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THE NATURAL PRODUCTS CHEMISTRY OF WEST INDIAN GORGONIAN OCTOCORALS

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1. INTRODUCTION

The octocoral fauna of the West Indies is unique in its profusion of gorgonian corals (also known as sea whips, sea fans, or sea plumes).[1] Faunistically, extensions of the West Indian region reach into the Gulf of Mexico, all the Antilles, the Bahamas, the Florida Keys, the Bermudas, the Islands of the Caribbean, and south along the northeast coast of South America to the reefs of Brazil. All over this region the families Gorgoniidae and Plexauridae flourish as they do nowhere in the world. Gorgonian corals (order Gorgonacea, phylum Cnidaria) are

conspicuous members of most tropical and subtropical marine habitats, being the most abundant octocorals found in the West Indies. With over 195 species documented from these two major families, gorgonian octocorals represent an estimated 38% of the known fauna.[1] Studies of the natural products chemistry of this interesting group of marine invertebrates began in the late 1950's. Since these early investigations, numerous studies of the chemistry of gorgonian corals have been published and summarized.[2-9] This Report documents the exciting chemistry that has been generated through the investigation of gorgonian octocorals from the West Indian region. It includes only research published in refereed journals up to December, 1994. A short communication in *Science* by Burkholder and Burkholder in 1958, highlighting the occurrence of antibiotic substances in gorgonian corals from Puerto Rico, was used as the starting point for the present review.[10] This Report is not intended to be comprehensive but instead concentrates on novel marine natural products with interesting biological and pharmaceutical properties. With the exception of several unusual sterols having interesting functionalities, marine sterols, carotenoids, fatty acids, and biopolymers isolated have not been included, since they have been reviewed by specialists.[11-15] Studies of the chemical ecology aiming at the elucidation of the defensive roles of secondary metabolites from West Indian gorgonians and the value of secondary metabolite composition as a chemotaxonomic tool are discussed. The cited articles were retrieved from computer literature searches by use of Chemical Abstracts (CA Selects), MarinLit, STN International and also NAPRALERT. Terms such as West Indian, Caribbean, gorgonian, sea whip, octocoral, and phylla names were used. The primary focus will be the structural chemistry and biological activities of the metabolites produced by a relatively small group of gorgonians found within a limited geographic area. Wherever possible, every effort was made to record the biological and pharmacological properties of new metabolites. Since marine natural products in general are often the targets of synthetic chemists, we include synthetic work, where available, on novel compounds isolated from these animals. We hope to illustrate the diversity of compounds produced by West Indian gorgonians, while highlighting their specialized ability to biosynthesize secondary metabolites with promising pharmacological activity.[16-19]

2. NATURAL PRODUCTS CHEMISTRY

Gorgonian metabolites possess novel structures that are largely unknown from terrestrial sources. These animals are now recognized to produce acetogenins, sesquiterpenoids, diterpenoids, prostanoids, and, in some cases, highly functionalized steroids.[7] The chemistry of West Indian gorgonian octocorals will be presented taxonomically according to genus and species (in alphabetical order) rather than by chemical class, although in some cases a given compound could be assigned equally well to different categories. This categorization was selected not only for its convenience but also because it reveals an interesting fact: so far only a small percentage of the many species of gorgonians from this region (less than 20%) appears to have been systematically scrutinized for their secondary metabolite content; and many species await chemical investigation.

2.1. *Briareum* (family Briareidae)

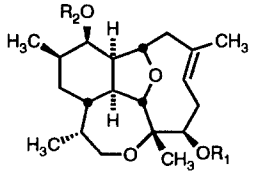
The phylogenetic position of the genus *Briareum*, which appears to be identical with the Pacific species *Solenopodium*, has long been the subject of debate.[1] Two documented species are known. One of them, *Briareum asbestinum*, is an exceedingly variable species commonly distributed from southern Florida through most of the West Indies. The second, *Briareum polyanthes*, is a recently discovered species that forms encrustations on rocks,

dead coral, and other living gorgonians. These animals are particularly rich in asbestinane and briarane diterpenoids.

A. *Briareum asbestinum* (Pallas)

(Common *Briareum*, corky sea fingers)

Studies of the chemistry of this interesting species began in the early 1960's with the discovery of a carbonyl-containing crystalline solid (later to be known as Briarein A) and the occurrence of taurobetaine in specimens collected near South Bimini (The Bahamas).[20-22] No appreciable amount of sesquiterpenes appears to have been found in this species. *Briareum asbestinum* elaborates diterpenes possessing the asbestinin and briarein ring systems. The asbestinins are a group of irregular diterpenoids that are related to the eunicellin-cladiellin group by 1,2-migration of the methyl group on the six-membered rings. Asbestinins 1-5 (**1-5**) were isolated from a sample of *B. asbestinum* collected in Belize,[23] whereas asbestinins -2, -3, -4, and -5 together with the derivatives asbestinin-5 acetate (**7**) and asbestinin epoxide (**8**) were obtained from samples collected in Honduras.[24] The structure of asbestinin-1 (**1**) was determined by single-crystal X-ray diffraction on the corresponding diol **6** and the structures of asbestinins 2-5 (**2-5**) were assigned from spectral analysis and chemical interconversions.[23] Structures for **7** and **8** were likewise derived from spectroscopic arguments and confirmed by chemical interconversions.[24] Several of the asbestinin derivatives show pharmacological activity. Compounds **1**, **5**, and **6** have the ability to antagonize the effects of acetylcholine on guinea pig ileum preparations. Compounds **5** and **6** also exhibit histamine antagonism in this same assay.[24]



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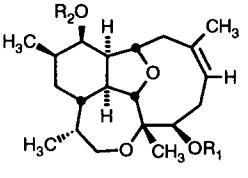
6 R_1 = H R_2 = H



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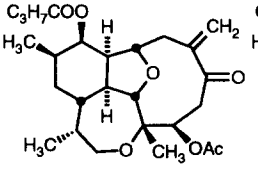

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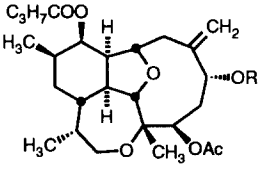

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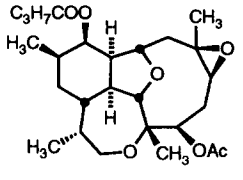

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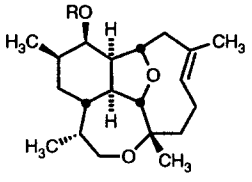

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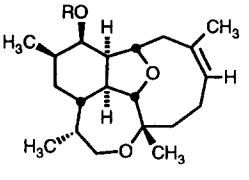

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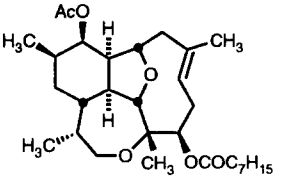

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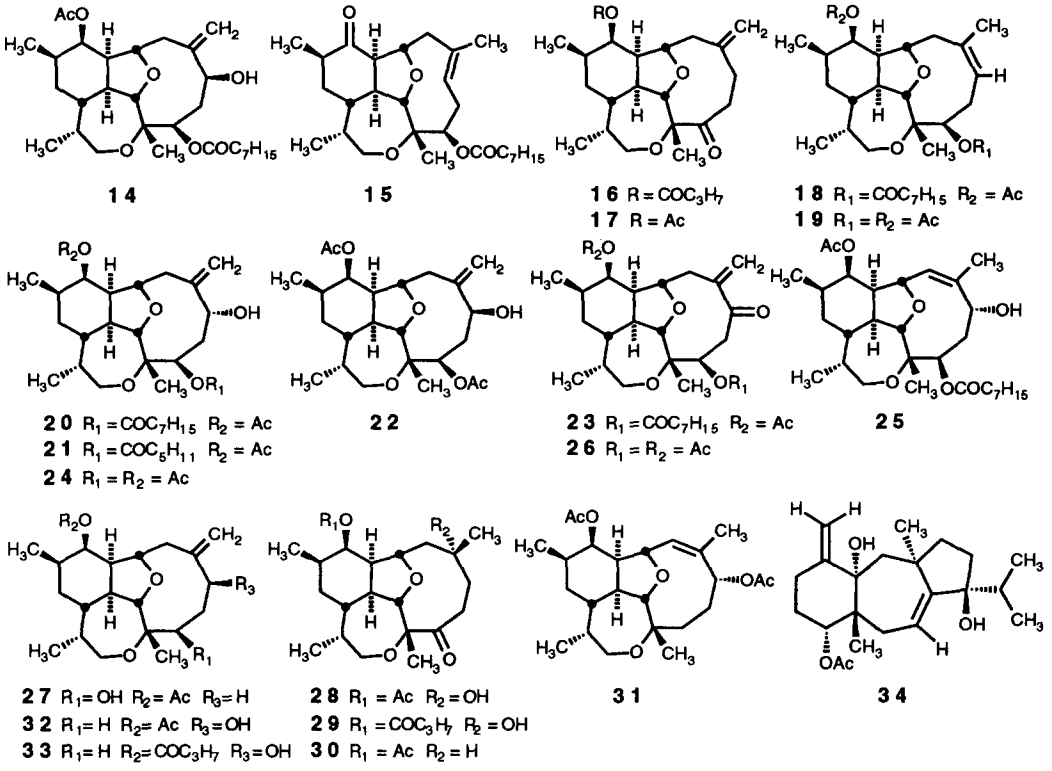
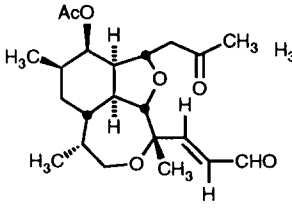
A specimen of *B. asbestinum* collected in Puerto Rico yielded four additional cytotoxic asbestins, 4-deoxyasbestinin A (**9**), 11-acetoxy-4-deoxyasbestinin B (**10**), 4-deoxyasbestinin C (**11**), and 11-acetoxy-4-deoxyasbestinin D (**12**).[25] The structures of the 4-deoxyasbestinins were elucidated from extensive NMR experiments,[26] and the structure of **10** was confirmed by X-ray crystallography.[27] All of the 4-deoxyasbestinin derivatives showed strong *in vitro* cytotoxicity against CHO-K1 cells and strong antimicrobial activity against *Klebsiella pneumoniae*. Compound **10**, however, proved inactive in the National Cancer Institute (NCI) test for

agents active against the human immunodeficiency virus (HIV).[25] Another five asbestinane diterpenes, asbestinins 6-10 (**13-17**), were isolated from specimens of *B. asbestinum* collected off the East and West coasts of Puerto



Rico. Their structures were defined by chemical and spectroscopic methods. Although diterpenoids **13-17** did not display significant antibacterial activity, they possess strong cytotoxicity when screened against a panel of five human tumor cell lines.[28] Recently, sixteen additional asbestinin diterpenes, asbestinins 11-23 (**18-30**), 11-acetoxy-4-deoxyasbestinin E (**31**), 11-acetoxy-4-deoxyasbestinin F (**32**), and 4-deoxyasbestinin G (**33**), were isolated from Puerto Rican specimens of *B. asbestinum* and identified by interpretation of spectral data and chemical methods.[29] That publication also includes structure revisions for asbestinin-6 (**13**) and asbestinin-7 (**14**).[29] The same study also resulted in the isolation of known diterpene (4S*,9R*,14S*)-4-acetoxy-9,14-dihydroxydolasta-1(15),7-diene (**34**) which has the dolastane carbon skeleton.[30] Compound **34** represents the first dolastane to be isolated from a species of the genus *Briareum* and extends the structural variability for this species. The hexane extract of the same specimen of *B. asbestinum* contained traces of a novel *seco*-asbestinin diterpenoid. The structure of **35**, the first representative of this novel class of diterpenoids, was assigned on the basis of extensive NMR analyses and by comparison with analogous spectral data from related asbestinane diterpenoids.[31] Confirmation of structure **35** was achieved by partial synthesis from known asbestinin-6 (**13**). Interestingly, *seco*-asbestinin derivative **35** was not cytotoxic against HeLa and CHO-K1 cells, suggesting a possible role for the ten-membered ring in the cytotoxic properties of asbestinane diterpenes. A collection of *B.*

asbestinum from South-West Tobago, West Indies, yielded the structure of an additional asbestinane containing one acetate at C-11 and a rare oxetane ring involving C-5 and C-7 along with five diterpenoids of the briarane class. The structure of **36** was determined by interpretation of spectroscopic data.[32]



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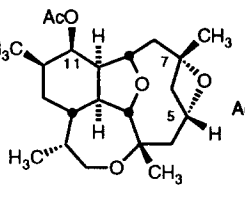

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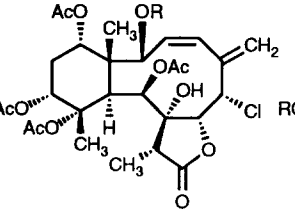

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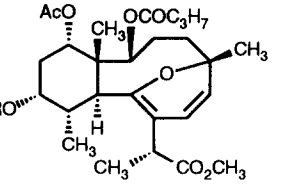

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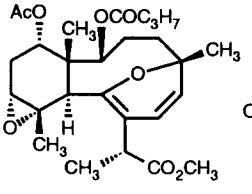

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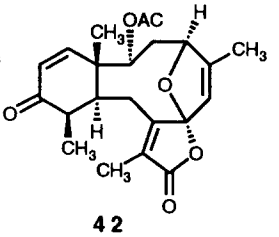

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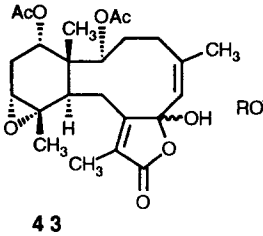

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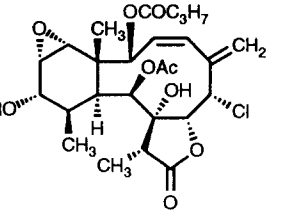


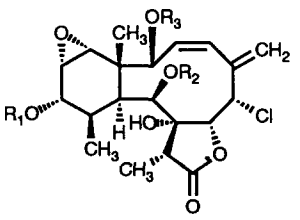
44 R = COC_3H_7

Briareum asbestinum also produces a series of interesting, highly oxidized diterpenes called briareins, which may sometimes contain chlorine, headed by briarein A (**37**). The X-ray structure of briarein A, isolated from *B. asbestinum* collected in Jamaica, has been reported.[33] The physical and chemical properties of briarein A as well as those for a tetraacetate monobutyrate analog of **37**, briarein B (**38**), which were obtained during collections of *B. asbestinum* from Belize[23] and Honduras,[24] have also been reported.[24] Extracts of *B. asbestinum* collected off the coast of Tobago, have afforded five diterpenes **39-43** that belong to the briarane class.[32] The structures of briaranes **39-43** were determined spectroscopically and that of methyl briareolate (**39**), a crystalline compound, was confirmed by X-ray crystal structure.[34] Briantheín V (**44**) is a cytotoxic and antiviral diterpene from *B. asbestinum* collected near Sandy Cay, Bahamas. X-ray analysis of a suitable crystal of **44** grown from a solution of methanol furnished the absolute structure and ring conformation.[35] The variation in defensive chemistry of colonies of *Briareum asbestinum*, which has been recognized as one of the most ubiquitous and chemically deterrent of the Caribbean gorgonians, has been sampled. The basis of deterrence appears to reside in the diverse complement of briarane and asbestinane diterpenoids found in individual colonies.[36] The structural variability for this species has been expanded even further with the recent discovery of five new diterpenoids possessing the eunicellin ring system from *B. asbestinum* collected in Puerto Rico. The isolation of asbestinins, briareins, and eunicellins from the same organism supports the theory that metabolites belonging to these skeleton classes are intimately related biogenetically.[37]

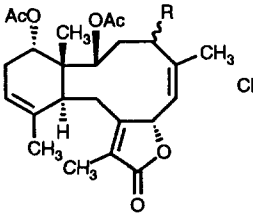
B. *Briareum polyanthes* (Duchassaing & Michelotti)

Prior to 1979, no species of *Briareum* from Bermudian waters had been assessed for their secondary metabolites composition. In 1979, a moderately large community of a new species, *Briareum polyanthes*, was

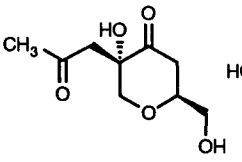
discovered at the eastern end of the Bermudian archipelago. These studies included the isolation and identification of three chlorinated diterpenes called briantheins X-Z (**45-47**).[38,39]



45 $R_1 = R_2 = Ac$ $R_3 = H$
46 $R_1 = R_2 = Ac$ $R_3 = COC_3H_7$
47 $R_1 = R_2 = R_3 = Ac$



48 R = H
49 R = OH



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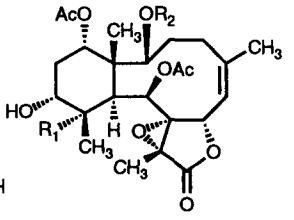
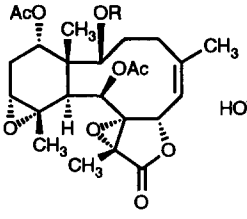


51 $R_1 = OH$ $R_2 = COC_3H_7$
52 $R_1 = OH$ $R_2 = Ac$
55 $R_1 = H$ $R_2 = COC_3H_7$
56 $R_1 = H$ $R_2 = Ac$



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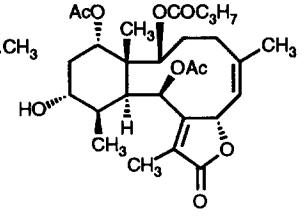
54 R = Ac



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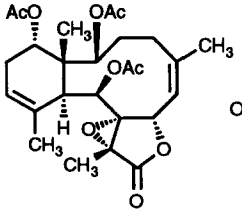

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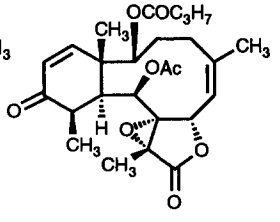

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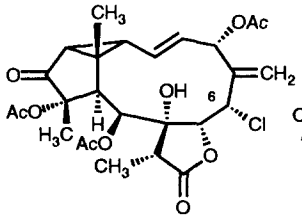
Detailed analysis of the spectral data and chemical correlation of briantheins X and Z established the gross structures of these highly oxidized, chlorinated diterpenes. X-ray diffraction confirmed the placement of the butyrate ester in brianthein Y and defined the absolute configuration for all three compounds.[39] Briantheins Y (**46**) and Z (**47**) have also been found in specimens of *B. asbestinum* collected in the Bahamas.[35] Two additional nonchlorinated diterpenes with the briarane skeleton, brianthein-W (**48**) and the unnamed compound **49**, were reported from the same organism shortly after. The structure of brianthein-W was defined from spectral data and X-ray diffraction studies.[40] The structure of brianthein **49** was described in 1986, but the spectral data for this metabolite were not reported.[41] Two of these compounds, brianthein Y (**46**) and brianthein W (**48**), have been tested to determine their effects on the feeding behavior of the grasshopper *Melanoplus bivittatus*, a major agricultural nuisance in the plain and plateau states.[40] Brianthein Y proved toxic at a high dose but inactive at a lower dose; brianthein W produced no deleterious effect at either dose.[42,43] Briantheins Y (**46**) and Z (**47**) showed viral inhibition in the *in vitro* mouse corona-virus assay, and **47** is also active *in vitro* against *Herpex simplex*-1 virus and P338 cells.[35] Brianthein Y was quite toxic at 250 ppm when subjected to the tobacco hornworm assay.[43] A unique antimicrobial pyranone, bissetone (**50**), was isolated from the very polar extracts of *B. polyanthes*. Spectroanalytical and chemical methods were used to develop plausible structures, but X-ray diffraction settled the correct structure and relative stereochemistry.[44] The (S,S) configuration of (-)-bissetone has been established by total synthesis from D-glucose.[45] In addition, a species of *Briareum* from Puerto Rico, which was identified as either *B. asbestinum* or *B. polyanthes*, contained nine new briarane diterpenes, which were named briareolides A-I (**51-59**).[46] Their structures were determined by spectroscopic methods, especially one-

and two-dimensional NMR. The structure and absolute stereochemistry of briareolide B (**52**) were determined by X-ray analysis.[46] Some of the briareolides [A(**51**), B(**52**), C (**53**), D (**54**), and E (**55**)] display antiinflammatory activity. However, these briarein type compounds, which are all nonchlorinated and highly oxygenated, were not cytotoxic against P-388 leukemia cells. All the briareolides except briareolide G (**57**), which has an α,β-unsaturated γ-lactone, contain an α,β-epoxy-γ-lactone, a feature found only in a few other briarane diterpenes isolated from *Briareum spp.*[46]

2.2. *Erythropodium* (family Briareidae)

Relatively uncommon, the only documented species of this genus, *Erythropodium caribaeorum*, can be found from southern Florida to the Virgin Islands. *E. caribaeorum* specializes in the biosynthesis of diterpenoids of the briarane skeleton class. These compounds, named erythrolides, are usually chlorinated at C-6 and are highly oxygenated.



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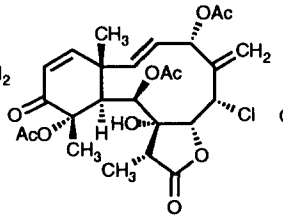

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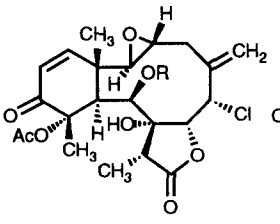
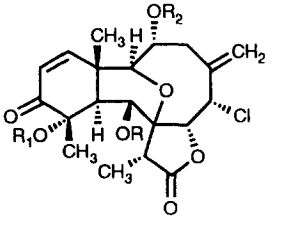
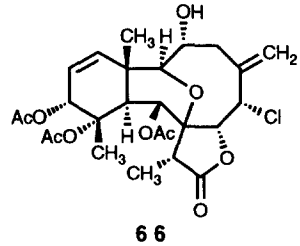


62 R = Ac
63 R = $COCH_2OAc$



64 R = R_1 = Ac R_2 = H
65 R = $COCH_2OAc$
R_1 = Ac R_2 = H
68 R = $COCH_2OH$
R_1 = Ac R_2 = H



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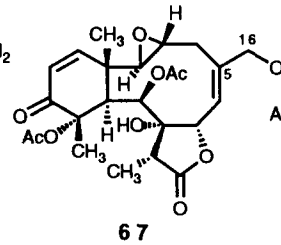

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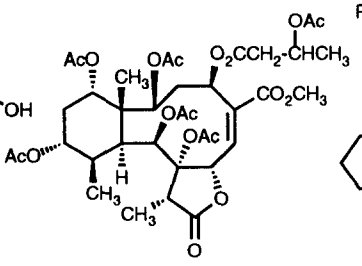

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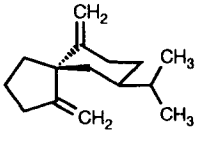


70

A. *Erythropodium caribaeorum* (Duchassaing & Michelotti)

Erythrolide A (**60**) and erythrolide B (**61**), isolated from the encrusting Caribbean gorgonian coral *Erythropodium caribaeorum* collected in Carrie Bow Cay, Belize, are two remarkably interesting chlorinated diterpenes. The structures of erythranes **60** and **61** were determined by X-ray analysis and from spectral data, respectively. Photochemical conversion of **61** into **60**, by a di-π-methane rearrangement, helped confirm their structural relationship.[47] Erythrolides A and B along with seven additional erythrolides have been isolated from *E. caribaeorum* collected in the U.S. Virgin Islands and Jamaica. The structures of erythrolides C-I (**62-68**) were elucidated from spectroscopic data.[46] All of these erythrolides, except erythrolide H (**67**), are chlorinated at the C-6 position. Erythrolide H (**67**) is unique among the compounds in this series in having a C-5,6 double bond and a

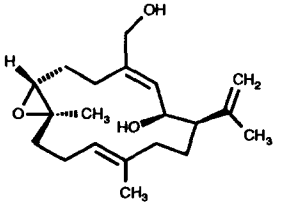
hydroxyl substituent at C-16 instead of an exocyclic C-5,16 double bond. *Erythropodium caribaeorum* obtained off the coast of Tobago yielded also the diterpenes erythrolide A (**60**), erythrolide B (**61**), and erythrolide E (**64**) along with a new diterpene, which has been designated erythrolide J (**69**). The structure of **69** was determined by high-resolution NMR.[48] Erythrodiene (**70**), a new sesquiterpene hydrocarbon of a rare structural class, has been isolated from *E. caribaeorum* collected at Chub Cay, Bahamas. The structure of **70** was assigned from spectral studies and through X-ray analysis of the diol obtained during ozonolysis of erythrodiene followed by reductive work up with $NaBH_4$.[49] Erythrodiene has been synthesized from 4-isopropylcyclohexanol in 8 steps and approximately 16% overall yield. The synthesis features a stereoselective intramolecular carbomercuration reaction as the key step.[50] When an extract of *E. caribaeorum* was incorporated into food strips, natural groups of fishes on the same reef from which the gorgonian had been collected were deterred from feeding. The feeding deterrent effects were present in a sample fraction containing erythrolides, but not in a fraction containing erythrodiene (**70**). Although the erythrolides appear to defend *E. caribaeorum* from reef predators, the function of sesquiterpene hydrocarbons remains unclear.[51]

2.3. *Eunicea* (family Plexauridae)

Gorgonians of the common Caribbean genus *Eunicea* were among the first marine invertebrates to be investigated chemically with over fifteen species documented. Although common and abundant, the genus *Eunicea* is taxonomically complex with many species varying only slightly in form and color. Consequently, secure species assignments were difficult to make and over the years a comprehensive chemical evaluation of this group was impeded. Animals belonging to this genus are usually rich in cembrane diterpenoids.

A. *Eunicea asperula* (Milne Edwards and Haime)

Asperdiol (**71**) is an antineoplastic agent (found in both *Eunicea asperula* and *Eunicea tourneforti* collected in the Caribbean region), whose structure was elucidated by X-ray analysis.[52] Asperdiol is unique in that it was the first cembrane lacking the lactone function that displays significant *in vitro* antitumor activity in the National Cancer Institute's KB, PS, and LE test systems. The ^{13}C-NMR spectral assignments of asperdiol,[53] its synthesis,[54,55] as well as the synthesis of two plausible precursors, have been reported.[56,57] Asperketals A-F (**72-77**) are diterpenes isolated from the Caribbean sea whip *E. asperula* collected along the offshore islands of the Tobago Cays. Compounds **72-76** are ketals and hemiketals related to the dilophol class of 10-membered-ring diterpenoids, while asperketal F (**77**) belongs to the fuscol class. Their structures were assigned on the basis of chemical and spectroscopic studies.[58] In addition, the isolation of the known diterpenoid obscuronatin (**78**) from the same organism was reported. Further studies to determine the stereochemistry of this compound were not pursued. The stereochemistry of asperketal B (**73**) was verified by an X-ray crystallographic experiment.[59]



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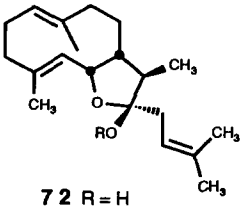
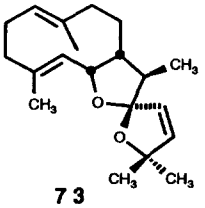


72 R = H
74 R = CH_3



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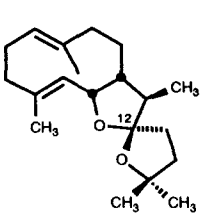

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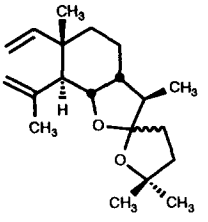

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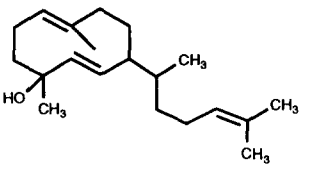


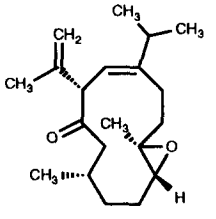
78

76 (epimer at C-12)

B. *Eunicea calyculata* (Ellis and Solander)

(Warty *Eunicea*)

Three representatives of the rare cubitane class were isolated as minor metabolites from the gorgonian *Eunicea calyculata* collected in Belize and the Bahamas Islands. The structure of the crystalline metabolite, calyculone A (**79**), was solved by single-crystal X-ray diffraction. The structures of calyculones B (**80**) and C (**81**) were proposed from comprehensive spectral analyses.[60] These compounds exemplify the rearranged cubitane class of diterpenoids. The cubitane carbon skeleton and the pseudopterane skeleton are the only known examples of a 12-membered monocyclic diterpenoid ring system that contains two isopropyl groups. In addition, the cembranoid diterpenoid crassin acetate was found as a minor metabolite.



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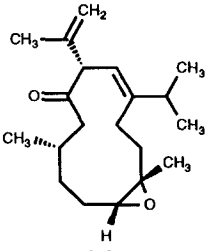

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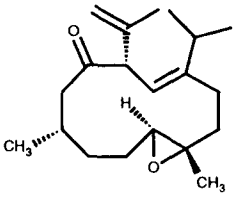

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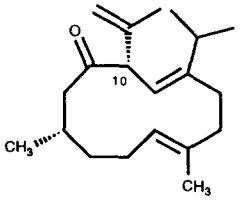
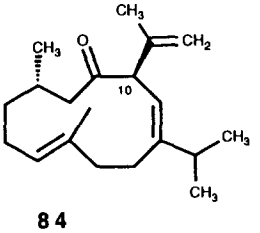


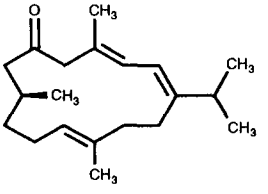
82

83 (epimer at C-10)



84

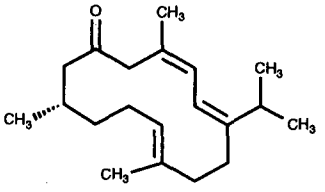
85 (epimer at C-10)



86

Isolation of crassin acetate from a *Eunicea* species is not surprising, however, since both *Eunicea* and *Pseudoplexaura* are taxonomically within the same family Plexauridae. The isolation of both diterpenoid ring systems from the same organism supports the theory that the cembranoid carbon skeleton is a logical biosynthetic precursor to the irregular isoprenoid cubitane ring system.[60] Seven diterpenoids, calyculones D (**82**), E (**83**), F

(**84**), and G (**85**), (1*E*,3*E*,11*E*)-1,3,11-cembratrien-6-one (**86**), (1*Z*,3*Z*,11*E*)-1,3,11-cembratrien-6-one (**87**), and (1*E*,3*Z*,11*E*)-1,3,11-cembratrien-6-one (**88**), from *E. calyculata* collected along the offshore islands of the Tobago Cays, were identified by spectroscopic methods and conversion of cembratriene **86** into the calyculones **82-85** by a photochemically induced 1,3-acyl migration.[61] We have here the first example of a 1,3-acyl migration in natural products and the first ring contraction involving the cembrene skeleton. This observation suggests that a similar cembrene ring contraction may also be responsible for production of the pseudopterane class of rearranged diterpenoids. Several dolabellane diterpenoids have been ascribed erroneously to *E. calyculata* (see reference 65).



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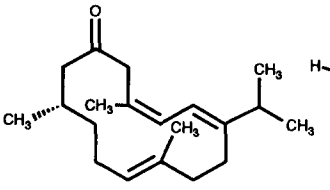

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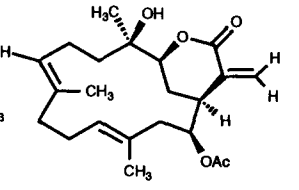
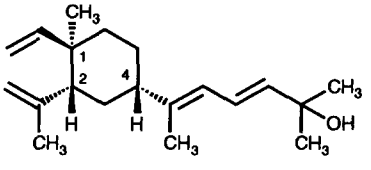


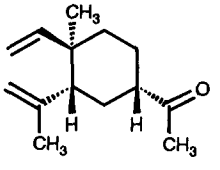
Crassin acetate

C. *Eunicea fusca* (Duchassaing and Michelotti)

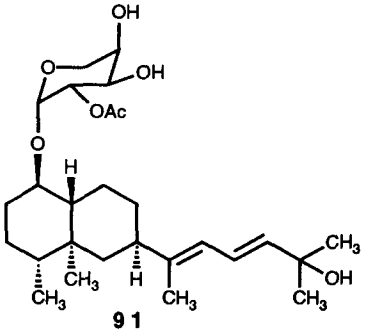
Fuscol (**89**) is an elemene-type diterpene that has been isolated from the gorgonian *Eunicea fusca* collected near South Caicos, W.I.[62] Although the data collected did not permit unequivocal assignment of the stereochemistry at C-4 in fuscol, the isolation of ketone **90** from the same animal implies that the side chain should be equatorial. An *E* configuration could be assigned to the disubstituted double bond. However, the geometry of the trisubstituted double bond could not be specified in the original report although it was later assigned as *E*.[63] The structures of **89** and **90** were identified by spectroscopic methods.[62] The total synthesis of fuscol, using a bicyclo[2.2.2]octane derivative prepared from D-mannitol as a synthetic precursor, has been described.[64] This synthesis indicated the absolute configurations of fuscol to be 1R, 2R, 4S. Fuscosides A (**91**), B (**92**), C (**93**), and D (**94**) are four diterpenoid arabinose glycosides isolated from *E. fusca* collected during an expedition to Martinique and the Tobago Cays and identified on the basis of chemical and spectral studies.[63]



89



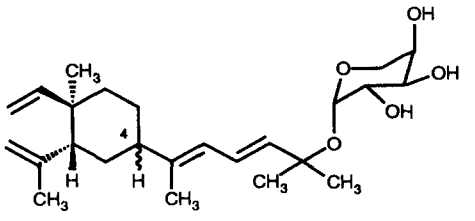
90



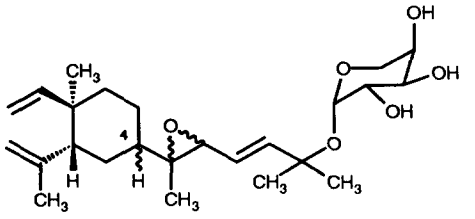
91

The spectral data of **92**, **93**, and **94** could not be used to determine the relative stereochemistry at C-4. Fuscoside A (**91**) possesses a novel carbon skeleton that has a bicyclic component related to the eremophilane class of

sesquiterpenoids, whereas fuscosides B-D are glycosides possessing fuscol (**89**) aglycons. Fuscosides A and B (**91**, **92**) are effective topical antiinflammatory agents with potencies equivalent to indomethacin and manoalide, two potent nonsteroidal antiinflammatory drugs. Fuscoside B (**92**) selectively inhibits the synthesis of leukotrienes LTB_4 and LTC_4, but not PGE_2, in the mouse peritoneal macrophage. This behavior suggests that **92** is a selective inhibitor of leukotriene synthesis. Samples of *E. fusca* collected in the Florida Keys and at St. Croix Island showed the same chemical compositions found in the animals from the earlier Martinique and Tobago Cays collections.[63]



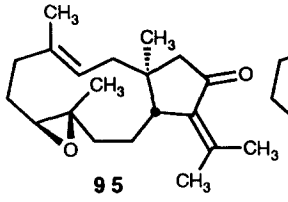
92



93 (RR or SS at the epoxide)
94 (bisepimer at the epoxide)

D. *Eunicea laciniata* (Duchassaing and Michelotti)

Two bicyclic diterpenoids of the dolabellane ring system, 7(S),8(S)-epoxy-13-keto-1(S),11(R)-dolabell-3(*E*),12(18)-diene (**95**) and 13-keto-1(S),11(R)-dolabell-3(*E*),7(*E*),12(18)-triene (**96**), were isolated from the Caribbean sea whip *Eunicea laciniata*[65] collected in Belize and in the Bahamas Islands. Their structures were assigned on the basis of chemical and spectral studies.[66] The facile BF_3-induced transannular cyclization of **95** to produce tricyclic compounds of the dolastane ring system revealed the chemical relationship between these two diterpenoid classes. Palominol is a dolabellane diterpene isolated from *E. laciniata* collected in Puerto Rico that was identified incorrectly as **97** by interpretation of spectral data and chemical evidence.[67] A subsequent investigation of *E. laciniata* collected at Tobago, produced four additional dolabellane diterpenes (**98**-**101**) in addition to palominol.



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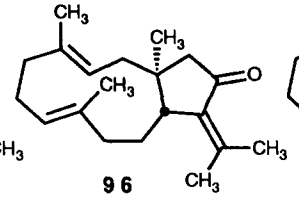
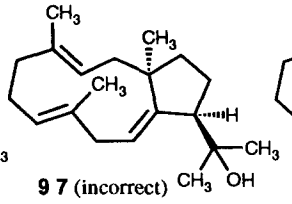
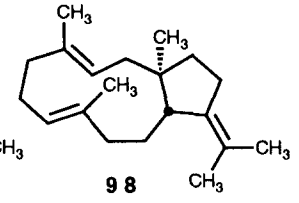


96



97 (incorrect)



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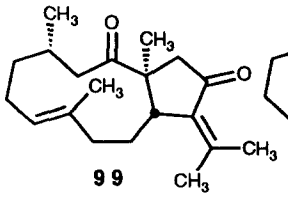

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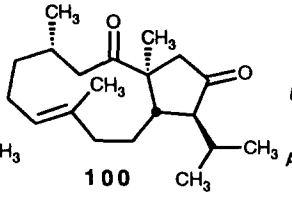

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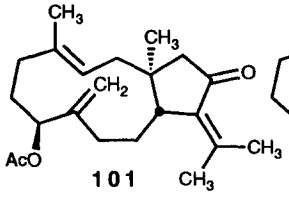

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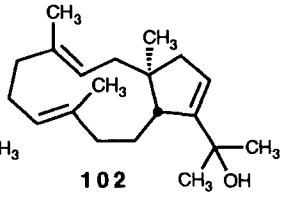
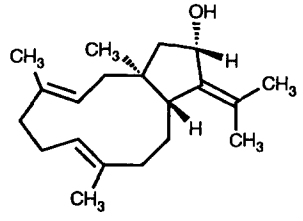
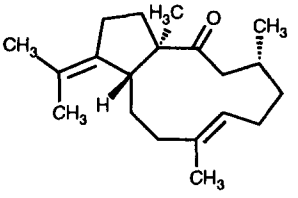


102

Their structures were elucidated by combined spectra and chemical methods and in that study the researchers established that the structure of palominol should be revised from **97** to **102**.[68] A brine shrimp assay, which was used as a simple lethality test to screen for biological activity in palominol, produced a 0% death response at an initial concentration of 30 μg/mL after a 24 hour count period. When screened for antimicrobial activity palominol was found to inhibit weakly the growth of Gram negative bacteria.[67] Palominol also displayed modest cytotoxic activity (IC_{50} = 10 μg/mL) against the human colon (HCT 116) cell line.[69] Isopalominol (**103**) along with dolabellanes **96**, **98**, and **102** were isolated from a specimen of *E. laciniata* collected from a different location at Puerto Rico. The structure of isopalominol, which also displayed weak cytotoxic activity against HCT 116 cells (IC_{50} = 30 μg/mL), was defined by spectral and chemical methods.[69] Five new dolabellane diterpenes, edunone (**104**), eduenone (**105**), edudione (**106**), edunol (**107**), and isoedunol (**108**), were isolated from *E. laciniata* collected near the east coast of Puerto Rico. The structures of **104**-**108** were established on the basis of spectral evidence. Dolabellane diterpenes **104**, **105**, **106**, and **107** displayed modest cytotoxicity against HeLa cells.[70] Dolabellanes have been prepared by the intramolecular condensations of α-sulfonyl carbanions with α,β-unsaturated aldehydes[71] and through an oxy-Cope rearrangement route.[72]



103



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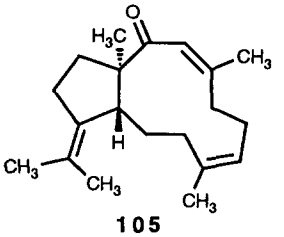

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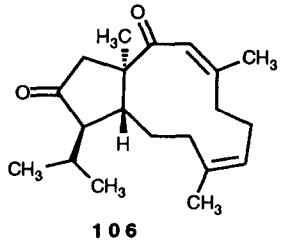

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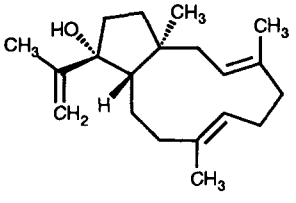

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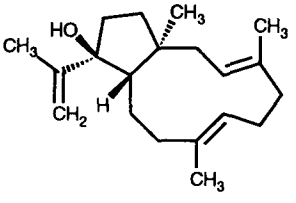


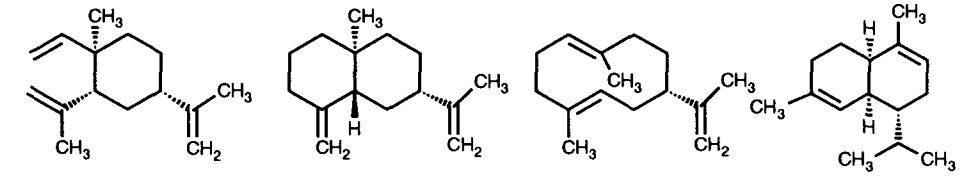
108

E. *Eunicea mammosa* (Lamouroux)

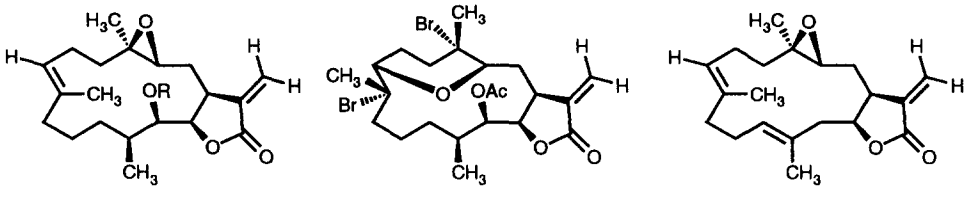
(Mammillated *Eunicea*)

Sesquiterpene hydrocarbons make up 0.8% of the dry weight of *Eunicea mammosa*.[3] Specimens of *E. mammosa* taken at Bimini, the Bahamas, contained several volatile hydrocarbons, some of which were subsequently identified as (+)-β-elemene (**109**), (-)-β-selinene (**110**) and (-)-germacrene-A (**111**).[5,73] Specimens collected at Jamaica and the Florida Keys contain (+)-α-muurolene (**112**) as the principal sesquiterpene hydrocarbon.[3,74] A direct route to (-)-β-selinene (**110**) via a site-specific, regioselective, Diels-Alder reaction, has been described.[75] Eupalmerin acetate (**113**) has been reported to occur in *E. mammosa* from Puerto Rico and in *Eunicea palmeri* and *Eunicea succinea* collected near Miami, Florida.[3,5,76,77] Its structure was established by chemical and spectral studies, and its absolute configuration was determined by X-ray anaysis of

crystalline eupalmerin acetate.[78] The same workers also determined the X-ray structure of the interesting dibromo tetrahydropyran derivative **114** obtained from **113** by reaction with bromine.[79] Compound **114** resulted from transannular participation of the epoxide oxygen in the reaction at the double bond, and possessed the configurations expected for a concerted process. The complete structural assignment of eupalmerin acetate (**113**) on the basis of extensive 2D-NMR studies, has been reported.[80] *In vitro* screening data for eupalmerin acetate showed potent cytotoxicity against CHO-K1 cells and antimicrobial activity against *Shigella flexneri* and *Proteus vulgaris* (MIC = 1 μg/mL).[80] Eupalmerin acetate, like other related cembranolides, displays strong anticiliary action[81-84] and functions as an uncharged noncompetitive inhibitor that displaces [^{3}H]PCP from its high-affinity binding site.[85] Cembranolide **113** inhibits with a similar potency the muscle (IC_{50}=6.4 μM) and electric organ (IC_{50}=4.9 μM) acetylcholine receptors (AChR's) expressed in *Xenopus laevis* oocytes.[85] Euniolide (**115**) has been found in significant amounts in specimens of *E. mammosa* collected off the west coast of Puerto Rico. The structure of this γ-lactonic cembranolide, which showed significant cytotoxicity against CHO-K1 cells, was assigned on the basis of spectral analysis.[76] The total synthesis of **115**, under the name isolobophytolide, has been reported.[86,87] Eupalmerin (**116**) is a minor constituent of *E. mammosa* from Puerto Rico.[88]

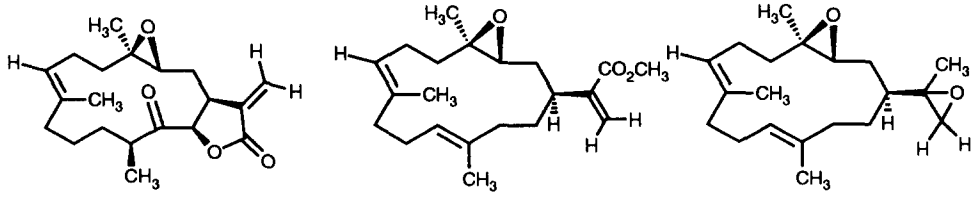


109 **110** **111** **112**



113 R = Ac
116 R = H

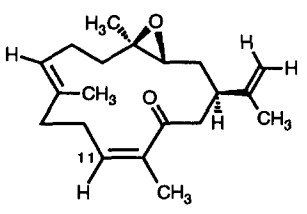
114 **115**



117 **118** **119**

The structure of this γ-cembranolide, which showed significant cytotoxicity against CHO-K1 cells, was assigned on the basis of spectral analysis.[88] The structures of six additional cembrane derivatives, eupalmerone (**117**), pseudoplexauric acid methyl ester (**118**), (7*E*,11*E*)-(1S,3R,4R)-3,4;15,17-diepoxycembra-7,11-diene (**119**), (-)-eunicenone (**120**), cembranoid chlorohydrin **121**, and diketone **122** (tentative structure), were determined by

means of spectroscopic analyses and chemical methods following their isolation from specimens of *E. mammosa* collected in Desecheo Island near Puerto Rico.[89]



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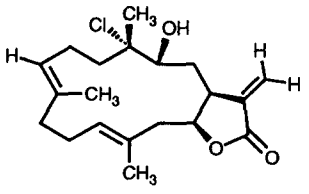

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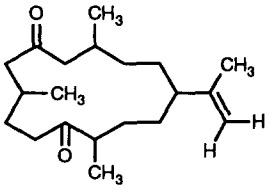
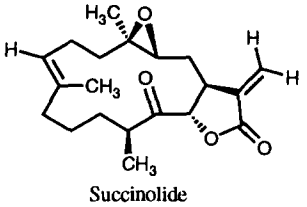
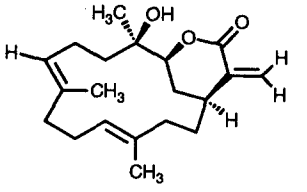


122 (tentative)

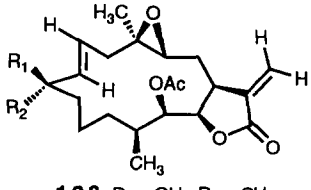


Succinolide

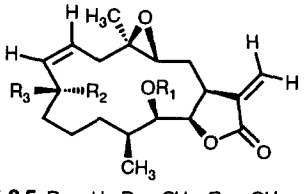


14-Deoxycrassin

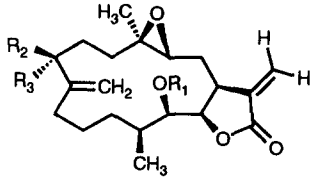
Also isolated from the same organism were four known α-methylene-γ-lactone derivatives, namely, euniolide (**115**), eupalmerin (**116**), eupalmerin acetate (**113**), and succinolide, and one α-methylene-δ-lactone 14-deoxycrassin. (-)-Eunicenone (**120**), a rare cembranoid diterpene having the uncommon 11-cis double bond, was found to be the (-)-antipode of a known cembranoid isolated from a South Pacific soft coral. The structure and stereochemistry of chlorohydrin **121** were established in conjunction with a single crystal X-ray analysis.[89] In addition to **113** (major), a large collection of *E. mammosa* from a different location near Puerto Rico, contained eighteen new γ-cembranolide diterpenes, which have been named collectively as the uprolides (**123-140**). The structure and absolute configuration of uprolide-A acetate (**123**) were determined by X-ray crystallographic and spectral analyses, and the structures of the remaining uprolides were elucidated from spectroscopic data and chemical evidence. Many of the uprolides are toxic *in vitro* to several human tumor cell lines.[90,91]



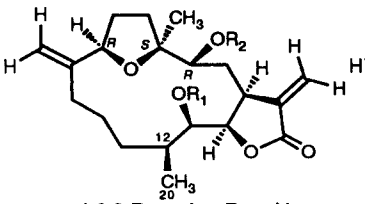
123 R_1 = OH R_2 = CH_3
124 R_1 = CH_3 R_2 = OH



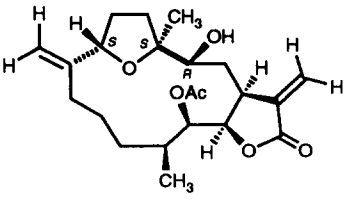
125 R_1 = H R_2 = CH_3 R_3 = OH
126 R_1 = Ac R_2 = CH_3 R_3 = OH
127 R_1 = Ac R_2 = CH_3 R_3 = OAc
128 R_1 = H R_2 = OH R_3 = CH_3
129 R_1 = Ac R_2 = OH R_3 = CH_3
130 R_1 = Ac R_2 = OAc R_3 = CH_3



131 R_1 = H R_2 = OH R_3 = H
132 R_1 = Ac R_2 = OH R_3 = H
133 R_1 = Ac R_2 = OAc R_3 = H
134 R_1 = Ac R_2 = H R_3 = OH
135 R_1 = Ac R_2 = H R_3 = OAc



136 R_1 = Ac, R_2 = H
137 R_1 = R_2 = H



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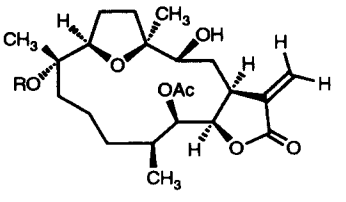
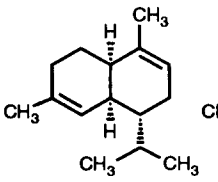


139 R = Ac
140 R = CH_3

F. *Eunicea palmeri* (Bayer)

(Palmer's *Eunicea*)

Eunicea palmeri from Miami contains (+)-α-muurolene (**112**) and (+)-β-copaene (**141**).[3] *E. palmeri* has also been reported to contain (+)-β-ylangene (**142**),[74] although this claim was later noted to be incorrect.[5] A study on a new route to the total synthesis of (±)-α- and β-copaene and (±)-ylangene has been reported.[92] The γ-cembranolide eupalmerin acetate (**113**) was isolated from the gorgonian *Eunicea palmeri* collected near Miami, Florida.[77] Eupalmerin acetate has been reported to occur also in the Caribbean gorgonians *E. succinea* and *E. mammosa*.[3,5,6,76]



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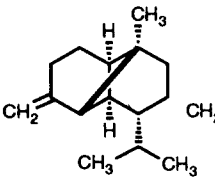

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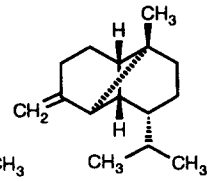

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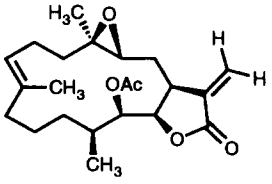
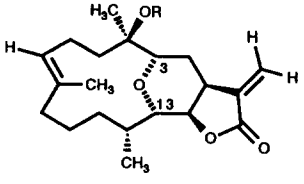


113

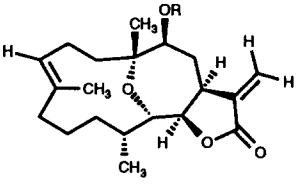
G. *Eunicea succinea* (Pallas)[93]

Collections made in the Bahamas (Bimini) yielded the antibacterial 3,13-oxabridge γ-lactone eunicin (**143**).[20] The structure of eunicin was proposed initially on chemical and spectral grounds and confirmed by X-ray crystallographic analysis of the corresponding iodoacetate **144**.[94,95] The total assignment of the ^{13}C-NMR spectrum of eunicin by 2D-NMR spectroscopy has been reported.[96] Collections of specimens from Jamaica yielded the related cembranolide jeunicin, which was unambiguously assigned structure **145** by crystallographic analysis of the p-iodobenzoate derivative **146**.[97] The identities of all the hydrogen and carbon resonances of jeunicin have been established through 2D-NMR techniques.[98] Both eunicin (**143**) and jeunicin (**145**) were found to be cytotoxic against the National Cancer Institute's KB cell line.[99] Examination of specimens collected in Curaçao led to the discovery of cueunicin (**147**), which occurs largely as the acetate **148**.[100,101] The structure of cueunicin (**147**) was proposed on the basis of spectral analyses and chemical degradation and that of cueunicin acetate (**148**) by X-ray crystallography.[102] A systematic fractionation of the crude extract of specimens collected in Bimini led to the discovery of (13αH, 14βH)-jeunicin (**149**). The molecular structure and absolute configuration of **149** (also known as 13,14-bis-epijeunicin)[6] were determined by X-ray crystallography.[99] This compound displayed *in vitro* cytotoxicity against KB and LE cell lines. The marine cembranolide peunicin (**150**) was isolated as the major component from the hexane extract of *E. succinea* collected in Panama.[103] The

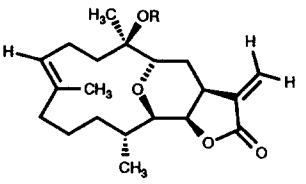
molecular structure and absolute configuration were determined from X-ray data.[104] Peunicin (**150**) is cytotoxic *in vitro* against KB and PS cell lines and, like eunicin (**143**), jeunicin (**145**), and eupalmerin acetate (**113**), shows strong anticiliary action.[81-84] Epipeunicin (**151**) is an unstable γ-lactonic cembranolide diterpene isolated from the same specimen of *E. succinea*, and its proposed structure is based on spectral data.[6,103]



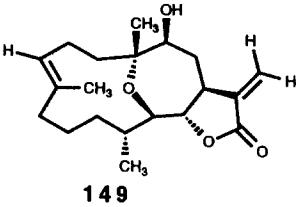
143 R = H
144 R = $COCH_2I$



145 R = H
146 R = COC_6H_4I



147 R = H
148 R = Ac



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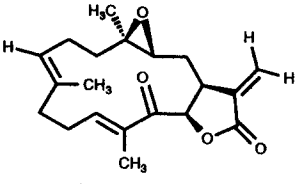

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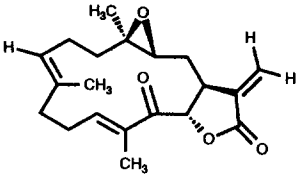
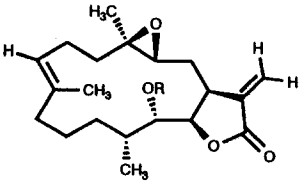
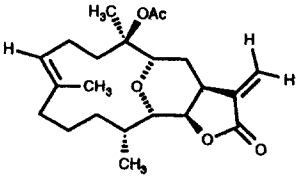


151

The γ-cembranolide 12,13-bisepieupalmerin (**152**) was isolated from specimens of *E. succinea* collected in St. Croix, U.S. Virgin Islands, and identified by X-ray methods.[105] 12,13-Bisepieupalmerin possesses the correct stereochemistry to be a biosynthetic precursor for the related cembranolides eunicin (**143**) and jeunicin (**145**), which were found to occur with **152** in the same organism. Eunicin (**143**) and its acetate **153** were obtained from a South Caicos collection.[105] Also from these collections complex mixtures of hydrocarbons in which (+)-β-elemene (**109**), (-)-germacrene-A (**111**), (+)-α-muurolene (**112**), (+)-β-copaene (**141**), and (+)-β-epibourbonene (**154**) were identified.



152 R = H
155 R = Ac



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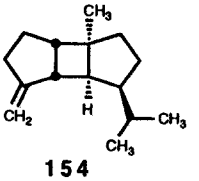
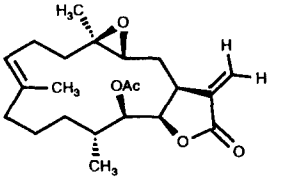


154

Euniolide (**115**), 12,13-bisepieupalmerin (**152**), and eunicin (**143**) were also found in Puerto Rican *E. succinea* specimens.[76] During this study 12,13-bisepieupalmerin was successfully converted chemically to eunicin (**143**) and jeunicin (**145**) under acidic conditions (SiO_2, P_2O_5) and thus provided evidence to establish **152** as their logical biosynthetic precursor. All three cembranolides **115**, **143**, and **152** displayed strong *in vitro* cytotoxicity against CHO-K1 cells.[76] In addition, 12,13-bisepieupalmerin and eunicin were found to be active

pharmacologically on the nicotinic acetylcholine receptor (AChR). The researchers concluded that these compounds act as noncompetitive inhibitors of peripheral AChR.[106] Extraction of a freshly collected sample of *E. succinea* from a different location near Puerto Rico yielded 12,13-bisepieupalmerin acetate (**155**), 12-epi-eupalmerin acetate (**156**), and succinolide (**157**) in addition to euniolide (**115**), 12,13-bisepieupalmerin (**152**), eunicin (**143**), and cueunicin (**147**). The structures of **155-157** were deduced spectroscopically, and those of **155** and **157** were confirmed by chemical correlations. All three cembranolides exhibited strong *in vitro* antitumor activity against several human tumor cell lines.[107]



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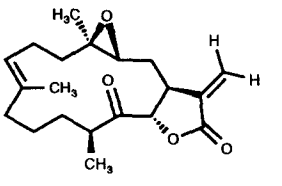

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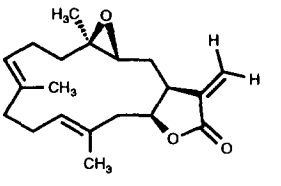
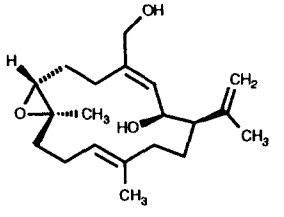


115

H. *Eunicea tourneforti* (Milne Edwards and Haime)

There are no data available with regard to the sesquiterpene hydrocarbon composition of the gorgonian *Eunicea tourneforti*. Asperdiol (**71**), an antineoplastic agent found in the Caribbean gorgonians *E. tourneforti* and *E. asperula*, has been discussed already.[52]

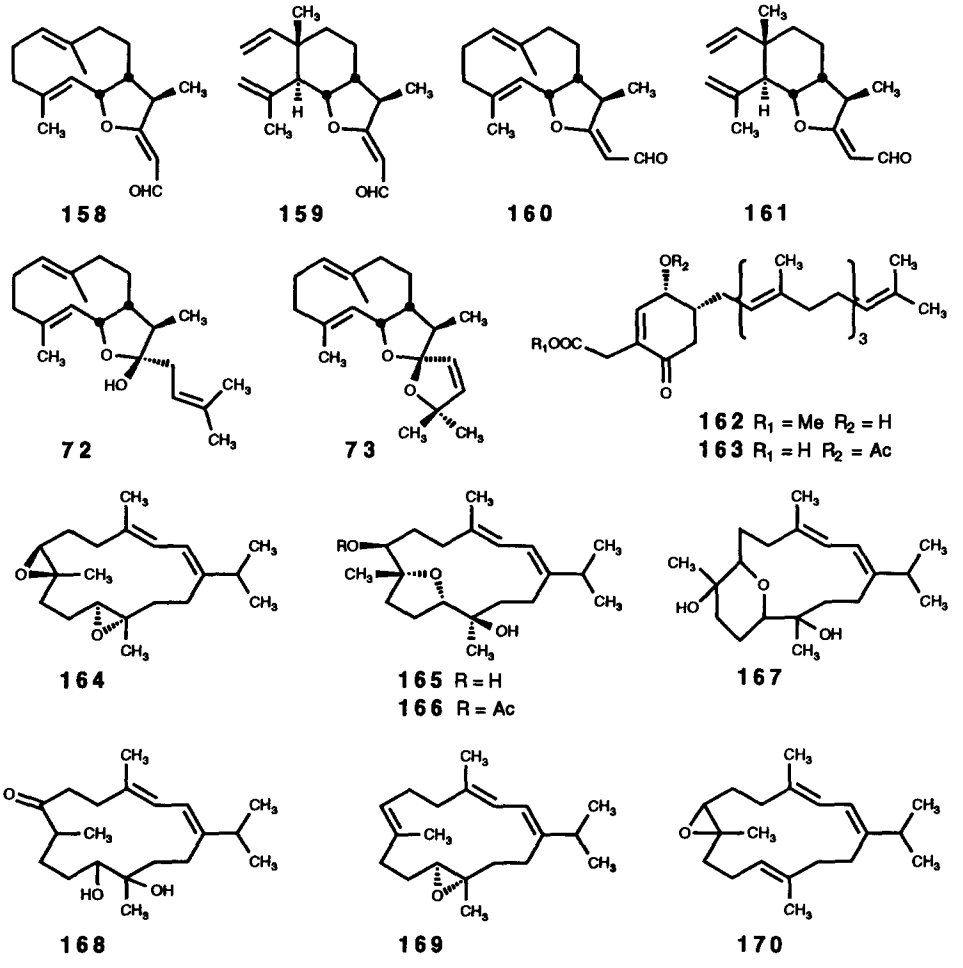


71

I. Other *Eunicea spp.*

Norasperenals A-D (**158-161**) are trisnorditerpenoids isolated from an undescribed Caribbean species of *Eunicea* collected in the Florida Keys. The structures of the isomeric norasperenals **158-161** were determined by combined spectral methods. Two previously described cyclic ketals, asperketal A (**72**) and asperketal B (**73**), were also isolated from the same animal.[108] The norasperenals appear to be produced by the loss of a C_3 fragment from a precursor closely related to the asperketals. Eunicenones A (**162**) and B (**163**), compounds of a mixed biosynthetic origin, were isolated from an undescribed species of the Caribbean gorgonian genus *Eunicea* collected in the Tobago Cays. The structures of these compounds, which are diterpenoid cyclohexanones of a new skeletal class related in part to the linear diterpenoid-substituted quinones and hydroquinones found in various plants and animals, were determined by spectral and chemical methods. The absolute stereochemistries of **162** and **163** were determined by CD methods.[109] Also isolated from an undescribed Caribbean gorgonian of the genus *Eunicea* collected in the Tobago Cays were five cembradiene diterpenoids **164-168** and two known

compounds (**169** and **170**) that have been previously isolated from Australian soft corals. The structures of these compounds were assigned on the basis of chemical and spectral studies, and the relative stereochemistry of cembradiene **166** was defined by X-ray crystallographic methods.[110]



2.4. *Gorgonia* (family Gorgoniidae)

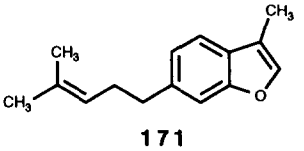
Among the sea fans of the West Indian region there is always a noticeable variation in color, size of meshes, flattening of branches, and form of spicules. The extremes of variation may differ from one another to a marked degree. Six species have been documented that can be found along the Bermudas and south Florida to Curaçao.

A. *Gorgonia ventalina* (Linnaeus)

(Common sea fan)

A liquid C_{15} benzofuran, furoventalene (**171**), was isolated from the steam volatile material of the purple sea fan, *Gorgonia ventalina*, collected at Bermuda. The structure of **171** was determined by interpretation of

spectral data and confirmed by total synthesis.[111] This nonfarnesyl sesquiterpene could be an artifact produced during the steam distillation of the gorgonian extract. When heated with concentrated sulfuric acid, *G. ventalina* liberates free iodine vapors. The iodine probably arises from the thermal degradation of covalently bonded iodine from 3,5-diiodotyrosine (**172**).[112] Extracts of this gorgonian collected in the Bahamas were reported to contain at least a dozen nonpolar terpenoids.[113] However, no structures were described in that report. Fractions containing these compounds reduced feeding by natural assemblages of tropical fishes by 87%; sclerites reduced feeding by fishes by 95%. In ship-board feeding experiments, artificial diet containing *G. ventalina* crude extracts was consumed 49% less by *Cyphoma gibbosum* (the flamingo tongue snail), an ovulid predatory gastropod that specializes on gorgonians.[113]



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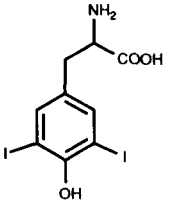


172

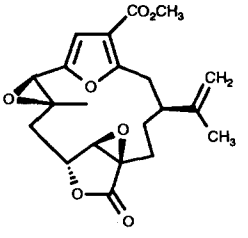
2.5. *Leptogorgia* (family Gorgoniidae)

There are five documented species of the genus *Leptogorgia* that occur along parts of the western Atlantic Ocean from the Chesapeake Bay to Brazil, including the Gulf of Mexico. Colonies of *L. setacea* are unbranched or with only one or two long, slender, flexible branches.

A. *Leptogorgia setacea* (Pallas)

("Spaghetti" coral)

The furanocembranolide 11β,12β-epoxypukalide (**173**) was isolated in trace quantities from the gorgonian *Leptogorgia setacea* collected in Mustang Island, Texas. The structure of **173** was determined from detailed ^{1}H- and ^{13}C-NMR analyses and comparison of these spectral data with those of closely related compounds.[114]



173

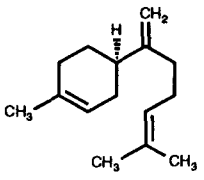
2.6. *Muricea* (family Plexauridae)

The genus *Muricea* can be found in the Bermudas, southern Florida and the Antilles, and in southern California to Panama. Six species have been documented. Colonies of *M. elongata* are bushy and commonly tall.

A. *Muricea elongata* (Lamouroux)

(Common *Muricea*)

Extraction of the gorgonian *Muricea elongata* from an undescribed location in the Caribbean region led to the isolation of the sesquiterpene hydrocarbons (+)-β-bisabolene (**174**), (-)-α-curcumene (**175**), and (-)-β-curcumene (**176**).[5,115] The identification of these sesquiterpenes was achieved by comparisons with authentic samples. Two stereoselective syntheses of optically active curcumenes have been reported.[116,117]



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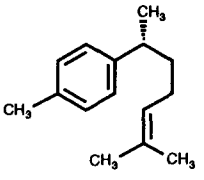

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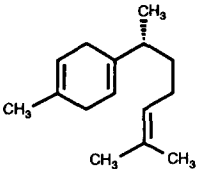


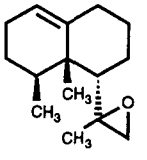
176

2.7. *Phyllogorgia* (family Gorgoniidae)

Several species and varieties of these leaf-corals have been described, largely because of their extraordinary variation in growth form. There is also a wide range of variation in the spicules. The gorgonian *P. dilatata* is a species endemic to Brazil.

A. *Phyllogorgia dilatata* (Esper)

A nardosinane sesquiterpene, 11,12-epoxynardosin-1(10)-ene (**177**), was isolated from the Brazilian gorgonian *Phyllogorgia dilatata*, and its structure has been deduced from chemical evidence and spectral data.[118]



177

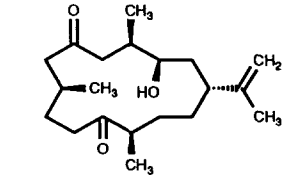
2.8. *Plexaura* (family Plexauridae)

There are five documented species belonging to the genus *Plexaura* in the West Indian region. The genus *Plexaura* occurs commonly in the Bermudas, southern Florida and the Gulf of Mexico south to Curaçao. The Indo-Pacific species attributed to this genus by various authors appear not to be congeneric with the West Indian species.[1] Gorgonians belonging to this genus are usually rich in cembrane diterpenes and prostanoids.

A. *Plexaura A* (spec. nov.)[119]

Plexaurolone (**178**) was first discovered from an undescribed gorgonian collected in Puerto Rico that appears to be related to the genus *Plexaura*, and that was found subsequently in the same species collected at Bonaire, Netherlands Antilles. The crystal structure and absolute configuration of the acetate derivative of plexaurolone were determined from three-dimensional X-ray diffraction data.[120] Plexaurolone (**178**) may represent the first example of a Caribbean cembranoid belonging to the α-series.[5] The same species collected at Tobago provided three new cembranoids, dihydroplexaurolone (**179**) and two dehydroplexaurolones **180** and

181, which also belong to the α-series. These specimens of *Plexaura A* also contained plexaurolone as the main constituent. The structure of **179** was established by X-ray crystallographic studies and those of **180** and **181** were established on the basis of spectral analyses and chemical modifications.[121]



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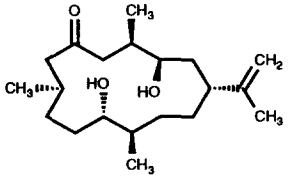

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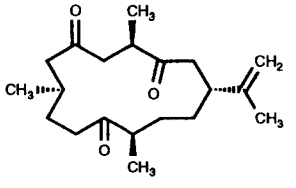

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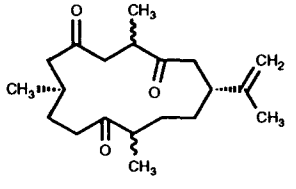
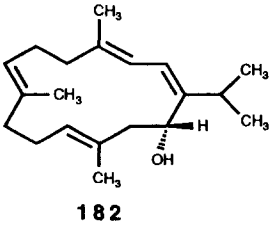


181

B. *Plexaura flexuosa* (Lamouroux)

(Bent *Plexaura*, sea rod)

The gorgonian *Plexaura flexuosa* from Puerto Rico was found to contain (1*E*,3*E*,7*E*,11*E*)-(14R)-cembra-1,3,7,11-tetraen-14-ol (**182**), the (-)-antipode of the potent antitumor promoter (+)-sarcophytol A (**183**). The bicyclic oxa-bridged 2,5-dihydrofuran-containing cembranoid diterpene (+)-marasol (**184**) was isolated as a minor constituent from samples of the same gorgonian. Their structures have been established through chemical and spectral studies.[122] Subsequent investigations by the researchers have shown that (-)-sarcophytol A (**182**) and (+)-marasol (**184**) are strongly cytotoxic against CHO-K1 and HeLa cells. A highly stereo- and enantioselective total synthesis of (+)-sarcophytol A (**183**) has been described, which could in principle be modified to obtain also (-)-sarcophytol A (**182**).[123-126] The synthesis of (±)-sarcophytol A benzyl ether has also been reported.[127]



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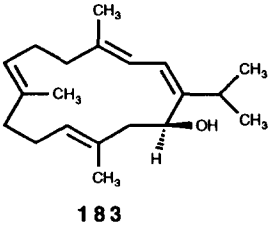

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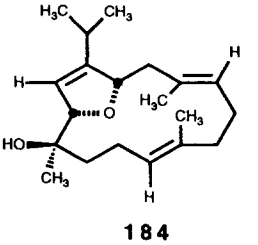
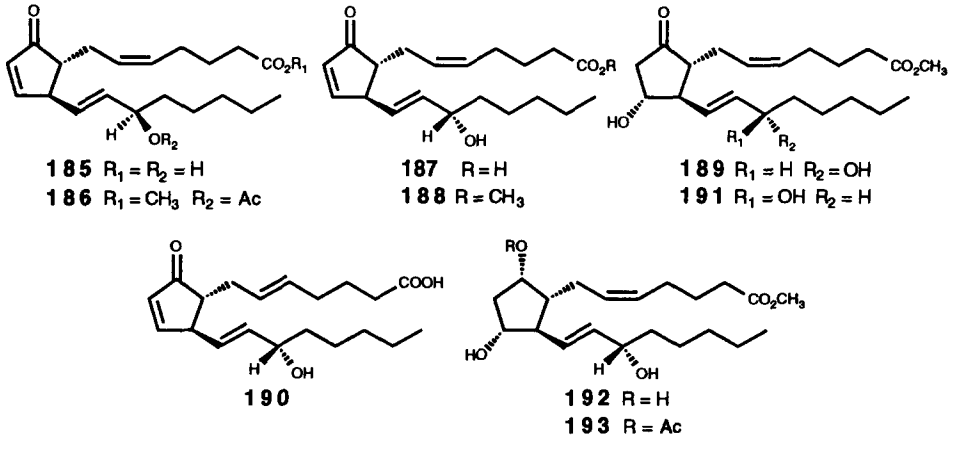


184

C. *Plexaura homomalla* (Esper)

(Black sea rod)

In 1969, Weinheimer and Spraggins reported the occurrence of relatively large quantities of two prostaglandin derivatives in the gorgonian *Plexaura homomalla* from coastal waters off Florida.[128] These compounds, 15-epi-PGA_2 (**185**) and its diester **186**, present in the air dried cortex to the extent of 0.2% and 1.3%, repectively, are epimeric with the potent hormones found in mammalians at the allylic hydroxyl center. They are devoid of the dramatic blood pressure lowering effect in dogs of PGA_2 itself. Most of the structure determination work was based on spectral data and chemical modifications, and was performed with the diester **186**.[128-130] These (15R)-prostaglandins, themselves possessed of no dramatic biological activity, were however, used as starting materials for the preparation of (15S)-prostaglandins such as PGE_2, $PGF_{2\alpha}$ and other closely-related highly active prostaglandins.[131-133] *Plexaura homomalla* collected in other locations throughout the Caribbean region has yielded prostaglandins with the (15S)-configuration [i.e. (15S)-PGA_2 (**187**), its methyl ester **188**, and (15S)-PGE_2 methyl ester (**189**)].[134] Also, both (15R)- and (15S)-prostaglandins may occur in some single specimens of this gorgonian. During the chromatographic purification of (15S)-PGA_2 obtained from *P. homomalla*, another natural prostaglandin, 5-trans-PGA_2 (**190**), was detected. Its structure was elucidated on the basis of spectral data and confirmed by chemical transformations.[135] The isolation and characterization of (15R)- and (15S)-prostaglandins A_2 and their esters from *P. homomalla* collected at Grand Cayman and the Florida Keys, have been described.[136] Small amounts of derivatives of prostaglandins (15R)-PGE_2 (**191**) and $PGF_{2\alpha}$ (**192**) were also reported. *P. homomalla* forma *kükenthali*, collected in Puerto Rico, yielded 50% of its weight as the mammalian prostaglandin (15S)-PGA_2 methyl ester (**188**). The freeze-dried gorgonian yielded (15S)-PGA_2 largely as the acetate of the methyl ester.[137] $PGF_{2\alpha}$-9-O-acetate methyl ester (**193**) was found as a natural product in extracts of *P. homomalla* collected in the Bahamas Islands. The structure of this prostaglandin derivative was assigned on the basis of spectral analysis.[138] Experiments performed underwater at Curaçao have shown that both (15R)-PGA_2 (**185**) and (15S)-PGA_2 (**187**) induce vomiting in fishes, which quickly learned aversion to pellets containing PGA_2. Thus, it was speculated that the PGA_2 of *P. homomalla* can serve as an effective defense against most predatory reef fish. These experiments, however, did not consider the role of PGA_2 as an allelopathic agent or as an antifoulant.[139]



Later data, however, suggested that the PGA_2 of *P. homomalla* is not used to compete allelopathically or to reduce fouling, but to provide protection from predators.[140] Interestingly, during a re-evaluation of the ichthyodeterrent role of prostaglandins in *P. homomalla*, it was found that the consumption of food strips containing the acetoxy methyl ester of (15R)-PGA_2 did not differ from consumption of control strips when presented to a natural assemblage of Caribbean coral reef fishes. However, treatment with the acetoxy acid, hydroxy methyl ester, and hydroxy acid of (15R)-PGA_2 inhibited consumption of food strips by reef fishes. Although the results of the latter study suggest that the esterified prostaglandins present in *P. homomalla* do not deter fish predators, these compounds may have very different effects on other potential predators of gorgonians, particularly invertebrates.[141,142] The mechanism of biosynthesis of prostaglandins of the A and E series from *P. homomalla*, which clearly follows a distinct pathway from the mammalian cyclooxygenase/endoperoxide route, has been the subject of intense research.[143-147] A major discussion of the chemistry and chemical ecology of *Plexaura homomalla* appeared in 1992.[9]

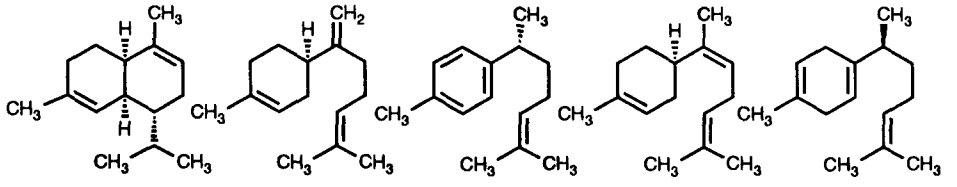
2.9. *Plexaurella* (family Plexauridae)

About six species of *Plexaurella* have been distinguished in the West Indian region. They occur in the western Atlantic from the Bermudas to Brazil. Gorgonians belonging to this genus are particularly rich in acyclic and cyclic sesquiterpenes.

A. *Plexaurella dichotoma* (Esper)

(Double-forked *Plexaurella*)

Plexaurella dichotoma from the Caribbean region has been reported to contain (+)-α-muurolene (**112**), (+)-β-bisabolene (**174**), (-)-α-curcumene (**175**), (+)-α-bisabolene (**194**), and (+)-β-curcumene (**195**).[3,5,74]



112 **174** **175** **194** **195**

B. *Plexaurella fusifera* (Kunze)

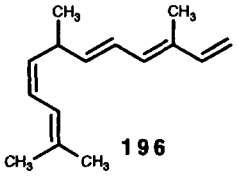
The gorgonian *Plexaurella fusifera* from the Caribbean region contains (+)-α-muurolene (**112**), (+)-β-bisabolene (**174**), (-)-α-curcumene (**175**), (+)-α-bisabolene (**194**), and (+)-β-curcumene (**195**).[3,5]

C. *Plexaurella grisea* (Kunze)

(Gray *Plexaurella*)

In addition to (+)-α-muurolene (**112**), (+)-β-bisabolene (**174**), (-)-α-curcumene (**175**), (+)-α-bisabolene (**194**), and (+)-β-curcumene (**195**),[3,5] two acyclic sesquiterpene hydrocarbons, **196** and **197**, have been reported from the gorgonian *Plexaurella grisea* collected near South Caicos Island. In addition, (+)-santalene (**198**), a well-known compound from terrestrial sources, was also isolated. The structures of **196** and **197** were

assigned from their spectral data and chemical evidence.[148] The acyclic sesquiterpene ketone **199** was isolated from a specimen of *P. grisea* collected in Puerto Rico and its structure was established from spectral data.[149]



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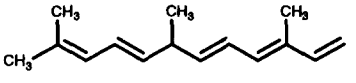

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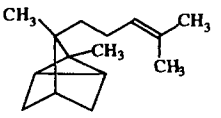

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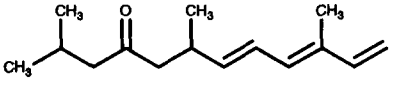
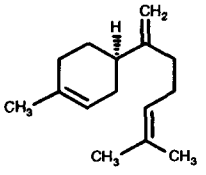


199

D. *Plexaurella nutans* (Duchassaing & Michelotti)

Extraction of the gorgonian *Plexaurella nutans* from an undescribed location in the Caribbean led to the isolation of the sesquiterpene hydrocarbons (+)-β-bisabolene (**174**), (-)-α-curcumene (**175**), and (-)-β-curcumene (**176**).[5,115]



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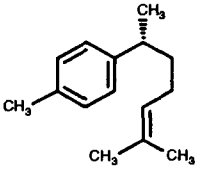

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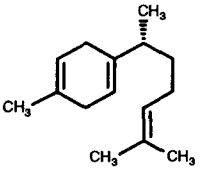

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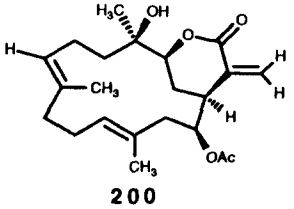
2.10. *Pseudoplexaura* (family Plexauridae)

The genus *Pseudoplexaura* is extremely common and abundant and can be found distributed along the Bermudas, Florida Keys, Bahamas and Antilles regions. Four species of *Pseudoplexaura* have been documented. This genus is characterized by a complex mixture of sesquiterpene hydrocarbons that have been consistently found in many species from well-separated geographical locations.[3]

A. *Pseudoplexaura crucis* (spec. nov.)

Trace quantities of the δ-lactonic cembranolide crassin acetate (**200**) were found to be responsible for the marginal KB activity of *Pseudoplexaura crucis* collected near St. Thomas, U.S. Virgin Islands. Crassin acetate has also been found in other gorgonians belonging to the genus *Pseudoplexaura* (see below).[150]



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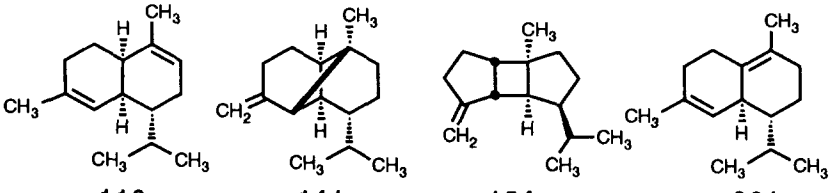
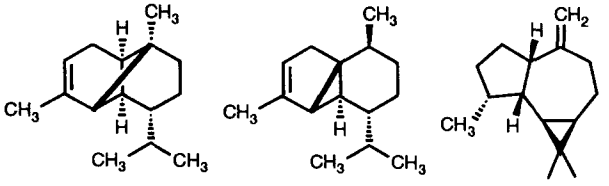
B. *Pseudoplexaura flagellosa* (Houttuyn)

P. flagellosa contains (+)-α-muurolene (**112**), (+)-β-copaene (**141**), (+)-β-epibourbonene (**154**), (-)-δ-cadinene (**201**), (+)-α-copaene (**202**), (+)-α-cubebene (**203**), and alloaromadendrene (**204**).[3,5] Synthetic studies on alloaromadendrane and aromadendrane-type compounds have been described.[151] The cembranolide crassin acetate (**200**) has also been isolated from *P. flagellosa* collected near Pigeon Key, Florida.[150]



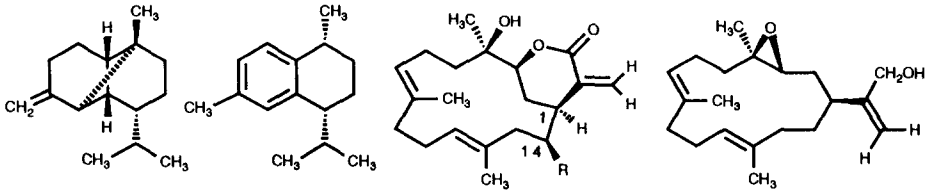
112 **141** **154** **201**



202 **203** **204**

C. *Pseudoplexaura porosa* (Houttuyn)

In addition to (+)-ylangene (**142**),[74] *Pseudoplexaura porosa* (originally referred to as *P. crassa*) contains the same complex mixture of sesquiterpene hydrocarbons (**112**, **141**, **154**, **201**, **202**, **203**, and **204**) described above.[3,5] (+)-Calamenene (**205**), which could be an artifact, was also isolated during steam distillation of the hydrocarbon fraction of *P. porosa*.[5,74,152] The synthesis of (±)-cis-calamenene has been reported.[153] The gorgonian *P. porosa* was among the first gorgonians to be investigated and,[20] after extensive chemical studies, the structure of crassin acetate (**200**) was elucidated by X-ray analysis of the corresponding p-iodobenzoate ester.[74,154] It was first isolated by Ciereszko, Sifford, and Weinheimer from specimens of *P. porosa* collected in Bermuda and Florida.[20] Ciereszko later reported that this diterpene lactone was present in very high concentrations in the symbiotic zooxanthellae isolated from this gorgonian.[22] The isolation, localization, and biosynthesis of crassin acetate in *P. porosa* have been studied extensively.[155,156]

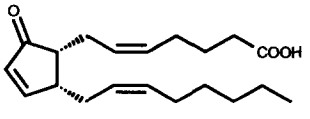


142 **205** **200** R = OAc **208**

206 R = OH

207 R = H

Subsequently, crassin acetate was also isolated from several gorgonians of the genus *Pseudoplexaura*, namely *P. flagellosa*, *P. wagenaari*, and *P. crucis*.[150,157] This lactone showed substantial activity in the KB test, an *in vitro* bioassay against a human carcinoma of the nasopharynx, and against P-388 lymphocytic leukemia.[150] The spectral characteristics of crassin acetate,[60] its total ^{13}C-NMR assignment,[158] and the total synthesis of crassin (**206**), obtained by saponification of crassin acetate, have been reported.[159-161] An intramolecular alkylation of a lithioalkyne with an allylic bromide has produced the 14-membered ring of crassin acetate (**200**).[162] A nitrile oxide cycloaddition furnished the lactone and the stereocenters at C-1 and C-14. The total synthesis of (±)-crassin acetate methyl ether has also been reported.[163] Crassin acetate (**200**), which may constitute as much as 1.5-2% of the dry weight of the cortex of the gorgonian *P. porosa*, functions in the marine ecosystem, along with other related compounds, by decreasing the viability of ciliated larvae of organisms which compete with gorgonians for space.[164,165] Recently, two additional cytotoxic antitumor diterpenoids of the cembrane class related to crassin acetate, named 14-deoxycrassin (**207**) and pseudoplexaurol (**208**), were isolated from a specimen of *P. porosa* collected in Puerto Rico. Both compounds displayed potent antitumor activity when screened against a small panel of five human tumor cell lines. The structures of **207** and **208** were established from spectral and chemical data.[166] Compound **207** appears to be a stereoisomer of the structure drawn for a minor metabolite isolated from the Indo-Pacific soft coral *Sinularia flexibilis* known as Uchio's toxin.[9] The prostanoid preclavulone-A (**209**) is biosynthesized by *P. porosa* collected off Key Largo, Florida. The biosynthesis of preclavulone-A from arachidonic acid involves a process that contrasts sharply with the mammalian (endoperoxide) route. Preclavulone-A may be a key intermediate from which other more highly oxygenated, bioactive marine prostanoids are formed.[143] Subsequent studies revealed that the Caribbean coral species *Plexaura homomalla*, *Plexaura nina*, *Plexaura flexuosa*, *Pseudopterogorgia americana*, *Muriceopsis flavida*, and *Eunicea asperula* have all been found to convert arachidonate to 8-R-HPETE (**210**) and preclavulone-A (**209**) demonstrating that this route to marine prostanoids is widespread among such corals.[144]



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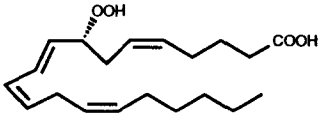
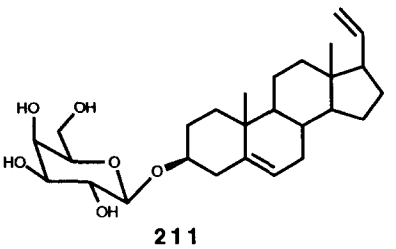


210

D. *Pseudoplexaura wagenaari* (Stiasny)

Pseudoplexaura wagenaari from Miami, Florida contains crassin acetate (**200**).[150] Specimens collected elsewhere in the Caribbean contain the following sesquiterpene hydrocarbons: (+)-α-muurolene (**112**), (+)-β-copaene (**141**), (+)-β-epibourbonene (**154**), (-)-δ-cadinene (**201**), (+)-α-copaene (**202**), (+)-α-cubebene (**203**), and alloaromadendrene (**204**).[3,5] The pregnene glycoside **211** was isolated from *P.wagenaari* collected from Key Biscayne, Florida, and its structure was determined by spectroscopic methods and finally confirmed by single crystal X-ray crystallography.[167]



211

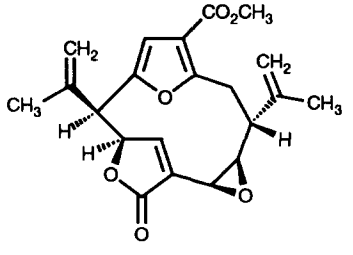
2.11. *Pseudopterogorgia* (family Gorgoniidae)

Gorgonians of the genus *Pseudopterogorgia* are best characterized as "sea plumes" based upon their large, highly finely branch (plumose) and physically soft forms. *Pseudopterogorgia* species are among the most common of the Caribbean species with over fifteen species documented. Chemical studies of *Pseudopterogorgia* species began in 1968, with investigations of the sesquiterpene hydrocarbons from the most common representative of this genus, *Pseudopterogorgia americana.*

A. *Pseudopterogorgia acerosa* (Pallas)

(Purple sea plume, Dry sea plume)

Pseudopterolide (**212**) was isolated by conventional chromatographic methods from the extract of *Pseudopterogorgia acerosa* collected in the Florida Keys. The structure of **212** was determined by X-ray analysis of the cyclic p-bromophenylurethane derivative obtained in two steps from pseudopterolide.[168] Pseudopterolide inhibits overall cell cleavage but does not inhibit nuclear division in the fertilized urchin egg assay. Although pseudopterolide can be dissected symmetrically into two geranyl units in two possible ways (perhaps suggesting a biogenesis involving dimerization) the prevalence of the 14-membered ring cembranoids in marine soft corals suggests a mechanism involving ring contraction.[168]



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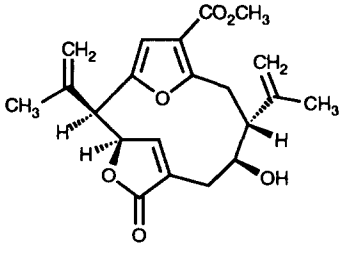

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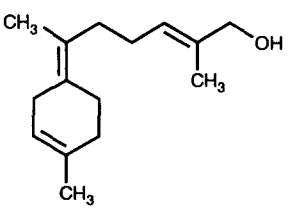

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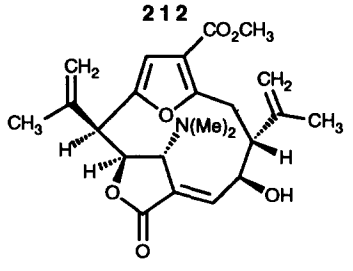

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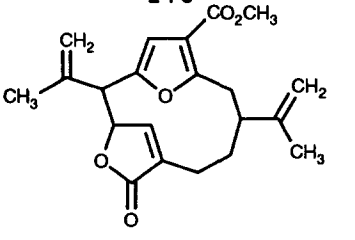

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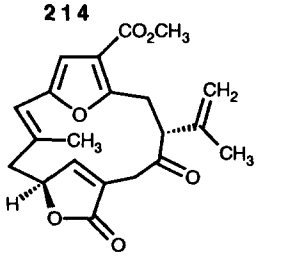
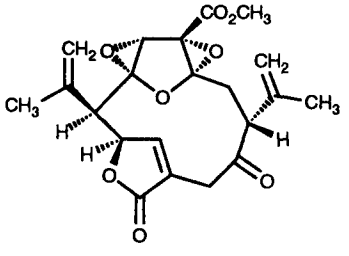


217

The first successful synthetic approach to a pseudopterane, viz., **213**, was reported.[169] A retrosynthetic strategy for the total synthesis of pseudopterolide (**212**) and allied pseudopteranes has been reported.[170,171] Several routes to the 2,5-furanocyclic ring system of the pseudopterane family of natural products along with prototype pseudopterane and furanocembrane systems have recently been described.[172-176] A collection of a *Pseudopterogorgia spp.* from Belize, whose spicule analyses closely related the animal to the Caribbean sea whip *P. acerosa*, produces exclusively the sesquiterpene 12-hydroxy-*E*-γ-bisabolene (**214**). The structure of this alcohol was based upon spectral analyses and chemical interconversions.[177] Tobagolide (**215**) is a nitrogenous pseudopterane derivative from a Tobago specimen of *P. acerosa*. 2D-NMR spectroscopy was used to establish the structure of tobagolide as the dimethylamino derivative **215**.[178] Pseudopterolide (**212**) can be transformed efficiently into tobagolide (**215**) by reaction with dimethylamine. Sequential treatment of tobagolide with methyl iodide and sodium hydride results in intramolecular S_N' displacement with reconstruction of pseudopterolide.[179,180] Two collections of *P. acerosa* from Tobago produced mixtures of acids that were esterified with diazomethane to obtain deoxypseudopterolide (**216**) and acerosolide (**217**) in the former collection and tobagolide (**215**) in the latter collection. The reported structural assignments for the pseudopterane **216** and the cembrane **217** were devoid of relevant stereochemistry and depended heavily on 2D-NMR spectroscopy.[181] The relative stereochemistry shown for acerosolide (**217**) has been tentatively established by total synthesis.[180,182,183] Notwithstanding, proof of its relative stereochemistry continues to be elusive and still must be considered to be an unresolved issue.[182]



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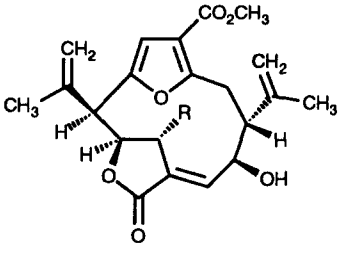
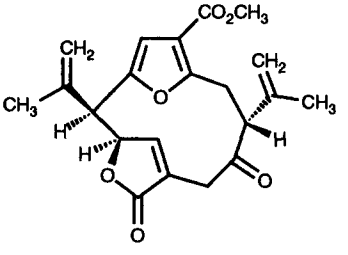
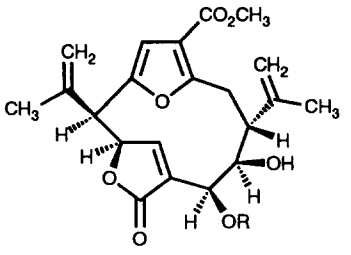


219 R = OCH_3
223 R = OH

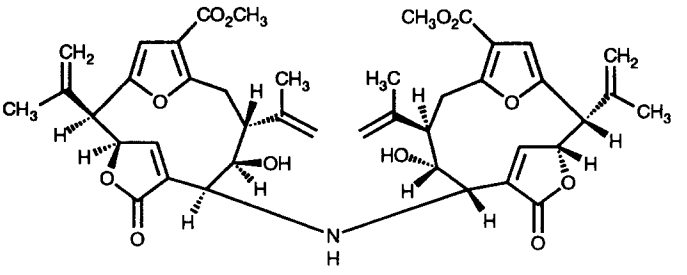


220

The structure of an additional pseudopterane, diepoxygorgiacerone (**218**), isolated from the same specimen of *P. acerosa*, was determined by 2D-NMR methods and confirmed by X-ray analysis, which also established its relative stereochemistry. This compound is an unusually stable diepoxyfuran derivative.[184] Six more pseudopteranoids, namely pseudopterolide-methanol adduct (**219**), gorgiacerone (**220**), gorgiacerodiol (**221**), methoxygorgiacerol (**222**), isogorgiacerodiol (**223**), and bis(gorgiacerol) amine (**224**) were also isolated from *P. acerosa* collected around the coast of Tobago and were identified by interpretation of spectral data.[185] The total synthesis of gorgiacerone (**220**) has been reported.[170,171,180]

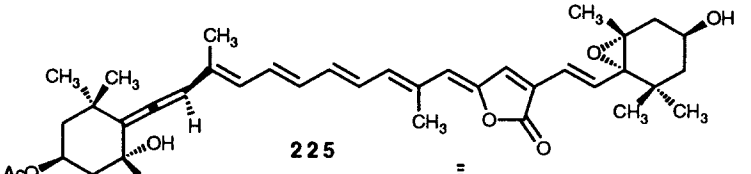


221 R = H
222 R = Me



224

The well-known carotenoid peridinin (**225**) was isolated from a sample of *P. acerosa* collected on the north coast of Tobago. After preliminary characterization by conventional spectral methods, the unambiguous ^{1}H- and ^{13}C-NMR assignments of peridinin were carried out.[186] The total synthesis of peridinin has been reported.[187-189] Further investigations of the polar extracts of this gorgonian led to the isolation and structure determination of the tetrahydroxysterol **226**. The structure of acerosterol (**226**) was determined on the basis of spectral data.[190] Assays on coral reefs have demonstrated that the crude lipid extract of *P. acerosa* collected at the Grenadine Islands and Belize, deterred natural predators at concentrations below their normal levels in gorgonian tissues. Assays conducted with purified sclerites from *P. acerosa* showed that the sclerites alone also function effectively to reduce predation on otherwise palatable food.[191,192] Similar results were also obtained with the crude lipid extracts of the Caribbean gorgonian *P. rigida* collected at the same sites.



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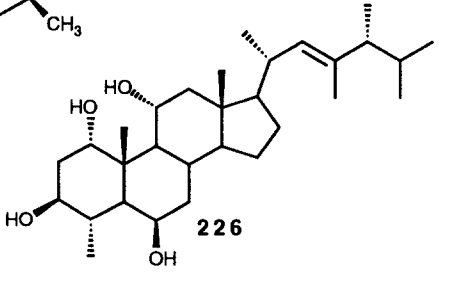


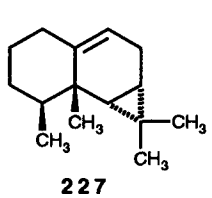
226

B. *Pseudopterogorgia americana* (Gmelin)

(Slimy sea plume)

The sesquiterpene hydrocarbon mixture occurring in the gorgonian *Pseudopterogorgia americana* (1% of its dry weight) collected in shallow waters at Bermuda and the Florida Keys, was found to consist primarily of (+)-9-aristolene (**227**), (-)-1(10)-aristolene (**228**), (+)-γ-maaliene (**229**), and (+)-β-gorgonene (**230**).[3,5,193] Extracts of powdered air dried *P. americana* collected off Havana, Cuba, produced, in addition to known β-

epibourbonene (**154**), calamenene (**205**), (-)-1(10)-aristolene (**228**), (+)-γ-maaliene (**229**), and α-chamigrene (**231**), a new compound, 1,1-dimethyl-7-isopropylidene-1,2,3,4,5,6,7,8-octahydronaphthalene (**232**). The latter compound was given the trivial name caridiene. The structure of **232** was elucidated by interpretation of spectroscopic data.[194] Two short syntheses of (±)-α-chamigrene have been reported.[195,196] Norzooanemonin (**233**) was isolated from the alcohol extract of *P. americana* (Florida Keys) by ion exchange followed by alumina chromatography. Its structure was deduced from its elemental composition and spectral features and has been confirmed by synthesis.[197]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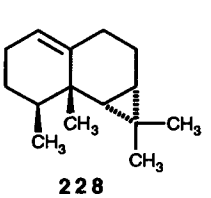
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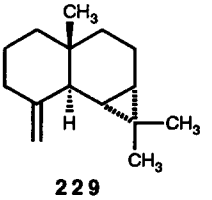
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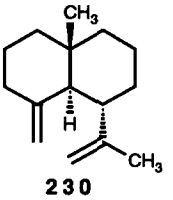
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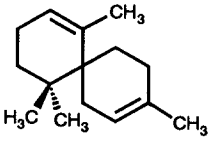
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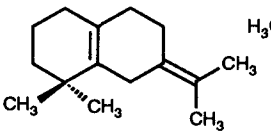
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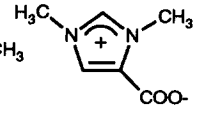
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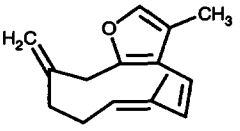
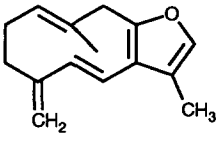

234 (incorrect)

In addition to norzooanemonin, the betaine fraction contained a mixture that appeared from its NMR spectrum to consist of trigonelline (N-methyl nicotinic acid betaine) and possibly homarine (N-methyl α-picolinic acid betaine).[197] The proposed structure for furanogermacrene derivative **234**, which was isolated from extracts of *P. americana* (Carrie Bow Cay, Belize) and identified from spectral measurements,[198] has been revised to structure **235**.[199] The structures of furanotriene **235**, (+)-germacrene-D (**236**), furanodienes **237** and **238**, along with **239**, isofuranotriene (**240**) and elemanolide (**241**), isolated from *P. americana* and a related species collected in Tobago, were established by spectroscopic methods.[199]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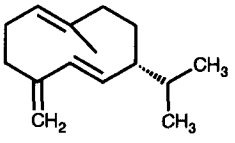
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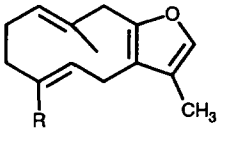
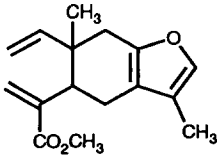

237 R = CH_3
238 R = CO_2CH_3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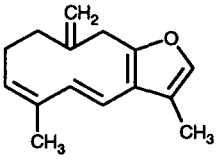
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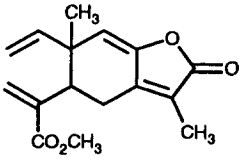
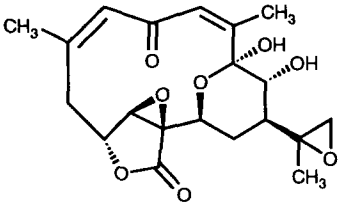

241

C. *Pseudopterogorgia bipinnata* (Verrill)

(Bipinnate sea feather)

The gorgonian *Pseudopterogorgia bipinnata*, a widely distributed member of the genus *Pseudopterogorgia*, produces a large variety of cembrene derivatives somewhat dependent upon collection site. The characteristic of *Pseudopterogorgia* cembrenes is their rather high levels of oxygenation. Two cembrene derivatives, the bipinnatolides **242** and **243**, were found to have antiinflammatory activity with potency equivalent to that of indomethacin. Their structures were established by spectroscopic, X-ray, and chemical methods.[200] Reportedly, over fifteen cembrane derivatives have been isolated from *P. bipinnata* but neither their structures nor the spectral data for **242** and **243**, appear to have been reported.



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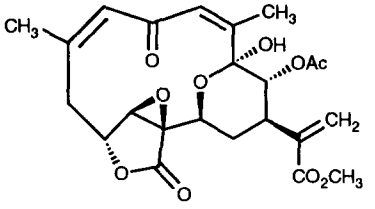
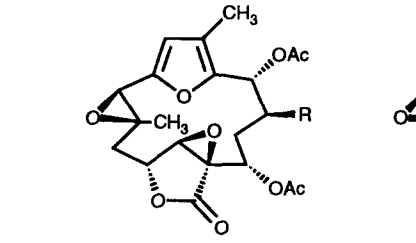


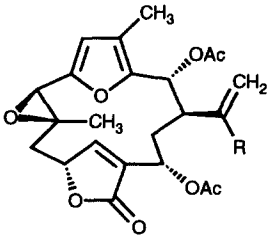
243

In 1989, four new cytotoxic cembranoids, denoted as bipinnatins A-D (**244-247**) were reported from *P. bipinnata* collected off Jamaica Cay, Acklins Islands, Bahamas.[201] Their structures were determined through a combination of spectroscopic and X-ray crystallographic methods. Bipinnatins A (**244**), B (**245**) and D (**247**) are active *in vitro* against P388 murine tumor cell lines with IC_{50}'s of 0.9, 3.2 and 1.5 μg/mL, respectively. Bipinnatin C (**246**), which lacks the α,β-unsaturated carbonyl functionality, is much less active, with an IC_{50} of 46.6 μg/mL.[201] Curiously, cembranes **244**, **245**, and **246**, along with related derivatives bipinnatin E (**248**) and bipinnatin F (**249**), all lophotoxin (**250**) analogs from a *Pseudopterogorgia sp.*, had been reported in 1985 by the Fenical group but their structures were not proposed nor their physical and chemical data reported.[202] They found then that one of these analogs, **245**, was equipotent as lophotoxin (**250**) for inhibition of [^{125}I]-α-toxin binding to intact cells and, notably, also blocked α-toxin binding to detergent-extracted receptor. Furthermore, **245** inhibited [^{125}I]-α-toxin binding to receptor-rich membrane fragments prepared from *Torpedo* electric organ, a preparation in which lophotoxin was inactive. Structure-activity relationships exhibited by these lophotoxin congeners suggest mechanisms for covalent binding to the receptor by way of a Michael addition or by Schiff base formation.[202,203] These lophotoxins are also unique in that they irreversibly inhibit nicotinic acetylcholine receptors by forming a covalent bond with a tyrosine residue at position 190 in the α-subunit of the receptor.[204,205,206] The bimolecular reaction constants for the interaction of the bipinnatins with the nicotinic receptor decreased in the order bipinnatin B > bipinnatin A > bipinnatin C for the acetylcholine-binding sites.[204] Although additional lophotoxin analogs have been reported [i.e. bipinnatins G (**251**), H (**252**), and I (**253**), as well as bipinnatolide-B (**254**)], their structures have not been proposed nor their physical and chemical data reported. Bipinnatin E and F (along with bipinnatins A, B, and C) were isolated from *P. bipinnata* collected in the Bahamas and bipinnatin G, H, and I were isolated from an unidentified species of *Pseudopterogorgia* collected in

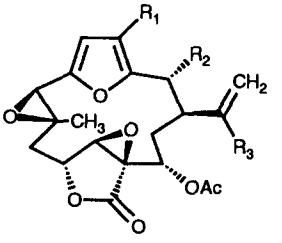
the Bahamas.[203] A concise synthesis of the furan-containing macrocyclic (cembranoid) ring system found in lophotoxin (**250**) and other members of this family of irreversible nicotinic receptor antagonists, has been described.[207]



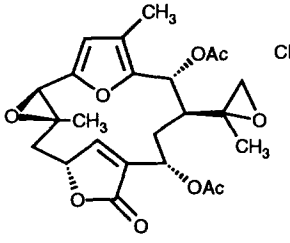
244 **245** **246**



247 R = CHO
251 R = CH_3
253 R = CO_2CH_3



248 R_1 = CO_2CH_3 R_2 = H R_3 = CHO
249 R_1 = R_3 = CH_3 R_2 = OAc
250 R_1 = CHO R_2 = H R_3 = CH_3



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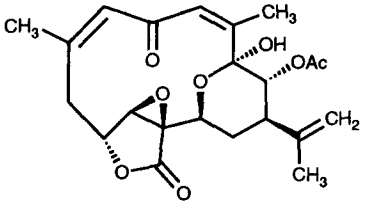
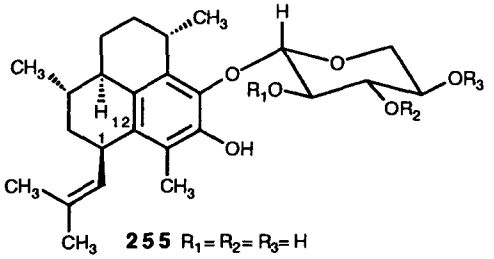


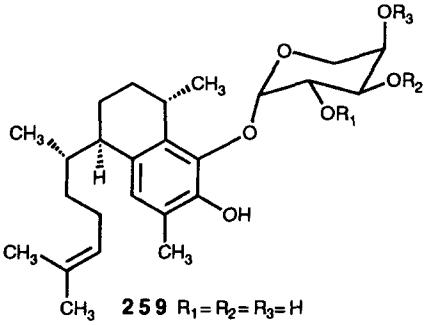
254

D. *Pseudopterogorgia elisabethae* (spec. nov.)

The Caribbean sea whip *Pseudopterogorgia elisabethae* collected in the central Bahamas Islands, was found to contain the pseudopterosins A-D (**255-258**), a new class of natural products which can be characterized as diterpene-pentose-glycosides. The pseudopterosins possess antiinflammatory and analgesic properties that exceed the potencies of existing drugs such as indomethacin. An X-ray-crystallographic study, together with degradation to obtain D-xylose, gave the structure of pseudopterosin C (**257**), to which pseudopterosins A (**255**), B (**256**), and D (**258**) were related by chemical interconversion.[208,209]

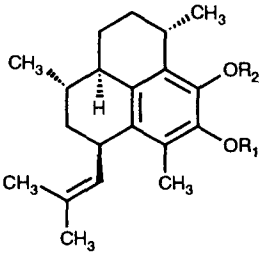


255 R_1 = R_2 = R_3 = H
256 R_1 = Ac R_2 = R_3 = H
257 R_2 = Ac R_1 = R_3 = H
258 R_3 = Ac R_1 = R_2 = H

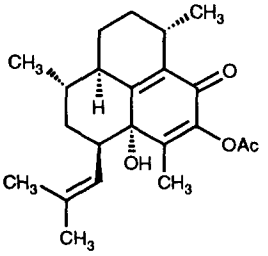


259 R_1 = R_2 = R_3 = H
260 R_1 = Ac R_2 = R_3 = H
261 R_2 = Ac R_1 = R_3 = H
262 R_3 = Ac R_1 = R_2 = H

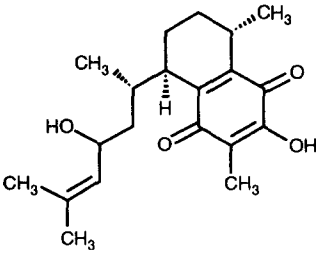
Pseudopterosin A (**255**) inhibits cell division in fertilized sea-urchin eggs with an IC_{50} of 25 μM.[210] (-)-Pseudopterosin A has been synthesized from (-)-limonene,[211] from (1S,2R,5S)-(+)-menthol,[212] and from (S)-citronellal.[213] The *seco*-pseudopterosins A-D (**259-262**) are potent antiinflammatory and analgesic compounds related to pseudopterosin A (**255**) by bond cleavage at the C1-C12 positions; they have been isolated from a Caribbean sea whip of the genus *Pseudopterogorgia* collected in the Florida Keys.[214] These compounds are arabinose glycosides possessing aglycones of the serrulatane class of diterpenoids encountered in composite plants of the genus *Eremophila*. The structures of the *seco*-pseudopterosins were suggested on the basis of comprehensive spectral analyses and upon chemical transformations. The selective reduction of serrulatenol, a diterpene isolated from *Eremophila rotundifolia*, as a route to compounds related to the *seco*-pseudopterosins but with different stereochemistry, has been reported.[215] An undescribed *Pseudopterogorgia* species from the Caribbean Sea (Bahamas Islands) was found to contain three additional pseudopterosins **263-265** and one new *seco*-pseudopterosin **266**, which were described on the basis of their NMR properties and chemical interconversions.[216]



263 R_1=H R_2= Ac
264 R_1= Ac R_2= H

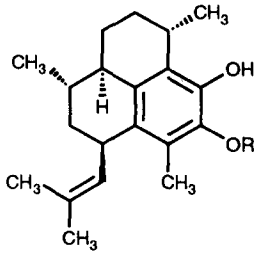


265

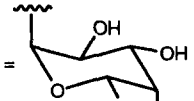


266

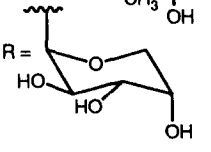
Eight new diterpene glycosides, pseudopterosins E-L (**267-274**), and the methylated aglycone of pseudopterosin E **275**, were isolated, together with pseudopterosins A-D, from two collections of *P. elisabethae*. A Bermudian collection contained pseudopterosins E-J (**267-272**) while K (**273**) and L (**274**) were obtained from a Bahamas collection.[217]

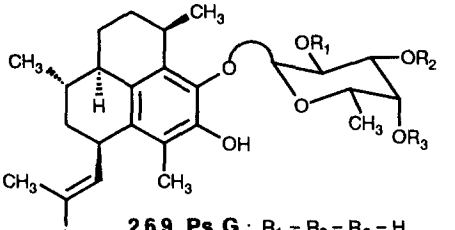


267 Ps E : R =



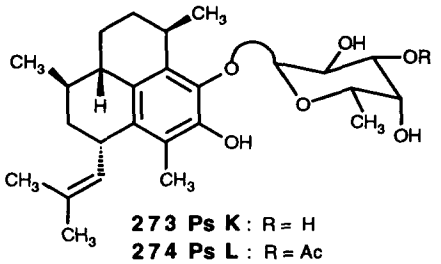
268 Ps F : R =



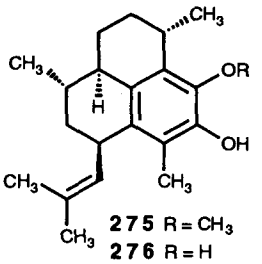


269 Ps G : $R_1 = R_2 = R_3 = H$
270 Ps H : R_1 = Ac $R_2 = R_3 = H$
271 Ps I : R_2 = Ac $R_1 = R_3 = H$
272 Ps J : R_3 = Ac $R_1 = R_2 = H$

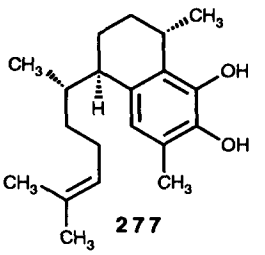
The structure of pseudopterosin F (**268**) was determined by X-ray analysis, and the remaining compounds were identified by spectroscopic methods.[217] Pseudopterosin E (**267**) has superior antiinflammatory properties to those of other compounds in this series, is less toxic, and appears to act by a novel mechanism. Two enantiospecific syntheses of pseudopterosin E from (1S,2R,5S)-(+)-menthol[212] and from (S)-citronellal[213] have been outlined. The aglycone of pseudopterosin E (**267**) has been synthesized from 5-methoxytetralone.[218] The aglycones **276** and **277** of the pseudopterosins and *seco*-pseudopterosins have been synthesized in a stereoselective manner.[219,220]



273 Ps K: R = H
274 Ps L: R = Ac



275 R = CH_3
276 R = H



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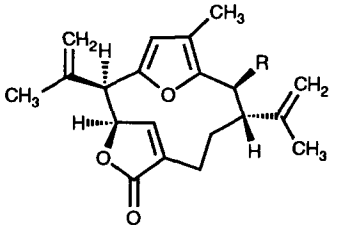
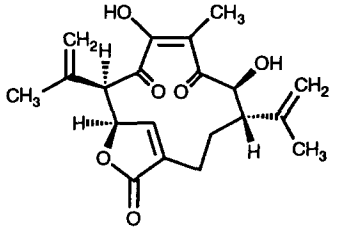
E. *Pseudopterogorgia kallos* (Bielschowsky)

Four new representatives of the pseudopterane skeleton class, namely kallolide A (**278**), kallolide A acetate (**279**), kallolide B (**280**), and kallolide C (**281**), were isolated from the gorgonian *Pseudopterogorgia kallos* collected in the Bahamas Islands.[221] The structure of kallolide A acetate (**279**) was provided by single-crystal X-ray diffraction analysis, and the remaining kallolide structures were established on the basis of spectral analyses and chemical interconversions. The major metabolite, kallolide A (**278**), is a potent inhibitor of phorbol ester induced inflammation in the mouse ear assay at concentrations and with efficacies equivalent to those of indomethacin.[221] A possible precursor of **278** has been prepared via [2,3] Wittig ring contraction of a macrocyclic furan diether.[222]



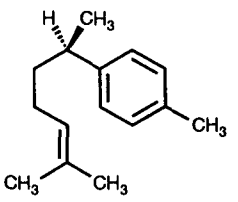
278 R = OH
279 R = OAc
280 R = H



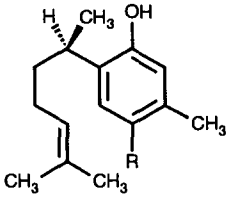
281

F. *Pseudopterogorgia rigida* (Bielschowsky)

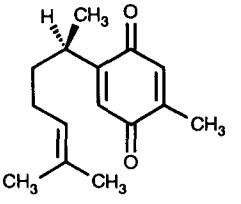
The gorgonian *Pseudopterogorgia rigida* can be easily distinguished from the more abundant *P. americana* because it is non-slimy and sparsely branched. The characteristic sesquiterpene components of *P. rigida* are the α, β, and γ-bisabolenes and (-)-α-curcumene (**175**).[223] Three derivatives of the aromatic sesquiterpene α-curcumene, (-)-curcuphenol (**282**), (-)-curcuquinone (**283**), and (-)-curcuhydroquinone (**284**), are, collectively, responsible for the antibiotic properties of *P. rigida*. The structures of these antibacterial metabolites were elucidated by spectral analysis and chemical interconversions.[223] The syntheses of **282-284** have been reported.[224,225] Assays on coral reefs have demonstrated that the crude lipid extract of *P. rigida* deters natural predators.[191,192] A hydrocarbon mixture consisting mainly of curcumene and the monoacetate of **284**, which are minor components of *P. rigida*, did not deter consumers significantly. Curcuhydroquinone (**284**) and curcuquinone (**283**), which exist in higher concentration at the edges of the colony, a region more susceptible to predation, had significant deterrent effects.[191]



175



282 R = H
284 R = OH



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2.12. *Pterogorgia* (family Gorgoniidae)

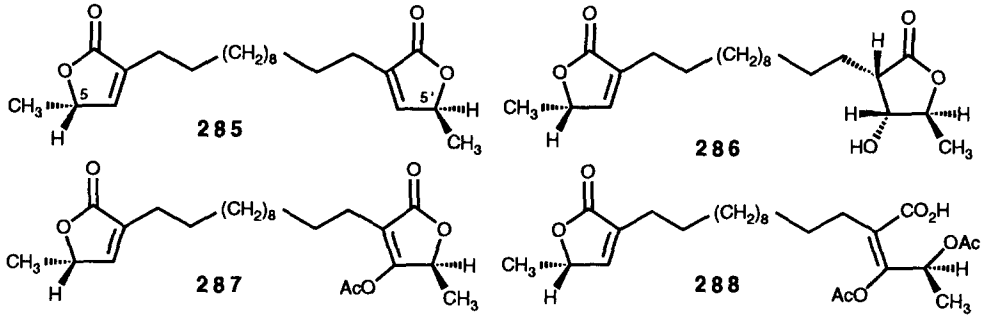
The three species documented as belonging to this genus occur along the Bermudas, southern Florida and the Keys, and the Greater Antilles south to Curaçao. The branches of *P. citrina* are flattened, and the colony is low and sparsely branched. The colonies of *P. anceps*, however, are bushy and more profusely branched, and larger. Sea whips of this genus are usually rich in polymethylene butenolides. On the other hand, they appear to have an insignificant hydrocarbon content.[74]

A. *Pterogorgia* (*Xiphigorgia*) *anceps* (Pallas)

(Angular sea whip)

The major component from the pentane extracts of *Pterogorgia anceps* collected in Bimini, Bahamas, was identified as ancepsenolide (**285**).[20] The structure of this crystalline bisbutenolide was elucidated by interpretation of spectroscopic data and by chemical degradation.[226] Three total syntheses for ancepsenolide have been reported.[227-229] The latest synthesis, which proceeded in 31% overall yield in seven steps, established the absolute stereochemistry of ancepsenolide as 5S, 5'S.[229] Another dilactone, hydroxyancepsenolide (**286**), was later isolated from this same organism and its structure was identified by spectroscopic and chemical methods.[230] Field and laboratory experiments have demonstrated the feeding-deterrent properties of lipid-soluble extracts of the octocoral *P. anceps*. Bioassay-directed fractionation of these extracts revealed that the deterrent property was restricted to an ancepsenolide-containing fraction.[231] Two additional acetogenin class compounds from two collections of *P. anceps*, one near the reefs surrounding the Bahama Island of San Salvador and a second from

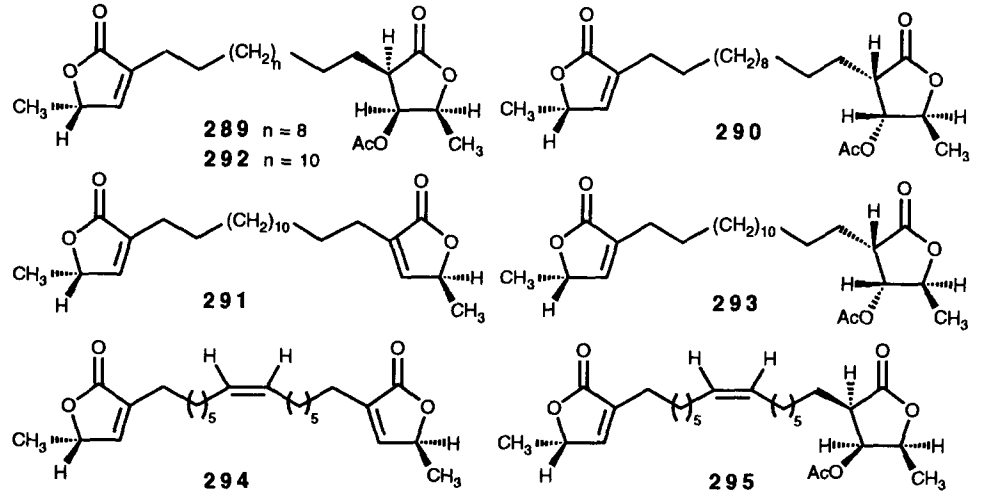
Belizian waters, have been reported. The structures of **287** and **288**, however, have not been elucidated nor their spectroscopic data reported.[231] Laboratory assays of purified metabolites isolated from *P. anceps* revealed a substancial feeding-inhibitory effect, which was restricted to the ancepsenolide diacetoxy derivative **288**.[231]



B. *Pterogorgia citrina* (Esper)

(Yellow sea whip)

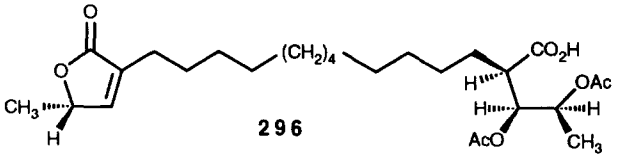
Previous investigations with *Pterogorgia citrina* had indicated the complete absence of lactones **285**, **286** and **296** in this gorgonian.[157] However, a recent investigation of *P. citrina* collected in Puerto Rico, revealed seven new polymethylene butenolides along with ancepsenolide (**285**). The structures of ancepsenolide acetate (**289**), hydroxyancepsenolide acetate (**290**), homoancepsenolide (**291**), homoancepsenolide acetate (**292**), hydroxyhomoancepsenolide acetate (**293**), 13,13'-dehydrohomoancepsenolide (**294**), and 13,14-dehydrohomoancepsenolide acetate (**295**), were elucidated on the basis of spectroscopic data and were confirmed upon chemical conversion to either ancepsenolide or to its homolog, homoancepsenolide. These butenolides were not active against *Escherichia coli* or *Staphylococcus aureus*, nor did they show cytotoxicity against a human colon tumor cell line (HCT 116).[232]



C. *Pterogorgia guadalupensis* (Duchassaing & Michelin)

(Flat sea whip)

Ancepsenolide (**285**), along with a crystalline lactone, 2-(13-carboxy-14,15-diacetoxyhexadecanyl)-2-penten-4-olide (**296**), was isolated from the gorgonian *Pterogorgia guadalupensis* collected in Jamaica.[233,234] The structure of **296**, which has been given the trivial name guadalupensic acid diacetate,[157] was proposed on the basis of spectroscopic data and conversion to ancepsenolide. Lactone **296** exhibited mild antibiotic activity against *Staphylococcus aureus* and *Mycobacterium smegmatis*.



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3. CONCLUDING REMARKS

The gorgonian fauna of the tropical and sub-tropical parts of the eastern American coasts, including Bermuda, the Gulf of Mexico, the Caribbean and the coasts of the West Indies, is very uniform, although not all the species (about 195 in number and including representatives of most of the principal families of the group) range throughout its whole extent. The Greater Antilles (Cuba, Hispaniola, Puerto Rico and Jamaica) lying not far from the center of the region, are within the area where the greatest variety of species occurs. Although up to the present time these islands are credited with about 53 species[1], a little less than one third of those of the entire region, yet it is probable that future collecting will eventually demonstrate that a large majority of the other West Indian and Atlantic gorgonians occur also along their shores.

The unprecedented structures obtained from the approximately 20% of West Indian gorgonians studied thus far constitute ample evidence that these animals are an important source of new classes of bioactive metabolites. These marine invertebrates are responsible for the production of over twenty different skeletal classes of terpenes with unique substitution patterns and functionalities. An example of both diversity and antipodal nature of West Indian gorgonian sesqui- and diterpenoid metabolites are those isolated from *Eunicea* and *Plexaura* octocorals. They are also the source of prostaglandins, sterols, carotenoids, and intriguing metabolites of mixed biogenesis. A chemical class distribution of the gorgonian natural products compiled in this Report, shows some interesting trends. The principal terpenoids elaborated by West Indian gorgonians are diterpenes and sesquiterpenes. Diterpenoids as a single class, represent the largest percentage of natural products isolated from these animals accounting for 73.5% of the approximately 290 metabolites reported from 1958 to December 1994. In general, gorgonians from this region appear to be quite consistent in that near 89% of their metabolites are terpenoid and only 1.4% and 5.2%, respectively, contain nitrogen or chlorine. Figure 1 shows a graphical breakdown by chemical class of the total number of metabolites isolated during this thirty-seven year period. The diterpenoids, the largest division, are in turn further analyzed and the distribution by skeleton classes of compounds in this group is shown in Figure 2. These figures profile the current interest in the field and demonstrate some pertinent differences between the secondary metabolism of West Indian gorgonians. For instance, the traditional clear dominance of cembranoid metabolites has been reduced significantly during the late

1980's and early 1990's with the discoveries of numerous diterpenoids of the asbestinane and briarane classes. They now represent, respectively, the second and third most frequently found types of diterpenoids in gorgonians from this region.

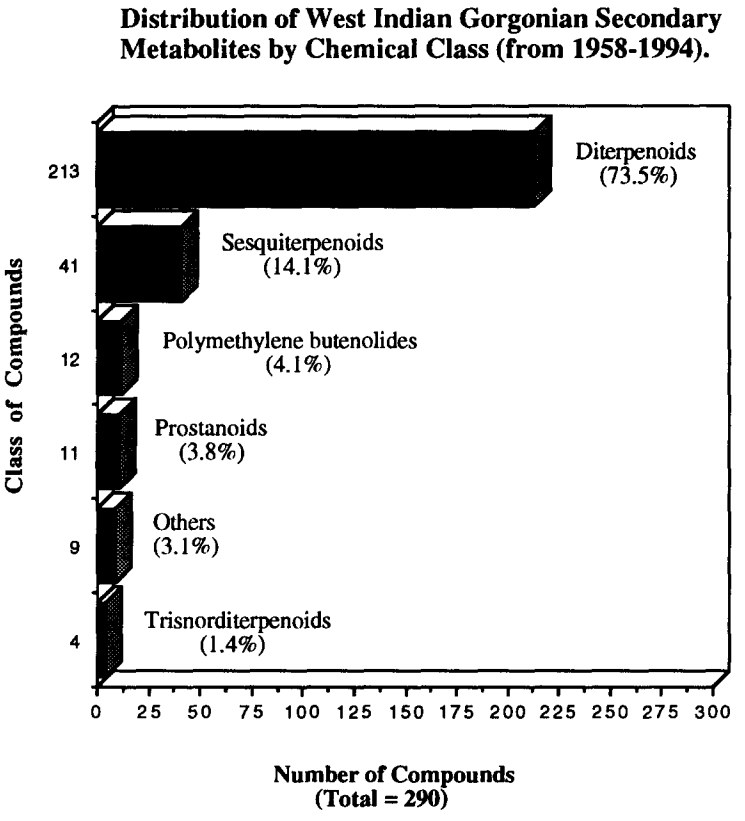

Figure 1. Excluding most sterols, carotenoids, phospholipids and biopolymers, a total of approximately 290 metabolites were isolated from West Indian gorgonians during the thirty-seven year period comprised between 1958 and December 1994.

A number of these compounds have offered special opportunities for advancing basic science and laying a foundation for new research. For instance, determining the natural functions of these secondary metabolites is currently an issue of more broad interest. Most marine scientists are now convinced about the defensive roles of these compounds and many suspect that they may have contributed to the evolutionary success of the producing organisms (the ecological roles of the majority of these compounds, however, have yet to be clearly defined). Their interest, coupled with the demonstration of potent feeding deterrence, has added a new dimension to

gorgonian biology. Moreover, metabolites isolated from West Indian gorgonians are frequently the subjects of biochemical and biosynthetic investigations. Some of these compounds have already found application as probes for new mechanisms of action, and a selected few may soon be found under development as pharmaceutical agents (i.e. the pseudopterosins are currently in clinical evaluation for topical skin diseases and fuscosides A (**91**) and B (**92**) are of possible interest. At this time, however, there are no other compounds isolated from West Indian gorgonians in preclinical study or in clinical evaluation).[235]

The majority of the species of gorgonians listed by Bayer (about 80%)[1] are not easily available as chemical targets, since they are either extremely rare or occur very deep. As a result, the emphasis of those already involved in the isolation of new compounds and those who may choose to enter this field, should inevitably move to the study of gorgonians that are rare or difficult to collect. The emphasis on new directions is well justified for it is becoming increasingly difficult to find new compounds from those specimens that are too obvious or easily collected using SCUBA. Notwithstanding, the recent literature provides confidence that many gorgonian species from the West Indian region will continue to yield fascinating and previously undescribed secondary metabolites with potent pharmacological activity. One can comfortably predict not only that the natural products isolated from these marine invertebrates will provide a rich source of biologically active compounds of medicinal importance but, even more importantly, that they will provide models on which to base extensive synthetic programs leading to still more efficacious pharmaceuticals.

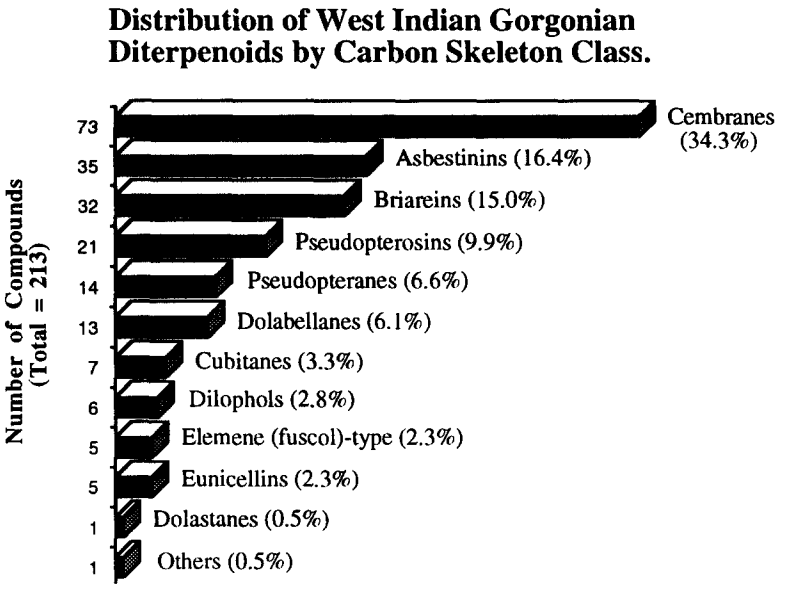

Figure 2. West Indian gorgonians are reponsible for the production of over twenty different skeletal classes of terpenes with about twelve skeletal classes, about half of those of the entire group, being ascribed to diterpenes. Most of them possess unique substitution patterns and functionalities.

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