

Marine natural products

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This review covers the literature published in 2003 for marine natural products, with 619 citations (413 for the period January to December 2003) 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 (656 for 2003), together with their relevant biological activities, source organisms and country of origin. Biosynthetic studies or syntheses that lead to the revision of structures or stereochemistries have been included (78), including any first total syntheses of a marine natural product.

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John Blunt obtained his BSc (Hons) and PhD degrees from the University of Canterbury, followed by postdoctoral appointments in Biochemistry at the University of Wisconsin-Madison, and with Sir Ewart Jones at Oxford University. He took up a lectureship at the University of Canterbury in 1970, where he is now a Professor. His research interests are with natural products, and the application of NMR techniques to structural problems.

Brent Copp received his BSc (Hons) and PhD degrees from the University of Canterbury, where he studied the isolation, structure elucidation and structure–activity relationships of biologically active marine natural products under the guidance of Professors Blunt and Munro. He undertook postdoctoral research with Jon Clardy at Cornell and Chris Ireland at the University of Utah. 1992–93 was spent working in industry as an isolation chemist with Xenova Plc, before returning to New Zealand to take a lectureship at the University of Auckland, where he is currently a Senior Lecturer.

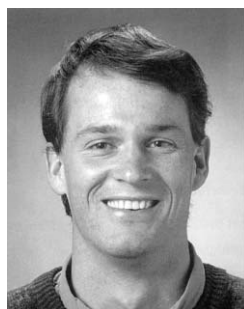
Murray Munro, a Professor in Chemistry at the University of Canterbury, Christchurch, New Zealand, has worked on natural products, mainly of New Zealand origin, for all of his professional career. A marine natural products research group was started in 1975 and in more recent years the research interests of the group have widened to include terrestrial as well as marine fungi and actinomycetes and drug delivery systems based on polymer therapeutics.

Peter Northcote, received his BSc and PhD degrees from the University of British Columbia, Canada where he was a member of R. J. Andersen's marine natural products research group. He carried out postdoctoral research with Professors Blunt and Munro at the University of Canterbury before taking a position as a senior research scientist at Lederle Laboratories, American Cyanamid Co. He joined the faculty of the Victoria University of Wellington in 1994 where he is currently a Senior Lecturer in organic chemistry.

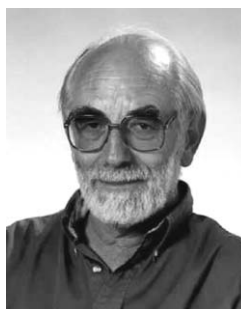
Michèle Prinsep received her BSc (Hons) and PhD degrees from the University of Canterbury, where she studied the isolation and structural elucidation of biologically active secondary metabolites from sponges and bryozoans under the supervision of Professors Blunt and Munro. She undertook postdoctoral research on cyanobacteria with Richard Moore at the University of Hawaii before returning to New Zealand to take up a lectureship at the University of Waikato, where she is currently a Senior Lecturer.



John W. Blunt



Brent R. Copp



Murray H. G. Munro



Peter T. Northcote



Michèle R. Prinsep

1 Introduction

This review is of the literature for 2003 and describes 656 new compounds from 243 articles. These numbers are comparable to those of the past few years. 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 separate structures are generally not shown.

2 Reviews

A number of reviews have dealt with classes of compounds: "Sterols in microorganisms",¹ "Bioactive macrolides and polyketides from marine dinoflagellates",² "Chemistry and biology of new marine alkaloids from the indole and annelated indole series",³ "Brominated diterpenes of marine origin",⁴ "Sulfur-containing natural products from marine invertebrates",⁵ "The cerebrosides",⁶ "Nonribosomal peptides from marine sponges",⁷ "Bioactive polyhydroxysterols and their sapogenins from marine organisms",⁸ "Sphingolipids from marine organisms",⁹ "A review of research on the cyanotoxin cylindrospermopsin",¹⁰ and "The manzamine alkaloids".¹¹

Reviews that focus on bioactivity and development as drug candidates include: "Natural products as sources of new drugs over the period 1981–2002",¹² "Marine natural products as prototype agrochemical agents",¹³ "Detection of pharmacologically active natural products using ecology",¹⁴ "Marine pharmacology in 2000: antitumour and cytotoxic compounds",¹⁵ "Bioactive natural products from marine invertebrates and associated fungi",¹⁶ "Marine pyridoacridine alkaloids and synthetic analogues as antitumour agents",¹⁷ "Drugs from the deep: marine natural products as drug candidates",¹⁸ "Marine-derived anticancer agents in clinical trials",¹⁹ "Marine natural products as lead anti-HIV agents",²⁰ "Natural products with anti-HIV activity from marine organisms",²¹ "Algae, a possible source for new drugs in the treatment of HIV and other viral diseases",²² and "Antimycobacterial natural products".²³

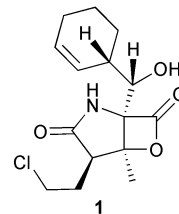
Chemical synthesis is the theme of a number of reviews covering specific types of compounds through to more generally applicable methodology: "Total synthesis of (+)-macrosphelides A, C, E, F and G based on enzymatic function",²⁴ "The total syntheses of phorbaxozoles—new classes in natural product synthesis",²⁵ "The development of a practical total synthesis of discodermolide",²⁶ "Synthesis of the pyrrole-imidazole alkaloids",²⁷ "Chemistry of bis-spiroacetal systems: natural products, synthesis and stereochemistry",²⁸ "Approaches towards the synthesis of cephalostatins, ritterazines and saponins from *Ornithogalum saundersiae*",²⁹ "New and old challenges in total synthesis. From concept to practise"³⁰ and "Microtubule-stabilizing marine metabolite laulimalide and its derivatives: synthetic approaches and antitumour activity".³¹

Other more general reviews include: "Molecular biodiversity. Case study: Porifera (sponges)",³² "Microalgal metabolites",³³ "Enhancing marine natural product structural diversity and bioactivity through semisynthesis and biocatalysis",³⁴ and "Marine natural products".³⁵ References to other reviews are more appropriately placed in the following sections. The Marinlit database³⁶ continues to be updated and has again been used as the basis for the preparation of this present review.

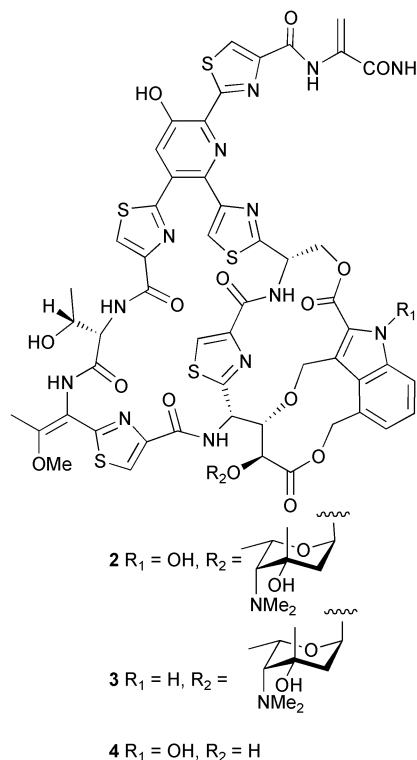
3 Marine microorganisms and phytoplankton

Probably the most important paper on marine microorganisms in 2003 was the first report on chemistry from the new obligate marine actinomycete taxon *Salinospora*.³⁷ In excess of 2500 strains from this taxon have now been isolated and the potent proteasome inhibitor salinosporamide A **1** was isolated from a culture of a *Salinospora* sp. originating from a heat-treated marine sediment sample from the Bahamas. The structure of

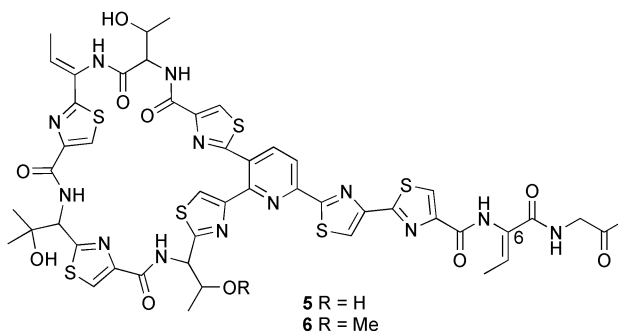
salinosporamide A, including the absolute stereochemistry, was deduced through spectral and X-ray analyses. Salinosporamide A displayed potent and selective *in vitro* cytotoxicity against cell lines in the NCI panel. Salinosporamide A also exhibited highly potent inhibition of the proteasomal chymotrypsin-like proteolytic activity of purified 20S proteasome. The unique functionalisation of the core-fused γ -lactam- β -lactone bicyclic ring structure of salinosporamide A **1** appears to contribute to



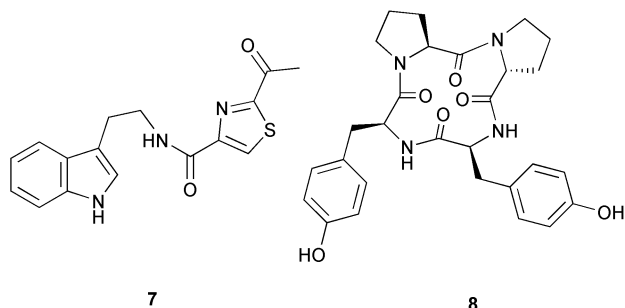
its potency. The thiazolyl peptide antibiotics, nocaithiacins I–III **2–4**, have been isolated from the culture broth of *Nocardia* sp.



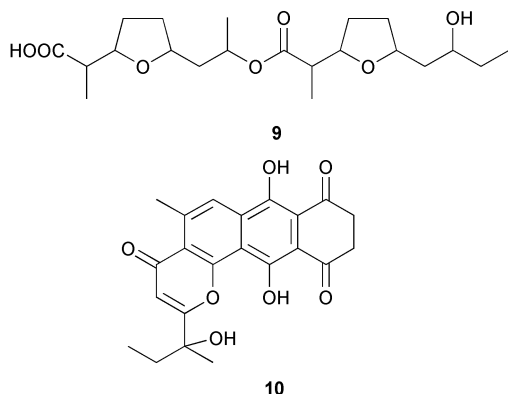
(source not given).³⁸ The nocaithiacins exhibit potent *in vitro* activity against a wide range of bacteria, including several multiple-drug resistant pathogens and also exhibit excellent *in vivo* efficacy in a systemic *Staphylococcus aureus* infection mouse model.³⁹ However, nocaithiacin I **2** was found to be identical to an antibiotic isolated from *Amycolatopsis* sp.⁴⁰ but spectral data and stereochemical details had not been originally reported for this compound. Two cyclic thiopeptides **5** and **6**, obtained from a culture of *Bacillus cereus* isolated from the marine sponge *Halichondria japonica*,⁴¹ exhibited potent antibacterial activities against *Staphylococci* and *Enterococci*



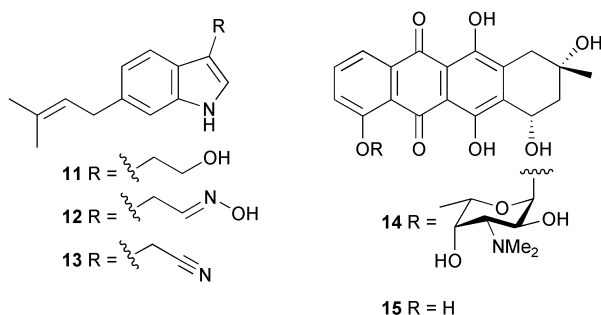
sp., and were active against multiple-drug resistant strains.⁴² (6*Z*)-Geometry for these compounds was implied by ROESY correlations. ¹H-¹⁵N HMBC analysis was used in determining the structure of bacillamide **7**, a peptidic metabolite of an algicidal marine *Bacillus* sp. isolated during the termination of a bloom of *Cochlodinium polykrikoides* in Masan Bay, Korea.⁴³ Bacillamide was shown to be active against a wide range of dinoflagellates and raphidophytes.⁴⁴ Culture of an exocellular extract of a *Pseudomonas* sp. associated with *Ircinia muscarum* from the Bay of Naples, Italy gave the cyclotetrapeptide **8**.⁴⁵



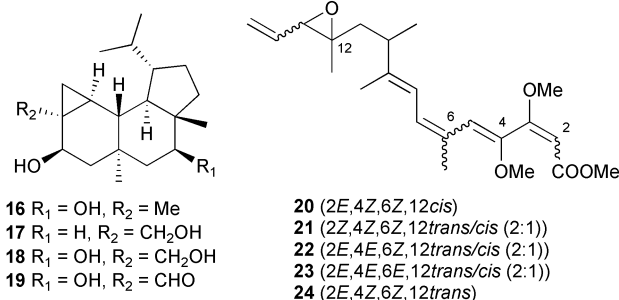
The amino acid stereochemistry was established by standard methods (for example, chiral HPLC analysis of the acid hydrolysate, Marfey's method *etc.*). Four *Streptomyces* sp. of diverse origin yielded a range of metabolites. Firstly, culture of a *Streptomyces* sp. from a sediment sample from Oahu, Hawaii, yielded the antibacterial and antifungal metabolite bonactin **9**.⁴⁶ Parimycin **10**, a new 1,4-anthraquinone, was isolated from



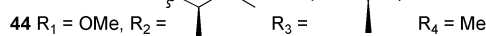
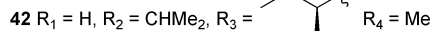
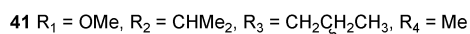
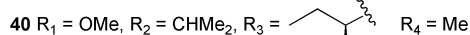
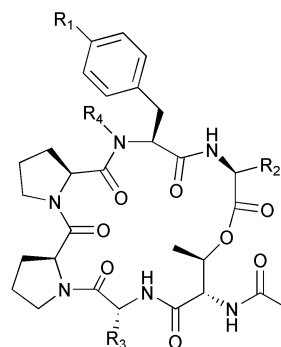
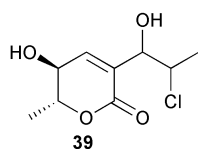
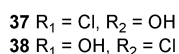
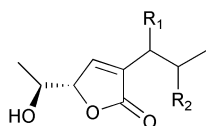
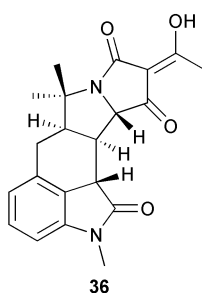
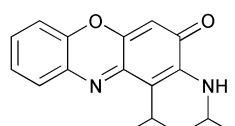
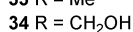
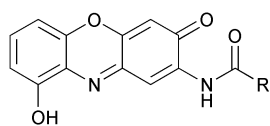
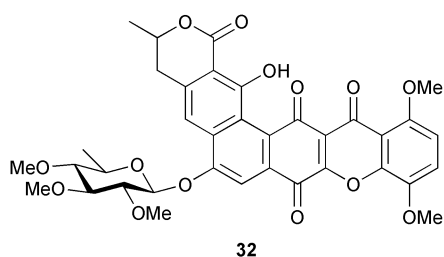
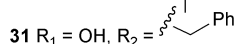
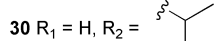
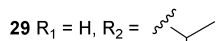
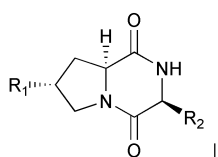
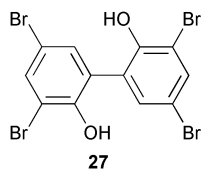
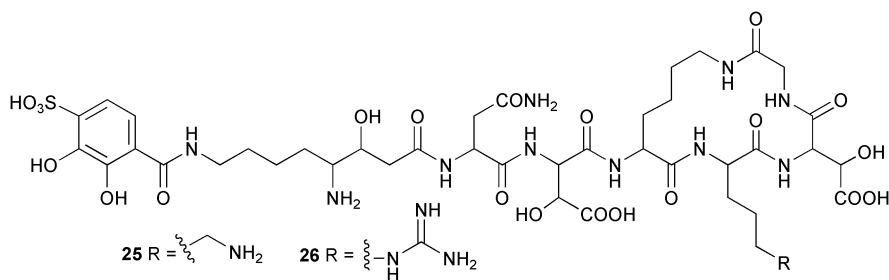
a *Streptomyces* sediment sample from Laguna de Terminos, Gulf of Mexico. Parimycin had moderate activity against *B. subtilis*, *Streptomyces viridochromogenes*, *S. aureus* and *E. coli*, in addition to activity against a number of human tumour cell lines.⁴⁷ A *Streptomyces* sp. cultured from an unidentified Mexican marine invertebrate yielded the cytotoxic indoles **11–13** which had moderate activity against a panel of 14 tumour cell lines.⁴⁸ Finally, the anthracycline komodoquinone **14** and the aglycone komodoquinone **15** were isolated from a culture of a *Streptomyces* sp. isolated from marine sediment off Komodo Island, Indonesia. Komodoquinone A displayed dose-dependent neurotogenic activity against the neuroblastoma cell line Neuro 2A.⁴⁹ A culture broth of an ATCC strain of the marine gliding bacterium *Saprospira grandis* yielded four



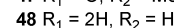
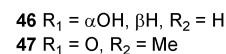
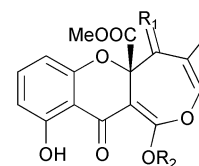
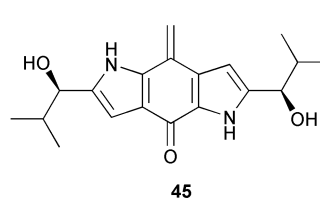
neoverrucosane diterpenoids, **16–19**. The relative and absolute stereochemistries of **16** were determined by standard methods⁵⁰ (for example, X-ray analysis, NOESY and ROESY NMR experiments, the modified Mosher method, chiral HPLC, comparison of circular dichroism (CD) or other optical data against standards or model compounds *etc.*). The marine myxobacterium *Haliangium ochraceum*,⁵¹ originally *H. luteum*, yielded several new isomers of the polyene antifungal antibiotic haliangicin.^{52,53} These are *cis*-haliangicin **20** and haliangicins B–D **21–23**, geometrical isomers of the polyene and epoxide moieties. The stereochemistry of the epoxide in the known haliangicin **24**⁵³



has been determined as *trans*. All of the haliangicins were active against the phytopathogenic fungus *Phytophthora capsici*.⁵⁴ Two siderophores, pseudoalterobactins **25** and **26**, were isolated from a culture of the bacterium *Pseudoalteromonas* sp. isolated from the marine sponge *Cinachyrella australiensis* collected in Palau. Both compounds displayed strong binding affinity for the ferric ion in the chrome azurol S (CAS) assay.⁵⁵ The bactericidal compound **27**, obtained from a culture of a new marine species *Pseudoalteromonas phenolica* sp. nov., isolated from seawater collected off Ogasawara Island Japan,⁵⁶ had potent activity against methicillin-resistant *S. aureus* (MRSA) and was also strongly active against *Enterococcus serolicida*, *E. faecium* and *E. faecalis*.⁵⁷ This compound is available commercially, but this is the first reported isolation as a natural product. Cultures of two marine bacterial strains isolated from cultures of *Pecten maximus* larvae in Galicia, Spain, led to the first reported isolation, as natural products, of a series of *DD*-diketopiperazines **28–31** and established them as potent inhibitors of the pathogenic marine bacterium *Vibrio anguillarum*. The structures were confirmed by synthesis.⁵⁸ A cytotoxic polycyclic xanthone **32** has been isolated from the culture broth of the actinomycete *Actinomadura* sp.⁵⁹ The phenoxazin-3-one antibiotics, chandrananimycins A–C **33–35**, were also isolated from a culture of *Actinomadura* sp. derived from sediment from Jiaozhou Bay, China. Chandrananimycins A–C were active against human tumour cell lines while **35** exhibited potent activity against the fungus *Mucor meihei* and the bacteria *B. subtilis* and *E. coli*, and antialgal activity against the microalga, *Chlorella vulgaris*, *C. sorokiniana* and *Scenedesmus suspicatus*.⁶⁰ The fungus *Aspergillus tamarii* was isolated from driftwood collected in Okinawa and cultured to yield a pentacyclic oxindole alkaloid, speradine **36**. The structure and relative stereochemistry of **36** were confirmed by X-ray analysis. Speradine **36** exhibited inhibitory activity against histone deacetylase and antibacterial activity against *Micrococcus luteus*.⁶¹ A culture of the fungus *Aspergillus ostianus*, isolated from an unidentified marine sponge from Pohnpei, was the source of three chlorinated antibiotics, the asperlactone derivatives **37** and **38** and the aspyrone derivative **39**. Compound **37** was the most potent, inhibiting the growth of the marine bacterium *Ruegeria atlantica* and that of *E. coli* and *S. aureus* to a lesser extent.⁶² Five novel depsipeptides, aspergillicins A–E **40–44**, were obtained from a culture of *Aspergillus carneus* collected from estuarine sediment in Tasmania, Australia. The amino acid sequences were assigned by MSⁿ ion-trap ESI mass spectrometry and stereochemistry was assigned by standard methodology. The aspergillicins exhibited

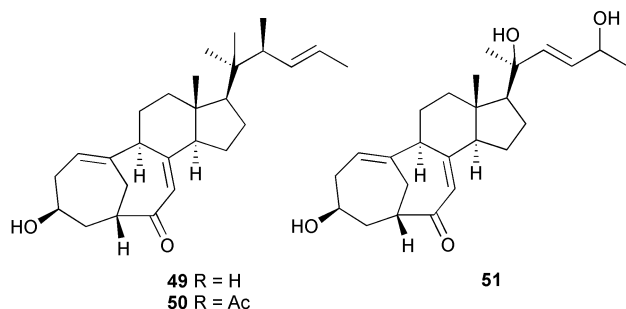


modest cytotoxicity against *Haemonchus contortus*.⁶³ A chiral dipyrrolobenzoquinone derivative, terreusinone **45**, has been obtained from a cultured strain of the marine algicolous fungus *Aspergillus terreus* isolated from the surface of the marine red alga *Halymenia acuminata* collected from Bijin Island, South Korea. The absolute stereochemistry was determined by a combination of Horeau's method and quantum chemistry calculations. Terreusinone has intense UV-A absorptivity.⁶⁴ A culture of *Penicillium brocae* from the tissue of the Fijian sponge *Zyzzya* sp. was the source of three novel cytotoxic polyketides, brocaenols A–C **46–48**. These contain the unusual enolised

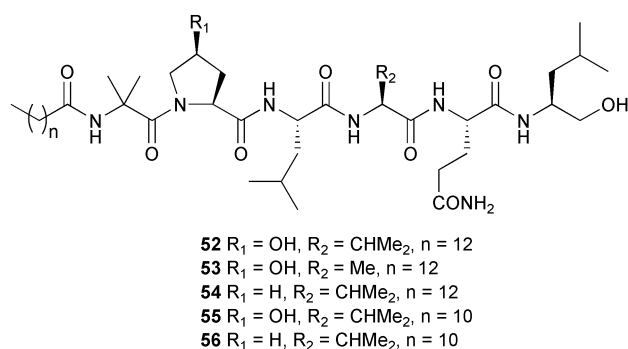


oxepine lactone ring system. Structure determination included an INADEQUATE experiment on brocaenol A. The absolute stereochemistry of **46** was established by a standard method and extended to **47** and **48** by comparison of CD and optical rotation data.⁶⁵ Brocaenols A–C displayed moderate activity against the HCT-116 cell line. Structures for brocaenols B and C were reversed in the original paper, but a correction has since been published.⁶⁶ The steroids isocyclocitrinol A **49** and 22-acetylisocyclocitrinol A **50** were extracted from a salt water culture of *Penicillium citrinum* isolated from an *Axinella* sp.

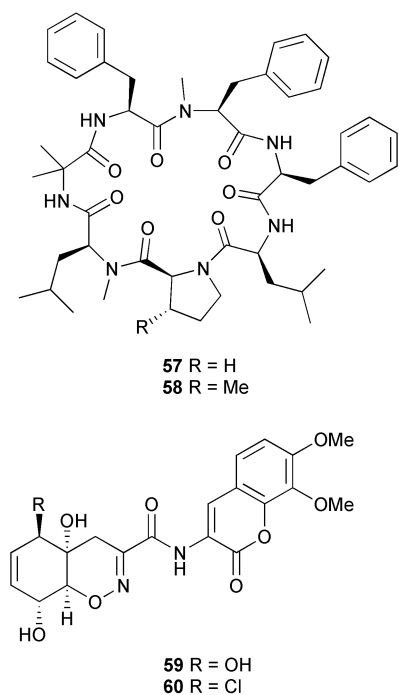
collected in Papua New Guinea.⁶⁷ The absolute stereochemistry of **50** was established by standard methods, extended to **49**, leading to the structural revision of cyclocitrininol, previously isolated from a terrestrial *P. citrinum*,⁶⁸ to **51**. Compounds **49** and



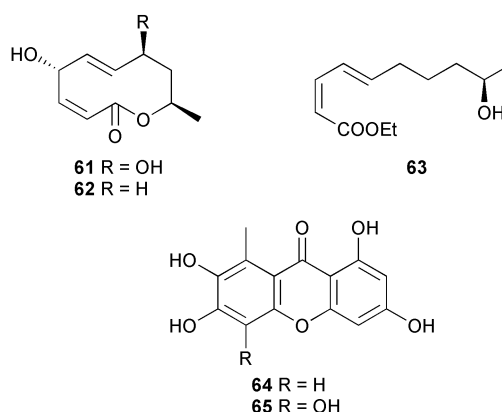
50 displayed weak antibacterial activity against *Staphylococcus epidermidis* and *Enterococcus durans*. The halovirs A–E **52–56**,



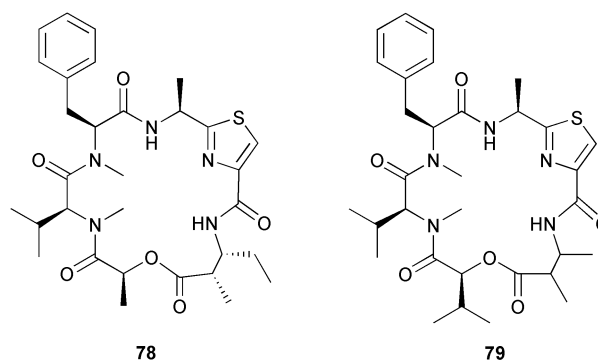
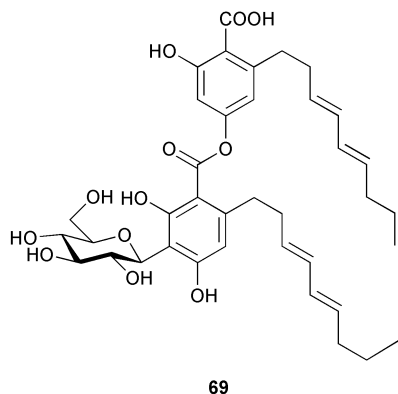
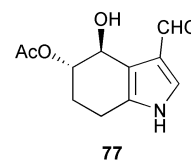
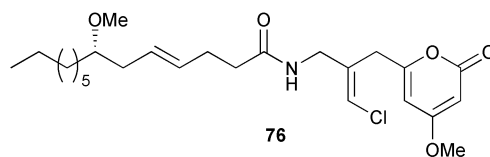
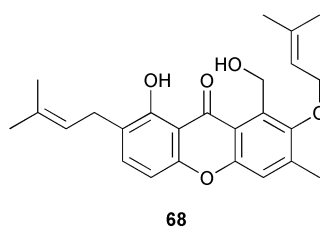
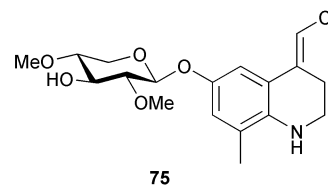
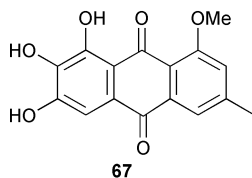
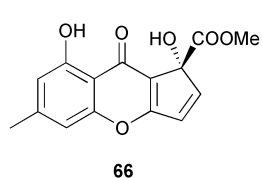
lipophilic linear peptides, are potent *in vitro* inhibitors of *Herpes simplex* viruses 1 and 2 and were isolated from a *Scytalidium* sp. sourced from the Caribbean seagrass *Halodule wrightii*.⁶⁹ Two cyclic heptapeptides, scytalidamides A **57** and B **58**, have been isolated from the culture broth of another *Scytalidium* sp. derived from the surface of the green alga *Halimeda* sp. collected off the Bahamas. The absolute configurations were confirmed by standard methods including CD measurements. Both scytalidamides displayed moderate cytotoxicity to the HCT-116 cell line *in vitro*.⁷⁰ Trichodermamides A **59** and B **60**,



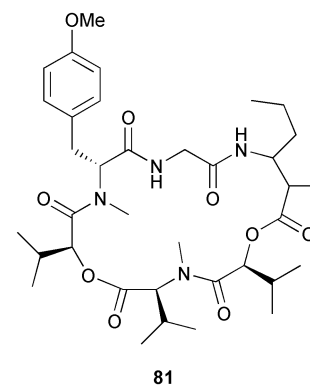
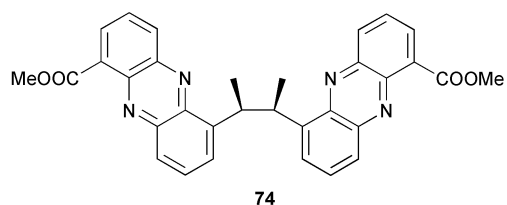
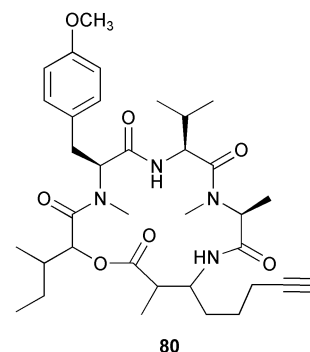
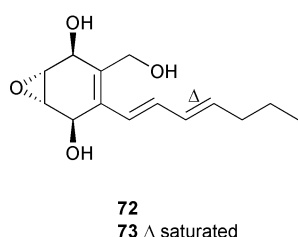
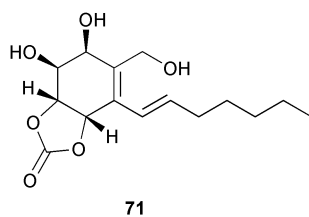
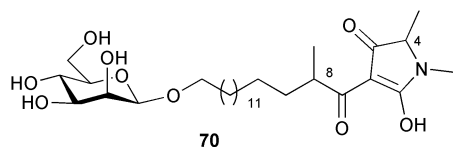
modified dipeptides, were isolated from cultures of *Trichoderma virens* isolated from the ascidian *Didemnum molle* and from the surface of a green alga of the genus *Halimeda*, both collected in Papua New Guinea. The ascidian-derived culture contained trichodermamide A with traces of trichodermamide B while a greater quantity of trichodermamide B was isolated from the algal-derived strain. The structure of **59** was assigned by X-ray diffraction while the absolute stereochemistry was determined using the modified Mosher method. Trichodermamide B displayed significant *in vitro* cytotoxicity against HCT-116 and moderate antimicrobial activity against amphotericin-resistant *C. albicans*, MRSA and vancomycin-resistant *E. faecium*.⁷¹ Trichodermamide A is closely related to penicillazine, reported from a marine-derived *Penicillium* sp.⁷² The reported structures differ only in the translocation of ester and amide bonds, but spectral data comparison suggests that these compounds may be identical. Two macrolides, modiolides A **61** and B **62**, and a linear pentaketide modiolin **63** have been isolated from the culture of *Paraphaeosphaeria* sp. separated from the marine horse mussel *Modiolus auriculatus*, collected in Okinawa. The absolute stereochemistry of **61** was determined by the exciton chirality method⁷³ using a *p*-methoxycinnamoyl ester, while the absolute stereochemistry of **63** was defined by the modified Mosher method. Modiolides A and B exhibited modest antibacterial activity against *Micrococcus luteus* and *Neurospora crassa*.⁷⁴ A culture of the marine fungus *Wardomyces anomalus*, isolated from the green alga *Enteromorpha* sp. collected in the Baltic Sea, yielded two xanthone derivatives, anomalins A **64** and B **65**.⁷⁵ The anomalins were only weakly antimicrobial, but



anomalin A possessed significant tyrosine kinase p56^{lck} enzyme inhibitor activity and antioxidative properties. Remisporine A **66**, a novel cyclopentachromenone, isolated from a culture of the marine fungus *Remispora maritima* from an unspecified wood source, is unstable under normal conditions and autocatalytically dimerises stereospecifically, *via* a Diels–Alder reaction, to remisporine B.⁷⁶ A new anthraquinone, evariquinone **67**, and the new prenylxanthone isoemicellin **68** were isolated from a culture of the fungus *Emericella varicolor* derived from the marine sponge *Haliclona valliculata* collected at Elba, Italy. The known C-glycosidic depside stromemycin **69**⁷⁷ was also isolated, and the previously undescribed double bond configurations established. Evariquinone **67** showed antiproliferative activity towards KB and NCI-H460 cells.⁷⁸ A culture of a marine strain of the fungus *Epicoccum purpurascens*, isolated from inner tissue of the jellyfish *Aurelia aurita* collected from the North Sea, Germany, yielded the tetramic acid derivative epicoccamide **70**. Attempts to resolve the stereochemistry at C-4 and C-8 by comparison of CD spectra with those of similar compounds were ambiguous.⁷⁹ Two highly oxygenated polyketides, phomoxin **71** and phomoxide **72**, are metabolites from a *Phoma* sp. isolated from a microbial mat collected from a Bahaman hypersaline pond, along with eupenoxide **73**, a previously synthesised, but unpublished fungal metabolite.⁸⁰

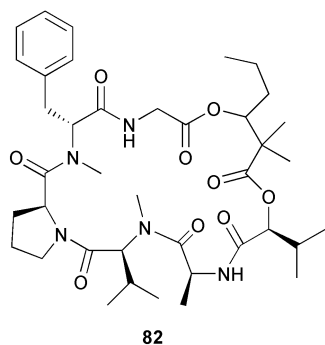


An actinomycete, *Pseudonocardia* sp., isolated from littoral sediment from Mauritius, Indian Ocean, was the source of a new phenazine derivative, phenazostatin D **74** which is

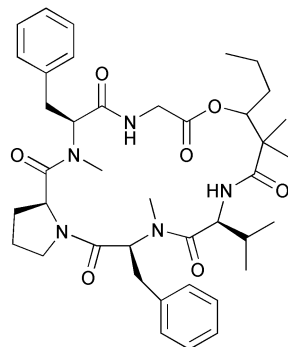


the *meso*- form of the known antibiotic phenazostatin B.^{81,82} Investigations of a collection of *Lyngbya majuscula* from Puerto Rico resulted in the isolation of three new metabolites, a quinoline alkaloid, **75**, malngamide T **76** and a tryptophan derivative **77**.⁸³ Geometries for the vinyl chloride functionalities of **75** and **76** were established as (*E*) by ¹H-¹³C coupling constant measurement from HSQMBC NMR experiments.⁸⁴ Six cyclic depsipeptides, guineamides A-F **78-83**, were isolated from a collection of *Lyngbya majuscula* collected from Papua New Guinea. Absolute stereochemistries for most of the amino acids

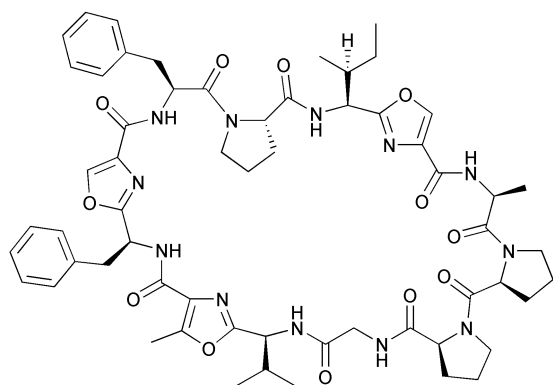
were determined by standard methods. Guineamides B and C were moderately cytotoxic to a mouse neuroblastoma cell line.⁸⁵ *L. majuscula* from Papua New Guinea was the source of the novel cyclic dodecapeptide wewakazole **84** which contains an unprecedented number of five-membered heterocyclic rings (six). Due to extensive signal overlap the structural assignment



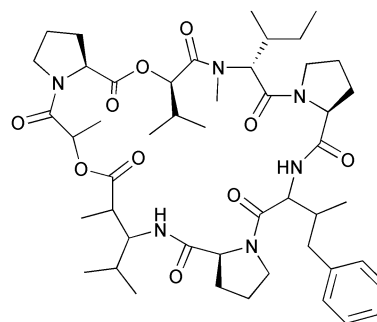
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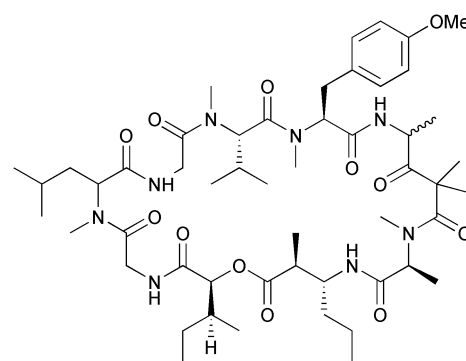
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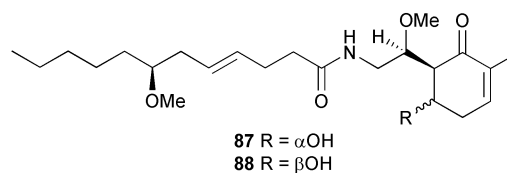
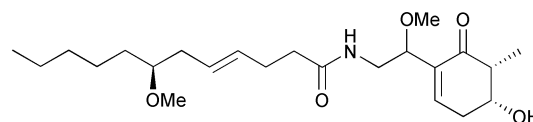
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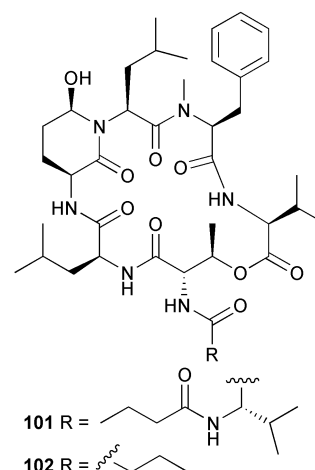
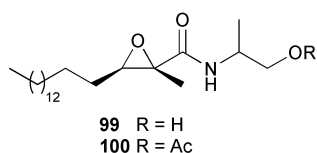
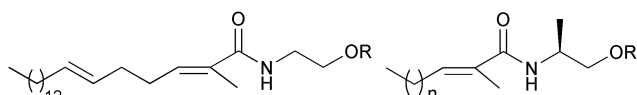
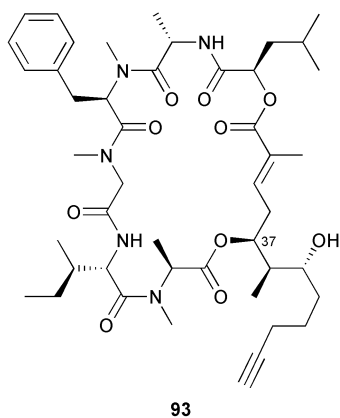
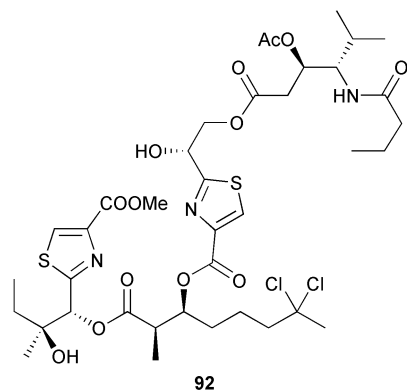
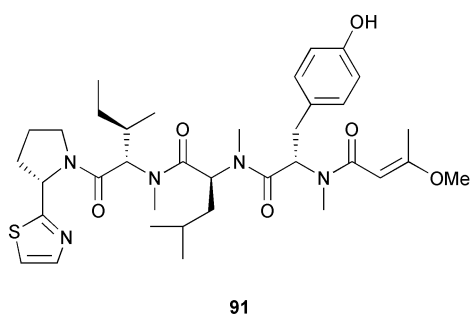
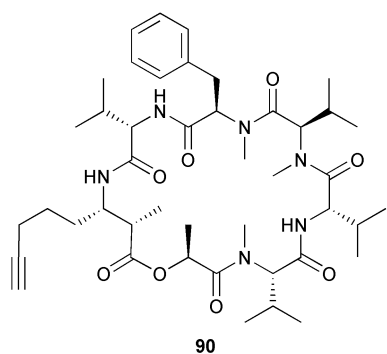
86

87 R = α OH
88 R = β OH

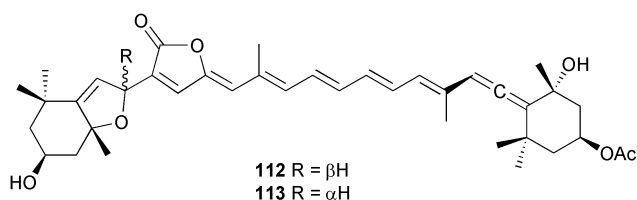
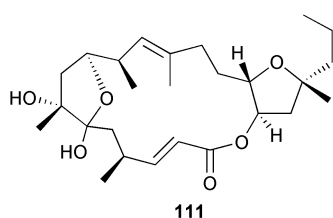
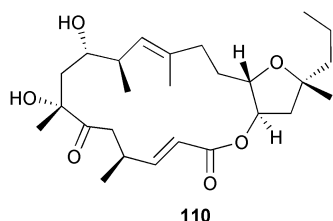
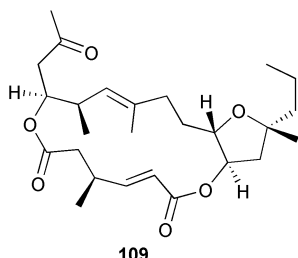
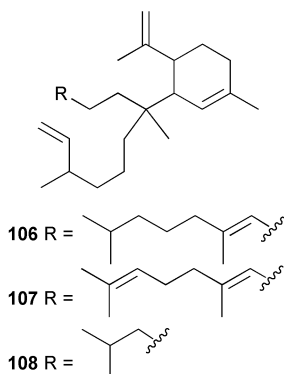
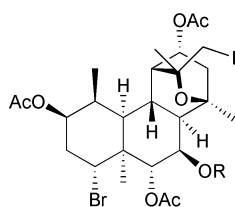
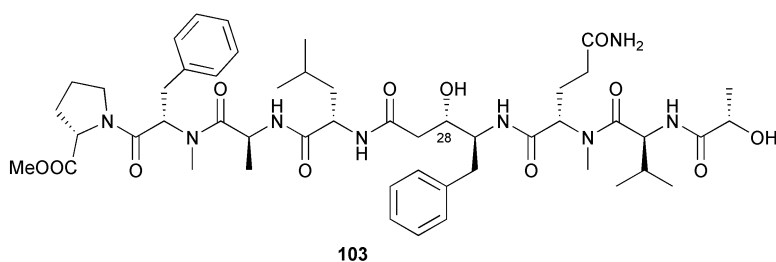
89

required multiple NMR and MS/MS experiments. The absolute stereochemistry was determined by standard methods.⁸⁶ *L. majuscula* from the southern Kenyan Coast was the source of the cyclic depsipeptide homodolastatin 16 **85**. The absolute stereochemistries of most of the amino acids in homodolastatin 16 were determined by standard methods. Homodolastatin 16 **85** displayed moderate activity against oesophageal and cervical cancer cell lines.⁸⁷ The cyclic peptide lyngbyastatin 3 **86**, isolated from *L. majuscula* collected from Guam, contains two unusual amino acid units, including 4-amino-2,2-dimethyl-3-oxopentanoic acid (Ibu). The configuration of the Ibu unit was established by acid hydrolysis and comparison with synthetic standards, while the absolute stereochemistries of the remaining residues were determined by standard methods. Lyngbyastatin 3, along with the previously isolated lyngbyastatin 1 and dolastatin 12,⁸⁸ are in fact diastereotopic mixtures of both Ibu epimers. Lyngbyastatin 3 **86** exhibited activity against KB and LoVo cell lines *in vitro*, but was poorly tolerated *in vivo* with little anti-tumour activity.⁸⁹ Three new malynгамides, U–W **87–89**, have been isolated from *L. majuscula* collected in Papua New Guinea. Partial relative stereochemistries only were determined.⁹⁰ A collection of *Lyngbya* sp. from Palau yielded ulongapeptin **90**, a cytotoxic cyclic depsipeptide,⁹¹ while a *Lyngbya* sp. from Guam yielded two new compounds, 15-norlyngbyapeptin A **91** and lyngbyabellin D **92**.⁹² The absolute stereochemistries

in each case were determined through degradative studies and/or comparison with commercially available and synthetic standards. Ulongapeptin was moderately cytotoxic against KB cells *in vitro*⁹¹ and lyngbyabellin D displayed activity against the KB cell line.⁹² Bioassay-guided fractionation of an extract from a *Lyngbya* sp. collected in Palau led to the isolation of palau'amide **93**. Effective use was made of a band-selective HMBC experiment to unambiguously assign ¹³C NMR signals that were separated by only 0.1 ppm.⁹³ Except for C-37, relative and absolute configurations were determined by standard methods. By modelling, and from NOE data, C-37 was assigned as having the (*S*) configuration. Palau'amide **93** exhibited potent cytotoxicity against KB cells.⁹⁴ Semiplenamides A–G **94–100**, anandamide-like fatty acid amides, were isolated from a collection of *Lyngbya semiplena* collected in Papua New Guinea. The absolute stereochemistries of the amino alcohols in semiplenamides C–E **96–98** were elucidated as all L by chemical derivatisation and chiral GCMS methods. All of the semiplenamides displayed toxicity in the brine shrimp assay, while semiplenamides A, B and G exhibited weak affinity for the rat cannabinoid CB1 receptor. Semiplenamide A was also a moderate inhibitor of the anandamide membrane transporter (AMT).⁹⁵ Samples of the marine cyanobacterium *Symploca* sp. collected in Palau were the source of the depsipeptides tasipeptins A **101** and B **102**,⁹⁶ and a cytotoxic peptide, tasiamide B **103**.⁹⁷ The relative and absolute configurations of the tasipeptins and tasiamide B were determined by standard



methods except for the configuration of C-28 in tasiamide B. This was tentatively suggested as (*S*) from NMR data analysis.⁹⁷ Both tasiptepsins exhibited moderate cytotoxicity towards KB cells *in vitro*. Also collected in Palau was an assemblage of a *Symploca* sp. cyanobacterium and an unidentified red alga. From this was isolated the iodinated diterpenes, tasihalides A **104** and B **105**. These compounds possess a novel cage structure with both an oxabicyclic ring system and a *cis*-decalin system. These are the only examples of iodinated diterpenes in nature. Since terpenoids are almost never reported from marine cyanobacteria, but halogenated terpenes are ubiquitous in red algae, the authors speculate that the more likely source of the tasihalides is the alga and not the cyanobacterium.⁹⁸ Two polyunsaturated monocyclic triterpenes **106** and **107** have been isolated from a culture of the common marine diatom *Rhizosolenia setigera*. The structure of a related monocyclic sesterterpene **108** was also proposed on the basis of mass spectral comparisons with compounds **106** and **107**.⁹⁹ Amphidinolide X **109**¹⁰⁰ and amphidinolide Y **110**¹⁰¹ are cytotoxic 16- and 17-membered macrodiolides isolated from cultures of the marine dinoflagellate *Amphidinium* sp., originally separated from the inside cells of the marine acol flatworm *Amphiscolops* sp. collected from Okinawa. Amphidinolide Y exists as a 9 : 1 equilibrium mixture of the 6-keto-**110** and 6(9)-hemiacetal **111** forms. Both amphidinolides X and Y were moderately cytotoxic against murine lymphoma L1210 and human epidermoid carcinoma KB cells *in vitro*. Feeding experiments with ¹³C-labelled acetates suggested that amphidinolide Y might be a precursor of amphidinolide X.¹⁰¹ A culture of the dinoflagellate *Symbiodinium* sp., a symbiont of the soft coral *Clavularia viridis* collected from Okinawa, yielded two diastereoisomeric norcarotenoids **112** and **113**. Both compounds exhibited moderate growth-inhibitory activity *in vitro* against a range of human cancer cell lines.¹⁰² A culture of the free-living marine dinoflagellate *Symbiodinium* sp. isolated from a tide pool, Coconut Island, Hawaii,¹⁰³ yielded the polyhydroxy compound zooxanthellamide A **114**.¹⁰⁴ Cultures of a strain of the dinoflagellate *Prorocentrum lima*¹⁰⁵ afforded okadaic acid methyl ester **115**, norokadanone **116** and an okadaic acid diol ester **117**.¹⁰⁶ Three hydroxybenzoate saxitoxin analogues, GC1–GC3 **118–120**, have been isolated from the cultured dinoflagellate *Gymnodinium catenatum* originally isolated from a planktonic bloom in Tasmania. GC1 and GC2 are the epimeric 11-hydroxysulfate derivatives of GC3, the 4-hydroxybenzoate ester derivative of decarbamoysaxitoxin. Preliminary investigations indicate that the compounds bind to rat brain sodium channels, in keeping with known PSP toxins.¹⁰⁷ Biosynthetic investigations using ¹³C-labelled precursors of the meroterpenoid neomarinone, originally isolated from culture of an unidentified marine actinomycete from sediment from Batiquitos Lagoon, California,¹⁰⁸ led to the structural revision of neomarinone to **121**.¹⁰⁹ A correction to the text of the article describing the structure and absolute stereochemistry of phormidolide from the

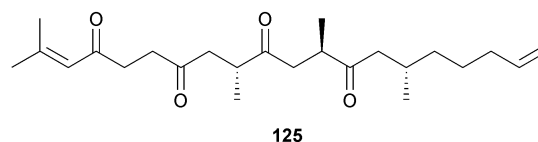
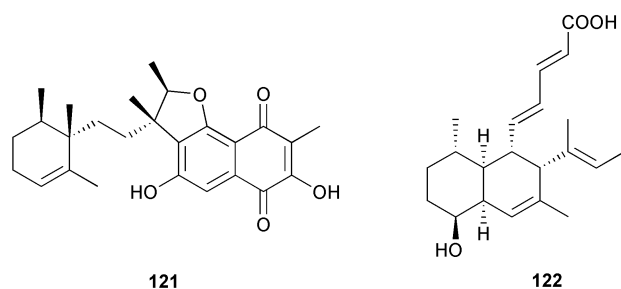
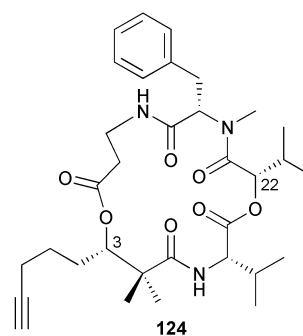
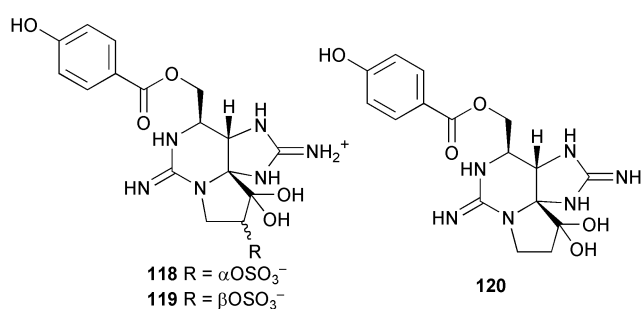
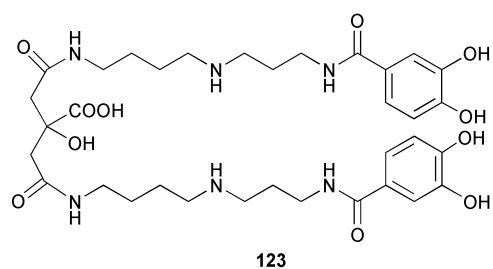
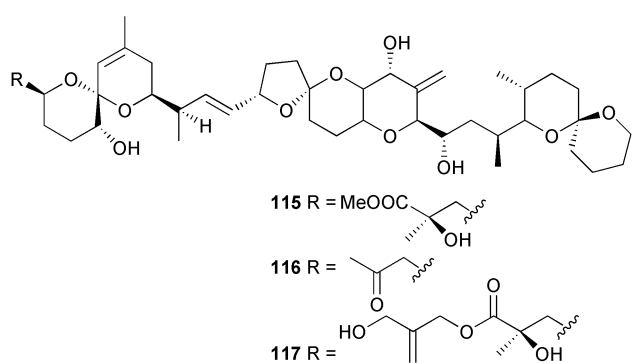
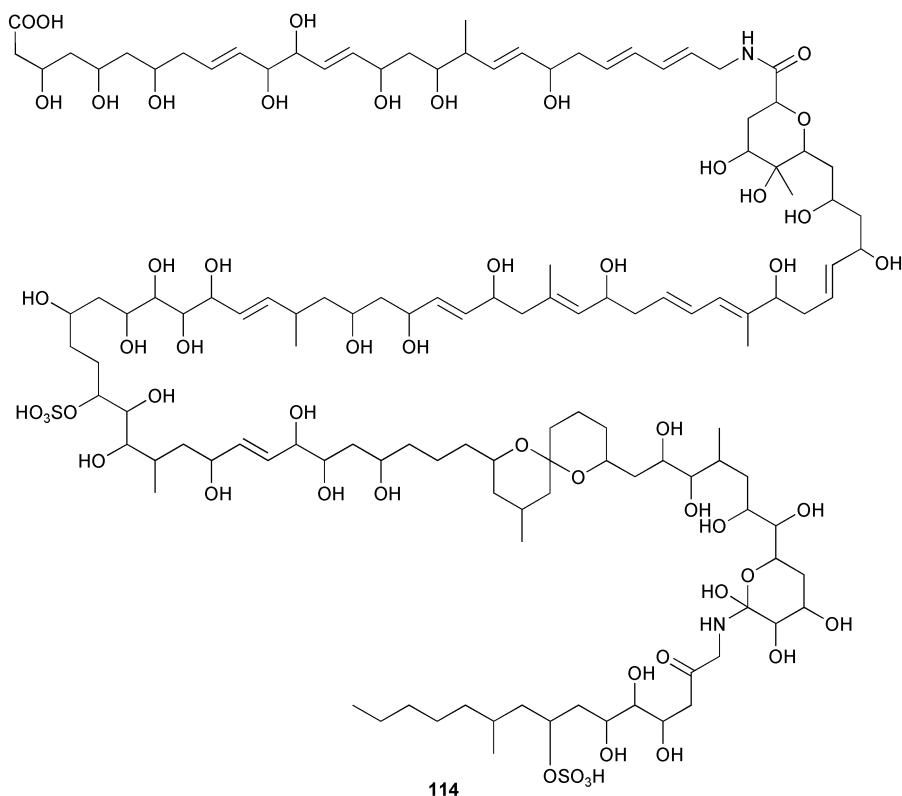


marine cyanobacterium *Phormidium* sp.¹¹⁰ has been published, amending two descriptors [(17*R*,26*R*) to (17*S*,26*S*)].¹¹¹ The absolute configuration of the fungal metabolite phomopsidin **122**, derived from a cultured strain of *Phomopsis* sp.,¹¹² has been determined by the exciton chirality method. Phomopsidin exhibited potent anti-microtubule activity in a microtubule assembly assay utilising purified porcine brain microtubule proteins.¹¹³ A total synthesis of petrobactin, a siderophore isolated from the marine bacterium *Marinobacter hydrocarbon-*

oclasticus has been completed. Comparison of the ¹H NMR spectrum of the synthetic product with literature data for the natural product¹¹⁴ resulted in a structural revision of petrobactin from 2,3-dihydroxybenzoyl- to 3,4-dihydroxybenzoyl-moieties. This 3,4-dihydroxybenzoyl analogue **123** was also synthesised, giving ¹H and ¹³C NMR spectra that were consistent with those of the natural product.¹¹⁵ The first total synthesis of yanucamide A **124**, which was isolated from an assemblage of *L. majuscula* and a *Schizothrix* species,¹¹⁶ has been achieved *via* amide and ester coupling methods. The synthesis established the configuration at C-3, originally unassigned due to ambiguity, and revised the configuration at C-22.¹¹⁷ In synthetic studies towards congeners of phomactin A, total syntheses of structures isomeric to that proposed for the phomactin known as Sch 49028, also isolated from the marine fungus *Phoma* sp.,¹¹⁸ are described. None of the isomers showed spectral data consistent with those of the natural product so it is proposed that Sch 49028 does not exist and that the NMR spectral data should have been assigned as phomactin A.¹¹⁹ Other first total syntheses reported include that of (\pm)-spiroxin C, originally isolated from culture of an unidentified fungal strain from a soft coral from Vancouver Island, Canada.¹²⁰ This involved a Suzuki–Miyaura cross-coupling reaction.¹²¹ Apratoxin A, a cyclodepsipeptide from *Lyngbya* sp. collected in both Guam¹²² and Palau,¹²³ has been synthesised.¹²⁴ The relative and absolute stereochemistries of amphidinoketide **125**, originally isolated from the dinoflagellate *Amphidinium* sp. collected in the Virgin Islands,¹²⁵ have been determined by total synthesis of all four diastereoisomers. Molecular modelling was used to infer that the natural product is not the thermodynamically preferred diastereoisomer.¹²⁶ Two syntheses of the 19-membered macrolide (+)-amphidinolide T1^{127,128} have been achieved,^{129,130} along with the synthesis¹³⁰ of amphidinolides T3¹³¹ and T5.¹²⁸ Synthesis of the structurally complex gymnocin-A, a polyether toxin with 14 contiguous rings, from the red tide dinoflagellate *Karenia mikimotoi*,¹³² has been accomplished through the use of *B*-alkyl Suzuki–Miyaura coupling-based methodology.¹³³ Following the first total synthesis of gambierol, a marine polycyclic ether toxin originally isolated from the marine dinoflagellate *Gambierdiscus toxicus*,¹³⁴ preliminary structure–activity relationship studies suggest that functionalities in the H ring and unsaturated sidechain are essential for potent murine toxicity.¹³⁵ A competitive inhibition assay using the isotopically labelled brevetoxin dihydro BTX-B (³H]PbTx-3), demonstrated that gambierol^{134,136} and gambieric acid-A^{137,138} from the dinoflagellate *Gambierdiscus toxicus* inhibit the binding of brevetoxins to site 5 of the voltage-gated sodium channel of excitable membranes,¹³⁹ while effects of brevetoxins produced by the dinoflagellate *Karenia brevis* (formerly *Ptychodiscus brevis* and *Gymnodinium brevis*)¹⁴⁰ on the murine myeloma cell line SP2/O, a possible model for *in vitro* studies for immune cells, suggest that the brevetoxins have an aberrant effect on cell division.¹⁴¹

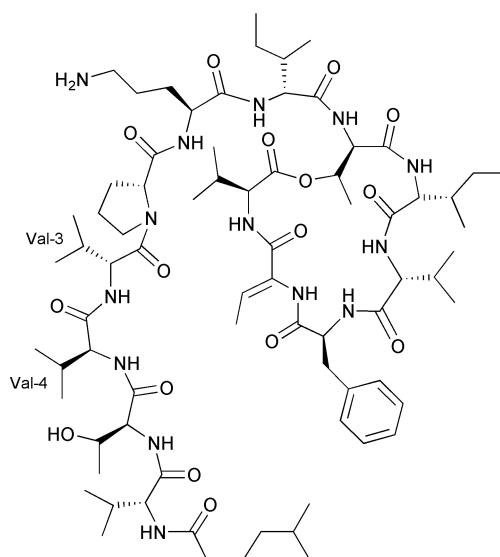
4 Green algae

As in 2002, very few new compounds have been reported from green algae. The cyclic depsipeptide kahalalide F **126**, originally isolated from both the mollusc *Elysia rufescens* and from the dietary source, the green alga *Bryopsis* sp.,¹⁴² was introduced

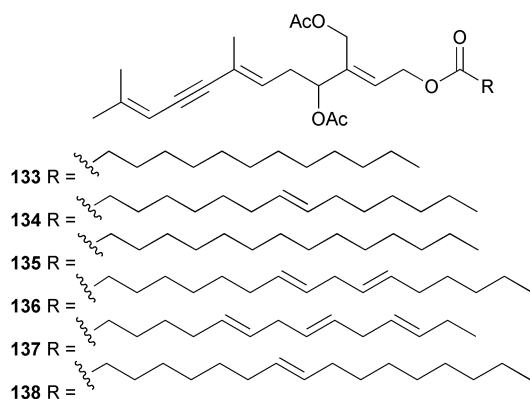
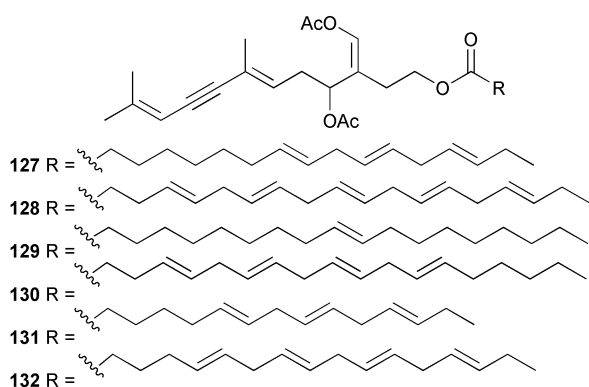


structure only was originally defined and the stereochemistry subsequently assigned.¹⁴³ The degradation results indicate that the correct structure is a stereoisomer **126**, in which the original assignments for Val-3 and Val-4 have been reversed. This stereochemistry is crucial for the observed bioactivity.¹⁴⁴ Twelve new terpene esters, **127**–**138** have been isolated from the green alga *Caulerpa prolifera* collected from Saronikos Gulf, Greece. The *C. prolifera* extract exhibited moderate to significant activity against three unidentified strains of marine bacteria, in addition

into Phase I trials by Pharma Mar SA as a lead compound against prostate cancer. The structure of kahalalide F has been corrected based on a series of degradation reactions. The planar



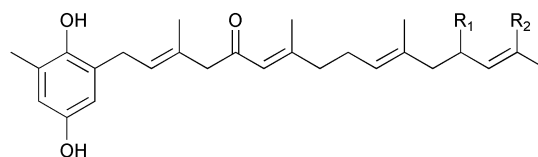
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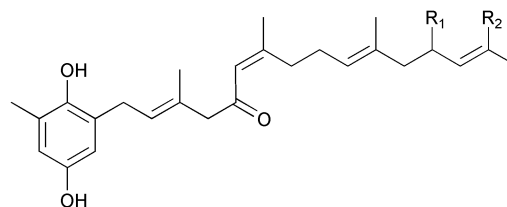
to strong growth inhibitory effects on the fouling microalga *Phaeodactylum tricornerutum*.¹⁴⁵ The first total synthesis of (\pm)-dihydrohipocephalin, a bioactive sesquiterpene isolated from Caribbean marine green algae of the genera *Penicillus* and *Udotea*,¹⁴⁶ has been reported.¹⁴⁷

5 Brown algae

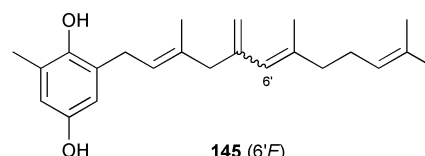
A wider range of compounds has been reported from brown algae in 2003 than in 2002, when terpenes and steroids were the predominantly reported compound classes. Six tetraprenyltoluquinols **139–144**, two triprenyltoluquinols **145** and **146** and two tetraprenyltoluquinones **147** and **148** were isolated from the brown alga *Cystoseira crinita* collected from the south coast of Sardinia. All compounds were tested for antioxidative properties in the α, α -diphenyl- β -picrylhydrazyl radical (DPPH) and thiobarbituric acid reactive substances (TBARS) assay systems. Compounds **139–146** exhibited potent radical-scavenging



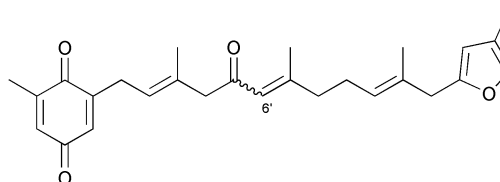
139 R₁ = H, R₂ = CH₂OH
 141 R₁ = OH, R₂ = Me
 143 R₁ = H, R₂ = Me



140 R₁ = H, R₂ = CH₂OH
 142 R₁ = OH, R₂ = Me
 144 R₁ = H, R₂ = Me

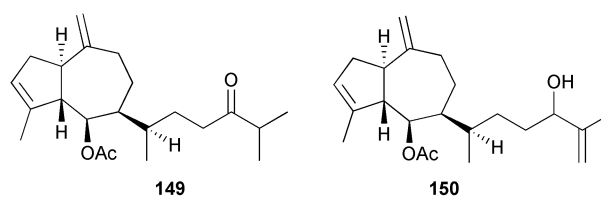


145 (6'E)
 146 (6'Z)



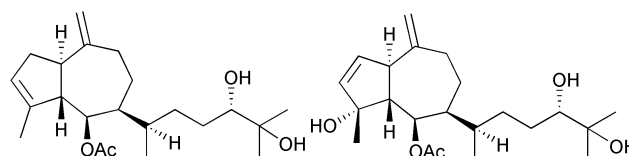
147 (6'E)
 148 (6'Z)

effects while **147** and **148** were significantly less active, but still comparable to that of butylated hydroxytoluene (BHT). The radical scavenging activity of compounds **142**, **144** and **148** was further assessed using the Trolox equivalent antioxidant capacity (TEAC) and photochemiluminescence (PCL) assays that confirmed the potent radical scavenging ability. Compounds **139** and **140** were moderately cytotoxic against several carcinoma cell lines.¹⁴⁸ Four hydroazulene diterpenes, dictyone acetate **149**, dictyol F monoacetate **150**, isodictytriol monoacetate **151** and cystoseirol monoacetate **152**, were isolated from the brown



149

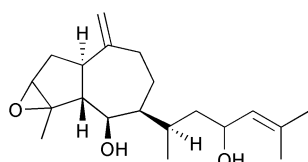
150



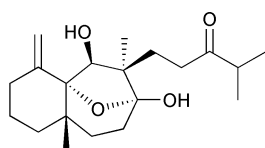
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152

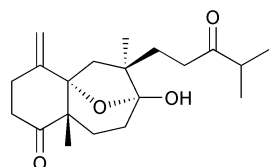
alga *Cystoseira myrica* collected in the Gulf of Suez. All four compounds exhibited moderate cytotoxicity against the murine cancer cell line KA3IT, but reduced cytotoxicity against normal NIH3T3 cells.¹⁴⁹ Dictyone acetate along with a pachydictyol A derivative **153** (incorrect structures shown in original reference) were also isolated from the brown alga *Dictyota dichotoma* collected from the Red Sea.¹⁵⁰ *D. dichotoma* from the Arabian Sea was the source of two seco-dolastanes dichotone **154** and dichotodione **155**,¹⁵¹ two dolastane diterpenoids, dichototetraol



153

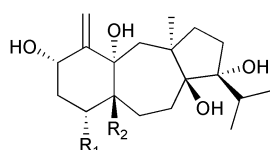
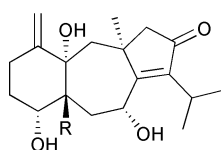


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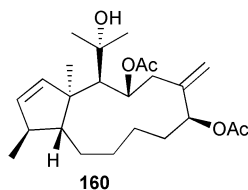
156 and dichopentaol **157**,¹⁵² and the related dichotenes A **158** and B **159**, two enone dolastane diterpenoids.¹⁵³ The

156 R₁ = H, R₂ = Me157 R₁ = OH, R₂ = CH₂OH

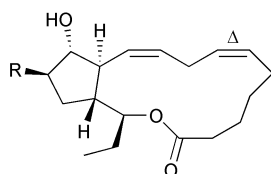
158 R = Me

159 R = OAc

configurations of **154** and **155** were determined by comparison of spectral data against those of known compounds. The new diterpene dictyocrenulol **160** was isolated from the brown alga *Dictyota crenulata* collected from Easter Island.¹⁵⁴ *Eisenia bicyclis* collected at Johgashima Island, Japan, was the source of nine novel oxylipin compounds **161–169**.¹⁵⁵ Five of these,



160

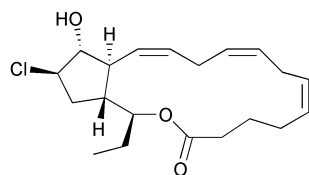


161 R = Cl

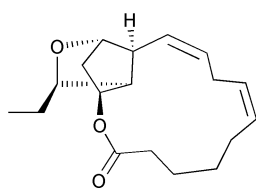
162 R = Cl, Δ saturated

163 R = I,

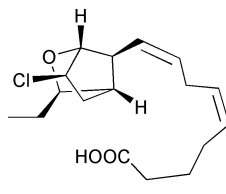
164 R = I, Δ saturated



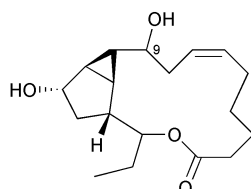
165



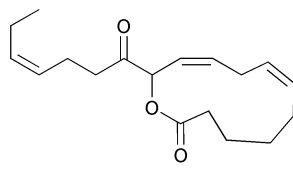
166



167

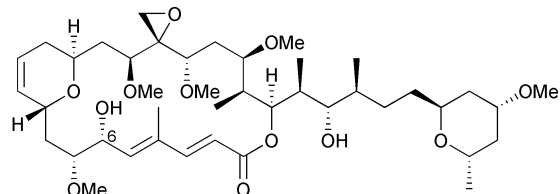


168



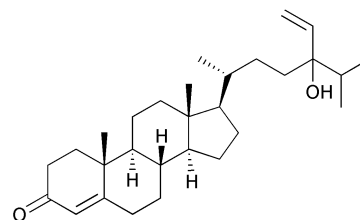
169

eiseniachlorides A–C **161–163** and eisenaiodides A **164** and B **165**, are ecklonialactone derivatives and two more, **166** and **167**, are cymathere type oxylipins. Stereochemistries of compounds **161–165** and **169** were elucidated by NMR analyses, but the relative stereochemistry at C-9 in **168** could not be determined unambiguously. Olefin geometry in **166** was ambiguous, but considered to be (*Z*) on biosynthetic grounds, and at least one olefin in compound **167** was (*Z*). A 22-membered cyclic lactone, lobophorolide **170**, was isolated from the common brown

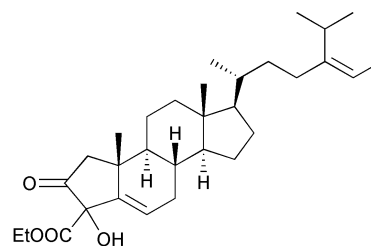


170

alga *Lobophora variegata*, collected at several reef locations in the Bahamas and from the Red Sea. The structure was elucidated by spectral data analysis and comparison against data published for tolytoxin¹⁵⁶ and swinholid A.^{157,158} It is proposed that lobophorolide and tolytoxin share the same relative configuration at all stereogenic centres in the macrolide portion of the molecule, while a (*6R*) configuration is suggested for both compounds rather than the (*6S*) configuration proposed previously for tolytoxin.¹⁵⁶ The absolute configuration of lobophorolide is proposed to be the same as that of tolytoxin based on optical rotation. Lobophorolide **170** displayed potent and highly specific activity against the marine filamentous fungi *Dendryphiella salina* and *Lindra thalassiae* in addition to potent activity against *C. albicans* and antineoplastic activity against the HCT-116 cell line.¹⁵⁹ The brown alga *Sargassum asperfolium*, collected in the Suez Gulf, was the source of the steroidal metabolite saringosterone **171**,¹⁶⁰ while a novel steroid **172** has

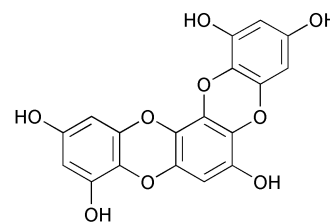


171



172

been isolated from the brown alga *S. carpophyllum* from the South China Sea.¹⁶¹ *Ecklonia stolonifera* collected from S. Korea yielded a new phlorotannin, eckstolonol **173**, which possessed



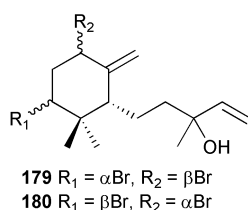
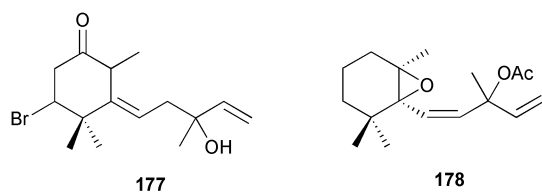
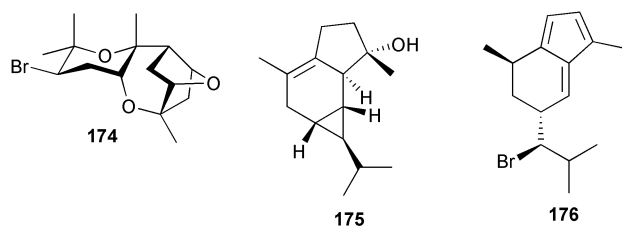
173

potent DPPH radical scavenging activity.¹⁶² Dolabellane **1**, originally isolated from the opisthobranch mollusc *Dolabella*

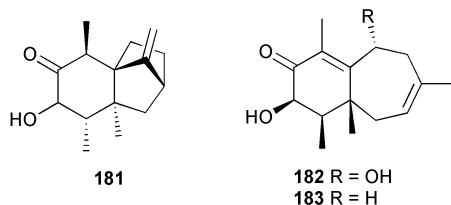
californica,¹⁶³ has been characterised as the major secondary metabolite and active chemical defense agent against herbivores (sea urchins and fish) in the brown alga *Dictyota pfaffi*.¹⁶⁴ (\pm)-Hedaol B, a bisnorditerpene isolated from the Japanese brown alga *Sargassum* sp.,¹⁶⁵ has been synthesised with geranyl acetone as a starting material and alkylation of silyl cyanide as the key step in the synthesis.¹⁶⁶

6 Red algae

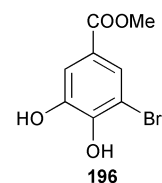
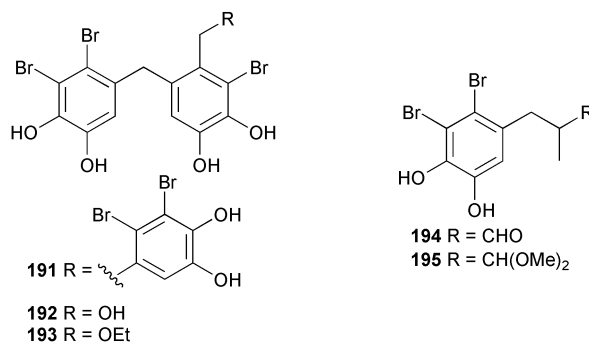
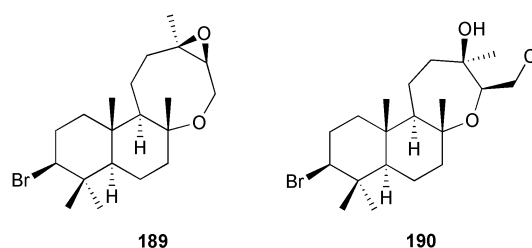
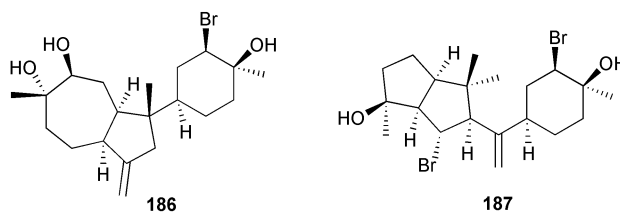
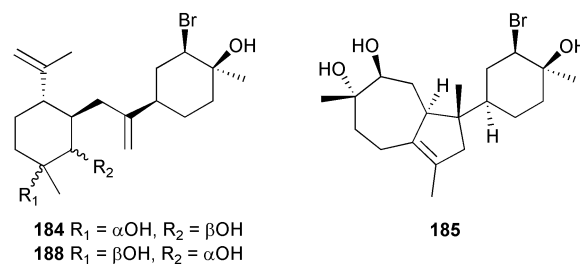
The genus *Laurencia* continues to be a prolific source of new metabolites. A brominated bisabolene derivative, aldingenin A **174**, was isolated from *Laurencia aldingensis* collected from Brazil. Biogenetic considerations were of value in the structural assignment.¹⁶⁷ From *L. microcladia* from Elba Island, a calenzanane sesquiterpene, debromoisocalenzanol **175** and an indene-type sesquiterpene **176** were isolated,¹⁶⁸ while four new sesquiterpenes, **177–180** including the snyderol derivatives **179**



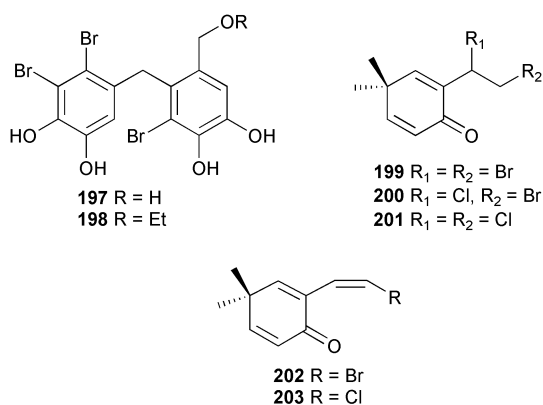
and **180**, have been isolated from *L. obtusa* collected from Bademli, Turkey. Compound **179** was active against D6 and W2 clones of the malaria parasite *Plasmodium falciparum*.¹⁶⁹ *Laurencia perforata*, collected from the Great Barrier Reef, Australia, was the source of the sesquiterpenes 4-hydroxy-1,8-*epi*-isotenerone **181** and two 3-*epi*-perforenone A derivatives, **182** and **183**.¹⁷⁰ A collection of *L. obtusa* from Greece yielded



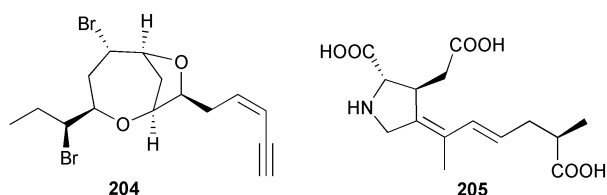
four new brominated diterpenes,¹⁷¹ prevezols C–E **184–186**, and neorgioldiol B **187**, together with the known prevezol B **188**, whose structure has been revised from that reported originally.¹⁷² Prevezol B and neorgioldiol displayed significant cytotoxicity against the human tumour cell lines MCF7, PC3, HeLa, A431 and K562 while prevezol C only exhibited significant cytotoxicity against HeLa and A431 cell lines. Prevezol D was moderately active against all cell lines.¹⁷¹ Two labdane type brominated diterpenes **189** and **190** have been isolated from *L. obtusa* from Greece. These structures contain unprecedented eight- and seven-membered ether rings respectively.¹⁷³ Six new bromophenols, **191–196** were isolated from *Rhodomela*



confervoides collected from the coast of Qingdao, China.¹⁷⁴ Compounds **193** and **195** may be artifacts of the extraction and isolation processes.¹⁷⁴ Compounds **194** and **195** were also reported in another paper by the same authors, along with the isolation of the known 3-bromo-4,5-dihydroxybenzoic acid methyl ester (but new as a natural product) from the same source (*R. confervoides*).¹⁷⁵ This benzoyl ester has previously been synthesised¹⁷⁶ but the spectral data were not reported. *R. confervoides* from Qingdao was also the source of bromophenols, **197** and **198**. The phenol **198**, which might also be derived from **197** during isolation,¹⁷⁷ exhibited moderate activity against five strains of bacteria.¹⁷⁸ Five monoterpenes **199–203** of the octadane class have been isolated from the red alga *Portieria hornemanni* (source not given).¹⁷⁹ The marine polyether triterpenoid dehydrothysiferol, originally isolated from the red alga *Laurencia pinnatifida*,¹⁸⁰ was shown to induce apoptosis in estrogen-dependent and independent breast cancer cells.¹⁸¹ Elatol, a halogenated sesquiterpene alcohol from the red alga *L. elata*¹⁸² inhibited six species of human pathogenic bacteria, with significant antibacterial activities against *Staphylococcus epidermidis*, *Klebsiella pneumonia* and *Salmonella* sp.¹⁸³ Iso-obtusol from the red alga *Laurencia obtusa*^{184,185} exhibited antibacterial activity against four bacterial species with significant activity

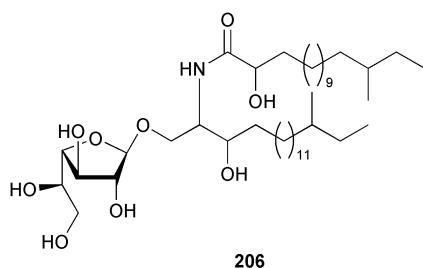


against *K. pneumonia* and *Salmonella* sp. Further tests indicated that both compounds were bacteriostatic rather than bacteriocidal against the bacteria tested.¹⁸³ Glutathione transferase specific activity in *Katharina tunicata* (black chiton) was shown to be affected by the brominated phenol lanosol,¹⁸⁶ which is prevalent among filamentous red algae of the Rhodomelaceae, and frequently consumed by *K. tunicata*.¹⁸⁷ The first asymmetric total syntheses of (+)-3-(*E*)- and (+)-3-(*Z*)-pinnatifidenyne, originally isolated from *Laurencia pinnatifida*,^{188,189} have been reported and utilise an “olefin geometry-dependent” internal alkylation to give excellent stereoselectivity.¹⁹⁰ The seven-membered ring ether (+)-neoisoprelaufucin **204**, originally isolated from *L. nipponica*,¹⁹¹ has also been synthesised, allowing the assignment of the absolute stereochemistry of the natural product.¹⁹² A nickel-catalysed coupling reaction of an alkynyl enone and an alkenylzirconium were the key steps in the synthesis of isodomoic acid **205**, originally isolated from the red alga *Chondria armata* from Kyushu Island.¹⁹³ The sidechain stereochemistry was established as (5*R*) by comparison of CD spectra of the natural and synthetic products.¹⁹⁴

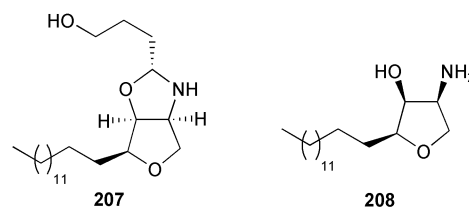


7 Sponges

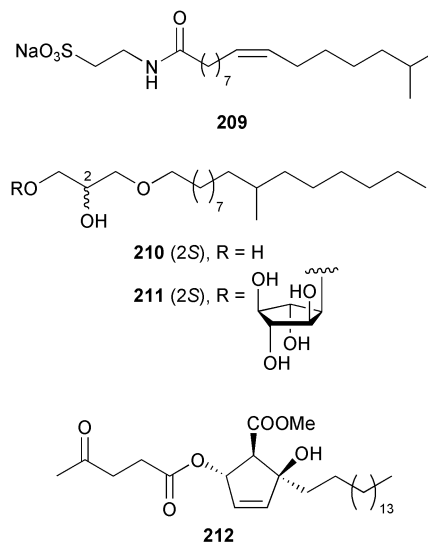
Sponges continue to be an important source of novel secondary metabolites and a notable growing trend is the characterisation of compounds from bacteria and fungi that have been isolated from sponges. Such compounds have been included in Section 3 of this review. There has also been increased interest in fatty acid derivatives, many of which have biological activities. An unusual galactofuranosylceramide, ectyoceramide **206**, was



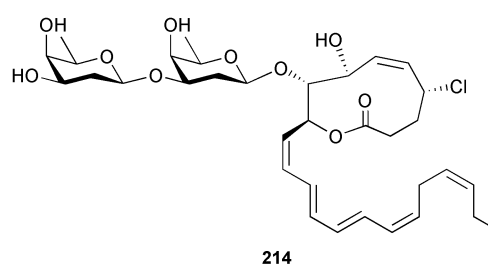
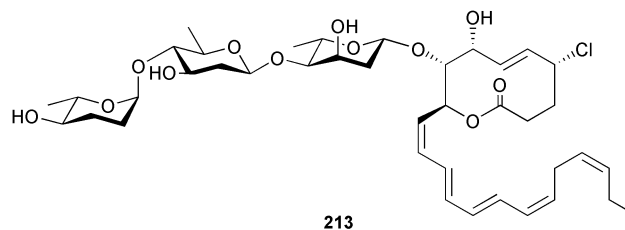
isolated from the Bahaman sponge *Ectyoplasia ferox*,¹⁹⁵ while a *Jaspis* species collected in Vanuatu was found to contain the cytotoxic sphingosine derivatives jaspines A **207** and B **208**.¹⁹⁶



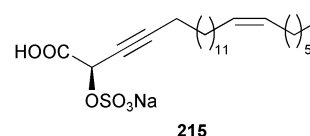
The Korean sponge *Erylus nobilis* was the source of the taurine derivative **209**.¹⁹⁷ Another Korean sponge, a *Stelletta* species, has yielded two cytotoxic compounds, glycerol ether **210**¹⁹⁸ and cyclitol derivative norsarcotride A **211**.¹⁹⁹ Plakevulin A **212**,



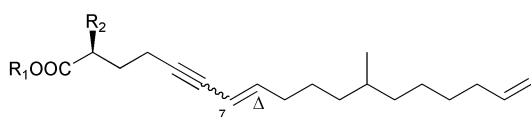
found to inhibit DNA polymerases α and γ , was isolated from the Okinawan sponge *Plakortis* sp.²⁰⁰ *Latrunculia corticata*, collected in the Gulf of Aqaba, Israel, was found to contain decalactone glycosides latrunculinoside A **213** and B **214**, which have anti-



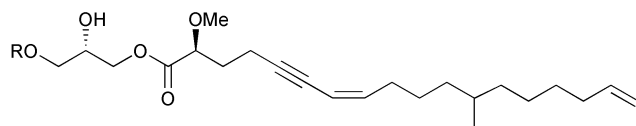
feedant activity against goldfish.²⁰¹ An inhibitor of membrane type 1 matrix metalloproteinase (MT1-MMP), callysponginal sulfate **215**, was isolated from *Callyspongia truncata* collected



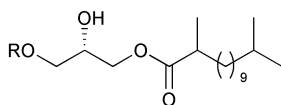
in Japan.²⁰² An undescribed Korean species of *Stelletta* was found to contain cytotoxic acetylenic acids: stellettic acid A **216**, (*Z*)- and (*E*)-stellettic acid B **217** and **218**, and stellettic



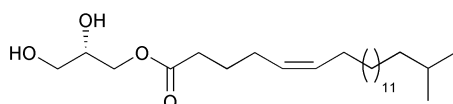
- 216** R₁ = H, R₂ = OMe, Δ saturated
217 R₁ = H, R₂ = OMe, (7Z)
218 R₁ = H, R₂ = OMe, (7E)
219 R₁ = R₂ = H, (7Z)
226 R₁ = dimeric anhydride, R₂ = OMe, Δ saturated
227 R₁ = R₂ = H, Δ saturated



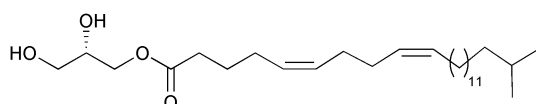
- 220** R = PO₃⁻CH₂CH₂N⁺Me₃
221 R = H



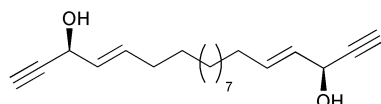
- 222** R = PO₃⁻CH₂CH₂N⁺Me₃
223 R = H



224

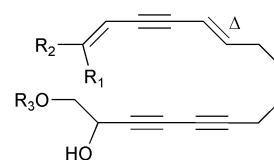


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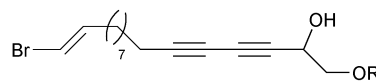


228

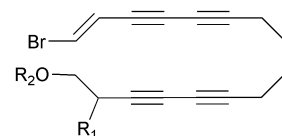
acid **C 219** that exhibited marginal to moderate toxicity to five human tumour cell lines.²⁰³ Interestingly, the same sponge also yielded the glycerol derivatives of **217**, the mildly cytotoxic **220** and **221** (inactive), along with other lysophosphatidylcholines and monoglycerides **222–225**.²⁰⁴ From a seemingly identical *Stelletta* species, collected at a different Korean location, a similar series of acetylenic acids was isolated including **216**, a dimeric anhydride **226** and a desmethoxy analogue **227**; all were mildly cytotoxic to human leukemia cells.²⁰⁵ The Indonesian sponge *Callyspongia pseudoreticulata* yielded the diyne **228**, which was found to be toxic in the brine shrimp assay.²⁰⁶ A *Diplastrella* species, collected in the Philippines, yielded a series of polyacetylenic diols, the diptynes A–E **229–233** and corresponding sulfates **234–236**.²⁰⁷ Three new chlorinated polyacetylenes **237–239** were isolated from the Californian sponge *Haliclona lunisimilis*²⁰⁸ along with known compounds originally isolated from the *Haliclona*'s nudibranch predator, *Di-aulula sandiegensis*.²⁰⁹ The moderately cytotoxic polyacetylenic amide, callyspongamide A **240**, was obtained from *Callyspongia fistularis* collected in the Red Sea.²¹⁰ Three new amides, **241–243**, along with the previously reported clathrynamide A **244**,²¹¹ were isolated from an Okinawan *Psammodemna* species.²¹² The stereochemistry of **244** was determined (Mosher method). All four compounds were found to be antifungal. The absolute stereochemistry of the amino alcohol xestoaminol C, originally isolated from a Fijian *Xestospongia* species,²¹³ has been established as (2*S*,3*R*) by the synthesis of the *N,O*-diacetyl derivative from (*S*)-alanine.²¹⁴ A racemic synthesis of 2-methoxy-13-methyltetradecanoic acid, isolated from a



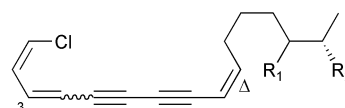
- 229** R₁ = R₃ = H, R₂ = Br, Δ saturated
230 R₁ = Br, R₂ = R₃ = H, Δ saturated
233 R₁ = R₃ = H, R₂ = Br
234 R₁ = H, R₂ = Br, R₃ = SO₃H, Δ saturated



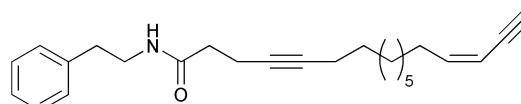
- 231** R = H
235 R = SO₃H



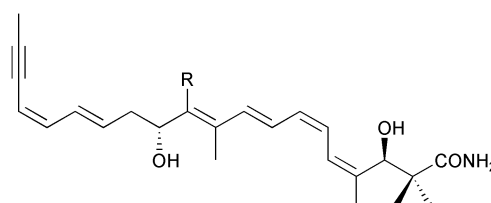
- 232** R₁ = OH, R₂ = H
236 R₁ = H, R₂ = SO₃H



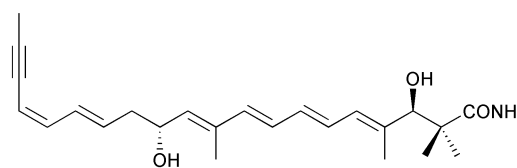
- 237** R₁ = OH, R₂ = H, (3*Z*), Δ saturated
238 R₁ = H, R₂ = OAc, (3*E*)
239 R₁ = OAc, R₂ = H, (3*E*), Δ saturated



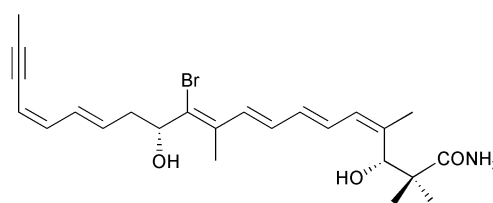
240



- 241** R = H
244 R = Br



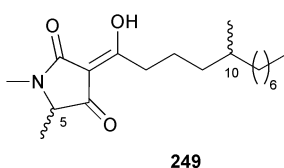
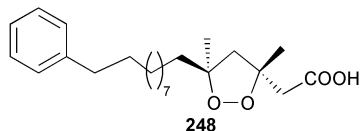
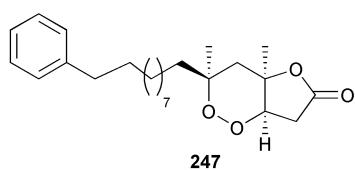
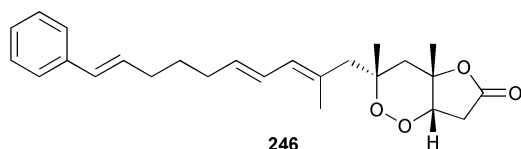
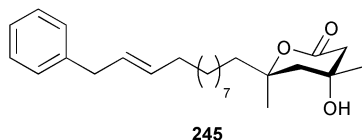
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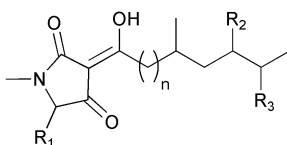
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Puerto Rican specimen of *Amphimedon complanata*,²¹⁵ has been reported.²¹⁶ (*R*)-Strongyloidiol B, originally isolated from a *Strongylophora* species,²¹⁷ was synthesised enantioselectively using a Zn(II) acetylide addition to an aldehyde.²¹⁸ Callyberynes A and B, also known as callypentaynes, obtained from Japanese specimens of *Callyspongia truncata*²¹⁹ and *Callyspongia* sp.,²²⁰

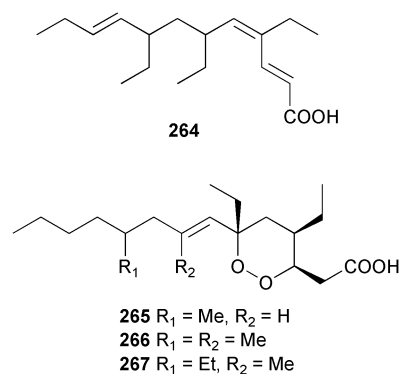
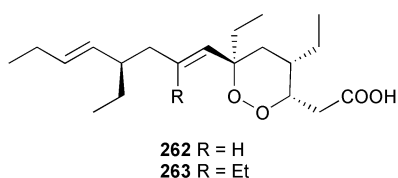
were synthesised using sequential Cadiot–Chodkiewicz cross-coupling reactions.²²¹ *Erylus trisphaerus*, collected in Dominica, was found to contain the mildly cytotoxic polyketide lactone, trisphaerolide A **245**.²²² A Madagascar specimen of *Plakortis* aff. *simplex* yielded three cyclic peroxides, the plakortolides H **246** and I **247** and andavadoic acid **248**, all of which were cytotoxic against a range of human tumour cell lines.²²³ The antimicrobial tetramic acid, melophlin C **249**, from an



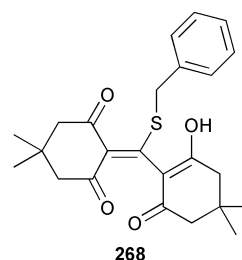
Indonesian specimen of *Melophlus sarassinorum*, was isolated as an inseparable mixture of four stereoisomers arising from the stereogenic centres at C-5 and C-10 (as evidenced by NMR and modified Marfey's method). A further twelve, less active tetramic acids, melophlins D–O **250–261**, were also isolated from the same sponge.²²⁴ Both plakortides M **262** and N **263**, isolated from a collection of *Plakortis halichondrioides* from Puerto Rico,



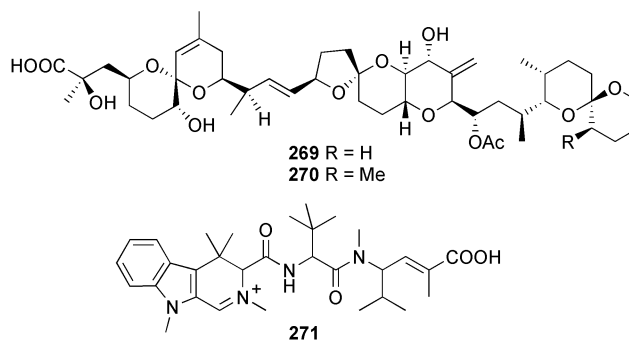
- 250** R₁ = R₂ = R₃ = H, n = 11
251 R₁ = R₂ = H, R₃ = Me, n = 11
252 R₁ = R₃ = H, R₂ = Me, n = 11
253 R₁ = R₂ = R₃ = H, n = 10
254 R₁ = R₂ = H, R₃ = Me, n = 10
255 R₁ = R₃ = H, R₂ = Me, n = 10
256 R₁ = Me, R₂ = R₃ = H, n = 10
257 R₁ = R₂ = H, R₃ = Me, n = 9
258 R₁ = Me, R₂ = R₃ = H, n = 9
259 R₁ = Me, R₂ = R₃ = H, n = 8
260 R₁ = R₃ = Me, R₂ = H, n = 8
261 R₁ = R₃ = H, R₂ = Me, n = 8

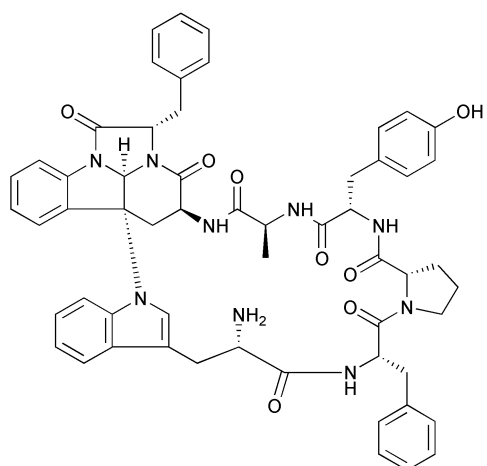


exhibited potent cytotoxicity to an array of human tumour cell lines.²²⁵ A Japanese specimen of *Monotria japonica* yielded the monotriajaponides A–D **264–267** which can lyse starfish oocytes without disruption of nuclear structure.²²⁶ Interestingly, the absolute stereochemistries of **265–267**, as determined by reduction and a modified Mosher method, were opposite to those determined for the plakortides **262** and **263**. The asymmetric synthesis of (+)-rottnebstol, originally isolated from a *Haliclona* species,²²⁷ using a Stille coupling firmly established the absolute stereochemistry as (12*R*). Similarly, syntheses of (+)-raspailol A and (+)-raspailol B, originally obtained from a *Raspailia* species,²²⁸ have established a (12*R*) configuration for these two metabolites also.²²⁹ An unusual bis-dimmedone thioether with strong UV A and B absorption, benzylthiocrellidone **268**, was isolated from a Great Barrier Reef collection

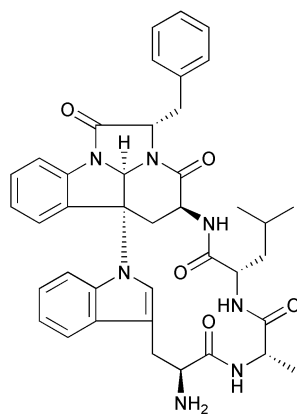


of *Crella spinulata*; the structure was reported in 2002,²³⁰ but was omitted from the 2002 review.²³¹ Okadaic acid, originally isolated from *Halichondria okadae*,²³² and subsequently found to be a dinoflagellate and shellfish toxin,^{233,234} has been investigated for potential as a defense molecule for the Adriatic sponge *Suberites domuncula*. Use of an ELISA assay established that okadaic acid was localised in the epithelium of the lacunae and water channels of the sponge, as well as in bacteria located in the sponge tissue. It was postulated that okadaic acid acts as a stimulant of the sponge immune system to the presence of bacteria, but in higher concentrations causes apoptosis.²³⁵ Two analogues of okadaic acid, 27-*O*-acetylokadaic acid **269** and 27-*O*-acetyldinophysistoxin 1 **270**, were isolated from a British Columbian sponge *Merriamum oxeato* and found to be potent G2 checkpoint inhibitors and highly cytotoxic.²³⁶ A Papua New Guinean sponge, *Cymbastela* sp., was found to contain the cytotoxic peptide milnamide D **271** along with the related peptides hemiamsterlin²³⁷ and milnamide A.²³⁸ All three

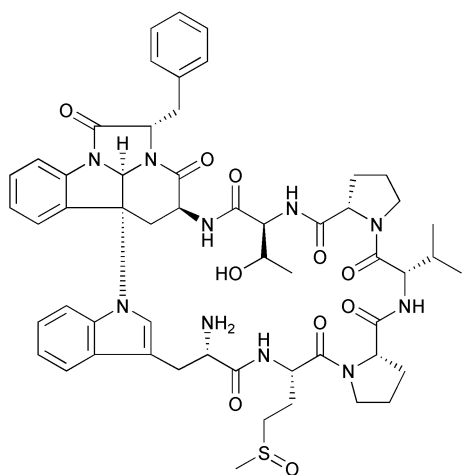




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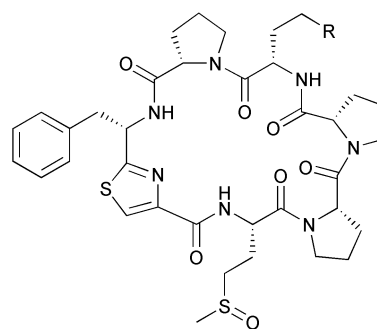


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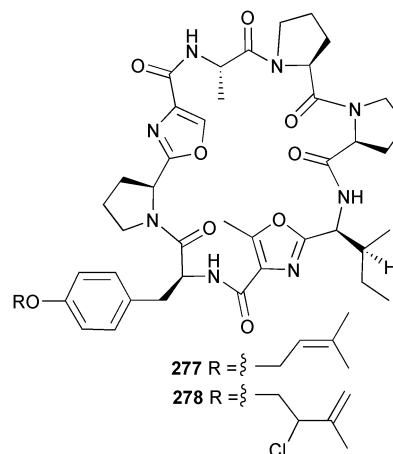


274

compounds were inhibitors of tubulin polymerisation.²³⁹ Three unusual new cyclic peptides, the kapakahines E–G **272–274**, have been isolated from a Micronesian collection of *Cribrochalina olemda* and reported as cytotoxic to P388 murine leukemia cells.²⁴⁰ The previously described sulfoxide, waiakeamide **275**, and a new sulfone analogue **276** were isolated from a *Haliclona* sp. collected in Palau. The sulfone **276** was found to inhibit the settlement of larvae of the blue mussel (*Mytilus edulis galloprovincialis*).²⁴¹ The myriastramides A–C **277–279** were isolated from the same Philippine collection of *Myriastria clavosa* that had previously yielded the clavoside macrolides.^{242,243} Leucamide A, originally isolated from the Australian sponge *Leucetta microraphis*,²⁴⁴ has been synthesised.²⁴⁵ Due to differences in biological activity, the *cis,cis*- **280** and reputed *trans,trans*- **281** isomers of ceratospongamide, originally isolated from the Indonesian symbiotic pairing of the red alga *Ceratodictyon*

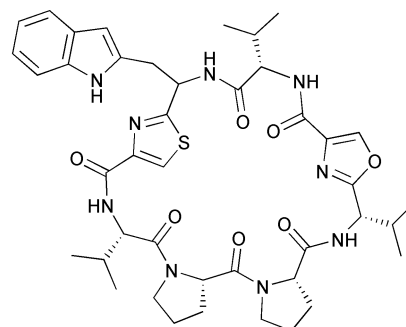


275 R = (SO)Me

276 R = (SO₂)Me

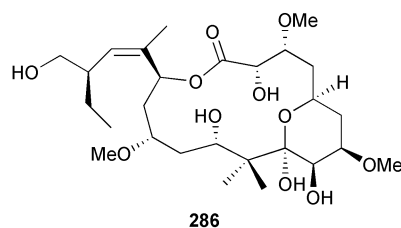
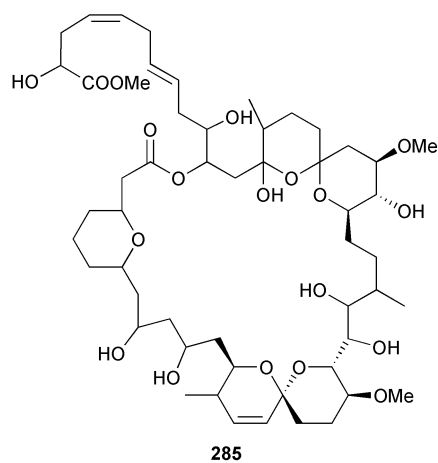
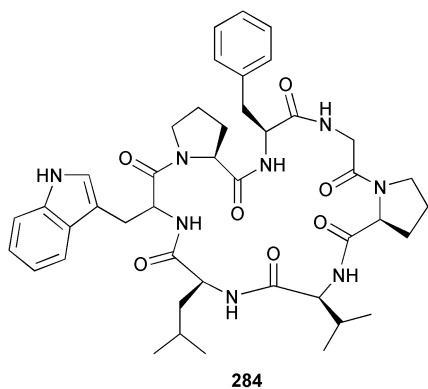
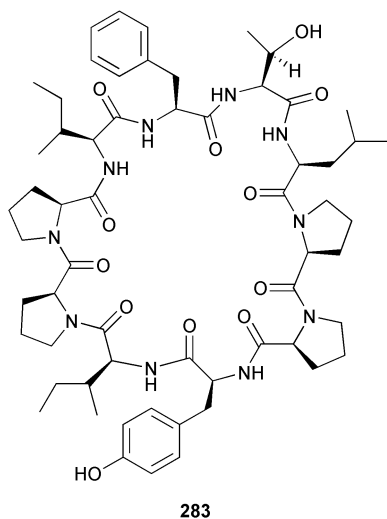
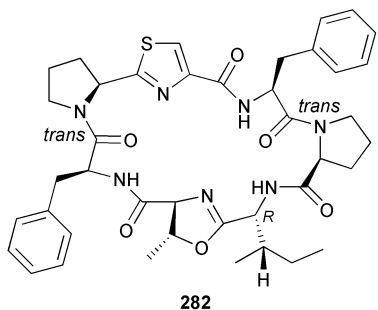
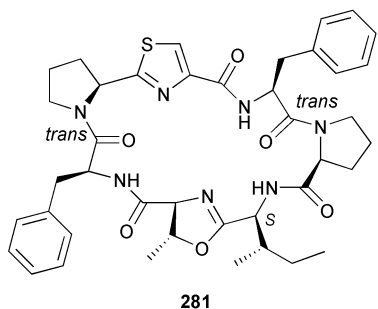
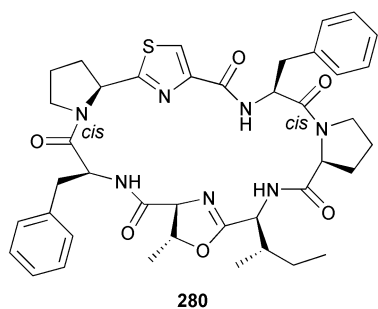
277 R =

278 R =

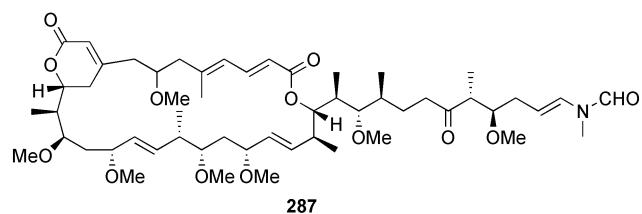


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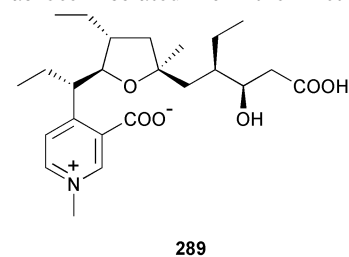
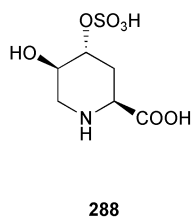
spongiosum and the sponge *Sigmadocia symbiotica*,²⁴⁶ continue to attract considerable attention from synthetic chemists. Although both rotamers had been synthesised previously,²⁴⁷ slight differences in the NMR spectra of the synthetic *trans,trans* isomer **281** and the isolated natural product were noted. Suspecting a possible epimerisation the *trans,trans*-[D-*allo*-Ile] isomer, **282** was synthesised, by two separate routes, to produce a compound that is identical in all respects to the natural isomerisation product.²⁴⁸ Phakellistatins 1²⁴⁹ and 10,²⁵⁰ have been synthesised.²⁵¹ Phakellistatin 1 was found to exist as the all-*cis* rotamer at the proline residues, while phakellistatin 10 was determined to be all-*trans*. Interestingly, both synthetic products were more than 100-fold less cytotoxic than the natural product.²⁵¹ A large (500 kg) collection of a *Phakellia* species from Chuuk, Micronesia, yielded the growth inhibitory phakellistatin 12 **283**,²⁵² while a Chinese collection of *Phakellia fusca* yielded the very cytotoxic phakellistatin 13 **284**.²⁵³ The macrolide spirastrellolide A was isolated as its methyl ester **285** from the Caribbean sponge *Spirastrella coccinea*. Unlike many other sponge-derived antimitotic macrolides, **285** does not effect tubulin polymerisation.²⁵⁴ An asymmetric synthesis of (–)-peloruside A, the antipode of the natural product **286** originally isolated from the New Zealand sponge *Mycale hentscheli*,²⁵⁵ has been achieved *via* a Mitsunobu-type lactonisation.²⁵⁶ The

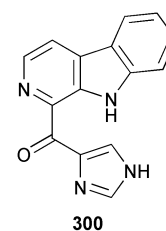
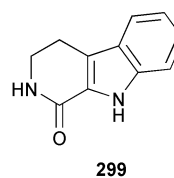
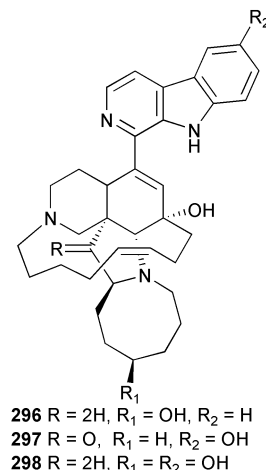
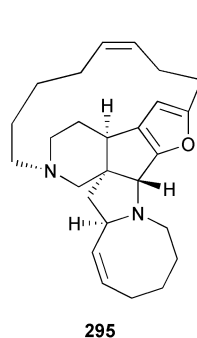
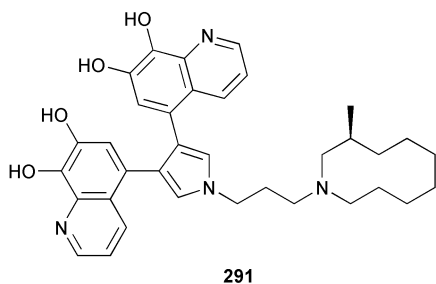
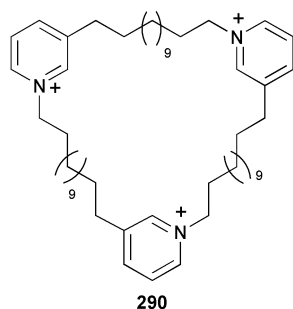


synthetic antipode proved to be biologically inactive in cytotoxicity assays, but established the absolute stereochemistry of the natural (+)-enantiomer **286** as drawn. The relative and absolute stereochemistries of the C23–C35 portion of reidispongiolide A **287**, isolated from the New Caledonian sponge *Reidispongia*

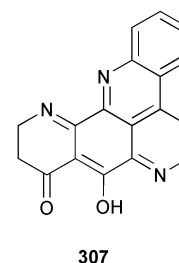
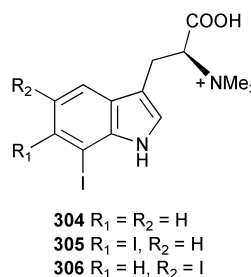
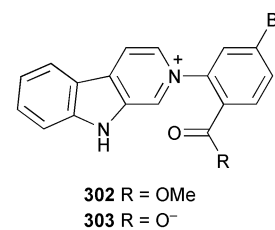
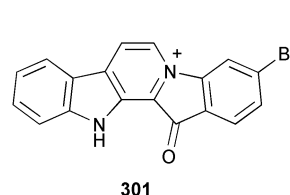
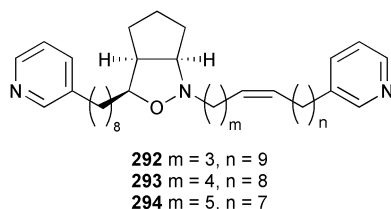


coerulea,²⁵⁷ have been established by synthesis of an ozonolysis fragment of the natural product.²⁵⁸ The total synthesis of (+)-13-deoxytedanolide, originally isolated from the Japanese sponge *Mycale adherens*,²⁵⁹ has been accomplished.²⁶⁰ The natural enantiomer of lasonolide A, isolated from a Caribbean *Forcepia* species,²⁶¹ has also been synthesised and found to be bioactive.²⁶² The hexabromobiphenylether from *Dysidea herbacea*²⁶³ has been synthesized and found to be a potent aldose reductase (ALR2) inhibitor.²⁶⁴ The Micronesian sponge *Cribrochalina olemda* was found to contain a new *N*-methyl-D-aspartate (NMDA) receptor ligand, cribronic acid **288**, which has potent convulsant activity in mice.²⁶⁵ The known antioxidant amino acid L-5-hydroxytryptophan was found to be a major constituent of the NW Atlantic intertidal sponge *Hymeniacidon heliophila* and was observed to suppress apoptosis in human lymphocytes at concentrations similar to those found in the sponge tissue. Since UV light induces apoptosis, it is proposed that the high concentrations of L-5-hydroxytryptophan act to protect this sponge species from sunlight UV damage.²⁶⁶ The pyridinium alkaloid simplakidine A **289** was isolated from the Caribbean sponge *Plakortis simplex*.²⁶⁷ The rather remarkable tris-pyridinium alkaloid viscosamine **290** has been isolated from the Arctic



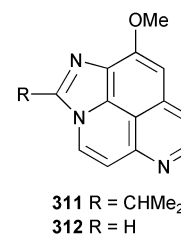
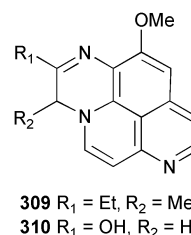
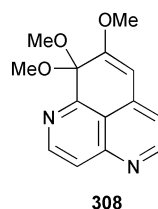


sponge *Haliclona viscosa*. The trimeric nature of this alkaloid was deduced from a series of ions in the mass spectrum.²⁶⁸ Halitulins **291**, isolated from a South African collection of *Haliclona tulearensis*,²⁶⁹ has been synthesised, establishing C-15 as (*S*).²⁷⁰ Clathryimine, originally isolated from *Clathria basilana*,²⁷¹ has been synthesised using palladium-catalyzed cross-coupling reactions.²⁷² Hachijodines F and G, isolated originally from *Xestospongia* and *Amphimedon* species,²⁷³ have been synthesised. The *N*-oxide moieties were introduced using modified Mukiyama conditions.²⁷⁴ Pyrinodemin A **292**, isolated from a Okinawan collection of an *Amphimedon* species,²⁷⁵ continues to attract considerable attention from synthetic organic chemists.²³¹ The position of the *cis* double bond has been contentious, with the originally published structure **292** being modified to **293**²⁷⁶ and **294**²⁷⁷ respectively. The structure **294**

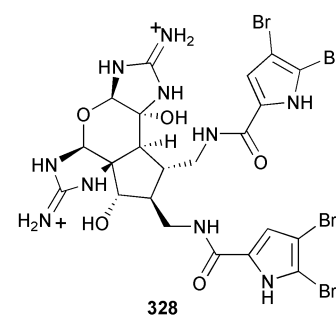
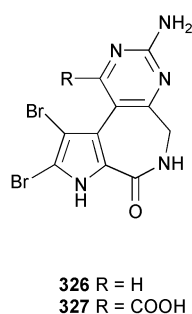
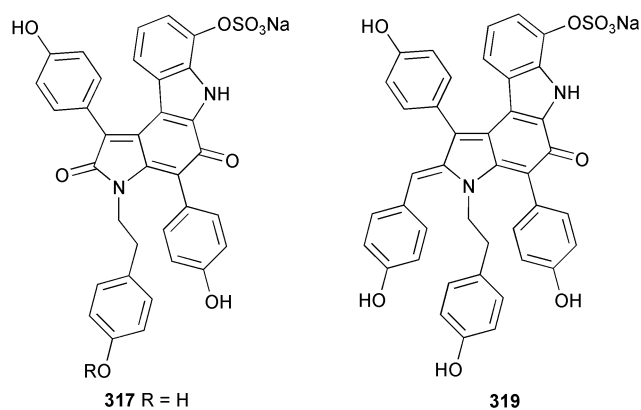
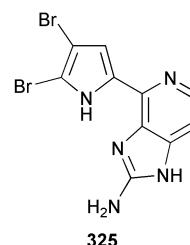
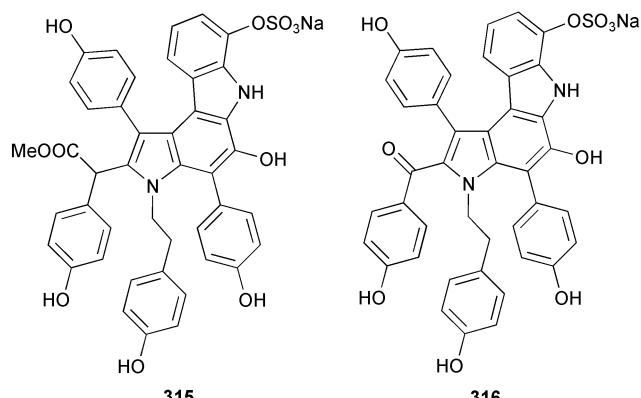
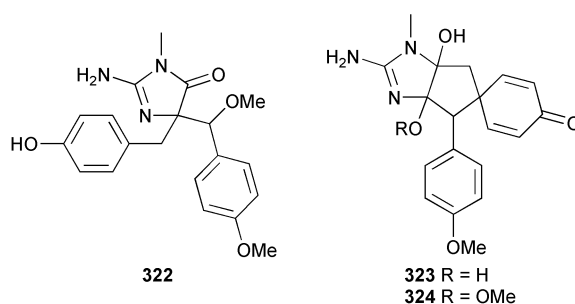
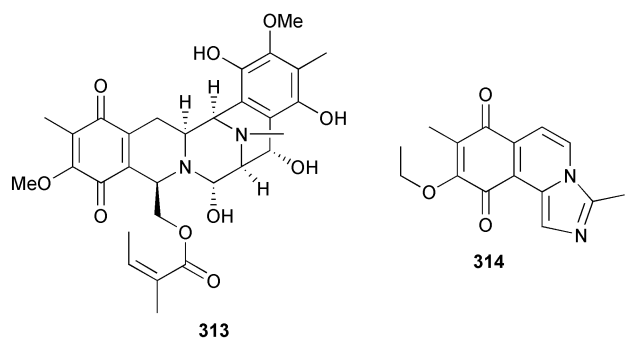


has now been synthesised asymmetrically by two independent groups establishing the absolute stereochemistry of the bicyclic core.^{278,279} One group was also able to compare the spectral data to the original spectra of the natural product and confirm the structure as **294**.²⁷⁸ Petosin and petosin A, originally isolated from *Petrosia seriata*,^{280,281} were found to inhibit HIV-1 replication and HIV-1 reverse transcriptase.²⁸² The total synthesis of the (+)-antipode of nakadomarin A **295**, originally isolated from an *Amphimedon* species,²⁸³ has established the absolute stereochemistry of the (–)-natural enantiomer as (*RRRR*).²⁸⁴ Three new manzamine alkaloids **296–298**, the related harman-1-one **299**, and des-*N*-methylxestomanzamine A **300** were isolated from an Indonesian sponge.²⁸⁵ Three β-carbolines, 3-bromofascaplysin **301**, 14-bromoreticulatine **302** and 14-bromoreticulatate **303**, have been reported as metabolites of *Fascaplysinopsis reticulata* from Indonesia and Fiji. 3-Bromofascaplysin was also reported as a metabolite of the tunicate *Didemnum* sp.²⁸⁶ Three iodine-containing indole alkaloids, plakohypaphorines A–C **304–306**, were also obtained from the same Caribbean *Plakortis simplex* collection that yielded simplakidine (*vide supra*). This is the first report of naturally occurring iodindole alkaloids.²⁸⁷ Damirones A and B²⁸⁸ have been prepared from the corresponding makaluvamines by alkaline hydrolysis, suggesting that

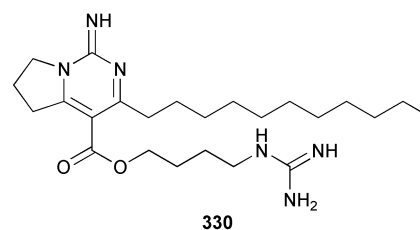
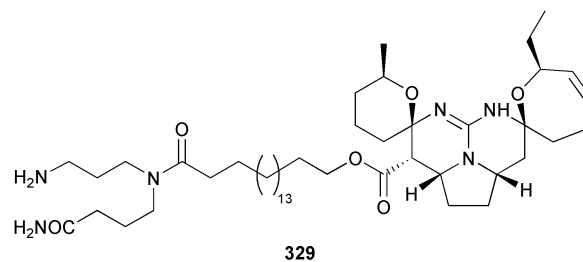
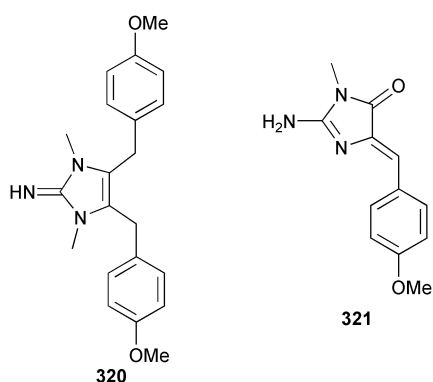
the damirones may be artifacts of isolation and not naturally-occurring compounds.²⁸⁹ The Indonesian sponge *Biemna fortis* yielded the pyridoacridine alkaloid labuanine **307**, which along with two related synthetic pyridoacridine alkaloids and the previously isolated biemnadin,²⁹⁰ were found to be inducers of neuronal differentiation.²⁹¹ Several new antimicrobial aaptamine type alkaloids **308–312** were isolated from an Indonesian



Xestospongia species,²⁹² while from a Japanese *Neopetrosia* sp. a further tetrahydroisoquinoline alkaloid, renieramycin J **313**, was reported.²⁹³ The dark blue, cytostatic and antimicrobial metabolite, cribrostatin 6 **314**, was isolated from a species of *Cribrochalina* from the Maldives.²⁹⁴ The dictyodendrins A–E **315–319**, isolated from the Japanese sponge *Dictyodendrilla verongiformis* were found to inhibit telomerase activity.²⁹⁵

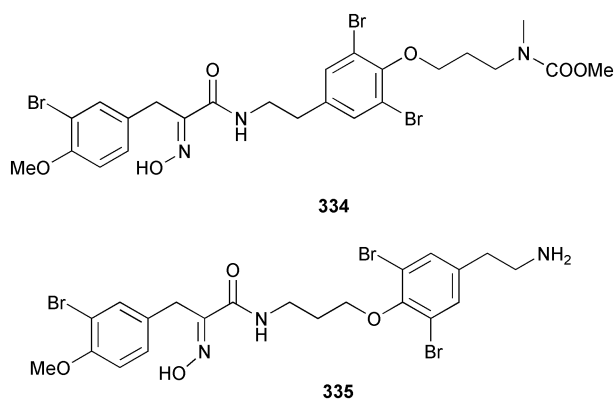
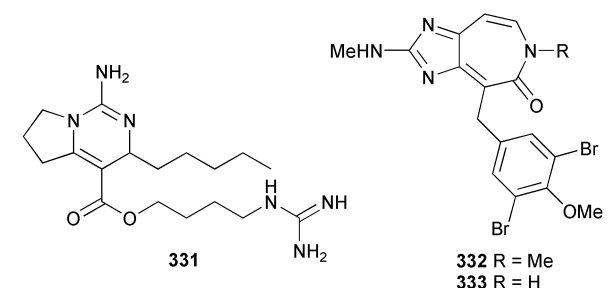


Japanese *Agelas nakamuri* collection.³⁰⁴ Oroidin-type alkaloids with novel skeletons, the latonduines A **326** and B **327**, were obtained from an Indonesian *Stylissa carteri* collection.³⁰⁵ A *Stylissa* aff. *massa*, obtained from Japanese waters, was found to contain a geranylgeranyltransferase type I inhibitor, massadine **328**.³⁰⁶ Crambescidin 826 **329**, isolated from a *Monanchora* sp. collected in Palau, was found to be a potent inhibitor of HIV-1 envelope-mediated fusion, along with the known compounds crambescidin 800³⁰⁷ and fromiamycalin,³⁰⁸ while dehydrocrambine A **330**, also isolated from this sponge, was

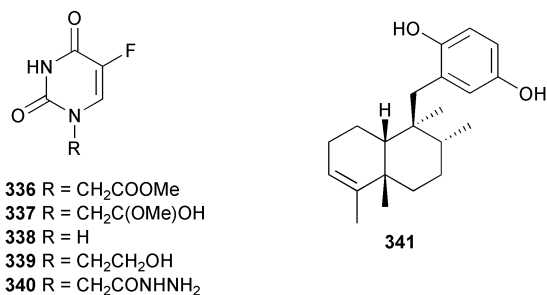


Phloeodictine A1, originally isolated from a New Caledonian sponge of the genus *Phloeodictyon*,²⁹⁶ has been synthesised.²⁹⁷ *N,N*-Dimethylamine D **320** and leucettamine C **321** are reported as new, mildly antimicrobial metabolites of two Fijian *Leucetta* species.²⁹⁸ The same research group has also isolated three further imidazole-containing alkaloids, calcaridine A **322** spirocalcaridine A **323** and spirocalcaridine C **324**, from one of the two *Leucetta* collections.²⁹⁹ Isonaamidines A and C, originally isolated from an Indo-Pacific *Leucetta* species,³⁰⁰ have been synthesised.³⁰¹ Sventrin, isolated from *Agelas sventes*,³⁰² has been synthesised by a Red-Al reduction of an alkyne.³⁰³ An MT1-MMP inhibitor, ageladine A **325**, was isolated from a

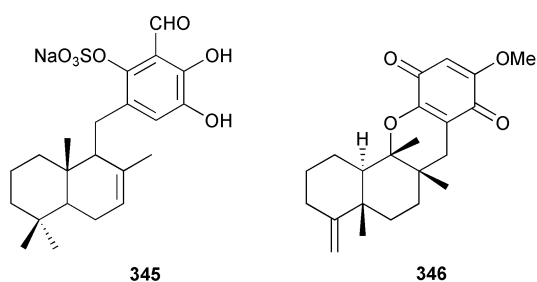
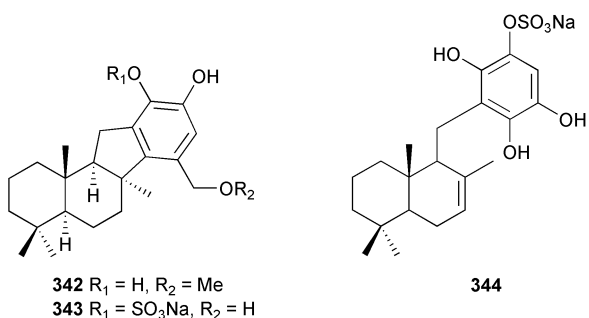
found to be a weak inhibitor only.³⁰⁹ A related antibacterial guanidine alkaloid, Sch 575948 **331**, was isolated from a *Ptilocalis spiculifer* (*Crambe crambe*) specimen.³¹⁰ Two antimitotic guanidine/bromotyrosine alkaloids, ceratamines A **332** and B **333**, were isolated from a Papua New Guinean *Pseudoceratina* sp.³¹¹ An Indian collection of *Psammaphysilla purpurea* was



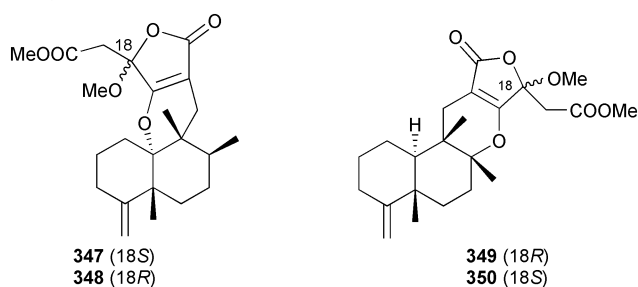
found to contain the antibacterial bromotyrosine-derived alkaloids purpuramine K **334** and L **335**.³¹² Aerothionin, originally isolated from *Verongia aerophoba*,³¹³ has been found to be active against drug-resistant strains of *Mycobacterium tuberculosis* and several other *Mycobacterium* sp.³¹⁴ A Chinese collection of the sponge *Phakellia fusca* yielded a remarkable series of fluorinated uracil derivatives **336–340**. The presence of fluorine was confirmed by X-ray diffraction and ¹⁹F NMR studies. This is the first report of fluorine-containing marine natural products.³¹⁵ Sponge-derived merosequiterpenoids continue to be a fruitful area of research for both natural product and synthetic chemists. Isoarenarol **341**, isolated from a Papua New



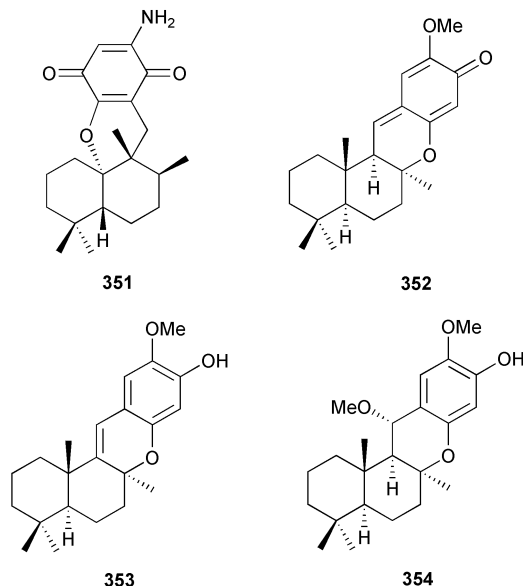
Guinean collection of *Dysidea arenaria*, was found to be a potent protein kinase inhibitor.³¹⁶ Spongiaquinone, isolated from *Stelospongia conulata*,³¹⁷ has been prepared in an asymmetric synthesis. The absolute stereochemistry was assigned based on comparison of the optical rotation of the synthetic methyl ether with that of the natural compound.³¹⁸ A Micronesian *Aka* species has yielded three new sesquiterpenoid quinols, akaol A **342**, **343**, and the tentatively assigned siphonodictyol I **344**.³¹⁹ Also isolated was siphonodictyal C **345**, originally



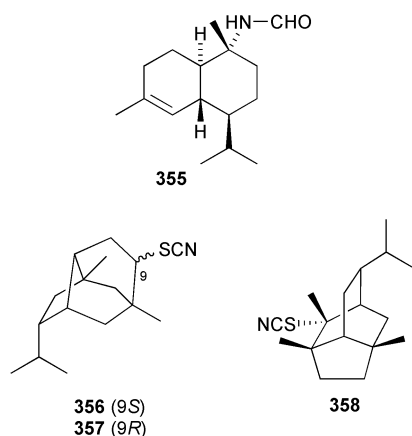
isolated from *Siphonodictyon coralliphagum*³²⁰ and previously described as a free phenol. However the sample isolated from the *Aka* sp. had identical NMR spectra and clearly shows the presence of SO₃Na by ESIMS.³¹⁹ The sulfate group is lost in EIMS, the technique used for characterisation in the original isolation procedure.³²⁰ Siphonodictyal C was a modest inhibitor of complexation in the CDK4/cyclin D1 assay.³²⁰ The moderately cytotoxic neodactyloquinone **346** and the dactyloactones A–D **347–350** were obtained from an Okinawan



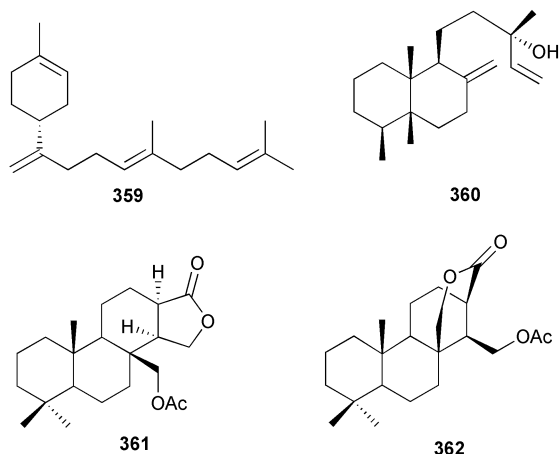
collection of *Dactylospongia elegans*.³²¹ A Great Barrier Reef species of *Spongia* yielded the sesquiterpenoid aminoquinone cyclosmenospongine **351**, which was found to be moderately cytotoxic to murine Ehrlich carcinoma cells.³²² Methanolic extracts of an Indonesian sponge of the genus *Hyrtios* yielded three new puupehenone derivatives **352–354**, but which are



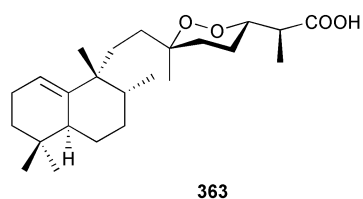
proposed to be artifacts of isolation from puupehenone.³²³ The biosynthesis of the sesquiterpenoid dichloroimines, stylotellanes A and B,³²⁴ was investigated. Incorporation of labelled farnesyl isocyanide and farnesyl isothiocyanate demonstrated the role of these compounds as intermediates in the formation of the stylotellanes.³²⁵ 10-Formamido-4-cadinene **355**, isolated from the Japanese sponge *Acanthella cavernosa*, was found to inhibit the settling of the cyprid (barnacle) larvae *Balanus aihnphritite*.³²⁶ The Indonesian sponge *Axinyssa aculeata* and its nudibranch predator *Phyllidia varicosa* were both found to contain the moderately antifungal 9-thiocyanatopupukeanane sesquiterpenoids **356** and **357**.³²⁷ 2-Thiocyanatoneopupukeanane **358**, originally



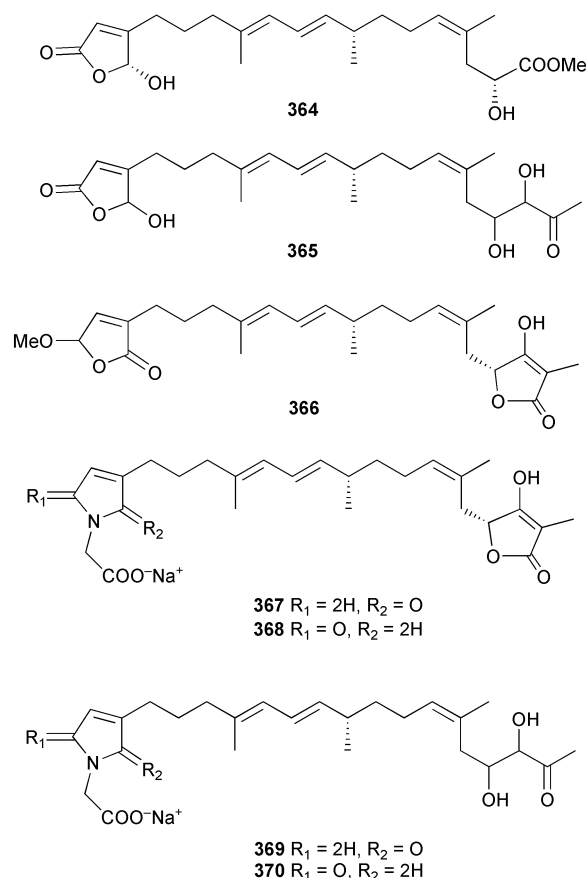
isolated from the sponge *Phycopsis terpnis*,³²⁸ was subsequently revised to the *endo* stereochemistry on the basis of long-range ^1H - ^1H coupling and NOE correlations.³²⁹ Both enantiomers have been synthesised from (*R*)-carvone *via* the corresponding alcohols³³⁰ and the stereochemistry of **358** has now been fully established *via* an X-ray structure of the nitrobenzoate derivative of the corresponding alcohol.³³¹ A Japanese *Axinissa* species yielded the mildly cytotoxic diterpene, axinysene **359**.³³² An enantioselective synthesis of (–)-nakamurol, originally isolated from the Okinawan sponge *Ageles nakamuri*,³³³ established the relative and absolute stereochemistries of the naturally-occurring **360** enantiomer.³³⁴ Synthesis of the proposed structure of aplyroseol-14 **361**, originally isolated from the New Zealand sponge *Aplysilla rosea*,³³⁵ did not yield spectra similar to those of the natural product. The revised structure, **362**, was synthesised



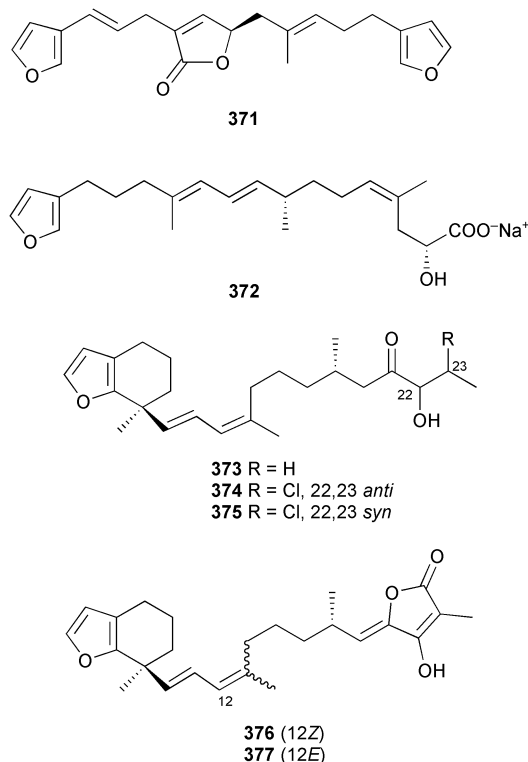
and found to be spectrally identical with aplyroseol-14.³³⁶ Six cycloamphilectenes isolated from an *Axinella* species collected in Vanuatu were found to be potent inhibitors of nitric oxide production by murine macrophages.³³⁷ Only one (*N*-formyl-7-amino-11-cycloamphilectene) of the six compounds in this study has had a structure determination published.³³⁸ The C-25 sesterterpenoids and related nor-compounds are characteristic of sponges, especially those of Dictyoceratid origin. A cytotoxic norsesterterpenoid, mycaleperoxide **363**, was isolated from a



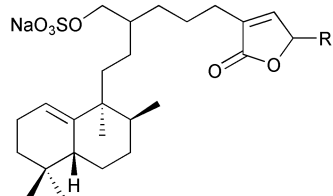
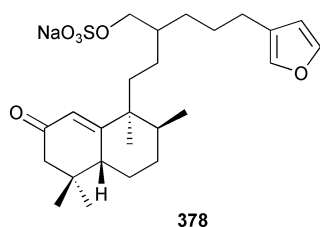
Mycale species collected in Thailand. The relative and absolute stereochemistries were established by standard methodology, including chemical interconversions.³³⁹ Two moderately cytotoxic norsesterterpenoids, sarcotins N **364** and O **365**, along with a sesterterpenoid **366**, four pyrroloesterterpenoids **367**–**370** and



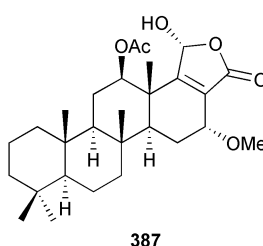
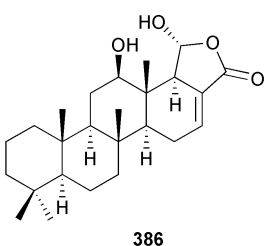
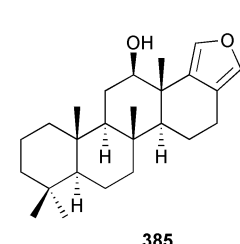
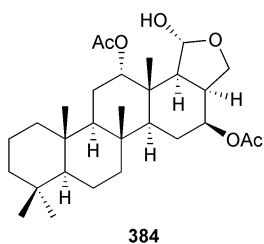
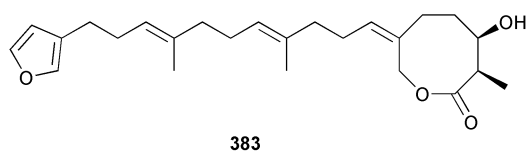
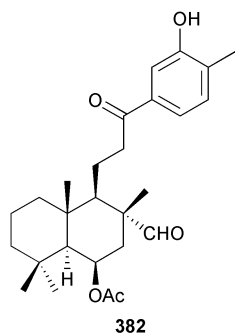
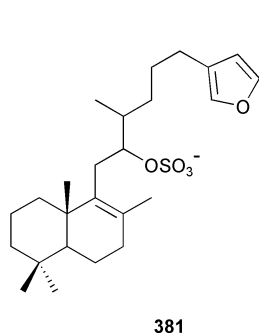
ent-kurospingin **371** were isolated from two Korean *Sarcotragus* species.³⁴⁰ The previously reported sarcotin I **372**³⁴¹ was found to have the (21*R*) configuration.³⁴⁰ Three norsesterterpenoids **373**–**375** and two sesterterpenoids **376** and **377**, isolated from an Ok-



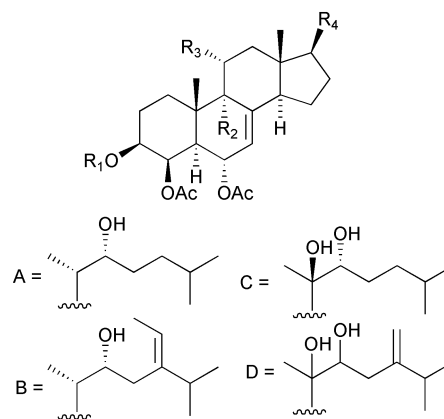
inawan *Ircinia* species, were found to be moderately cytotoxic.³⁴² *Darwinella australensis* collected from NW Australia contained sesterterpenoid sulfates **378**–**380** that inhibited the cell division of sea urchin eggs, but were not cytotoxic to human leukemia cells.³⁴³ An *Ircinia* species collected at -70 m by dredging in the Gulf of Mexico contained a tricyclic sesterterpenoid, Sch 599473



381,³⁴⁴ while the Antarctic sponge, *Suberites caminatus* yielded the rearranged sesterterpenoid aldehyde caminatal **382**.³⁴⁵ An asymmetric synthesis of (–)-cacospongionolide F, isolated from *Fasciospongia cavernosa*,³⁴⁶ confirmed the original stereochemical assignments.³⁴⁷ The bicyclic lactone astakolactin **383** and the pentacyclic diacetate 16-acetoxy-dihydrodeoxoscalarin **384** were obtained from specimens of *Cacospongia scalaris* collected in Greece.³⁴⁸ A *Spongia* species collected in Japan yielded three cytotoxic pentacyclic sesterterpenoids **385–387**.³⁴⁹ Seven new

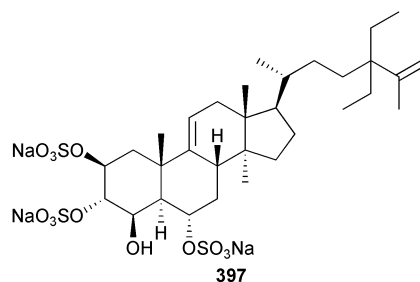
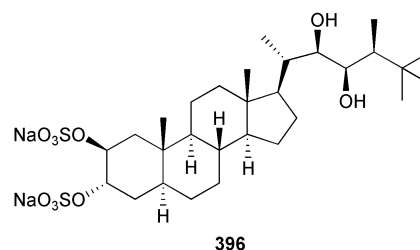
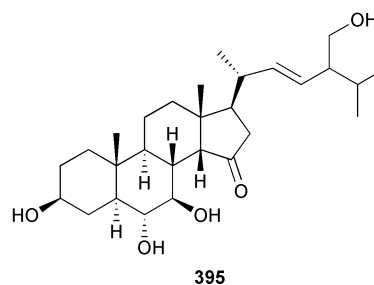


polyhydroxy sterols **388–394** were isolated from a Japanese *Acanthodendrilla* species along with three known agosterols. These were found to be proteasome inhibitors.³⁵⁰ Clathriol B

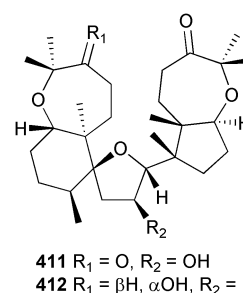
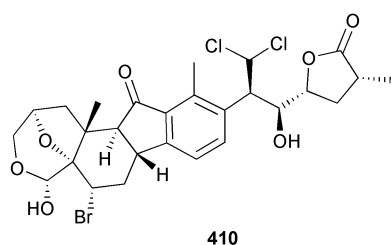
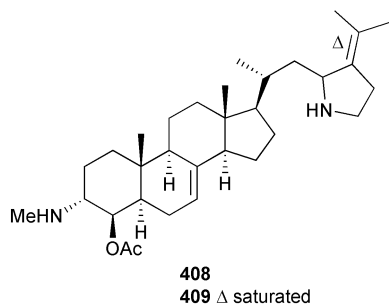
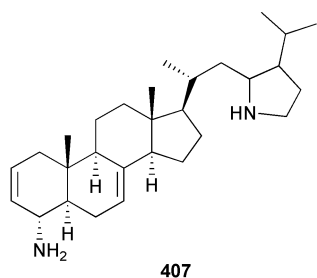
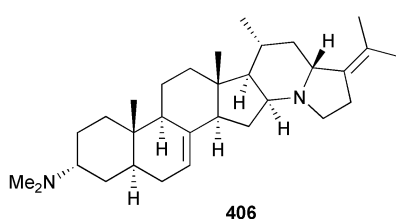
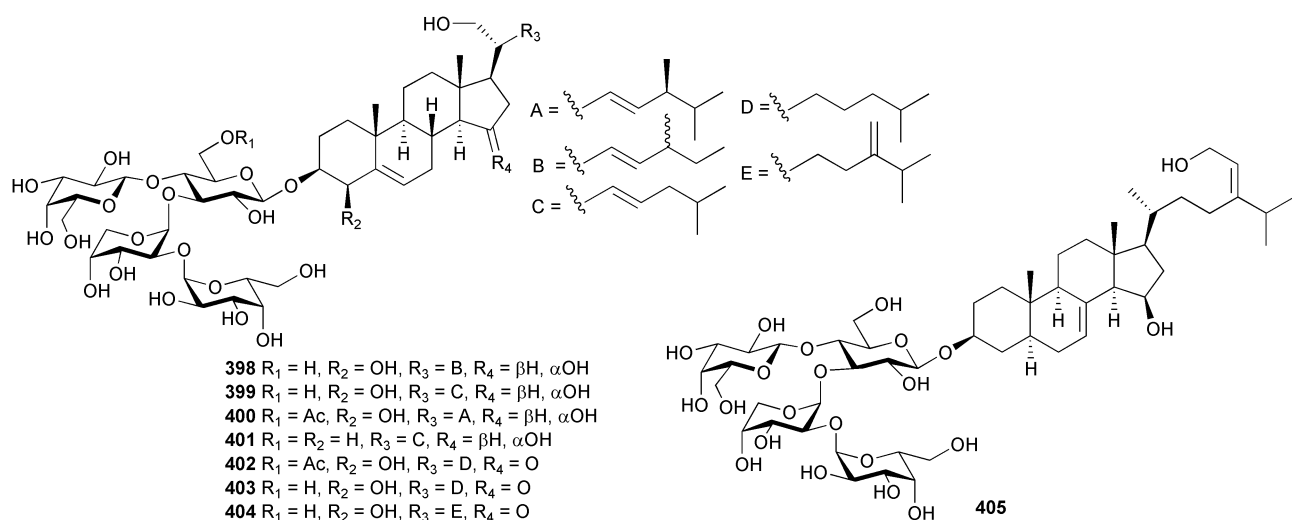


- 388 R₁ = Ac, R₂ = OH, R₃ = H, R₄ = A
389 R₁ = Ac, R₂ = OH, R₃ = H, R₄ = B
390 R₁ = R₂ = R₃ = H, R₄ = C
391 R₁ = R₂ = R₃ = H, R₄ = D
392 R₁ = R₂ = H, R₃ = OH, R₄ = A
393 R₁ = R₂ = H, R₃ = OAc, R₄ = A
394 R₁ = Ac, R₂ = H, R₃ = OH, R₄ = B

395, isolated from the New Zealand sponge *Clathria lissosclera*, was found to inhibit the production of superoxide from human neutrophils.³⁵¹ A sterol sulfate, Sch 572423 **396**, along with the previously described halistanol sulfate,³⁵² isolated from a *Topsentia* species collected in the Bahamas, were found to bind to P2Y₁₂ receptors.³⁵³ Another deep-water Bahaman sponge, belonging to the family Astrocleridae, yielded the trisulfated sterol Sch 575867 **397**,³⁵⁴ while a series of steroidal

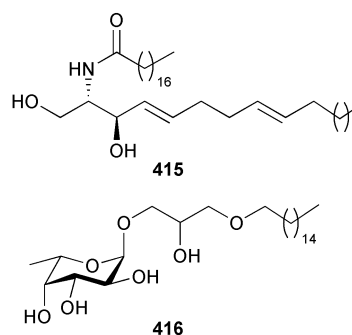
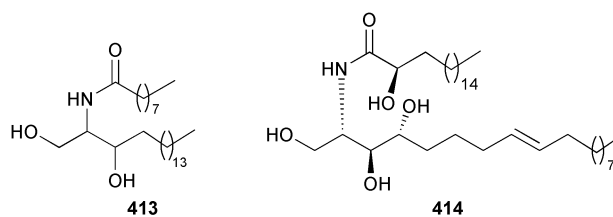


oligoglycosides, the mycalosides B–I **398–405**, have been isolated from the Cuban sponge *Mycale laxissima*. The mycalosides are inhibitors of the fertilisation of sea urchin eggs.³⁵⁵ Four significantly cytotoxic steroidal alkaloids, plakinamines I–K **406–408** and dihydroplakinamine K **409**, were isolated from a Philippine sponge *Corticium niger*.³⁵⁶ The halogenated and rearranged norsteroid, nakiterpiosin **410**, isolated from the



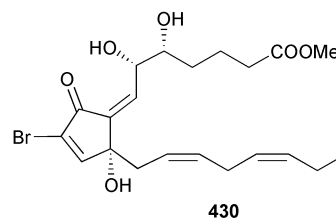
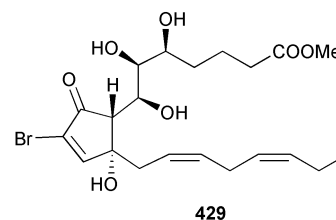
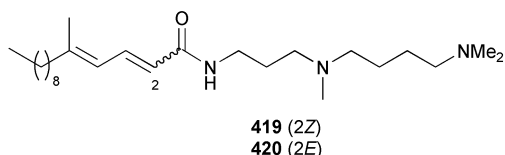
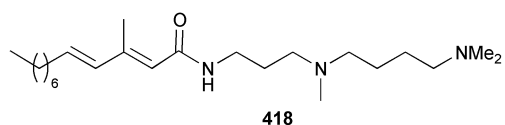
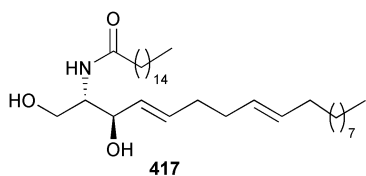
8 Coelenterates

The number of new metabolites reported annually from coelenterates has remained relatively constant over the 2002–2003 period. A new sphingosine derivative **413** was reported from a soft coral *Nephthea* sp. collected at the Andaman and Nicobar Islands, Indian Ocean,³⁶¹ while investigations of *Simularia grandilobata* and *Simularia* sp. specimens from the same location afforded **414–416** as antimicrobial metabolites.³⁶² The

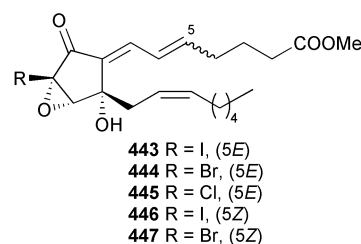
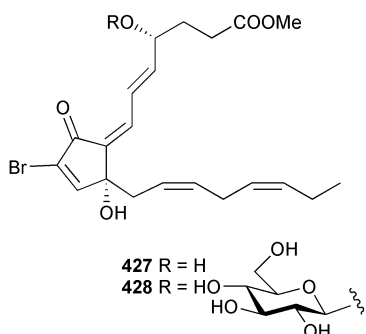
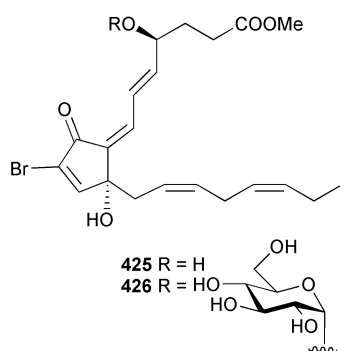
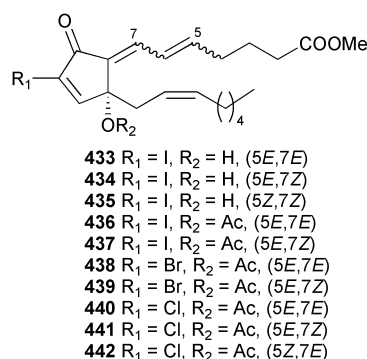
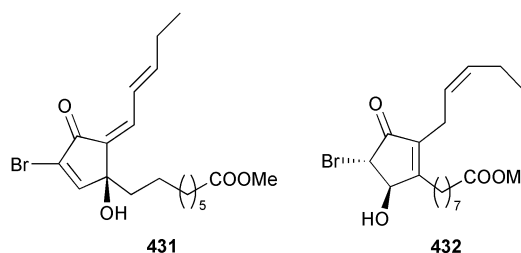
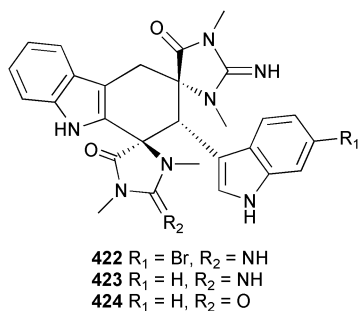
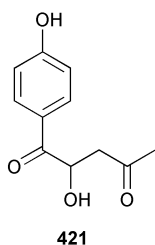


Okinawan *Terpios hoshinota*, was found to be cytotoxic to murine P388 leukemia cells.³⁵⁷ Hippospongiic acid A, originally isolated from a Japanese *Hippospongia* species,³⁵⁸ inhibits all classes of vertebrate DNA polymerases and human topoisomerases I and II, but is inactive towards DNA polymerases from plants, insects and prokaryotes.³⁵⁹ Two mildly cytotoxic polyoxygenated triterpenes, yardenones A **411** and B **412** were isolated from a Yemenese collection of *Axinella cf. bidderi*.³⁶⁰

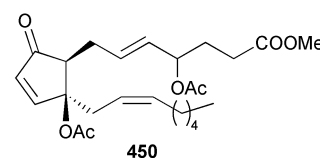
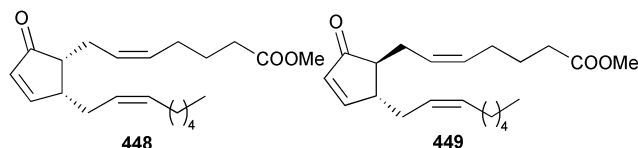
absolute stereochemistry of the *N*-palmitate **417**, isolated from a Bay of Bengal collection of *Nephthea* sp., was deduced by analysis of 1H - 1H coupling constants of the acetone derivative and comparison of optical properties with known compounds.³⁶³ Acylspermidines **418–420**, isolated from an Okinawan collection of *Simularia* sp. soft coral,³⁶⁴ were all potently cytotoxic towards A431 cells. In a separate study **419** and **420** were found to be potent inhibitors of plant vacuolar H^+ -pyrophosphatase.³⁶⁵ The



phenol **421** was isolated from a Taiwanese collection of *Isis hippuris*,³⁶⁶ while investigation of a Japanese collection of the stony coral *Tubastraea* sp. afforded bisindole alkaloids **422–424**.³⁶⁷ From Israel, eight new oxylipin derivatives were reported from Gulf of Aqaba collections of *Dendronephthya* sp. (**425–428**), *Tubipora musica* (**429** and **430**) and *Dendrophyllia* sp. (**431**

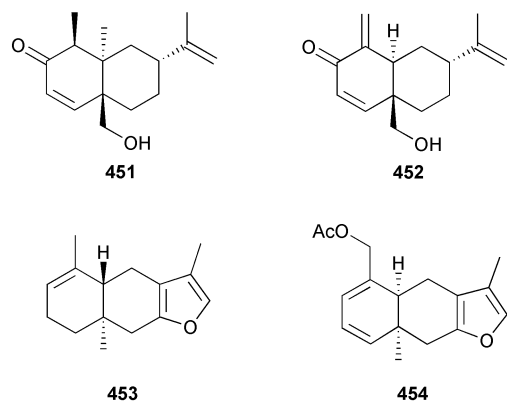


The absolute configurations of **433–443**, **445** and **446** were secured by analysis of CD data while those of **444** and **447** were proposed based upon biogenetic considerations. Prostanoids **448–450**, possible biosynthetic precursors to the clavulones, were also isolated from an Okinawan collection of *C. viridis*.³⁷⁰ By utilising protease and detergent fractionation methodology, clavulones and arachidonic acid have been located in host

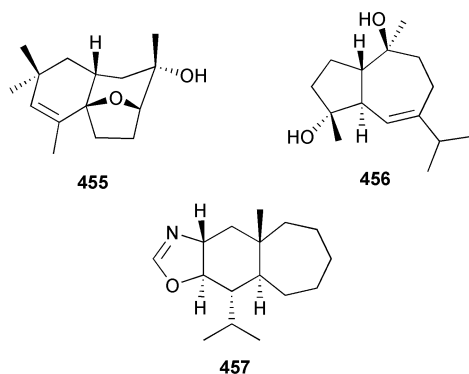


and **432**) coelenterates.³⁶⁸ Stereochemical configurations were secured by standard methods. All eight metabolites exhibited biological activity towards bacteria, brine shrimp, sea urchin egg development and crown gall potato tumours. Fifteen new members of the clavulone family of prostanoids **433–447** were reported from an Okinawan collection of *Clavularia viridis*.³⁶⁹

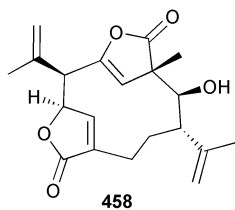
C. viridis membranes, as opposed to the closely associated symbiont *Symbiodinium* sp.³⁷¹ Sesquiterpenes ainigmaptilonones A **451** and B **452** were isolated from a Weddell Sea, Antarctica, collection of *Ainigmaptilon antarcticus*.³⁷² Ainigmaptilone A demonstrated activity in a number of ecologically-relevant assays, including antibiotic and feeding deterrence properties. Furanosquiterpene **453**, reported from the Antarctic gorgonian *Dasystenella acanthina*, bears a *trans*-ring junction as determined by NOESY NMR experiments and comparison with related *cis*-fused isomers.³⁷³ Asymmetric synthesis of both enantiomers of acetoxytubipofuran **454**, originally isolated



from a Japanese collection of *Tubipora musica*,³⁷⁴ defined the absolute stereochemistry as shown,³⁷⁵ while the structure of echinofuran³⁷⁶ has been confirmed by racemic synthesis.³⁷⁷ Confertol **455** and nephalbidol **456** were isolated from the soft corals *Simularia conferta* and *Nephthea albida* respectively,³⁷⁸ while cladioxazole **457** was isolated from an Andaman Island,

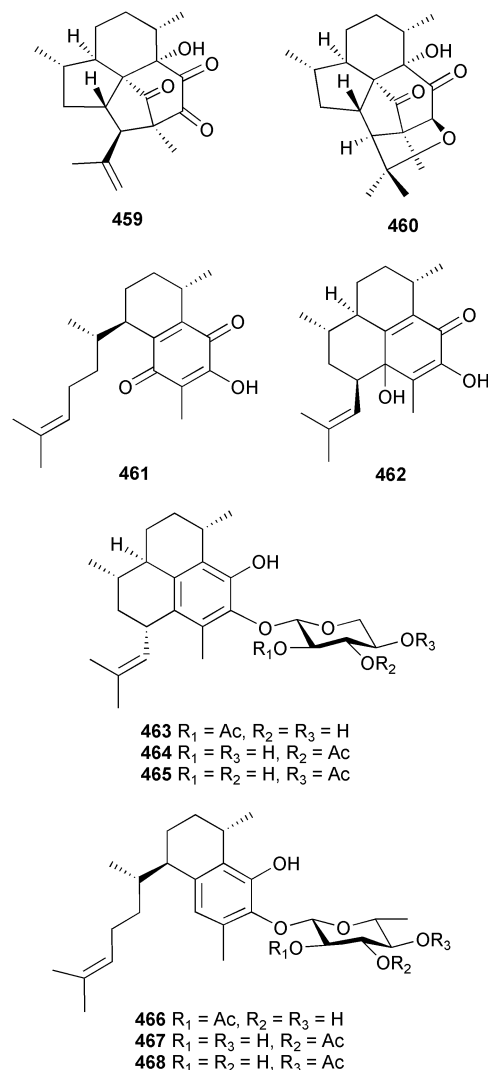


Indian Ocean, collection of *Cladiella* sp.³⁷⁹ A full account of the synthesis of the dolabellane diterpene claenone, previously reported from *Clavularia* sp.,³⁸⁰ the first synthesis of palominol, from *Eunicia laciniata*,³⁸¹ and a new route to dolabellatrienone, also from *E. laciniata*,^{381,382} have also been reported.³⁸³ Stereoselective synthesis of (+)-4,5-deoxyneodolabellane, a metabolite of an Australian collection of *Cespitularia* sp.,³⁸⁴ has been reported.³⁸⁵ The structure of kallosin A **458**, a rearranged

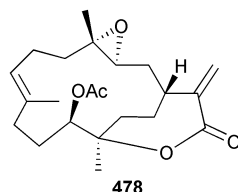
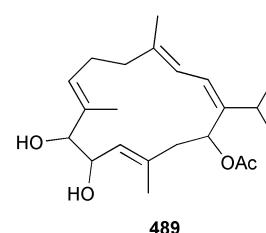
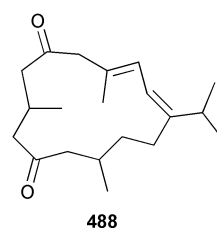
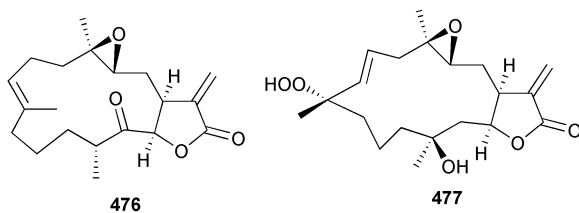
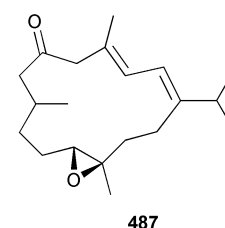
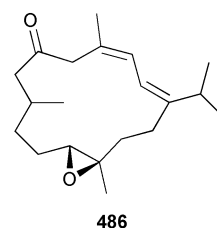
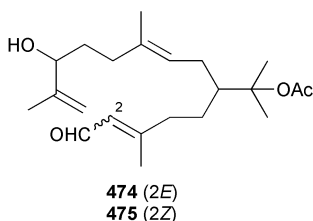
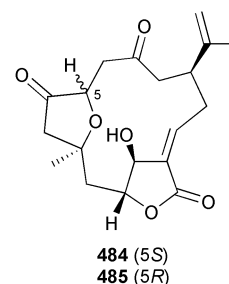
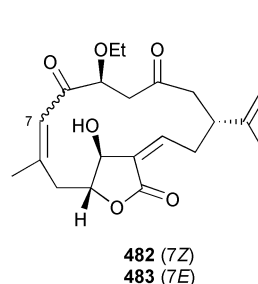
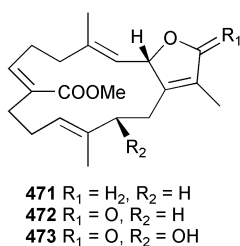
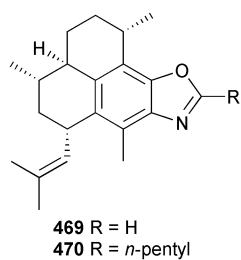


pseudopterane diterpenoid isolated from a Caribbean collection of *Pseudopterogorgia kallos*, was secured by spectroscopic and X-ray analyses.³⁸⁶ Elisabethin A, isolated from *P. elisabethae*,³⁸⁷ has been synthesised utilising intramolecular [4 + 2] cyclisation under biomimetic conditions.³⁸⁸ The first synthesis of the related diterpene elisapterosin B and a new route to colombiasin A, also isolated from *P. elisabethae*,^{389,390} have been achieved based on

[5 + 2] and [4 + 2] intramolecular cyclisations of a common diene intermediate.³⁹¹ New members of the elisapterosin family, D **459** and E **460**, were reported from a Caribbean collection of the same organism.³⁹² *P. elisabethae* is also a well recognised source of anti-inflammatory diterpenes, new examples of which include elisabethadione **461**, elisabethol **462**, pseudopterossins M–O **463–465** and seco-pseudopterossins E–G **466–468**.³⁹³ Of the

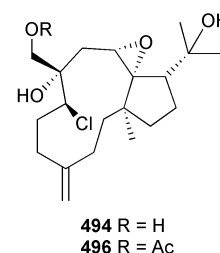
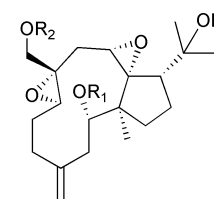
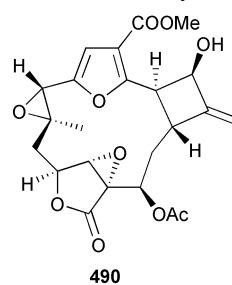
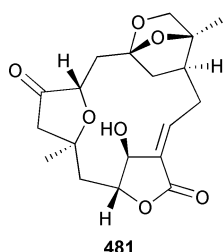
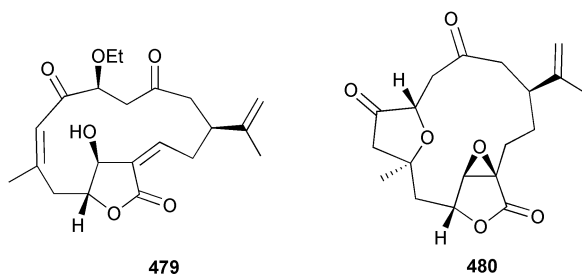


eight diterpenes, **461**, **464** and **466** were the most potent in the mouse ear edema assay. The chemical steps involved in the biosynthesis of the pseudopterossins in *P. elisabethae* have been studied using ³H-labelled precursors,³⁹⁴ with a subsequent study showing that diterpene production is occurring within the dinoflagellate symbiont *Symbiodinium* sp.³⁹⁵ Preparation of all four C-1 and C-7 stereoisomers of pseudopterossazole **469**, a mildly antimycobacterial diterpene isolated from *P. elisabethae*,³⁹⁶ required a revision of assigned stereochemistry to that shown,³⁹⁷ while a new bioactive congener, homopseudopterossazole **470**, has been reported from the same organism collected near San Andrés Island, Colombia.³⁹⁸ The structures of the *P. elisabethae* metabolites, elisabatins B³⁹⁹ and C,⁴⁰⁰ have been confirmed by X-ray studies.⁴⁰¹ Investigation of a Great Barrier Reef collection of *Sarcophyton cherbonnieri* yielded furanocembranoids **471–473**, while the same study⁴⁰² also reported new seco-cembranoids **474** and **475** from a Fijian collection of *Nephthea* sp. in addition to the known cembrane decaryiol.⁴⁰³ Modest cytotoxicity towards a panel of tumour cell lines was exhibited by **471**, **473** and decaryiol while the latter was shown to arrest the cell cycle at G2/M. Structures of sarcocrossolide B **476**⁴⁰⁴ and sarcophycrossolide A **477**,⁴⁰⁵ cytotoxic cembrane diterpenes isolated from a Chinese collection of *Sarcophyton crassocaule*, were secured by X-ray studies,⁴⁰⁶ as was that of



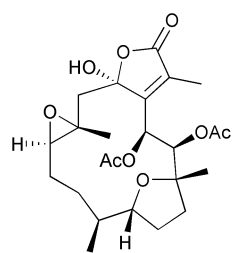
11-*epi*-sinulariolid acetate **478**,⁴⁰⁷ previously reported from gorgonians collected from the Gulf of Elat. 11-*epi*-Sinulariolid acetate was found to exhibit moderate cytotoxicity towards a range of tumour cell lines. In addition to a number of known metabolites, new nor-cembrane diterpenes leptocladolides A **479**, B **480** and C **481** were isolated from a Taiwanese collection

incorrect relative stereochemistry at C-11. Cembranes **486–489** were isolated from an eastern Caribbean collection of *Eunicea tourniforti*.⁴⁰⁹ The structure and relative stereochemistry of the highly oxygenated diterpene providencin **490**, purified from Caribbean collections of *Pseudopterogorgia kallos*, was secured by X-ray analysis.⁴¹⁰ Mild cytotoxicity towards human tumour cell lines was observed for **490**. In addition to the known metabolites stolonidiol **491** and stolonidiol monoacetate **492**, two new dolabellane diterpenes, clavinflols A **493** and B **494**, were isolated from a Taiwanese collection of *Clavularia inflata*.⁴¹¹ While **491**, **492** and **494** exhibited selective cytotoxicity towards the KB cell line, **493** was selective towards the Hepa cell line. In contrast, the acetoxy derivatives **495** and **496** were essentially

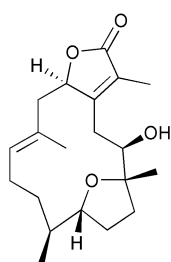


of *Simularia leptocladus*, while **479** and related compounds 1-*epi*-leptocladolide A **482** and (7*E*)-leptocladolide A **483** were isolated from an ethanolic extract of *S. parva*.⁴⁰⁸ Both **479** and **483** exhibited modest cytotoxicity towards two tumour cell lines, but **482** was less active. Two known diterpenes, sinuleptolide **484**⁴⁰⁹ and norcembrenolide **485**,⁴¹⁰ inhibit LPS-induced TNF- α production by murine macrophage-like cells in a dose-dependent manner.⁴¹¹ Note that while the characterisation data for the two diterpenes reported in the reference agree with original and recent reports,⁴⁰⁸ the structures are represented with

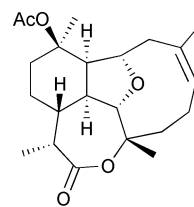
inactive in the same assays. Pachyclavariolides M–R **497–502** were isolated from a Taiwanese collection of *Pachyclavularia violacea*.⁴¹² P388 cell line growth inhibition was observed for **497**. (*Z*)-Sarcodictyin A **503** is a potent cytotoxic diterpenoid isolated from a Japanese collection of *Bellonella albiflora*.⁴¹³



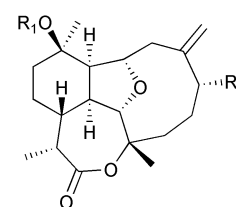
497



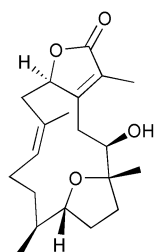
498



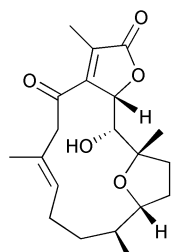
509



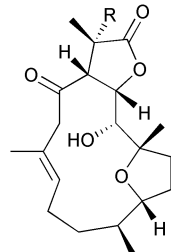
510 R₁ = Ac, R₂ = OH
 511 R₁ = COC₃H₇, R₂ = OAc
 516 R₁ = Ac, R₂ = OOH
 517 R₁ = COC₃H₇, R₂ = OOH



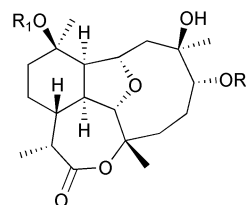
499



500

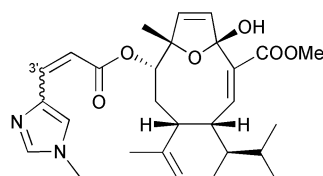


501 R = H
 502 R = OH

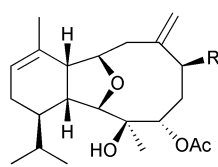


512 R₁ = Ac, R₂ = H
 513 R₁ = Ac, R₂ = Me
 514 R₁ = COC₃H₇, R₂ = H
 515 R₁ = COC₃H₇, R₂ = Me

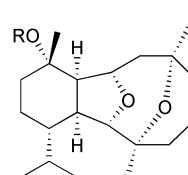
The absolute stereochemistry of **503** was related to sarcodictyin A **504** by transesterification and comparison of CD spectra. Spectroscopic discrepancies observed for the enantioselectively synthesised structure originally proposed for alcyonin **505**, isolated from the Okinawan soft coral *Simularia flexibilis*,⁴¹⁴ have led to the proposal that the correct structure of the natural product is the allylic peroxide **506**.⁴¹⁵ The structures of briarellins E **507** and F **508**, isolated from a Puerto Rican collection of



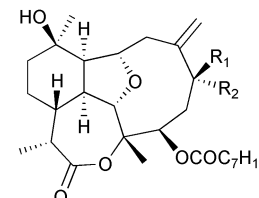
503 (3'Z)
 504 (3'E)



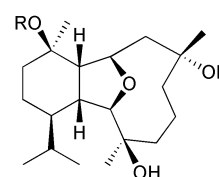
505 R = OH
 506 R = OOH



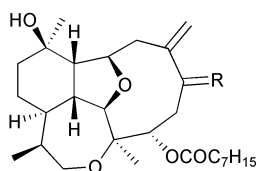
518 R = Ac
 523 R = H



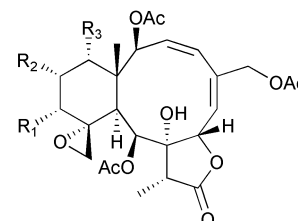
519 R₁ = OH, R₂ = H
 520 R₁ = H, R₂ = OOH



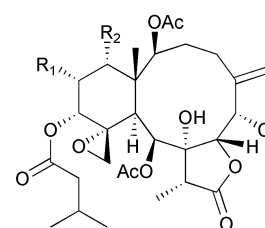
521 R = Ac
 522 R = H



507 R = βOH, αH
 508 R = O



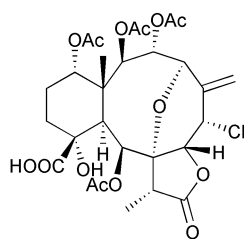
524 R₁ = R₃ = OAc, R₂ = OCOCH₂CHMe₂
 525 R₁ = R₂ = OCOCH₂CHMe₂, R₃ = OAc
 526 R₁ = R₃ = OCOCH₂CHMe₂, R₂ = H



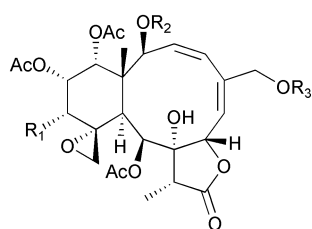
527 R₁ = OCOCH₂CHMe₂, R₂ = OAc
 528 R₁ = H, R₂ = OCOCH₂CHMe₂

Briareum asbestinum,⁴¹⁶ were confirmed by enantioselective total synthesis, which also established the absolute configuration of the diterpenes.⁴¹⁷ In addition to a number of known compounds, new briarellins J–P **509–515**, two unnamed congeners **516** and **517** and polyanthellin A **518** were reported from a Puerto Rican collection of *Briareum polyanthes*.⁴¹⁸ Spectroscopic evidence was also presented for revision of the structure of briarellin A from **519**⁴¹⁹ to peroxide **520**, and reformulation of the structures of **521** and **522**, isolated from an Australian collection of *Briareum* sp. in 1989,⁴²⁰ to the enantiomers of **518** and **523** respectively. Antimalarial testing against *Plasmodium falciparum* indicated **511**, **516** and **517** to be the most active. Two investigations of the chemistry of *Junceella juncea*, one using specimens collected from the Tuticorin coast of the Indian Ocean, yielded juncins I–M **524–528**,⁴²¹ while a Taiwanese collection of the same organism afforded juncin N **529**.⁴²² Additional studies of *J. juncea* from Taiwan afforded juncenolides B–D **530–532**⁴²³ and juncenolide E **533**,⁴²⁴ of which **531** exhibited mild cytotoxicity towards Hepa and KB cell lines.⁴²³ A different diterpene structure **534**, isolated from an Indian Ocean collection of *J. juncea*, was also given

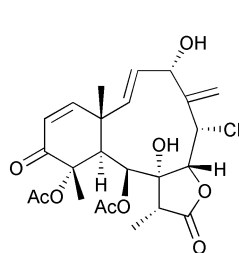
the trivial name juncenolide B.⁴²⁵ A Taiwanese collection of *Junceella fragilis* yielded 9-*O*-deacetylumbraiculolide A **535**.⁴²⁶ The structurally related epoxides briaexcavatulides S–V **536–539** were isolated from Taiwanese specimens of *Briareum excavatum*,⁴²⁷ while a Taiwanese collection of *J. fragilis* was



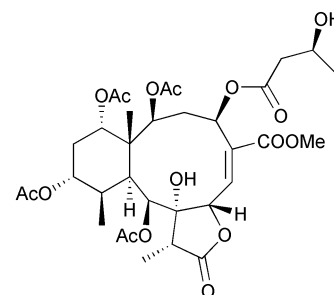
529



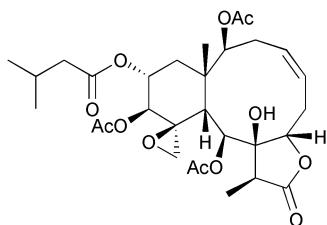
530 $R_1 = R_3 = H, R_2 = Ac$
 531 $R_1 = OAc, R_2 = Ac, R_3 = H$
 532 $R_1 = OAc, R_2 = Ac, R_3 = Me$
 533 $R_1 = R_3 = H, R_2 = 3\text{-methylbutanoyl}$



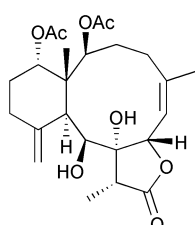
549



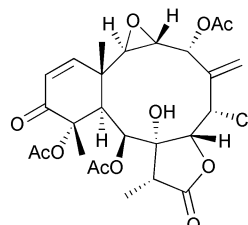
550



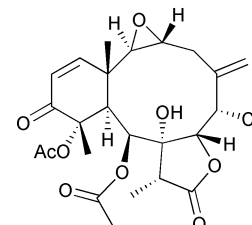
534



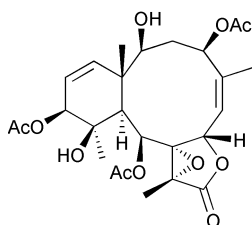
535



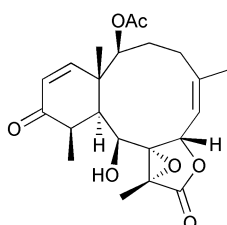
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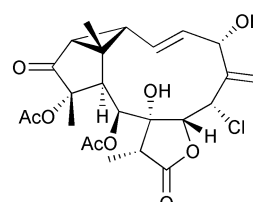
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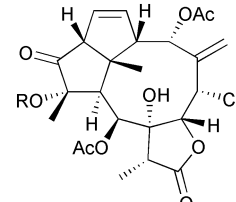
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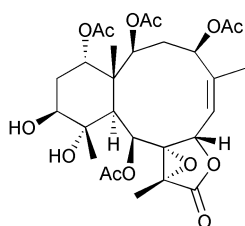
537



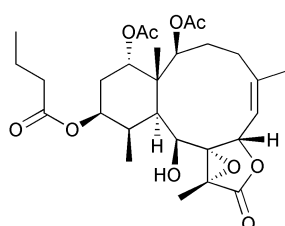
553



554 $R = Me$
 555 $R = Ac$
 556 $R = H$

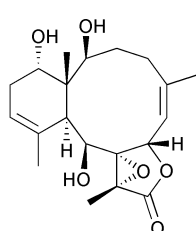


538

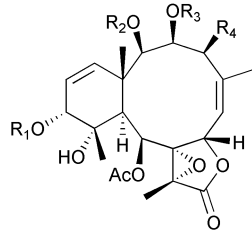


539

the source of juncellolide H **540**.⁴²⁸ Briarilides A–H **541–548**, obtained from Amami Oshima, Kagoshima Prefecture collections of *Briareum* sp., were evaluated for cytotoxicity towards Vero and MDCK cell lines where modest activity was observed for **541**, **544–546**, weak activity for **542**, **543** and **547** while **548** was inactive.⁴²⁹ In addition to a number of known



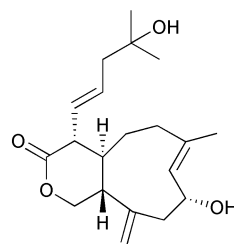
540



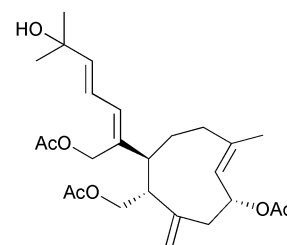
541 $R_1 = R_2 = R_3 = Ac, R_4 = OAc$
 542 $R_1 = R_2 = Ac, R_3 = H, R_4 = OAc$
 543 $R_1 = Ac, R_2 = R_3 = H, R_4 = OAc$
 544 $R_1 = R_2 = Ac, R_3 = H, R_4 = OCO(CH_2)_6Me$
 545 $R_1 = R_2 = Ac, R_3 = H, R_4 = OCO(CH_2)_4Me$
 546 $R_1 = R_2 = Ac, R_3 = CO(CH_2)_6Me, R_4 = OH$
 547 $R_1 = R_2 = R_3 = Ac, R_4 = H$
 548 $R_1 = R_2 = R_4 = H, R_3 = Ac$

metabolites, seven new briaranes, erythrolides R–U **549–552**, an erythrane, erythrolide V **553**, and two aquariane-skeletoned diterpenes, aquariolides B **554** and C **555**, were reported from a Caribbean collection of *Erythropodium caribaeorum*.⁴³⁰ Aquariolide A **556**, previously isolated from aquarium-grown

specimens of *E. caribaeorum*,⁴³¹ was also identified from the organism collected in the wild. The relative stereochemistries of **549–555** were determined either by conversion to known related derivatives, or by interpretation of ROESY NMR data, while for erythrolide **550**, Mosher methodology established the absolute configuration of the 3-hydroxybutanoyl side chain as (3*S*). The biosynthetic relationships between a number of erythrolide diterpenes, involving possible enzymatic-mediated di- π -methane and vinyl-propane rearrangements were discussed. The study also reported that the known metabolites erythrolides **P**⁴³² and **J**⁴³³ exhibited modest cytotoxicity towards the MCF7 tumour cell line. An Okinawan collection of *Xenia* sp. yielded the known metabolite xeniolide A⁴³⁴ as well as new xenicane diterpenes dihydroxeniolide A **557** and isoxeniatriacetate **558**.⁴³⁵

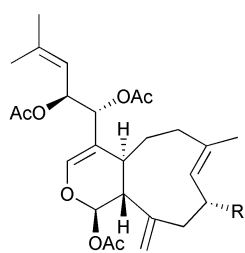


557

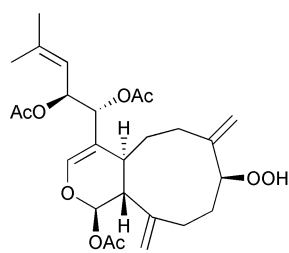


558

The absolute configuration of **557** was established (Mosher method), while the absolute configuration of **558** was determined by synthesis from the stereochemically-defined xeniolide A.⁴³⁶ 13-*Epi*-9-deacetyxenicin **559** was isolated as a cytotoxic component of *Asterospicularia laurae* collected on the Great Barrier Reef, Australia.⁴³⁷ Good activity was observed for **559** against P388D1 cells, while the known metabolite 13-*epi*-9-deacetyxenicin **560**⁴³⁸ was less active. DCM or ether solutions of **559** readily underwent autoxidation to afford the hydroperoxide **561**, while **560** was found to be resistant to further reaction. The stereochemistries of sesterterpenes cladocorans

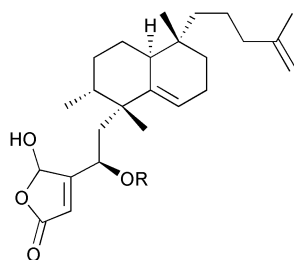


559 R = H
560 R = OH

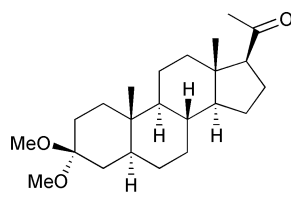


561

A **562** and B **563**, isolated from Mediterranean collections of *Cladocora cespitosa*,⁴³⁹ have been revised by total synthesis,⁴⁴⁰ while preparation and testing of related stereoisomers indicated the series exhibits cytotoxicity towards a panel of human tumour cell lines.⁴⁴¹ Pregnane acetal **564** was isolated from an ethanol

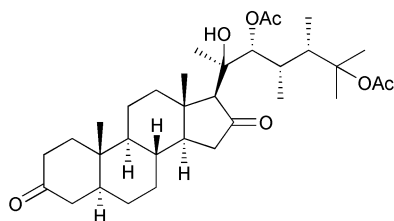


562 R = Ac
563 R = H

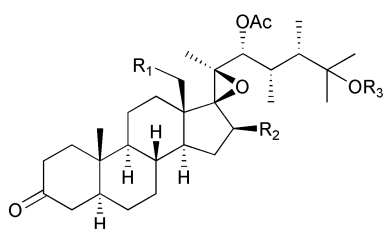


564

extract of *Subergorgia suberosa*, collected off the Mandapam coast, Indian Ocean,⁴⁴² while a Taiwanese collection of *Isis hippuris* afforded the polyoxygenated steroids hippuristerones E-1 **565**–**569**.⁴⁴³ New gorgosterol and ergosterol derivatives **570**–

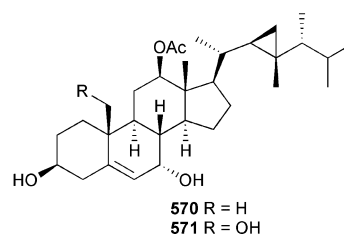


565

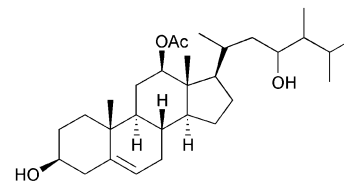


566 R₁ = OAc, R₂ = OH, R₃ = H
567 R₁ = OAc, R₂ = OH, R₃ = Ac
568 R₁ = R₃ = H, R₂ = OH
569 R₁ = R₂ = R₃ = H

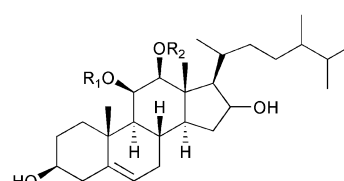
574 were isolated from a Great Barrier Reef collection of *Capnella lacertiliensis*.⁴⁴⁴ All compounds exhibited weak antifungal activity while **573** and **574** also weakly inhibited tyrosine kinase p56^{lck}. The spiroketal steroid **575** was isolated from a Tuticorin coast, Indian Ocean collection of *Gorgonella umbraculum*,⁴⁴⁵ while the mildly cytotoxic gibberoketosterol **576** was isolated from a Taiwanese collection of *Simularia gibberosa*.⁴⁴⁶ A South China Sea collection of *Nephtea chabroli* afforded the weakly cytotoxic sterols **577** and **578**,⁴⁴⁷ and the arabinopyranosylsterol **579** was isolated from *Cladiella krempfi*, also collected in Chinese waters.⁴⁴⁸ APETx1, a 4,552 Da 42-amino acid peptide cross-linked by three disulfide bonds, was isolated from the sea anemone *Anthopleura elegantissima*.⁴⁴⁹ The toxin inhibits HERG voltage-dependent K⁺ channels *via* gating modification rather than channel pore occlusion. Pore formation by equinatoxin II, a protein toxin isolated from the Mediterranean sea anemone



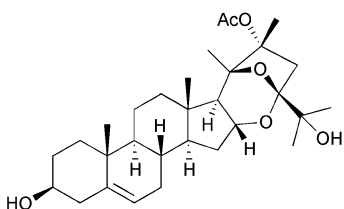
570 R = H
571 R = OH



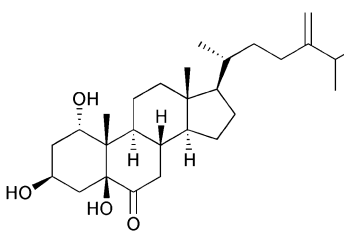
572



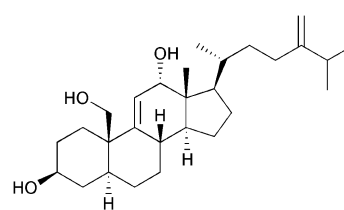
573 R₁ = H, R₂ = Ac
574 R₁ = Ac, R₂ = H



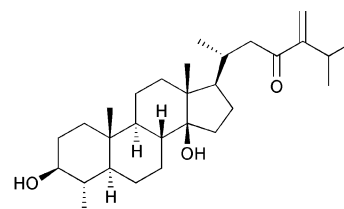
575



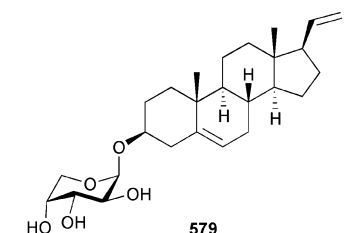
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577



578

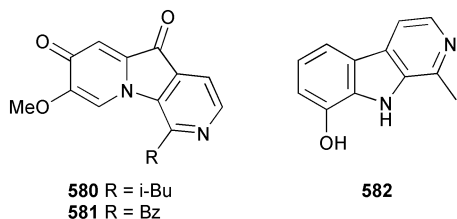


579

Actinia equina,⁴⁵⁰ has been examined using combinations of ³¹P NMR, ³¹P MAS NMR, electron microscopy,⁴⁵¹ FTIR⁴⁵² and toxin mutagenesis.⁴⁵³ The ability of surface plasmon resonance to study membrane binding processes of pore forming toxins has been reviewed.⁴⁵⁴

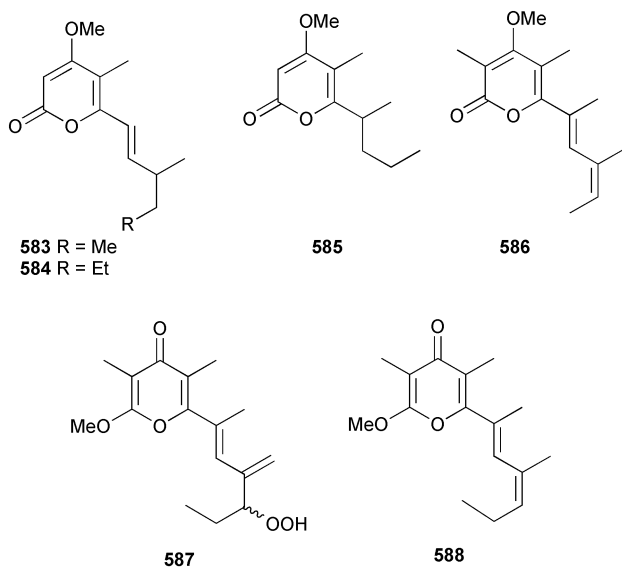
9 Bryozoans

Once again, few new compounds have been reported from bryozoans. The structural determination of the alkaloids pterocellins A **580** and B **581**, isolated from the marine bryozoan *Pterocella vesiculosa* collected in New Zealand, relied in part on an X-ray diffraction study of pterocellin A **580**. Both pterocellins A and B exhibit potent antimicrobial and antitumour activity *in vitro*, but only displayed modest activity in an *in vivo* hollow fibre assay.⁴⁵⁵ The β -carboline alkaloid 8-hydroxyharman **582** was isolated from a sample of the New Zealand marine bryozoan *Cribricellina cribraria*.⁴⁵⁶ A number of brominated alkaloids and a diterpene from the North Sea bryozoan *Flustra foliacea*^{457,458,459,460,461} were tested against bacteria derived from marine and terrestrial environments. These compounds exhibited significant activities against one or more marine bacterial strains originally isolated from *F. foliacea*, but only weak activities against the terrestrial bacteria. Dihydroflustramine C⁴⁶² and flustramine D⁴⁶¹ exhibited *N*-acyl-homoserine lactone (AHL)-antagonistic activity as determined by using the biosensors *Pseudomonas putida* (pKR-C12), *P. putida* (pAS-C8) and *E. coli* (pSB403).⁴⁵⁸ A synthesis of the cytotoxic isoquinoline alkaloid perfragilin A, originally isolated from the bryozoan *Membranipora fragilis*,⁴⁶³ has been reported.⁴⁶⁴



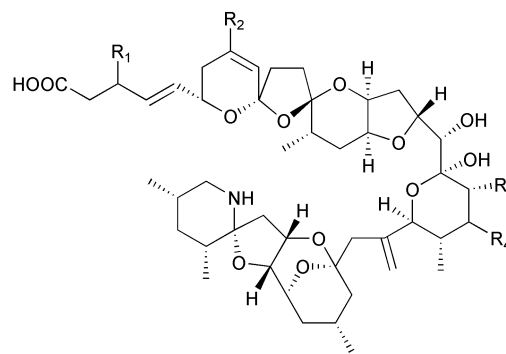
10 Molluscs

There was a slight increase in new chemistry identified from molluscs in 2003 over that reported for the time frame of the previous review. Irregular polypropionates placidenes C–F **583–586** and hydroperoxide **587** were isolated from a Mediterranean collection of *Placida dendritica*.⁴⁶⁵ It is likely that **587** is derived from the known metabolite placidene A **588**,⁴⁶⁶ but



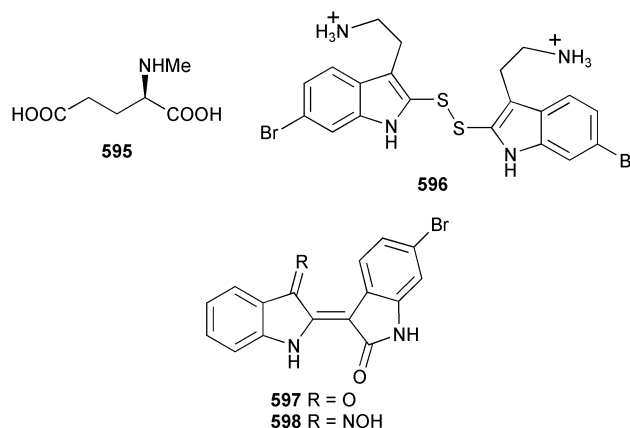
whether the hydroperoxide is an artifact of isolation, or a true natural product is unclear. The first synthesis (racemic) of the unsaturated polypropionate photodeoxytridachione, isolated

from *Placobranchus ocellatus*⁴⁶⁷ and other molluscs,⁴⁶⁸ has been reported.⁴⁶⁹ Five new azaspiracid analogues **589–593**, identified using tandem mass spectrometric techniques, were isolated from *Mytilus edulis* collected off the west coast of Ireland.⁴⁷⁰ The stereochemistries of the new azaspiracid analogues are arbitrarily shown as matching that of azaspiracid-1 **594**,⁴⁷¹ the



589 R₁ = OH, R₂ = R₄ = H, R₃ = Me
590 R₁ = R₂ = H, R₃ = Me, R₄ = OH
591 R₁ = OH, R₂ = Me, R₃ = R₄ = H
592 R₁ = R₃ = H, R₂ = Me, R₄ = OH
593 R₁ = OH, R₂ = R₃ = Me, R₄ = H
594 R₁ = R₂ = R₄ = H, R₃ = Me

structure and stereochemistry of which has been called in to question by stereoselective synthetic studies.^{472,473} The isolation of *N*-methyl-D-glutamic acid **595** from the Japanese mollusc *Scapharca broughtonii* is the first report of this amino acid derivative as a natural product.⁴⁷⁴ Monterey Bay, California, collections of *Calliostoma canaliculatum* afforded the disulfide-linked dimer of 6-bromo-2-mercaptotryptamine **596** as a channel-gating antagonist of voltage-gated potassium channels.⁴⁷⁵ 6-Bromoindirubin **597**, isolated from the Mediterranean mollusc *Hexaplex trunculus*, and the synthetic oxime **598** were found



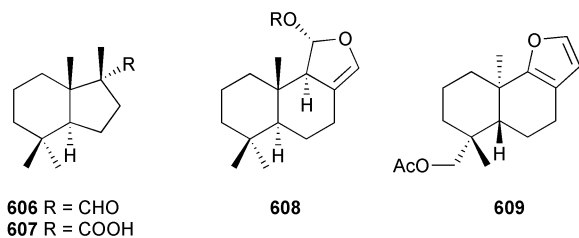
to be potent inhibitors of glycogen synthase kinase-3 (GSK-3).⁴⁷⁶ The molecular geometry of GSK-3 β inhibition by **598** was determined by a co-crystallisation X-ray study. Radio- and stable isotope incorporation studies have identified nicotinic acid and acetate as biosynthetic precursors of haminol-2,⁴⁷⁷ a *de novo* biosynthesised metabolite of the Mediterranean mollusc *Haminocoe orbignyana*.⁴⁷⁸ The ability of the fungal alkaloid gliotoxin to act as a bioaccumulated toxin of shellfish has been examined using *Mytilus edulis*.⁴⁷⁹ Lamellarin D, a polycyclic alkaloid first isolated from molluscs of the genus *Lamellaria*,⁴⁸⁰ has been found to be a potent inhibitor of the DNA-processing enzyme topoisomerase I.⁴⁸¹ Japanese and US collections of *Aplysia kurodai* and *A. californica* were sources of the gut and vasculature contraction inhibitory pentapeptide Pro-Arg-Gln-Phe-Val-amide (PRQFVa).⁴⁸² Precursoral peptide cDNA was successfully cloned while PRQFVa-positive neuron distribution in CNS and peripheral tissue was mapped using *in situ* hybridisation and immunocytochemistry. Five excitatory peptides, r11a-e **599–603** were isolated from the venom of the fish-hunting

599 GOSFCKADEKOCEYHADCCNCLSGICAOSTNWILPGCSTSSFFKI
 600 GOSFCKANGKOCYSYHADCCNCLSGICKOSTNVILPGCSTSSFFRI
 601 GOSFCKADEKOCKYHADCCNCLGICKOSTSWIGCSTNVFLT
 602 GCKKDRKOCYSYHADCCNCLSGICAOSTNWILPGCSTSTFT
 603 ECKTNKMSCSL γ γ CCRFRCCFHGKCQTSVFGCVWDP*

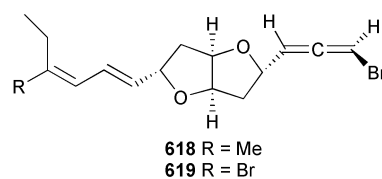
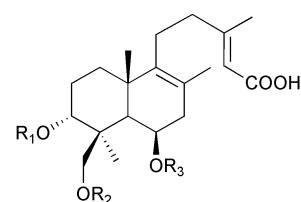
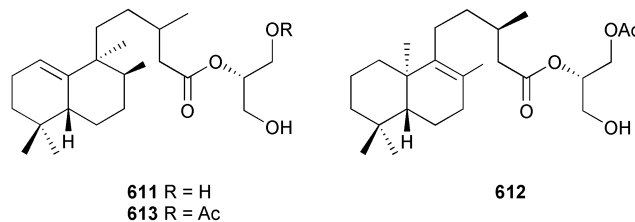
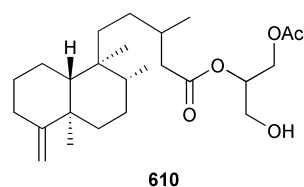
604 GCGPYONAACHOCGCKVGRROYCDROSGG*
 605 CRA γ GTYC γ NDSQCCLN γ CCWGGCGHOCRHP*

O = hydroxyproline, γ = γ -carboxyglutamic acid, * indicates C-terminal amidation

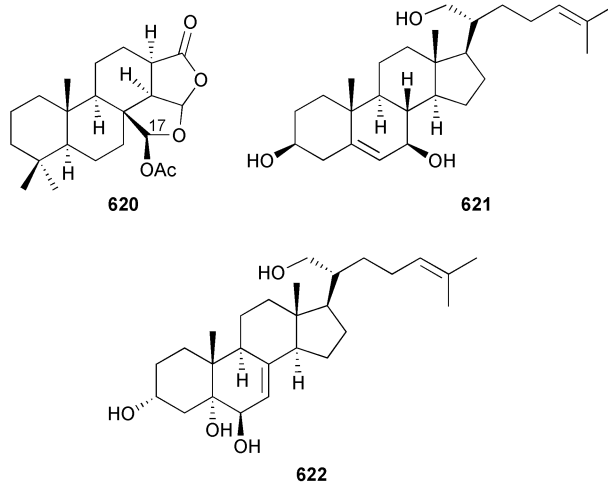
cone snail *Conus radiatus* collected in the Philippines.⁴⁸³ Further molecular analysis of cDNA clones defined the isolated peptides as belonging to a new class, the I-superfamily, of conotoxins, which contain a scaffold with four disulfide bonds (linkages not defined). The solution conformation of α A-conotoxin EIVA **604**, originally isolated from the Atlantic cone shell *C. ermineus*,⁴⁸⁴ was determined by NMR experiments and restrained molecular dynamics calculations.⁴⁸⁵ A South China Sea collection of *Conus betulinus* yielded κ -conotoxin BtX **605**, a 31 residue four disulfide bond-containing K⁺ channel up-modulator.⁴⁸⁶ As noted in Section 4, the revised structure⁴⁸⁷ of kahalalide F **126**, a potently cytotoxic⁴⁸⁸ depsipeptide isolated from the mollusc *Elysia rufescens* and the algal dietary source *Bryopsis* sp.,¹⁴² has been confirmed by careful analysis of degradation products and chiral derivatisation.¹⁴⁴ The mechanism of biological action of dolastatin 11, a cytotoxic depsipeptide isolated from the sea hare *Dolabella auricularia*,⁴⁸⁹ involves stabilisation of F-actin, which has been studied using X-ray fibre diffraction of oriented filament sols.⁴⁹⁰ Also isolated from a Japanese collection of the sea hare *D. auricularia*, dolabellin B2, a 33 amino acid residue peptide, exhibits a broad spectrum of antimicrobial activity.⁴⁹¹ The solution structure of attractin, a 58-residue water-borne protein pheromone isolated from *Aplysia californica* has been determined by NMR methods.⁴⁹² Austrodol **606** and austrodoric acid **607** are new nor-sesquiterpenes isolated from the Antarctic nudibranch *Austrodoris kerguelensis*, but with **607** most likely being an artifact of isolation.⁴⁹³ As noted in Section 7, the thio-cyanatopupukeanane sesquiterpenes **356** and **357** were isolated as an epimeric mixture from the nudibranch *Phyllidia varicosa* and the nudibranch's dietary sponge *Axinyssa aculeata*.³²⁷ While both compounds were isolated from the digestive gland of the nudibranch, epimer **357** was found to accumulate in the mantle, suggestive of a role in chemical defense. Both compounds exhibited mild toxicity towards brine shrimp and antimicrobial activity with **357** being more potent. *De novo* biosynthesis, via mevalonic acid, of fatty acid ester derivatives of drimane **608** and sesquiterpene **609**⁴⁹⁴ in the nudibranch *Doriopsilla areolata*



has been determined by feeding studies utilising [1-¹³C]glucose, [1,2-¹³C₂]glucose and [1,2-¹³C₂]acetate.⁴⁹⁵ Investigation of the diterpenoid acylglycerol fraction of an extract of the mantle of the Antarctic nudibranch *Austrodoris kerguelensis* afforded the acylglycerols **610** and **611**.⁴⁹⁶ Also isolated were two known 1,2-diacylglyceryl esters, previously reported from the same organism,^{497,498} the structures of which were corrected to **612** and **613** based upon interpretation of HMBC NMR correlations. The *de novo* biosynthesis of the structurally related diterpenoid glyceride verrucosin A^{499,500} by the Mediterranean nudibranch *Doris verrucosa* has been investigated using both ¹³C- and ¹⁴C-labelled precursors.⁵⁰¹ Four new labdane diterpenes **614**–**617** were isolated from the pulmonate *Trimusculus peruvianus*, collected near the Antofagasta Coast of Chile.⁵⁰² Absolute



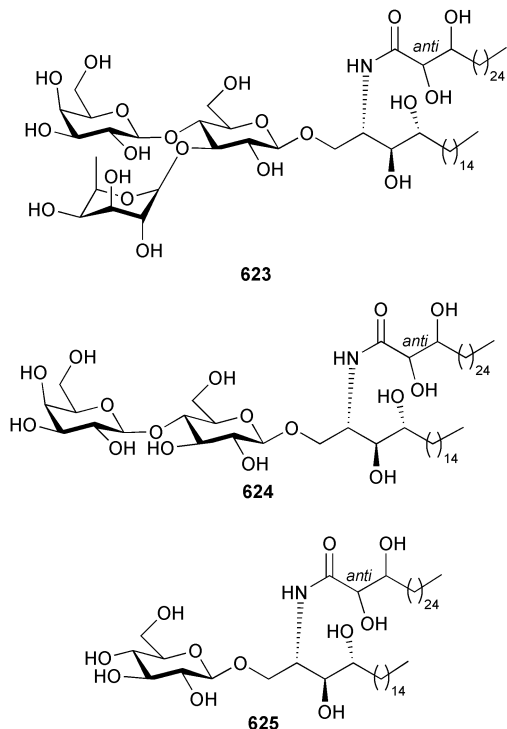
stereochemistry was secured by standard methods. Compounds **616** and **617** exhibited mild cytotoxicity towards human tumour cell lines *in vitro*. The structure of aplysiallene **618**, deduced from a metabolite isolated from a Japanese collection of the sea hare *Aplysia kurodai*,⁵⁰³ has been retracted⁵⁰⁴ and corrected to the known bromoallene algal metabolite **619**.⁵⁰⁵ The first diastereoselective synthesis of (–)-spongian-16-oxo-17-al, originally isolated from the nudibranch *Ceratosoma brevicaudatum*,⁵⁰⁶ has confirmed the absolute stereochemistry of the metabolite, while synthesis of the related compound (–)-acetyldendrillo-1 **620**, isolated from the nudibranch *Cadlina luteomarginata*,⁵⁰⁷ has led to correction of stereochemistry at C-17.³³⁶ A further collection of *Trimusculus peruvianus*, again from the Antofagasta Coast of Chile, yielded two mildly cytotoxic polyhydroxylated steroids **621** and **622**.⁵⁰⁸ The stereochemistries of **621** and **622** were



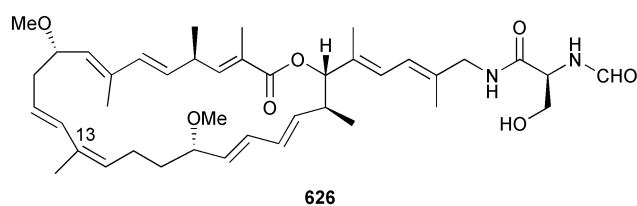
determined by interpretation of NOESY NMR data and comparison of chemical shifts with stereochemically-defined related compounds.

11 Tunicates (ascidians)

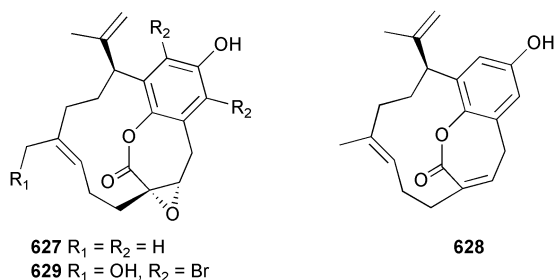
The number of new secondary metabolites reported from ascidians has remained essentially static for each of 2002 and 2003. Three new glycosphingolipid molecular species, the major component of each being represented by **623–625**, were isolated



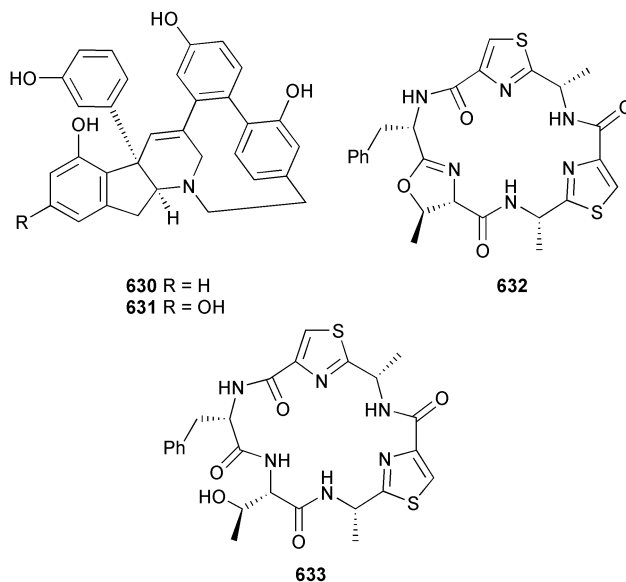
from a Mediterranean collection of *Microcosmus sulcatus*.⁵⁰⁹ A full account of the synthesis of lobatamide C, a cytotoxic macrolide isolated from *Aplidium lobatum* collected off the southwestern coast of Australia,⁵¹⁰ has been reported.⁵¹¹ In addition, preliminary V-ATPase inhibition structure–activity data was reported indicating the importance of the salicylate ring and enamide moieties for activity. The absolute configuration of iejimalide B **626**, a cytotoxic 24-membered macrolide isolated



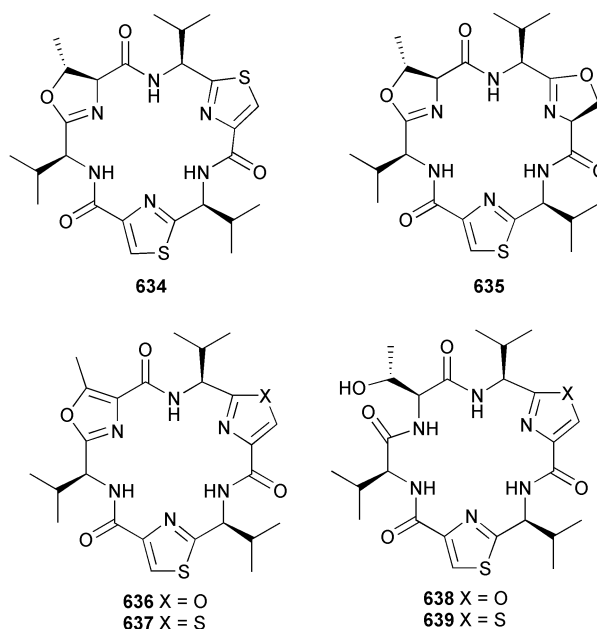
from a Japanese collection of *Eudistoma cf. rigida*,⁵¹² has been defined by analysis of ^1H - ^1H and ^1H - ^{13}C coupling constants, distance geometry calculations and analysis of oxidative degradation products.⁵¹³ During the study the gross structure was also corrected to that shown (13Z). Floresolides A **627**, B **628** and C **629** are moderately cytotoxic cyclofarnesylated hydroquinones isolated from an *Aplidium* sp. ascidian collected



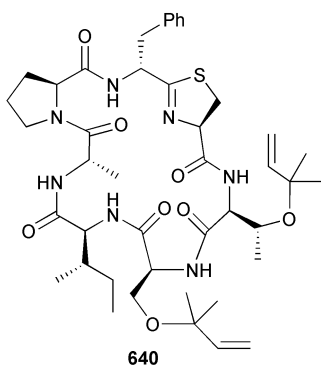
at Flores Island.⁵¹⁴ The structures and absolute configurations of all three metabolites were secured by X-ray analysis of **629**. The structures of the 3-aza-[7]-paracyclophane-containing alkaloids haouamines A **630** and B **631**, isolated from *Aplidium haouarianum* collected off Tarifa Island, Cádiz, were also secured by X-ray analysis.⁵¹⁵ Both haouamines exhibited two sets of NMR signals, attributed to the presence of isomers resulting from either atropisomerism or slow pyramidal inversion of the bridgehead amine. Of the two compounds, haouamine A was the more potent antitumour agent. Ascidians are a well-established source of cyclic peptides, many of which exhibit cytotoxicity. Didmolamides A **632** and B **633** are cyclic hexapep-



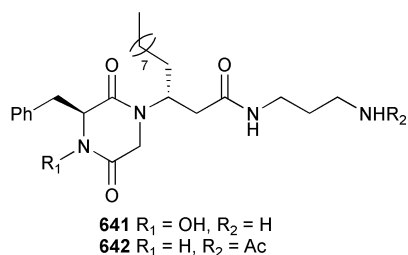
tides containing all (*S*)-configuration amino acids isolated from *Didemnum molle* collected in Madagascar.⁵¹⁶ Both compounds exhibited modest cytotoxicity towards a panel of tumour cell lines. Six new congeners of the bistratamide family of cyclic hexapeptides, E–J **634–639**, were reported from a Tablas Island,



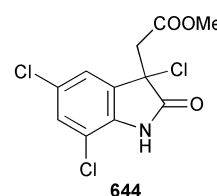
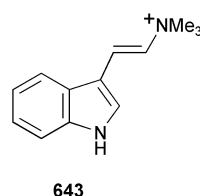
Philippines collection of *Lissoclinum bistratum*.⁵¹⁷ All six compounds showed weak to moderate activity towards the HCT-116 tumour cell line. A full account of the synthesis of mollamide, a cytotoxic cycloheptapeptide isolated from an Australian collection of *Didemnum molle*,⁵¹⁸ has been reported.⁵¹⁹ The solution structure of the cytotoxic cycloheptapeptide trunkamide A **640**^{520,521} has been determined using 2D-NMR data and simulated annealing methods.⁵²² Fluorescent analogues of



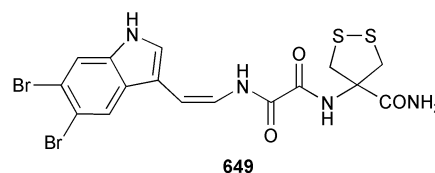
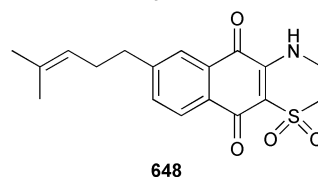
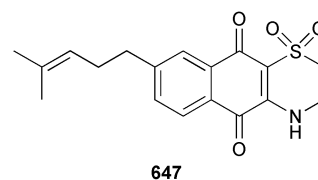
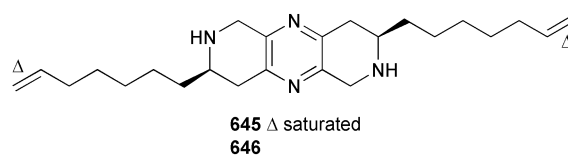
ascidian-derived depsipeptides didemnin B and tamandarin A have been used to study short-term predator-prey relationships between fish and marine invertebrate larvae.⁵²³ Plicatamide, a modified octapeptide isolated from the blood of a San Diego Bay specimen of *Styela plicata*,⁵²⁴ and several synthetic analogues have been found to exhibit potent antimicrobial activity, to cause K⁺ efflux in *Staphylococcus aureus*, were potently hemolytic for human red blood cells, and formed cation-selective channels in model lipid bilayers.⁵²⁵ Structure–activity studies of halocidin, an antimicrobial peptide (3443 Da) isolated from hemocytes of the solitary ascidian *Halocynthia aurantium*,⁵²⁶ identified one congener with potent antimicrobial activity, but reduced hemolytic activity.⁵²⁷ Further biological investigation of the cytotoxic depsipeptide aplidine, isolated from *Aplidium albicans*,⁵²⁸ indicates that the compound inhibits the growth and induces apoptosis in MOLT-4 cells through inhibition of vascular endothelial growth factor (VEGF) secretion which blocks the VEGF-VEGFR-1 autocrine loop necessary for growth of these cells.⁵²⁹ In addition, aplidine prevents the *in vitro* aggregation of the prion peptide PrP 106–126.⁵³⁰ EPR studies of vanadium-binding proteins, isolated from the vanadocytes of the ascidian *Ascidia sydneiensis samea*, indicate that up to 24 vanadium ions bind per protein molecule in a mononuclear state and that coordination is through amine nitrogens.⁵³¹ The absolute configuration of etzionin **641**, an antifungal diketopiperazine hydroxamate originally isolated from an unidentified Red Sea ascidian,⁵³² has been secured by synthesis of all four stereoisomers of derivative **642**, and direct comparison of optical rotation



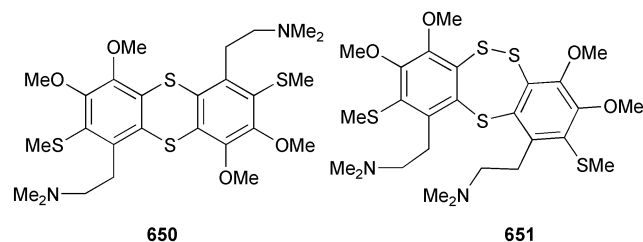
values with the same natural derivative.⁵³³ An initial attempt at expanding the structure–activity relationship of the cytotoxic quinolizidine alkaloid clavectipine B isolated from the Bermudian ascidian *Clavelina picta*,⁵³⁴ has indicated the importance of sidechain unsaturation, and that relative stereochemistry about the ring system does not seem to be important for cytotoxicity.⁵³⁵ Two full accounts of the stereoselective synthesis of lepadiformine, a biologically active alkaloid isolated from the ascidians *Clavelina lepadiformis* and *C. moluccensis*,^{536,537} have been reported.^{538,539} The structurally related ascidian alkaloids (+)-cylindricines C–E, isolated from an Australian collection of *Clavelina cylindrica*,⁵⁴⁰ were prepared using ruthenium-catalysed hydrolytic diene cyclisation methodology.⁵⁴¹ The quaternised indole-enamine conicamin **643** was isolated as a histamine antagonist from a Mediterranean collection of *Aplidium conicum*.⁵⁴² Cynthichlorine **644**, previously known as a synthetic product from the chlorination of methylindolyl methylester,⁵⁴³ was isolated from a Moroccan collection of *Cynthia savignyi*.⁵⁴⁴



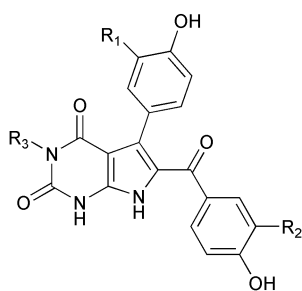
The alkaloid exhibited antifungal activity towards two tomato pathogenic fungi and bacteria and was also cytotoxic in the brine shrimp lethality assay. Studies of an unidentified ascidian collected in Madagascar have afforded the mildly cytotoxic alkaloids barrenzine A **645** and B **646**.⁵⁴⁵ The structures of the barrenzines were secured by use of ¹H-¹⁵N HMBC NMR experiments, while the observance of optical rotatory properties for **645** suggested the (*R**,*R**) configuration. Further investigation of the Mediterranean collection of *Aplidium conicum* yielded conicaquinones A **647** and B **648**, both of which exhibited cytotoxicity towards a rat glioma cell line.⁵⁴⁶ Kottamide E **649**,



the first example of a natural product bearing the amino acid 4-amino-1,2-dithiolane-4-carboxylic acid (Adt), was isolated from the New Zealand ascidian *Pycnoclavella kottae*.⁵⁴⁷ Benzotrithiols related to the cytotoxic pentathiepin ascidian alkaloids varacin⁵⁴⁸ and lissonclintoxin A^{549,550} have been prepared and optical rotatory properties and crystal structures investigated.⁵⁵¹ Lissoclinotoxins E **650** and F **651** were isolated as mildly

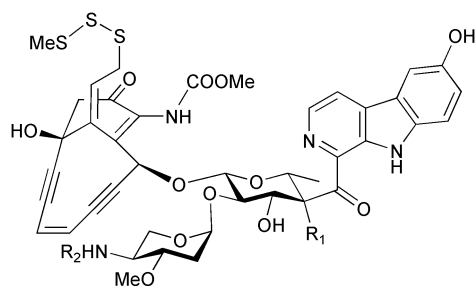
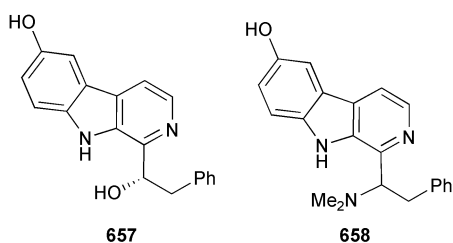


cytotoxic components of a Philippine didemnid ascidian.⁵⁵² The relative orientation of the aromatic rings of **650** and **651** were deduced, as shown, based upon molecular modeling studies. New members of the rigidin family of pyrrolopyrimidine alkaloids, rigidins B–D **652–654**, were isolated from an Okinawan collection of *Cystodytes* sp.,⁵⁵³ while rigidin E **655** was isolated from a Papua New Guinea collection of a *Eudistoma* species.⁵⁵⁴ Rigidins B–D were mildly cytotoxic towards the L1210 murine



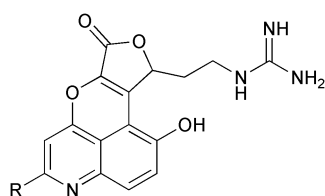
- 652** $R_1 = R_3 = \text{H}, R_2 = \text{OMe}$
653 $R_1 = \text{OMe}, R_2 = R_3 = \text{H}$
654 $R_1 = R_2 = \text{OMe}, R_3 = \text{H}$
655 $R_1 = R_2 = \text{H}, R_3 = \text{Me}$
656 $R_1 = R_2 = R_3 = \text{H}$

leukemia cell line⁵⁵³ while rigidin **656**⁵⁵⁵ and rigidin E were not cytotoxic towards A431 and wild-type and p53 deficient HCT-116 human tumour cell lines.⁵⁵⁴ Two β -carboline alkaloids, eudistomins W **657 and X **658**, were isolated from Chuuk Atoll, Micronesia collections of a *Eudistoma* species.⁵⁵⁶ The absolute stereochemistry of **657** was ascertained (Mosher method), and **658** was found to be more potent in antimicrobial assays. Shishijimicins A–C **659–661** are extraordinarily potent cytotoxic**



- 659** $R_1 = \text{SMe}, R_2 = 2\text{-propyl}$
660 $R_1 = \text{H}, R_2 = 2\text{-propyl}$
661 $R_1 = \text{SMe}, R_2 = \text{Et}$

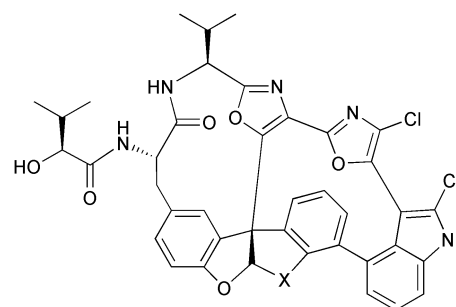
enediynes isolated from a South Japan collection of *Didemnum proliferum*.⁵⁵⁷ Relative and absolute stereochemistries were determined by standard methods and by comparison of CD data with that reported for the calicheamicins, terrestrial microbe-derived enediyne antibiotics. Distomadines A **662** and B **663** are new 6-hydroxyquinoline alkaloids from the New



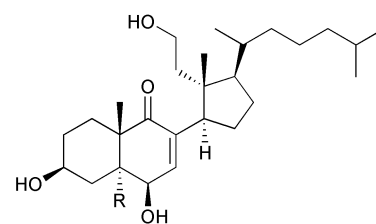
- 662** $R = \text{H}$
663 $R = \text{COOH}$

Zealand ascidian *Pseudodistoma aureum*.⁵⁵⁸ The structure of styelsamine C, an hydroxylpyridoacridine alkaloid isolated from the Indonesian ascidian *Eusynstyela latericius*,⁵⁵⁹ has been confirmed by synthesis.⁵⁶⁰ As noted in Section 7, 3-bromofascaplysin **301** was isolated from extracts of a *Didemnum* species ascidian collected at Chuuk Atoll, Micronesia, as well as from Fijian collections of *Fascaplysinopsis* sponges.²⁸⁶ The structure of

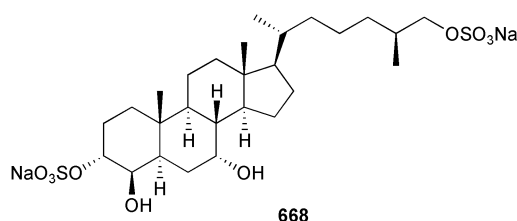
sebastianine A, a pentacyclic alkaloid isolated from a Brazilian collection of *Cystodytes dellechiaiei*,⁵⁶¹ has been confirmed by total synthesis.⁵⁶² Continued study of ascididemin, isolated from a Japanese collection of a *Didemnum* sp.,⁵⁶³ indicates that derivatives are also active in antiparasitic assays,⁵⁶⁴ that the antitumour activity can be varied somewhat predictably,^{565,566} and that a mechanism of reductive activation to form reactive oxygen species also contributes to the cytotoxicity of the parent alkaloid.⁵⁶⁷ The structure of bengacarboline, a cytotoxic alkaloid isolated from a Fijian collection of a *Didemnum* sp.,⁵⁶⁸ has been confirmed by total racemic synthesis.⁵⁶⁹ A convenient solid-phase synthesis of the ascidian metabolites lamellarin L⁵⁷⁰ and U⁵⁷¹ has been reported.⁵⁷² New improved syntheses of (–)-diazonamide A **664** have been reported,^{573,574} and investigation of the mechanism of action of **664** and analogue **665** indicate that the alkaloids are potent inhibitors of microtubule assembly, possibly at a unique site.⁵⁷⁵ Efficient syntheses of the naturally occurring cytotoxic ecteinascidins ET-729, -745, -759B, -736, -637 and -594^{576,577,578,579,580} from the fermentation product cyanosafrafracin B have been reported.⁵⁸¹ The parent compound, ET-743, continues to progress through clinical trials.^{582,583,584} Ritterazine B, a dimeric steroidal alkaloid isolated from *Ritterella tokioka*,⁵⁸⁵ induces apoptosis in HL-60 cells and causes cell cycle accumulation at G2/M, but has no caspase activation effect nor does it alter phosphorylation of bcl-2.⁵⁸⁶ Aplidiasterols A **666** and B **667** are new cytotoxic secosterols isolated from a Mediterranean collection of *Aplidium conicum*.⁵⁸⁷ The structure and absolute stereochemistry of a steroidal sperm-activating and attracting factor **668** isolated from the ascidian *Ciona intestinalis*⁵⁸⁸ has been unambiguously determined by total synthesis.⁵⁸⁹



- 664** $X = \text{NH}$
665 $X = \text{O}$

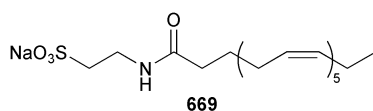


- 666** $R = \text{H}$
667 $R = \text{OH}$

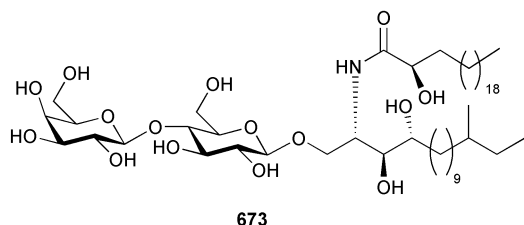
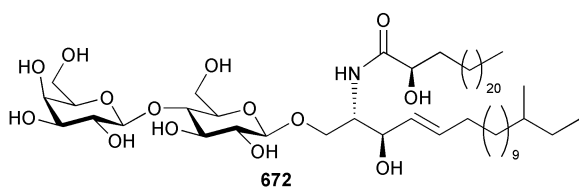
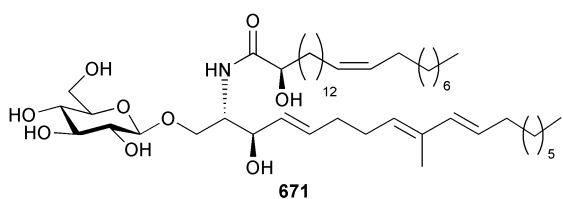
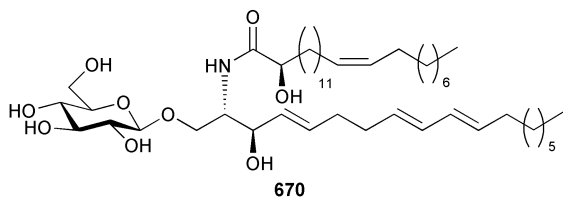


12 Echinoderms

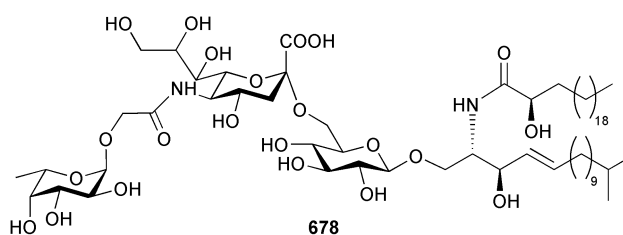
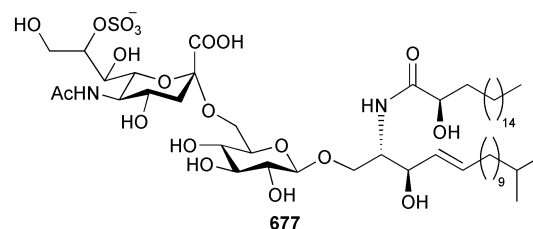
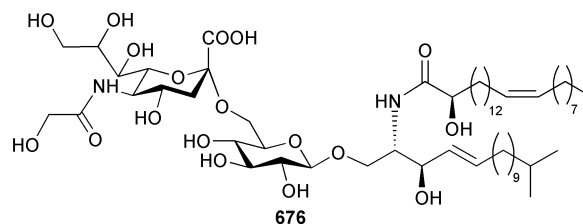
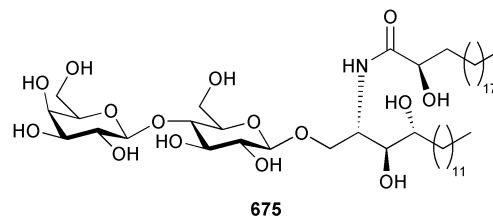
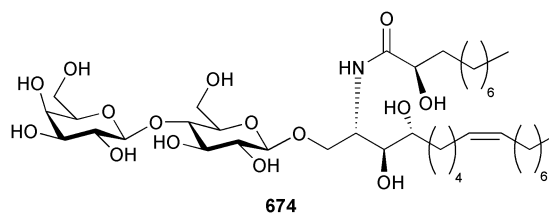
A similar number of new compounds were reported from echinoderms in 2003 compared with 2002. This field continues to be dominated by glycosylated ceramides and saponins. Taurine derivative **669** was isolated from a Gomun Island, Korea,



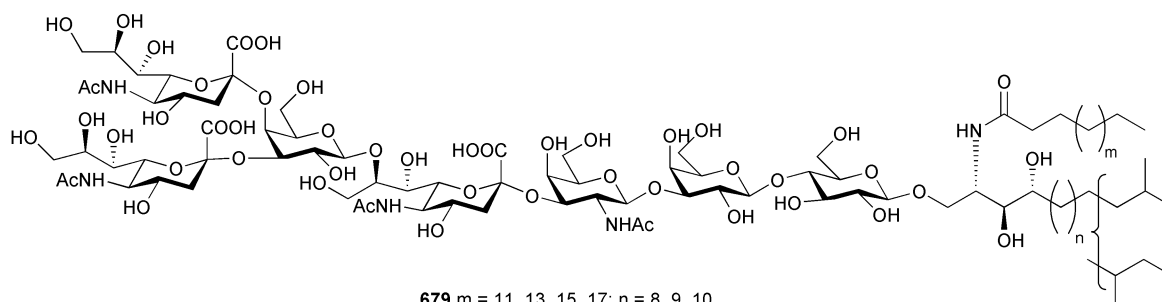
collection of the starfish *Certanaroda semiregularis*.¹⁹⁷ Investigation of the Patagonian starfish *Anasterias minuta* afforded a range of metabolites including the new glucosylceramide anasterocerebroside A **670**.⁵⁹⁰ The known ceramide **671**^{591,592} was also characterised for the first time. A Japanese collection of the starfish *Luidia maculata* yielded four ceramide lactosides, luidialactosides A–D **672–675**.⁵⁹³ The position of the olefin in

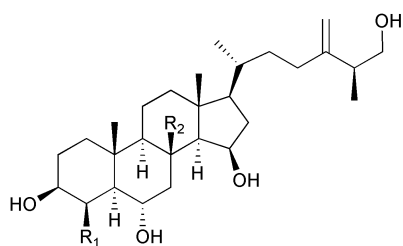


the long chain base of **674** was deduced by FABMS analysis of a dimethyl disulfide derivative. Three ganglioside molecular species, SCG-1–3, the major species of which are represented by **676–678**, were isolated from the Japanese sea cucumber *Stichopus chloronotus*.⁵⁹⁴ All three species displayed neuritogenic activity against PC12 cells in the presence of nerve growth factor. A structurally more complex ganglioside molecular species SJG-2 **679**, isolated from a Japanese collection of *Stichopus japonicus*, also exhibited neuritogenic activity.⁵⁹⁵ Brine shrimp lethality assay-directed fractionation of the starfish *Certanaroda semiregularis*, collected off Komun Island, Korea, afforded thirteen new polyhydroxysterols. These were certanardosterols A–M **680–692**,⁵⁹⁶ as well as the known **693**.⁵⁹⁷ Side chain

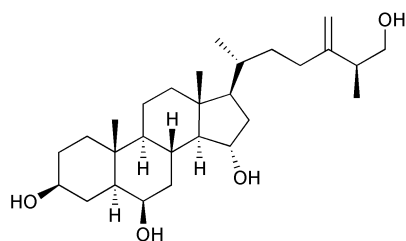


configurations at C-24 (for **686** and **693**), C-25 (for **680**) and both C-24 and C-25 (for **688**) were determined (Mosher method). All of the sterols, with the exception of **692**, exhibited modest *in vitro* cytotoxicity towards a panel of human tumour cell lines. A range of hemolytic steroid disulfates, including new examples **694** and **695**, were reported from the starfish *Pteraster pulvillus* collected by trawling in the Sea of Okhotsk in the Far East.⁵⁹⁸ Unusual alkaloid cation and steroidal anion compounds **696–698** were isolated from the starfish *Lethasterias nanimensis chelifera* collected by trawling near the Kuril Islands in the Far East.⁵⁹⁹ Comparison of optical rotation values identified the cation as being the (*R*)-isomer of salsolinol. Steroid glycosides (saponins), commonly isolated from echinoderms, present challenges in structural elucidation and exhibit a diverse range of biological activities, both aspects of which have been reviewed.^{600,601} Four

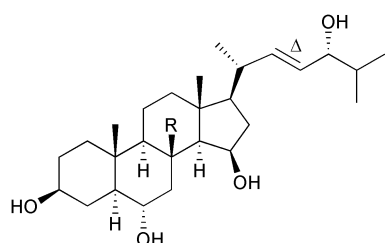




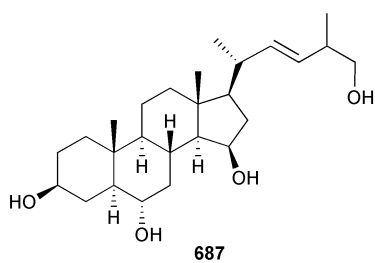
- 680 $R_1 = R_2 = OH$
 681 $R_1 = OH, R_2 = H$
 682 $R_1 = H, R_2 = OH$
 683 $R_1 = R_2 = H$



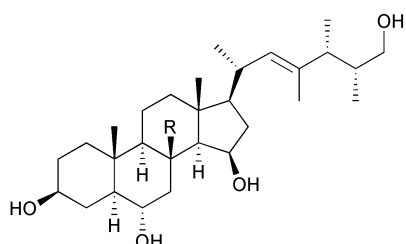
684



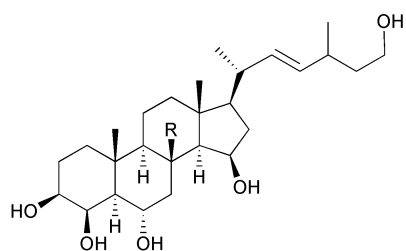
- 685 $R = H, \Delta$ saturated
 686 $R = H$
 689 $R = OH, \Delta$ saturated



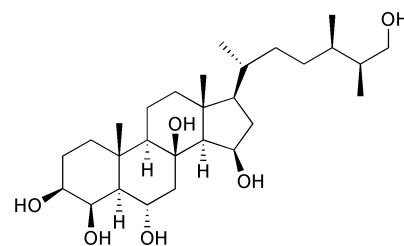
687



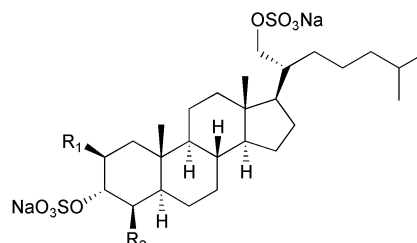
- 688 $R = OH$
 689 $R = H$



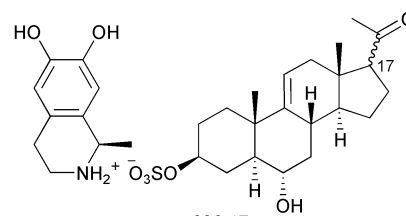
- 690 $R = OH$
 691 $R = H$



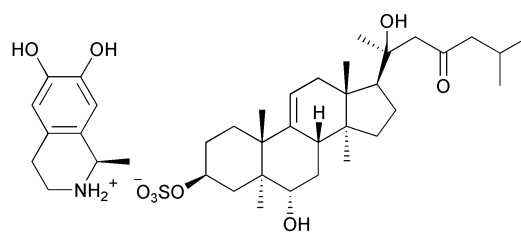
692



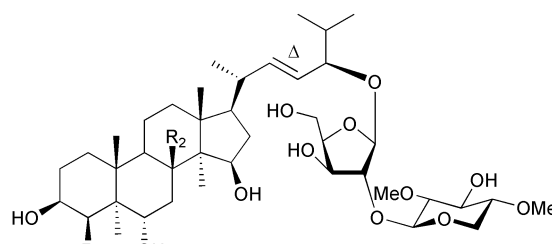
- 694 $R_1 = H, R_2 = OH$
 695 $R_1 = OH, R_2 = H$



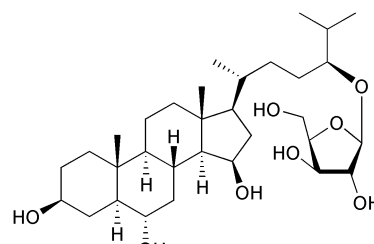
- 696 17β
 697 17α



698

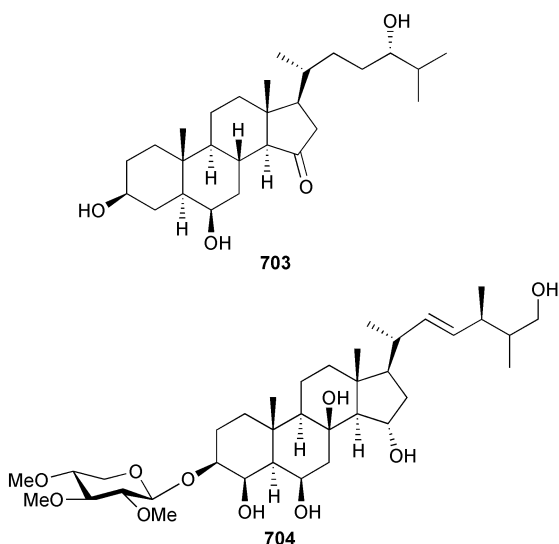


- 699 $R_1 = R_2 = OH, \Delta$ saturated
 700 $R_1 = R_2 = H, \Delta$ saturated
 701 $R_1 = OH, R_2 = H$



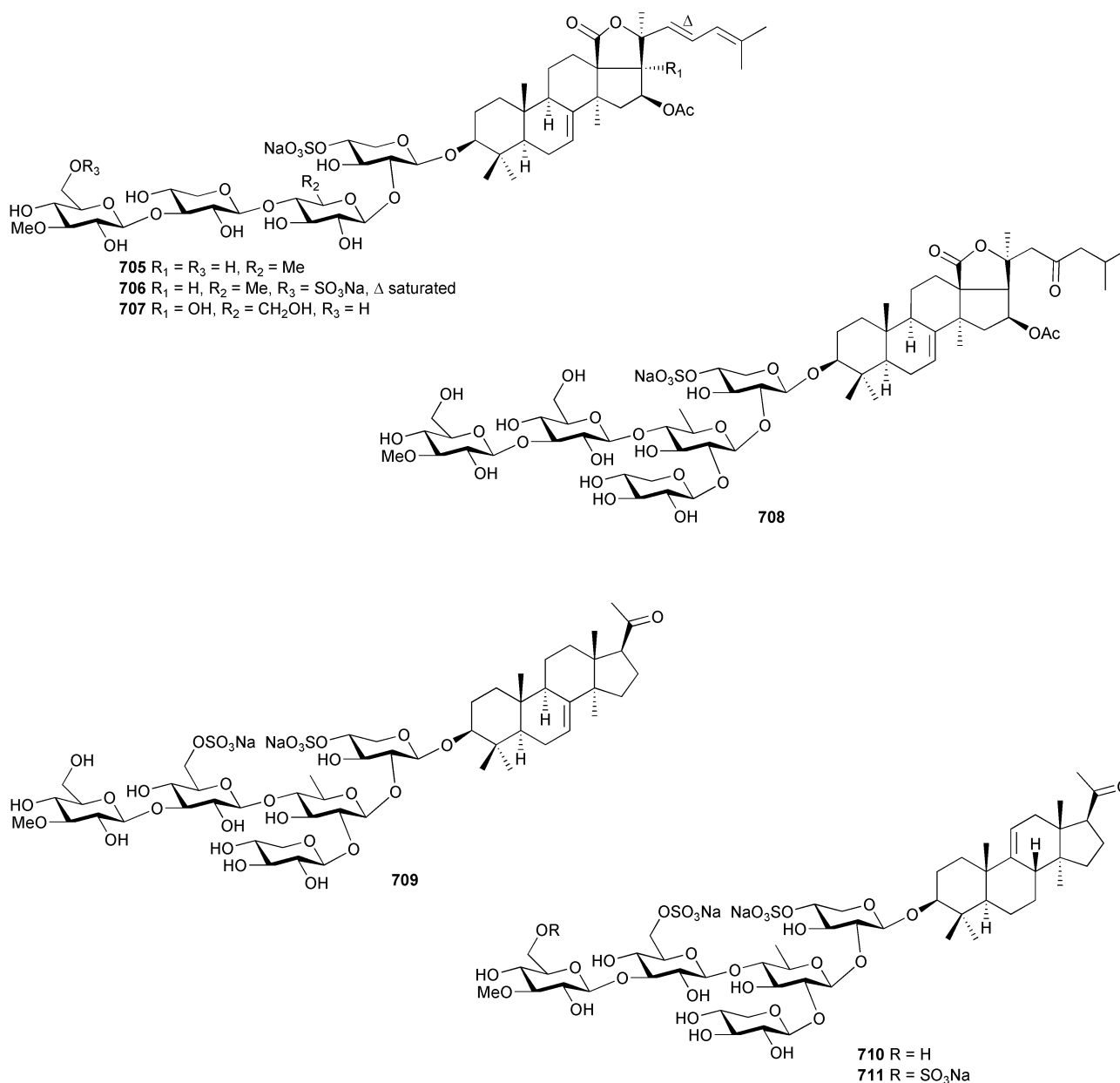
702

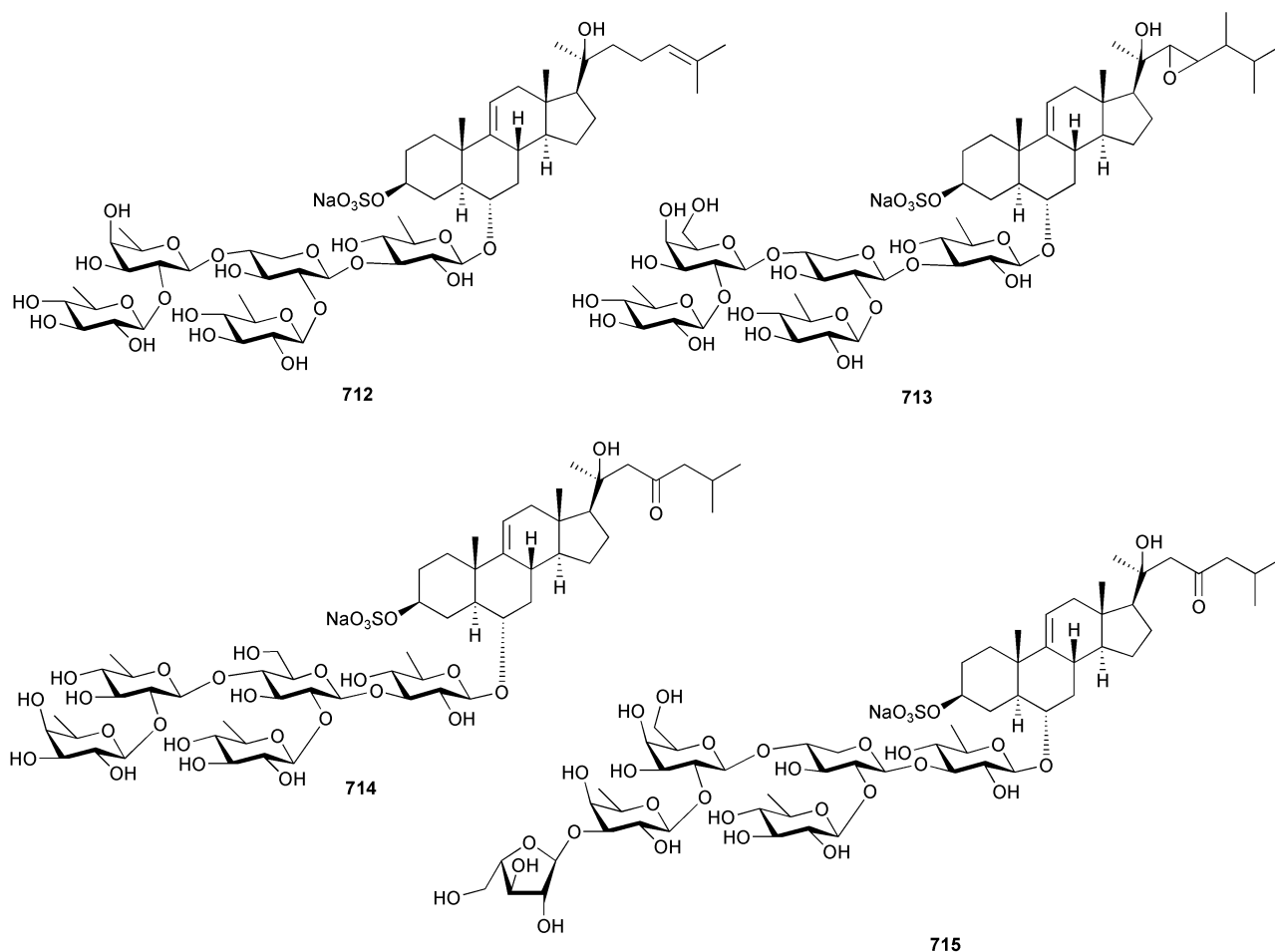
new saponins, certonardosides K–N **699–702**, isolated from the starfish *Certonardoa semiregularis* collected off Komun Island, Korea, exhibited varied biological activity towards a range of tumour cell lines and bacteria.⁶⁰² Configuration at C-24 in **699**,



701 and **702** was secured by methanolysis and analysis of MTPA ester derivatives. The polyhydroxylated steroid ketone **703** and monoglycosylated steroid **704** were reported from collections of

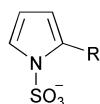
the Far Eastern starfish *Henricia sanguinolenta* and *H. leviuscula leviuscula*.⁶⁰³ Both compounds mildly inhibited division of fertilised sea urchin eggs. A South China Sea collection of the sea cucumber *Mensamaria intercedens* yielded intercedensides A–C **705–707**, novel triterpene glycosides that exhibited *in vitro* cytotoxicity towards a panel of human tumour cell lines.⁶⁰⁴ Intercedenside A also exhibited *in vivo* activity towards Lewis lung and mouse S180 sarcoma tumour models. A Sea of Japan collection of the sea cucumber *Cucumaria conicospermium* also afforded triterpene glycosides, cucumariosides A₂-5 **708**, A₃-2 **709**, A₃-3 **710** and isokoreoside A **711**, all of which contain the same pentasaccharide moiety, but differ in the number and position of the sulfate groups and the aglycone.⁶⁰⁵ Limited quantities of two new saponins ruberoside E **712** and F **713** were isolated from specimens of the starfish *Asterias rubens* collected in the Baltic Sea.⁶⁰⁶ The structures of both compounds were secured using a cryogenic NMR probe in an LC-NMR-MS configuration. Two mildly cytotoxic saponins, luidiaquinoside **714** and psilasteroside **715**, were reported from collections of the starfish *Luidia quinaria* collected at Sendai (Japan) and *Psilaster cassiope* collected in the northern Gulf of Mexico respectively.⁶⁰⁷ The pathological effects of sea urchin toxins has been reviewed.⁶⁰⁸





13 Miscellaneous

Three alkylnaphthalene sulfamates **716–718** were isolated as fish-feeding deterrent metabolites from the annelid *Cirriiformia tentaculata*, collected in Florida.⁶⁰⁹ Close to forty years after the structure of tetrodotoxin was elucidated,^{610,611,612} the first asymmetric syntheses of the alkaloid have been reported.^{613,614}



716 R = C₈H₁₇
717 R = C₇H₁₅
718 R = C₆H₁₃

14 Conclusion

In the early years of marine natural products research there was less emphasis on biological testing, but increasingly there has been a focus on the biological properties of these compounds. In the first of the Faulkner reviews (1977),⁶¹⁵ mention was made of the antibiotic properties of only a handful of compounds and reference made to the P388 activity of some *Dolabella auricularia* metabolites. In this review of the literature for 2003, over 720 compounds are included with biological activities being reported for 354 of these. The distribution of biological activities and source phyla for these compounds in 2003 is shown graphically in Figs. 1 and 2. The sponges and coelenterates continue to dominate as source phyla of new compounds, with microorganisms being the other major source. The relative incidence of bioactivity detected was greatest from the green algae followed by tunicates, echinoderms and sponges, but in absolute numbers the sponges dominated. The reported biological testing has been grouped into five categories, but is dominated by various tests for anticancer and antimicrobial/antiinfective properties.

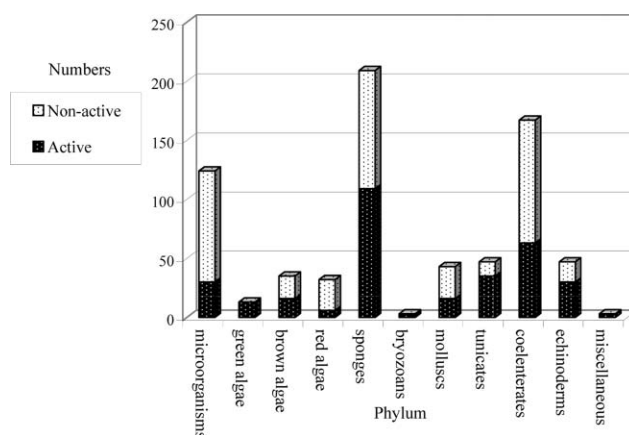


Fig. 1 Distribution of biologically-active and non-active marine natural products by phylum, 2003. (**Non-active**—compounds for which no biological activity has been reported; **Active**—compounds that are active in at least one bioassay).

Tunicates, echinoderms and sponges were prime sources for the detection of potential anti-cancer properties. This combination of source and biological activity is very much in keeping with the data presented in the timely review on marine natural products and related compounds in clinical and advanced clinical trials.⁶¹⁶ A graphical representation of the tabular data presented in that review is shown in Fig. 3. Progress towards marine anticancer drugs dominates with the prime source phyla being sponges followed by microorganisms, tunicates and molluscs. The other categories where marine natural products are progressing are in drugs for pain and asthmatic conditions where the interest is centered on *Conus* toxins and analogues of sponge sterols respectively.⁶¹⁶

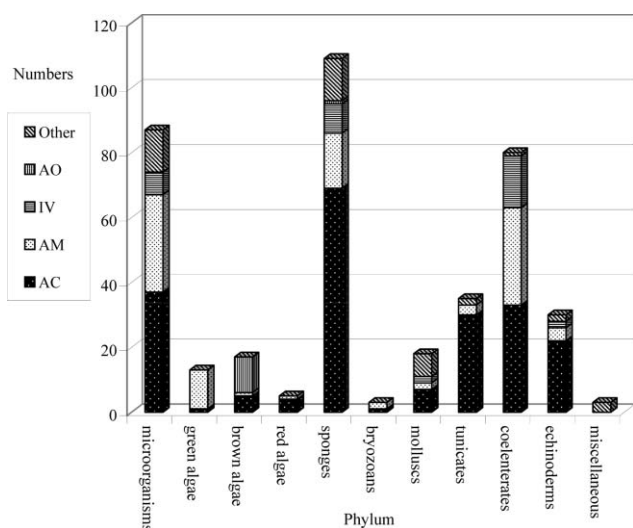


Fig. 2 Distribution of biological activity by phylum. (AC—cancer related assays including cytotoxicity, antimetabolic, histone deacetylase, proteasome, TNF, a range of kinases, DNA binding and matrix metalloproteinase; AM—antimicrobial, anti-infective, anti-Tb, antimalarial assays; AO—antioxidant assays; IV—*in vivo* assays such as brine shrimp and sea urchin eggs; Other—includes antiviral assays, assays based on central nervous system responses, feeding deterrent assays, ion channel assays, antifouling assays and assays for Fe siderophores, neuronal differentiation, oocyte lysis, sperm attractant and UV-A activity).

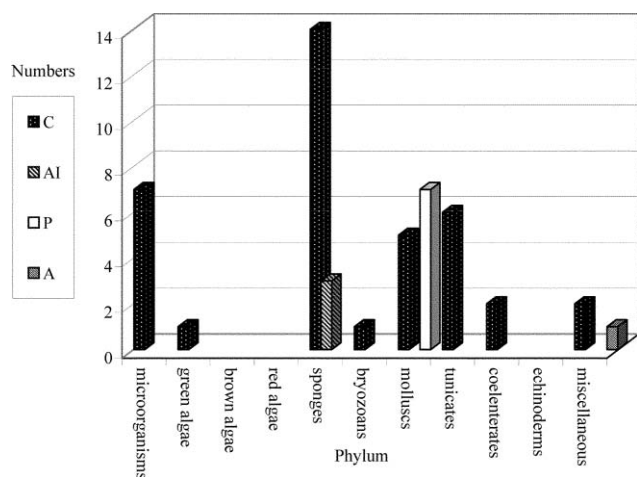


Fig. 3 Numbers and distribution of marine and marine-derived compounds in clinical and pre-clinical trials. (Data extracted from Table 1 in reference 616) (C—anticancer drugs; AI—anti-inflammatory drugs; P—drugs for intractable pain; A—Alzheimers).

Since the discovery of the arabinose-based nucleosides by Bergman over 50 years ago,⁶¹⁷⁻⁶¹⁹ the explosion of interest in alternative nucleoside compositions and the subsequent development of Ara-C and Ara-A as drugs with obvious linkages to later antiviral drugs such as acyclovir and AZT, there has been a tacit assumption that marine-based drugs would soon be forthcoming. That has not yet happened, but the first truly marine drugs should be licensed within the next two years.⁶¹⁶ Yondelis, better known as ecteinascidin 743, is in Phase II and III trials in Europe and the USA against soft tissue sarcoma, while the *Comus* toxin known as Ziconotide or Prialt is in Phase III clinical trials for intractable pain with plans for launching as a new drug in 2005. Despite problems in 2003 with the European Agency for the Evaluation of Medicinal Products, Yondelis will probably also be launched in 2005.⁶¹⁶

Acknowledgements

We thank Ekkehard Unger for the collection of data for this review.

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