

## NEW METABOLITES FROM AUSTRALIAN MARINE SPECIES

Robert J. Wells

Roche Research Institute of Marine Pharmacology,  
P.O. Box 255, Dee Why, N.S.W., 2099, Australia.

**Abstract** - New metabolites isolated from marine species collected in Australia since 1975 are discussed. Emphasis is placed on work performed by Australian research groups but contributions from other workers on marine species collected from Australia are reviewed briefly.

### INTRODUCTION

During the 1st IUPAC Symposium on Marine Natural Products at Aberdeen in 1975, J.T. Baker presented a plenary lecture entitled "Some Metabolites from Australian Marine Organisms" (Ref. 1). This was a general review of metabolites isolated from Australian marine species to 1975, including some preliminary results from the Roche Research Institute of Marine Pharmacology, situated near the coast about 20 km north of the centre of Sydney.

This paper will continue the same general theme and the plethora of novel compounds which have been discovered from Australian marine species will be discussed. Work carried out at the Roche Research Institute of Marine Pharmacology and University departments in Australia sponsored by Roche will be emphasised, but metabolites isolated by other workers from marine species collected in Australia will also be reviewed briefly.

The usual arrangement of new metabolites by structural type has not been adopted and a survey based on biological classification has been preferred. It is felt that this gives a better overview of the similarities and variations to be expected within various phyla.

The prime target of the Roche Research Institute of Marine Pharmacology has been the discovery and structural elucidation of marine natural products with biological activity. However, many substances with no detectable biological activity have also been isolated. Logistics of collecting material to yield enough extract to allow biological evaluation and fractionation to a pure compound stage suggested that, in earlier ventures, the study of abundant phylogenetically simple sessile organisms would be wise. Australian work has therefore concentrated on those phyla studied in many other laboratories - Porifera, Algae and Coelenterata. These three phyla have produced the vast majority of the many novel compounds isolated from Australian sources in the last three years. Several other phyla have been investigated and have given interesting results which will be reviewed.

### PORIFERA

Previously reported work on sponge metabolites has demonstrated that this phylum has yielded metabolites with the greatest structural diversity (Ref. 2). Much of recent Australian research has centred on two families of the sponge order Dictyoceratida, the Spongidae and Dysideidae, which have yielded an array of new terpenoids.

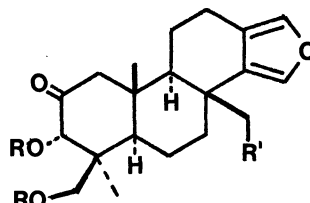
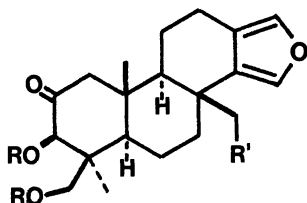
### SPONGIDAE (DICTYOCERATIDA)

The most interesting compounds to be isolated from the family Spongidae are C<sub>25</sub>-C<sub>27</sub> sesterterpenes and C<sub>21</sub> difuranoterpenes, presumably derived by degradation of a sesterterpene precursor (Ref. 2). A considerable number of Australian Spongidae have been examined and a series of new sesterterpenes, diterpenes and C<sub>21</sub> difuranoterpenes has been characterised. Initial work in Australian species has been reviewed previously (Ref. 1) and work on C<sub>21</sub> difuranoterpenes from *Spongia* species (Refs. 3, 4), furanoid sesterterpene lactones from *Thorecta marginalis* (Ref. 5) and a tetracyclic sesterterpene from *Heteronema erecta* (Ref. 6) have been published.

### Spongia

Many collections of several species of *Spongia*, closely related to *S. officinalis*, collected on the Australian Great Barrier Reef, gave between 2% and 8% of a mixture of diterpenes 1 - 8. All these diterpenes have been separated and related to 8, the structure of which was confirmed and the relative stereochemistry determined by a single crystal X-ray structure. The absolute configuration was determined by CD studies (Ref. 7).

The ratios of the diols 1 and 3 to the triols 5 and 7 and their acetates were extremely variable between separate collections but in the majority of collections triols 5 and 7 predominated.



- 1 R = H, R' = H  
2 R = Ac, R' = H  
5 R = H, R' = OH  
6 R = Ac, R' = OAc

- 3 R = H, R' = H  
4 R = Ac, R' = H  
7 R = H, R' = OH  
8 R = Ac, R' = OAc

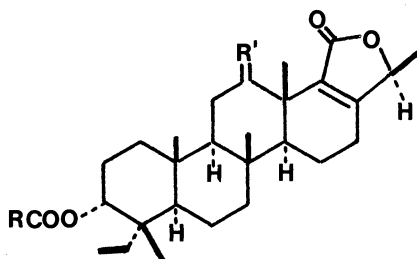
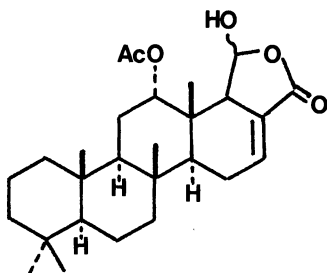
### Phyllospongia

The genus *Phyllospongia*, confined to the Indo-Pacific region, has been investigated intensively by Roche chemists. Two independent major studies on different species have been involved. Hofheinz, working on materials supplied by Dunstan from Barrier Reef collections of *P. radiata* and *P. foliascens*, isolated a number of novel C<sub>26</sub> and C<sub>27</sub> sesterterpenes (Ref. 8) related to scalarin 9, previously reported by Italian workers (Ref. 9). Concurrently Australian chemists isolated closely related C<sub>26</sub> sesterterpenes from *P. dendyi* and an unnamed *Phyllospongia* species (Refs. 10, 11).

#### *Phyllospongia radiata* and *P. foliascens*

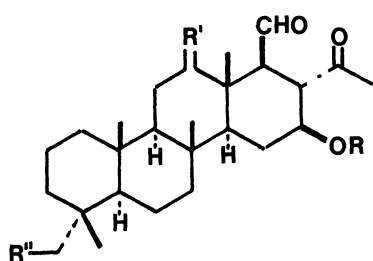
The lipid soluble extract of *P. radiata* was a complex mixture from which six related terpenoid metabolites were isolated by exhaustive chromatography on silica gel. The gross structures of the C<sub>27</sub> lactones 10 - 12 and the C<sub>26</sub> ketoaldehydes 13 - 15 were derived from spectral data and chemical interconversions. These structures were confirmed and the relative and absolute stereochemistry established by a single crystal X-ray structure on 16, derived from 11 by oxidation with Jones' reagent (Ref. 12) and by a CD comparison of all related compounds (Ref. 8).

*P. foliascens* yielded four further related metabolites 17 - 20, all with an α-ethyl group at C4.



9

- 10 R = CH<sub>3</sub>; R' = H (β), OH (α)  
11 R = CH<sub>2</sub>CH<sub>3</sub>; R' = H (β), OH (α)  
12 R = CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>; R' = H (β), OH (α)  
16 R = CH<sub>2</sub>CH<sub>3</sub>; R' = O  
20 R = CH<sub>2</sub>CH<sub>3</sub>; R' = M (β), OAc (α)



13 R = Ac; R' = O;

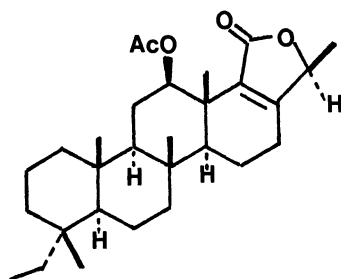
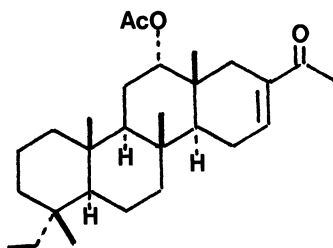
R'' = H

18

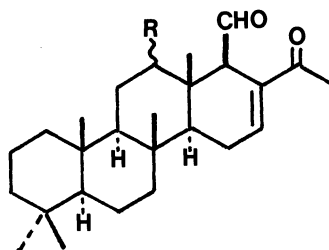
14 R = Ac; R' = H ( $\alpha$ ), OH ( $\beta$ ); R'' = H

15 R = H; R' = H ( $\alpha$ ), OH ( $\beta$ ); R'' = CH<sub>3</sub>

17 R = H; R' = H ( $\beta$ ), OAc( $\alpha$ ); R'' = CH<sub>3</sub>

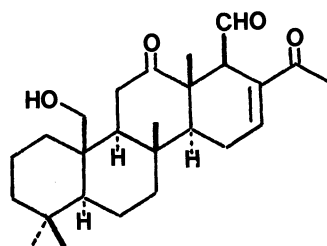


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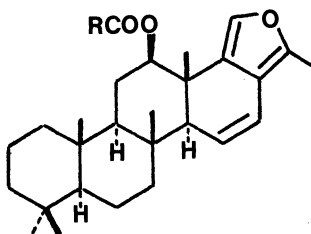


21 R = OCOCH<sub>2</sub>CH(OH)CH<sub>3</sub> ( $\beta$ )

22 R = OAc ( $\alpha$ )



26



23 R = CH<sub>2</sub>CH(OH)CH<sub>3</sub>

24 R = CH=CHCH<sub>3</sub>

25 R = CH<sub>3</sub>

#### Phyllospongia dendyi and Phyllospongia sp.

Two further species of Phyllospongia have been investigated in Australia. P. dendyi gave two C<sub>26</sub> sesterterpenes, dendalone 3-hydroxybutyrate 21 and epidendalone acetate 22, in a 20:1 ratio. The gross structural determination was aided, as for a previously reported sesterterpene (Ref. 6), by brief pyrolysis of 21 to give a high yield of the vinyl furans 23 - 25 in which 23 predominated. The absolute stereochemistry of 21 and 22 was established by comparison of CD spectra with those of P. radiata compounds (*vide supra*).

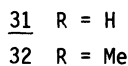
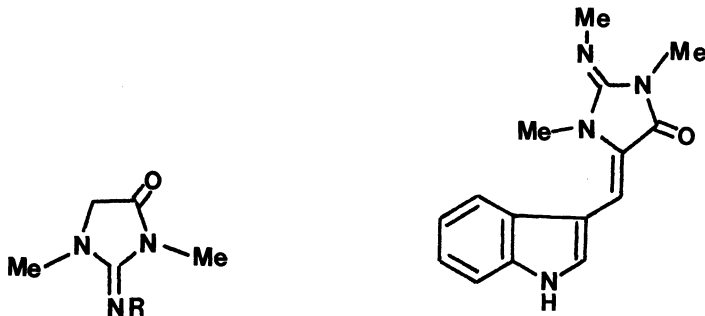
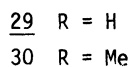
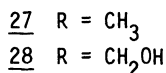
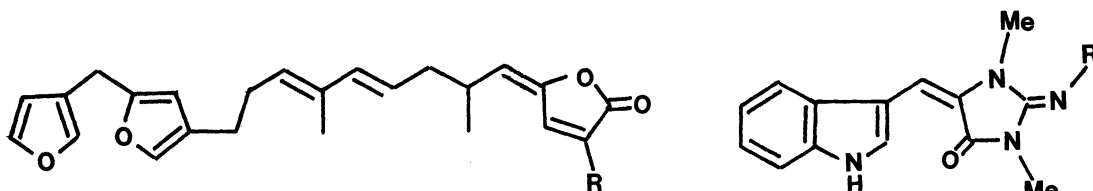
The origin of the "extra" methyl groups in these C<sub>26</sub> and C<sub>27</sub> sesterterpenes is obscure. One possibility is methylation of a suitable precursor by methionine but the specific incorporation of homomevalonate (as the terminal unit, in the case of C<sub>26</sub> compound, and as both starter and terminal units for C<sub>27</sub> compounds) in an acyclic precursor cannot be discounted. An interesting variation on Phyllospongia sesterterpenes was the isolation of 26 as the major sesterterpene of an as yet unnamed Phyllospongia species. The structure was established by X-ray analysis of the acetate of 26 (Ref. 13).

### Thorecta

*Thorecta* is a large Indo-Pacific genus which has been split by some authorities into two genera, *Thorecta* and *Aplysinopsis* (Ref. 14). We have previously described the isolation of two sesterterpenes, 27 and 28, from *Thorecta marginalis* and another unnamed species of this genus. We have subsequently investigated a further ten species of this diffuse genus. Six species were found to contain the sesterterpenes 27 and 28, whilst in a further six species these lactones were absent, but all contained the sparingly soluble tryptophan derivative 29.

All species in which 29 was detected best fit the description of the genus *Aplysinopsis* (Ref. 14). One of these species, collected near Lizard Island on the northern section of the Great Barrier Reef, contained, in addition to 29, the methyl analogue 30. We have coined the name aplysinopsin for 29 and methylaplysinopsin for 30. Interest in 30 was intense when it was found that the compound protected mice from tetrabenazine induced ptosis (Ref. 15), indicative of antidepressant properties.

Structural elucidation of 29 has been reported (Ref. 16) and synthesis of 29 and 30 by piperidine catalysed condensation of indole-3-aldehyde with the requisite creatinine derivatives 31 and 32 has been effected. Many analogues have also been prepared by the same general method (Refs. 17, 18), and are being tested for biological activity. The crystalline compounds 29 and 30, isolated from the sponge, have the *E*-configuration about the double bond. This was shown by an X-ray crystal structure of 30 (Ref. 19) and was established by NOE studies of the <sup>1</sup>H n.m.r. spectrum for 29 by Schmitz et al. on an independently isolated sample from the sponge *Verongia spengeli* (Ref. 20). The isolation of 30 from natural and synthetic sources is due to the sparing solubility of the *E*-isomer and it has been found that 30 can be isomerised to a ca. 1:1 mixture of the *E*-isomer 30 and the *Z*-isomer 33 (Ref. 18). An X-ray crystal structure of the *Z*-isomer 33 (Ref. 21), which has drastically reduced antidepressant properties (Ref. 15), confirms that 33 exists in the crystalline state as shown.



### DYSIDEIDAE (DICTYOCERATIDA)

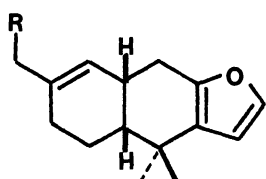
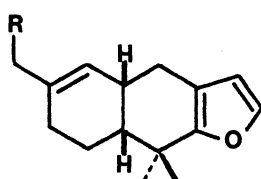
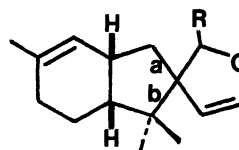
The family Dysideidae has proved to be of particular interest and, at first sight, some of the metabolites isolated from Australian collections of this family are perplexing. Three Australian species of the genus *Dysidea* have been investigated and, in the case of *D. herbacea*, many different collections have been extracted with startlingly variable results.

Dysidea sp. (unidentified)

An as yet unnamed Dysidea species collected in the Sydney region of New South Wales has yielded four new sesquiterpenes of considerable chemical interest. Chromatography of the crude dichloromethane extract on silica gel gave the two furanoid sesquiterpenes 34 and 35. The gross structures were indicated by spectroscopic methods and established by single crystal X-ray studies (Ref. 22). It was surprising that the rearranged furanoid sesquiterpene 34 predominated over the unrearranged metabolite 35 by 3:1.

The more polar compounds 36 and 37 were shown, by spectroscopic techniques and desulphurisation with Raney nickel, to be acetates of thio-derivatives of 34 and 35. The rearranged sesquiterpene 36 was again predominant (ratio 20:1).

An attractive precursor for the furans 34 - 37 would be a spiro-compound of the general structure 38 which could form 34 or 35 by alternative rearrangement by cleavage of bonds a or b. A member of this new sesquiterpene class, the acetate 39, has been recently isolated from Dysidea herbacea (vide infra). A Barrier Reef Dysidea sp. has yielded a 6% dry weight yield of avarol (Ref. 23).

34 R = H36 R = SAc35 R = H37 R = SAc38 R = leaving group39 R = OAcDysidea herbacea

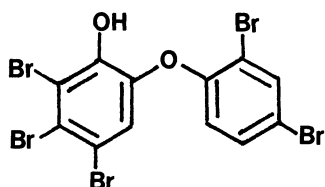
Two previous studies of Dysidea herbacea have been reported. A collection from the Caroline Islands yielded a series of polybrominated diphenyl ethers exemplified by 40 (Ref. 24), whereas the trichloro-metabolite dysidin 41 was isolated from a Barrier Reef collection (Ref. 25a). We have recently investigated several individual collections of D. herbacea from various locations on the Barrier Reef with some interesting results. Some samples contained polybromo-diphenyl ethers similar to 40, other samples yielded specifically hexachlorinated metabolites and from a few samples no halogenated metabolites were discovered. The constituents of two collections containing hexachloro-compounds are now considered.

A small collection of D. herbacea from north of Cooktown gave a high yield of dysidenin 42 which contained two trichloromethyl-groups and the unusual thiazole ring system (Ref. 25b). The structure was solved by spectral studies of 42 and the non-halogenated analogues 43 and 44 formed by Zn-AcOH and Zn-AcOD reduction of 42. Dysidenin 42a is obviously amino-acid derived, probably from four amino acids. Recently isodysidenin 42b has been isolated from an Indonesian collection of D. herbacea (Ref. 25c). The stereochemical detail shown in structure 42 is that of 42b (Ref. 25c). Dysidenin, 42a, is possibly the C5 epimer of 42b (Ref. 25c).

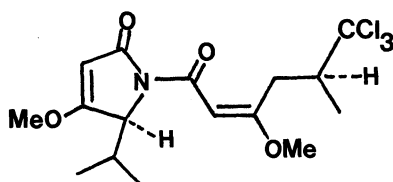
A collection of D. herbacea from the southern end of the Barrier Reef gave the two compounds 45 and 39 (4:1).

The isolation of the spiro-sesquiterpene 39 from the same collection was gratifying because it was the only metabolite which was typical of other reported Dysidea species (Ref. 2) and also the possible biosynthetic origin of the furanoid sesquiterpenes 34 - 37 was uncovered. Treatment of 39 with BF<sub>3</sub>-etherate in benzene gave a 1:1 mixture of 34 and 35 which established the gross structure and relative stereochemical details at the AB ring junction. <sup>13</sup>C and <sup>1</sup>H n.m.r. shifted spectra (Eu(fod)<sub>3</sub>) indicated that the carbon bearing acetoxy group was α but the stereochemistry at the spiro-centre remains to be determined unambiguously.

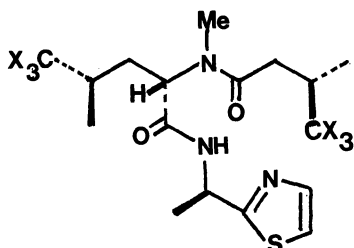
The atypical occurrence of halogenated metabolites in D. herbacea, often in a total isolable yield of 2 - 4% based on dry sponge, could well be explained by the presence of symbiotic blue-green algae. Microscopic examination of some specimens has demonstrated the presence of a "red" blue-green alga, the algal cells often predominating over all other cells in the sponge matrix. The variation in halogenated compounds between individual specimens may well be explained by the variable presence of different dominant blue-green algal symbionts.



40



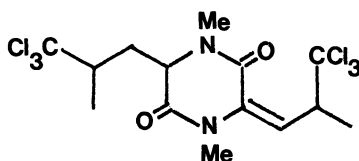
41



42 X = Cl

43 X = H

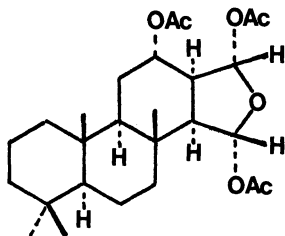
44 X = D



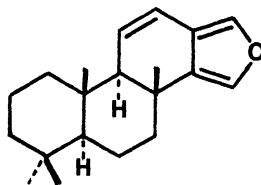
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## DENDROCERATIDA

*Aplysilla rosea* is the only Dendroceratid sponge studied in Australia. Aplysillin 46 was the major compound isolated. The structure followed from spectral data on 46 and the vinyl furan 47, readily formed from 46 on brief heating at 230°, and the relative stereochemistry obtained by a single crystal X-ray study of 46 (Ref. 26).



46

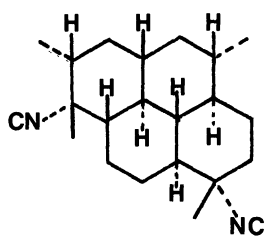


47

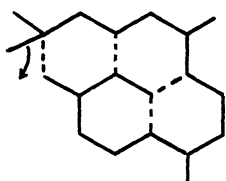
## SPICULATE SPONGES

A single example of metabolites from a spiculate sponge is considered. An *Adocia* species from the Barrier Reef produced a closely related series of diterpene mono- and diisocyanides in 3% dry weight yield. Diisocyanoadociane 48 constituted 70% of the crude extract and was crystallised directly. Details of the X-ray structural determination have been published (Ref. 27) and it was suggested that this unique rearranged diterpene skeleton was formed by a single methyl migration of a precursor represented formally by 49.

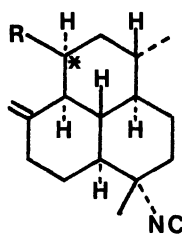
The remaining metabolites were very difficult to separate pure but a mixture of two monoisocyanides deposited crystals of 50 on prolonged storage at -20° in pentane. The structure of 50 (relative configuration only) came from spectral studies and a single crystal X-ray study (Ref. 28) which showed it to be an unusually cyclised but regular tricyclic diterpene. The proposed biosynthesis of 48 is supported by the presence of 50; presumably an isomer of 50 at the position marked is a biosynthetic precursor. Two more related compounds 51 and 52 have also been isolated and further investigation of this sponge for bicyclic compounds is in progress.



48



49

50 R = Me<sub>2</sub>C=CH-51 R = CH<sub>2</sub>=C(Me)CH<sub>2</sub>-52 R = Me<sub>2</sub>C(NC)CH<sub>2</sub>-

## COELENTERATA

Most Australian research on the chemistry of the coelenterata has concentrated on the alcyonarians (soft corals) with some studies on gorgonians which are less prevalent on the Barrier Reef than in Caribbean waters. Interesting compounds isolated by the Oklahoma group from Australian coelenterate collections are reviewed but emphasis is placed on those studies conducted at RRIMP and those supported by RRIMP at the James Cook University of North Queensland.

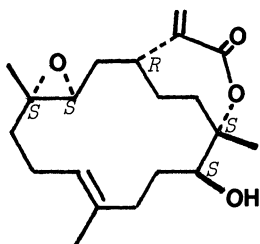
## ALCYONARIANS (SOFT CORALS)

Soft corals have been well studied and Australian work has been under way for the last three years. The majority of metabolites reported have the ubiquitous cembrane skeleton or bicyclic variations but some novel terpenoid and terpenoid quinol variations have been uncovered recently.

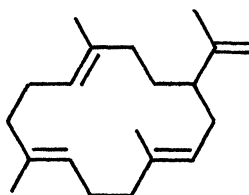
Various cembranoid compounds are shown in formulae 53 - 63, although these are representative rather than encyclopedic. *Sinularia flexibilis* has been studied by three groups (Refs. 29, 30, 31). Australian specimens have yielded a variety of cembranoids including the previously reported lactone sinulariolide 53, neo-cembrene-A 54 and the novel cyclopentadecane 55. Two new lactones flexibilide 56 and dihydroflexibilide 57 were isolated at RRIMP and 56 was reported in 1976 (Ref. 29) in connection with studies on an Indonesian collection of *S. flexibilis*. Subsequently both 56 and 57 have been reported independently (Ref. 31) under the names sinularin and dihydrosinularin.

Dehydroepoxyneophthenol 58 was isolated from a *Sarcophyton* species (Ref. 32) and the  $\alpha$ -methylene lactone 59 occurs in *Lobophytum michaelae* (Ref. 33). A new cembrene 60 was isolated by two Australian groups (Refs. 34, 35) from *Sarcophyton* species and the epoxide analogue 61 has also been characterised (Ref. 34).

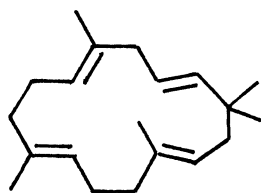
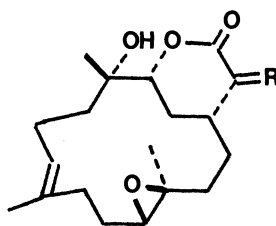
The gross structures of most cembranoids are available from spectral data and routine chemical reactions but fine stereochemical detail is obscure and often requires X-ray studies to be definitive. Thus much of RRIMP and other Australian work will be omitted in that stereochemically correct structures cannot be obtained without a major chemical study. As an example the structure 62 or 63 could be written for the major metabolite of a *Lobophytum* species but the choice between these structures and relative stereochemistry requires further study.



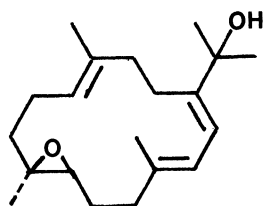
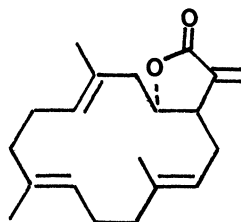
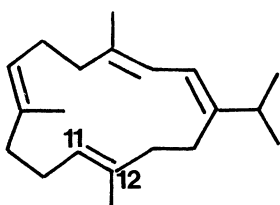
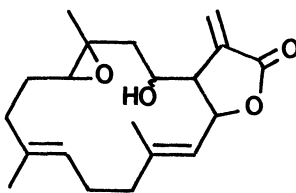
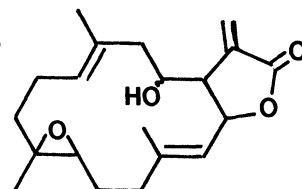
53



54

55

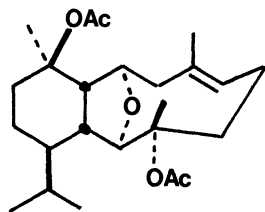
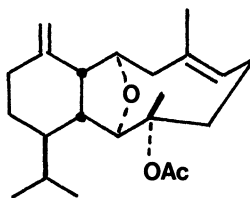
56 R = CH<sub>2</sub>  
57 R = CH<sub>3</sub>,H

5859 R = H6061 11,12 epoxy-606263

More unusual compounds from soft corals will be considered in more detail.

#### Cladiella sp.

Two related bicyclic diterpenes of the eunicellin type (Ref. 36) were isolated from a Cladiella species. The structure and relative stereochemistry of acetoxycladiellin 64 was established by an X-ray crystal structure determination and the structure of cladiellin 65 obtained by chemical correlation. An interesting feature of the chemistry of the cladiellins was the effect of the ether oxygen which, by anchimeric assistance, produced the cis-hydroxy-m-chlorobenzoate on reaction of 64 with m-chloroperbenzoic acid (Ref. 37).

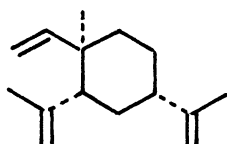
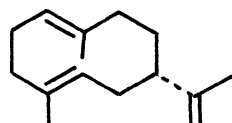
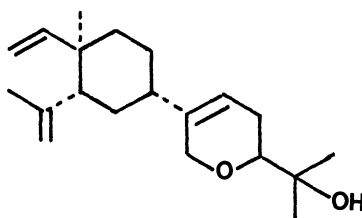
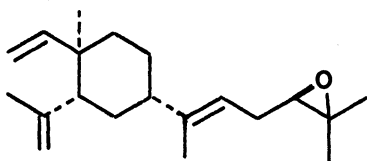
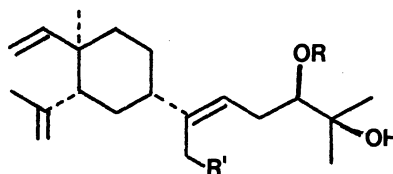
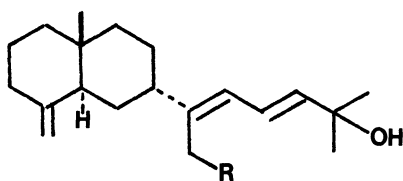
6465



## Non-cembrane diterpenes

A Barrier Reef *Lobophytum* species gave a complex extract from which a range of sesqui- and diterpenes has been isolated (Ref. 38). The two known sesquiterpenes,  $\beta$ -elemene 66 and germacrene-A 67, were found in the hydrocarbon portion of the dichloromethane extract, whereas more polar compounds were found to be diterpenes which can be regarded as *iso*-pentenyl analogues of the  $\beta$ -elemene system.

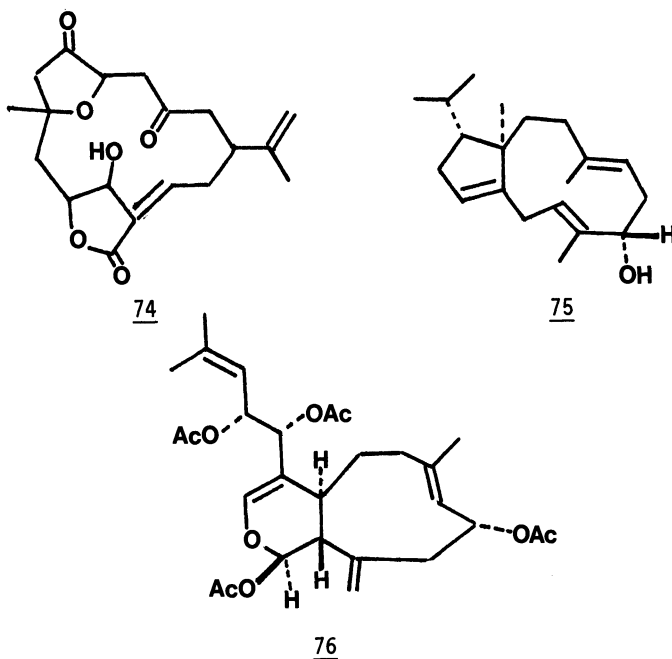
Structural elucidation of four new diterpenes 68 - 71 followed from spectral evidence, in particular  $^{13}\text{C}$  n.m.r. comparisons with  $\beta$ -elemene 66 and  $\beta$ -elemol and chemical interconversions. No trace of diterpene analogues of the germacrene system could be detected, even after cold extraction of a frozen fresh sample of the soft coral. It is interesting that 68 has also been isolated from an unidentified red alga at RRIMP.

6667686970 R = Ac, R' = OAc71 R = H, R' = OAc72 R = H73 R = OH

*Lobophytum hedleyi* has yielded the diterpene analogues 72 and 73 of the selinane sesquiterpene skeleton (Ref. 39).

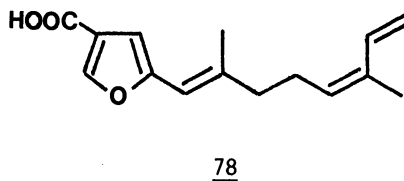
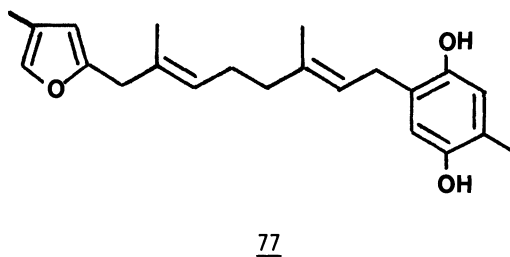
## Modified diterpenes

The novel *nor*-cembrane 74 was isolated from a *Sinularia* species. The structure was obtained from a single crystal X-ray study of the material which crystallised directly from a dichloromethane extract (Ref. 40). The structure of the rearranged bicyclic diterpene 75, from an unidentified soft coral, was also established by an X-ray study (Ref. 40). The interesting compound xenicin 76 has recently been reported from *Xenia elongata*, collected at the southern end of the Barrier Reef (Ref. 41).



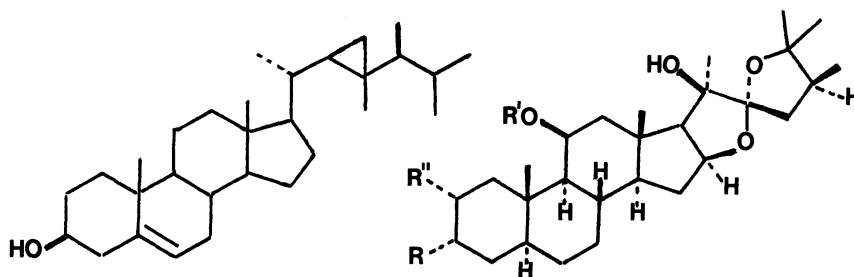
## Miscellaneous

The quinol 77 has been obtained from *Sinularia lochmodes*. The structure was obtained from a careful  $^1\text{H}$  n.m.r. study (Ref. 42); *Sinularia gonatodes* yielded the new furanoid sesquiterpene 78 (Ref. 43).



## GORGONIANS

The Barrier Reef gorgonian *Isis hippuris* yielded a complex extract from which gorgosterol 79 and the unusual steroids, hippurin-1 80 and hippurin-2 81, were isolated and characterised by single crystal X-ray studies and CD studies of derivatives (Refs. 44, 45).

7980 R = OH, R' = H, R'' = OAc81 R = OAc, R' = Ac, R'' = H

## ECHINODERMATA

## Crinoids

Sutherland and Rideout (Ref. 46) have continued the investigation of crinoid pigments (cf. Ref. 1). *Himerometra robustipinna* elaborates rhodoptilometrin 82, together with a minor amount of 83 and a trace of the dimer 84. The pigment mixture of *Lampometra palmata gyges* was more complex. Major products were 83, 85 ((-) enantiomer) and 86 with minor amounts of 82, 87, 88 ((-) enantiomer) and 89. *Zigometra microdiscus* also gave metabolites in the same series with 83 predominating, 90 present as a minor constituent, and traces of 82 and 85.

Anthraquinone pigments of *Comactinia meridionalis* were 91 (major) and 92 (minor), whilst *Comulata pectinata* form *purpurea* gave the interesting sulphated anthraquinones 93 and 94 (major), and 95 (minor). *Comantheria briareus* elaborated the pyrones 96 (major), 97 (major) and 98 (minor), all of which are sulphonic acids.

Although crinoids are highly coloured and very conspicuous on coral reefs, they are not subject to major predation. Sutherland *et al.* have shown that the sulphated pigments are fish repellents (Ref. 46).

## MOLLUSCA

The major toxin of the blue-ringed octopus *Hapalochlaena maculosa* has been positively identified as tetrodotoxin 99 (Ref. 47). This is the first reported case in which tetrodotoxin is utilised as a venom.

## ARTHROPODA

Arsenobetaine 100 has been identified as the relatively non-toxic organo-arsenic constituent of the western rock lobster *Panulirus longipes cygnus* George. The structure of arsenobetaine isolated from the tails of lobsters containing 26 p.p.m. of arsenic was determined by an X-ray crystal structure determination and further confirmed by synthesis (Ref. 48).

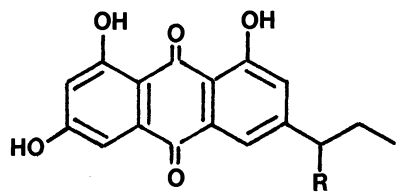
## ALGAE

Probably the most intensively investigated of marine genera from the chemical aspect is the red algal genus *Laurencia*. Australian research on algae has emphasised no particular group, although the chemically most fruitful families Dictyotaceae and Bonnemaisoniaceae and the genera *Laurencia*, *Plocamium*, *Polysiphonia*, etc. have received some attention, particularly because of *in vitro* antimicrobial activity of many extracts (e.g. Ref. 57).

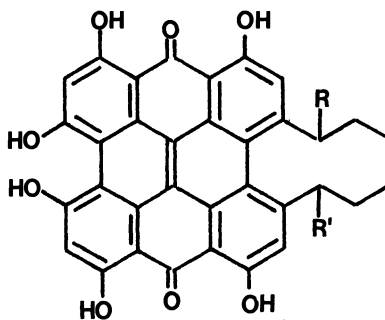
## RHODOPHYTA (RED ALGAE)

*Laurencia filiformis* f. *heteroclada*

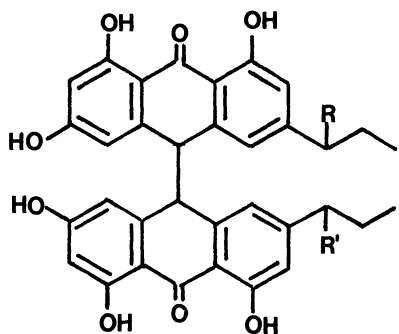
Two separate collections of this alga, from Victoria, have been investigated. One collection contained dihydrolaurene 101, laurene 102, allolaurinterol 103 and filiforminol 104 (Ref. 49), whereas the second collection contained these laurane derivatives, together with 0.27% of the selinane derivative heterocladol 105 (Ref. 50). The co-occurrence of 105 and laurane derivatives cannot be rationalised in terms of the rather rigid postulates which propose that different sesquiterpene classes arise exclusively from 2E,6E and 2Z,6E-farnesol respectively (Ref. 50).



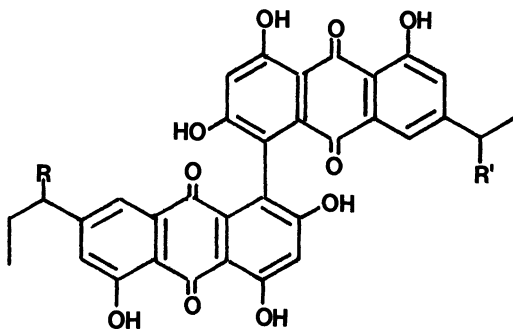
82 R = OH  
83 R = H



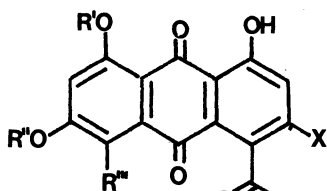
84 R = R' = OH  
89 R = H, R' = OH



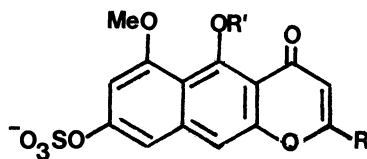
85 R = R' = H  
86 R = H, R' = OH  
87 R = R' = OH



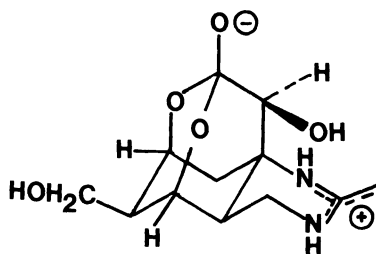
88 R = R' = OH  
90 R = R' = H



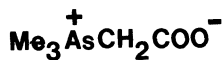
91 R = CH<sub>3</sub>, X = OH, R' = R'' = R''' = H  
92 R = CH<sub>3</sub>, X = OH, R' = R'' = H, R''' = OH  
93 R = CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, X = OSO<sub>3</sub><sup>-</sup>, R' = R'' = CH<sub>3</sub>, R''' = H  
94 R = CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, X = OSO<sub>3</sub><sup>-</sup>, R' = R''' = H, R'' = CH<sub>3</sub>  
95 R = CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, X = OXO<sub>3</sub><sup>-</sup>, R' = H, R'' = CH<sub>3</sub>, R''' = OH



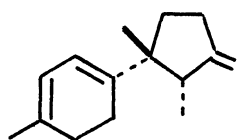
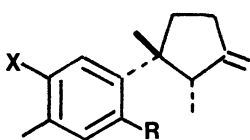
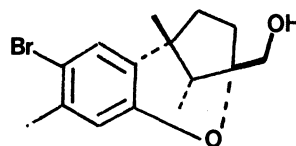
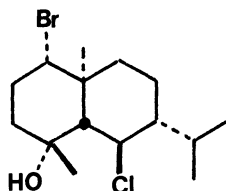
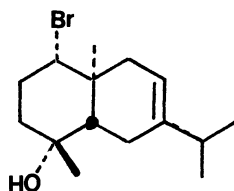
96 R = CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, R' = CH<sub>3</sub>  
97 R = CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, R' = H  
98 R = CH<sub>3</sub>, R' = H



99



100

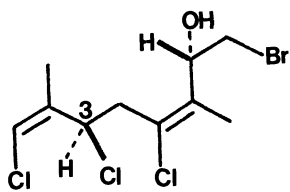
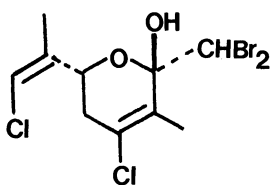
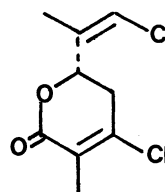
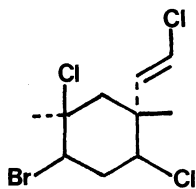
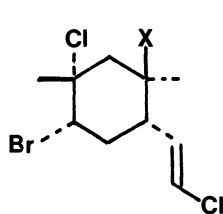
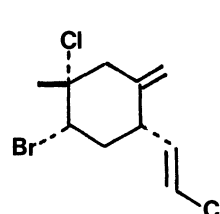
101102 X = R = H103 X = Br, R = OH104105106Laurencia sp.

A collection of a Laurencia species, collected from southern New South Wales by Sims, yielded the selinane derivative 106 as one of the metabolites but yields were only 0.005% (Ref. 51).

Plocamium

Several new polyhalogenated monoterpenes have been isolated from Australian Plocamium species. In independent studies two groups isolated a number of acyclic monoterpenes from different southern Australian collections of P. costatum. Separate X-ray studies on costatol 107 (Ref. 52) and costatone 108 (Ref. 53) established the structures and absolute configuration of each compound. In addition to 108, 109 occurred in this collection (Ref. 53). It is interesting to note that the stereochemistry at C3 of 107 is *R*, whereas that at C3 of 108 is *S*, suggesting that 108 is formed by internal SN2 substitution of a precursor similar to 107.

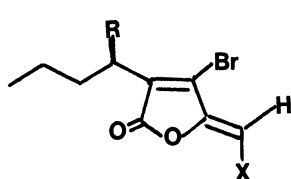
Plocamium mertensii yielded the monocyclic bromotrichloro-monoterpene 110 (Ref. 54), whilst an Australian collection of P. cartilagineum gave the major metabolites 111 and 112 (Ref. 54) with minor metabolites including 113. The halogen substitution pattern was solved by the differing  $^{13}\text{C}$  n.m.r. relaxation times and NOE values for chlorinated and brominated carbon atoms respectively. An English collection of P. cartilagineum gave a series of related compounds including 112 and 113 (Ref. 55).

107108109110111 X = Cl112 X = Br113

## Bonnemaisoniaceae

Members of the red algal family Bonnemaisoniaceae studied to date have all produced halogenated metabolites of polyketide precursors. Studies on three Australian species are now surveyed.

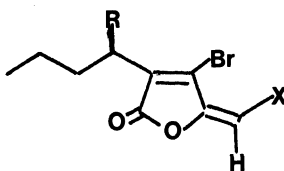
*Delisea fimbriata*, collected on the Sydney coastline, yielded a series of polyhalogenated lactones, the fimbrolides, represented by the general formulae 114 - 116, 117 - 119 and 120 - 122 (Ref. 56). The acetyxfimbrolides 116 and 119 were isolated from a south polar collection of the same species and the R-configuration of the acetyl-group determined by an X-ray study of a derivative of 116 (Ref. 57).



114 R = H, X = Br

115 R = OH, X = Cl, Br or I

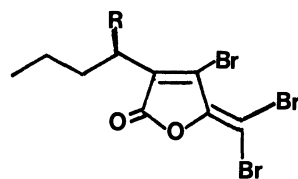
116 R = OAc, X = Cl, Br or I



117 R = H, X = Br

118 R = OH, X = Cl, Br or I

119 R = OAc, X = Cl, Br or I

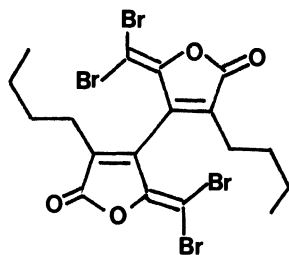


120 R = H

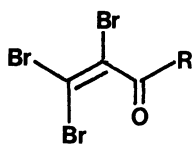
121 R = OH

122 R = OAc

*Delisea hypnoides* (slender form), collected in Tasmania, gave pure 120, together with the interesting dimer 123 (Ref. 58).



123

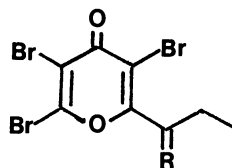


124 R = CH<sub>2</sub>Br

125 R = CH=CHCBr<sub>2</sub>Et

126 R = CHBr(CH<sub>2</sub>)<sub>3</sub>Me

127 R = CBr<sub>2</sub>(CH<sub>2</sub>)<sub>3</sub>Me



128 R = Br, Br

129 R = O

The extract of *Ptilonia australasica* was complex with the non-polar fraction comprising a series of tribromovinyl ketones including 124 - 127 (Ref. 56). From the more polar fractions the pyrones 128 and 129 were isolated. The highly crystalline pentabromo-pyrone 128 was the dominant metabolite, representing half of the 3% dry weight dichloromethane extract (Ref.10).

## PHAEOPHYTA (BROWN ALGAE)

Brown algae have not been chemically examined to the same extent as red algae. The single exception to this generalisation is the family Dictyotaceae which has received considerable attention recently. Australian species of brown algae have been studied only recently with some interesting results.

## Sargassaceae

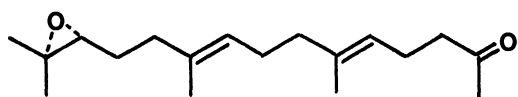
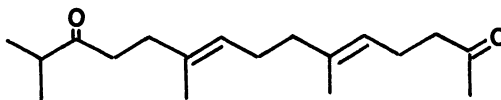
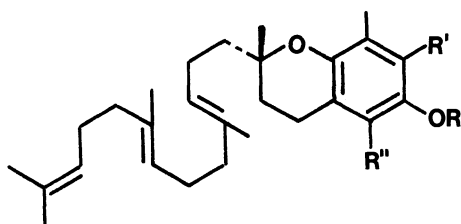
The Australian genus *Cystophora* and related genera have yielded a series of polyketide derived compounds, terpenoid metabolites or mixtures of both classes. Algae of this genus are also a rich source of catecholamines.

## Cystoseiraceae

*Cystophora moniliformis* yielded the farnesyl acetone derivatives 130 and 131 in dry weight yields of 0.6% and 0.05% respectively. The absolute configuration of 130 was determined on the derived diol (Ref. 59).

*Cystophora expansa* and *C. platylobium* are extremely rich sources of  $\delta$ -tocotrienol 132, whilst other species contain a preponderance of acetogenins accompanied by minor quantities of tocotrienols.

*C. torulosa* produced small amounts of the methyl ether of  $\delta$ -tocotrienol 133 and a homologue for which formulae 134 and 135 could not be excluded with the material available. The dominant proportion of the 5% dichloromethane extract comprised a mixture of alkenyl resorcinols in which 136 was major but 137 - 139 were detected. A phloroglucinol derivative 140, probably formed from the precursor of 136 by an alternative cyclisation mechanism, was also isolated in low yield (Ref. 60). *C. congesta* yielded 141 as the major metabolite.

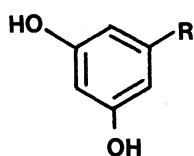
130131

132 R = R' = R'' = H

133 R = Me, R' = R'' = H

134 R = R' = Me, R'' = H

135 R = R'' = Me, R' = H

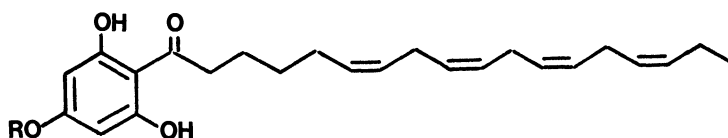


136 R =

137 R =

138 R =  $-(\text{CH}_2)_{12}\text{Me}$

139 R =  $-(\text{CH}_2)_{14}\text{Me}$



140 R = Me

141 R = H

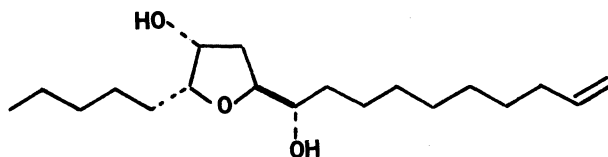
*Caulocystis cephalornithos*, a species closely related to *Cystophora* has yielded a series of metabolites, including tridecylphenol 142, pentadec-1-ene 143 and hexadec-1-en-3-one 144.

142 R = 3-hydroxyphenyl

Me(CH<sub>2</sub>)<sub>11</sub>CH<sub>2</sub>R

143 R = CH=CH<sub>2</sub>

144 R =  $\begin{matrix} \text{O} \\ || \\ \text{-C-CH=CH}_2 \end{matrix}$



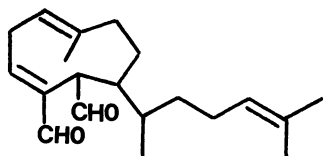
145

*Notheia anomala*, a member of the order Fucales, yielded the unusual lipid 145 as the major metabolite. The structure was obtained by degradative methods and the relative stereochemistry from an X-ray crystal structure by J.F. Blount.

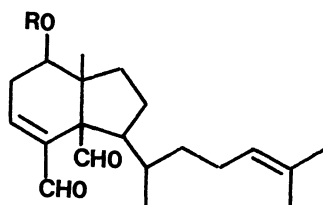
#### Dictyotaceae

Considerable work on the metabolites of the Dictyotaceae has been published, particularly by Fenical and coworkers (Ref. 61). Two studies on Australian representatives are reported here.

*Dictyota dichotoma* yielded a complex mixture of diterpenes including several known compounds with the pachydictyol skeleton (cf. Ref. 61) and the recently reported cyclononane derivative 146 (Ref. 62). Amongst new terpenes isolated were the new bicyclic dialdehyde 147 and its acetate 148 (Ref. 38).



146



147 R = H

148 R = Ac

A series of diterpenes containing the previously unreported bicyclo[8.1.0]undecane skeleton has been isolated from a *Dilophus* species collected near Sydney. The structure and relative stereochemistry of 149 was established by a single crystal X-ray determination and spectral comparisons secured the structures of the closely related compounds 150 - 153 (Ref. 45).

A Tasmanian collection of a *Perithalia* species yielded the phenol 154 with both an isoprene and a "reverse" isoprene unit (Ref. 58).

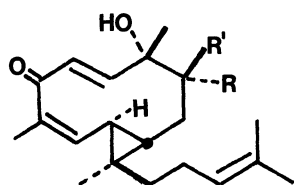
#### CHLOROPHYTA

Australian work on green algae has centred on the genus *Caulerpa*. Three species have been investigated to date and, in contrast to other chemical researches on this genus, have yielded moderate to high yields of diterpenes and sesquiterpenes.



*Caulerpa brownii* gave an extremely high hexane soluble extract from which 9.5% of caulerpol 155, closely related to vitamin A, was isolated, together with a low yield of the acetate 156 (Ref. 63).

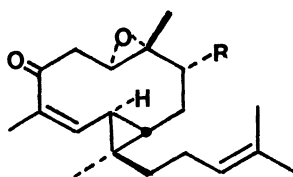
*Caulerpa flexilis* gave a 3% dry weight yield of an unusual sesquiterene, the diacetoxybutadiene 157, whereas *C. trifaria* yielded the diterpenoid diacetoxybutadiene 158.



149 R' = H, R = OAc

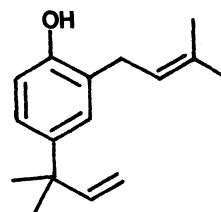
150 R' = R = H

151 R' = OAc, R = H

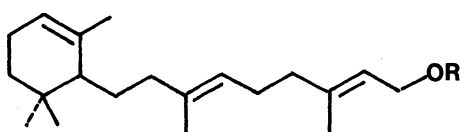


152 R = H

153 R = OAc

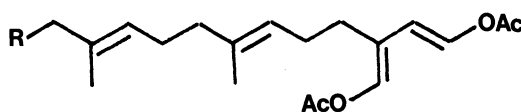


154



155 R = H

156 R = Ac



157 R = H

158 R = Me<sub>2</sub>CH-CH<sub>2</sub>-CH<sub>2</sub>

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