-valine by leucine and were isolated as two carboxy-terminal variants with either valine or isoleucine in the 7-position.[48] The *bis*-catechol α-hydroxy acid siderophore, petrobactin **10**, was isolated from the cultured oil-degrading marine bacterium *Marinobacter hydrocarbonoclasticus*.[49] The cyclic hexapeptide halolitoralin A **11** and tetrapeptides halolitoralins B **12** and C **13** were isolated from the fermentation broth of *Halobacillus litoralis*, which had originated from a high-salt sediment from the Huanghai Sea, China. All amino acid residues were established as (*S*) by hydrolysis and subsequent Marfey's analysis. The halolitoralins A–C **11**–**13** exhibited moderate antifungal activity against *C. albicans*, *T. rubrum* and four crop-threatening fungi, in addition to moderate activity against the human gastric tumour BGC cell line.[50] The macrolide antibiotic chalcomycin B **14** was isolated from the culture broth of a *Streptomyces* sp. derived from mangrove sediment collected near Pohoiki, Hawaii.[51] Chalcomycin B **14** exhibited activity against a variety of microorganisms and microalgae. Cultures of *Humicola grisea*, a

filamentous fungus isolated from drift wood in New Caledonian waters, were the source of humicolone **15**, a phenolic tetralone in acetal form that exhibited appreciable cytotoxicity towards KB cell lines. The absolute configuration of humicolone **15** was established by Mosher's method and molecular modelling.[52] A cyclic tetrapeptide, designated JM47 **16**, was isolated from a marine *Fusarium* species isolated from the green alga *Codium fragile* subsp. *atlanticum* collected in Scottish waters and was determined to be cyclo(Ala-Ala-Aoh-Pro), where Aoh is (2*S*,9*S*)-2-amino-8-oxo-9-hydroxydecanoic acid.[53] The absolute stereochemistry of the core was determined by acidic hydrolysis and chiral TLC analysis of the proline residue.[53] A culture of a strain of the mangrove fungus *Eutypa* sp. isolated from wood in the South China Sea yielded eutypoid A **17** from the culture mycelium.[54] Four new epipolysulfanyldioxopiperazines, leptosins M **18**, M1 **19**, N **20** and N1 **21** were isolated from a culture of the fungus *Leptosphaeria* sp. originating from the Japanese brown alga *Sargassum tortile*.[55] Absolute stereochemistries were determined by chemical analyses and transformations. Each compound possessed significant cytotoxic activity against the P388 cell line while leptosin M **18** also exhibited appreciable cytotoxicity against a disease-oriented panel of 39 human cancer cell lines and specifically inhibited two protein kinases and topoisomerase II.[55] A carotenoid glycosyl ester **22** was isolated from cultured cells of a *Fusarium* species isolated from the seawater surface at Tanegashima, Japan.[56] Cultured *Fusarium chlamydosporum,* isolated from the Japanese marine red alga *Carpopeltis affinis*, was the source of fusaperazines A **23** and B **24**, two new sulfur-containing dioxopiperazine derivatives, and two known compounds **25** and **26** which had been originally isolated from a fermentation of the fungus *Tolypocladium* sp.[57] In the current report, the absolute configurations of **25** and **26** were determined by chemical transformations and the stereostructures of **23** and **24** established by comparison.[58] A new gabosine derivative, parasitenone **27** was isolated from a culture of the fungus *Aspergillus parasiticus* from the Korean red alga *Carpopeltis cornea*. The absolute configuration of parasitenone **27** was determined to be (4*S*,5*S*,6*S*) on the basis of CD data and a chemical transformation.[59] Aspergilloxide **28**, a sesterterpene epoxy-diol, was isolated from an extract of an

undescribed *Aspergillus* species from the Bahamas. The absolute configuration was assigned by application of the modified Mosher method.[60] The fungus *Curvularia lunata*, isolated from the marine sponge *Niphates olemda* from Indonesian waters, was the source of lunatin **29**, shown to be active against *S. aureus*, *E. coli* and *B. subtilis* but inactive against *C. albicans*.[61] Two new α-pyrones, herbarin A **30** and herbarin B **31** along with a new phthalide herbaric acid **32** were isolated from two cultured strains of the fungus *Cladosporium herbarum* isolated from the sponges *Aplysina aerophoba* and *Callyspongia aerizusa* collected in the French Mediterranean and in Indonesian waters respectively.[61] Herbarins A **30** and B **31** displayed activity in the brine shrimp assay.[61] A culture of the fungus *Emericella variecolor* isolated from a sponge collected in the Caribbean Sea off Venezuela yielded varitriol **33**, varioxirane **34**, dihydroterrein **35** and varixanthone **36** which were characterised by spectroscopic methods and chemical transformations.[62] Varitriol **33** displayed increased potency toward some renal, CNS and breast cancer cell lines in the NCI's 60-cell line panel while varixanthone **36** displayed antimicrobial activity against a range of bacteria.[62] Macrosphelide L **37** was obtained from a strain of the fungus *Periconia byssoides* cultured from the sea hare *Aplysia kurodai*.[63] The absolute stereostructure, along with that of macrosphelide H **38**, previously isolated from the same fungal species,[64,65] was determined by spectroscopic analyses and chemical transformations. Both compounds inhibited the adhesion of human-leukemia HL-60 cells to human-umbilical-vein endothelial cells (HUVEC).[63] The triester *seco*-macrosphelide E **39** was isolated from a strain of the fungus *P. byssoides* separated from the sea hare *Aplysia kurodai*. The absolute stereostructure was elucidated by spectroscopic analyses and synthesis.[66] The syntheses of macrosphelides H **38** and G,[65] also from *P. byssoides*, have been published.[67,68] The Japanese fish *Halichoeres bleekeri*[69] was the source of a cultured strain of *Streptomyces hygroscopicus* from which halichoblelide **40**, a macrolide with potent cytotoxicity against the murine P388 cell line and 39 human cancer cell lines, was isolated. The absolute configuration of halichoblelide **40** was established by spectroscopic analyses and chemical transformation.[70] The source of the 14-membered resorcylic macrolides aigialomycins A–E **41**–**45** was a culture of the mangrove fungus

*Aigialus parvus*. The structures, including absolute configurations, were determined by spectroscopic methods, chemical conversions and X-ray analysis of a derivative of aigialomycin C **43**. Aigialomycin D **44** displayed antimalarial activity *in vitro* against *Plasmodium falciparum* in addition to moderate cytotoxicity against the KB, BC-1 and Vero cell lines.[71] Ten new sesquiterpenoids, isosativenetriol **46**, drechslerines A **47** and B **48**, 9-hydroxyhelminthosporol **49**, drechslerines C–G **50–54** and sativene epoxide **55** were isolated from a culture of the fungus *Drechslera dematioidea* from the red alga *Liagora viscida*. Drechslerines E **52** and G **54** exhibited antiplasmodial activity against two strains of *P. falciparum*.[72] Two γ-pyrone derivatives, microsphaerones A **56** and B **57**, were isolated from a culture of the fungus *Microsphaeropsis* sp. from the marine sponge *Aplysina aerophoba* collected in French waters.[73] The presence of an (*S*)-2-methylsuccinic acid moiety in microsphaerone A **56** was established by GC-MS analysis of a (–)-menthylated hydrolysis product.[73] Three diterpene glycosides, virescenosides O–Q **58–60** have been isolated from a cultured strain of *Acremonium striatisporum* associated with the holothurian *Eupentacta fraudatrix*.[74] Virescenosides O–Q **58–60** were cytotoxic against Ehrlich carcinoma cells *in vitro* while virescenoside P **59** was also cytotoxic to developing eggs of the sea urchin *Strongylocentrotus intermedius*.[74] Cultures of the marine fungus *Hypoxylon oceanicum*[75] from mangrove wood from Shenzen, China, yielded the macrocyclic polyesters **61** and **62** and the linear polyesters **63–67**.[76] The absolute configurations of the polyesters were deduced from CD spectral studies. Compounds **61** and **62** exhibited modest activity against the phytopathogenic fungus *Neurospora crassa*.[76] The marine sponge *Xestospongia exigua* collected from the Bali Sea, Indonesia, was the source of fungal isolates of *Penicillium cf. montanense*. Cultures of these isolates gave the xestodecalactones A–C **68–70**, 10-membered macrolides with a fused 1,3-dihydroxybenzene ring. Xestodecalactones **69** and **70** are diastereoisomeric but only **69** was active against *C. albicans*.[77] A culture of the facultative marine ascomycete *Zopfiella latipes*, originally isolated from Indian Ocean soil, was the source of zopfiellamides A **71** and B **72** which were moderately active against *Arthrobacter citreus*, *B. brevis*, *B. subtilis*, *B. licheniformis*,

*Corynebacterium insidiosum*, *Micrococcus luteus*, *Mycobacterium phlei*, *Streptomyces* sp. and *Acinetobacter calcoaceticus*.[78] Halorosellins A **73** and B **74** were isolated from the culture broth of the marine fungus *Halorosellinia oceanica* of Thai origin. In addition, **75**–**77** were isolated. The isobenzofuran-1-one **76** exhibited moderate antimycobacterial activity.[79] A culture of an unidentified fungus from the South China Sea yielded the cyclic tetrapeptides **78**–**80**,[80] which are very similar to the bacterial metabolites, the halolitoralins B **12** and C **13** (*vide supra*). The filamentous marine fungus *Keissleriella* sp. isolated from a Yellow Sea sediment source gave a dihydronaphthalen-1(4H)-one **81** which was antifungal *in vitro* against *C. albican*s, *T. rubrum* and *A. niger*.[81] 5-Hydroxyramulosin **82** originated from the fungus *Phoma tropica*, isolated from the brown alga *Fucus spiralis*. The structure was secured by an X-ray analysis.[82] A Palauan collection of the marine cyanobacterium *Lyngbya* sp. was the source of the brominated glycoside macrolide, lyngbyaloside B **83**. The relative stereochemistry of the 12 stereocentres has been proposed on the basis of coupling constant and ROESY NMR data. Lyngbyaloside B **83** exhibited weak cytotoxicity against KB cells.[83] A related glycosidic macrolide, lyngbouilloside **84**, was isolated from *L. bouillonii* collected from Papua New Guinea. Lyngbouilloside **84** exhibited modest cytotoxicity to neuro-2a neuroblastoma cells.[84] A Guam collection of *Lyngbya* sp. yielded apratoxin B **85** while a collection of the same species from Palau afforded apratoxin C **86**. The chirality of the constituent amino acids was determined as (*S*) by chiral HPLC analysis of the hydrolysis products. Apratoxin C **86** exhibited appreciable cytotoxicity against KB and LoVo cells, while apratoxin B **85** and the semisynthetic (*E*)-dehydroapratoxin A were considerably less active.[85] *Lyngbya* sp. from Palau also yielded the dichlorinated thiazole hydroxy acid-containing cytotoxic macrolide lyngbyabellin C **87**, the modified tetrapeptides lyngbyapeptins B **88** and C **89** and a cytotoxic *N*-acylpyrrolinone, palau'imide **90**.[86] The absolute stereochemistry of lyngbyabellin C **87** could not be determined as only minute amounts were available but cytotoxicity to both KB and LoVo cell lines was noted. One ester linkage of lyngbyabellin C was particularly prone to methanolysis. Regioselective ester cleavage at C-16 caused conversion to the methyl ester

homohydroxydolabellin and led to the speculation that the sea hare metabolite dolabellin[87] is likely to be an artifact rather than a natural product. Homohydroxydolabellin had virtually identical activity against KB and LoVo cell lines to lyngbyabellin C **87**. The absolute stereochemistries of lyngbyapeptins B **88** and C **89** were found to be all (*S*) by chiral HPLC analysis of hydrolysis products and the (*E*) stereochemistry for the olefin in lyngbyapeptin C **89** was established by a ROESY NMR experiment. The configurations of C-4 and C-15 of palau'imide **90** were deduced by analysis of degradation products but that at C-20 was not determined due to lack of material. Palau'imide was cytotoxic to KB and LoVo cells.[86] The first total syntheses of the lipopeptides lyngbyabellin A, originally isolated from collections of *L. majuscula* from Guam,[88] and lyngbyabellin B isolated from collections of *Lyngbya* sp. from Guam[89] and Florida[90] respectively, have been described. The functionalised thiazole carboxylic acids were prepared by oxidative dehydrogenation of the corresponding thiazolidines with manganese dioxide.[91] Collections of *Lyngbya* sp. from various Palauan dive sites were the source of six new β-amino acid-containing cyclic depsipeptides, the ulongamides A–F **91**–**96**. The absolute stereochemistries of the hydroxy acid and all α-amino acid-derived units were elucidated as (*S*) by chiral HPLC analysis of hydrolysis products. Advanced Marfey's analysis of the acid hydrolysates determined the stereochemistry of 3-amino-2-methylhexanoic acid as (2*R*,3*R*) in ulongamides A–C **91**–**93** and (2*S*,3*R*) in ulongamides D–F **94**–**96**. Ulongamides A–E **91**–**95** were weakly cytotoxic against KB and LoVo cells *in vitro*, while ulongamide F **96** was inactive.[92] A Madagascan collection of *L. majuscula* was the source of further depsipeptides, the antanapeptins A–D **97**–**100**. Structures were deduced by 2D NMR and mass spectral analysis.[93] A 36-membered macrolactone (25*S*,27*S*,29*S*,33*S*)-caylobolide A **101** was isolated from *L. majuscula* from the Bahamas. The relative stereochemistry of the 1,3,5-triol was determined using Kishi's Universal NMR database while the absolute stereochemistry at C-25, C-27, C-29 and C-33 was determined by Mosher's analysis. Caylobolide A **101** displayed cytotoxicity against human colon tumor cells (HCT-116) *in vitro*.[94] Hectochlorin **102** was isolated from *L. majuscula* collected from Hector Bay, Jamaica, and

Boca del Drago Beach, Panama. The absolute stereochemistry of **102** was determined as (2*S*,3*S*,14*S*,22*S*) by X-ray analysis. Hectochlorin **102**, a potent stimulator of actin polymerisation, shows a unique profile of cytotoxicity by the COMPARE algorithm in the NCI panel and is strongly inhibitory towards *C. albicans*.[95] A total synthesis of hectochlorin **102** has now been accomplished.[96] A mixed assemblage of *L. majuscula* and a *Schizothrix* sp. from Fijian waters yielded the cytotoxic disulfide dimer somocystinamide A **103**. The absolute stereochemistry was established as (2*R*,2'*R*) by HPLC analysis of hydrolysis products.[97] A collection of *L. confervoides* from Saipan in the Commonwealth of the Northern Mariana Islands was the source of a cytotoxic cyclic depsipeptide, obyanamide **104**. The absolute stereochemistry was determined by chiral chromatography of hydrolysis products and comparison with authentic and synthetic standards. Obyanamide **104** was cytotoxic to KB cells.[98] An antifungal cyclododecapeptide, lobocyclamide B **105** has been isolated from a benthic mat of *L. confervoides* from the Bahamas. The absolute stereochemistry of **105** was established by a combination of chiral HPLC and Marfey's methods. Lobocyclamide B **105** displays antifungal activity against fluconazole-resistant *C. albicans*.[99] Maculalactone M **106**, a benzofuranone derivative, was isolated from the epilithic encrusting cyanobacterium *Kyrtuthrix maculans* collected in Hong Kong. The planar structure was established by spectral analysis but an attempt to determine the absolute stereochemistry by CD spectroscopy was unsuccessful.[100] A new dolastatin 10[101] analogue, symplostatin 3 **107**, has been isolated from a tumour-selective extract of an Hawaiian collection of *Symploca* sp. VP452 which taxonomically appears to be *S. hydnoides*. The absolute stereochemistry of **107** was established by chiral HPLC of acid hydrolysis products. Symplostatin 3 **107** only differs from dolastatin 10 in the C-terminal unit, where the dolaphenine unit is substituted by a 3-phenyllactic acid residue. Symplostatin 3 also displays strong *in vitro* cytotoxicity towards a range of human tumour cell lines and disrupts microtubules but at a higher concentration than dolastatin 10.[102] A cytotoxic peptide ester, malevamide D **108**, closely related to isodolastatin H,[103] was isolated from an Hawaiian collection of *S. hydnoides*. Partial stereochemical assignments were made by chiral HPLC analysis of

hydrolysates. Malevamide D **108** displayed toxicity against P388, A-549, HT-29 and MEL-28 cell lines in the sub-nanomolar range.[104] A Palauan collection of *Symploca* sp. was the source of the acyclic peptide tasiamide **109**. The absolute stereochemistry of **109** was established by chiral HPLC of degradation products. Tasiamide **109** was cytotoxic against KB and LoVo cells.[105] A laboratory culture of a *Phormidium* sp. from Sulawesi, Indonesia yielded phormidolide **110**, a bromine-containing macrolide. The absolute stereochemistry of the 11 stereocentres was determined on a *bis*-acetonide derivative using the variable temperature Mosher ester method. Phormidolide **110** was a potent brine shrimp toxin.[106] A new cytotoxic polyether, gymnocin-A **111** has been isolated from a culture of the red tide dinoflagellate *Gymnodinium mikimotoi* from Japanese waters. The structure, which consists of 14 contiguous ether rings and a 2-methyl-2-butenal sidechain, was determined by NMR and mass spectral analysis while the absolute stereochemistry of **111** was elucidated by the modified Mosher method. Gymnocin-A **111** was cytotoxic in a cell-based assay but only weakly toxic to fish.[107] The first total synthesis of the polycyclic ether toxin (–)-gambierol, isolated from cultured cells of the ciguatera-causative dinoflagellate *Gambierdiscus toxicus*,[108] has been achieved.[109,110] The synthesis features a Stille coupling for the stereoselective construction of the triene sidechain.[110] The absolute stereochemistry at eight chiral centres in amphidinolide E **112**, a cytotoxic 19-membered macrolide isolated from the marine dinoflagellate *Amphidinium* sp.,[111] has been determined as (2*R*,7*R*,8*R*,13*S*,16*S*,17*R*,18*R*,19*R*) by NMR spectroscopic data analysis, modified Mosher's method and the exciton chirality method.[112] Meanwhile, six new macrolides, amphidinolides H2–H5 **113**–**116**, G2 **117** and G3 **118** were isolated from the dinoflagellate *Amphidinium* sp. obtained from an Okinawan acoel flatworm *Amphiscolops* sp.[113] The absolute stereochemistries of compounds **113**–**117** were determined from coupling constant data, distance geometry calculations and chemical means, while that of amphidinolide G3 **118** was established by comparison of NMR data with those of amphidinolide G.[114] Compounds **113**–**117**, in addition to amphidinolides G–H, [114] B,[115] D[116] and five derivatives of amphidinolide H, exhibited varying levels of cytotoxicity against murine L1210

cells and human epidermoid carcinoma KB cells.[113] A further cytotoxic 12-membered macrolide, amphidinolide W **14160/1**, has also been isolated from an *Amphidinium* sp. from the flatworm *Amphiscolops* sp.[117] Spectroscopic means, including analysis of $^{13}C$-$^{13}C$ INADEQUATE correlations for a $^{13}C$-enriched sample, established the structure, while the absolute stereochemistry of **14160/1** was assigned by *J*-based configuration analysis and the modified Mosher method. Amphidinolide W **119** is the first macrolide without an exomethylene unit among all amphidinolides obtained to date.[118] Three groups more or less simultaneously succeeded in achieving total syntheses of the originally proposed structure of amphidinolide A,[119] via a ring-closing metathesis,[120] ruthenium-catalysed alkene-alkyne coupling[121] or employing extensive use of inter-and intramolecular Stille reactions.[122] It was concluded that the structure of amphidinolide A needed revision. A total synthesis of amphidinolide T4[123] has been accomplished.[124] A digalactosyl diacylglycerol **120** was isolated from a culture of the Japanese marine dinoflagellate *Heterocapsa circularisquama*. Compound **120** exhibits cytolytic activity towards oyster heart cells.[125] The first stereoselective synthesis of the cytotoxic peptide aspergillamide B from an *Aspergillus* sp.[126] has been reported[127] as well as the first total synthesis of somamide A, a 19-membered macrocyclic depsipeptide isolated from assemblages of the cyanobacteria *L. majuscula* and *Schizothrix* sp.[128] The anti-inflammatory and anti-proliferative properties of scytonemin, an extracellular sheath pigment originally isolated from the cyanobacterium *Stigonema* sp.,[129] have been reported.[130,131] Goniodomin A, an antifungal polyether macrolide from the dinoflagellate *Goniodoma pseudogoniaulax*[132] has been shown to inhibit angiogenesis by inhibition of endothelial cell migration and basic fibroblast growth factor (bFGF) induced tube formation and is active *in vivo*.[133]

## 4 Green algae

Relatively few compounds have been reported from green algae recently. From the Cuban green alga *Cymopolia barbata* six new prenylated bromohydroquinones were isolated **121–126**.[134] The

NMR data for five known but related cymopol compounds were also assigned, as literature data[135,136] were either incomplete or unassigned.[134] The green alga *Codium iyengarii* from the Karachi coast of the Arabian Sea was the source of a new steroid, iyengadione **127** and two new steroidal glycosides, iyengarosides A **128** and B **129**. Iyengaroside-A **128** displayed moderate activity against a range of bacteria.[137] Two novel carotenoid C14:1 *trans*-$\Delta^2$ esters, siphonaxanthin C14:1 *trans*-$\Delta^2$ ester **130** and 6'-hydroxy siphonaxanthin C14:1 *trans*-$\Delta^2$ ester **131** were isolated from the green alga *Pterosperma cristatum* collected in Japanese waters.[138] An inseparable mixture of nitrogenous glycerolipids **132–134** was isolated from the green alga *Ulva fasciata* collected from the Indian Coast. **133** was the major component of the mixture.[139] Some glycoglycerolipids from the green alga *Ulvella lens* have been identified as chemical inducers to settlement and metamorphosis of planktonic larvae of the sea urchin *Strongylocentrotus intermedius*.[140]

## 5 Brown algae

Terpenoids and steroids dominate the compounds reported from brown algae. In the course of examination of the sterol composition of the brown alga *Cystoseira crinita* collected in the Mediterranean off Turkey, a new sterol 24-norchola-5,22-dien-3β-ol, was identified by GC-MS analysis.[141] Stypolactone **135**, a diterpenoid of mixed biogenesis has been isolated from the brown alga *Stypopodium zonale*. The structure and relative stereochemistry were determined from spectroscopic evidence and biogenetic considerations. Stypolactone **135** displayed weak cytotoxicity *in vitro* against the A-549 and H-116 cell lines.[142] Two diterpenoids with a novel skeleton, dictyterpenoids A **136** and B **137**, were isolated from the brown alga *Dilophus okamurae* collected from the Japan Sea Coast and displayed antifeedant activity against young abalone.[143] *S. carpophyllum* from the South China Sea was the source of two new bioactive sterols **138** and **139**. These sterols induced morphological abnormality in the plant pathogenic fungus *Pyricularia oryzae* and **138** also exhibited cytotoxic activity against several cultured cancer cell lines.[144] *S. polycystum*

collected in the North China Sea yielded a new sterol, stigmast-5,23,25-triene **140**.[145] The absolute configuration of the secondary alcohol in fucoxanthin **141**, isolated in this case from the brown alga *Turbinaria triquatra* but otherwise ubiquitous in brown algae,[146] was determined by the Mosher method. The *T. triquatra* extract displayed activity against NINH3T3 fibroblast and KA3IT murine cancer cell lines.[147] Three loliolide derivatives, **142–144** have been isolated from the brown alga *Undaria pinnatifida* from Japanese waters. Containing a hemiacetal group, **142** is a unique loliolide derivative. The relative stereochemistry of **142** was determined by NOE measurements while **143** and **144** were determined to be diastereomers.[148] The tropical brown alga *Stypopodium zonale* collected off the coast of Tenerife was the source of three terpenoids **145–147**. Structures and relative stereochemistries were determined from the derived methyl esters. The methyl ester of **147** exhibited *in vitro* cytotoxic activity against HT-29 H-116 and A-549.[149] Two shikimate derivatives **148** and **149** were isolated from the brown alga *Spatoglossum variabile* collected from the coast off Karachi.[150] Total syntheses of sporochnols B and C, fish feeding deterrents originally isolated from the brown alga *Sporochnus bolleanus*,[151] have been reported, using the C-H insertion reaction of alkylidenecarbene as the key step.[152] Total syntheses of dictyochromenol **150** from the brown alga *Dictyopteris undulata* from Japan[153] and the (*Z*)-stereoisomer have been reported and it was established that the natural enantiomer has an (*R*) configuration.[154] A total synthesis of yahazunol, originally isolated from the brown alga *Dictyopteris undulata*,[155] has been achieved, starting from (+)-albicanic acid.[156]

## 6 Red algae

As for the brown algae, terpenoids and steroids are the dominant metabolite classes reported from red algae. A monoterpene, prefuroplocamioid **151**, has been isolated from a Chilean sample of *Plocamium cartilagineum*. The (*Z*)-stereochemistries of the double bonds along with the C-6 relative stereochemistry were determined from NMR analyses but instability problems prevented

assignment of absolute stereochemistry.[157] This *P. cartilagineum* was also the source of the plocamenols A–C **152–154**, linear polyhalohydroxylated monoterpenes,[158] and three other halogenated monoterpenes **155–157**.[159] The structures and relative stereochemistries of these compounds were elucidated by spectroscopic means and led to assignment of the relative stereochemistry at C-7 as (*S**) for furoplocamioids A-C, also from *P. cartilagineum*.[160] *P. cartilagineum* was the source of yet another new halogenated monterpene **158**.[161] The antifeedant effects of a range of halogenated monoterpenes, originally isolated from *P. cartilagineum*[160, 162–166] and *Pantoneura plocamioides*,[167] were tested against several divergent insect species including the Colorado potato beetle *Lepinotarsa decemlineata*, the aphids *Myzus persicae* and *Ropalosiphum padi*, and *Spodoptera frugiperda*-derived Sf9 cells.[161] Two C15 acetogenins containing a terminal bromoallene moiety, itomanallenes A **159** and B **160**, and a brominated sesquiterpene itomanol **161**, have been isolated from *Laurenica intricata* from Okinawa.[168] Another Okinawan red alga, *L. yonaguniensi,* was the source of neoirietetraol **162**, a brominated diterpene based on the rare neoirieane skeleton. Also isolated was a chlorinated C15 acetogenin, (3*Z*)-laurenyne **163**. The relative stereochemistry of **162** was determined from spectral data but an attempt to determine the absolute configuration was unsuccessful. Both neoirietetraol **162** and (3*Z*)-laurenyne **163** were toxic to brine shrimp and **162** was active against the marine bacteria *Alcaligenes aquamarinus* and *E. coli*.[169] Three halogenated rearranged sesquiterpenes **164–166** containing the brasilane skeleton and a 1,6-epoxy moiety have been isolated from *L. obtusa* collected off Symi Island in the Aegean Sea, Greece. The structures and relative stereochemistries were established by spectral data analyses and molecular modelling.[170] Bromocyclococanol **167**, a sesquiterpene possessing a novel skeleton, was isolated from *L. obtusa* from Cayo Coco, Cuba. The structure and stereochemistry were established from spectroscopic data and biogenetic considerations.[171] The 5-acetate derivative **168** of prepacifenol was isolated from both *L. filiformis* and the sea hare predator *Aplysia parvula* collected from Taroona, Tasmania. Also isolated was the known prepacifenol, originally found in a *Laurencia* sp. seaweed.[172] An X-ray analysis was reported for **168** and the NMR spectra of

prepacifenol were fully assigned for the first time. Both compounds exhibited moderate activity in the brine shrimp bioassay.[173] The first 6,8-cycloeudesmane sesquiterpene of marine origin **169**, has been isolated from *L. microcladia* from the Baia di Calenzana, Elba Island.[174] *L. obtusa*, collected from off Symi Island in the Aegean Sea, Greece was the source of four C15 acetogenins, 13-epilaurencienyne (3*Z*) **170**, 13-epipinnatifidenyne (3*E*) **171** and two diacetoxypentadec-3-en-1-yne derivatives **172–173**. **170** and **173** exhibited strong toxicity to ants with considerable knockdown effect on the first day, while compounds **171** and **172** exhibited gradual toxicity that escalated at the fourth day with >70% mortality.[175] The structures and relative stereochemistries of four undecane-3-one sequiterpenes **174–177** and perforenone D **178** have been reported from *L. obtusa* collected at Milos Island in the Aegean Sea, Greece. The relative stereochemistry of the known compound perforatone **179** was also revised.[176] Two sesquiterpenes with an oxacyclic chamigrene skeleton, oxachamigrene **180** and 5-acetoxyoxachamigrene **181**, have been isolated from *L. obtusa* from Cayo Coco, Cuba.[177] *L. viridis* from Tenerife, Canary Islands was the source of three polyethers, clavidol **182**, 3-*epi*-dehydrothyrsiferol **183** and lactodehydrothyrsiferol **184**. The relative stereochemistries were proposed on the basis of ROESY and NOEDIFF data and biogenetic considerations.[178] The Indonesian red alga *Vidalia* sp. was the source of the phenolic metabolite vidalenolone **185**,[179] while a new 3,6-diketosteroid **186** was isolated from the red alga *Hypnea musciformis* collected on the Atlantic Coast of Morocco. **186** exhibited anti-elastase activity against porcine pancreas elastase (PPE). Two novel steroids **187** and **188** were also isolated as an inseparable mixture.[180] A sulfoglycolipidic fraction from the red microalga *Porphyridium cruentum*, shown to contain large amounts of palmitic acid, arachidonic acid and eicosapentaenoic acid, strongly inhibited production of the superoxide anion and growth of DLD-1, MCF-7, PC-3 and M4 Beu cell lines.[181]

Several syntheses of red algal metabolites were reported in 2002. 2,3,6-Tribromo-1-methylindole, originally isolated from *L. brongniartii*[182] has been synthesised from 2,3-dibromo-1-

methylindole,[183] and the first asymmetric total synthesis of (+)-laurenyne, a metabolite of *Laurencia obtusa*,[184] has been achieved.[185]

## 7 Sponges

The phylum Porifera (sponges) continues to be a rich source of novel secondary metabolites, with a diversity of biological activities that continue to inspire the efforts of synthetic organic chemists. A pair of ceramides with variable alkyl chain lengths **189** and **190** were isolated from *Clathria fasciculata* collected in southern China.[186] Pachastrissamine **191**, a sphingosine derivative, was reported from the Okinawan sponge *Pachastrissa* sp. and the absolute stereochemistry determined from analysis of the MTPA amides.[187] The relative and absolute stereochemistry of the immunosuppressive sphingolipid, plakoside A **192**, isolated from the Caribbean sponge *Plakortis simplex*,[188] was finally determined by degradation and derivatisation.[189,190] The cyclopropyl-containing side chains were cleaved off as carboxylic acids from the natural product. These acids were synthesised with known absolute stereochemistry and derivatives with (1*S*,2*S*)- and (1*R*,2*R*)-2-(2,3-anthracenedicarboximido)-cyclohexanol were prepared and compared by HPLC. Previous syntheses of plakoside with the correct,[191] and incorrect[192] relative stereochemistry had resulted in compounds with the same optical rotation. The methyl ester of 5,9,23-triacontatrienoic acid **193**, isolated from *Chondrilla nucula* collected from the French Mediterranean coast, was found to inhibit elastase.[193] Two further new cytotoxic cyclitol derivatives, sarcotride B **194** and C **195** were isolated from a Korean *Sarcotragus* sp.[194] The isocrasserides **196–206** were isolated from the Caribbean sponge *Plakortis simplex*.[195] The authors report that the isocrasserides **196–206** and the related, previously described crasserides,[196] were found in all sponges examined from a wide variety of genera within the phylum and propose that they are a characteristic, distinguishing metabolite of the phylum Porifera. The antimicrobial glycolipid caminoside A **207**, isolated from Dominican specimens of *Caminus sphaeroconia*, was found to be a potent inhibitor of the bacterial type III secretion system.[197] The lembehynes B **208** and C **209**, isolated from an Indonesian species of

*Haliclona*, were found to possess neuritogenic activity against neuroblastoma cells.[198] Strongylodiol A, originally isolated from an Okinawan *Strongylophora* species,[199] has been synthesised confirming the (*R*) stereochemistry.[200] Japanese specimens of *Callyspongia truncata* yielded the α-glucosidase inhibitor callyspongynic acid **210**[201] while corticatic acids D **211** and E **212** along with the previously reported corticatic acid A,[202] were isolated from a Japanese *Petrosia corticata* and found to be geranylgeranyltransferase type I inhibitors.[203] A cytotoxic fatty acid, (*5Z,9Z*)-22-methyl-5,9-tetracosadienoic acid **213** was isolated from *Geodinella robusta* collected from the Sea of Okhotsk, Russia.[204] A series of polymethoxydienes **214**–**218**, similar to the alkenes isolated from the cyanophyte *Tolypothrix conglutinata*,[205] were isolated from a Philippine specimen of *Myriastra clavosa*, and found to be moderately cytotoxic.[206] *Plakortis nigra*, collected from a depth of 115 m in Palau, was found to contain epiplakinic acids G **219** and H **220** and the γ-lactones **221** and **222** along with several β-carbolines (*vide infra*). All compounds were found to inhibit the growth of HCT-116 cells.[207] A peroxylactone, originally isolated from a *Plakinastrella* species,[208] has been synthesised as a racemic mixture.[209] Two new 1,2-dioxolane peroxide acids **223** and **224**, isolated from *P. onkodes* collected in Florida, possessed moderate antifungal activity.[210] A 1,2-dioxane peroxide acid **225,** also with moderate antifungal activity, was isolated from a Jamaican specimen of *Plakortis halichondrioides*.[210] The relative and absolute stereochemistry of the cyclic peroxide **226**, originally isolated from *P. angulospiculatus*,[211] has been proposed by comparison to the optical rotation and NMR spectral data of synthesised diastereomers.[212] Seven methyl esters, plakortethers A–G **227**–**233** with selective toxicity towards murine macrophage cells (RAW 264-7), were obtained from a Bahaman specimen of *P. simplex*.[213] Plakortone D **234**, originally isolated from *P. halichondrioides*,[214] has been synthesised thereby establishing the relative stereochemistry of C-10 and its absolute configuration as illustrated.[215] The plakortides named I and J, recently isolated from the Jamaican sponge *Plakortis* sp.,[216] have been renamed plakortides M and N as the names plakortide I and J had been used previously for related metabolites isolated from *P. simplex* collected in the Bahamas.[217] *Theonella cf. swinhoei* from Indonesia was found to contain the

bitungolides A–F **235**–**240** which were shown to weakly inhibit dual-specificity phosphatase.[218] Subereatensin **241** was isolated from a Thailand specimen of *Suberea aff. praetensa*.[219] An Okinawan collection of *Terpios hoshinota* contained the cytotoxic alcohol terpiodiene **242**.[220] The symbiotic complex of the sponge *Haliclona cymaeformis* and the red alga *Ceratodictyon spongiosum* collected in the Philippines was found to contain *p*-sulfooxyphenylpyruvic acid **243** and its phenol congener **244**.[221] Five new cytotoxic discodermolide analogues **245**–**249** were isolated from several different *Discodermia* sp. specimens collected in the Bahamas.[222] The highly cytotoxic metabolite swinhoeiamide A **250**, related to calyculinamide A, was obtained from *Theonella swinhoei* collected in Papua New Guinea.[223] The same compound with similar optical activity was isolated from an Australian collection of *Luffariella geometrica* and named geometricin A.[224] Another calyculin A congener, hemicalyculin A **251** with potent cytotoxicity, has been obtained by bioassay-guided fractionation of Japanese specimens of *Discodermia calyx*, the original organism from which calyculin was isolated.[225] An enantioselective synthesis of bengamide Z, originally isolated from a *Jaspis* sp.,[226] has been reported.[227,228] Two potently cytotoxic amides, theopederins K **252** and L **253**, were obtained from a *Discodermia* species collected from Honduras.[229]

Sponges continue to be a rich source of novel and biologically active peptides. The inhibitor of factor VIIa and thrombin, dysinosin A **254**, was isolated from a new genus of dictyoceratid sponge of the family Dysideidae from Australia.[230] The structure of dysinosin A has been confirmed by stereoselective synthesis.[231] The cyclic tripeptide renieramide **255**, which was isolated from a new species of *Reniera* collected in Vanuatu, showed immunomodulatory activity.[232] Interestingly, the structure of **255** proved to be identical to a patented synthetic analogue of the microbial product OF4949.[233] A Northern Australian collection of *Leucetta microraphis* yielded the cytotoxic heptapeptide leucamide A **256**.[234] Cyclotheonamides E2 and E3, originally isolated from a *Theonella* species,[235] have been synthesised.[236,237] Two new cyclotheonamides E4 **257** and E5 **258** were obtained from an *Ircinia* sp. from Japan and were found to be potent tryptase

inhibitors.[238] The *trans, trans* rotamer of ceratospongamide has been synthesised along with the previously reported *cis, cis* isomer.[239,240] Both forms of ceratospongamide were originally isolated from the symbiotic complex of *Sigmadocia symbiotica* and its host red alga *Ceratodictyon spongiosum*.[241] The two rotamers were remarkably stable at temperatures up to 95 °C, but could be interconverted at 175 °C in DMSO. The *trans, trans* rotamer was found to be a potent inhibitor of the expression of secreted phospholipase $A_2$ ($sPLA_2$) while the *cis, cis* form was inactive.[241] Similarly, two distinct conformers of the previously reported peptide phakellistatin 2 **259** were isolated and characterised from the Fijian specimen of *Stylotella aurantum*.[242] The less polar conformer was found to contain an intramolecular hydrogen bond. Phakellistatin 2 was originally isolated from *Phakellia carteri* and reported to be potently cytotoxic.[243] A subsequent reisolation and a total synthesis failed to reproduce the biological activity. The less polar conformer isolated from *Stylotella* was found to have a similar activity to that originally reported, and was found to lose activity at room temperature on standing for several weeks.[242] Isolated from the same sponge was the weakly cytotoxic octapeptide axinellin C **260**.[244] The structures proposed for halipeptins A **261** and B **262**, originally isolated from a *Haliclona* species from Vanuatu,[245] have been revised.[246] The molecular formulae have been revised to include sulfur, replacing the proposed oxazetidine ring with a thiazoline moiety **263** and **264**. A new compound, halipeptin C **265** was obtained from the same sponge.[246] A Palauan specimen of the genus *Haliclona* was found to contain the new haliclonamides C–E **266–268** which were found to repel the settlement of *Mytilus edulis* adults.[247] Two depsipeptides with nematocidal activity, phoriospongins A **269** and B **270**, were isolated from both a *Phoriospongia* species and *Callyspongia bilamellata* from southern Australia.[248] Callipeltins D **271** and E **272** were isolated from a *Latrunculia* species collected from Vanuatu.[249] The determination of the presence of (*R*)-*allo*-threonine and (*R*)-alanine in their structures by use of Marfey's reagent led to the re-examination of the stereochemistry of callipeltin A **273**, originally isolated from a *Callipelta* species.[250] The stereochemistry has been revised as illustrated. A

Japanese collection of *Theonella swinhoei* was found to contain an antibacterial depsipeptide nagahamide A **274**.[251]

Sponge derived macrolides have proven to be of considerable interest to both synthetic and natural product research groups. Callipeltoside A **275**, originally isolated from a Lithistid sponge of the genus *Callipelta*,[252] has been synthesised stereoselectively independently by two groups, establishing the relative and absolute stereochemistry of the chlorocyclopropyl side chain.[253–255] The structure of lasonolide A, isolated from a Caribbean *Forcepia* species,[256] has been revised to **276** by enantioselective synthesis of its antipode.[257,258] (+)-Dactylolide **277**, isolated from a *Dactylospongia* species,[259] has been synthesised, establishing both the relative stereochemistry of the acyloxymethine and overall absolute stereochemistry.[260,261] Interestingly, it appears to be a pseudo-enantiomer of the closely related sponge metabolite (–)-zampanolide.[262] Clavosides A **278** and B **279** were isolated from the Philippine sponge *Myriastra clavosa*.[263] The same compounds were described independently from *M. clavosa*, along with clavosides C **280** and D **281**.[264] A new mycalolide, 30,32-dihydroxymycalolide **282**, with potent cytotoxicity, was obtained from *Mycale izuensis* from Japan.[265] A macrolide lactam, poecillastrin A **283**, related in structure to the chondropsins,[266] was isolated from a Bahamas collection of a deep water *Poecillastra* species.[267] Poecillastrin A was found to have cytotoxicity and antiproliferative properties similar to those of the chondropsins. Two brominated dibenzo-*p*-dioxins, spongiadioxin C **284** and the methyl ether **285**, found to inhibit the division of fertilised sea urchin eggs, were isolated from an Australian collection of *Dysidea dendyi*.[268] The moderately cytotoxic thioester irciniamine **286** was isolated from an *Ircinia* species collected in Japan.[269] The previously reported motuporins A–C **287**–**289**[270] along with the new congeners D–F **290**–**292** were found to inhibit the invasion of breast carcinoma cells into new tissues. These compounds were isolated from *Xestospongia exigua* collected in Papua New Guinea along with an unresolved mixture of three isomers **293**.[271] Xestamine D, originally isolated from *Calyx podatypa*,[272] has been synthesised employing a palladium coupling strategy.[273] The syntheses of hachijodines F and G, originally isolated from an *Amphimedon*

species,[274] have also been reported.[275] The structure **294**, originally proposed for pyrinodemin A isolated from an *Amphimedon* species,[276] was synthesised independently by two groups but did not have spectral characteristics identical to the natural compound.[277,278] The alternative structure **295** was proposed and synthesised by both groups. Recently, a third structure **296** has been synthesised which matches the spectral data reported for the natural compound more closely. The researchers note "that it would be hasty to conclude that **296** is the correct structure of natural pyrinodemin A".[279] A *Halichondria* species collected from Eritrea was found to contain the bispiperidine alkaloid halichondramine **297**.[280] The relative stereochemistry of each piperidine ring was determined but their stereochemical relationship remains unresolved due to severe spectral overlap. Two novel *N*-oxide containing alkaloids araguspongines K **298** and L **299** were isolated from Saudi Arabian specimens of *Xestospongia exigua*.[281] A Western Australian *Xestospongia* species yielded (7*S*)-hydroxyxestospongin A **300**; its absolute stereochemistry, and that of the previously reported[282] (+)-xestospongin D **301**, was determined by X-ray analysis.[283] Three novel manzamine type alkaloids, *ent*-12,34-oxamanzamines E **302**, F **303** and 12,34-oxamanzamine A **304** were isolated from three closely related species of an undescribed genus of the family *Petrosiidae* (Order Haplosclerida) from Indonesia.[284] An intramolecular Stille/Diels-Alder reaction has been employed in the enantioselective synthesis of ircinal.[285] The bromoindole **305**, isolated from a South Australian *Hymeniacidon* species was found to have nematocidal activity.[286] A Micronesian sponge belonging to the order Haplosclerida, and probably representing a new genus, contained a cathepsin inhibitor haploscleridamine **306**.[287] *N*-3'-Ethylaplysinopsin **307**, isolated from the Jamaican sponge *Smenospongia aurea*, has a high affinity for the human serotonin 5-$HT_2$ receptor.[288] A diketopiperazine **308**, isolated from *Geodia barretti* collected at 300 m from Norwegian waters, was found to have spectral data identical to that of barettin previously isolated from the same sponge and originally assigned as structure **309**.[290] A subsequent synthesis of **309** disproved this structure for barettin.[291] A *Smenospongia* species from Queensland, Australia, yielded the bisindole **310**.[292] *Hyrtios reticulata* from Indonesia was found to contain 1,6-dihydroxy-1,2,3,4-tetrahydro-β-

carboline **311**, while *Hyrtios erectus*, also from Indonesia, yielded hyrtiosulawesine **312** and 5-hydroxy-3-(2-hydroxyethyl)-indole **313**.[293] Piperazine-based bisindole metabolites have received considerable synthetic attention. Hamacanthin B **314** from a deep water *Hamacantha* species[294] has been synthesised and the absolute stereochemistry determined as (*S*).[295] The *cis* and *trans* diastereomers of 6'-debromo-3,4-dihydrohamacanthin A, originally isolated from *Rhaphisia lacazei*,[296] have been synthesised as a diastereoisomeric and a racemic mixture; similarly, 6'-debromo-*cis*-3,4-dihydrohamacanthin B was also prepared.[297] The *trans* isomer of dihydrohamacanthin A from the same sponge was also synthesised along with the *cis* isomer of dragmacidin C.[298] Dragmacidin D, isolated from a *Spongosorites* species,[299,300] has been synthesised as a racemic mixture.[301] The plakortamines A–D **315**–**318** were isolated from the same deepwater *Plakortis nigra* specimens that yielded the epiplakinic acids (*vide supra*).[207] A series of sulfamate indoles **319**–**322** and an indolocarbazole **323** were isolated from a New Zealand *Ancorina* species.[302] Makaluvamine O **324** was isolated from the same Jamaican collection of *Smenospongia aurea* that was found to contain *N*-3'-ethylaplysinopsin **307**.[288] The Indopacific sponge *Zyzzya fuliginosa* yielded batzelline D **325** and isobatzelline E **326** which was found to inhibit the cell fusion of HIV-1.[303] A synthesis of discorhabdin A, originally isolated from a *Latrunculia* species,[304] has been reported.[305] Thorectandamine **327**, a β-carboline alkaloid with weak cytotoxicity, was obtained from a Palauan *Thorectandra* species.[306] Four new cytotoxic bisannulated acridines 5-methoxyneoamphimedine **328**, neoamphimedine Y **329**, neoamphimedine Z **330**, and alpkinidine **331** were isolated from *Xestospongia cf. exigua* (**328**) and *X. cf. carbonaria* (**328**–**331**).[307] Slagenins B and C, originally isolated from *Agelas nakamurai*,[308] were synthesised with the correct absolute stereochemistry.[309] The stereochemistry of slagenin A **332**, also from *Agelas nakamurai*, was established by an independent stereoselective approach that also produced slagenins B and C.[310] Racemic syntheses of both dibromophakellstatin from *Phakellia mauritiana*[311] and dibromophakellin from *Acanthella carteri*[312] have been achieved.[313] An *Agelas* species collected in the Bahamas was found to contain monobromoisophakellin **333** which along with related

bromopyrroles was found to inhibit feeding by the reef fish *Thalassoma bifasciatum*.[314] (*E*)-Debromoaxinohydantoin isolated from a *Hymeniacidon* species,[315] and (*Z*)-debromoaxinohydantoin, also known as spongiacidin C, isolated from *Stylotella aurantium*[316] and a *Hymeniacidon* species,[317] have both been synthesised.[318] Stereoselective syntheses of agelastatins A and B from *Agelas dendromorpha*[319] have been reported.[320,321] The cytotoxic imidazole alkaloids naamine C from *Leucetta chagosensis*,[322] and pyronaamidine from a *Leucetta* species[323] have been synthesised.[324] Two related imidazole alkaloids **334** and **335** have been isolated from an Australian specimen of *L. chagosensis* while a third compound **336** was obtained from a Fijian specimen of a closely related sponge.[325] Bromosceptrin **337**, a dimeric pyrrole alkaloid, was obtained from a Florida Keys specimen of *Agelas conifera*.[326] Crambescidin 359 **338**, isolated from *Monanchora arbuscula*,[327] has been synthesised stereoselectively establishing the absolute stereochemistry.[328] A Verongid sponge of the family Aplysinellidae collected in Okinawa yielded nakirodin A **339** and the absolute stereochemistry was established by the hydrolytic release of *N*,*N*,*N*-trimethyl-(*R*)-homoserine.[329] Psammaplins K **340** and L **341** were obtained from the Fijian sponge *Aplysinella rhax*.[330] Psammaplin A, previously described from a *Psammaplysilla* species,[331] was found to be a chitinase inhibitor. A *Druinella* species, also from Fiji, was found to contain purealidin S **342** and purpuramine J **343**, which were both moderately cytotoxic.[332] The endemic Brazilian sponge *Aplysina caissara* yielded caissarines A **344** and B **345**.[333] Bastadin 21 **346** was isolated from *Ianthella quadrangulata* from Queensland, Australia.[334] The formamide-containing *seco*-xanthine hymeniacidin **347** was obtained from the same specimen of an Australian *Hymeniacidon* species from which bromoindole **305** was reported (*vide supra*).[286] Pseudoanchynazines A–C **348**–**350**, containing a methylcarbamate moiety, were isolated from an Argentinian *Clathria* species.[335] Stereoselective syntheses of 18-methoxyavarone isolated from *Dysidea cinerea*[336] and *D. avara*,[337] and 19-methoxyavarone from a *Dysidea* species[338] and *D. avara*[337] have been accomplished.[339] Aureol, originally isolated from *Smenospongia aurea*,[340] has been synthesised with the correct absolute stereochemistry via a rearrangement of (+)-arenarol.[341] The Okinawan sponge

*Dactylospongia elegans* yielded dactyloquinones C–E **351**–**353**.[342] A sulfated hydroquinone, phuklona sulfate **354** that displayed modest cytoprotection against HIV-1, was obtained from a *Haliclona* species collected in Thailand.[343] An Okinawan *Axinyssa* species contained the monocyclic sesquiterpene (*E*)-3-isocyanobisabolane-7,10-diene **355** that is toxic to brine shrimp,[344] while exiguamide **356** from a Japanese collection of *Geodia exigua* inhibited sea urchin embryogenesis.[345] A Jamaican specimen of *Myrmekioderma styx* yielded styxones A **357** and B **358** as well as the degraded terpenoid styxlactone **359**.[346] *Axinyssa ambrosia*, collected from the Caribbean coast of Columbia, was the source of two nitrogenous eudesmane-type sesquiterpenes, **360** and **361**. Compound **360** was cytotoxic to P388, HT-29 and A-549 cell lines and the polyps of the scleractinian coral *Madracis mirabilis*.[347] A total synthesis of the spirocyclic sesquiterpene (+)-axenol, originally isolated from an *Eurypon* sp. of sponge from New Zealand,[348] has been achieved via a "one-pot" reaction.[349] Kalihinene X **362**, originally isolated from *Acanthella cavernosa*,[350] was synthesised stereoselectively establishing the absolute stereochemistry.[351] Seven tricyclic diterpenes, the gagunins A–G **363**–**369**, with widely varying cytotoxicity were obtained from a Korean *Phorbas* species.[352] A quite remarkable number of new diterpenes, the cyanthiwigins E to AA **370**–**392**, with cytotoxic and anti-HIV–1 activity were obtained from the Jamaican sponge *Myrmekioderma styx*.[353] A Vanuatuan collection of an *Axinella* species yielded the tetracyclic diterpene *N*-formyl-7-amino-11-cycloamphilectene **393**.[354] A Korean collection of a sponge of the genus *Sarcotragus* was found to contain two bisfuranoditerpenoids, sarcotins K **394** and L **395** which displayed weak cytotoxicity.[355] In the same report are also described the isolation of an additional seven pyrrolosesterterpenoids **396**–**402**, five furanosesterterpenoids **403**–**407**, and two trinorsesterterpenoids **408** and **409** which had varying levels of cytotoxicity. The stereochemistries of the previously reported **410**–**412**[356] were revised on the basis of a re-interpretation of CD spectral data.[355] Compound **411** was inadvertently drawn with (8*Z*) geometry in this and the previous report.[355,356] A series of five sesterterpenoids, barangcadoic acid **413** and rhopaloic acids D–G **414**–**417**, were isolated from an Indonesian *Hippospongia* species.[357] All compounds were found to

inhibit the protease activity of human RAS converting enzyme (hRCE1) and are the first natural products reported with this activity. An Okinawan *Luffariella* species yielded two new luffariolides H **418** and J **419** that were found to be cytotoxic and antimicrobial.[358] Three further cytotoxic sesterterpenes, thorectandrols C–E **420**–**422** were isolated from a *Thorectandra* species collected in Palau.[359] Both the natural (+) and unnatural (–) enantiomers of cacospongionolide B, originally isolated from *Fasciospongia cavernosa*,[360] have been synthesised; the natural enantiomer is more than twice as active as an inhibitor of $sPLA_2$.[361] *Hyrtios erecta* collected from the Egyptian Red Sea was found to contain salmahyrtisol A **423** and B **424** and 3-acetyl- and 19-acetyl-sesterstatin **425** and **426**, all of which showed significant cytotoxicity in human cancer cell lines.[362] A species of *Phyllospongia* collected in Indonesia yielded the scalarane sesterterpenoids **427**–**433**.[363] Three further scalarane-type sesterterpenoids **434**–**436** were obtained from a Papua New Guinean specimen of *Ledenfeldia frondosa*.[364] A Jamaican sample of *Agelas sceptrum* was found to contain the $C_{29}$ steroid **437**.[365] A peroxy steroid, 9(11)-dehydroxyaxinysterol **438**, from an Okinawan species of the genus *Axinyssa*, was found to inhibit the growth of several human cancer cell lines.[344] Three oxygenated sterols **439**–**441** were obtained from a collection of *Polymastia tenax* obtained from the Caribbean Coast of Columbia. Compounds **439** and **440** were found to have significant cytotoxicity to a range of human and murine cancer cell lines.[366] The absolute stereochemistry of contignasterol **442** was established by the preparation of MPA and MTPA esters as well as CD curve analysis, confirming the customary steroid configuration.[367] A polyoxygenated steroid, clathriol **443**, also with anti-inflammatory activity, was obtained from a New Zealand collection of *Clathria lissosclera*.[368] The *abeo*-sterol orostanal, recently isolated from *Stelletta hiwasaensis*,[369] has been synthesised from hyodeoxycholic acid.[370] An Indonesian specimen of *Petrosia strongylata* yielded two thymidine phosphorylase inhibiting sulfated sterols, lembehsterols A **444** and B **445**.[371] Four new plakinamine type steroidal alkaloids **446**–**449** have been isolated from a Vanuatuan *Corticium* species.[372] The steroidal tetraglycoside, mycaloside A **450**, was obtained from a Cuban specimen of *Mycale laxissima*.[373] A Philippine specimen of *Rhabdastrella globostellata* yielded the

isomalabaricane type triterpenoids stellettins H **451** and I **452** along with the antipode **453** of (+)-stellettin E[374] originally isolated from a *Stelletta* species.[375] (–)-Stellettin E and the previously reported stellettin B were found to be selectively cytotoxic towards a p21-deficient HCT cell line.[375] Both enantiomers (*S,S*) and (*R,R*) of the acyclic diketotriterpene **454**, originally isolated from *Hyrtios erectus*,[376] have been synthesised asymmetrically, establishing the absolute stereochemistry of the natural product as (*R,R*).[377] Eight further raspacionins **455**–**462** were isolated from a Sicilian collection of *Raspaciona aculeata*; all were found to be both ichthyotoxic and cytotoxic.[378] The triterpenoid trisaccharide nobiloside **463**, obtained from the Japanese sponge *Erylus nobilis*, is a neuraminidase inhibitor.[379]

## 8 Coelenterates

There was a slight increase in the number of metabolites reported from coelenterates in 2002. The examples reported continue to be dominantly of terpenoid biogenesis. Bioassay guided fractionation of extracts obtained from an Indian Ocean collection of the soft coral *Lobophytum crassum* afforded ceramide **464** as a moderately antibacterial component.[380] Specimens of the soft coral *Sinularia* sp. collected from the Andaman and Nicobar Islands contained the ceramides **465** and **466**.[381] Cervicoside **467**, a new glycoside, was isolated from a Chinese collection of *Sinularia cervicornis*.[382] In a study of soft corals from the Karwar region of India, xanthine **468** and pyrazole **469** were isolated from *Echinomuraceae splendens*.[383] New examples of cadinene-skeleton sesquiterpenes, xenitorins A–F **470**–**475**, were isolated from a Taiwanese collection of *Xenia puerto-galerae*.[384] The relative stereochemistries of **470**–**475** were secured by NOESY NMR experiments. Xentorins A **470** and E **474** exhibited cytotoxicity towards the A-549 and P388 tumour cell lines. The structure and absolute stereochemistry of alcyopterosin E **476**, a nitrate ester-containing sesquiterpene isolated from a sub-Antarctic collection of *Alcyonium paessleri*,[385] was secured by total synthesis.[386] Subergorgiol **477** and 2β-acetoxysubergorgic acid **478** were

isolated from Taiwanese collections of *Subergorgia suberosa*.[387] Relative stereochemistry was determined by NOESY NMR experiments. Both **477** and **478** failed to exhibit cytotoxicity towards either KB or HeLa tumour cells, while subergorgic acid methyl ester, also isolated from the extract, exhibited mild cytotoxicity towards the HeLa cell line. A racemic synthesis of pathylactone A **479**, isolated from the soft coral *Paralemnalia thyrsoides*,[388] and 1-*epi*-pathylactone A has raised doubts about the spectral assignments of the norsesquiterpene natural product.[389] A further study of a Taiwanese collection of *Subergorgia suberosa* yielded the sesquiterpenes suberosols A–D **480**–**483**.[390] Relative stereochemistries were determined by NOESY NMR experiments. All four metabolites exhibited cytotoxicity towards the P388 murine leukaemia cell line while suberosols C **482** and D **483** also exhibited cytotoxicity towards the A-549 and HT-29 tumour cell lines. The first chemical study of the soft coral *Lemnalia flava*, collected off Mombasa, Kenya, has yielded lemnaflavoside **484** and three monoacetate derivatives **485**–**487**.[391] *seco*-Sethukarailin **488** was isolated from a collection of *Sinularia dissecta* from the Mandapam Coast, South India.[392] However, the compound may be an artifact arising from the use of methanol in the extraction process. The Caribbean sea whip *Pseudopterogorgia elisabethae* was the source of ileabethin **489**, a diterpene representing the first example of the ileabethane skeleton.[393] Relative stereochemistry was ascertained through the interpretation of NOESY NMR data. The absolute configuration of elisabethin C **490**, a bisnorditerpenoid also isolated from *P. elisabethae*,[394] has been secured by total synthesis.[395] Three cytotoxic prostanoids, claviridenones E–G **491**–**493**, were isolated from a Taiwanese collection of *Clavularia viridis*.[396] Claviridenone B exhibited pronounced cytotoxicity towards the A-549, HT-29 and P388 cell lines. The same publication also reported the isolation of cembranoid claviolide **494** from a Taiwanese collection of *C. violacea*. An Okinawan collection of *C. viridis* yielded the prostanoid-related oxylipins tricycloclavulone **495** and clavubicyclone **496**.[397] Relative stereochemistries of both compounds were principally determined by interpretation of NOESY NMR data, with the exception being a biogenetic argument that was used to assign the configuration of the sidechain acetoxy stereogenic centre. Clavubicyclone **496** exhibited mild

cytotoxicity towards MCF-7 and OVCAR-3 tumour cell lines. Bioassay-directed fractionation of a Taiwanese collection of the soft coral *Cespitularia hypotentaculata* yielded diterpenes cespitularins A–D **497**–**500**, a norditerpene cespitularin E **501** and three further diterpenes, cespitularins F–H **502**–**504**, with a novel skeleton.[398] Variable potency and selectivity was observed for the eight compounds towards tumour cell lines A-549, HT-29 and P388. Two new dolabellane-type diterpenoids **505** and **506**, as well as the known diterpene claenone **507**,[399] were isolated from an Okinawan collection of *Clavularia* species.[400] The relative stereochemistries of **505** and **506** were secured by X-ray analysis, with absolute stereochemistry in both cases being inferred by the co-occurrence of **507** which has defined absolute configuration.[401] The facile chemical conversion of **507** to **506** suggested that **506** was an artifact of isolation. Moderate *in vitro* cytotoxicity towards tumour cell lines was observed for **506**. *Clavularia koellikeri* collected in Okinawa yielded two cembrane diterpenoids **508** and **509** and a dolabellane diterpene **510**.[402] The absolute configuration of **508** was secured by comparison with the known enantiomer,[403] the relative stereochemistry of **509** was determined by interpretation of NOESY NMR data while the absolute configuration of **510** was obtained by NOESY NMR experiments, preparation of Mosher esters and comparison with the known absolute stereochemistry of the related metabolite stolonidiol. Diterpene **508** was found to exhibit cytotoxicity to a wide range of tumour cell lines. Investigation of the chemistry of *Eunicea pinta* collected from San Andrés Island, Colombia led to the report of eight γ-cembranolide-type diterpenes, 12-epieupalmerone **511** and uprolides H–K **512**–**515**, K acetate **516**, L **517** and M **518**.[404] The structure and stereochemistry of **511** was established by X-ray analysis, which in turn led to a correction of the stereochemistry of the co-occurring diterpene succinolide **519**.[405] The structure and relative stereochemistry of uprolide H **512** was also secured by X-ray analysis, allowing the stereochemistries of **513**–**518** to be determined by NOESY NMR experiments. The presence of (6*E*) geometry and a hydroperoxide group at C-8 in **512** also precipitated a revision of the structures of uprolide B **520**,[406] uprolide B acetate **521**,[406] uprolide B diacetate **522**,[406] 8-epi-uprolide B **523**,[406] 8-epi-uprolide B acetate **524**,[406] 8-epi-uprolide B diacetate **525**,[406] 12,13-

bisepiuprolide B **526**,[407] 12,13-bisepiuprolide B acetate **527**,[407] uproeunicin **528**,[407] uprolide C **529**,[406] uprolide C acetate **530**[406] and uproeuniolide **531**.[407] A Madagascan collection of *Sarcophyton* sp. was the source of cembrane diterpenes **532** and **533**.[408] The relative stereochemistry of **533** was deduced by interpretation of NOESY NMR data. An Australian collection of *Sarcophyton* sp. yielded cembranes **534**–**537** as two pairs of stereoisomers.[409] Cembrane **534** is a previously reported semi-synthetic compound with defined absolute stereochemistry which in turn allowed the determination of absolute configuration for **535**. The absolute stereochemistries of **536** and **537** were established by the preparation of Mosher ester derivatives of **536**. Both **534** and **535** inhibited ligand binding to rat-brain adenosine $A_1$ receptors. Scabrolides A–D **538**–**541** were isolated from a Taiwanese collection of *Sinularia scabra*.[410] Relative stereochemistries were determined by the use of NOESY NMR experiments. Norditerpene **540** exhibited mild cytotoxicity towards KB and Hepa59T/VGH tumour cell lines. The structure and relative stereochemistry of cembrane **542**, isolated from the soft coral *Sinularia tenella*, was established by X-ray analysis.[411] Milolides G **543**, 16-acetoxymilolide G **544**, H–M **545**–**550**, 16-hydroxymilolide M **551**, 16-acetoxymilolide M **552**, milolide N **553** and 16-acetoxymilolide N **554** were isolated from a collection of *Briareum stechei* from Yap, Micronesia.[412] Relative stereochemistries were deduced by interpretation of NOESY NMR data. Artificial cultures of *Erythropodium caribaeorum* were found to produce a range of diterpenes including the antimitotic agent eleutherobin and aquariolide A **555**.[413] Inspection of ROESY NMR data and comparison with known related compounds led to the proposed absolute stereochemistry of **555**. A Caribbean collection of the same gorgonian species led to the isolation of six new briarane diterpenes, erythrolides L–Q **556**–**561**.[414] Relative stereochemistries were established by interpretation of NOESY NMR data and by an X-ray analysis of **560**. The structure and absolute stereochemistry of juncenolide A **562**, a mildly cytotoxic briarane diterpene isolated from a Taiwanese collection of *Junceella juncea*, was also established by X-ray analysis.[415] Two full accounts have been given of the structural and stereochemical reassessments of sclerophytins A **563** and B **564**. Strong

circumstantial evidence is also provided for suggested structural revisions of several other sclerophytin-type diterpenes.[416,417] A Far-Eastern collection of the gorgonian *Plumarella* sp. was the source of diterpenes plumarellide **565** and a possible artifact, the ethyl ester of plumarellic acid **566**.[418] Relative stereochemistry was deduced from NOESY NMR data and both compounds exhibited mild haemolytic activity towards mice blood erythrocytes. Pachyclavulariaenones D–G **567**–**570** were isolated from a Taiwanese collection of *Pachyclavularia violacea*.[419] The relative configurations of the compounds were secured by NOESY NMR experiments and an X-ray analysis of **569**. **570** exhibited mild cytotoxicity. An Indian Ocean collection of *Sinularia* sp. was the source of horiolide **571**.[420] Cyclobutenbriarein A **572** and five new examples of briarane skeleton diterpenes 11-hydroxybrianthein V **573**, 11-hydroxybrianthein U **574**, 11-hydroxybrianthein Y **575**, 3,4-dihydro-11-hydroxybrianthein V **576** and 3,4-dihydro-11-hydroxybrianthein U **577** were isolated from a Bahamian collection of *Briareum asbestinum*.[421] The absolute configuration of **573** was secured by an X-ray analysis while the relative stereochemistries of the other compounds were established by interpretation of NOESY NMR data. An Indonesian collection of *Xenia* sp. yielded xeniolide F **578** and 9-hydroxyxeniolide F **579**. The relative stereochemistries were established by NOESY NMR experiments.[422] Seven mildly cytotoxic xenicane-skeletoned diterpenes **580**–**586** were isolated from *Xenia umbellata* collected off Taiwan.[423] Secosterol **587** was reported from *Pachyclavularia violacea* collected near Sulawesi Island, Indonesia.[424] The degraded pregnanes muricenones A **588** and B **589**, were isolated from *Muricea* sp. collected in the Bay of Mazatlán, Mexico.[425] The collection of *Eunicea pinta* from San Andrés Island, Colombia that afforded diterpenes **511**–**518** (*vide supra*) also yielded the saponin **590** which was characterised by X-ray analysis of the peracetate derivative.[404] Saponin **591** was isolated from *Lobophytum* sp. collected from Sanya Bay, Hainan Island.[426] The Taiwanese collection of *Clavularia viridis* that yielded prostanoids **491**–**493** (*vide supra*) also afforded three cytotoxic steroids, stoloniferones E–G **592**–**594**.[396] Both the (20*R*) and (20*S*) stereoisomers of **595**, isolated from the octocoral *Dendronephthya* sp.,[427] have been prepared leading to the conclusion that the natural product has the (20*S*)

configuration.[428] *Nephthea bayeri*, collected off Nanji Island China, yielded nanjiols A–C **596–598**.[429] The structure of 22,23-dimethylcholest-5-en-3β-ol **599**, isolated as the major sterol component of an Andaman and Nicobar Island collection of *Sinularia* species, must remain tentative as it was derived solely from mass fragmentation analysis of the monoacetate derivative.[381] A study of Japanese collections of *Isis hippuris* led to the isolation of steroids **600–610**[430] in addition to the previously reported **611**.[431] X-ray analysis established the stereochemistries of **611** and **610**, the latter result also establishing the stereochemistry of **612**, previously reported from the same species.[432] Most of the compounds showed moderate cytotoxicity towards drug-resistant cells expressing P-gp but not against cells expressing multidrug resistance protein-1 (MRP-1). Further investigation of a Korean collection of the stony coral *Montipora* sp. yielded diacetylenes **613–615** of which **615** was the most potent cytotoxin towards a range of tumour cell lines.[433] The structures proposed for cladocorans A **616** and B **617**, isolated from the Mediterranean anthozoan *Cladocora cespitosa*,[434] are in question as spectroscopic data of synthetic material were not identical to data reported for the natural products.[435] Ecdysteroid zoanthusterone **618** was isolated from a Thai collection of *Zoanthus* species.[436] Tridentatols D–H **619–623** were isolated from the marine hydroid *Tridentata marginata* collected off North Carolina.[437] Enzyme-mediated hydrolysis of the sulfate esters leads to the corresponding phenols, which include the potent feeding deterrent **624**. The sea anemone *Anthopleura pacifica* yielded ceramide (4*E*,8*E*)-spingol-*n*-hexadecamide **625**.[438] The solution structure of equinatoxin II, a 19.8 kDa cytolysin isolated from the Mediterranean anemone *Actinia equina*,[439] has been determined by NMR analysis.[440] The structure provides some clues as to how the peptide may bind to cell membranes and form pores, while a separate study has utilised lipid monolayers and surface plasmon resonance to further examine the events leading to pore formation.[441] A polypeptide toxin, PsTX-20A, of molecular mass 20 kDa was purified from an Okinawan collection of the anemone *Phyllodiscus semoni*.[442] *Radianthus macrodactylus*, collected in the Seychelles, yielded RTX-A, RTX-S and RTX-G, three high molecular weight (20 kDa) cytolysins, two low molecular weight cytolysins, RmI (5100 Da) and RmII (6100 Da) and InI, a

7100 Da trypsin inhibitor.[443] The first total syntheses of montipyridine[444] and montiporynes A and B,[445] metabolites of the stony coral *Montipora* species,[446,447] have been reported. Further investigation of the diterpene glycoside lemnabourside, originally isolated from the soft coral *Lemnalia bournei*,[448] has shown it to be an inhibitor of 5α-reductase and to exhibit antiproliferative activity via the caspase-3 apoptotic pathway.[449] The sodium channel toxins Bg II and Bg III, isolated from the sea anemone *Bunodosoma granulifera*,[450] have been found to be especially potent towards insect sodium channels.[451]

## 9 Bryozoans

Despite their promise as excellent sources of novel, bioactive metabolites, only a handful of new compounds have been reported from bryozoans. Most of these are alkaloids. Four new bromotryptamine derivatives **626**–**629** have been isolated from the North Sea bryozoan *Flustra foliacea* collected in German waters, and the complete $^{13}C$ NMR spectral data for the known compound flustrabromine[452] have been reported for the first time.[453] A sample of *F. foliacea* collected in the southern North Sea also yielded deformylflustrabromine **628** which displayed moderate cytotoxicity against the HCT-116 cell line.[454] The complete $^{1}H$ and $^{13}C$ NMR assignments for the *F. foliacea* alkaloids dihydroflustramine C,[455] flustramine A,[456] flustramine E,[457] debromoflustramine B,[457] and flustramine B[456] have been published, reconciling deficiencies and ambiguities from earlier literature assignments.[458] The marine bryozoan *Amathia convoluta* collected from the East coast of Tasmania, was the source of the tribrominated alkaloids, convolutamine H **630** and convolutindole A **631**. Compounds **630** and **631** displayed potent and selective activity against *Haemonchus contortus*, a parasitic nematode of ruminants.[459] *Watersipora subtorquata* from Tsutsumi Island, Japan was the source of bryoanthrathiophene **632**. This compound **632** exhibited potent antiangiogenic activity on bovine aorta endothelial cell (BAEC) proliferation.[460] Three disulfides, pentaporins A–C **633**–**635**, have been isolated from the

Mediterranean bryozoan *Pentapora fascialis*. Energy dispersive X-ray analysis assisted in the determination of the existence of sulfur atoms. The pentaporins **633**–**635** displayed anthelmintic activity against *Trichinella spiralis*.[461] Several synthetic firsts have also been reported for bryozoan metabolites: the total syntheses of dihydroflustramine C[455] and flustramine E[457] have been achieved,[462] as has the total synthesis of amathaspiramide F,[463] an alkaloid from a New Zealand collection of *Amathia wilsoni*.[464] Asymmetric syntheses of amathamides A and B, alkaloids from the bryozoan *A. wilsoni* collected in Tasmania,[465] have been accomplished starting from 3-hydroxybenzaldehyde.[466]

## 10 Molluscs

Fewer examples of new metabolites were reported from molluscs in 2002 than during the time period of the previous review. The absolute stereochemistries of membrenones A–C **636**–**638**, γ-dihydropyrone-containing polypropionates isolated from the skin of the Mediterranean mollusc *Pleurobranchus membranaceus*,[467] have been determined by stereocontrolled syntheses of the enantiomers.[468] The stereochemical assignment of **638** is a correction of an earlier synthetic effort[469] necessitated by the conclusion that the sign of the optical rotations of **637** and **638** were misreported in the original isolation publication.[467] Stereoselective syntheses have led to correction of the relative stereochemistry and established the absolute stereochemistry of siphonarienolone **639** and siphonarienedione **640**,[470] polypropionates originally isolated from the mollusc *Siphonaria grisea*.[471] The first synthesis of siphonarin B **641** has confirmed the absolute stereochemistry of the metabolite,[472] isolated from the molluscs *Siphonaria zelandica* and *S. atra*.[473] The structure and stereochemistry of a new polychlorinated sulfolipid **642** was reported from collections of the mussel *Mytilus galloprovincialis* made in the Adriatic Sea.[474] The relative stereochemistry of **642** was established by $^{1}H$-$^{13}C$ and $^{1}H$-$^{1}H$ coupling constant analysis while absolute stereochemistry was established by the preparation and analysis of Mosher MTPA esters. Mild cytotoxicity to murine

fibrosarcoma and monocyte/macrophage cell lines was observed for **642**. In a separate study of the same mollusc species, LC-MS/MS was used to identify a new yessotoxin analogue **643** designated noroxoYTX.[475] The novel chlorinated pyrrolidone **644** was isolated from extracts of a Philippino collection of the dorid nudibranch *Asteronotus cespitosus*.[476] As similar metabolites have been reported previously from the sponge *Dysidea herbacea*, the study concluded that the carnivorous mollusc in question acquired the metabolite as part of its diet as opposed to *de novo* synthesis. A new member to the malyngamide series of metabolites, malyngamide S **645**, was reported from a New Zealand collection of the sea hare *Bursatella leachii*.[477] The compound also exhibited mild cytotoxicity and anti-inflammatory activities. Kulokekahilide-1 **646** is a moderately cytotoxic depsipeptide isolated from the mollusc *Philinopsis speciosa* collected off Pupukea, O'ahu.[478] The absolute stereochemistry of **646** was determined by degradation combined with Marfey analysis as well as the synthesis of all stereoisomers of the two unusual amino acids, 4-phenylvaline and 3-amino-2-methylhexanoic acid. Bursatellanin-P, a 60 kDa protein was purified from the purple ink of the sea hare *Bursatella leachii*.[479] The protein exhibited anti-HIV activity. In an intriguing twist to the usual natural product isolation paradigm, PCR amplification, using primers of the α-conotoxin gene sequence, of genomic DNA from the predatory marine snail *Conus geographus* yielded a single specific α-conopeptide gene product.[480] Subsequent cloning and sequencing identified the α-conotoxin GIC sequence. The predicted mature toxin, a 16-amino acid peptide, was then synthesised and found to act as a potent antagonist of the neuronal nicotinic receptor. The biosynthesis of 2,6-dimethyl-5-heptenal, a volatile component of skin extracts of the dendronotid nudibranch *Melibe leonina*,[481] has been investigated using stable isotope incorporation experiments.[482] Successful incorporation of $^{13}C$ demonstrated that the metabolite was the product of *de novo* terpenoid biosynthesis by the nudibranch. The first enantiospecific synthesis of (–)-9-pupukeanone **647**, a degradation product of the volatile defensive isonitrile 9-isocyanopupukeanane **648** isolated from the nudibranch *Phyllidia varicosa*,[483] has been reported.[484] The synthesis confirms the absolute stereochemistry of the pupukeanane skeleton. The absolute stereochemistry

of ibhayinol **649**, a sesquiterpenoid metabolite isolated from a South African collection of the sea hare *Aplysia dactylomela*,[485] was established by X-ray analysis.[486] MS-MS studies have firmly established the position of the methyl ester moiety in the purple pigment aplysiaviolin **650**, isolated from a Tasmanian collection of the sea hare *Aplysia parvula*.[173] This study included an investigation of the sea hare's algal diet *Laurencia filiformis* which revealed the presence of the 5-acetate derivative **168** of prepacifenol, as well as prepacifenol and a range of other known metabolites (*vide supra*). Sardinian collections of the sea hare *Aplysia punctata* afforded a range of metabolites including four new diterpenes, **651**–**654**, and three new sesquiterpenes **655**–**657**.[487] Relative stereochemistries of **651**–**657** were secured by NOESY NMR experiments – the absolute configurations were not established. A progesterone homologue **658** was isolated from the skin of the dorid nudibranch *Aldisa smaragdina* collected off Cabo Cope, Spain.[488] The absolute stereochemistry was secured by synthesis from stigmasterol.

The first total syntheses of aplyolides B–E, ichthyotoxic macrolides isolated from the skin of sea hare *Aplysia depilans*,[489] have been reported confirming the absolute stereochemistry reported for the metabolites.[490,491] A new synthesis of 3-isocyanotheonellin, a nitrogenous bisabolene sesquiterpene isolated from a Sri Lankan collection of the nudibranch *Phyllidia* sp.,[492] was also amenable to the synthesis of related compounds all of which exhibited potent *in vitro* antifouling activity towards barnacle larvae.[493] (–)-Doliculide, a cytotoxic depsipeptide isolated from a Japanese collection of the sea hare *Dolabella auricularia*,[494,495] exhibits cytotoxicity by enhancing actin assembly.[496]

## 11 Tunicates (ascidians)

A similar number of new metabolites were reported in 2002 compared to 2001 and they continue to be dominantly amino acid-derived. The inhibitor of matrix metalloproteinase 2 (MMP2) from an ascidian of the family Polyclinidae collected off Kii Peninsula, Western Japan was identified as

sodium 1-(12-hydroxy)octadecanyl sulfate **659**.[497] MTPA ester analysis indicated that **659** occurs naturally as a 55:45 mixture of the (12*R*) and (12*S*) enantiomers. Synthesis from (*R*)-12-hydroxystearic acid confirmed the structure of **659**. Both natural and synthetic material inhibited MMP2 with equal potency. The absolute stereochemistry of lobatamide C **660**, a cytotoxic macrolide isolated from *Aplidium lobatum* collected off the southwestern coast of Australia,[498] has been defined by stereospecific synthesis.[499] A novel triglycosylceramide derivative, sulcaceramide **661**, was reported from a Mediterranean collection of the ascidian *Microcosmus sulcatus*.[500] The structure was solved by a combination of spectroscopic techniques and degradation/derivatisation studies. Two unusual 1,2,3-trithiocane derivatives, **662** and **663** were isolated from the ascidian *Perophora viridis* collected off the Atlantic coast of North Carolina.[501] Relative stereochemistries were deduced from NOESY NMR experiments while MTPA derivatisation of the hydroxyl at C-7' helped secure the absolute configuration of **662**. Both compounds exhibited mild antibacterial activity as well as toxicity towards brine shrimp. The total synthesis of a stereoisomer of bistramide C, a cytotoxic polyether isolated from the ascidian *Lissoclinum bistratum*,[502] combined with chiroptical analysis led to the proposal of **664** as the predicted relative and absolute configuration of the natural product.[503] The relative and absolute stereochemistries of didemnaketals B **665** and C **666**, reported from an undescribed Palauan ascidian of the genus *Didemnum*,[504,505] were established by a combination of degradation and derivatisation experiments.[506] The structure of (+)-didemniserinolipid B **667**, a serinolipid isolated from an Indonesian collection of *Didemnum* sp.,[507] has been revised to the 31-sulfate and the relative and absolute configuration of the natural product established by synthesis.[508] A new member of the tunichrome family of modified peptides, tunichrome *Sp*-1 **668** was isolated from the hemocytes of *Styela plicata*, collected in Mission Bay, California.[509] The sequence of **668** was determined by Edman degradation while stereochemistry was determined by acid hydrolysis followed by derivatisation and GC-MS and HPLC analysis. The ascidian *Didemnum molle*, collected at Ibo Island north of Mozambique, was the source of the cycloheptapeptide cyclodidemnamide B **669**.[510] Hydrolysis followed by Marfey's derivatisation and

HPLC analysis allowed determination of configuration at many of the stereogenic centres with final confirmation being achieved by total synthesis. Localisation studies of the related cyclic peptides patellamides A-C suggested that the natural products are distributed throughout the tunic of the ascidian *Lissoclinum patella* and not located in the *Prochloron* sp. symbiotic cyanobacteria.[511] Halocidin was isolated as an antimicrobial peptide (3443 Da) from the hemocytes of the solitary ascidian *Halocynthia aurantium*.[512] Cloning of a peptide precursor from a cDNA library prepared from pharyngeal tissues of the tunicate *Styela clava* identified clavaspirin as a 23-residue antibacterial peptide.[513] Synthetic clavaspirin inhibited the growth of Gram-positive and negative bacteria, permeabilised *E. coli* membranes and was potently haemolytic towards human and bovine erythrocytes. Polyclonal antibodies, raised against clavanin A, have been used to locate the clavanin family of antibacterial peptides in the eosinophilic granulocytes and macrophages of the ascidian *Styela clava*.[514] Lepadins D **670**, a salt of **670** with an unidentified counterion, E **671** and F **672** were isolated as antiplasmodial and antitrypanosomal alkaloid constituents of a *Didemnum* sp. ascidian collected from Stanley Reef, the Great Barrier Reef.[515] The relative stereochemistries of substitution about the decahydroquinoline ring system in **670–672** were determined by NOESY NMR experiments and are illustrated here with the defined ring junction absolute stereochemistry of lepadin A.[516] Lepadins F–H **672–674** were reported from extracts of the ascidian *Aplidium tabascum* collected from Swains Reef, Great Barrier Reef.[517] In two separate accounts, the absolute stereochemistry of lepadiformine **675**, a biologically active alkaloid isolated from the ascidians *Clavelina lepadiformis* and *C. moluccensis*,[518,519] has been defined by stereoselective total synthesis.[520,521] Two new 2-aminoimidazolone alkaloids, polyandrocarpamines A **676** and B **677**, were isolated from a Fijian collection of the ascidian *Polyandrocarpa* sp. and the structures confirmed by synthesis.[522] Coproverdine **678** is a cytotoxic alkaloid isolated by bioassay-directed fractionation of an unidentified ascidian collected at the Three Kings Islands, New Zealand.[523] Cytotoxicity towards a variety of murine and human tumour cell lines was observed. Rubrolide M, recently isolated from a Spanish collection of the ascidian *Synoicum blochmanni*,[524] was synthesised

using palladium-catalysed coupling methodology.[525] The compound and related congeners were found to exhibit cytotoxicity towards human tumour cell lines. The first syntheses of rhopaladins A–C and a new route to rhopaladin D have been reported,[526] confirming the structures of the alkaloids isolated from a *Rhopalaea* sp. ascidian collected in Okinawa.[527] Bioassay-directed fractionation of extracts of the New Zealand endemic ascidian *Pycnoclavella kottae* afforded the cytotoxic and anti-inflammatory alkaloids kottamides A–D **679**–**682**.[528] The structures were solved by spectroscopic techniques, including the use of $^{1}H$-$^{15}N$ 2D NMR experiments. Sebastianines A **683** and B **684** were isolated as biologically active pyridoacridine metabolites from a Brazilian collection of the ascidian *Cystodytes dellechiajei*.[529] The relative stereochemistry of **684** was determined by interpretation of NOESY NMR data. The cytotoxicities of both compounds towards human colon tumour cells were determined to be p53 dependent by use of p53 and p21 knockout cell lines. The New Zealand ascidian *Lissoclinum notti* was found to contain the cytotoxic and antibacterial pyridoacridine alkaloids isodiplamine **685**, cystodytin K **686** and lissoclinidine **687** in addition to several known related compounds including diplamine **688**.[530] Conversion of diplamine **688** to lissoclinidine **687** was achieved by photochemical-induced isomerisation, but the natural product status of lissoclinidine was confirmed by rapid analysis of extract that was collected underwater and kept away from light. Two new pyridoacridine alkaloids, kuanoniamines E **689** and F **690**, and a putative biosynthetic precursor subarine **691** were isolated from a Singaporean collection of an unidentified ascidian.[531] The mildly cytotoxic perophoramidine **692** was isolated from a Philippines collection of the ascidian *Perophora namei*.[532] The carbon skeleton of **692** was established by analysis of HMBC and 2D INADEQUATE NMR data, while relative stereochemistry was determined by analysis of ROESY NMR data. The structures of the pyrrole alkaloids polycitones A and B, originally isolated from a South African collection of the ascidian *Polycitor* sp. and Madagascan collections of *Polycitor africanus*,[533,534] have been confirmed by synthesis.[535] A new member of the lamellarin class of alkaloids, lamellarin β **693** was reported from a collection of the ascidian *Didemnum* sp.[536] Investigation of the ascidian *Eudistoma toealensis* and

its predatory flatworm *Pseudoceros* sp., collected in Chuuk, Micronesia, yielded three new staurosporine derivatives **694–696**.[537] The absolute stereochemistries of **694–696** were established by comparison of CD data with those observed for staurosporine which has defined absolute stereochemistry.[538] The study also led to revision of the absolute stereochemistries of derivatives **697** and **698**, previously reported from the same organisms.[539] A study of the Thai ascidian *Ecteinascidia thurstoni*, using a KCN-pretreatment isolation procedure, afforded the known alkaloid ecteinascidin 770 **699** and the novel analogue ecteinascidin 786 **700**.[540] Both **699** and **700** exhibited potent cytotoxicity towards tumour cell lines and growth inhibition of *M. tuberculosis* $H_{37}$Ra. The structure of **699** was confirmed in a separate study that also reported the stereoselective synthesis of ecteinascidin 743.[541] The mechanism of cytotoxic action of ecteinascidin 743 has been reviewed.[10] A *Lissoclinum* species collected off Hateruma Island, Okinawa contained haterumaimides J **701** and K **702** with the relative stereochemistry being deduced from NOESY NMR experiments.[542] Both of the diterpene alkaloids exhibited potent cytotoxicity towards the P388 cell line. A range of meroterpenoids including the new examples **703–706** were isolated from a Tarifa Island, Cádiz collection of the ascidian *Aplidium conicum*.[543] The relative stereochemistry was determined by 1D and 2D NOE NMR experiments. The sulfated steroid **707** was found to be responsible for sperm activation and attraction in Japanese collections of the ascidians *Ciona intestinalis* and *C. savignyi*.[544] The absolute stereochemistry of (–)-longithorone A **708**, a dimeric prenylated quinone isolated from the ascidian *Aplidium longithorax*,[545,546] has been deduced in an elegant study that utilised Diels-Alder reactions in a biomimetic fashion.[547] The structure of ritterazine M **709**, a cytotoxic steroidal alkaloid isolated from the Japanese collection of the ascidian *Ritterella tokioka*,[548] has been corrected by total synthesis.[549,550] The structure presented for **709** in the synthesis papers contains an inadvertent error in the depicted C-25' stereochemistry of the isolated natural product – the correct structure of ritterazine M is shown in this review.

Further investigation has shown that the mechanism of cytotoxic action of vitilevuamide, a bicyclic peptide isolated from Fijian collections of the ascidians *Didemnum cuculliferum* and

*Polysyncraton lithostrotum*,[551] involves the inhibition of tubulin polymerisation possibly via interaction at a unique site.[552] The *in vivo* antitumour activity of the dimeric disulfide alkaloid polycarpine, isolated from the ascidians *Polycarpa clavata*[553] and *P. aurata*,[554] and related synthetic analogues has been investigated.[555]

## 12 Echinoderms

Glycosylated ceramides and saponins continue to be the major classes of metabolites identified in echinoderms. A full account of the isolation and characterisation of hedathiosulfonic acids A and B, isolated from a Japanese collection of the deep-sea urchin *Echinocardium cordatum*,[556] has been reported.[557] In addition, the compounds are the subject of a Japanese patent claiming the use of the compounds as antitumour, antibacterial and antifouling agents.[558] Luidiacerebrosides A **710** and B **711** were isolated from the starfish *Luidia maculata* collected in Hakata Bay, Fukuoka, Japan.[559] The stereochemistries of **710** and **711** were determined by degradation, fragment derivatisation and subsequent comparison with published data. In a separate study of *L. maculata*, the same research group also reported the new ganglioside molecular species LMG-3, of which **712** is the major component.[560] A collection of the Patagonian starfish *Allostichaster inaequalis* afforded two new glucosylceramides **713** and **714**.[561] Ten glucocerebrosides, HPC-3-A to HPC-3-J **715–724** and two glucocerebroside molecular species HPC-1 **725** and HPC-2 **726** were isolated from the Japanese sea cucumber *Holothuria pervicax* (Torafunamako).[562] While the ceramide portions of HPC-1 and HPC-2 were comprised of extensive heterogeneous mixtures of alkyl homologues, use of reversed-phase HPLC was effective in purifying **715–724**, although regio-isomer ambiguity still exists. All eight stereoisomers of pulcherrimine, a bitter principle isolated from the ovary of the sea urchin *Hemicentrotus pulcherrimus*,[563] have been synthesised, leading to the revision of the structure for the (2'*S*,2*R*,4*S*) isomer **727**.[564] Investigation of the water-soluble components of crinoids collected at Goza, Japan afforded, in addition to a range of known quinones, the 6-*O*-sulfate of ptilometric acid

**728** from *Tropiometra afra macrodiscus* and **729** from *Oxycomanthus japonicus* respectively.[565] The new sulfated steroid **730** was isolated from both *Leptasterias alaskensis asiatica* and *L. fisheri*, starfish collected at the Kiril Islands.[566] A study of the starfish *Diplopteraster multipes,* also collected in the Far East, afforded a range of sterol sulfates including the new example **731**.[567] Lysastroside A **732**, a new steroidal glycoside was isolated from the starfish *Lysastrosoma anthosticta*, collected in the Sea of Japan.[568] Ten new saponins, certonardosides A–J **733–742** were isolated from the starfish *Certonardoa semiregularis*, collected off the coast of Komun Island, Korea.[569] The absolute configurations of the side chains were secured by the $^{1}$H NMR analysis of MTPA esters. All compounds were evaluated for a range of antiviral properties towards HIV, HSV, CoxB, EMCV and VSV, but only mild potency was observed for **741** and **742**. Linckosides A **743** and B **744**, neuritogenic steroidal glycosides, were reported from an Okinawan collection of the starfish *Linckia laevigata.*[570] Both compounds induced neuronal differentiation in PC12 cells, with **744** being more potent. Significant synergistic effects on NGF-induced neuronal differentiation in PC12 cells were also observed for **743** and **744**. Brine shrimp lethality-directed fractionation of the Patagonian starfish *Anasterias minuta* afforded anasterosides A **745** and B **746**.[571] Anasteroside A **745** exhibited antifungal activity towards the plant pathogen *Cladosporium cucumerinum*, while **746** was inactive at all tested concentrations. Hydrolysis of the crude triterpenoid glycosides purified from Andaman and Nicobar Islands, Indian Ocean collections of the sea cucumbers *Holothuria nobilis* and *Bohadschia aff. tenuissima* afforded the new genins **747–749**.[572] Hemoiedemosides A **750** and B **751** are cytotoxic and antifungal triterpene glycosides isolated from the Patagonian sea cucumber *Hemoiedema spectabilis*.[573] Hemoiedemoside A **750** was more potent in the brine shrimp assay and more antifungal towards *Cladosporium cucumerinum* than **751**, while the desulfated analogue of **750** was significantly less active in the same assays. In the search for antagonists of the chemokine receptor subtype 5 (CCR5) as possible anti-HIV agents, bioassay guided fractionation of an Andaman and Nicobar Island collection of the sea cucumber *Telenata ananas* afforded two triterpene glycosides, **752** and **753**.[574] Both

compounds exhibited inhibitory activity in a CCR5 while no activity was observed towards the related receptor CXCR2.

Two reports of new syntheses of echinoderm metabolites appeared in 2002. A new route for the synthesis of (2*S*,2'*R*,3*S*,4*R*)-2-(2'-hydroxy-21'-methyldocosanoylamino)-1,3,4-pentadecanetriol, a ceramide sex pheromone isolated from the female Hair Crab, *Erimacrus isenbeckii*,[575,576] was reported,[577] while squaric acid ester-based methodology was used in a new synthesis of echinochrome A, a polyhydroxylated napthoquinone pigment commonly isolated from sea urchin spines.[578]

## 13 Miscellaneous

A series of flavones, the thalassiolins A–C **754–756** has been isolated from the Caribbean sea grass *Thalassia testudinum* (turtle grass). Thalassiolins A–C **754–756** are HIV integrase inhibitors, of which thalassiolin A **754** is the most potent.[579]

## 14 Conclusion

Despite the greater number of people working in more diverse areas on marine natural products the rate of discovery of new compounds during 2002 (677) was only comparable to that for any year in the last decade or so (~718 per annum on average). This could perhaps be explained by a steady state being reached where the greater effort is balanced against the difficulties of finding new compounds. As in previous years new compounds from sponges and coelenterates dominate (37% and 20% respectively: see Figure 1). Notable in 2002 was the decrease in compounds reported from molluscs (down from 7% to 2%).

The presumed biogenetic origins of the new compounds for 2002 have been systematically assigned. In assigning biogenetic origins divisions were made into peptide, terpenoid, alkaloid,

polyketide and shikimate categories. Glycosides were classified by the origins of the aglycone; compounds of mixed biogenetic origins were classified as to the probable source of the majority of the carbon atoms; peptides, depsipeptides and peptide esters were grouped together separate from alkaloids, for which the criterion of a basic nitrogen was applied. Non-basic aromatic compounds of shikimate or tryptophan origin were classified as shikimate. Divisions were made within each category. The terpenoids were divided up into mono, sesqui etc, but steroids and triterpenoids and higher terpenoids were clustered and a category of meroterpenoids introduced. Alkaloids were sub-divided into five categories that included compounds of polyketide, 3-alkylpyridine, shikimate, tryptophan as well as other origins. Three subdivisions only were used for the polyketides – regular polyketides, compounds of fatty acid, ceramide or sphingolipid origin, and the macrolides.

The overall biogenetic distribution is shown in Figure 2. The dominant pathway is that of terpenoid biogenesis (48%), which is perhaps not surprising as the chemistry of the two largest groups examined, the sponges and coelenterates, is dominated by terpenoid compounds. A more detailed breakdown of biogenetic origins is shown in Figure 3. For clarity the algae are shown as just one grouping and compounds of direct shikimate origin have been omitted. It is emphasised that these distributions are for compounds reported in 2002, and should not taken to necessarily reflect the distributions for all reported marine natural products.

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