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Marine natural products

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This review covers the literature published in 2004 for marine natural products, with 693 citations (491 for the period January to December 2004) 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 (716 for 2004), together with their relevant biological activities, source organisms and country of origin. Biosynthetic studies (8), and syntheses (80), including those that lead to the revision of structures or stereochemistries, have been included.

Covering: 2004. Previous review: *Nat. Prod. Rep.*, 2005, **22**, 15.

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1 Introduction

Previous reviews in this series, published in 2003 and 2004, noted the passing of D. John Faulkner and Paul J. Scheuer, and acknowledged their contributions to the field of marine natural products. Sadly, we now have to note the death of Professor Kenneth L. Rinehart in June 2005. Professor Rinehart had an academic career at the University of Illinois that spanned nearly five decades (1954-2001). Rinehart, like Faulkner and Scheuer, was a pioneer in the study of natural products with significant contributions in the application of mass spectrometry to the solving of natural product structures and the emphasis placed on the search for bioactive compounds sourced from marine organisms. Professor Rinehart pioneered the use of bioassays in the field during collecting expeditions, thus identifying species that should be recollected in larger amounts while still at the site of collection. Lasting contributions from Professor Rinehart will be from his work on the ecteinascidins and didemnins, two of the still relatively few marine natural products in advanced stages of clinical trials (Yondelis™ and Aplidine™).

This review is of the literature for 2004 and describes 716 new compounds from 259 articles, numbers that have increased by ~10% from those of each of the past few years. As in previous reviews, 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

In 2004 a larger than customary number of reviews were published covering many different aspects of marine natural products, with two reviews^{1,2} giving overall coverage of the 2003 literature. Several reviews describe work derived from regional collections, including Southern Africa,³ the Japanese coasts with emphasis on drug leads from marine invertebrates,⁴ ecosystem comparisons in New Caledonia,⁵ cytotoxic natural products from Taiwan,⁶ bioactive compounds from Brazil,⁷ diterpenes from Dictyotacean brown algae from the tropical Atlantic American region,⁸ and the efforts of Faulkner, Scheuer, Paul and the NCI in Palau.⁹

Reviews with an ecological and/or antifouling focus include an account of biogenic compounds from marine algae with potential as antifouling agents,¹⁰ a general discussion of biofouling and antifouling,¹¹ a review of the recent literature on marine chemical ecology,¹² an account of chemical defense strategies of marine organisms,¹³ and some insights into the antimicrobial defenses of selected marine invertebrates.¹⁴ There have been three articles that explore the nature of immune systems in various phyla, including marine invertebrates.^{15,16,17} A somewhat speculative article compares selected marine and non-marine toxins, raising issues such as convergence and the role of symbiotic organisms.¹⁸

Synthetic efforts on marine natural products continue to expand, with reviews covering a variety of topics including *trans*-fused polycyclic ethers,¹⁹ the convergent

syntheses of polycyclic ethers,²⁰ the use of Suzuki-Miyaura cross-couplings for polycyclic ethers,²¹ and the total syntheses of oxazole-containing natural products.²²

Several reviews focus on studies on compounds from specific types of organisms, such as cytotoxic metabolites from marine algae,²³ anticoagulants from marine algae,²⁴ metabolites of marine-derived fungi,²⁵ antimicrobials and antifungals from marine microorganisms,²⁶ toxins from microalgae,²⁷ enzyme inhibitors from marine microbes,²⁸ glycosides from sea cucumbers,²⁹ medicinal and pharmaceutical products from macroalgae,³⁰ bioactive polypeptides from *Anemonia sulcata*,³¹ metabolites from several species of sponges of the genus *Plakortis*³² and specifically from *Plakortis simplex*,³³ peptide and peptide-like pheromones and kairomones from crustaceans,³⁴ toxins from Northern Adriatic mussels,³⁵ metabolites from the gorgonian corals of the genus *Junceella*,³⁶ and metabolites from symbiotic bacteria.³⁷

A broad range of bioactivities of marine natural products is reviewed in several articles, including marine pharmacology in 2000,³⁸ the merging of the potential of microbial genetics with biological and chemical diversity,³⁹ drugs and cosmetics from the sea,⁴⁰ unconventional natural sources for future drug discovery,⁴¹ new structures and bioactivities for small-molecule natural products,⁴² and marine natural products and related compounds in clinical and advanced preclinical trials.⁴³

Treatments for specific disease types is the subject of several reviews including the search for new candidates for cancer chemotherapy from natural products,⁴⁴ antitumour and cytotoxic compounds reported in 2001-2,⁴⁵ mechanism-targeted discovery of antitumour marine natural products,⁴⁶ antiviral marine natural products,⁴⁷ antifungal compounds from marine organisms,⁴⁸ and natural antimycobacterial metabolites.⁴⁹

Specific compound classes are reviewed in antimicrobial peptides from marine invertebrates,⁵⁰ bioactive peptides from marine sources,⁵¹ mycosporine-like amino acids,⁵² simple indole alkaloids and those with a nonrearranged monoterpene unit,⁵³ bioactive alkaloids,⁵⁴ bisindole alkaloids from sponges,⁵⁵ quinolizidine alkaloids from marine sources,⁵⁶ purines from marine organisms,⁵⁷ siderophores from marine microorganisms,⁵⁸ secosteroids of marine origin (1972-2004),⁵⁹ biologically active natural glycosides,⁶⁰ drimane sesquiterpenoids (1990-2002),⁶¹ diterpenoids (2002),⁶² diterpenoids (2003),⁶³ organohalogen compounds,⁶⁴ marine isocyanides and related compounds,⁶⁵ and allenic compounds.⁶⁶

Research on specific compounds is reviewed in articles on discodermolide,⁶⁷ curacin A,⁶⁸ agelasphin KRN7000,⁶⁹ ecteinascidin 743, aplidine and kahalalide F,^{70,71} amphidinolides (1986-2003),⁷² shark-repelling saponins mosesins and pavoninins,⁷³ lamellarins,⁷⁴ and the bisindole alkaloids dragmacidins and hamacanthins.⁷⁵

A brief review on “Drugs from the Sea – Who are the producers?” explores the hypothesis that microorganisms, either by way of ingestion or as symbionts, are the true source of bioactive compounds from marine invertebrates.⁷⁶ Two reviews on the use of mass spectrometry in peptidomics⁷⁷ and analysis of marine toxins⁷⁸ should be of general interest. The Marinlit database⁷⁹ continues to be updated and has again been used as the basis for the preparation of this present review.

3 Marine Microorganisms and phytoplankton

Increasingly, the field of marine microbes is becoming a focal point for research and rising numbers of novel compounds continue to be identified. An actinomycete, *Micromonospora* sp. obtained from *Didemnum proliferum* (Shishijima Is., Japan), produced the dibenzodiazepine alkaloid, diazepinomicin **1**, which exhibited modest antimicrobial activity against selected Gram-positive bacteria.⁸⁰ Gutingimycin **2** is a highly polar trioxacarcin derivative from a *Streptomyces* species isolated from sediment (Laguna de Terminos, Gulf of Mexico).⁸¹ The absolute configuration was determined by X-ray analysis.⁸² The same *Streptomyces* species⁸¹ also yielded trioxacarcins D–F **3–5**, in addition to the known trioxacarcins A–C.^{83,84,85} The structures and absolute configurations of the new trioxacarcins followed from the X-ray analysis of gutingimycin **2** and the known stereochemistry of L-trioxacarcins A and B.⁸⁵ The trioxacarcins and gutingimycin **2** exhibited strong antibacterial activity against a range of test organisms. The antitumour activity of trioxacarcin D **3** was similar to that previously reported for trioxacarcins A–C,^{83,84,85} while trioxacarcin A and trioxacarcin D **3** were also potently antiplasmodial.⁸⁶ *S. acrimycini*, isolated from sediment (São Sebastião channel, Brazil), provided two dipeptide derivatives, 8-amino-[1,4]diazonane-2,5-dione **6** and leucyl-4-hydroxyproline **7**.⁸⁷ A cultured Nereus™ strain of *S. aureoverticillatus* isolated from marine sediment (source not given) produced a macrocyclic lactam, aureoverticillactam **8**, possessing moderate activity against human tumour cell lines. Some stereochemistry (2*E*,6*E*) could be determined, but other olefins could not be assigned due to spectral overlap.⁸⁸ Two caprolactones **9** and **10** were produced from a *Streptomyces* species (mangrove sediment, Papua New Guinea). The proposed structures were based on GCMS experiments and proven by synthesis, while the absolute configurations of **9** and **10** were

established using chiral GC to compare the natural and synthetic stereoisomers.

Compounds **9** and **10** displayed moderate phytotoxicity and concentration-dependent inhibition of human cancer cell lines, with concomitant low general cytotoxicity.⁸⁹ A *Bacillus* species obtained from mud near the Arctic pole yielded three cyclopeptides, mixirins A–C **11–13**. The absolute stereochemistries of the amino acid residues were determined (Marfey's), but not those of the fatty acid residues. The mixirins A–C inhibited the growth of human colon tumour cells (HCT-116).⁹⁰ Petrobactin sulfonate **14**, along with petrobactin,⁹¹ was isolated from the oil-degrading marine bacterium *Marinobacter hydrocarbonoclasticus*,^{91,92} and is the first marine siderophore containing a sulfonated 3,4-dihydroxy aromatic ring. The structure of petrobactin sulfonate was elucidated from spectral data, resulting in a revision of the NMR assignments for petrobactin.⁹³ An actinomycete, *Verrucosispora* sp. (deep sediment, Sea of Japan), yielded the abyssomicins B–D **15–17**, whose structures and relative stereochemistries were supported by X-ray analyses. The absolute stereochemistry of abyssomicin D **17** was determined (Mosher and Helmchen methods) and, through structural analogy, assumed to be the same for abyssomicins B **15** and C **16**.⁹⁴ Abyssomicin C **16** was identified as an inhibitor of the pathway between chorismic and *para*-aminobenzoic acids and was strongly active against Gram-positive bacteria.⁹⁵ Helquinoline **18**, and the *N*-acetylkynuramine **19**, were produced by a North Sea bacterium *Janibacter limosus*. Helquinoline displayed moderate activity against *B. subtilis*, *Streptococcus viridochromogenes* and *Staphylococcus aureus*.⁹⁶ Two cyclic peptides **20** and **21** were isolated from a bacterial *Ruegeria* species associated with cell cultures of a sponge *Suberites domuncula* (Gulf of Naples, Italy).⁹⁷ Two further peptides from the culture

were known synthetic compounds,^{98,99} but isolated for the first time from nature. A known peptide¹⁰⁰ and a new diastereoisomer **22** were also obtained, in addition to a peptide first reported from rabbit skin tissue.¹⁰¹ Cyclopeptides **20** and **21** exhibited moderate activity against *B. subtilis*.¹⁰² Two cyclodepsipeptides, petrosifungins A **23** and B **24**, have been isolated from *Penicillium brevicompactum* derived from a sponge *Petrosia ficiformis* (Elba, Italy). The absolute configurations of the amino acids were determined (Marfey's).¹⁰³ A mixed culture of two *P. corylophilum* strains, (deep water sediment, Fiji/Matuka), provided the known fungal pigments anserinones A and B¹⁰⁴ along with three other pentaketides, (+)-formylanserinone B **25**, (-)-epoxyserinone A **26** and (+)-epoxyserinone A **27**. Two further minor constituents of the extract, hydroxymethylanserinone B **28** and deoxyanserinone B **29**, were isolated but not completely purified. The relative stereochemistries of **25** and **26** were determined (NOE experiments and molecular mechanics calculations), but the stereochemistry of (+)-formylanserinone B **25**¹⁰⁵ was subsequently revised from (9*S*) to (9*R*) based on recognition of discrepancies in published data.^{104,106} Similarly, the structure of (-)-epoxyserinone A **26** has been clarified as the structure was incorrectly drawn in the original report.¹⁰⁵ The revised stereochemistry for **25** requires the absolute stereochemistry of **26** to be (2*R*,3*S*,4*S*,9*R*).¹⁰⁷ Anserinone B and (+)-formylanserinone B **25** were the most active against a range of tumour cell lines.¹⁰⁵ *P. citrinum*, isolated from a red alga *Actinotrichia fragilis* (Okinawa, Japan), was the source of citrinadin A **30** that displayed modest cytotoxicity against L1210 and KB cell lines.¹⁰⁸ A *Penicillium* species, from a sponge *Axinella verrucosa* (Elba, Italy), produced the known compound communesin B¹⁰⁹ and the new congeners communesins C **31** and D **32**. Communesins B–

D exhibited moderate antiproliferative activity against several human leukemia cell lines and were active against brine shrimp.¹¹⁰ A mussel *Mytilus edulis* (Toyama Bay, Japan Sea) was the source of an *Aspergillus* species that yielded a polyketide, aspermytin A **33**, with the absolute configuration being deduced from the CD spectrum. Aspermytin A **33** induced neurite outgrowth in rat pheochromocytoma cells.¹¹¹ Golmaenone **34**, a diketopiperazine alkaloid, was obtained from an *Aspergillus* species isolated from a red alga *Lomentaria catenata* (Ulsan City, Korea). The absolute stereochemistry was established (Marfey's) as were significant radical scavenging and UV-A protecting properties.¹¹² *A. pseudodeflectus*, isolated from an alga *Sargassum fusiform* (Miura Peninsula, Japan), was the source of pseudodeflectusin **35**, an isochroman cytotoxic against human cancer cell lines.¹¹³ A diketopiperazine dimer **36** was obtained from a marine-derived *A. niger* supplied by the Australian Institute of Marine Sciences, and the absolute stereochemistry determined (chiral HPLC).¹¹⁴ *A. niger*, isolated from a sponge *Axinella damicornis* (near Elba, Italy), yielded seven metabolites; the bicoumanigrin **37**, the structurally unusual 4-benzyl-1*H*-pyridin-6-one derivatives aspernigrins A **38** and B **39** and the pyranonigrins A–D **40–43**, which contain the unprecedented pyrano[3,2-*b*]pyrrole skeleton. The absolute configurations of aspernigrin B **39** and pyranonigrin A **40** were established by quantum chemical calculations of the CD spectra. Also isolated was the known fungal pigment cycloleucomelone,^{115,116} which was moderately cytotoxic against human cancer cell lines *in vitro*, while aspernigrin B **39** was established as strongly neuroprotective.¹¹⁷ Cultivated mycelium of *A. flavipes*, isolated from a sea anemone *Anthopleura xanthogrammica* (Qingdao Bay, eastern China Sea), produced two cerebroside analogues, flavicerebrosides A **44** and B **45**, with moderate activities against

the KB cell line.¹¹⁸ *Aigialus parvus*, isolated from mangrove wood (Thailand), provided the ketene acetal aigialone **46** and the spiroacetal aigialospirol **47**. X-ray analysis of **46** established the relative stereochemistry only.¹¹⁹ The moderately cytotoxic oxopiperazine metabolites, gliocladins A–C **48–50**, and glioperazine **51** were isolated from a strain of *Gliocladium* species separated from a sea hare *Aplysia kurodai* (Kata coast, Japan). Relative stereochemistries at all centres, except for C-3 in **48** and **49** and for C-8 in **51**, were determined (NOESY).¹²⁰ Four cytotoxic diterpene glycosides, virescensides R–U **52–55**, were isolated from *Acremonium striatisporum* originating from a holothurian *Eupentacta fraudatrix* (Kitovoe Rebro Bay, Sea of Japan).¹²¹ The stereochemistry of C-13 in **55** was determined by comparison against known compounds.¹²² *Apiospora montagnei*, isolated from the inner tissue of an alga *Polysiphonia violacea* (North Sea near Helgoland), was the source of myrocin A **56**, apiosporic acid **57**, methyl 9-hydroxyhexylitaconate **58** and the (–)-enantiomer **59** of the known (+)-hexylitaconic acid.^{123,124,125} Five leptosins O–P **60–64** were obtained from a *Leptosphaeria* species, originally separated from *Sargassum tortile* (Tanabe Bay, Japan),¹²⁶ but structural and absolute stereochemistry determinations were performed on the derived acetates. Leptosins O **60** and P **61** exhibited significant cytotoxicity against P388 cells while leptosins O **60** and S **64** were moderately cytotoxic to 39 human tumour cell lines.¹²⁷ *Emericella variecolor*, (marine sediment, Gokasyo Gulf, Japan), provided two new sesterterpenes, 6-*epi*-ophiobolin G **65** and 6-*epi*-ophiobolin N **66** along with six previously reported ophiobolins. All isolated compounds were cytotoxic against a neuroblastoma cell line.¹²⁸ The modestly cytotoxic cyclic dipeptides rostratins A–D **67–70** were isolated from *Exserohilum rostratum*, a fungal strain associated with a marine

cyanobacterial mat (Lanai, Hawaii). Absolute configurations of the rostratins were determined (Mosher's).¹²⁹ Peribysins A–D **71–74**, from a strain of *Periconia byssoides* originating from *Aplysia kurodai*,¹³⁰ are eremophilane sesquiterpenoids of which **73** and **74** represent a new class of furanofuran, and are potent inhibitors of the adhesion of HL-60 cells to HUVEC, with **74** being the most active.¹³¹ An eremophilane sesquiterpene, 7H239-A **75**, was obtained from a xylariaceous fungus isolated from a *Nypa* (mangrove) palm frond (Kuala Selangor, Malaysia) and was cytotoxic towards a variety of cancer cell lines, with some selectivity for the CCRFCM leukemia line.¹³² The diterpene phomactin H **76**, with a novel skeleton including an oxepane moiety, was obtained from an unidentified surface fungus isolated from a brown alga *Ishige okamurae* (Tateishi, Japan). The structure and relative stereochemistry were determined by X-ray analysis.¹³³ Two halogenated alkenoates, **77** and **78** were isolated from an unidentified surface fungus of a red alga *Gracillaria verrucosa* (Jinha, Korea).¹³⁴ A total synthesis, using a Cr(II)/Ni(II) macrocyclisation, has been reported¹³⁵ for racemic phomactin G, from a marine fungal *Phoma* species.¹³⁶ A *Cladosporium* species from a brown alga *Actinotrichia fragilis* (Okinawa, Japan), produced two cytotoxic macrolides, sporiolides A **79** and B **80**. Sporiolide A **79** was also moderately antifungal against a range of organisms, while both sporiolides were active against *Micrococcus luteus*.¹³⁷ Fuscoatrol A **81**, a caryophyllene sesquiterpene, was isolated from *Humicola fuscoatra* associated with an unidentified colonial ascidian (Shikotan Is., Kuril Isles) with the structure being confirmed by X-ray analysis. Fuscoatrol A **81** displayed moderate antimicrobial activity and was cytotoxic against sea urchin eggs.¹³⁸ *Lyngbya majuscula* (Hector's Bay, Jamaica) was the source of three lipopeptides, jamaicamides A–C **82–84**. Structural elucidation

included the use of the Accordion 1,1-ADEQUATE experiment.¹³⁹ This experiment detects ^1H - ^{13}C - ^{13}C spin systems for a wide range of ^{13}C - ^{13}C coupling values and permits unequivocal distinction between 2- and 3-bond HMBC correlations. Only the C-23 stereochemistry of jamaicamide A **82** could be determined (Marfey's). Biosynthetic experiments suggested that the jamaicamides result from alternating PKS and NRPS assembly units, confirmed through cloning and identification of the biosynthetic gene cluster. The jamaicamides displayed cytotoxic, sodium channel blocking and ichthyotoxic activities.¹⁴⁰ Eleven chlorinated lipids, taveuniamides A–K **85–95**, were isolated from two mixed samples of *L. majuscula* and *Schizothrix* sp. (Taveuni Is., Fiji). Taveuniamides F **90**, G **91** and K **95** exhibited relatively potent brine shrimp toxicity.¹⁴¹ From a total synthesis of kalkitoxin and its congeners, the absolute stereochemistry of this potent neurotoxin isolated from *L. majuscula*¹⁴² could be assigned as (3*R*,7*R*,8*S*,10*S*,2'*R*).¹⁴³ Kalkitoxin, from a second total synthesis, exhibited potent activity against HCT-116.¹⁴⁴ A *Symploca* species (Fingers Reef, Guam) was the source of two cytotoxic compounds, micromide **96** and guamamide **97**. Chiral HPLC and chemical derivatisation followed by comparison with synthetic standards established the absolute stereochemistry of **96**.¹⁴⁵ Isolation of 8-hydroxy-3,5-dimethyl-isochroman-1-one¹⁴⁶ from a mangrove fungus (coastal South China Sea) is the first report of this compound from a marine source.¹⁴⁷ A symbiotic dinoflagellate *Symbiodinium* species, from an acoel flatworm *Amphiscolops* species (source not given), produced the amphoteric iminium compound symbioimine **98**. The absolute stereochemistry was determined by X-ray analysis. Symbioimine **98** inhibited osteoclastogenesis of the murine monocytic cell line RAW264 and therefore has potential for use as an antiresorptive for prevention and

treatment of osteoporosis in postmenopausal women.¹⁴⁸ The cytotoxic 25-membered macrolide amphidinolide C2 **99** was obtained from a dinoflagellate *Amphidinium* species isolated from an acoel flatworm *Amphiscolops* species (Sunabe, Okinawa).¹⁴⁹ Structural elucidation of (+)-amphidinolide A **100**, also from an *Amphidinium* species,^{150,151} has been completed through a combination of NMR analysis and total synthesis.¹⁵² Amphidinolide H¹⁵³ attenuated actin depolymerisation induced by diluting F-actin and enhanced the binding of phalloidin to F-actin and is therefore a useful tool for analyzing actin-mediated cell function.¹⁵⁴ A total synthesis of amphidinolide W **101**, a 12-membered macrolide isolated from an *Amphidinium* species,¹⁵⁵ has been completed with revision of the C-6 stereochemistry.¹⁵⁶ A total synthesis of amphidinolide X¹⁵⁷ has also been reported.¹⁵⁸ A dinoflagellate *Amphidinium* species, originally isolated from the surface wash of seaweeds (Lingshui Bay, Hainan Province, China), was the source of the potent cytotoxin lingshuiol **102**.¹⁵⁹ The same culture yielded two further lingshuiols, A **103** and B **104**.¹⁶⁰ Two strains of a dinoflagellate *Protoceratium cf. reticulatum* (Sanriku, Iwate, Japan) were the source of four potent antitumour compounds, protoceratins 1–4. Protoceratin 1 was identical to the shellfish toxin 2-homoyessotoxin,¹⁶¹ while protoceratins 2–4 **105–107** were determined to be the di-, mono- and tri-arabinosides of 2-homoyessotoxin respectively.¹⁶² A *Symbiodinium* species, isolated in the free-living state from a Hawaiian tide pool, gave the polyhydroxy metabolite zooxanthellamide B **108**, a δ -lactone analogue of zooxanthellamide A¹⁶³ which had previously been obtained from the same dinoflagellate.¹⁶⁴ Several *Symbiodinium* strains obtained from different researchers around Japan produced zooxanthellactone **109**. The original strain used for the production was isolated from the foraminifer, *Amphisorus hemprichii*. The absolute

stereochemistry of zooxanthellactone **109**, which was modestly cytotoxic against two human squamous cell carcinomas, was also established.¹⁶⁵ The polyether brevenal **110**, obtained from laboratory cultures of *Karenia brevis* as well as collections off the west coast of Florida during a red tide, competes with brevetoxin for a site associated with the voltage-sensitive sodium channel thus protecting fish from the neurotoxic effects of brevetoxin exposure. Brevenal may have utility as a model compound for the development of therapeutics to prevent, or reverse intoxication in red tide exposures.¹⁶⁶ A study in rats using short-term inhalation exposure to brevetoxin 3¹⁶⁷ suggested that the immune system may be a target of toxicity following brevetoxin inhalation.¹⁶⁸ The rapid effects of brevetoxin-2¹⁶⁹ and saxitoxin¹⁷⁰ on embryonic murine frontal cortex neuronal networks on microelectrode arrays have been reported.¹⁷¹ NMR studies on two synthetic diastereomeric models corresponding to the CDE/FG ring of prymnesins,^{172,173} suggested that the earlier stereochemical assignment of the E/F ring juncture in the prymnesins needs to be revised.¹⁷⁴ A total synthesis of oscillarin **111**, an antithrombotic peptide from *Oscillatoria agardhii*,¹⁷⁵ has been achieved, confirming the absolute stereochemistry proposed and correcting the structure of a subunit to the Δ^3 -pyrroline-containing unit shown. Bioassays confirmed that **111** is a potent thrombin inhibitor while the originally assigned structure is inactive. An X-ray analysis of a ternary complex between oscillarin and α -thrombin has been reported.¹⁷⁶ Synthetic (1*S*,2*S*) grenadamide had equal but opposite optical rotation from natural grenadamide from *Lyngbya majuscula*,¹⁷⁷ which is therefore the (1*R*,2*R*)-enantiomer **112**.¹⁷⁸ Both enantiomers of xestodecalactone A¹⁷⁹ have been synthesised, and CD and chiral HPLC comparisons have confirmed the (*R*)-configuration for the natural product.¹⁸⁰ Using inexpensive starting materials, concise

total syntheses of the maculalactones A,¹⁸¹ B¹⁸² and C,¹⁸² from a cyanobacterium *Kyrtuthrix maculans*, have been achieved. Results from optical rotation measurement, chiral HPLC and NMR spectroscopy in the presence of a chiral shift reagent established that natural maculalactone A is present in *K. maculans* as a partially racemic mixture.¹⁸³ Total synthesis of the *Bacillus laterosporus* polyketide antibiotics basiliskamide A and B¹⁸⁴ confirmed the assignment of absolute configuration as (7*S*,8*S*,9*R*,10*S*).¹⁸⁵ The first total synthesis of (+)-phomopsidin, a microtubule assembly inhibitor and isolated from a *Phomopsis* species,¹⁸⁶ has been achieved via a diastereoselective transannular Diels-Alder reaction.¹⁸⁷ The total synthesis of halovir A,¹⁸⁸ one of a series of linear, lipophilic peptides produced by a *Scytalidium* species, has been completed as part of a structure-activity relationship study of the series.¹⁸⁹ A one-pot multistep domino reaction from a starting enone of established absolute configuration was used to complete a total synthesis of the mangrove fungus metabolite (+)-xyloketal D.^{190,191} The dinoflagellate metabolite yessotoxin¹⁹² has been shown to induce a cyclosporin A-sensitive permeability transition in rat liver mitochondria and Morris Hepatoma 1C1 cells in the presence of permissive levels of calcium, and also induces membrane depolarisation.¹⁹³ The potent ichthyotoxin antillatoxin from *Lyngbya majuscula*,¹⁹⁴ along with three synthetic stereoisomers, were assessed for ichthyotoxicity and cytotoxicity in five different assay systems. In all assays the natural antillatoxin was the most potent.¹⁹⁵ Euplotin C,¹⁹⁶ a sesquiterpene from a marine ciliate protist *Euplotes crassus*, displayed moderate activity against the protozoa *Leishmania major* and *L. infantum* and mild activity against *Candida albicans*.¹⁹⁷ An assay for inhibitors of lymphocyte function-associated molecule 1/intercellular cell adhesion molecule-1 (LFA-1/ICAM-1) mediated cell-cell adhesion

was used to identify new pharmacologically active compounds from marine cyanobacteria and algae.¹⁹⁸ Six of the sixty marine natural products tested significantly inhibited LFA-1/ICAM-1 mediated cell adhesion after primary and secondary testing. These compounds were cymathere aldehyde,¹⁹⁹ microcolins B²⁰⁰ and D,¹⁹⁸ avrainvilleol,²⁰¹ cymopol²⁰² and hormothamnione diacetate.^{203,204,205} The stereochemistry of a cyclisation product, and results of incorporation experiments with [1-¹³C]- and [1,2-¹³C₂]-acetates, were used to propose the course of geranylgeranyl diphosphate cyclisation in the biosynthesis of the phomactins^{206,207,208,136} from a marine fungal *Phoma* species.²⁰⁹ Incubation of a diatom *Rhizosolenia setigera* with [1-¹³C]-acetate indicated that the polyunsaturated monocyclic sesterterpene and triterpene metabolites are produced predominantly via the mevalonate pathway.²¹⁰

4 **Green algae**

Very few new secondary metabolites from green algae have been reported. Capisterones A **113** and B **114** are triterpene sulfate esters isolated from *Panicillus capitatus* (Cat Cay, Bahamas). Both compounds exhibited potent antifungal activity against the marine algal pathogen *Lindra thallasiae*.²¹¹

5 **Brown algae**

As noted in previous reviews, terpenes and polyphenolic compounds are the predominant metabolite classes found in brown algae. A sample of *Eisenia bicyclis*, a very common

Pacific-coast Japanese species, was purchased from a Japanese company and yielded a new phloroglucinol derivative **115**, and two known phloroglucinols, eckol²¹² and dieckol.^{213,214} All three compounds inhibited glycation and α -amylase, so may have an effect on complications of diabetes.²¹⁵ Phloroglucinol²¹⁶ and the derivatives eckstolonol,²¹⁷ eckol,²¹² phlorofucofuroeckol A²¹⁸ and dieckol,²¹³ isolated from *Ecklonia stolonifera* are tyrosinase inhibitors.²¹⁹ Five meroditerpenes, amentol chromane diacetate **116**, cystoseirone diacetate **117**, preamentol triacetate **118**, 14-*epi*-amentol triacetate **119** and 14-methoxyamentol chromane **120** were obtained from a *Cystoseira* species (Canary Islands).²²⁰ Two cytotoxic trihydroxylated diterpenes based on 12-hydroxygeranylgeraniol, **121** and **122**, were isolated from *Bifurcaria bifurcata* (Atlantic coast of Morocco). The absolute configuration at C-12 in both compounds was established (Mosher's), but the stereochemistries of C-6 in **121** and C-7 in **122** could not be unambiguously determined.²²¹ *Scytosiphon lomentaria*, cultured in deep seawater, produced the bisnorditerpene **123**.²²² The secondary metabolite composition of *Dictyota dichotoma* (Aegean Sea) and *D. linearis* (Chios Is., Greece), were examined and new diterpenes isolated; isopachydictyolal **124** from *D. dichotoma* and 4 α -acetyldictyodial **125** from *D. linearis*.²²³ *D. dichotoma* (Karachi coast in the Arabian Sea) yielded three C-16 oxidised *seco*-dolastanes, dichotenols A-C **126–128**.²²⁴ A new dolabelladiene derivative **129** and the previously isolated 10,18-diacetoxy-8-hydroxy-2,6-dolabelladiene²²⁵ were characterised from *D. pfaffii* (Northeast Brazil).²²⁶ Both compounds showed strong anti-HSV-1 activity *in vitro* but little inhibition of HIV-1 reverse transcriptase. 10,18-Diacetoxy-8-hydroxy-2,6-dolabelladiene²²⁵ was the antifeedant component of *D. pfaffii* against the sea urchin *Lytechinus variegatus* and

generalist fishes.²²⁷ The diterpenes (6*R*)-6-hydroxydichotoma-3,14-diene-1,17-dial, and the 6-acetate derivative, from *D. menstrualis*,²²⁸ originally isolated from *D. dichotoma*,²²⁹ exhibited antiretroviral activity *in vitro*.²²⁸ Two glycerol derivatives, **130** and **131**, were obtained from *Sargassum parvivesiculosum* (Hainan Province, China).²³⁰ The sesquiterpene-substituted benzoic acid, dictyvaric acid **132**, was isolated from *Dictyopteris divaricata* (Shandong coast, China),²³¹ while seven cadinane sesquiterpenes, **133–139**, were obtained from *D. divaricata* (Qingdao coast, China). Structures and absolute configurations of **133–139** were established from spectroscopic data and X-ray analysis of **133** and **136**.²³² Six dibenzyl bromophenols **140–145**,²³³ with different dimerisation patterns, and two propyl bromophenol derivatives, **146** and **147**,²³⁴ were isolated from *Leathesia nana* (Shandong Province, China). X-ray analysis determined that **145** was a racemate. Compound **142** showed moderately selective cytotoxicity, and **140** may have been an artifact of isolation.²³³ Surprisingly, compound **146** was reported in another paper by the same authors.²³⁵ The moderately cytotoxic diphlorethohydroxycarmalol **148**, from *Ishige okamurae* (Boso Peninsula, Japan),²³⁶ was characterised by conversion to the known nonaacetate.²³⁷ An enantioselective synthesis of the proposed structures for the bioactive (*E*)- and (*Z*)-usneoidones, from *Cystoseira usneoides*,²³⁸ has been completed by a convergent strategy.²³⁹ However, the spectroscopic data of the synthetic products differed significantly from the reported values. The phlorotannin derivatives 8,8'-bieckol²⁴⁰ and 8,4'''-dieckol,²⁴¹ from *Ecklonia cava* (Korean coasts), are inhibitors of HIV-1 reverse transcriptase (RT) and protease. Both compounds inhibited the RT more potently than the protease and the inhibitory activity of 8,8'-bieckol against HIV-1 RT was comparable to that of nevirapine, a reference

compound.²⁴² Fucosterol^{243,244} was isolated from *Pelvetia siliquosa* and *in vivo* testing demonstrated that it is the main antidiabetic principle from *P. siliquosa*.²⁴⁵

6 Red algae

As for the brown algae, terpenes and polyphenolic compounds continue to be the predominant metabolite classes reported from red algae. *Laurencia obtusa* (Isla Grande, Panama), contained the oxygenated sesquiterpene chamigrenelactone **149**.²⁴⁶ The sesquiterpene **150** and a halogenated C15 acetogenin **151**, a stereoisomer of neoisoprelaufucin,²⁴⁷ were isolated from *L. obtusa* (Tekirova, Turkey).²⁴⁸ Two halogenated diterpenes, 15-bromoparguer-9(11)-ene-16-ol **152** and 15-bromoparguer-7-ene-16-ol **153**, were obtained from *L. nipponica* (Troitsa Bay, Sea of Japan).²⁴⁹ Bioassay-guided fractionation of an extract from *L. intricata* (Discovery Bay, Jamaica), gave the diterpene laurenditerpenol **154** and the absolute configuration at C-1 was established (Mosher's). **154** was a potent inhibitor of hypoxia-activated hypoxia-inducible factor-1 and of the angiogenic factor hypoxia-induced VEGF in T47D cells.²⁵⁰ Two phenylpropanoic acid derivatives, tichocarpols A **155** and B **156**, were isolated from *Tichocarpus crinitus* (Katsurakoi coast of Japan). These two compounds, along with floridoside,²⁵¹ also isolated from the alga, exhibited antifeedant activity against the sea urchin *Strongylocentrotus intermedius*.²⁵² Inositol phosphoceramide **157** was isolated from *Gracilaria verrucosa* (Sea of Japan) and identified by GC and GCMS analysis.²⁵³ *Peyssonnelia caulifera* (Yanuca Is., Fiji) was the source of two enediene ω 3 monoacyl glycerides, peyssonenynes A **158** and B **159**, and a pyrone-containing ω 3 fatty acid

methyl ester, peyssopyrone **160**, but the instability of the peyssonenynes prevented complete stereochemical assignment. Both peyssonenynes displayed activity at a similar level in a DNA methyltransferase enzyme inhibition assay.²⁵⁴ *Rhodomela confervoides* (Qingdao coast, China) was the source of seven new bromophenol derivatives **161–167**, together with two known bromophenol compounds. X-ray analysis of **161** and **162** supported the structural assignments. The known synthetic compounds 3-bromo-5-hydroxy-4-methoxyphenylacetic acid²⁵⁵ and 3-bromo-5-hydroxy-4-methoxybenzoic acid,²⁵⁶ were obtained as natural products for the first time.²⁵⁷ Seven brominated diterpenes of the parguerene and isoparguerene series isolated from *Jania rubens* (Red Sea coast of Egypt) included the novel deoxyparguerol-7-acetate **168**. All the isolated diterpenes had anthelmintic activity and exhibited antitumour activity against Ehrlich ascites carcinoma *in vitro* with isoparguerol derivatives being slightly more effective than parguerol derivatives.²⁵⁸ The first total synthesis of (–)-presphaerene **169**²⁵⁹ from *Sphaerococcus coronopifolius* was achieved from (*R*)-glyceraldehyde²⁶⁰ and established the relative and absolute stereochemistries of **169** as well as the absolute stereochemistries of the co-occurring sphaeroanes (+)-presphaerol,^{261,262} isosphaerodiene 1²⁶³ and isosphaerodiene 2.²⁶³ The first enantioselective total synthesis of (+)-brasilenyne^{264,265} was reported, starting from (*S*)-malic acid.²⁶⁶ Also reported in 2004 was the first total synthesis of the sesquiterpenoid (+)-palisadin B from *Laurencia cf. palisada*,²⁶⁷ utilising a new method for the formation of *trans-anti* cyclogeranyl-oxepene systems.²⁶⁸ Furoplocamioid C, prefuroplocamioid, pirene and a tetrachlorinated cyclohexane from *Plocamium cartilagineum*²⁶⁹ exhibited selective cytotoxicity against human tumour cell lines with pirene showing a specific and irreversible effect on SW480

cells.²⁷⁰ Halogenated metabolites from several species of *Laurencia* were tested for antibacterial activity against 22 strains of human pathogenic bacteria, including seven strains of antibiotic-resistant bacteria. Laurinterol,²⁷¹ isolaurinterol,²⁷² *allo*-laurinterol,²⁷³ cupalaurenol²⁷⁴ and 2,3,5,6-tetrabromoindole²⁷⁵ displayed a wide spectrum of antibacterial activity against Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus*, penicillin-resistant *Streptococcus pneumoniae* and vancomycin-resistant *Enterococcus faecalis* and *E. faecium*. Laurinterol and *allo*-laurinterol were particularly effective.²⁷⁶ Studies on vanadium bromoperoxidase isolated from marine red algae have established it as a catalyst in the biosynthesis of brominated cyclic sesquiterpene structures in the algae.²⁷⁷

7 Sponges

Unusual fatty acid derived metabolites are often isolated from sponges, and some motifs seem to be characteristic of the phylum; 2-methoxylated fatty acids are one such group of metabolites. A series of these compounds were synthesised, found to be active against mycobacteria, and proposed as a possible chemical defense mechanism in sponges.²⁷⁸ Two long 2-methyl substituted fatty acids **170** and **171** were isolated as methyl esters from *Halichondria panicea* (Sea of Japan, Russia).²⁷⁹ A Chinese *Spongia* species yielded the ceramides spongiamines A **172** and B **173**.²⁸⁰ Clarhamnoside **174**, a glycolipid containing an unusual L-rhamnose unit, was isolated from the Bahamian *Agelas clathrodes*.²⁸¹ The relative stereochemistry of the sugar units was determined from proton coupling constants determined with the use of a ¹³C-coupled HMQC experiment. The

absolute stereochemistry of the alkyl chain oxymethine of caminoside A, originally isolated from *Caminus sphaeroconia*,²⁸² has been determined as (10*R*) by the preparation of a TPP diester of the aglycone.²⁸³ An inhibitor of bacterial proteases, pachymoside A **175**, was isolated from *Pachymatisma johnstonia* (Isle of Man).²⁸⁴ An α -glycosidase inhibitor, penasulfate A **176**, was obtained from a Japanese *Penares* species using recycling HPLC.²⁸⁵ *Mycale cecilia* (Gulf of California, Mexico) yielded fourteen cytotoxic long chain pyrroles, mycalazals 3–13 **177–187**, and three nitrile-containing congeners, the mycalenitriles 1–3 **188–190**.²⁸⁶ A Korean *Homaxinella* species yielded three weakly cytotoxic butenolides, homaxinolides A–C **191–193**, along with the moderately cytotoxic cyclopentenone, homaxinone A **194**. Also isolated from the same collection was an unsaturated alcohol **195** previously known only as a synthetic intermediate.²⁸⁷ A pair of isomeric bithiocyanates, thiocyanatins D₁ **196** and D₂ **197**, and the related thiocyanate-thiocarbamates, thiocyanatins E₁ **198** and E₂ **199**, were obtained as inseparable pairs from a South Australian *Oceanapia* species; all compounds were potent nematocides. Several related compounds were also tentatively identified by mass spectrometry.²⁸⁸ An acetylenic acid **200** has been obtained from a Chinese *Cinachyrella australiensis*.²⁸⁹ A *Plakortis* species (Canary Islands) contained plakolide A **201**, a γ -lactone that inhibits inducible nitric oxide synthase activity.²⁹⁰ Two isomeric cytotoxic *trans* epoxides, plakorstatins 1 **202** and 2 **203**, were isolated from *Plakortis nigra* (Sulawesi, Indonesia).²⁹¹ A Dominican *Plakortis anglospiculatus* provided two highly branched tricyclic acids, spiculoic acids A **204** and B **205** which are thought to be the result of a Diels Alder-ase-catalyzed intramolecular [4+2] cycloaddition.²⁹² A series of glycosphingolipids were partially characterised from four *Agelas* species using tandem

HPLC/ESIMS and HPLC/LSIMS.²⁹³ Dideoxypetrosynol A, a polyacetylene originally obtained from a *Petrosia* species,²⁹⁴ induced apoptosis in human melanoma cells.²⁹⁵ Manzamenone A²⁹⁶ was a potent inhibitor of β DNA polymerase and only weakly active against the α form of the enzyme.²⁹⁷ A lysophosphatidylcholine, originally isolated from *Spirastrella abata*,²⁹⁸ has been shown to increase intracellular Ca^{2+} concentration in human leukemia cells.²⁹⁹ Mycalazal 2 and mycalazol 11, pyrrole-containing lipids isolated from *Mycale micranthoxea*,³⁰⁰ have been synthesised using a Stille coupling.³⁰¹ A synthesis of (2*R*,5*Z*,9*Z*)-2-methoxyhexacos-5,9-dienoic acid, from *Topsentia roquensis*,³⁰² has been accomplished using a novel HgO mediated O-alkylation.³⁰³ A racemic synthesis of plakortone E **206**³⁰⁴ has established the relative stereochemistry,³⁰⁵ and an asymmetric synthesis of plakortone G **207**³⁰⁶ defined both the relative and absolute stereochemistries.³⁰⁷ Two dimeric peroxides, dihalenaquinolides A **208** and B **209**, were isolated from a Taiwanese *Petrosia elastica*.³⁰⁸ A very potent cytotoxin, psymberin **210**, related to the pederin family of metabolites, was obtained from a series of Papua New Guinean collections of *Psammocinia* species.³⁰⁹ In an independent study, a compound named irciniastatin A, having the same NMR characteristics as **210** but claiming different stereochemistry at C-8, and the keto analogue irciniastatin B **211** were isolated from *Ircinia ramosa* (Borneo).³¹⁰ Four calyculin analogues, calyculin J **212**, calyculinamide F **213**, des-*N*-methylcalyculin A **214** and the known calyculinamide A,³¹¹ were obtained from a Japanese *Discodermia calyx*. All four compounds were potent inhibitors of protein phosphatase 2A.³¹² A prokaryotic gene cluster, proposed to be responsible for the biosynthesis of onnamide A, has been isolated from the metagenome of *Theonella swinhoei*. The specific PKS cluster is distinct from many others by the lack

of an acyltransferase domain, a characteristic that it shares with the pederin gene cluster. The *onnA* cluster was found only in the chemotypes of *T. swinhoei* that produce onnamide A and the theopederins.³¹³ In a series of five consecutive papers the large-scale synthesis of discodermolide is described, culminating in the production of 60 g of enantio-pure material.³¹⁴ Discodermolide, a microtubule stabilizing agent, was originally isolated from a deepwater *Discodermia dissoluta*.³¹⁵ The level of commitment involved in this large-scale synthesis of a highly complex marine natural product is a measure of the importance of the field of marine natural products to medical research and the pharmaceutical industry. Sponges continue to be a rich source of novel and biologically active peptides. The dysinosins B–D **215–217**, from a Queensland *Lamellodysidea chlorea*, were inhibitors of serine protease factor VIIa and thrombin.³¹⁶ The microtubule-destabilizing peptide, milnamide C **218**, was obtained from an *Auletta* species (Papua New Guinea).³¹⁷ Milnamide D **219**, isolated from a *Cymbastela* species and reported in 2003,³¹⁸ was inadvertently omitted from the previous review.¹ An asymmetric synthesis of milnamide A **220**³¹⁹ and the subsequent autoxidation to milnamide D established the relative and absolute stereochemistry of these two potent antimitotic compounds.³²⁰ *Scleritoderma nodosum* (Philippines) contained the cytotoxic cyclic peptide scleritodermin A **221**.³²¹ Another Philippine sponge, *Clathria (Thalysias) abietina*, yielded two isomeric disulfide-bridged heptapeptides, microcionamides A **222** and B **223**, with cytotoxic and antitubercular activities.³²² An unusually cyclised peptide, callynormine **224**, isolated from *Callyspongia abnormis* (Kenya), represents a new class of heterodectic cyclic peptide, the endiamino peptides, which contain an α -amido- β -aminoacrylamide functionality.³²³ *Axinella carteri* (Caroline Islands) yielded the

octapeptide cyclonellin **225**.³²⁴ Kendarimide A **226**, a linear peptide obtained from a *Haliclona* species (Sulawesi, Indonesia), reversed P-glycoprotein-mediated multi-drug resistance in mammalian cells.³²⁵ A large depsipeptide, neamphamide A **227**, with potent cytoprotective activity against HIV-1 was isolated from a Papua New Guinean *Neamphius huxleyi*.³²⁶ Phakellistatin 13, recently isolated from *Phakellia fusca*,³²⁷ has been synthesised, confirming the natural L configuration of the tryptophan residue.³²⁸ Phakellistatin 13 was also converted by photo-oxidation into phakellistatin 3 and isophakellistatin 3, both originally obtained from *P. carteri*.³²⁹ Miraziridine A, isolated from *Theonella* aff. *mirabilis*,³³⁰ has been synthesised and is an inhibitor of three classes of proteases.³³¹ Callipeltin A, originally isolated from a New Caledonian *Callypelta* species,³³² acts as an ionophore, increasing the contraction of vascular tissues in the presence of Na⁺ ions.³³³ The complex structures and often spectacular biological activity of sponge-derived macrolides and their related congeners provide attractive targets and considerable challenges to natural product and synthetic chemists alike. Examples of these include the two oxazole-containing macrolides neohalichondramide **228**, (19Z)-halichondramide **229** and a related ring opened compound secohalichondramide **230** obtained from *Chondrosia corticata* (Guam),³³⁴ and the three cytotoxic mycalolides, 30-hydroxymycalolide A **231**, 32-hydroxymycalolide A **232**, and 38-hydroxymycalolide B **233** isolated from a Japanese *Mycale magellanica*.³¹² Latrunculeic acid **234**, from *Negombata (Latrunculia) magnifica*³³⁵ (Gulf of Eilat, Red Sea), is clearly related to the latrunculin macrolides, isolated previously from the same sponge.³³⁶ Spongidepsin **235**, originally isolated from a *Spongia* species (Vanuatu),³³⁷ has been synthesised independently by two groups defining both relative and absolute configurations.^{338,339}

The relative stereochemistry of dictyostatin **236**, originally obtained from a *Spongia* species,³⁴⁰ has been determined (Murata's method), revising the original structure.³⁴¹ Two independent groups have confirmed this relative stereochemistry and absolute configuration by synthesis.^{342,343} Five antiproliferative lasonolide congeners, lasonolides C–G **237–241**, were isolated from a *Forcepia* species (west coast of Florida).³⁴⁴ A larger recollection of the producing organism, *Spirastrella coccinea*, yielded sufficient spirastrellolide A **242** for further spectroscopic examination and derivative preparation. Originally reported with a molecular formula of C₅₃H₈₆O₁₉,³⁴⁵ an extensive re-analysis led to the determination of a new molecular formula, exchanging H₃O₂ for Cl, and structural revision (as shown). The relative stereochemistries of segments C-3–C-7, C-9–C-24, and C-27–C-38 were established from ROESY data obtained at 800 MHz.³⁴⁶ The synthesis of a series of diastereomers of a degradation fragment of reidispongiolide A **243**, originally isolated from *Reidispongia coerulea*,³⁴⁷ has led to a reassignment of the relative stereochemistry of the C-7–C15 fragment.³⁴⁸ The potent cytotoxin 13-deoxytedanolide, from *Mycale adhaerans*,³⁴⁹ has been shown to bind to the 60S large ribosomal subunit.³⁵⁰ Two brominated biphenyl ethers **244** and **245** were isolated from *Phyllospongia dendyi* (Palau), along with a series of related known compounds. Some of the known dihydroxy congeners showed inhibitory activity towards the assembly of microtubules.³⁵¹ A tricyclic dipeptide betaine, dysibetaine PP **246**, and two cyclopropane betaines, dysibetaines CPa **247** and CPb **248**, were isolated from an aqueous extract of *Dysidea herbacea* (Yap, Micronesia).³⁵² A Japanese *Spongia* species produced the moderately antifungal spongiacysteine **249**.³⁵³ Three aromatic amino acid-derived alkaloids, hamigeroxalamic acid **250**, hamigeramine **251**, and hamigeramide **252** were

isolated from a Mediterranean *Hamigera hamigera*.³⁵⁴ Esmodil **253**, known previously as a synthetic drug, has been found as a metabolite of a South Australian *Raspailia* species.³⁵⁵ A series of twenty new phloeodictine alkaloids **254–273**, together with several known congeners, were obtained from *Oceanapia fistulosa* (New Caledonia). The compounds were characterised by LCMS from a complex mixture that showed antiplasmodial activity against chloroquine-resistant *Plasmodium falciparum*.³⁵⁶ Alkylpyridine-derived alkaloids are a characteristic of sponges that continue to provide an assortment of unusual metabolites. Viscosaline **274** was obtained from *Haliclona viscosa* (Russian Arctic Ocean).³⁵⁷ The same sponge, but from Svalbard in the Norwegian Arctic, yielded haliclamines C **275** and D **276**.³⁵⁸ Three inhibitors of histone deacetylase, cyclostelletamine G **277** and dehydrocyclostelletamines D **278** and E **279**, were isolated from a Japanese *Xestospongia* species.³⁵⁹ A Brazilian *Pachychalina* species yielded the cytotoxic ingenamine G **280**, the previously described cyclostellattamine G, and four new congeners, cyclostellattamines H, I, K and L **281–284**.³⁶⁰ An *Amphimedon* species (Southern Japan) contained tetrahydrohalicyclamine **285** and 22-hydroxyhalicyclamine **286**, both of which inhibit the growth of mammalian cells.³⁶¹ A new araguspongine/xestospongine analogue, araguspongine M **287**, has been described from *Neopetrosia exigua* (formerly *Xestospongia exigua*) from Palau.³⁶² Hachijodine B, originally isolated from a *Xestospongia* species,³⁶³ has been synthesised, along with the proposed structure of ikimine B originally isolated from an unidentified sponge,³⁶⁴ but the spectra of the synthetic ikimine B did not match that of the natural product suggesting a possible incorrect assignment of the original structure.³⁶⁵ Three manzamine alkaloids **288–290** have been isolated from an Indonesian *Acanthostrongylophora* species. The

activities of several known manzamine alkaloids as potent antiinflammatory, antifungal, and anti-HIV-1 agents were also reported.³⁶⁶ Indole-based alkaloids are well represented among sponge metabolites. Three further iodinated indole alkaloids, plakohypaphorines D–F **291–3** are reported from *Plakortis simplex* (Bahamas). Plakohypaphorines B–D have significant antihistamine activity.³⁶⁷ The weakly cytotoxic guanine-containing 6-hydroxydiscodermindole **294** was obtained from *Discodermia polydiscus* (Bahamas).³⁶⁸ An antifouling alkaloid, 8,9-dihydrobarettin **295**, has been isolated from *Geodia barretti*.³⁶⁹ The recently reported revised structure for barettin,³⁷⁰ from *G. barretti*,³⁷¹ has been synthesised confirming the revised structure.³⁷² Using LCMS, barettin has been detected at biologically-significant concentrations in water surrounding live *G. barretti* specimens.³⁶⁹ An enantiospecific synthesis of the (+)-dragmacidin F has established the absolute configuration of the natural product as (4'S,6"S,6"'"S).³⁷³ Two thiomethyl-containing β -carbolines, dragmacidonamines A **296** and B **297**, were isolated from a *Dragmacidon* species (Adaman Islands, India).³⁷⁴ A *Thorectandra* species (Palau) produced a β -carboline alkaloid **298** with moderate cytotoxicity.³⁷⁵ A series of fused bisindole-derived compounds **299–306** in the fascaplysilin series were isolated from *Fascaplysinosia reticulata* (Indonesia).³⁷⁶ Pyrroloquinones and pyrroloiminoquinones are associated with sponges, particularly members of the Order Poecilosclerida. Zyzzyanone A **307**, which is moderately cytotoxic and inhibits division of fertilised sea urchin eggs, was isolated from an Australian *Zyzya fuliginosa*.³⁷⁷ Two β -D-ribopyrroloquinoline alkaloids **308** and **309** were obtained from a South African *Strongylodesma aliwaliensis*.³⁷⁸ Four new discorhabdins, 3-dihydro-7,8-dehydrodiscorhabdin C **310**, 14-bromo-3-dihydro-7,8-dehydrodiscorhabdin C **311**,

discorhabdin V **312**, and 14-bromo-1-hydroxydiscorhabdin V **313** were isolated from the South African *Tsitsikamma pedunculata*. In the same article, the tsitsikammanamines A **314** and B **315** are reported from *T. favus* along with 1-methoxydiscorhabdin D **316** and 1-aminodiscorhabdin D **317** from *Latrunculia bellae*.³⁷⁹ Also isolated from *L. bellae* was discorhabdin G*, identical in structure with discorhabdin I **318** which was reported, along with discorhabdin L **319**, from *Latrunculia brevis* (Argentina).³⁸⁰ Fortunately, some of the confusion over the earlier naming of the discorhabdin series has been resolved in a 2005 review on pyrroloiminoquinones.³⁸¹ Cribrostatin 7 **320**, a cytotoxic quinone alkaloid was obtained from a *Petrosia* species (Philippines).³⁸² A Chinese *Cinachyrella australiensis* contained isolumichrome **321**.²⁸⁹ Bisdemethylaaptamine **322** and the 9-*O*-sulfate analogue **323** were isolated from an Indonesian *Aaptos* species.³⁸³ The racemic spiro-polycyclic aromatic alkaloid lihouidine **324**, obtained from a new species of *Suberea* (Lihou reef, Coral Sea), showed cytotoxic activity.³⁸⁴ Syntheses of 7-methoxy-1,6-dimethylisoquinoline³⁸⁵ from a *Xestospongia* species,³⁸⁶ 6-hydroxy-7-methoxyisoquinolinemethanol³⁸⁷ from a *Haliclona* species,³⁸⁸ and cribrostatin 6³⁸⁹ from a *Cribochalina* species,³⁹⁰ have been completed. Renieramycin A, from a *Reniera* species,³⁹¹ had antileishmanial activity.³⁹² A *Leucetta* species (Papua New Guinea) provided spiroleucettadine **325** which showed antibacterial activity against *Enterococcus durans*.³⁹³ *Leucetta chagosensis* (Sulawesi, Indonesia) contained naamines F **326** and G **327** as well as kealiinines A–C **328–330**. Naamine G was strongly antifungal.³⁹⁴ *Monanchora unguifera* (Jamaica) provided 1,8a;8b,3a-didehydro-8 α -hydroxyptilocaulin **331**, together with the known 8 β isomer, which co-crystallised in perfect order with an approximate inversion centre.³⁹⁵ Monanchorin **332**, a new bicyclic metabolite and the

pentacyclic crambescidin acid **333**, previously reported as the ethyl ester,³⁹⁶ have both been isolated from *Monanchora unguiculata* (Maldive Islands).³⁹⁷ Two phakellin alkaloids, **334** and **335**, active as human lipoxygenase inhibitors, were found in an *Agelas* species (Papua New Guinea).³⁹⁸ An Okinawan *Agelas* species provided the nagelamides A–H **336–343** and 9,10-dihydrokeramadine **344**. The nagelamides were antibacterial, while nagelamide G inhibited protein phosphatase 2A activity.³⁹⁹ A systematic analysis of CD spectra and Mosher acid derivatives suggested that the configuration of longamide A, from *Agelas longissima*,⁴⁰⁰ be revised to (4*R*).⁴⁰¹ (±)-Sceptrin,^{402,403} from *Agelas sceptrum*,⁴⁰⁴ and (±)-dibromosceptrin⁴⁰³ from *Agelas conifera*,⁴⁰⁵ have both been synthesised. The conversion of ageliferin into sceptrin using microwave irradiation also revealed a possible alternative biosynthetic pathway linking the pyrrole-imidazole alkaloids.⁴⁰⁶ The synthesis of dehydrobatzelladine C, originally isolated from two *Monanchora* species³⁹⁶ has been reported.⁴⁰⁷ The first enantiospecific synthesis of agelastatin A, isolated from *Agelas dendromorpha*,⁴⁰⁸ has been achieved.⁴⁰⁹ The HIV-active alkaloid batzelladine A, from a *Batzella* species,⁴¹⁰ has been synthesised in an enantio-pure form.⁴¹¹ Crambescidin 800, originally isolated from *Crambe crambe*,⁴¹² caused myelogenous leukemia cells to differentiate into erythrocytes.⁴¹³ The schulzeines A–C **345–347** were isolated from *Penares schulzei* (Hachijo-kojima Is., Japan).⁴¹⁴ The configurations of these unusual sulfonated long chain aromatic alkaloids, potent inhibitors of yeast α -glucosidase, were determined from a combination of chemical degradation and modified Mosher's method. A series of bromotyrosine alkaloids, the purpurealidins A–H **348–355**, were reported from a *Psammaphysilla purpurea* (India).⁴¹⁵ Purpurealidin B **349** was antibacterial. Two potent antagonists of the sarcoplasmic

reticulum calcium channel RyR1-FKBP12, the sulfonates **356** and **357**, were isolated from *Ianthella basta* (Guam), along with 34-*O*-sulfatobastadin-9 **358**.⁴¹⁶ A sulfur-containing nucleoside, hamiguanosinol **359**, was obtained from a Mediterranean *Hamigera hamigera*.³⁵⁴ A bromotyrosine oxime that inhibits mycothiol-S-conjugate amidase, isolated from an *Oceanapia* species,⁴¹⁷ has been synthesised.⁴¹⁸ The same molecule was also synthesised independently through a trifluoromethyloxazole intermediate.⁴¹⁹ A total synthesis of the eurypamides, first isolated from a Palauan *Microciona eurypa*,⁴²⁰ resulted in revised stereochemistry for eurypamide A **360** and confirmed the structures of eurypamides B–D.⁴²¹ Two macrocyclic merosesquiterpenoids, likonides A **361** and B **362**, were obtained from a Kenyan *Hyatella* species.⁴²² 17-*O*-isoprenyldictyoceratin-C **363** was isolated from a Philippine *Spongia* species.⁴²³ An amino-merosesquiterpenoid, 5-*epi*-smenospongine **364**, isolated from *Dactylospongia elegans* (Flores, Indonesia), caused the differentiation of K562 leukemia cells into erythrocytes.⁴²⁴ A Papua New Guinean *Psammocinia* species contained chromarols A–E **365–369**, inactivators of human 15-lipoxygenase through a redox mechanism similar to that reported for a range of known meroterpenoids.⁴²⁵ Makassaric acid **370** and subersic acid **371**, isolated from an *Acanthodendrilla* species (Sulawesi, Indonesia), were inhibitors of MAPKAP kinase 2.⁴²⁶ *Petrosia (Strongylophora) corticata* (Papua New Guinea) contained the anti-invasion active meroditerpenoid strongylophorine-26 **372**.⁴²⁷ A series of merosesquiterpenoids from a variety of sponge sources were assessed for hemolytic and cytotoxic properties.⁴²⁸ Similarly, a further range of sponge-derived merosesquiterpenoids were active as antioxidants.⁴²⁹ Smenospongine, originally isolated from a *Smenospongia* species,⁴³⁰ caused K562 leukemia cells to differentiate into

erythrocytes.⁴³¹ A series of polyprenylated hydroquinones and benzoic acids of sponge origin inhibited phosphatase CDC25A.⁴³² Puupehenone, originally isolated from a Hawaiian sponge,⁴³³ inhibited the differentiation of endothelial cells into tubular structures, an important step in angiogenesis.⁴³⁴ Chloropuupehenone⁴³³ has been synthesised.⁴³⁵ An aromatic sesquiterpenoid **373** was isolated from a *Didiscus* species (Thailand).⁴³⁶ *Stylorella aurantium* (Great Barrier Reef) yielded a carbonimidic dichloride stylorellane D **374**.⁴³⁷ The weakly antibacterial hyrtiosenolides A **375** and B **376** were isolated from a Red Sea *Hyrtios* species.⁴³⁸ The boneratamides A–C were isolated as their methyl esters **377–379** from an Indonesian *Axinyssa aplysinoides*.⁴³⁹ The relative stereochemistry of boneratamide A **377** was established by X-ray analysis, while boneratamides B **378** and C **379** differ in their relative configurations at either one or both of C-18 and C-23. The antimicrobial germacrane sesquiterpenoid **380**, and the bis-urea analogue **381**, were obtained from an *Axinyssa* species (Thailand).⁴⁴⁰ Two sesquiterpene isothiocyanates **382** and **383** were obtained from an Okinawan *Stylissa* species.⁴⁴¹ The biosynthesis of the carbonimidic dichloride sesquiterpenoids, the stylorellanes A and B, was examined in the producing organism *Stylorella aurantium* (Great Barrier Reef). Feeding experiments with ¹⁴C-labeled metabolites established that CN, SCN, and farnesyl isothiocyanate were intermediates in the biosynthetic pathway to these dichloroimines.⁴⁴² A total synthesis of hamigeran E,⁴⁴³ from a New Zealand *Hamigera tarangaensis*, has been reported.⁴⁴⁴ (6*R*,7*S*)-7-amino-7,8-dihydro- α -bisabolene, from a *Halichondria* species,⁴⁴⁵ has been synthesised.⁴⁴⁶ Helianane, isolated from *Haliclona fascigera*,⁴⁴⁷ was synthesised employing a vacuum thermolytic ring expansion step.⁴⁴⁸ A Kenyan *Raspailia* species gave two purine alkaloid-derivatised

diterpenes asmarines G **384** and H **385** and the diterpenoid barekol **386**, together with several related known compounds.⁴⁴⁹ A *Raspailia* species (Madagascar) produced further asmarines, I–K **387–389**, and the diterpenoid nosyberkol **390**.⁴⁵⁰ A furanoditerpenoid **391**, and two related norditerpenoids **392** and **393**, that inhibit the lyase activity of DNA polymerase β , were obtained from an unidentified Dictyoceratid sponge from Papua New Guinea.⁴⁵¹ A bright yellow encrusting Aplysillid sponge, tentatively identified as *Aplysilla sulphurea* from S. E. Queensland, contained the cytotoxic and nematocidal compound chromodorolide C **394**, along with the known A and B congeners.⁴⁵² *Acanthella cavernosa* (Philippines) provided 10-formamido-kalihinol F **395** and 15-formamido-kalihinol F **396**, both of which inhibited bacterial folate biosynthesis.⁴⁵³ A norgracilane- **397** and three new aplysulphurane-type spongian diterpenoids **398–400** were isolated from *Dendrilla membranosa* (South Shetlands, Antarctic),⁴⁵⁴ and by forming complexes between (*R*) and (*S*) 2,2,2-trifluoro-1-(9-anthryl)ethanol and the γ -methylbutenolide of **397** the absolute stereochemistries were established (as drawn). Aplysulphurane-type spongian diterpenoids, with antiinflammatory properties, were also reported from a New Zealand *Chelonaplysilla violacea*.⁴⁵⁵ Two compounds from this series, named as pourewic acid A **398** and cadlinolide C **399**, were found in both collections along with the formate-containing pourewanone **401**, methyl pourewate B **402**, 15-methoxypourewic acid B **403**, and an inseparable mixture of the diastereoisomeric cadlinolides D **404**, with relative stereochemistries established as drawn. The optical rotation of the New Zealand-derived pourewic acid A, which was small, was comparable to but opposite in sign to that reported for the Antarctic sample, but the measurements were made in different solvents (CH_2Cl_2 vs. CHCl_3). Further

resolution of the absolute stereochemistries will require more rigorous chiroptical evaluation of the samples. In contrast, an Anvers Is., Antarctic, collection of *Dendrilla membranosa* yielded the aromatic antimicrobial spongian diterpenoids, membranolides B–D **405–407**.⁴⁵⁶ The three diterpenoid isocyanides **408–410**, isocyanate **411**, and isothiocyanate **412** were isolated from the same Okinawan *Stylissa* species that had yielded the previously described isothiocyanate sesquiterpenes **382** and **383**.⁴⁴¹ All metabolites displayed weak cytotoxicity. The biosynthetic origins of the isocyanide and isothiocyanate carbon of a variety of sesqui- and diterpenes isolated from *Amphimedon terpenensis* and an *Axinyssa* species (Great Barrier Reef), have been investigated. For all compounds specific incorporation of ¹⁴C-thiocyanate was demonstrated.⁴⁵⁷ A racemic synthesis of kalihinol C, first isolated from an *Acanthella* species,⁴⁵⁸ has been reported.⁴⁵⁹ Three cytotoxic norsesquiterpenoids, tasnemoxides A–C **413–415**, have been isolated from a Red Sea *Diacarnus erythraenus*.⁴⁶⁰ An *Acanthodendrilla* species (Indonesia) provided the cytotoxic acantholides A–E **416–420**. Acantholide B **417** was antimicrobial.⁴⁶¹ A Korean *Psammocinia* species contained three cytotoxic sesterterpenoids, psammocinins A₁ **421**, A₂ **422** and B **423**.⁴⁶² (6*Z*)-Neomanoalide-24,25-diacetate **424** was obtained from a Palauan *Luffariella* species.⁴⁶³ A *Brachiaster* species (Thailand) yielded the same manoalide congener **424**, the (*E*) isomer **425** and the potentially antitubercular 12-deacetoxy-scalarin-19-acetate **426**.⁴⁶⁴ Five moderately cytotoxic sesterterpenoids, three scalaranes **427–429** and two linear furanoterpenoids **430** and **431**, were obtained from a Korean *Smenospongia* species.⁴⁶⁵ *Hyrtios erectus* (Hainan Is., China) contained the linear furanoterpenoid 5,10-dihydroxyfurospinulosine-1 **432**, two formylhyrtiosal congeners **433** and **434**, and 12 α -*O*-acetylhyrtiolide **435**.⁴⁶⁶ *Stoeba*

extensa (Japan) gave the cytotoxic furanosesterterpenoid shinsonofuran **436** along with halisulfate **7** **437**.⁴⁶⁷ The C-8 stereochemistry of halisulfate **7**, originally isolated from a *Coscinoderma* species,⁴⁶⁸ has been revised to that shown on the basis of careful NOE analysis.⁴⁶⁷ A scalarane-type sesterterpenoid **438**, and a related oxycyclic congener **439**, were obtained from a Madagascan *Phyllospongia madagascarensis*.⁴⁶⁹ Two different, undescribed Madagascan species of *Lendenfeldia* contained a linear furanoterpenoid **440** with potent HIV-1 reverse transcriptase inhibitory activity, along with four scalarane-type sesterterpenoids **441–444**.⁴⁷⁰ *Suberites caminatus* (King George Is., Antarctica) contained oxaspirosuberitenone **445** and 19-*epi*-suberitenone **446**.⁴⁷¹ In an independent study, a *Suberites* species, also collected from King George Is., Antarctica, yielded suberitenones C **447** and D **448**, and suberiphenol **449**.⁴⁷² Untenospongins B from an Okinawan *Hippospongia* species,⁴⁷³ has antimicrobial activity.⁴⁷⁴ A structural comparison of the PLA₂ inhibitory activity of the petrosaspongiolides, isolated from *Petroaspongia nigra*,⁴⁷⁵ was reported.⁴⁷⁶ Using bioassay-guided fractionation, heteronemin⁴⁷⁷ was reisolated as a farnesyl transferase inhibitor from *Hyrtios reticulata*.⁴⁷⁸ Cacospongionolide E from *Fasciospongia cavernosa*⁴⁷⁹ has been synthesised.⁴⁸⁰ A synthesis of (–)-(18*S*)-variabilin from *Ircinia variabilis*⁴⁸¹ has been achieved.⁴⁸² Four cytotoxic steroids **450–453** were obtained from *Axinella* cf. *bidderi* (Yemen, Indian Ocean).⁴⁸³ *Phorbas amaranthus* (Florida) contained four moderately cytotoxic *nor*-ring A steroids, phorbasterones A–D **454–457** of which **456** and **457** were isolated as C-24 epimeric mixtures.⁴⁸⁴ Nakiterpiosin **458** and nakiterpiosinone **459**, both potent cytotoxins, were obtained from *Terpios hoshinota* (Okinawa).⁴⁸⁵ An Italian *Cliona nigricans* produced the potently cytotoxic polychlorinated steroids clionastatins A **460** and B

461.⁴⁸⁶ The C31 steroid, ophirasterol **462**, was isolated from a Colombian *Topsentia ophiraphidites*.⁴⁸⁷ Two steroidal saponins, erylosides K **463** and L **464**, were isolated from a Jordanian specimen of the same sponge, *Erylus lendenfeldi*, from which eryloside A was originally isolated.^{488,489} *Rhabdastrella* aff. *distincta* (Hainan Is., China) provided four isomalabaricane-type triterpenoids isogeoditins A **465** and B **466**, 13-(*E*)-isogeoditin A **467**, and 22,23-dihydrostelletin B **468**.⁴⁹⁰

8 Coelenterates

There was a slight increase in new chemistry identified from coelenterates in 2004 compared to the number reported in 2003. The glycerol derivative **469** was reported from a gorgonian *Junceella juncea* (South China Sea).⁴⁹¹ The acyl glycerol ethers **470** and **471** and ceramide **472** were isolated from a *Lobophytum* species (Indian Ocean).⁴⁹² The stereochemical assignment of **472** was achieved by analysis of derivatives of hydrolysis products. The sphingosines **473** and **474** were obtained as mildly antibacterial components of an Indian Ocean gorgonian *Pseudopterogorgia australiensis*.⁴⁹³ Structurally-related lipids **475**⁴⁹⁴ and **476**⁴⁹⁵ were isolated from *Junceella juncea* and a *Lobophytum* species respectively, with stereochemical assignments of **475** being made by analysis of hydrolysis products. An *Alcyonium* species (Senegal) was the source of glycolipids **477** and **478**.⁴⁹⁶ The chloromacrolactones, lytophilippines A **479**, B **480** and C **481**, were isolated as bioactive constituents from a Red Sea hydroid *Lytocarpus philippinus*.⁴⁹⁷ The absolute configuration of **479** was established based upon comprehensive derivatisation and chemical degradation studies in concert with *J*-based

analysis and molecular modeling. The moderately cytotoxic pentapeptide gymnangiamide **482** was isolated from a Philippines hydroid *Gymnangium regae*.⁴⁹⁸ Chemical degradation and derivatisation, followed by HPLC analysis allowed the determination of the absolute configuration of **482**. The related clavulazols, A **483** and B **484**, are two new pyrazine derivatives from *Clavularia viridis* (Taiwan).⁴⁹⁹ Furanones **485** and **486** were obtained, in addition to a number of other compounds, from a Taiwanese soft coral *Sinularia nanolobata*.⁵⁰⁰ The absolute configuration of **485**, and by association **486**, was established by comparison with spectroscopic data previously reported for synthetically-derived **485**. Prostanoids **487–493** were also isolated from a Taiwanese *C. viridis*.⁵⁰¹ The absolute configurations of all compounds were assigned by comparison of CD spectra with that for clavulone I. **492** was the most potent cytotoxin in the series. The structurally-related punaglandins, originally isolated in 1985 from a Hawaiian *Telesto riisei*,^{502,503} inhibit ubiquitin isopeptidase activity⁵⁰⁴ while several members of a synthetically-derived library of punaglandin-related analogues exhibited similar cytotoxic potency to that observed for the natural product punaglandin 3.⁵⁰⁵ An unusual bicyclic prostanoid, carijenone **494**, was obtained from an Eastern Pacific octocoral *Carijoa multiflora*.⁵⁰⁶ The absolute configuration of (+)-tricycloclavulone **495**, from an Okinawan *Clavularia viridis*,⁵⁰⁷ has been established by enantioselective total synthesis.⁵⁰⁸ The guaiane-skeleton sesquiterpenes menverins A–D **496–499** were isolated from *Menella verrucosa* (South China Sea).⁵⁰⁹ The instability of the compounds was noted, particularly that of **497** which was observed to dehydrate to **500** in the NMR tube (CDCl₃). Bioassay-guided fractionation of a Taiwanese soft coral *Lemnalia cervicorni* yielded the known mildly cytotoxic sesquiterpene lemnalol as well as the inactive

metabolites cervicol **501**, isolemnalol **502** and the ketone **503**.⁵¹⁰ The ketone **503** was isomeric with 4-oxo- α -ylangene⁵¹¹ and exhibited identical ¹³C and NOESY NMR data consistent with an α -orientation of the isopropyl group. *Sarcophyton glaucum* (Kitungamwe Reef, Kenya) yielded, in addition to other known compounds, the mildly cytotoxic sesquiterpene guaiacophine **504**.⁵¹² Five nardosinane-skeletoned sesquiterpenes, armatins A–E **505–509**, were isolated from a Taiwanese *Nephthea armata*.⁵¹³ Diketone **510** was also reported for the first time as a natural product. *Isis hippuris* (coast of Taiwan) was the source of isishippuric acids A **511** and B **512**.⁵¹⁴ Sesquiterpene **512** exhibited moderate *in vitro* cytotoxicity towards tumour cell lines. Cladidiol **513**, a mild inhibitor of acetylcholinesterase, was obtained from a *Cladiella* species (Andaman Is., India).⁵¹⁵ Sesquiterpenes **514–517** were isolated from *Clavularia koellikeri* (Okinawa).⁵¹⁶ Mosher's method secured the absolute stereochemistry of **515**, which on acetylation gave **514** securing the absolute configuration of this compound as well. The absolute configuration of **517**, previously reported as a synthetic intermediate,⁵¹⁶ followed from comparison of the $[\alpha]_D$ with literature values.⁵¹⁶ (+)-Cyclocolorone **518**, previously known as a terrestrial metabolite, and the 1 α -OH analogue **519** were isolated from a soft coral *Nephthea* species (Andaman and Nicobar Islands, Indian Ocean).⁵¹⁷ Nanonorcaryophyllenes A **520** and B **521** were obtained from *Sinularia nanolobata* (Taiwan).⁵⁰⁰ The absolute configuration of **520** was the opposite of a stereochemically-defined microbially-derived metabolite of caryophyllene. The structure of the sesquiterpene alcyopterosin N, from the sub-Antarctic soft coral *Alcyonium paessleri*,⁵¹⁸ has been confirmed by total synthesis.⁵¹⁹ Nine meroditerpenoids, chabrolonaphthoquinone A **522**, chabrolhydroxybenzoquinones A–D **523–526**, and

chabrolbenzoquinones A–D **527–530**, were isolated from a Taiwanese *Nephthea chabrolii*.⁵²⁰ The merosesquiterpene **531**, previously reported as a synthetic intermediate,⁵²¹ has been obtained from a *Scleronephthya* species (South China Sea).⁵²² Three publications in 2004, presenting new pterosin diterpene glycosides from the soft coral *Pseudopterogorgia elisabethae*, unfortunately led to duplication in structures and trivial names. Ata *et al.* reported structures of pseudopterosins P **532** and Q **533** in addition to elisabethins E **534** and F **535** from *P. elisabethae* (Bahamas).⁵²³ Hydrolysis and comparison of optical rotation data supported the presence of β -L-xylose in both **532** and **533**. Both pseudopterosin P and Q, as well as previously reported analogues pseudopterosins A–E and K isolated from the same soft coral specimens, exhibited antibacterial activity towards Gram-positive bacteria, but not towards Gram-negative organisms. Elisabethins E **534** and F **535** were inactive in the same assays. Working with *P. elisabethae* (Colombian Caribbean), Duque *et al.* isolated seven diterpene glycosides, pseudopterosins P–V **536–542**.⁵²⁴ The absolute configuration of the aglycone of **536** was established by phenolic *O*-benzylation at C-9, sugar removal by hydrolysis and comparison of NMR and chiroptical data reported for the known benzyl ether. In the case of **536–539**, the sugar was identified as an appropriately acetylated α -L-fucopyranoside by hydrolysis, derivatisation and chromatographic analysis, while β -D-arabinopyranoside was the sugar moiety present in **540–542**. The structures presented for pseudopterosins U **541** and V **542** are isomeric with those previously reported for pseudopterosins O and N respectively.⁵²⁵ Confusingly, in the original publication that reported pseudopterosins N and O,⁵²⁵ the structures were drawn as bearing xyloside sugar moieties, while the text suggested the structures contained D-arabinose sugars. The NMR data reported for

pseudopterosins U and V are not coincident with the values previously reported for pseudopterosins O and N. Rodriguez *et al.*, also working with *P. elisabethae* (Colombian Caribbean), isolated eleven diterpene glycosides that they named pseudopterosins P **537**, Q **538**, R **543**, S **544**, T **536**, U–Z **545–550**, and two *seco*-pseudopterosins, H **551** and I **552**.⁵²⁶ The absolute configuration of the sugars in **551** and **552** were not determined – they are arbitrarily represented in this review as D. Of the metabolites reported by Rodriguez *et al.*, **543** and **544** represent unique diacetate derivatives. Whereas Duque *et al.* reported **540–542** claiming the presence of a β -D-arabinose sugar, Rodriguez *et al.* reported the apparently isomeric structures **549**, **545** and **546** respectively as containing an α -D-arabinoside moiety, together with **547** and **548**, also containing this moiety. The NMR and optical rotation data reported for the α -/ β - anomer pairs **541/545** and **542/546** were identical (but different to pseudopterosins N and O, see above), indicating a lack of congruity between the structures and their stereochemistries. As of October 2005 these issues had not been addressed and resolved in the scientific literature. Diterpenes **537**, **538**, **545–548**, **551** and **552** displayed activity in a number of biological assays including antiinflammatory, cytotoxicity and antiinfective evaluation.^{524,526} The relative stereochemistry of the cubitane-skeleton diterpene **553**, from *Eunicea laciniata* (Barbados), was determined by use of a T-ROESY NMR experiment.⁵²⁷ Cembranes 7,8-dihydroflabellatene A **554** and B **555** were isolated from extracts of a sea pen *Gyrophyllum sibogae* (South Africa).⁵²⁸ The relative stereochemistry of **554** was secured by X-ray analysis (Mosher's method failed), while the absolute configurations of **554** and **555** were equated to those of the known sponge metabolites **556** and **557**.⁵²⁹ Cembrane **554** exhibited potent antiproliferative activity towards tumour cell lines. Sarcophydol

558 was isolated from a *Sarcophyton* species (Hainan Is., China).⁵³⁰ Cembradienes **559–563** were obtained from a *Eunicea* species (Colombian Caribbean).⁵³¹ The structure and relative configuration of **559** was established by X-ray analysis, confirming that **559–562** contained the unusual C2-C12 ether linkage, while the inter-relationships between **559–562** were established by chemical conversion. Mild growth inhibition of *Plasmodium falciparum* was observed for **559**, **560** and **562**. Of three norditerpenoids, scabrolides E–G **564–566**, from a Taiwanese *Sinularia scabra*, **564** was a modestly potent growth inhibitor against two tumour cell lines.⁵³² Cembratrienes **567** and **568**, containing the rare (12*Z*) geometry, were isolated from a new species of *Sarcophyton* (Great Barrier Reef).⁵³³ The same study also led to the determination of the absolute configuration (MPA ester) of sarcoglaucol-16-one **569**⁵³⁴ and, by comparison of CD spectra, sarcophine **570**.⁵³⁵ The acetate derivative **571**, also present in a Kenyan *Sarcophyton glaucum*, was identified as a natural product.⁵¹² A number of rearranged and halogenated semisynthetic derivatives of sarcophine have been prepared and evaluated in a range of biological assays.^{536,537} Neodolabellan-skeleton diterpenes **572** and the modestly cytotoxic **573** were isolated from an Okinawan soft coral *Clavularia koellikeri*.⁵¹⁶ The structure and relative stereochemistry of **572** were established by X-ray analysis, while oxidation of **573** yielded **572**. The absolute configuration of **573**, and hence of **572**, was secured (Mosher's). Nanolobatins A–C **574–576** were reported from *Sinularia nanolobata* (Taiwan).⁵⁰⁰ All three diterpenes exhibited modest cytotoxicity towards tumour cell lines. The structure and relative configuration of ciereszkolide **577**, a rearranged cembrane from a Caribbean sea plume *Pseudopterogorgia kallos*, was established by X-ray analysis.⁵³⁸ Further examination of the same species from the same location also afforded

the hexacyclic diterpene, bielschowskysin **578**, secured by X-ray analysis.⁵³⁹ Modest biological activity towards *Plasmodium falciparum* and human tumour cell lines was observed. A number of new briarane-skeleton diterpenes were isolated from coelenterates in 2004. Fragilide A **579**⁵⁴⁰ and junceollolide I **580**⁵⁴¹ were obtained in separate studies from the same collection of *Junceella fragilis* (southern coast of Taiwan). Another collection of *J. fragilis*, this time from the South China Sea, afforded junceallonoids A **581** and B **582**,⁵⁴² while extracts of *J. juncea*, (also South China Sea) yielded juncins O–Q **583–585**.⁵⁴³ Briaexcavatolides W **586**,⁵⁴⁴ and X–Z **587–589**,⁵⁴⁵ were obtained from a Taiwanese *Briareum excavatum*. A sea whip *Ellisella* species (Okinawa) was the source of briaranes **590–593**, of which **591** and **592** were inhibitors of cytokinesis.⁵⁴⁶ The same paper also reported **594–597** and a number of known diterpenes from a sea pen *Pteroides* species (Indonesia). One of the known diterpenes, 12-*O*-desacetyl-12-*O*-benzoylpteroidine,⁵⁴⁷ demonstrated *in vitro* reversal of multi-drug resistance properties. The absolute stereochemistry of minabein-4 **598** was established by X-ray analysis.⁵⁴⁸ From this it was concluded that the C-2/C-9 diastereomeric structure reported for nui-inoalide-D, isolated from *Junceella gemmacea*,⁵⁴⁹ which exhibits identical ¹³C NMR data to **598**, was incorrect. Kitungolides A–C **599–601** are unusual coumarin-containing diterpenes from a new genus of Kenyan soft coral.⁵⁵⁰ Pregnanes **602** and **603**, previously reported as synthetic intermediates,^{551,552} were isolated from a *Scleronephthya* species (South China Sea).⁵²² The Δ^{20} -pregnanes **604** and **605**, from an Indopacific *Carijoa* species, were identified as moderately potent inhibitors of the mitochondrial respiratory chain.⁵⁵³ *Carijoa multiflora* (Panama) gave the unusual chlorinated pregnanes **606** and **607**.⁵⁵⁴ Pregnane **608**, previously known as a synthetic intermediate,⁵⁵⁵ and the diacetoxy-

analogue **609** were isolated from a Taiwanese *Subergorgia mollis*.⁵⁵⁶ The pregnane saponin **610**, from a Panamanian *Muricea cf purpurea*, is unusual because it contains L-galactose linked to the aglycone by an α -glycosidic bond.⁵⁵⁷ The sugar configuration was determined by hydrolysis, derivatisation and comparison of CD spectra with the corresponding synthetically-prepared α -D and β -D-galactose derivatives. Interestingly, a saponin bearing the same overall structure and comparable $[\alpha]_D$ value, but with a β -glycosidic linkage **611**, was reported from *Eunicea laciniata* (Barbados).⁵²⁷ The natural product **612** was isolated from a *Lobophytum* species (Andaman and Nicobar Islands),⁵⁵⁸ while the 19-hydroxylated steroids acanthovagasteroids A–D **613–616** were reported from *Acanthogorgia vagae* (South China Sea).⁵⁵⁹ The 19-acetoxysterols armatinols A **617** and B **618** were isolated as mildly cytotoxic components from a Taiwanese *Nephthea armata*.⁵¹³ Two new, **619** and **620**, and three known sterols were obtained from *Sarcophyton glaucum* (Taiwan).⁵⁶⁰ Whilst **619** and **620** were inactive, two of the known sterols exhibited modest cytotoxicity towards a panel of mouse and human tumour cell lines. The modestly cytotoxic steroids **621–627** were isolated from an Antarctic octocoral *Dasystenella acanthina*.⁵⁶¹ The absolute configuration at C-24 in **621** was established (Mosher's). Bioassay-directed fractionation of extracts of *Dendronephthya gigantea* (Green Is., Taiwan) yielded dendronesterones A–C **628–630** of which **628** exhibited mild cytotoxicity.⁵¹⁰ In addition to the diterpenes reported above, the cholic acid derivatives **631** and **632** were obtained from an *Eleutherobia* species (Pohnpei, Micronesia).⁵⁴⁸ The structure of the first A-nor-hippuristanol steroid **633**, a mildly cytotoxic constituent of a Taiwanese *Isis hippuris*, was established by X-ray analysis.⁵¹⁴ Steroidal glycoside **634** was isolated from *Junceella juncea* (South China Sea).⁴⁹¹ The structure of 24-methylene-

cholesta-3 β ,5 α ,6 β ,19-tetraol, a mildly cytotoxic sterol from *Nephthea albida* and *N. tiexieral verseveldt*,⁵⁶² has been confirmed by synthesis from stigmasterol.⁵⁶³ A number of steroids, from a range of coelenterates, exhibited significant inhibition of the 5 α -reductase enzyme.⁵⁶⁴ The structures of three mildly cytotoxic biscembranoids, methyl tortuoates A **635** and B **636** from *Sarcophyton tortuosum* (Hainan Is.),⁵⁶⁵ and nyalolide **637**, from a Kenyan *Sarcophyton glaucum*,⁵¹² were established by X-ray analyses of **635** and **637**. The structures of all three are arbitrarily presented in this review as bearing the purported absolute configuration of the related metabolite methyl sartortuoate.⁵⁶⁶ Two unusual mixed-skeleton terpenoids were also reported from soft corals in 2004. Stolonilactone **638**, putatively derived from condensation of a cembrane diterpenoid and trisnorsesquiterpene fragments, was obtained from an Okinawan *Clavularia koellikeri*.⁵⁶⁷ The structure of polymaxenolide **639**, from a hybrid soft coral *Sinularia maxima* x *S. polydactyla* (Guam), was established by X-ray analysis,⁵⁶⁸ and represents the fusion of a cembrane diterpene with an africanane-type sesquiterpene.

9 Bryozoans

The number of new secondary metabolites reported from bryozoans in 2004 remains small. Six alkaloids, calibugulones A-F **640–645**, were isolated from *Calibugula intermis* (Palau) with the structures of **641** and **642** being confirmed by chemical interconversion. All calibugulones displayed cytotoxicity against murine IC-2^{WT} tumour cells *in vitro* with **644** being the most potent.⁵⁶⁹ Two syntheses of calibugulones employing similar methods from an isoquinoline dione,⁵⁷⁰ or 5-aminoisoquinoline⁵⁷¹ were reported almost

simultaneously. The potent and selective inhibition of the dual specificity phosphatase Cdc25B was also reported for these compounds.⁵⁷⁰ Larvae of *Bugula neritina* (Morehead, North Carolina) were the source of bryostatin 20 **646**, along with the known bryostatin 10⁵⁷² and an as yet uncharacterised bryostatin.⁵⁷³ Proof that *Endobugula sertula*, the bacterial symbiont of *Bugula neritina*, is the producer of the bryostatins was recently obtained.⁵⁷⁴ The bryostatins are concentrated in the bryozoan larvae and give protection against predation by fish, but the adults are unprotected. The bryostatins represent the first marine example of a microbial symbiont producing an antipredator defense for its host.⁵⁷⁴ *Flustra foliacea* (“Steingrund”, North Sea) was the source of deformylflustrabromine B **647** along with a number of previously reported compounds. All compounds were tested *in vitro* for affinity towards the $\alpha 4\beta 2^*$ and $\alpha 7^*$ subtype of the neuronal nicotinic acetylcholine receptor using radioligand binding assays, with deformylflustrabromine⁵⁷⁵ and deformylflustrabromine B **647** showing affinities in the lower micromolar range.⁵⁷⁶ Myriaporones are polyketide-derived compounds originally isolated from a bryozoan *Myriapora truncata*.^{577,578} The total syntheses of myriaporones 1 **648**, 3 **649** and 4 **650** have been reported by two groups allowing determination of the previously undetermined C-5 and C-6 configurations.^{579,580} The first enantioselective synthesis of the *Flustra foliacea* metabolite (–)-flustramine B⁵⁸¹ has been accomplished, employing a cascade addition-cyclisation strategy.⁵⁸²

10 Molluscs

There was a decrease in new chemistry identified from molluscs in 2004. Bioassay-directed fractionation of extracts from *Mytilus galloprovincialis* (coast of Italy) afforded the cytotoxic chlorosulfolipid **651**.⁵⁸³ The relative configurations were deduced from NMR data, while the absolute configuration was based upon comparison with related compounds from the same source. Collections of *Mytilus edulis* and *Cerastoderma edule* in the presence of a *Dinophysis acuta* bloom (coast of Norway) afforded PTX-12 **652**, a new member of the pectenotoxin family that occurs as a pair of C-36 equilibrating diastereoisomers.⁵⁸⁴ A brevetoxin analogue, brevetoxin B5 **653**, was isolated from a New Zealand cockle *Austrovenus stutchburyi* and also detected in two other mollusc species, *Perna canaliculus* and *Crassostrea gigas*.⁵⁸⁵ The structure was elucidated by comparison with related toxins brevetoxin B1 and PbTx-2 and confirmed by chemical conversion from PbTx-2. A sea hare *Dolabella auricularia* (Japan) afforded the cytotoxic depsipeptide aurilide **654**.⁵⁸⁶ The absolute stereochemistry of **654** was determined by analysis of hydrolysis products and confirmed by enantioselective synthesis. Aurilide exhibits potent *in vitro* cytotoxicity, toxicity in *in vivo* evaluation and strongly stabilises microtubules, but with a different mechanism from that exhibited by taxol. The relative stereochemistry was established for the cytotoxic glycosidic macrolide dolastatin 19 **655** from *D. auricularia* (Gulf of California).⁵⁸⁷ It has been demonstrated that mate attraction in sea hares of the genus *Aplysia* is mediated via attractin peptides that contain a conserved Ile-Glu-Glu-Cys-Lys-Thr-Ser heptapeptide sequence.⁵⁸⁸ Haterumaimides L **656** and M **657** and 3 β -hydroxychlorolissoclimide **658** were obtained as cytotoxic components from *Pleurobranchus albiguttatus* and *P. forskalii* (Philippines).⁵⁸⁹ Structurally-related chlorinated diterpenes have been reported previously from

Lissoclinum ascidians,^{590,591} supporting the assertion that the mollusc compounds are diet-derived. The isolation of a number of scalarane-skeleton metabolites, including **659** and **660** from a nudibranch *Glossodoris rufomarginata* (South China Sea), was proposed to be dietary-linked as the nudibranchs were found on an unidentified sponge which contained scalaradiol.⁵⁹² Tribromoimidazole **661** was reported for the first time as an antimicrobial natural product from the egg masses of Spanish and Chilean collections of *Trunculariopsis trunculus*, *Ceratosoma erinaceum* and *Trophon geversianus*, with the structure confirmed by synthesis.⁵⁹³ Sesquiterpenes **662–664** were isolated from a nudibranch *Phyllidiella pustulosa*, (Hainan Is., South China Sea).⁵⁹⁴ The absolute configuration of **662** was established by chemical conversion to a known diene. The absolute stereochemistry of oxazin-3 **665**, from North Adriatic Sea mussels,⁵⁹⁵ was established by synthesis,⁵⁹⁶ while the structure and absolute stereochemistry of azaspiracid-1 **666**, originally obtained from Irish collections of *Mytilus edulis*,⁵⁹⁷ has been revised as a consequence of stereoselective total synthesis.^{598,599} The structure of cyercene A, a pyrone polypropionate from a Mediterranean *Cyerce cristallina*,⁶⁰⁰ has been confirmed by synthesis.⁶⁰¹ Austrodoric acid **667**, from an Antarctic nudibranch *Austrodoris kerguelenensis*,⁶⁰² has been synthesised with comparison of CD spectra being used to establish the absolute configuration of the natural product.⁶⁰³ The structure proposed for onchidin,⁶⁰⁴ a cytotoxic depsipeptide from a pulmonate *Onchidium* species but possibly of cyanobacterial origin, has been synthesised and exhibited different spectroscopic data to that observed for the natural product.⁶⁰⁵ A full account of the stereoselective synthesis of (+)-brasilenyne, an antifeedant haloether from a sea hare *Aplysia brasiliiana*,²⁶⁴ has been reported.²⁶⁶ Enantioselective syntheses of (–)-tochuinyl

acetate **668** and (–)-dihydrotochuinyl acetate **669**⁶⁰⁶ defined the absolute configurations of the sesquiterpenes that were isolated from a nudibranch *Tochuina tetraquetra* and its dietary soft coral *Gersemia rubiformis*.⁶⁰⁷ Dolastatin 18 **670**, from *Dolabella auricularia*,⁶⁰⁸ has been synthesized, confirming the original (*R*) stereochemistry of the *N*-Me-Phe unit.⁶⁰⁹ The absolute configuration of ulapualide A **671**, the renowned bioactive macrolide from egg masses of a nudibranch *Hexabranhus sanguineus*,⁶¹⁰ has been solved by X-ray analysis of a complex with G-actin.⁶¹¹ The sponge metabolite renieramycin M can be converted to jorumycin **672**,⁶¹² a cytotoxic isoquinoline alkaloid comparable in potency to ecteinascidin 743, which was originally isolated from a nudibranch *Jorunna funebris* (Mandapam, India).⁶¹³ The absolute configuration of (+)-norrisolide **673**, from a nudibranch *Chromodoris norrisi*,⁶¹⁴ has been established by stereoselective synthesis,⁶¹⁵ while the biogenetically-proposed stereoisomer of acanthodorol **674**, from a nudibranch *Acanthodoris nanaimoensis*,⁶¹⁶ has also been synthesised.⁶¹⁷ The *de novo* biosynthesis of aglajnes-1 and -3, linear and 4-hydroxy- α -pyrone polypropionate metabolites previously isolated from opisthobranch molluscs *Aglaja depicta*⁶¹⁸ and *Bulla striata*⁶¹⁹ respectively, has been established by [^{1-¹⁴C}]-propionate feeding experiments.⁶²⁰ Cell-free preparations of *Oxynoe olivacea* can convert the dietary algal metabolite caulerpenyne⁶²¹ into oxytoxin-2,⁶²² the main defensive metabolite of the mollusc.⁶²³ The biosynthesis of 3-alkylpyridine alkaloids haminol-1 and -2, from a Mediterranean *Haminoea orbignyana*,⁶²⁴ has been studied using [1,2-¹³C₂]-acetate incorporation, establishing elongation with acetate of a nicotinic acid starter unit.⁶²⁵ Parguerol and isoparguerol, originally from *Aplysia dactylomela*,⁶²⁶ induced neurite outgrowth in PC-12 cells with modest potency.⁶²⁷ The shellfish biotoxin

yessotoxin¹⁹² was a potent opener of the permeability transition pore on inner mitochondrial membranes.¹⁹³

11 Tunicates (ascidians)

While the number of new metabolites isolated from ascidians has remained essentially static for each of 2002 and 2003, a slight decrease was reported in 2004. As with previous years, the majority of the metabolites reported from ascidians are derived from amino acids. (2*S*,3*R*)-2-Aminododecan-3-ol **675** was reported as an antifungal component of *Clavelina oblonga* (Brazil).⁶²⁸ The absolute stereochemistry was secured by preparation of the dibenzoyl derivative and comparison of CD data with structurally-defined model compounds. The first examples of acetylenic lipids from an organism of the phylum Chordata **676–679** were isolated from an unidentified ascidian of the family Polyclinidae (Spain).⁶²⁹ Biselides A **680** and B **681** were obtained from an Okinawan ascidian from the family Didemnidae.⁶³⁰ Absolute stereochemistry was implied by comparison of NMR and CD data with those reported for the corrected absolute configuration of haterumalide NA.^{631,632} A stereoselective total synthesis⁶³³ has confirmed the structure and absolute configuration of bistramide A **682** from *Lissoclinum bistratum*.⁶³⁴ The absolute configurations of lepadins D⁶³⁵ **683**, E⁶³⁵ **684** and H⁶³⁶ **685**, from a *Didemnum* species⁶³⁵ and *Aplidium tabascum*,⁶³⁶ have been ascertained by stereoselective total synthesis.⁶³⁷ 1,3-Dimethyl-8-oxoisoguanine **686** was isolated from an ascidian *Pseudodistoma cereum* (New Zealand).⁶³⁸ An Australian *Atrialum robustum* was the source of amino acid-derived metabolites **687–691**.⁶³⁹ The absolute stereochemistries of **687** and **688** were

established by degradative derivatisation studies while only the relative configurations of methylthioadenosine analogues **690** and **691** were determined. Compound **690** was a relatively potent partial agonist of human A₃ adenosine receptors. A Palaun *Botrylloides tyreum* afforded the weakly cytotoxic tyrosine analogues botryllamides E–H **692–695**.⁶⁴⁰ *Cystodytes cf. violatinctus* (Kenya) gave violatinctamine **696**, which in solution was proposed to exist as a rapidly interconverting mixture of imino-phenol (shown) and amino quinone-methide tautomers.⁶⁴¹ Lissoclibadin 1 **697** was isolated as a mildly antibacterial component of an Indonesian *Lissoclinum cf. badium*.⁶⁴² The relative orientations of the aromatic rings were based upon molecular modelling studies. Fascaplysin analogues **301** and **698–701** were obtained from a *Didemnum* species (Chuuk Atoll, Micronesia), while **301** was also isolated from a sponge *Fascaplysinopsis reticulata* (Fiji).³⁷⁶ Asymmetric syntheses of (+)-arborescidine A, (–)-arborescidine B and (–)-arborescidine C, antipodes of the natural products **702–704** from a New Caledonian *Pseudodistoma arborescens*,⁶⁴³ have been achieved *via* use of the Noyori catalytic asymmetric hydrogen transfer reaction.⁶⁴⁴ The synthetic arborescidines had opposite optical rotations to those of the natural products, establishing the absolute configurations as drawn and claimed originally,⁶⁴³ but opposite to those claimed in a subsequent revision.⁶⁴⁵ Three lamellarin alkaloids, lamellarins γ **705**, α **706** and ϵ **707** were reported from *Didemnum obscurum* (Indian Ocean),⁶⁴⁶ while solid-phase syntheses of lamellarins Q and O have been reported.⁶⁴⁷ Four further ecteinascidins, ETs 731 **708**, 745b **709**, 808 **710** and 815 **711** from *Ecteinascidia turbinata* were disclosed in a patent.⁶⁴⁸ Full accounts of the biomimetic synthesis of the dimeric prenylated quinone (–)-longithorone A⁶⁴⁹ from *Aplidium longithorax*,^{650,651} of the corrected structure of diazonamide A,⁶⁵² and the

isolation and synthesis of an endogenous sperm-activating and attracting factor from *Ciona intestinalis*⁶⁵³ have been reported. The structures of cyclic peptides bistratamides E, G and J,^{654,655} from *Lissoclinum bistratum*,⁶⁵⁶ botryllazine B,⁶⁵⁷ from a Spanish *Botryllus leachi*,⁶⁵⁸ and subarine,⁶⁵⁹ a potentially ring-opened pyridoacridine alkaloid from an unidentified Singaporean ascidian,⁶⁶⁰ have been confirmed by syntheses. Molecular dynamics simulations have modelled the interaction of didemnins A and B^{661,662} with human elongation factor eEF1A in the presence of GTP, an interaction that leads to inhibition of protein synthesis.⁶⁶³ Monomeric analogues of the heterodimeric antimicrobial peptide halocidin from *Halocynthia aurantium*⁶⁶⁴ have been prepared, leading to the identification of a more potent antimicrobial and less haemolytic variant.⁶⁶⁵ Further biological investigation of the meridianins, aminopyrimidineindole alkaloids originally from *Aplidium meridianum*,⁶⁶⁶ has revealed that they inhibit various protein kinases, prevent cell proliferation and induce apoptosis,⁶⁶⁷ while polycarpine, an alkaloid from *Polycarpa clavata*,⁶⁶⁸ and a dimethyl analogue both induced apoptosis via p53 and caspase-3 dependent pathways.⁶⁶⁹

12 Echinoderms

There was a slight increase in new compounds identified from echinoderms in 2004 compared to 2003. In addition to a number of known metabolites, xanthosine **712** was isolated from a starfish *Asterias rollestoni* (Yellow Sea, China).⁶⁷⁰ A ganglioside molecular assemblage, LMG-4, the major entity of which is represented by **713**, was obtained from a Japanese starfish *Luidia maculata*.⁶⁷¹ The ganglioside displayed

neuritogenic activity against PC12 cells in the presence of nerve growth factor. A structurally more complex ganglioside molecular entity CJP4 **714**, also exhibiting neuritogenic activity, was isolated from a Japanese feather star *Comanthus japonica*.⁶⁷² The progesterone derivative **715** was obtained from a Russian starfish *Lethasterias nanimensis chelifera*,⁶⁷³ while the polyhydroxysterol **716** was isolated from a Pacific starfish *Asterina pectinifera*.⁶⁷⁴ Brine shrimp assay-directed fractionation of a starfish *Certonardoia semiregularis*, (Komun Is., Korea) extract, afforded twelve polyhydroxysterols **717–728** and two saponins **729** and **730**.⁶⁷⁵ Side-chain configurations were determined either by Mosher analysis (certonardosterols Q₂ **718**, A₃ **725**, A₄ **726**, B₄ **727** and certonardoside H₄ **730**) or biogenetic arguments (certonardosterols Q₁ **717**, Q₃ **719**, Q₄ **720**, Q₅ **721**, Q₆ **722**, Q₇ **723**, D₅ **728** and certonardoside H₃ **729**). All of the compounds tested exhibited modest *in vitro* cytotoxicity towards a panel of human tumour cell lines. In a separate study of the same organism from the same location, a further eleven sterols **731–741** and eight saponins **742–749** were identified.⁶⁷⁶ A glycoside, phrygioside A **750** and the corresponding aglycone **751**, were isolated from a starfish *Hippasteria phrygiana* (Sea of Okhotsk).⁶⁷⁷ The steroid-taurine conjugate, triseramide **752**, was a mildly bioactive component of a Fijian starfish *Astropecten triseriatus*.⁶⁷⁸ The Far-Eastern starfish *Henricia sanguinolenta* and *H. leviuscula leviuscula* yielded the saponins sanguinosides A **753** and B **754**.⁶⁷⁹ The C-24 configuration of **754** was based on biogenetic considerations. Further investigation of the side-chain absolute stereochemistries of henriciosides H₁ **755**, H₂ **756** and H₃ **757**, originally isolated from a Far-Eastern starfish *H. derjugini*,⁶⁸⁰ (Mosher's) established that **755** is, in fact, identical to the previously reported steroid laevisculoside I,⁶⁸¹ and that **756**

has the (24*R*,25*S*) configuration while **757** is (24*R*,25*R*).⁶⁸² Linckosides C–E **758–760**, from the Okinawan starfish *Linckia laevigata*, induced neurite outgrowth in PC12 cells.⁶⁸³ The relative configurations of C-24 and C-28 in **759** were established, with the same configurations implied for **758**. The triterpene aglycones, philinopgenins A–C **761–763**, were obtained from the acid hydrolysate of the crude glycoside fraction from a sea cucumber *Pentacta quadranglasis* (South China Sea).⁶⁸⁴ The philinopgenins are possibly artefacts. Two saponins, thyonosides A **764** and B **765**, were isolated from the sea cucumber *Thyone aurea* (Namibia).⁶⁸⁵

13 Miscellaneous

Two 21-residue antimicrobial peptides, arenicin-1 **766** and arenicin-2 **767** were obtained from a polychaete worm *Arenicola marina* (White Sea, Russia).⁶⁸⁶ Diatom-derived conjugated aldehydes such as (2*E*,4*E*)-decadienal continue to be of interest, exhibiting cytotoxicity towards a number of different organisms including bacteria, algae, fungi, echinoderms, molluscs and crustacea⁶⁸⁷ in addition to inhibiting fertilization success in broadcast-spawning invertebrates.⁶⁸⁸ The structure of the antipredatory chemical defense compound 2,3,4-tribromopyrrole from a hemichordate worm *Saccoglossus kowalevskii*,⁶⁸⁹ has been confirmed by synthesis.⁶⁹⁰ Mass spectrometric analysis of stable isotope incorporation experiments determined that Cypridina luciferin, an alkaloid utilised by the bioluminescent crustacean *Cypridina (Vargula) hilgendorffii*, is biosynthesised from L-tryptophan, L-arginine and L-isoleucine.⁶⁹¹ Gymnorrhizol **768**, an unusual macrocyclic polydisulfide possessing an unprecedented carbon skeleton, has

been isolated from a mangrove *Bruguiera gymnorrhiza* (Guangxi Province, China). The structure was confirmed by X-ray analysis.^{692,693}

14 Conclusions

In this review, the structures of 767 compounds have been reported. The biological testing on, or biological properties of, 380 compounds is included. Using numbers extracted from MarinLit,⁷⁹ the geographic origins of compounds reported in 2004 are compared with those up to 2003 (Fig. 1a). The geographical descriptors used in MarinLit are somewhat imprecise, ranging from exclusive to inclusive, but Australia, the Caribbean, the Indian Ocean, Japan, the Mediterranean and the Western Pacific clearly stand out as the sources for two-thirds of the reports on marine natural products, with Japan being the clear leader. What is most notable about the data for 2004 (Fig. 1b) is the marked increase in citations relating to the China Sea. Also shown in Fig. 1 is the relative proportion of articles for each region reporting bioactivity (“bioarticles”). These, taken collectively, suggest the possibility that greater attention is being paid to searching for, or commenting on, bioactive compounds (55% in 2004 vs. 49% up to 2003).

Insert Figures 1a and 1b

A second point of comparison is the type of biological activity reported which can be grouped into eight areas - Anticancer, Antibiotic (which includes antifungal and antimalarial), Antiinflammatory, Antiviral, Immunomodulatory, Various, Agricultural and Methodology. Fig. 2 shows the types of the testing carried out up to, and including, 2004.

Insert Figure 2

The actual data for 2004 did not vary significantly from that reported cumulatively, but was suggestive that the “catch-all” category of Methodology was increasing. Testing with an anticancer outcome remains far and away the most used assay, but increasingly results are appearing in the literature for antimalarial, antitubercular and antiinfective assays against drug-resistant microorganisms and in time these areas will stand out against the cumulative record. There can be no doubt of the urgent need for new therapeutics in those areas, but also in agricultural areas where resistance to the standard anthelmintics is becoming a serious problem.

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