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INTERESTING ASPECTS OF MARINE NATURAL PRODUCTS CHEMISTRY

D. JOHN FAULKNER
Scripps Institution of Oceanography, La Jolla, CA 92093, U.S.A.

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Marine natural products chemistry has experienced an explosive growth during the past five years. Whereas it was possible to present a fairly exhaustive review[1,2] of the field just two or three years ago, such a task is now impractical. A compilation of marine natural products is available,[3] but it is only a matter of time before this too becomes unreasonable. For this report on marine natural products, I have selected those groups of compounds which I believe to be of greatest interest to organic chemists. I have tried to attract the attention of the synthetic chemist seeking novel target molecules or the practical spectroscopist seeking unusual arrangements of functional groups. My report emphasizes unusual molecules, both simple and complex, their interrelationships and, where possible, their effects on other organisms.

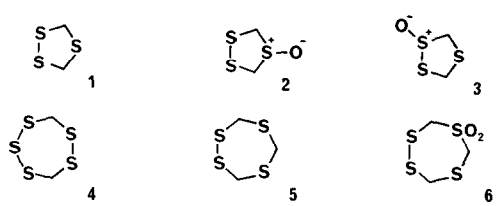
The rate at which new structures have been published reflects the power of modern spectroscopic techniques. Structural elucidation by single crystal X-ray diffraction analysis is particularly well suited to studies of marine natural products, since many compounds contain heavy atoms. However, the fashionable reliance on interpretation of spectral data, particularly proton NMR spectroscopy, coupled with an apparent reluctance to perform chemical degradations or correlations, has led to some erroneous structural assignments. There are many communications which, due to space limitations, contain insufficient data for a reviewer to judge whether the structure assigned is correct or simply the most likely of several alternatives. In some cases, a carbon skeleton has been assumed on the basis of biosynthetic probability and no chemical correlation has been performed. In a few cases, structures have been proposed on the basis of mass spectral fragmentation data only; these structures require proof by synthesis. Inevitably, a few of the proposed structures will be incorrect. I have reported the structures as presented in the literature; individual readers must evaluate the reliability of each structural elucidation.

One of the major problems faced by the marine natural products chemist is that his ability to identify compounds exceeds his ability to identify the marine organisms from which the compounds were obtained. This is particularly true for the identification of sponges, since expert taxonomists often fail to agree. Since it is difficult to name a new compound after an unknown organism, some marine natural products have been given irrelevant and unpronounceable names, but it is hoped that this practice will be curtailed.

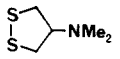
A positive feature of marine natural products chemistry is the desire to determine the functions of new compounds in the marine environment. This is leading to interdisciplinary research involving the chemist with marine biologists and ecologists, a trend which can only serve to strengthen both fields.

In a report of this length, I have been obliged to omit whole areas of study. Exciting developments in the areas of marine sterols[4] and marine carotenoids[5] are being reviewed by experts in these fields. Other groups of compounds, particularly the simple hydrocarbons, amines, choline esters, amino acids and quinonoid pigments, were not included as a result of personal choice.

If the cyclic polysulfides **1–6** from *Chondria californica* had not possessed antibiotic activity, I have no doubt that they would have been discarded, since the unusually simple PMR spectra of these compounds resemble those of solvents at first glance. The major component is the sulfone **6**, which is also the most effective antibiotic.[6] Both lenthionine **4** and 1,2,4,6-tetrathiepane **5** had previously been found in the mushroom *Lentinus edodes*.[7] The sulfoxide **3** exhibited slight optical activity in the CD spectrum, but we could not detect an optical rotation at 589 nm. The cyclic polysulfides **1**, **4**, and **5** have been synthesized from dichloromethane and sodium polysulfide, while the sulfoxides **2** and **3** were prepared by oxidation of **1** with sodium periodate; the sulfone **6** has not been synthesized.



There are relatively few polysulfides in nature, yet those which have been discovered often possess biological activity. Considering the relatively high sulfate concentration in seawater, and particularly the high sulfide concentrations in anoxic environments, we might expect to find many more sulfides in the marine environment. One of the most useful marine natural products is nereistoxin **7**, responsible for the insecticidal activity of the marine polychaete worm *Lumbriconereis heteropoda*.[8] A synthetic analog of nereistoxin called Padan is now used commercially as an insecticide.[9]



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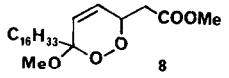
An observation that I have always found intriguing was that n-alkyl disulfides were formed when gorgonian corals (*Pseudoplexaura porosa*) were allowed to decompose under flowing seawater.[10] The sulfides are probably formed by bacterial action on the lipids of the coral, but this remains to be confirmed experimentally. A series of sulfur-containing lipids, which may be considered derivatives of 3-oxoundecyl mercaptan, has been isolated from the brown algae *Dictyopteris plagiogramma* and *D. australis*.[11]

On preliminary investigation, many marine organisms appear to contain mainly fatty acid-derived lipids and are therefore relegated to the "uninteresting" category. However, some recent results indicate that lipids from marine organisms may contain interesting functional groups. A sponge of the genus *Chondrilla* has been shown to contain a cyclic peroxyketal, chondrillol **8**, whose structure was established by chemical degradation.[12] In a most unusual reaction, treatment of an ethereal solution of **8** with aqueous hydrochloric acid gave a β-chlorovinyl ketone **9**.



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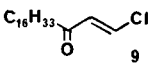

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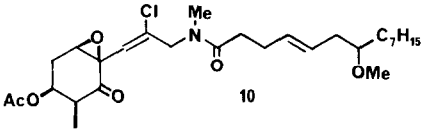
The Hawaiian sea hare *Stylocheilus longicauda* contains stylocheilamide **10** and deacetylstylocheilamide **11**, which are chlorinated amide derivatives of *trans*-7-methoxytetradec-4-enoic acid, which is a major constituent of the Hawaiian alga *Lyngbya majuscula*.[13] The structure of stylocheilamide **10** has been determined by chemical degradation, but stereochemical details remain unknown.[14]



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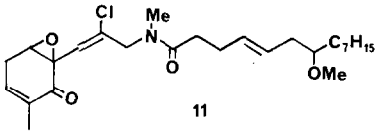

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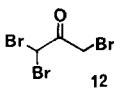
Two concurrent investigations of constituents of the red alga *Asparagopsis taxiformis* led to the isolation of two very different sets of metabolites because the isolation procedures were biased to obtain different classes of compounds. Fenical[15] obtained seven polyhalogenated acetones and four polyhalogenated 3-buten-2-ones from chloroform extracts of air-dried algae. The major constituents were 1,1,3-tribromoacetone **12** and a tribromo-3-buten-2-one **13** with minor constituents containing chlorine. The structures were proposed on the basis of GC–MS data. Although the polyhalogenated acetones were synthesized by bromination of acetone and chloroacetone, none of the compounds, natural or synthetic, was isolated in pure form. I do not believe that the comparison of a natural mixture with a synthetic mixture using GC–MS constitutes an absolute confirmation of structure.



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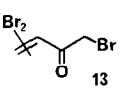

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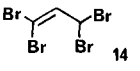
Moore *et al.*[16] deliberately obtained only the volatile constituents of *A. taxiformis*. Examination of the crude oil by PMR and GC–MS revealed that bromoform was the major constituent and $CHBr_2I$, $CHBrI_2$ and CHI_3 were minor constituents. The assignments were confirmed by comparisons with authentic samples. Among the very minor constituents, identified only by GC–MS, was CHClBrI. Moore also identified 1,1,3,3-tetrabromopropene **14** and three other tetrahalopropenes, dibromoacrolein, bromoacetone and iodoacetone, by GC–MS studies. Three polyhalogenated 3-buten-2-ones were observed by GC–MS, and one of these, subsequently identified as 1,1,4,4 - tetrabromo - 3 - buten - 2 - one **15**, was isolated.



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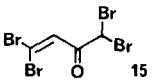

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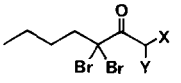
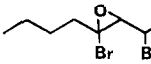
Comparison of the two studies is difficult because the data are insufficiently detailed. It is significant that Fenical did not obtain any iodinated compounds, which may have decomposed on silica gel chromatography, while Moore obtained fewer chlorinated metabolites. Moore's subsequent research[17] on methylene chloride extracts of *A. taxiformis* has revealed the presence of a total of 74 halogenated metabolites, the majority of which were detected by GC–MS and identified by comparison with authentic materials. This array of metabolites contains 11 one-carbon compounds, including carbonyl di-iodide, 8 two-carbon compounds, including a variety of halogenated acetamides, 39 three-carbon compounds, including halogenated acetones, isopropanols and propenes and 16 four-carbon compounds, both halogenated 3-buten-2-ones and 3-buten-2-ols. Fenical[18] has recently shown that halogenated acetic acids were present in the aqueous extracts of *A. taxiformis* and that these acids were converted into ethyl esters when ethanol was used as the extraction solvent.

A. taxiformis is eaten by Hawaiians, who prepare the seaweed in a way which should preserve many of the halogenated compounds, including those which are lachrymatory and which may be toxic. The life cycle of *A. taxiformis* is complex: *A. taxiformis*, having male and female plants, alternates with a heteromorphic sporophyte called *Falkenbergia rufanulosa*. While both male and female plants of *A. taxiformis* contain halogenated metabolites in specialized "vesicular cells", *F. rufanulosa* does not contain these compounds.

A related red alga, *Bonnemaisonia hamifera*, contains 1,1,3,3 - tetrabromo - 2 - heptanone **16** as the major halogenated metabolite. Four minor constituents, including 3,3-dibromo - 1 - iodo - 2 - heptanone **17**, were detected by GC–MS.[19] *Bonnemaisonia nootkana* also contains halogenated heptane derivatives. The major constituent, 2,3 - epoxy - 1,1,3 - tribromoheptane **18**, has been isolated and characterized.[20]

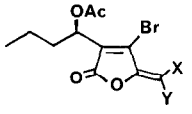


16 X=Y=Br
17 X=I Y=H

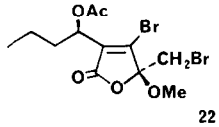


18

Two groups[21,22] have reported a series of halogenated lactones called fimbrolides from *Delisea fimbriata* (Bonnemaisoniaceae) which are responsible for the antibiotic activity of these red algae. The major component **19** was treated with methanol under basic conditions to obtain a mixture of two diastereoisomeric addition products which were separated by HPLC. The structure of the crystalline diastereoisomer **22** was obtained by X-ray diffraction.[22] Two other acetoxyfimbrolides **20** and **21** have been isolated and characterized, while a total of seventeen fimbrolides have been detected by GC–MS.[21]



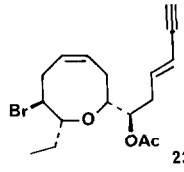
19 X=H Y=Br
20 X=Br Y=H
21 X=H Y=I



22

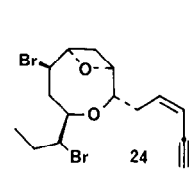
The acetylenes from red algae of the genus *Laurencia* have presented rather difficult problems of structural elucidation so that it is not surprising that several incorrect structures were corrected using X-ray analysis. The acetylenes are all halogenated cyclic esters based on a linear pentadeca-3-ene-1-yne carbon chain. The structures of those acetylenes not identified by X-ray analysis have been elucidated by stepwise degradation and detailed analysis of PMR spectra. Because the signals due to protons α to oxygen, bromine and chlorine often occur in the same region of the spectrum, it is difficult to assign signals in this region, even though it may be possible to determine all vicinal and geminal relationships between protons through careful spin decoupling. The difficulty in assigning these signals has led to some very interesting examples of incorrect structure assignment.

Laurencin **23**, isolated from *Laurencia glandulifera*, was shown to contain a *trans* enyne system attached to an 8-membered ether ring. The interpretation of the richly detailed PMR spectrum is a classic example of the use of spin decoupling in structure elucidation.[23] The structure determined by spectral methods was confirmed by X-ray analysis,[24] and the absolute configuration was determined by Prelog's atrolactic acid method.

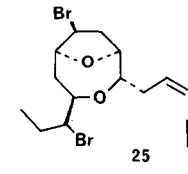


23

The structure determinations of laureatin **24** and isolaureatin **25** required a lengthy degradation sequence, in addition to careful spectral analysis.[25] In these compounds, as in all acetylenes containing two ether rings, the major problem was to determine which four of the six possible methine carbon atoms were involved in ether linkages and to determine the ring sizes. A feature of the PMR spectrum of laureatin **24** is that the signals due to protons on the oxetane ring are strongly deshielded, as is the C-12 proton, which is assumed to be situated close to oxetane oxygen atom. The structure of isolaureatin **25** has been confirmed by X-ray analysis.[26] Both laureatin **24** and isolaureatin **25** contain the *cis* enyne system, although the corresponding *trans* isomers were subsequently described.[27] Some *Laurencia* acetylenes have been isolated



24

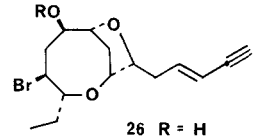


25

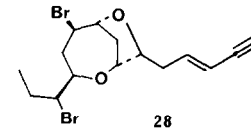
as mixtures of geometrical isomers about the Δ^3 olefinic bond. Since such mixtures are very difficult to separate, it seems best to estimate the *cis* : *trans* isomer ratio by GLC or PMR and convert the mixture into a single derivative by hydrogenation or hydration of the acetylene.

The structural elucidation of laurefucin **26** and acetyllaurefucin **27**, both isolated from *Laurencia nipponica*, provided the first hints of just how difficult these structural assignments could be. An incorrect structure for laurefucin resulted from the logical interpretation of a series of degradation experiments.[28] After the correct structure had been revealed by X-ray analysis,[29] it was discovered that a key intermediate in the degradation scheme had undergone an unobserved molecular rearrangement during chromatography, but the details of the rearrangement have not been revealed.

Laurefucin **26** and acetyllaurefucin **27**, together with isoprelaurefucin **28**,[30] were all isolated from *L. nipponica* as the *trans* olefins. We have recently found that *L. subopposita* contains the same three metabolites but as mixtures of *cis* and *trans* isomers.

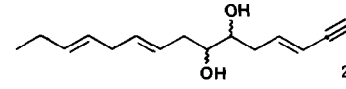


26 R = H
27 R = OAc



28

Irie and coworkers have suggested that *cis*- and *trans*-laurediol **29**, isolated in low yield from *L. nipponica*, might be biosynthetic precursors of the cyclic ethers **23–28** that they had described.[27] While this is a reasonable suggestion for **23–28**, the chlorinated acetylene (see below) appear to require a chlorohydrin precursor, However, the suggestion that the biosynthetic routes involve bromonium ion initiated cyclizations has not been challenged.



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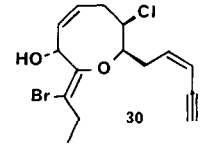
A series of acetylenes containing both bromine and chlorine has recently been described. The presence of chlorine introduces another degree of difficulty into the assignment of the PMR spectrum and the proportion of incorrect structural elucidation based on spectroscopic methods has increased accordingly. In the case of chondriol, the incorrect structure **31** was assigned, even though the published PMR spectrum does not contain the usual signals observed for the methylene protons of the bromopropyl group in model compounds,[31] and yet authors, reviewers and readers alike accepted the incorrect structure!



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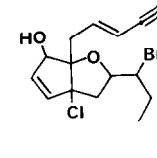
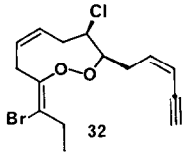


31

The correct structure of chondriol **30** resulted from an X-ray analysis performed after signals due to a tetrasubstituted olefinic bond had been observed in the CMR spectrum.[32] The structural similarities between chondriol **30** and the *Laurencia* metabolites such as laurencin **23** led to a taxonomic reexamination of the algal source, with the results that *Chondria oppositiclada* was reclassified as *Laurencia yamada*.[33]

A second metabolite of *L. yamada* called rhodophytin **32** is the most interesting of the halogenated acetylenic ethers.[34] Comparison of the CMR and PMR spectra with those of chondriol **30** and its derivatives revealed that portions of the two molecules were almost identical. The structural elucidation of this stable cyclic peroxide was complicated by the fact that neither rhodophytin **32** nor its rearrangement product **33** shows a molecular ion in its mass spectrum, which instead shows an [M-16] cluster as the highest molecular weight peak. However, hydrogenation of rhodophytin **32** to 7 - chloro - 6 - hydroxypentadeca - 12 - one showed that rhodophytin must contain two oxygen atoms. The existence of the cyclic peroxide functionality was demonstrated by the reaction of rhodophytin **32** with acidified methanolic potassium iodide to generate iodine. Unlike most peroxides, rhodophytin **32** is stable to strong base but slowly undergoes rearrangement to the conjugated diene **33** in CCl_4 solution, a reaction which is probably acid catalyzed.



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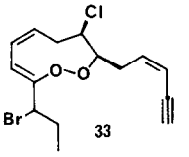
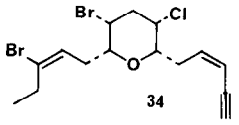


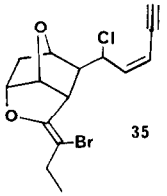
33

Dactylyne **34** was isolated from the opisthobranch mollusc *Aplysia dactylomela*. Due to difficulties in assigning the PMR spectrum, the structure of this interesting molecule was not firmly established until an X-ray analysis had been performed.[35] Dactylyne **34** is unique among the *Laurencia* acetylenes, where it undoubtedly belongs, in having a 6-membered ether ring, rather than a medium-sized ether ring. The corresponding *trans* enyne, isodactylyne, was also isolated from the same source.[36]



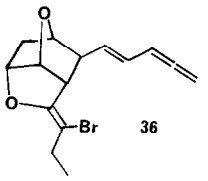
34

The Hawaiian alga *Laurencia nidifica* (green variety) produces halogenated acetylenes which contain a carbocyclic ring and have a chlorine at C-5.[37] The structure of *cis*-maneonene A **35** was established by interpretation of the PMR data and by limited chemical degradation, including a reaction with chromous sulfate to obtain an



35

α,β-unsaturated allene **36**. Two geometrical isomers of manoenene A were also isolated. Isomanoenone-A **37** and isomanoenone-B **38**, both obtained from the same alga, *L. nidifica*, have two carbocyclic rings.[38] The structures were determined by analysis of spectral data, particularly the PMR spectra.



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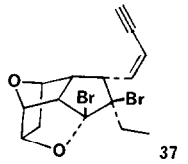

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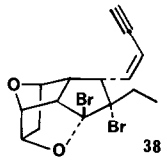
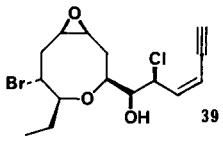


38

There is ample evidence that many more *Laurencia* acetylenes will be described in the near future. Among these is an interesting epoxide **39** from *L. poitei*, whose structure was determined by X-ray analysis.[39]

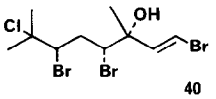


39

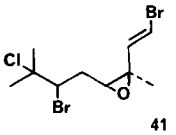
Although the halogenated monoterpenes may appear to be among the more simple compounds isolated from marine organisms, the structural elucidation of these metabolites has been complicated by the high degree of halogen substitution in the molecules. To the X-ray crystallographer, the highly halogenated monoterpene **44** resembled an inorganic molecule, with electron-dense halogen atoms dominating the diffraction pattern. In polyhalogenated compounds containing both chlorine and bromine, it is often difficult to determine the relative locations of the halogen atoms by spectroscopic methods. Assignment of α-halogen protons in the NMR spectrum of a polyhalogenated monoterpene using Schoolery apparent shielding coefficients is quite unreliable due to "through-space" shielding by other halogen atoms in the molecule. Nonetheless, the structures of many halogenated monoterpenes have been determined by a mixture of spectroscopic methods, often involving empirically-derived correlations.

Halogenated monoterpenes were first found in the digestive gland of the California sea hare *Aplysia californica*. The structure of the alcohol **40** was derived using a combination of spectroscopy and partial synthesis. The basic carbon skeleton and substitution pattern was apparent from the NMR spectrum, but the position of the chlorine atom could not be determined by spectroscopic means. Treatment of the alcohol with mild base gave an epoxide **41**, showing that bromine had been at C-4. Jones oxidation of the alcohol gave a ketone **42**, indicating that the chlorine must be at either C-6 or C-7 of the alcohol **40**. At that time, the three known molecules having chlorine and bromine on adjacent carbon atoms all contained a secondary bromine and tertiary chlorine and were assumed to be derived by the "Markovnikoff" addition of Br^+Cl^- to a trisubstituted olefin of a suitable precursor.

Synthesis of the ketone was therefore accomplished by a "biomimetic synthesis", treatment of the acetate **43** with NBS in ether containing lithium chloride and a trace of hydrogen chloride.



40



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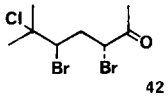

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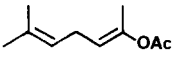
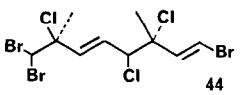


43

The relative stereochemistry of the epoxide **41** was determined using a combination of PMR measurements.[41] The *cis* arrangement of hydrogen and methyl about the epoxide ring was established by observing a 15% NOE. For once, the high degree of halogen substitution was advantageous, for the molecule was held in a preferred conformation in solution. Interpretation of lanthanide-induced shift data, using a PDIGM computation in conjunction with the coupling constants from a richly detailed first order 220 MHz PMR spectrum, allowed the assignment of the conformation of the epoxide **41** in solution and, consequently, the relative stereochemistry of the alcohol **40**.

The structure of the monoterpene **44** was determined by X-ray crystallography.[42] Although **44** was first isolated from the sea hare, the true source was found to be the red alga *Plocamium cartilagineum*, a principal component of the sea hare's diet.[43] *P. cartilagineum* contained a mixture of twelve linear halogenated monoterpenes which were very difficult to separate.[44] The compounds were closely related, each having a Δ^1 olefinic group and a $\Delta^{5,7}$ dienic function. Since these molecules rarely showed a molecular ion in the mass spectrum, we found that the most convenient method of checking the molecular weight was to sum the two fragments which resulted from cleavage of the 3,4-bond. It was soon obvious that the compounds could be grouped according to molecular formula. The pair of compounds **48** and **49**, having the molecular formula $C_{10}H_{11}Br_3Cl_2$, could be related to **44** by loss of HCl, while the $C_{10}H_{12}Br_2Cl_2$ pair **46** and **47** were related to **44** by loss of BrCl. We could not cleanly eliminate HCl from **44**, but the reaction of **44** with lithium triethylborohydride gave a mixture of two $C_{10}H_{12}Br_2Cl_2$ isomers, one of which was identical to **46** and the other the expected geometrical isomer **45**. The structure of the second natural isomer **47** was assumed to be the diastereoisomer about the 3,4-bond since the mass spectra of the two isomers were almost identical and the major differences in the NMR spectra were associated with groups flanking the 3,4-bond. We considered the possibility of interchanging halogen atoms but felt that this should give rise to greater differences in mass spectra and NMR spectra than those observed. In addition, the possibility of interchanging halogen atoms is not available for the diastereoisomeric pair **53** and **54**. The structures of the remaining monoterpenes **50–56** were assigned on the basis of the observed spectral data, using empirical rules to assign the relative stereochemistry of the diastereoisomeric pairs.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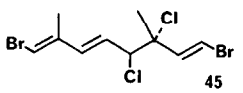
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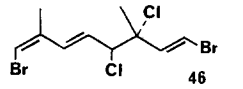
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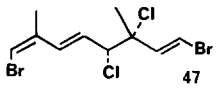
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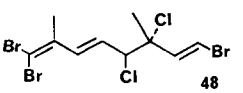
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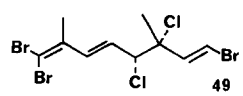
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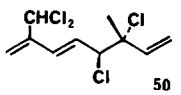
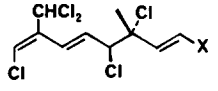
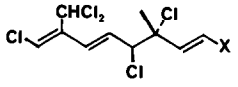


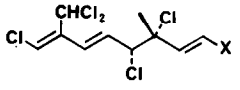
50



51 X = H
52 X = Br

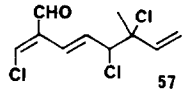


53 X = H
55 X = Br



54 X = H
56 X = Br

There are many aspects of this research which are still puzzling. Why were the diastereoisomers of **51** and **52** not observed when other diastereoisomeric pairs were always found in approximately equal amounts? Since all halogenated *Aplysia* metabolites are assumed to be of dietary origin, why did the samples of *Plocamium* not contain the alcohol **40** and other linear polyhalogenated monoterpenes **58–60** subsequently found in *Aplysia californica*?[45] Why did we not find cartilagineal **57**, which has been isolated as a major constituent of *P. cartilagineum* collected in the vicinity of Santa Cruz,[46] approximately 400 miles northwest of La Jolla?



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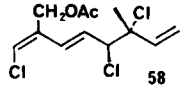

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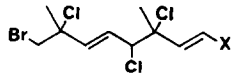
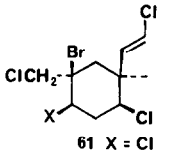


59 X = H
60 X = Br

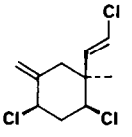
In an attempt to answer some of these questions, we analyzed the halogenated monoterpene content of single branches of *Plocamium* from several plants at different locations and depths. We found that there were (at least) three different "chemical types" of *P. cartilagineum* distributed in a random manner throughout the La Jolla area.[47] In similar vein, Crews has observed that the halogenated monoterpene content of *Plocamium* species depended on the collecting site, while Moore has observed a similar diversity in halogenated monoterpene content of *Chondrococcus hornemanni* with location. All these observations indicate that the natural products chemistry of red algae which contain halogenated monoterpenes is both complex and unpredictable.

It would appear that *P. violaceum* collected in the vicinity of La Jolla is a chemically homogeneous

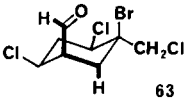
population, for all samples collected contained four monocyclic halogenated monoterpenes in approximately the same proportions. The major component was violacene **61**.[48] Since the richly detailed 220 MHz NMR spectrum clearly showed the positions of the hydrogens on the 6-menbered ring, the problem of assigning a structure could be summarized in two questions: where was the sole bromine atom and how were the four substituents at the tetrasubstituted carbon atoms arranged? With so many halogen atoms in the molecule, it is difficult to perform selective dehalogenation reactions. In this case, we found that reduction of **61** with chromous sulfate in aqueous DMF gave a reasonably good yield of the methylenecyclohexane derivative **62**, which was also identified as a minor natural product. Observation of an $[M^+-CH_2Cl]$ cluster but no $[M^+-CH_2Br]$ cluster in the mass spectrum indicated that C-5 must be bonded to a bromine atom and a $-CH_2Cl$ group. The stereochemistry of violacene resulted from careful analysis of the PMR spectrum, the observation of a small W-coupling in the aldehyde **63** obtained by ozonolysis of violacene, and analysis of lanthanide-induced shifts in the PMR spectrum of the acetate **64**. This simple cyclohexanoid skeleton had not previously been encountered among monoterpenes.



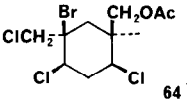
61 X = Cl
67 X = Br



62

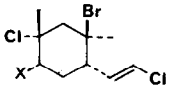


63



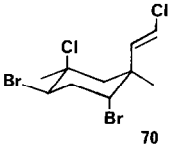
64

A second cyclic monoterpene from *P. violaceum* was based on a second novel carbon skeleton. The structure of (1*R*,2*S*,4*S*,5*R*) - 1 - bromo - *trans* - 2 - chlorovinyl - 4,5 - dichloro - 1,5 - dimethylcyclohexane **65** was determined by X-ray crystallography.[49] Treatment of **65** with hydrogen chloride in carbon tetrachloride gave the diene **66**, which was identified as a fourth natural product. We had suspected that the diene might be an artifact of the workup procedure, but extraction with cold hexane and immediate analysis by GLC proved that **66** was indeed a natural product. The diene **66** was isolated as the major component of *P. violaceum* collected near Santa Cruz and the structure determined from a detailed analysis of both the PMR and CMR spectra.[50] The equatorial stereochemistry of the methyl group was proposed on the basis of the chemical shift (δ = 30.3 ppm) of the methyl signal in the CMR spectrum. This seems to be a risky assignment since the position of this signal lies midway between the methyl signals (δ = 28.0 and 32.1 ppm) in **65**, which has both axial and equatorial methyl groups.

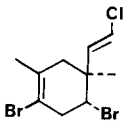


65 X = Cl **66**
68 X = Br **69**

We are currently investigating the mixture of halogenated monoterpenes from *P. cartilagineum* collected from the English Channel.[51] Three of the components **67–69** have been identified as analogues of known compounds where the chlorine at C-4 was replaceed by bromine. The major constituent **70** is also the most interesting of the new metabolites, for it has an axial bromine at C-2. This is the stereochemical arrangement which would be required for rearrangement to **68** (Br to C-1; chlorovinyl to C-2). Treatment of **70** with silver acetate in acetic acid gave **69**, the rearranged diene, while the reaction of **70** with lithium chloride and lithium carbonate in DMF gave the vinyl bromide **71**. A fifth metabolite is the nonconjugated diene **72**.



70



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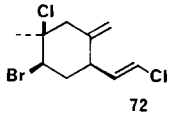
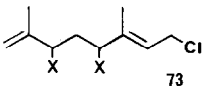


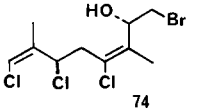
72

Crews is currently investigating a series of linear halogenated monoterpenes from *P. violaceum*.[52] These compounds, which have the general structure **73** (X = Br or Cl), may prove to be the biosynthetic precursors of the cyclic metabolites **61**, **62**, **65** and **66** of *P. violaceum*.

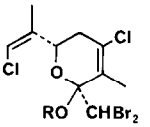


73

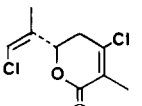
Two research groups have studied the halogenated monoterpenes of *Plocamium costatum* from South Australia, Wells *et al.*[222] isolated costatol **74** and costatone **75**, while Sims *et al.*[223] isolated costatone **75** and costatolide **76**. The structures of both costatol **74** and costatone **75** were determined by X-ray analysis. Costatolide **76** was synthesized from costatone **75** by treatment with DBU in ether, a reaction which is analogous to the haloform reaction. Costatone **75** underwent spontaneous decomposition with loss of water to form a 70:30 mixture of *trans* and *cis* trienones **77** and **78** and gave the corresponding ketal **79** on treatment with methanolic hydrogen chloride.



74



75 R = H
79 R = Me



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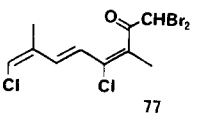

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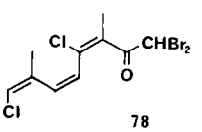
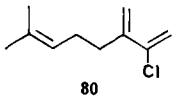


78

Linear halogenated monoterpenes related to myrcene have been isolated from *Chondrococcus hornemanni* by Ichikawa *et al.*[53] (Japan) and by Burreson *et al.*[54] (Hawaii). The major constituent in the Japanese sample and in the Hawaiian sample from Black Point was 2 - chloro - 7 - methyl - 3 - methylene - 1,6 - octadiene **80**, while in the Hawaiian sample from Halona Blowhole the major constituent was *Z* - 3 - bromomethylene - 2 - chloro - 7 - methyl - 1,6 - octadiene **81**. The structural elucidations of the linear monoterpenes depended on detailed interpretation of mass spectra and NMR spectra.



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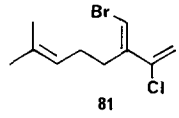
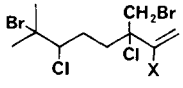
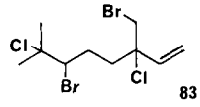


81

In a second communication, Burreson *et al.*[55] have described different halogenated monoterpenes as major constituents from *C. hornemanni* from these same locations. In this case, the major component in the alga from Black Point was 7 - bromo - 3 - bromomethyl - 7 - methyl - 2,3,6 - trichloro - 1 - octene **82**. Comparison of PMR and CMR data of **82** with those of model compounds clearly shows that all data support the "anti-Markovnikoff" location of chlorine at C-6 and bromine at C-7. *C. hornemanni* from Halona Blowhole contained a 3 : 1 mixture of **83** and **84** in which the product of "Markovnikoff" addition of BrCl to the olefinic bond predominated.

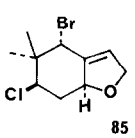


82 X = Cl
84 X = H

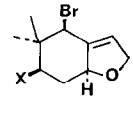


83

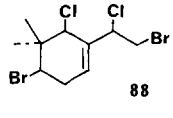
The second collection from Halona Blowhole gave chondrocole A **85** as the major monoterpene constituent. Two closely related bicyclic monoterpenes, chondrocole B **86** and C **87**, have been identified as minor constituents of other collections. Chondrocole A **85** and chondrocole B **86** differ in configuration at the carbon bearing bromine. The PMR spectra have been analyzed in great detail, with particular reference to long-range coupling. The homoallylic coupling constant across the dihydrofuran ring is unexpectedly large (5 Hz) and is, in fact, larger than the vicinal coupling constant (2 Hz). The differences in chemical shifts of like protons in the two compounds are consistent with the expected effects of changing the configuration of the bromine atom from axial to equatorial. Chondrocole C **86** has the same relative stereochemistry as chondrocole B **87** but contains two bromine atoms. A monocyclic monoterpene **88** has been tentatively assigned the structure shown.



85



86 X = Cl
87 X = Br



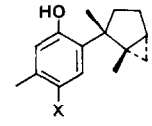
88

It would appear that the observations regarding variation of metabolites in *Plocamium* species may also apply to *Chondrococcus*. I was intrigued to find that *Plocamium* and *Chondrococcus* are so similar in appearance that they are difficult to differentiate in the field. They are, however, classified in different Orders.

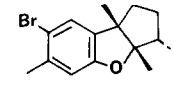
It has been said that if you wish to find new marine natural products you have only to find an uninvestigated species of *Laurencia*. This genus of red algae has yielded such a variety of halogenated sesquiterpenes, diterpenes and acetylenes that this statement, while not always accurate, provides good advice to those wishing to enter this field.

Among the sesquiterpenes from *Laurencia* we now recognize eleven different carbon skeletons, and it is known that more are currently under investigation. Since the halogenated metabolites of *Laurencia* species have recently been reviewed,[189] I will select only a few compounds to illustrate various aspects of the research.

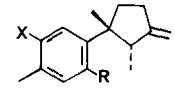
The antibiotic activity of *Laurencia* species is usually due to phenolic sequiterpenes such as laurinterol **89** or debromolaurinterol **90**.[56] Although laurinterol **89** is a very effective antibiotic,[58] the cyclic ether aplysin **91**[57] formed from laurinterol **89** under mild acidic conditions, is inactive.[59] The phenols **92** and **93**, isomers of laurinterol **89** and debromolaurinterol **90**, are also strongly antibiotic and also isomerize into cyclic ethers.[60,61] Since the isomers **89** and **92** have very similar GC retention times and mass spectra, identification of these compounds by PMR spectroscopy is advisable. α-Bromocuparene **94** and α-isobromocuparene **95** have been isolated from *L. glandulifera* and *L. nipponica*, respectively.[62] It has been implied that the bromocuparenes are the biosynthetic precursors of laurene **96** and other aromatic sesquiterpenes from *Laurencia* species.



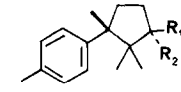
89 X = Br
90 X = H



91



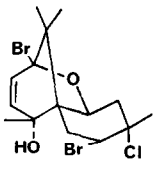
92 R = OH X = Br
93 R = OH X = H
96 R = H X = H



94 R_1 = Br R_2 = H
95 R_1 = H R_2 = Br

In the 5 years since Sims *et al.*[63] reported the presence of pacifenol **97** in *Laurencia pacifica*, the halogenated chamigrene derivatives have become one of the most frequently encountered groups of marine natural products. As fate would have it, the first two halogenated chamigrenes, pacifenol **97** and johnstonol **98**,[64] were probably artifacts of the work-up procedure, resulting from acid-catalyzed rearrangement of prepacifenol **99**[65] and prepacifenol epoxide **100**,[66] respectively, although they can occur as natural products from some specimens of *Laurencia*.

After the key compounds in this series had been identified by X-ray analysis, there were sufficient model compounds to enable others to be identified by comparison of spectral data. The structures derived by X-ray analysis have revealed that the absolute configuration at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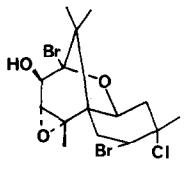
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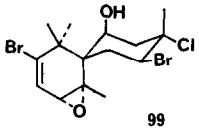
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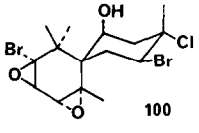
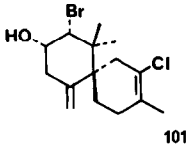

100

the spiro carbon atom is not the same for all chamigrenes, with elatol **101**[67] differing from the remaining compounds. González *et al.*[68] have recently obtained two pairs of chamigrenes from *L. obtusa* which have *trans*-diequatorial 2-bromide and 3-chloride on a (−)β-chamigrene skeleton **102** and *trans*-diaxial 3-bromide and 2-chloride on a (+)β-chamigrene skeleton **103**. Two structures derived by interpretation of spectral data, nidificene **104**[69] and intricatene **105**,[70] have been assigned the same structure but have slightly different PMR spectra. If the two compounds are indeed different but have the same gross structure, then they too must be diastereoisomeric about the spiro carbon atom.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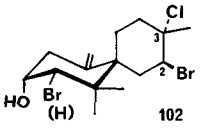
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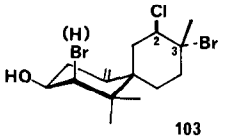
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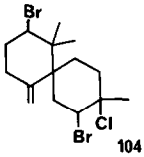
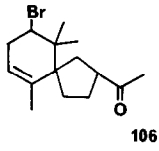

104,105

Spirolaurenone **106**[71] can formally be considered the ring contraction product of the epoxide **107**, with which it co-occurs in *L. glandulifera*.[72]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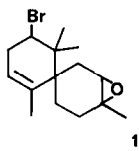
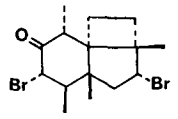

107

A most unusual series of sesquiterpenes has been isolated from *Laurencia perforata*. The structure of perforatone **108** was elucidated by detailed analysis of the coupling constants in a lanthanide-shifted PMR spectrum.[73] Two minor products, **109** and **110**, were assigned solely on the basis of the PMR spectra,[73] but the structure of a fourth product, **111**, was assigned by synthesis of the dehalogenation product.[74] Since these compounds represent a radical departure from familiar *Laurencia* metabolites, the interrelationships between these compounds and their relationship to the chamigrenes, if any, should be established.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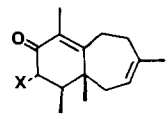
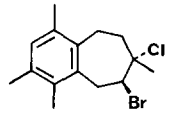
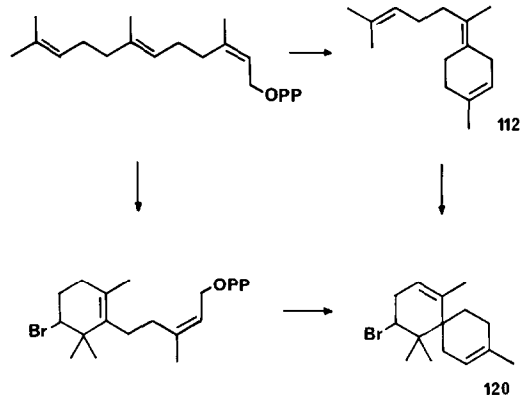

109 X = OH
110 X = Cl


111

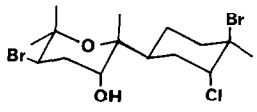
Although it should be recognized that biosynthetic intermediates are often present as minor constituents of an organism, there have been numerous proposals for biosynthetic pathways to the halogenated chamigrenes, based on the major metabolites of a *Laurencia* species. When stripped of embellishments, two basic biosynthetic pathways emerge (Fig. 1). The "bisabolene" route has


112

120

Fig. 1. Two possible biosynthetic routes to 10 - bromo - α - chamigrene **120**.

been proposed for *L. caespitosa* and *L. intricata*, from which bisabolene **112** based metabolites, such as isocaespitol **113**,[75] caespitol **114**,[76] and preintricatol **115**[70] have been isolated.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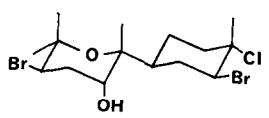
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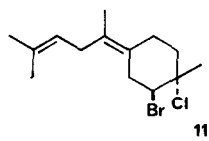
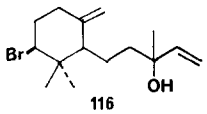

115

The structure of isocaespitol **113**, which was determined by X-ray analysis, has a secondary axial chlorine atom and a tertiary axial bromine atom, unlike caespitol **114** and the majority of chamigrenes, which have a tertiary equatorial chlorine atoms and a secondary equatorial bromine atom. Isocaespitol **113** rearranged to caespitol **114** on melting. Proponents of the "monocyclofarnesol" route point to the isolation of β-snyderol **116**[77] from *L. Snyderae* and α-synderol **117**[77] and 3β-bromo-8-epicaparrapi oxide **118**[78] from different

samples of *L. obtusa*. The "missing" isomer **119** of snyderol has been synthesized and was shown to undergo acid-catalyzed cyclization to give 10-bromo-α-chamigrene **120** as the major product.[79] Subsequent to its synthesis, 10-bromo-α-chamigrene **120** was isolated as a minor metabolite of *L. pacifica*.[80]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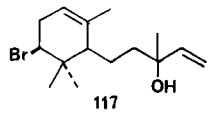
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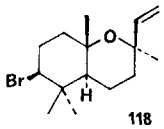
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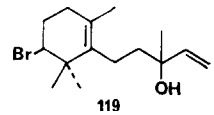
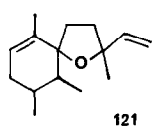
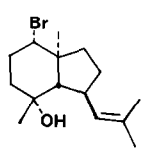

119

Since the halogenated sesquiterpenes were usually the major metabolites of *Laurencia* species and were therefore the simplest compounds to isolate, there has been relatively little research on non-halogenated and minor metabolites. Those who have studied non-halogenated metabolites have often been rewarded by the isolation of compounds with unusual carbon skeletons, such as dactyloxene-B **121**, which can result from rearrangements accompanying the loss of a halogen atom.[81]


121

A good example of the benefits to be derived from more detailed investigations of the metabolites of algae is found in a recent study of *Laurencia subopposita*. We had previously reported the structure of the major metabolite oppositol **122**, which has a novel carbon skeleton.[82] On reexamination, we have found a total of eighteen metabolites: seven acetylenes, three aromatic sesquiterpenes, three derivatives of oppositol, and five sesquiterpene alcohols. The sesquiterpene alcohols include the diol **123**, oplopanone **124**, and three aromadendrene alcohols.[61]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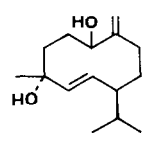
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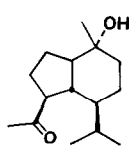
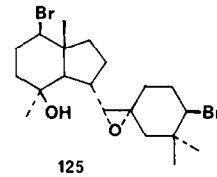
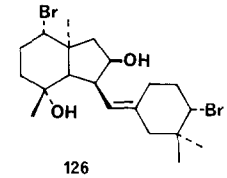
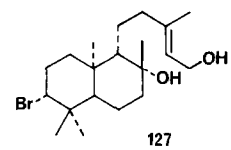

124

There is a striking relationship between oppositol **122** and the diterpenes from an undescribed *Laurencia* species, ireol A **125** and iriediol **126**. Both structures were elucidated by X-ray analysis and were found to have the same ring system but opposite absolute configuration.[83] Although many sesquiterpenes from marine organisms are the optical enantiomers of the corresponding compounds from terrestrial sources, it is most unusual to find molecules of both absolute configurations in the same organism.


125


126

Two brominated diterpenes having the labdane skeleton are known. Although aplysin-20 **127** was isolated from *Aplysia kurodae*,[84] its structural similarity to concinndiol **128**, a metabolite of *Laurencia concinna*,[85] leads to the suggestion that aplysin-20 **127** is also a *Laurencia* metabolite.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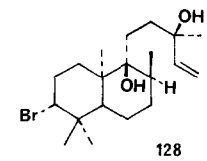
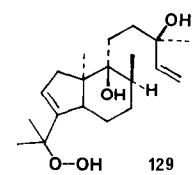
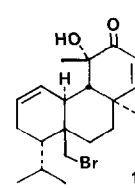

128

The structure determination of concinndiol hydroperoxide **129**, a metabolite of *Laurencia snyderae*,[86] proved to be a difficult X-ray analysis problem.[87] Using an incorrect molecular formula ($C_{20}H_{34}O_3$), the initial results indicated that twenty-three non-hydrogen atoms had been located; four oxygen atoms, eighteen "normal" carbon atoms, and one very large carbon atom. After further chemical studies had indicated that the correct molecular formula contained twenty-four non-hydrogen atoms, with two of the four oxygens present as a hydroperoxide, the structure was shown to be **129**.


129

The only brominated diterpenes which were not *Laurencia* metabolites were obtained from the red alga *Sphaerococcus coronopifolius*. The structure of sphaerococcenol A **130** was obtained by X-ray analysis.[88] The structure of bromosphaerol **131** was determined by X-ray analysis of a suitable degradation product, together with interpretation of the PMR spectra.[89]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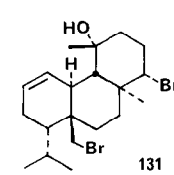
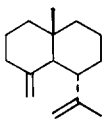
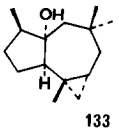

131

Two orders of coelenterates, the gorgonians (Gorgonacea) and the soft corals (Alcyonacea) have been shown to contain both sesquiterpenes and diterpenes. With one exception, β-gorgonene **132** from *Pseudopterogorgia americana*,[90] the sesquiterpenes from gorgonians are remarkable only because they are usually the enantiomers of the same terpenes from terrestrial sources.[1,2]


132

Whereas there have been no recent reports of sesquiterpenes from gorgonians, several interesting sesquiterpenes having unusual carbon skeletons have been reported from the soft corals. Africanol **133**, isolated from *Lemnalia africana*, was shown to be a tricyclic sesquiterpene alcohol by X-ray analysis.[91] The structures of lemnacarnol **134**, from *Lemnalia carnosa*,[92] and $\Delta^{9(12)}$ - capnellene - 3β,8β,10α - triol **135**, from *Capnella imbricata*,[93] were also determined by X-ray analysis. In a subsequent publication, three additional alcohols based on the capnellane skeleton were discussed.[94] All four capnellanes were interrelated through a common degradation product. The capnellane composition of various samples of *C. imbricata* was found to vary with location.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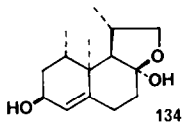
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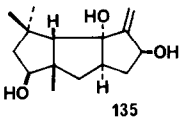
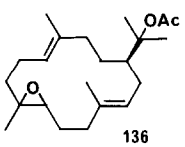

135

Cembranolide diterpenes have been isolated in very high yields (> 1% of dry weight) from both gorgonians and soft corals. Crystals of crassin acetate **144** can be obtained from *Pseudoplexaura crassa* by squeezing the "juice" from the fresh gorgonian.[95] Few chemical studies of marine cembranolides have been reported, since the majority of structures were determined by X-ray analysis. This is quite understandable, since stereochemical assignments in this 14-membered ring system are notoriously difficult. For example, the gross structure of epoxynephthenol acetate **136**, isolated from *Nephthea* sp. (soft coral), was determined by stepwise oxidation to (−) homoterphenyl methyl ketone **138** and the lactone **137**, allowing determination of the position of the epoxide ring and the configuration at the carbon bearing the isopropyl side chain. The assignment of *trans* geometry to the olefinic and epoxide groups was based on negative evidence, the failure to observe nuclear Overhauser effects between the methyl signals and their respective olefinic or α-epoxy proton signals. A survey of X-ray derived structures shows that trisubstituted olefinic bonds in cembranolides normally have the *trans* geometry. In this example, as in many others, the effort required to pursue the stereochemical assignment further is probably greater than the reward.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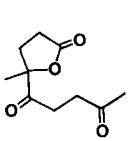
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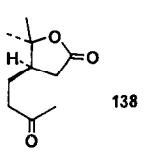
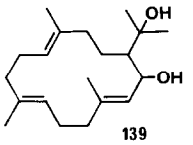
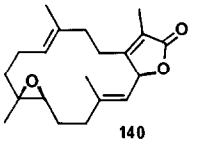

138

The positions of the olefinic bonds in 2-hydroxynephthenol **139**, obtained from *Litophyton vividis*, were determined by analysis of the ozonolysis products. The relationship of the two alcohol functions became apparent when the corresponding 2-ketone underwent a retro-aldol reaction, but the stereochemistry of the molecule was not determined.[97]


139

The structures of sarcophine **140**, from *Sarcophytum glaucum*,[98] lobophytolide **141**, from *Lobophytum cristagalli*,[99] and sinularolide **142**, from *Sinularia flexibilis*,[100] were all determined by X-ray analyses, which did not reveal the absolute configurations. The minor cembranolides of *S. glaucum* have also been reported.[101]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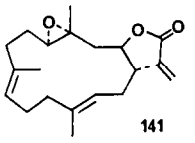
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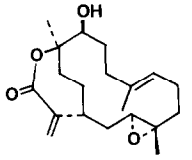
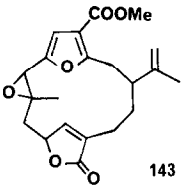
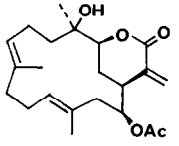

142

In contrast to the abundance (> 1%) of the cembranolides from tropical soft corals, the Hawaiian soft coral *Sinularia abrupta* contains less than 0.05% of a more highly functionalized cembranolide which has been named pukalide **143** (contrary to the useful tradition of naming compounds after the species). The structure of pukalide **143** was determined by detailed analysis of spectral data.[102]


143

Interest in the cembranolides from gorgonians lies less in the novelty of the structures than in their distribution and biosynthetic origin. Crassin acetate **144** is an exceptionally toxic metabolite which has been isolated from several species of *Pseudoplexaura*.[103] In contrast, the major metabolites of *Eunicea mammosa* vary according to the collection site, eunicin **145** from Bimini[104] and jeunicin **146** from Jamaica.[95] Eupalmerin acetate **147** was isolated from *E. palmeri*.[95]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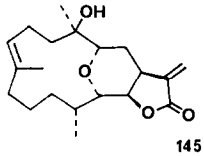
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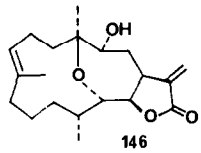
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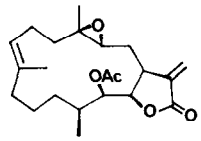
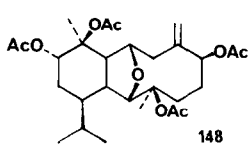

147

Many of the cembranolide lactones have been reported to be toxic in a variety of assays. It is possible that the gorgonians and soft corals may owe their survival to the presence of these toxic compounds which can be synthesized by symbiotic zooxanthellae (unicellular algae).[105] Gorgonians from temperate waters do not have symbiotic zooxanthellae and do not appear to synthesize diterpenes.

Some non-cembranolide diterpenes have also been reported from gorgonians and soft corals. Eunicellin **148**, isolated from the gorgonian *Eunicella stricta*, was shown to be a tricyclic diterpene by X-ray analysis of the dibromide derivative.[106] Although one can easily relate eunicellin **148** to the cembranolides by the introduction of a carbon–carbon bond, xenicin **149**, isolated from *Xenia elongata*,[107] does not resemble any known soft coral metabolite. At a conference in Aberdeen (1975), Weinheimer, speaking on behalf of the Oklahoma group, announced the structure of briarein A **150**, a chlorinated diterpene from *Briareum asbestinum*.[108] Similar compounds have been isolated from sea pens.[109]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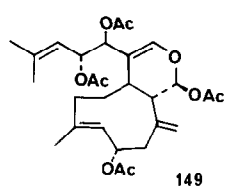
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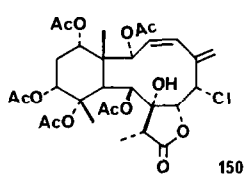
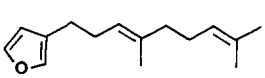

150

The terpenoids isolated from sponges often contain furan groups. The simplest furanosesquiterpene, isolated from *Oligoceras hemorrhages*,[110] was shown to be dendrolasin **151**, a compound previously isolated from an ant, *Dendrolasius fuliginosus*. Dehydrodendrolasin **152** had previously been isolated in high yield (~5% of dry weight) from *Pleraplysilla spinifera*,[111] together with pleraplysillin-1 **153** and pleraplysillin-2 **154**.[112] The structural elucidations of these compounds were particularly dependent on detailed analysis of decoupling in the PMR spectra.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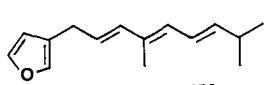
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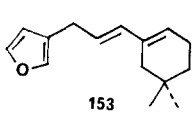
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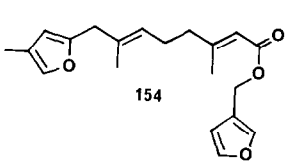
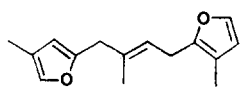

154

A second subspecies of *P. spinifera* which grows on the coelenterate *Paramuricea camaleon* (the two sponges are morphologically different but identical according to spicule analysis), contains longifolin **155** and two novel sesquiterpenes, spiniferin-1 and -2. On the basis of the PMR spectrum, which contained a one-proton signal at δ 0.75, spiniferin-1 was tentatively identified as **156** or **157**.[113] The structure of spiniferin-1 was recently revised after it was shown that the CMR spectrum contained ten sp^2 carbons. The revised structure **158**, which satisfies all the spectral data, is supported by chemical degradation studies.[114] Spiniferin-2 has been tentatively identified as **159** or **160**, but, in view of the revision of the spiniferin-1 structure, these structures should also be viewed as uncertain.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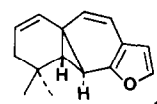
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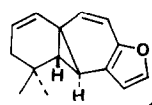
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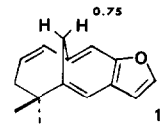
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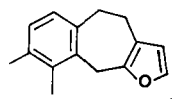
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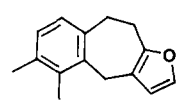
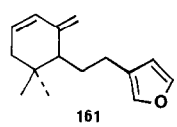

160

Ten furanosesquiterpenes have been isolated from *Disidea pallescens*. The structures of these compounds are based on interpretation of spectral data, coupled with biosynthetic considerations, and again cannot be considered as rigorously established.[115,116] It is argued that the compounds are all based on a monocyclofarnesane ring system (e.g. pallescensin-2 **161** and pallescensin-3 **162**).[115] A further four furanosesquiterpenes **163–166** have been isolated from *Microciona toxystila*.[117] Microcionin-2 **164** can be converted into microcionin-1 **163** by treatment with boron trifluoride etherate.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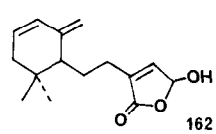
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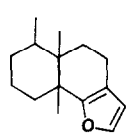
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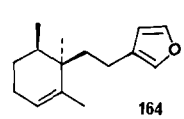
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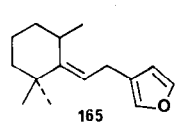
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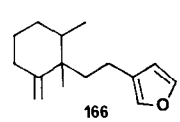
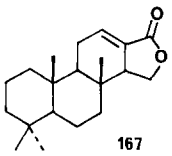

166

Although a group of diterpenes was described at the Aberdeen conference, the literature contains only one example of a diterpene from a sponge. Isoagatholactone **167**, isolated from *Spongia officinalis*, has a carbon skeleton which had not previously been encountered in nature.[118] The structure was assigned on the basis of spectral data and confirmed by chemical correlation with grindelic acid **168**.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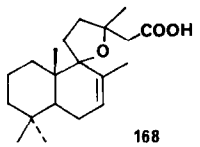
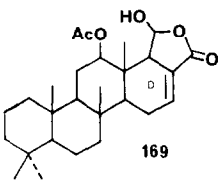

168

Although sesterterpenes are rare in nature, sesterterpenes and related C-21 furanoterpenes are the typical secondary metabolites of sponges of the family Spongidae. The pentacyclic sesterterpenes scalarin **169**,[119] deoxyscalarin **170**,[120] and scalaradial **171**[120] were isolated from *Cacospongia scalaris*, *Spongia officinalis* and *Cacospongia mollior*, respectively. The three compounds have been interrelated by simple chemical manipulations, but the stereochemistry of the three compounds was not determined. The gross structure of scalarin was based on interpretation of spectral data and an interesting chemical degradation.[119]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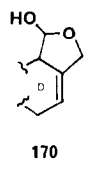
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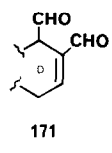
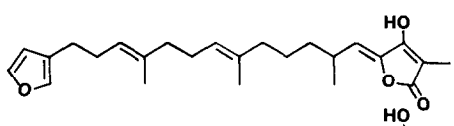

171

Five "linear" sesterterpenes having a tetronic acid functionality have been isolated from sponges of the genus *Ircinia*. Crude extracts of *Ircinia variabilis* showed strong antibiotic activity against *S. aureus*, the activity being due to a tetronic acid, variabilin **172**.[121] The β-substituted furan and tetronic acid functions of variabilin **172** were easily identified from spectral data and define the two "ends" of the molecule. PMR data indicate two trisubstituted olefinic bonds, and their locations were determined by ozonolysis. The stereochemistry of this molecule and of the other tetronic acid sesterterpenes remain undetermined. Strobilin **173**, from *Ircinia strobilina*,[122] and fasciculatin **174**, from *I. fasciculata*,[123] are both double bond isomers of variabilin **172**, while ircinin-1 **175a** and ircinin-2 **175b**, from *I. oros*,[124] both contain a second furan ring.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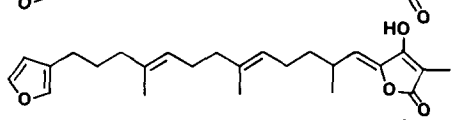
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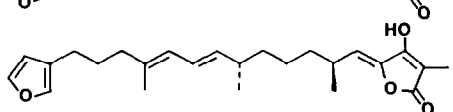
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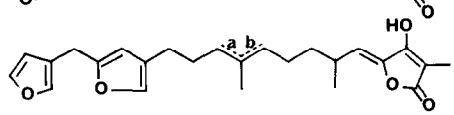
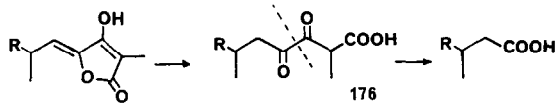

175

It is quite easy to imagine the loss of a four-carbon fragment if one considers mild oxidation of a "hydrolyzed" tetronic acid **176**. Thus one may propose the formation of ircinin-3 **177a** and ircinin-4 **177b** from ircinin-1 and ircinin-2, respectively. The stereochemistry of the trisubstituted olefinic bonds in ircinin-3 (*E*) and -4 (*Z*) were assigned on the basis of the chemical shift of the methyl signal,[125] but the validity of assigning the stereochemistry of *regioisomeric* trisubstituted olefinic bonds on this basis is doubtful.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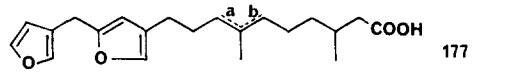
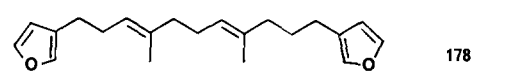

177

The largest group of furanoterpenes are eleven C-21 difurans having a furan group at each end.[126-129] The compounds vary according to the oxygenation pattern in the center of the prenyl chain and may be considered to be based on anhydrofurospongin-1 **178**.[126] Many of the subsequent structures were related to furospongin-1 **179**, one of the few compounds in this series for which the absolute configuration is known.[127] The two β-substituted furans, identified by PMR signals, must form the two ends of the molecule. The position of the trisubstituted olefin was determined by analysis of ozonolysis products. The position of the alcohol function was determined by decoupling, while the absolute configuration at the carbon bearing oxygen was determined by the Horeau method. Finally, dehydration of the alcohol to two dienes, followed by ozonolysis of the non-conjugated diene, gave (*R*)-2-methyladipic acid to establish the absolute configuration at the carbon bearing methyl. Again, the stereochemistry of the trisubstituted olefin was assigned *trans* on the basis of the chemical shift of the methyl signal in the PMR spectrum.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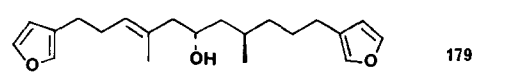
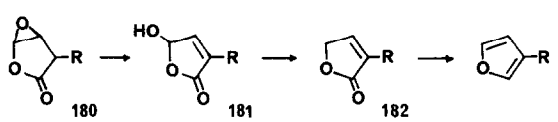
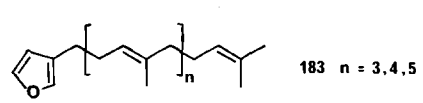
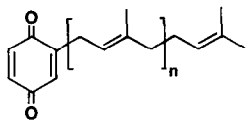

179

A number of minor constituents of *Spongia officinalis* closely related to furospongin-1 but having oxidized furan rings have been described.[130] None of the compounds was obtained pure, but evidence is advanced for the presence of β,γ-epoxy-γ-lactones **180** and γ-hydroxy-α,β-butenolides **181**. The epoxides rearrange to γ - hydroxy - α,β - butenolides, which were reduced with sodium borohydride to α,β - unsaturated - γ - lactones **182**, which were, in turn, reduced to furospongin-1 **175** with di-isobutyl aluminum hydride in tetrahydrofuran.

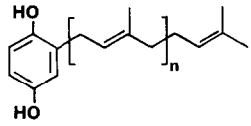

180 181 182

The polyprenyl derivateves from sponges of the genus *Ircinia* consist of a series of polyprenylated furans **183** from *I. spinulosa*[131] and polyprenylated quinones **184** and hydroquinones **185** from *I. spinulosa* and *I. muscarum*.[132]


183 n = 3,4,5

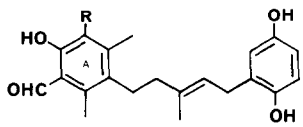


184 n = 3,5,6,7

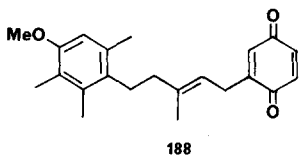


185 n = 3,5,6,7

The sesquiterpenoid hydroquinones from *Halichondria panicea* are among the more interesting sponge metabolites.[133] The major isomers, panicein-B_3 **186** and panicein-C **187**, were shown to have two aromatic rings with an aromatic aldehyde and three and four phenolic groups, respectively. The structural elucidations are based on detailed analysis of spectral data. The isolation of panicein-A **188** indicates that the aldehyde group might be derived biosynthetically from a methyl group, while the discovery of monocyclofarnesol **189** in the same sponge[134] suggests that the A-ring has a sesquiterpenoid origin.



186 R = H
187 R = OH



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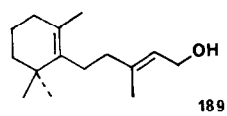
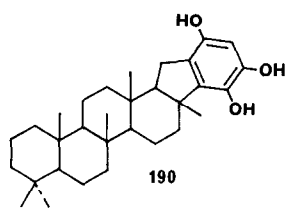


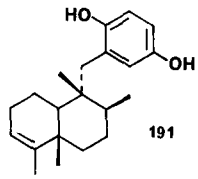
189

The structure of disidein **190**, from *Disidea pallescens*, was suggested as the "most likely" structure for the compound, based on analysis of spectral data and limited degradation.[135]



190

Sesquiterpenoid hydroquinones and quinones have been isolated from both sponges and brown algae. The gross structure of avarol **191**, from the sponge *Disidea avara*, was established by chemical degradation of ring A and by acid-catalyzed rearrangement of the corresponding dimethyl ether to a tetrasubstituted olefin **192**.[136] The relative stereochemistry of avarol **191** was determined by detailed analysis of the PMR and CMR of avarol and its derivatives. The absolute configuration of avarol was determined by applying the method of Nakanishi and Dillon to the diol **193**.[137] Two isomers of avarol **191** have been isolated from the brown alga *Dictyopteris undulata* (formerly *D. zonaroides*). Each of the two double-bond isomers, zonarol **194** and isozonarol **195**, was reduced to a saturated hydroquinone mixture which was oxidized to a dihydrotauric acid mixture.[138]



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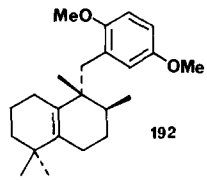

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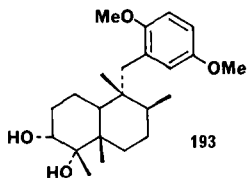

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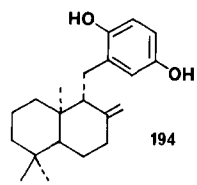

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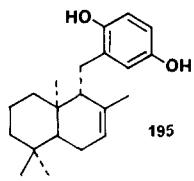
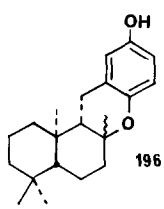


195

Acid catalyzed isomerization of zonarol **194** gave chromazonarol **196**, which was shown to be a natural product of *D. undulata*.[139] The sponge *Disidea pallescens* contained the enantiomer *ent*-chromazonarol **197**.[140] Catalytic hydrogenation of the methyl ester of zonaroic acid **198**, a minor constituent of *D. undulata*, gave a single saturated phenol, which was oxidized to a single dihydrotauranic acid, the enantiomer of that isolated from ambrein and manool. Thus the absolute configurations of all compounds in this series were established.[141]



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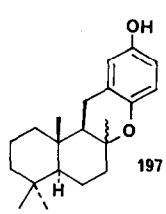

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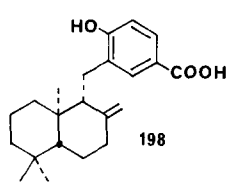
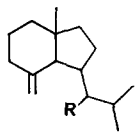


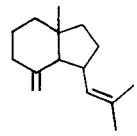
198

Although the isonitriles have traditionally been described as having the odor of "rotting fish", naturally-occurring isonitriles are now firmly established as metabolites of sponges, mainly of the Order Halichondrida. Axisonitrile-1 **199**, isolated together with the corresponding isothiocyanate **200** from *Axinella cannabina*,[142] was shown to possess the same carbon skeleton as oppositol **122**, a skeleton which has not been encountered among terrestrial natural products. The isonitrile functionality (IR 2130 cm^{-1}) could be removed by reduction with sodium in liquid ammonia to obtain the parent hydrocarbon **201** or by lithium aluminum hydride reduction to the methylamine, followed by Hofmann degradation to form the diene **203**. The structure of the hydrocarbon skeleton was established by a classical degradation procedure which did not reveal stereoche-

mical details. Axisonitrile-2 **204** was shown to be an isonitrile having the aromadendrane skeleton.[143] An interesting feature of the NMR spectrum is the appearance of the methyl group (*) signal as a 1:1:1 triplet (J = 2 Hz) due to long-range ^{14}N–^{1}H coupling. In a later paper, axisothiocyanate-2 **205** and two formamides **202** and **206** were described.[144] A third isonitrile-isothiocyanate-amide trio has recently been isolated from *Axinella cannabina*. The structure of axisonitrile-3 **207**, determined by X-ray analysis, is based on a new sesquiterpene skeleton containing a spiro[4, 5] decane ring system.[145]



199 R = NC
200 R = NCS
201 R = H
202 R = NHCHO



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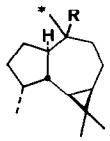
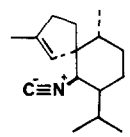
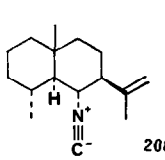


204 R = NC
205 R = NCS
206 R = NHCHO



207

Minale *et al.* have isolated a sesquiterpene isonitrile from *Acanthella acuta*.[146] Acanthellin-1 **208** was reduced to a hydrocarbon which was shown to be 4-*epi*-eudesmane. Analysis of the PMR spectrum revealed that the isonitrile function was located at C-6 and that both the isonitrile and isopropylidene groups were equatorial. Scheuer *et al.* have isolated two isonitriles, together with the corresponding isothiocyanates and formamides, from a marine sponge, *Halichondria* sp. The structure of the sesquiterpene isonitrile **209** was established by its conversion to zizanene.[147] Formation of Δ^1 and Δ^9 olefins by Hofmann degradation of the methylamine resulting from lithium aluminum hydride reduction of the isonitrile **209** indicated that the isonitrile group was axial (*trans*-diaxial elimination). The diterpene isonitrile **210** was shown to be the isonitrile analogue of geranyllinalool.[147] Although it is theoretically possible, the allylic isonitrile **210** was not reported to undergo a [3,2]-sigmatropic rearrangement to a nitrile.



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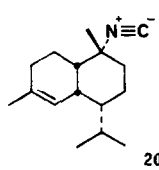

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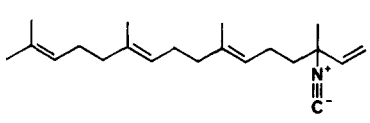
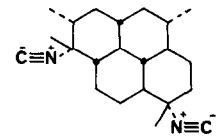


210

The most unusual compound in this series is a deterpene diisocyanide, diisocyanoadociane **211**, isolated from a sponge of the genus *Adocia*.[148] This structure, which

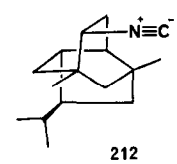


211

was the result of X-ray analysis, is one of the few diterpenes which does not contain any angular methyl groups.

Among the most important marine natural products research is that which explains biological phenomena. It had been known for a decade that the nudibranch *Phyllidia varicosa* secretes a toxic mucus containing a volatile active component. Isolation of the active component went very slowly until *Phyllidia* was observed to feed on a sponge, *Hymeniacidon* sp., which contained the same toxin in greater quantities. The nudibranch is thought to be protected from potential predators by a compound obtained from a specific food source, a phenomenon which is fairly frequently encountered among opisthobranchs. Other isonitriles have been reported to show antibiotic activity, often an indication of wider biological activity.

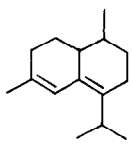
The active component was shown to be a sesquiterpene isonitrile called 9-isocyanopupukeanane **212**, which has a novel carbon skeleton elucidated by an X-ray crystallographic study of the corresponding phenylthiourea.[149]



212

There have been refreshingly few speculations on the biosyntheses of the isonitrile - isothiocyanate - amine - formamide families. It is assumed that there must be interconversion between the four derivatives, but the biosynthetic sequence must be determined experimentally. It has been suggested that the nitrogen-containing derivatives are derived from the corresponding carbonium ions, but the nature of the nitrogen source is unknown. Several of the terpenoid skeletons were previously unknown, and the biosynthesis of the carbon skeletons require unusual rearrangements of presumed isoprenoid intermediates. Most investigators have recorded the presence of a terpenoid hydrocarbon fraction from isonitrile-containing sponges, but the hydrocarons, which could hold clues to biosynthetic schemes, have not been identified. Above all, it should be remembered that sponges are invertebrates and therefore may lack the ability to perform *de novo* isoprenoid biosynthesis. I can see no more interesting biosynthetic study among the marine natural products.

Among the brown algae, members of the family Dictyotaceae have provided the majority of the interesting secondary metabolites described to date. In addition to zonarol **194** and isozonarol **195**, *Dictyopteris undulata* also contains a sesquiterpene hydrocarbon, zonarene **213**.[150] Sesquiterpenes had previously been reported from *Dictyopteris divaricata*, which contains dicytopterol **214** as an inseparable mixture of double-bond isomers, and dictyopterone **215**.[151]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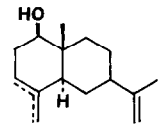
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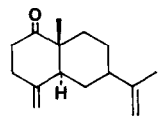
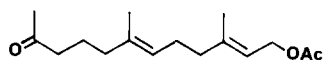

215

Recent research has indicated that diterpenes will figure more frequently as metabolites of brown algae. A truncated terpene, oxycrinol acetate **216**, and the linear diterpene crinitol **217** have been isolated from *Cystoseira crinita*.[152] *Trans*-phytol is often found as an algal metabolite, but it is normally regarded as a primary metabolite arising from the degradation of chlorophyll and is seldom reported. *Cis*-phytol **218**, a minor metabolite of *Gracilaria andersoniana*, should, in all probability, be considered a secondary metabolite.[153] A monocyclic diterpene **219** having the same skeleton as retinol was isolated from *Caulerpa brownii*.[154]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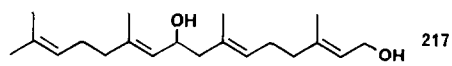
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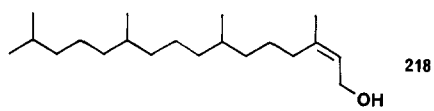
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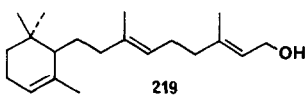
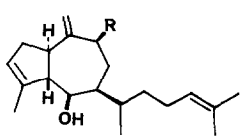
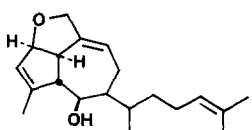

219

A number of diterpenes have been isolated from the Dictyotaceae and from sea hares which feed upon them. Pachydictyol A **220**, first isolated from *Pachydictyon coriaceum*,[155] has also been found in *Aplysia vaccaria*.[156] Two similar compounds, dictyol A **221** and dictyol B **222**, have been isolated from both *Dictyota dichotoma*[157] and *Aplysia depilans*.[158] The structure of pachydictyol A **220** was determined by X-ray methods, and the structures of **221** and **222** were deduced from analysis of spectral data and conversion to pachydictyol A. Three additional compounds, all related to pachydictyol A, have been isolated from Mediterranean *D. dichotoma*,[159] while two other related compounds have been obtained from Bristol Channel *D. dichotoma*.[160] An epoxide **223** of pachydictyol A has been isolated from *D. flabellata* and its structure determined by chemical degradation.[161]


220 R = H
222 R = OH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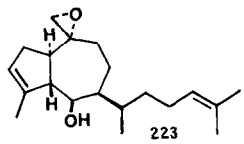
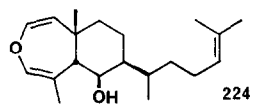

223

Recently, some related compounds having different carbon skeletons have been isolated from *D. acutiloba*. The structure of dictyoxepin **224** was determined by X-ray analysis, while the structure of dictyolene **225** was deduced from chemical and spectral data.[162] The structure of dilophol **226**, a monocyclic compound from *Dilophus ligulatus*, was assigned on the basis of chemical and spectral information.[159]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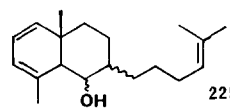
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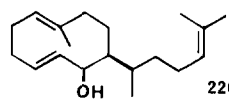
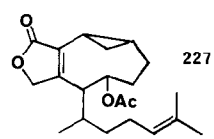
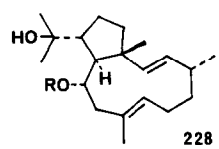
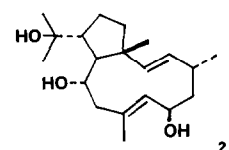

226

Acetoxycrenulatin **227**, isolated from *D. crenulata*, has a carbon skeleton which is quite different from other *Dictyota* diterpenes.[161] The gross structure was deduced from its chemical reactions and spectral data, but the stereochemical details have not yet been elucidated.


227

Sea hares of the genus *Dolabella* are nocturnal, and their feeding habits are generally unknown. However, the diterpenes that have been found in two species of *Dolabella* are probably from an algal source and can be reviewed most conveniently with the diterpenes from brown algae. We have found a series of fourteen diterpenes from two collections of *Dolabella californica*.[163] The structure of **228** was determined by X-ray analysis,[164] and the structures of the remaining compounds have been established by chemical interconversions. The compounds all contain different patterns of acetylation but are based on the diol **229** and the triols **230** and **231**.


228 R = Ac
229 R = H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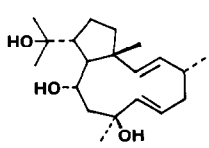
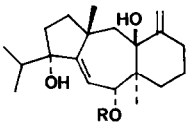

231

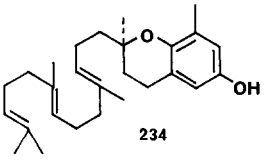
The active constituents of *Dolabella auricularia* in the P-388 assay (lymphocytic leukemia) were shown to be

dolatriol **232** and a related acetate **233**. The structure of dolatriol 6-acetate **233** was established by X-ray analysis.[165] There is a striking similarity between the carbon skeletons of **229** and **232**, both of which were previously unknown, with **232** containing an extra ring.

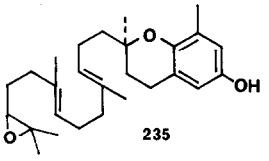


232 R = H
233 R = Ac

Conjue uchidai is a hydroid which is epiphytic on *Sargassum tortile*, a brown alga. The "juice" of *S. tortile* was shown to cause settling of *C. uchidai*.[166] Structures of molecules which will induce settling have been determined and the compounds synthesized, but the testing of the synthetic materials was not quantitative. The active fraction of *S. tortile* contains δ-tocotrienol **234** and the corresponding 2,3-epoxide **235**, together with four unidentified compounds. The epoxide **235** appeared to be more effective than δ-tocotrienol **234** in inducing settling.[167]

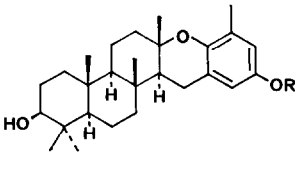


234

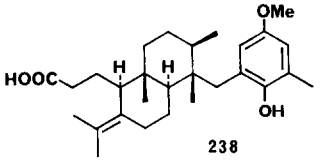


235

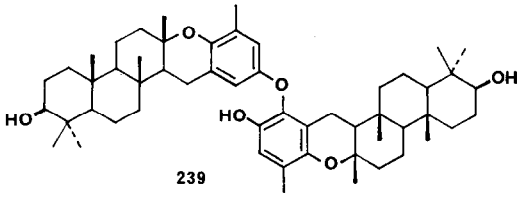
Taondiol **236**, isolated from *Taonia atomaria*, is a pentacyclic isomer of δ-tocotrienol epoxide **235**. The structure was determined by analysis of spectral data and confirmed by X-ray analysis[168] and the synthesis of 11'-desoxytaondiol methyl ether and taondiol methyl ether **237**.[169] A second collection of *T. atomaria* contained only atomaric acid **238**, which may be regarded as an oxidation product of taondiol methyl ether in which a series of concerted 1,2 shifts have occurred along the backbone of the molecule.[170] The structure and stereochemistry shown for atomaric acid were consistent with the spectral data but were heavily dependent on the biosynthetic assumptions. A dimer **239**, formed by phenol oxidation of taondiol **236**, has also been isolated from *T. atomaria*.[171]



236 R = H
237 R = Me

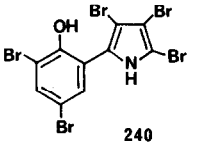


238



239

Many marine bacteria produce compounds which inhibit the growth of marine and terrestrial bacteria. In some cases, these antibacterial compounds may be toxic to the organism which produces them. The first antibiotic isolated from a marine bacterium, designated *Pseudomonas bromoutilis*, was the pentabromophenol **240**.[170] This same antibiotic has been found in *Chromobacter* sp., which also contained tetrabromopyrrole, hexabromo-2,2' - bipyrrole, and *p*-hydroxybenzaldehyde, all of which showed some antibacterial activity.[173] A marine pseudomonad has been shown to contain the antibiotics 2 - *n* - pentyl - 4 - quinolinol **241** and 2 - n - heptyl - 4 - quinolinol **242**, together with *p*-hydroxybenzaldehyde, indole - 3 - carboxaldehyde, and 6 - bromoindole - 3 - carboxaldehyde.[174] Although it is reasonable to suppose that some of these compounds, particularly the brominated metabolites, may be produced in the marine environment, it is probable that *p*-hydroxybenzaldehyde and indole - 3 - carboxaldehyde result from partial degradation of tyrosine and tryptophan, which are constituents of the enriched agar medium. Each of these compounds has been identified by analysis of spectral data and confirmed by synthesis.[173-5]



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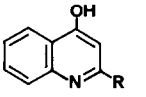
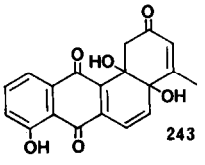


241 R = C_5H_{11}
242 R = C_7H_{15}

Marine fungi are rarely studied, but a recent investigation resulted in the isolation of the antibiotic SS-228Y **243** from *Chainia* sp.[176] The antibiotic was shown to be unstable to heat and light, being converted into a naphthacenequinone **244**.



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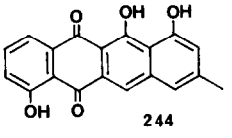
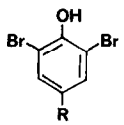
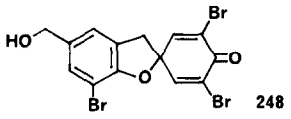


244

Marine worms have been shown to contain halogenated aromatic and heteroaromatic compounds. Some acorn worms (Hemichordata) have been described as having an iodoform-like odor, although no iodoform-like compounds have even been isolated from them. The odor of *Balanoglossus biminiensis* was attributed to the presence of 2,6-dibromophenol **245**.[177] Two brominated phenols **245** and **246** have been isolated from the tubeworm *Phoronopsis viridis*.[178] The annelid worm *Thelepus setosus* contained five brominated phenols; the major metabolites were 3,5 - dibromo - 4 - hydroxybenzyl alcohol **247** and thelepin **248**, an antifungal compound which resembles griseofulvin in both structure and activity.[179] Reduction of thelepin with sodium borohydride gave a mixture of the corresponding dienol and thelephenol **249**, a minor natural product. The other minor products were 3,5 - dibromo - 4 - hydroxybenzaldehyde **250** and *bis* - (3,5 - dibromo - 4 - hydroxyphenyl) methane **251**. Although thelepin **248** was probably formed by oxidation of thelephenol **249**, the reaction could not be performed *in vitro*.



245 R = H
246 R = Br
247 R = CH_2OH
250 R = CHO



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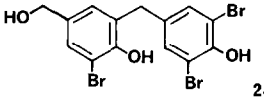

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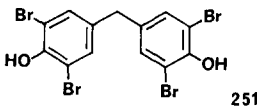
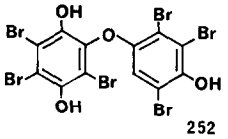
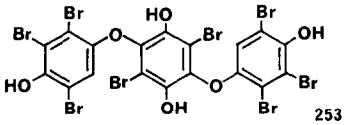


251

The acorn worm *Ptychodera flava laysanica* also contains many halogenated phenols, the simplest of which was 2,4,6 - tribromophenol **246**.[180] The major phenolic constituents were tetrabromohydroquinone or tribromohydroquinone, depending on the extraction solvent used. Smaller quantities of dimeric phenolic ethers, such as **252**, or a trimeric phenol ether **253**, were also isolated.



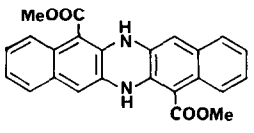
252



253

The iodoform-like odour of *P. flava* was attributed to the presence of 3-chloroindole **254**.[181] Three other halogenated indoles, 3-bromoindole **255**, 6 - bromo - 3 - chloroindole **256** and 5,7 - dibromo - 6 - methoxyindole **257** have been isolated from various samples of the worms. Perhaps the most interesting discovery was that one population of *P. flava* which was coloured green rather than yellow contained the known purple dye **258** and two new congeners **259** and **260**. The Tyrian purple dye **258**, obtained from various *Murex* species (molluscs), was one of the first marine natural products to find commercial use. Its history and chemistry have been reviewed by Baker.[182]

A review of pigments from marine organisms is beyond the scope of this paper, but the structure of one pigment, caulerpin, from green algae of the genus *Caulerpa*, is of particular interest. On the basis of spectral properties, caulerpin was assigned the structure **261**.[183] However, the biosynthesis of this structure could not be rationalized. The alternative structure **262**, formally derived from two units of tryptophan, has recently been shown to be the correct structure.[184]



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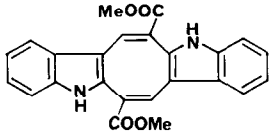
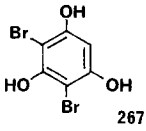


262

A number of brominated phenols have been isolated from red algae, especially from members of the Rhodomelaceae.[185] The brominated phenols generally show antibiotic activity.[186] Lanosol **263** is the most abundant and widely distributed of the brominated phenols, being found in more than twelve species of marine algae.[185] Lanosol was first isolated as the dipotassium salt of a disulphate which was originally[187] assigned structure **264** but later reassigned[188] structure **265**. Other brominated phenols from red algae have been reviewed in detail elsewhere.[189] Recently, many algae have been screened for the presence of brominated phenols using GC–MS analysis of the per-trimethylsilyl derivatives.[186] Some brominated phenols were found in non-rhodomelaceous algae, albeit in very low concentrations, and both lanosol **263** and its ethyl ether **266** have been detected in seawater.[185] *Rytiphlea tinctoria*,[190] obtained from the Mediterranean Sea, contained lanosol **263** and its ethyl ether **266**. When collected along the Atlantic coast of France, the same alga contained dibromophloroglucinol **267** (or perhaps a corresponding methyl ether) and the tetrabromo compound **268**, which

263 R_1 = R_2 = R_3 = H
264 R_1 = H R_2 = R_3 = SO_3K
265 R_2 = H R_1 = R_3 = SO_3K
266 R_1 = Et R_2 = R_3 = H



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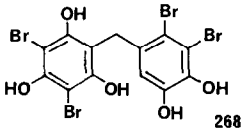
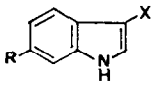
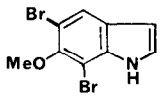


268

appears to be a condensation product of **263** and **267**. Two brominated antimicrobial compounds, 1 - (2',4' - dibromophenoxy) - 2 - hydroxy - 4,5,6 - tribromobenzene **269** and 1 - (4' - dibromophenoxy) - 2 - hydroxy - 5 - bromobenzene **270**, were isolated from *Dysidea herbacea*, a sponge from the western Caroline Islands.[191]



254 R = H X = Cl
255 R = H X = Br
256 R = Br X = Cl



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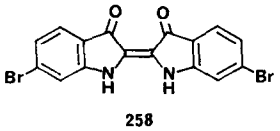

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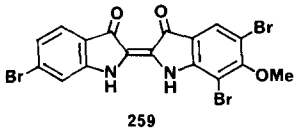

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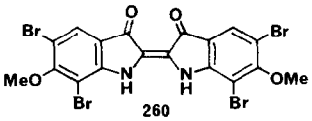

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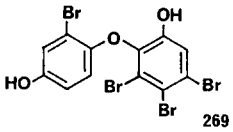
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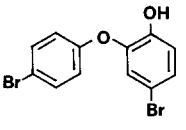
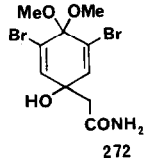

270

The brominated metabolites from sponges of the genus *Verongia* and other related sponges pose an interesting but unsolved problem; many of the metabolites which have been isolated are obviously the products of reaction of an unknown metabolite with nucleophilic reagents or solvents. In the course of his research on antibiotics from marine organisms, Burkholder showed that both *Verongia fistularis* and *V. cauliformis* contained potent antibiotics.[192] The antibiotic dienone **271** and the inactive dimethoxy ketal **272** were isolated from both sources, and it was at first assumed that the ketal came from addition of the solvent methanol to the dienone.[193] By extracting an undescribed *Verongia* species from the Gulf of California with ethanol, we obtained a 1:1 mixture of two diastereoisomeric mixed ketals **273**.[194] By extracting the same sponge with acetone containing sodium azide or propyl mercaptan, we obtained a mixture of azides **274** or a dithioketal **275**, respectively.[195] Although we have proposed that the highly reactive metabolite might be the arene oxide **276**, we have no direct proof of its existence and acknowledge that there are other possible precursors for this array of extraction products.


271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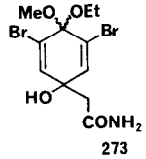
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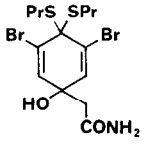
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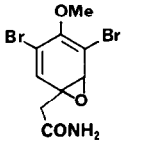
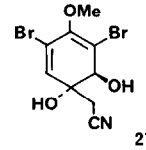

276

Several other related compounds have been isolated from sponges. The nitrile, aeroplysinin-I **277**[196] and the lactone, aeroplysinin-II **278**[197] have both been isolated from *Verongia* and *Ianthella* species, surprisingly as both racemates and optical enantiomers. Three aromatic compounds, the hydroquinone **279**,[198] which could be the NIH shift product from **276**, the isoxizolidone **280**,[199] and the phenol **281**,[200] which could well be an artifact, have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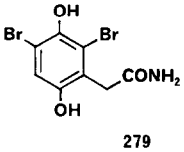
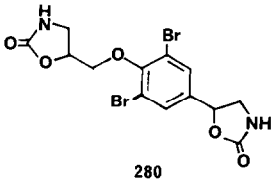
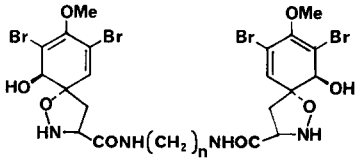

279

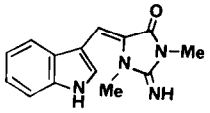

280


281

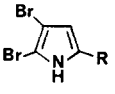
all been isolated from various *Verongia* species. *Verongia thiona* is a rich source of two "dimeric" metabolites, aerothionin **282** and homoaerothionin **283**.[201] A major feature of all these sponges is the pronounced antibiotic activity associated with fresh tissue sections. In at least two *Verongia* species, the antibiotic activity of the fresh tissue appears to exceed that of the pure compounds isolated from the sponges and could indicate the presence of a very active but unstable antibiotic.

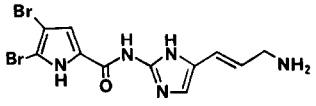

282 n = 4 283 n = 5

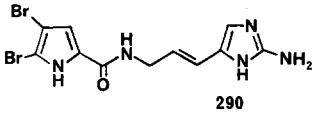
An unusual characteristic of *Verongia* species is that the yellow-coloured tissues rapidly turn black on removal from water and exposure to air. A yellow pigment **284** has recently been isolated from *Verongia spengelii*, but this pigment is not involved in the colour change.[202]

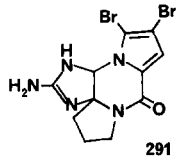

284

A number of brominated pyrroles (cf. bacterial metabolites) have been isolated from sponges. *Agelas oroides* contained the 2-carboxylic acid **285**, amide **286** and nitrile **287** of 4,5-dibromopyrrole,[203] while an unidentified species of *Agelas* yielded the corresponding guanimide **288**.[204] The structure of oroidin, from *Agelas oroides*, was once a controversial matter. The original structure **289** was proposed on the basis of spectral data and chemical degradation.[203] However, the structure of the isomeric dibromophakellin **291**, a metabolite of *Phakellia flabellata* whose structure was established by X-ray analysis,[205] suggested that oroidin might have an alternative structure **290**. Further support for the revised structure came from the synthesis of the dihydro derivative of structure **290**.[206]


285 R = COOH
286 R = $CONH_2$
287 R = CN
288 R = CONHC(NH)NH_2

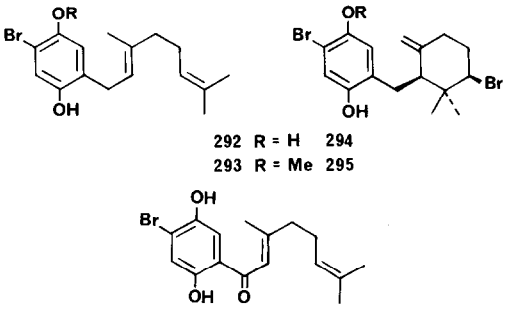

289


290


291

An unusual group of aromatic compounds have been isolated from the calcareous green alga *Cymopolia barbata*.[207] The simplest compounds, cymopol **292** and its monomethyl ether **293**, are prenylated hydroquinones in which the aromatic ring has been brominated. Cyclocymopol **294** and its monomethyl ether **295** may be presumed to result from bromonium ion initiated cycliza-

tion of the prenyl chain. The structure and absolute stereochemistry of cyclocymopol monomethyl ether acetate were established by X-ray crystallography. A ketone, cymopolone **296** was also obtained.



292 R = H 294
293 R = Me 295

296

The discovery of metabolites such as cyclocymopol **294**, the snyderols **116** and **117**, 3β - bromo - 8 - epicaparrapi oxide **118**, aplysin-20 **127**, oppositol **122**, 10 - bromo - α - chamigrene **120**, and related compounds has led to investigation of the efficacy of a bromonium ion initiated cyclization reaction as a synthetic tool. Although the yields are not high (20% yield is the best achievement to date) due to competing reactions, the reaction sequence in Fig. 2 can be accomplished.[208-211] α-Snyderol **117**[209] and 10 - bromo - α - chamigrene **120**[208] have been synthesized by routes incorporating this reaction sequence.

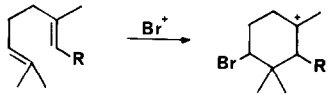
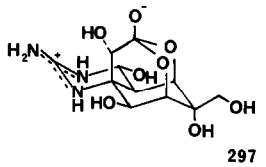


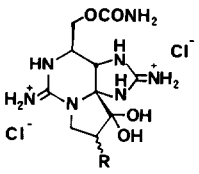
Fig. 2. Cyclization of a 1,5 diene initiated by a "bromonium" ion.

No review of marine natural products would be complete without a discussion of marine toxins. Many marine organisms have been labelled toxic, but relatively few chemical structures have been reported. Yet the toxins are among the most interesting marine natural products and remain the most potentially useful compounds. Nereistoxin **7** has been adopted from use as an insecticide, while tetrodotoxin **297** is used as a research tool in neurophysiology. The isolation, structural elucidation, and synthesis of tetrodotoxin **297** have been reviewed elsewhere.[212]

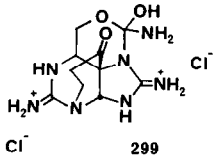


297

The toxins associated with "red tides" continue to attract considerable attention. Paralytic shellfish poisoning can occur when toxin-producing dinoflagellates (or other microorganisms) undergo a spectacular and rapid growth to form "blooms". The filter-feeding organisms, particularly edible clams and mussels, concentrate the toxins unchanged and are rendered unfit for consumption. The structure of saxitoxin **298**, the toxin of the dinoflagellate *Gonyaulax catanella*, was determined by single crystal X-ray analyses of suitable derivatives.[213,214] Prior to that time, many of the structural features had been determined by chemical degradation, but an incorrect structure **299** had been deduced.[215] The structure **299** was not challenged until shown to be incompatible with the ^{13}C NMR spectrum. In the past year, the toxin of *Gonyaulax tamarensis* has been shown to contain a 3:1 mixture of two hydroxylated derivatives **300** and **301** of saxitoxin.[216]

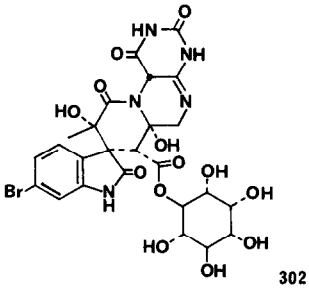


298 R = H
300 R = α-OH
301 R = β-OH



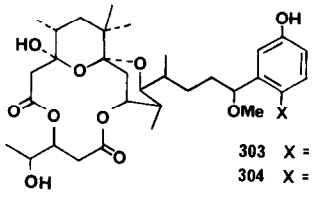
299

When shellfish suddenly become toxic, there is always good reason to suspect that the toxin from a microorganism has become concentrated by passage through the marine food chain. When the gastropod *Babylonia japonica* was collected from a small area of Suruga Bay, Japan, it contained a powerful toxin in the midgut gland.[217] The structure of surugatoxin **302** was determined by X-ray analysis.[218] Recent research suggests that the toxin was produced by a marine bacterium which proliferated in water polluted by pulp-mill wastes.[219] We should be warned by this event!



302

Many sea hares have been reported to be toxic. The toxin in the Hawaiian sea hare *Stylocheilus longicauda* was shown to be an inseparable mixture of aplysiatoxin **303** and debromoaplysiatoxin **304**. The structures of these compounds were determined by a series of chemical degradations, but some stereochemical features remain unknown.[220] Recently, debromoaplysiatoxin has been detected in several blue-green algae and isolated from *Lyngbya gracilis*.[221] Although debromoaplysiatoxin was obtained as a crystalline compound, the X-ray analysis may prove impossible, since there are two molecules per unit cell.



303 X = Br
304 X = H

There are many other compounds which may be classed as marine toxins, ranging from simple amines to

complex peptides. I have selected those toxins which provide the most challenging target molecules for the synthetic organic chemist.

The many new and complex marine natural products are an obvious challenge to synthetic chemists. They should not, however, neglect the highly halogenated small molecules, which provide excellent tests for the regioselectivity and stereoselectivity of halogenation reactions. There are also many examples where biomimetic syntheses can be attempted.

I feel that there has been an overabundance of biosynthetic speculation concerning marine natural products. Since many of the key organisms, such as macro-algae, are difficult (perhaps even impossible) to maintain in culture, there is a danger that these speculations might be considered truths through default. Until such time as one can successfully carry out true biosynthetic studies involving the use of isotopically-labelled compounds, the biomimetic syntheses must be regarded as the best method of gaining insight into biosynthetic routes, although the limitations of this research must be recognized.

Throughout this report I have mentioned the source organism for each compound, for it is clear that there are chemotaxonomic relationships at the Genus level. From my own experience with *Plocamium* species, I doubt that secondary metabolites can be used as taxonomic features at the species level, for there are too many other environmental factors which may affect the production of secondary metabolites.

There is some evidence that marine organisms may contain a relatively large number of biologically active compounds, when compared with terrestrial organisms. However, with the exception of the "in-house" research of RRIMP in Australia, few marine natural products have received adequate pharmaceutical or agricultural screening.

There seems to be considerable interest in chemical communication between marine organisms. Ironically, although both marine biologists and organic chemists share this interest, there is a lack of communication between them and very little of the interdisciplinary research which is needed to solve these problems.

I have reported on the marine natural products literature as of November 1976. The literature coverage is not complete and represents a personal selection. I know that there are many more interesting compounds under investigation. For the next few years, at least, marine natural products chemistry will continue to expand and will be an area of research worthy of the organic chemist's attention.

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