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SURVEY OF BRIARANE-TYPE DITERPENOIDS OF MARINE ORIGIN

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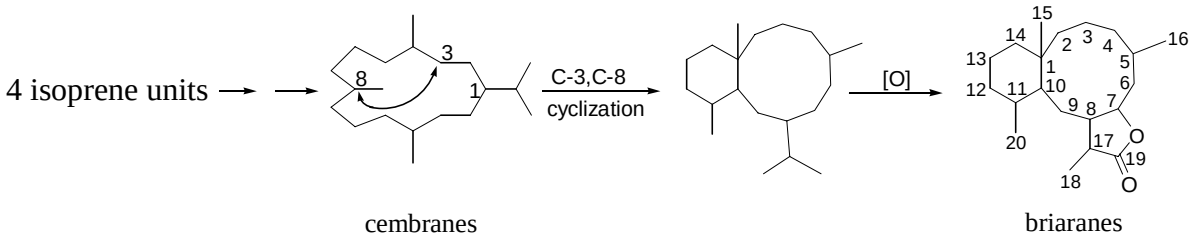
Abstract – The structures, names, biological activities, and references of two hundred ninety-nine marine original briarane-type metabolites are described and compiled in tabular form in this review. All briarane-type natural products are obtained from marine invertebrates, including various octocorals, a nudibranch, and a sponge. Some of these compounds showed potential biological activities.

1. INTRODUCTION

Since the discovery of the first briarane-type metabolite (briarein A) in 1977 by Burks *et al*. from a West Indian gorgonian coral *Briareum asbestinum*,[1] two hundred ninety-nine 3,8-cyclized cembranoid compounds have been reported. They all feature the briarane carbon skeleton (Scheme 1), containing a bicyclo[8.4.0] system, and most possess a γ-lactone in their structures. Two hundred ninety-seven compounds of this type have been isolated from the soft coral subclass Octocorallia (Phylum cnidaria, class Anthozoa), including Gorgonacea, Pennatulacea, Alcyonacea, and Stolonifera. In addition, two briaranes were obtained from a nudibranch and a sponge, respectively. Briarane-type diterpenoids continue to attract the attentions of investigations because of the structural complexity and interesting biological activities (e.g., cytotoxicity, antiinflammatory, antiviral, immunomodulatory activity, insect control, antifouling, biotoxin, and ichthyotoxicity) associated with numerous compounds of this type. This survey of briarane-type compounds will be presented taxonomically according to genus and species.



Scheme 1. Possible biogenetic origin of briarane-type metabolites. The numbering system shown is those presently in use.

2. GORGONACEA

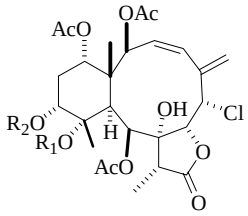
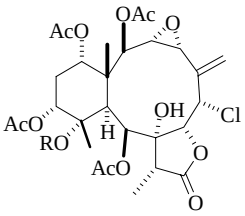
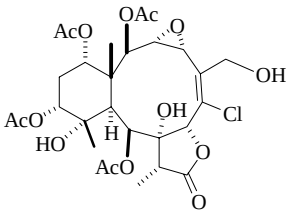
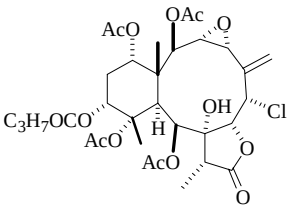
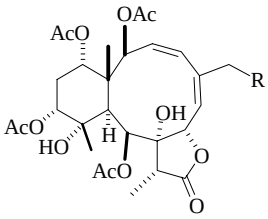
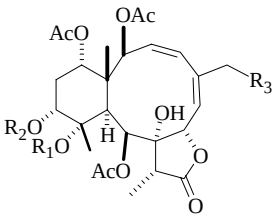
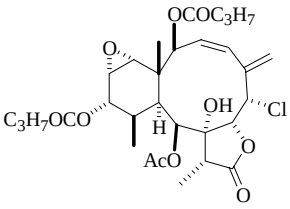
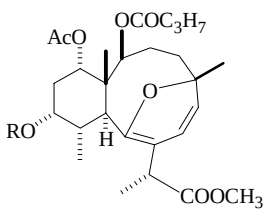
2.1. *Briareum* (= *Solenopodium*)[2] (family Briareidae)

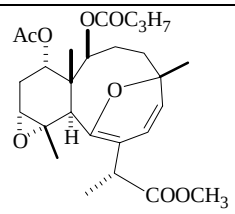
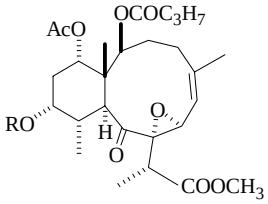
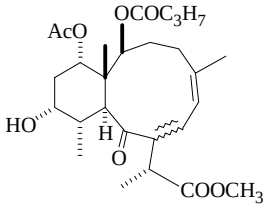
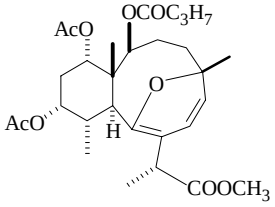
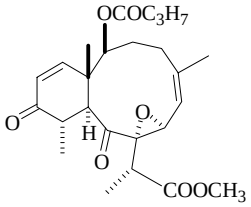
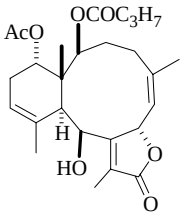
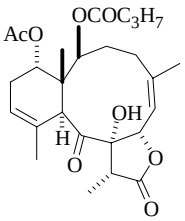
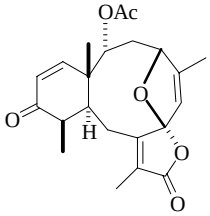
A. *Briareum asbestinum*

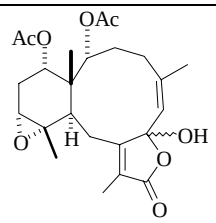
The octocoral genus *Briareum* has been the subject of a number of investigations which have uncovered various oxygenated terpenoids, the majority of which possess the briarane skeleton.[3,4] The structure, including the absolute stereochemistry of the first briarane-type compound, briarein A (**1**), was determined by X-Ray analyses.[1] Briarein B (**2**) had been reported in 1980's,[5,6] however, the complete spectral data (UV, IR, MS, ^{1}H and ^{13}C NMR) and structure elucidation of briareins A (**1**) and B (**2**) with those of the other ten new metabolites, briareins C–L (**3**–**12**), were reported by Rodríguez *et al*. in 1996.[7] Brianthein V (**13**) is a cytotoxic and antiviral briarane from *B. asbestinum*, collected near Sandy Cay, Bahamas. The structure and absolute configuration of briarane (**13**) were established by spectroscopic methods (IR, MS, ^{1}H and ^{13}C NMR) and X-Ray analyses.[8]

Moreover, eleven novel 2-*n*-butyryloxybriaranes, briareolate esters A–I (**14**–**22**) and briareolides J (**23**), and K (**24**) and two unnamed new diterpenoids (**25**) and (**26**) that belong to the briarane class compounds, were isolated from the organic extracts of *B. asbestinum*, collected off the coast of Tobago. The structures of **14**–**26** were elucidated by spectroscopic methods, including 1D and 2D NMR spectral analyses.[9–11] The structures and relative configurations of briareolate esters A (**14**) and D (**17**) were further confirmed by X-Ray analyses.[9,11] It is noted that briareolate esters A–I (**14**–**22**) containing C-19 methyl ester groups in their structures;[9–11] briareolate esters A–C (**14**–**16**) and H (**21**) possessing cyclic ether groups in the ten-membered rings;[9–11] the 9-keto group in briareolate esters D–G (**17**–**20**), and I (**22**), and briareolide K (**24**);[11] the spiroketal-lactone-dihydrofuran system in briarane (**25**);[10] and the epoxy groups attaching at the C-7/C-8 positions in briareolate esters D–F (**17**–**19**) and I (**22**),[11] respectively, are rarely found in briarane class metabolites. However, the geometry across the C-7/C-8 double bond in briareolate ester G (**20**) and the stereochemistry of C-7 hydroxyl group in briarane (**26**) are still unknown.[10,11] Briareolate esters D (**17**), G (**20**), and I (**22**), and briareolide K (**24**) showed activity in the brine shrimp bioassay.[11]

Table 1. The Briarane-Type Metabolites from *B. asbestinum*

Structure	No.	Name	Biological activity	Ref.
	**1**	briarein A (R_1 = R_2 = Ac)		1,7
	2	briarein B (R_1 = Ac, R_2 = COC_3H_7)		5–7
	3	briarein C (R_1 = H, R_2 = COC_3H_7)		7
	**4**	briarein D (R = Ac)		7
	5	briarein E (R = H)		7
	**6**	briarein F		7
	**7**	briarein G		7
	**8**	briarein H (R = OAc)		7
	9	briarein I (R = $OCOC_7H_{15}$)		7
	10	briarein J (R = Cl)		7
	**11**	briarein K (R_1 = H, R_2 = COC_7H_{15}, R_3 = $OCOC_3H_7$)		7
	12	briarein L (R_1 = Ac, R_2 = COC_3H_7, R_3 = OAc)		7
	**13**	brianthein V	show *in vitro* cytotoxicity in the P-388 assay at 13 μg/mL; show viral inhibition at 50 μg/mL in the *in vitro* mouse corona virus assay.	8
	**14**	briareolate ester A (R = COC_3H_7)		9,11
	15	briareolate ester B (R = H)		10,11

Structure	No.	Name	Biological activity	Ref.
	**16**	briareolate ester C		10,11
	**17**	briareolate ester D (R = H)	LD_{50} (brine shrimp) = 400–500 μg/mL	11
	18	briareolate ester E (R = Ac)		11
	19	briareolate ester F (R = COC_3H_7)		11
	**20**	briareolate ester G	LD_{50} (brine shrimp) = 400–500 μg/mL	11
	**21**	briareolate ester H		11
	**22**	briareolate ester I	LD_{50} (brine shrimp) = 400–500 μg/mL	11
	**23**	briareolide J		11
	**24**	briareolide K	LD_{50} (brine shrimp) = 400–500 μg/mL	11
	**25**			10

Structure	No.	Name	Biological activity	Ref.
	**26**			10

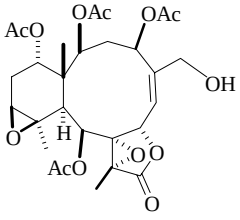
B. *Briareum excavatum*

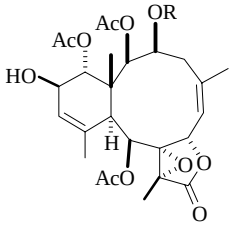
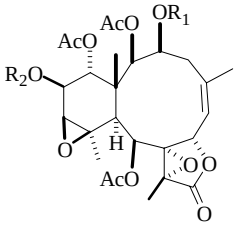
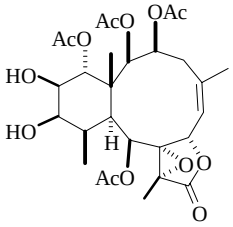
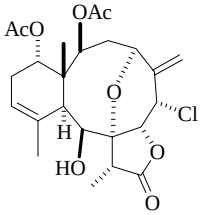
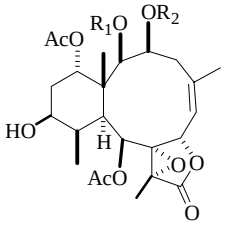
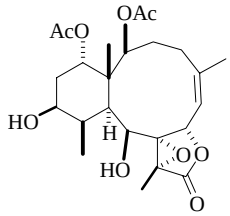
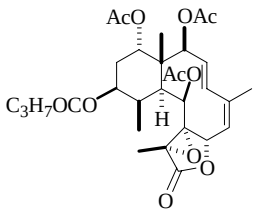
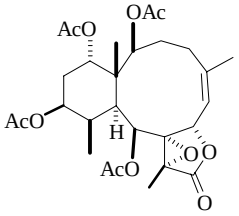
Seven new briaranes, including 16-hydroxystecholide C acetate (**27**) and stecholides I–N (**28**–**33**), were isolated from the Papua New Guinea gorgonian coral, *B. excavatum*. The structures of these metabolites were established by the interpretations of spectral analyses (and conformational energy calculations. The structure, including the relative configuration of stecholide I (**28**) was further confirmed by X-Ray diffraction analyses.[12] Besides, a series of briarane-type metabolites have been isolated from *B. excavatum*, that were collected along the coast of Southern Taiwan, Great Barrier Reef, and the Sulawesi Island, Indonesia. These metabolites are excavatolides A–Z (**34**–**59**),[13–16] briaexcavatolides A–R (**60**–**77**),[17–19] and briantheins A–C (**78**–**80**),[20] respectively. The structures of compounds (**34**–**80**) were elucidated by extensive spectroscopic methods. Structures of excavatolides B (**35**) and U (**54**); and briaexcavatolides B (**61**), K (**70**), O (**74**), and P (**75**) were further confirmed by X-Ray diffraction analyses, respectively.[13,16–19] The absolute configuration of brianthein A (**78**) was established by the modified Mosher's method and supported by restrained molecular dynamic calculations.[20]

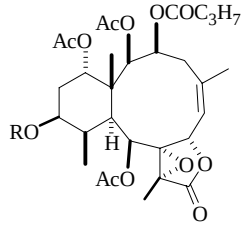
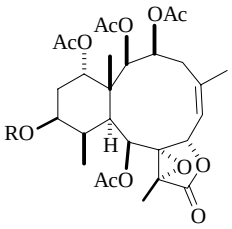
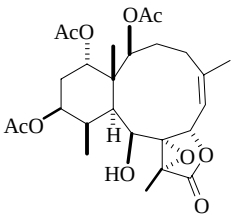
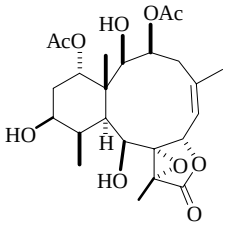
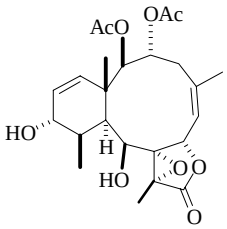
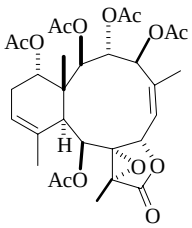
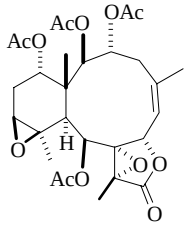
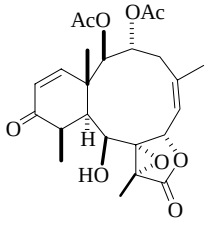
Among the above compounds, excavatolide F (**39**) is the first briarane derivative containing a 3(*E*),5(*Z*)-diene moiety in a *S-trans* conformation.[14] Briaexcavatolides K (**70**) and L (**71**) are the only briarane diterpenoids known to possess hydroxyl groups at the C-8β and C-17α positions.[18] Brianthein B (**79**) is the only hydroperoxybriarane that had been isolated.[20]

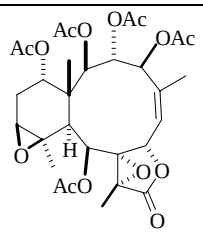
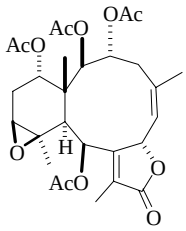
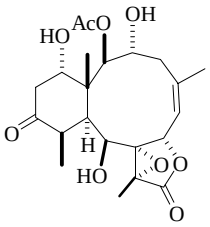
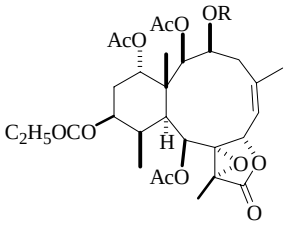
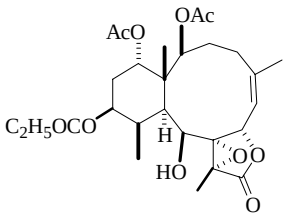
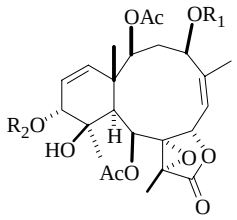
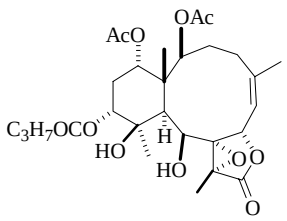
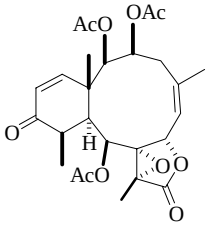
All briaranes from *B. excavatum* were studied for their potential cytotoxicity toward P-388 and various human tumor cell lines. The cytotoxic data of these compounds that were reported previously are presented in Table 2. It is noted that brianthein A (**78**) exhibited reversing multidrug resistance in KB cells.[20] In a later study, stecholide L (**31**) was isolated from an Indonesian gorgonian coral, *Briareum* sp. too.[21]

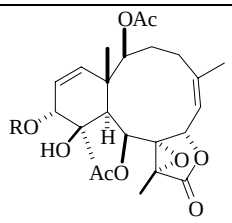
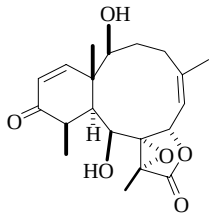
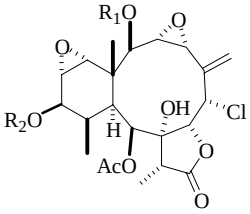
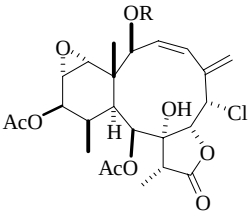
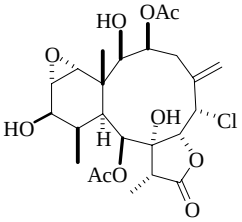
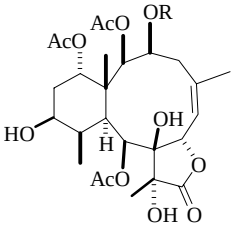
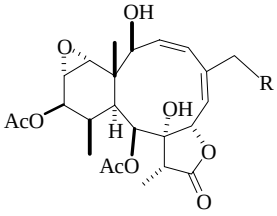
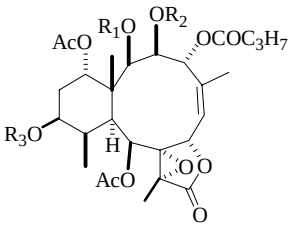
Table 2. The Briarane-Type Metabolites from *B. excavatum*

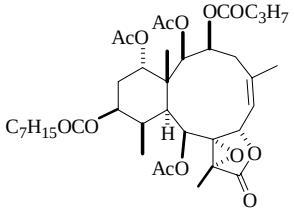
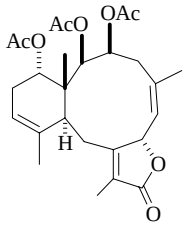
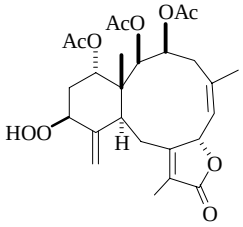
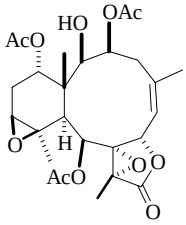
Structure	No.	Name	Biological activity	Ref.
	**27**	16-hydroxystecholide C acetate		12

Structure	No.	Name	Biological activity	Ref.
	**28**	stecholide I (R = COC_3H_7)	ED_{50} (P-388) = 23 μg/mL[a]	12
	29	stecholide J (R = Ac)		12
	**30**	stecholide K (R_1 = R_2 = Ac)		12
	31	stecholide L (R_1 = Ac, R_2 = H)	IC_{50} (P-388, A-549, HT-29, MEL-28) = 10, 2.5, 5, 5 μg/mL[b]	12,21
	32	stecholide M (R_1 = COC_3H_7, R_2 = H)		12
	**33**	stecholide N		12
	**34**	excavatolide A	ED_{50} (P-388, KB, A-549, HT-29) = >50, 2.5, 21.9, >50 μg/mL	13
	**35**	excavatolide B (R_1 = Ac, R_2 = COC_3H_7)	ED_{50} (P-388, KB, A-549, HT-29) = >50, >50, >50, >50 μg/mL	13
	36	excavatolide C (R_1 = R_2 = Ac)	ED_{50} (P-388, KB, A-549, HT-29) = 0.3, 1.9, 1.9, 1.9 μg/mL	13
	37	excavatolide D (R_1 = H, R_2 = Ac)	ED_{50} (P-388, KB, A-549, HT-29) = 1.8, 4.2, >50, 1.3 μg/mL	13
	**38**	excavatolide E	ED_{50} (P-388, KB, A-549, HT-29) = 1.6, 0.8, 1.2, 1.6 μg/mL	13
	**39**	excavatolide F	ED_{50} (P-388, KB, A-549, HT-29) = 6.2, 7.0, 5.2, 5.5 μg/mL	14
	**40**	excavatolide G	ED_{50} (P-388, KB, A-549, HT-29) = 15.7, >50, 22.8, >50 μg/mL	14

Structure	No.	Name	Biological activity	Ref.
	**41**	excavatolide H (R = COC_3H_7)	ED_{50} (P-388, KB, A-549, HT-29) = >50, >50, >50, >50 μg/mL	14
	42	excavatolide I (R = Ac)	ED_{50} (P-388, KB, A-549, HT-29) = >50, >50, >50, >50 μg/mL	14
	**43**	excavatolide J (R = COC_3H_7)	ED_{50} (P-388, KB, A-549, HT-29) = 3.8, 6.5, 5.2, 5.2 μg/mL	14
	44	excavatolide K (R = Ac)	ED_{50} (P-388, KB, A-549, HT-29) = 0.9, 3.3, 3.0, 1.3 μg/mL	14
	**45**	excavatolide L	ED_{50} (P-388, KB, A-549, HT-29) = 5.8, >50, 37.2, 4.4 μg/mL	13,14
	**46**	excavatolide M	ED_{50} (P-388, KB, A-549, HT-29) = 0.001, 1.0, 0.1, 2.2 μg/mL	14
	**47**	excavatolide N	IC_{50} (P-388, A-549, HT-29, MEL-28) = 5, >10, >10, >10 μg/mL	15
	**48**	excavatolide O	IC_{50} (P-388, A-549, HT-29, MEL-28) = 5, 5, 5, 10 μg/mL	15
	**49**	excavatolide P	IC_{50} (P-388, A-549, HT-29, MEL-28) = 5, >10, >10, >10 μg/mL	15
	**50**	excavatolide Q	IC_{50} (P-388, A-549, HT-29, MEL-28) = 5, 10, 10, 10 μg/mL	15

Structure	No.	Name	Biological activity	Ref.
	**51**	excavatolide R		15
	**52**	excavatolide S		15
	**53**	excavatolide T		15
	**54**	excavatolide U (R = COC_3H_7)	ED_{50} (P-388, KB, A-549, HT-29) = >50, >50, > 50, >50 μg/mL	16
	55	excavatolide V (R = Ac)	ED_{50} (P-388, KB, A-549, HT-29) = 3.9, 7.0, 19.1, 20.4 μg/mL	16
	**56**	excavatolide W	ED_{50} (P-388, KB, A-549, HT-29) = 19.4, >50, >50, >50 μg/mL	16
	**57**	excavatolide X (R_1 = Ac, R_2 = COC_3H_7)	ED_{50} (P-388, KB, A-549, HT-29) = >50, >50, >50, >50 μg/mL	16
	58	excavatolide Y (R_1 = COC_2H_5, R_2 = Ac)	ED_{50} (P-388, KB, A-549, HT-29) = 9.5, >50, >50, 15.1 μg/mL	16
	**59**	excavatolide Z	ED_{50} (P-388, KB, A-549, HT-29) = 1.3, 6.5, 11.2, 2.8 μg/mL	16
	**60**	briaexcavatolide A		17

Structure	No.	Name	Biological activity	Ref.
	**61**	briaexcavatolide B (R = COC_3H_7)	ED_{50} (P-388, KB) = 1.3, 1.5 μg/mL	17
	62	briaexcavatolide C (R = Ac)		17
	**63**	briaexcavatolide D		17
	**64**	briaexcavatolide E (R_1 = R_2 = Ac)		17
	65	briaexcavatolide F (R_1 = H, R_2 = COC_3H_7)	ED_{50} (A-549) = 1.3 μg/mL	17
	66	briaexcavatolide G (R_1 = R_2 = H)		17
	**67**	briaexcavatolide H (R = H)		17
	68	briaexcavatolide I (R = Ac)		17
	**69**	briaexcavatolide J		17
	**70**	briaexcavatolide K (R = Ac)		18
	71	briaexcavatolide L (R = COC_3H_7)	ED_{50} (P-388) = 0.5 μg/mL	18
	**72**	briaexcavatolide M (R = Cl)		18
	73	briaexcavatolide N (R = OH)		18
	**74**	briaexcavatolide O (R_1 = R_3 = H, R_2 = Ac)		19
	75	briaexcavatolide P (R_1 = Ac, R_2 = R_3 = H)	ED_{50} (P-388, A-549, HT-29) = 0.9, 4.8, 3.1 μg/mL	19
	76	briaexcavatolide Q (R_1 = R_3 = Ac, R_2 = H)		19

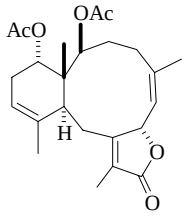
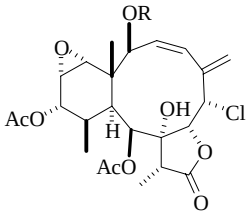
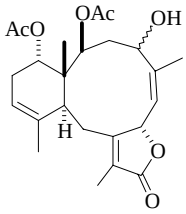
Structure	No.	Name	Biological activity	Ref.
	**77**	briaexcavatolide R		19
	**78**	brianthein A	cytotoxic toward the human epidermoid carcinoma KB 3-1 cell line and the multidrug resistance cell line KB-C2.	20
	**79**	brianthein B	cytotoxic toward the human epidermoid carcinoma KB 3-1 cells.	20
	**80**	brianthein C	cytotoxic toward the human epidermoid carcinoma KB 3-1 cells.	20

[a]For significant activity of pure compounds, an ED_{50} value $\leq$ 4.0 μg/mL is required. See ref. 22.
[b]These cytotoxic data were reported by Rodríguez *et al.* See ref. 21.

C. *Briareum polyanthes*

B. polyanthes, a new gorgonian species, was discovered at the eastern end of the Bermuda archipelago. This gorgonian coral was found to contain five new metabolites, including briantheins W–Z (**81**–**84**)[23–25] and an unnamed briarane (**85**).[26] The structures (**81**–**84**) were determined by spectral analyses (IR, UV, MS, ^{1}H and ^{13}C NMR), but the related spectral and physical data for metabolite (**85**) were not reported.[26] In addition, the ^{13}C NMR spectral data of brianthein X (**82**) was reassigned by Linz *et al*. in 1986 with 2D NMR techniques.[27] Besides, the structure of brianthein W (**81**) was further confirmed by single-crystal X-Ray diffraction analyses.[23] The absolute configuration of brianthein X (**82**) was established by chemical methods and X-Ray diffraction analyses.[28,29] In the insecticidal activity testing, brianthein Y (**83**) exhibited toxicity at a high dose but inactive at a low dose to the grasshoppers, *Melanoplus sanguinipes* and *M. bivitattus*.[26] Brianthein W (**81**) was also obtained from a Taiwanese gorgonian, *Briareum* sp.[30] and briantheins X–Z (**82**–**84**) were isolated from the *B. asbestinum*, that collected in Caribbean water.[8,29] Briaranes (**81**) and (**84**) exhibited cytotoxicity in the P-388 assay, and briaranes (**83**) and (**84**) displayed antiviral activity, respectively.[8,30]

Table 3. The Briarane-Type Metabolites from *B. polyanthes*

Structure	No.	Name	Biological activity	Ref.
	**81**	brianthein W	ED_{50} (P-388, KB, A-549, HT-29) = 0.76, >50, >50, >50 μg/mL[a]	23,30
	**82**	brianthein X (R = H)		24,27–29
	83	brianthein Y (R = COC_3H_7)	toxic at 3 mg/insect against grasshoppers, *M. sanguinipes* and *M. bivitattus*; show viral inhibition at 400 μg/mL in the *in vitro* mouse corona virus assay.[b]	8,24,26
	84	brianthein Z (R = Ac)	show *in vitro* cytotoxicity in the P-388 assay at 10 μg/mL; show viral inhibitions at 80 and 80 μg/mL in the *in vitro* mouse corona virus and Herpes simplex-1 virus assays, respectively.[b]	8,25
	**85**			26

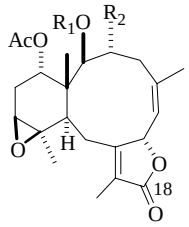
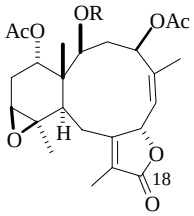
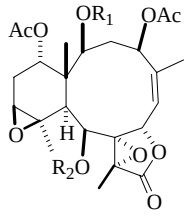
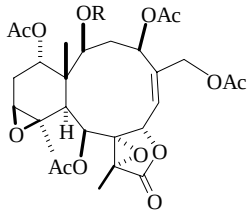
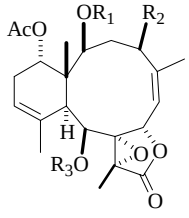
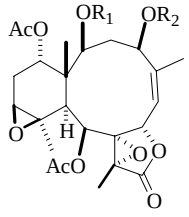
[a]The cytotoxic data of brianthein W (**81**) were reported by Sheu *et al*. See ref. 30.
[b]The antiviral and cytotoxic data of briantheins Y (**83**) and Z (**84**) were reported by Coval *et al*. See ref. 8.

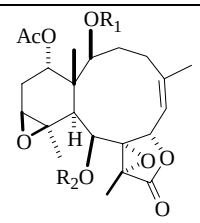
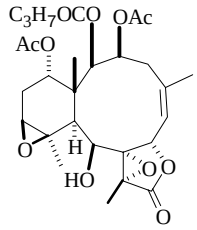
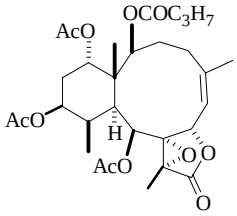
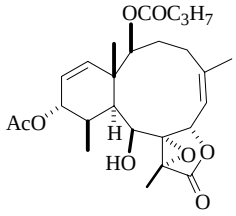
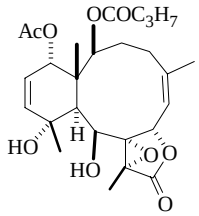
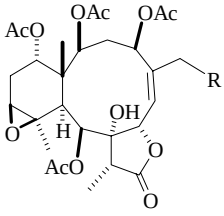
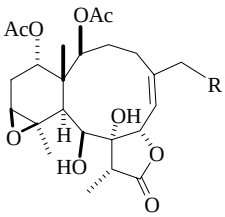
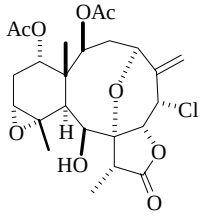
D. *Briareum stechei*

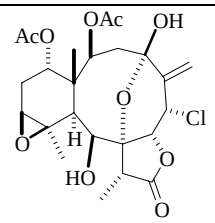
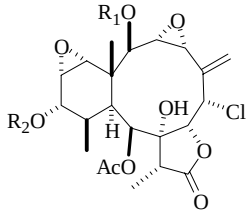
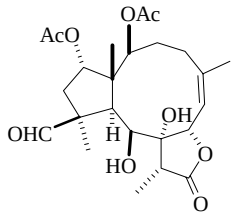
In the Great Barrier Reef water, *B. stechei* grows in shallow water reef habits as encrusting sheets exposed on living and dead hard coral skeletons, and in the vicinity of the growing edge of this organism, the hexacoral, *Porites andrewsi* (a hard coral) was dying. This interesting ecological phenomenon indicated the possibility of allelopathy in *B. stechei*. Based on above ecological character, the chemical constituents of *B. stechei* were studied and led to the isolation of four new briarane-type derivatives (**86**–**89**). The structures and relative stereochemistry of **86**–**89** were elucidated by NMR studies, and the single-crystal X-Ray determinations were performed on briaranes (**88**) and (**89**). However, the possible ecological roles of these metabolites are uncertain.[31] Twenty novel metabolites, designated stecholides (**90**–**109**), featuring the briarane carbon skeleton were isolated from the gorgonian coral, *B. stechei*, that was collected from the Dalton Reef area of the Australian Great Barrier Reef. The structures of metabolites (**90**–**109**) were deduced by extensive spectral analyses (IR, MS, ^{1}H and ^{13}C NMR). Briaranes (**90**, **92**, and **109**) showed cytotoxicity to P-388 tumor cells.[32] Moreover, eleven new briarane-type diterpene lactones, which were named miolides (**110**–**120**), were isolated from this organism that collected at the Mil channel, Yap, Federated States of Micronesia.[33] Briarane (**120**) is the first of the naturally occurring briarane lactones to

have a contracted ring-A with a bicyclo[8.3.0] system. Excavatolide A (**34**) was also obtained from this organism.

Table 4. The Briarane-Type Metabolites from *B. stechei*

Structure	No.	Name	Biological activity	Ref.
	**86**	(R_1 = COC_3H_7, R_2 = OAc)[a]		31
	87	(R_1 = COC_3H_7, R_2 = H)[b]		31
	**88**	(R = COC_3H_7)[c]		31
	89	(R = COC_2H_5)[d]		31
	90	stecholide A (R_1 = COC_3H_7, R_2 = H)	ED_{50} (P-388) = 4.5 μg/mL	32
	**91**	stecholide A acetate (R_1 = COC_3H_7, R_2 = Ac)		32
	92	stecholide B (R_1 = COC_2H_5, R_2 = H)	ED_{50} (P-388) = 5.4 μg/mL	32
	93	stecholide B acetate (R_1 = COC_2H_5, R_2 = Ac)		32
	94	stecholide C (R_1 = Ac, R_2 = H)		32
	95	stecholide C acetate (R_1 = R_2 = Ac)		32
	**96**	16-acetoxystecholide A acetate (R = COC_3H_7)		32
	97	16-acetoxystecholide B acetate (R = COC_2H_5)		32
	98	16-acetoxystecholide C acetate (R = Ac)		32
	**99**	11,12-deoxystecholide A acetate (R_1 = COC_3H_7, R_2 = OAc, R_3 = Ac)		32
	100	11,12-deoxystecholide E (R_1 = COC_3H_7, R_2 = R_3 = H)		32
	**101**	stecholide D (R_1 = COC_3H_7, R_2 = H)		32
	102	stecholide D butyrate (R_1 = R_2 = COC_3H_7)		32

Structure	No.	Name	Biological activity	Ref.
	**103**	stecholide E (R_1 = COC_3H_7, R_2 = H)		32
	104	stecholide E acetate (R_1 = COC_3H_7, R_2 = Ac)		32
	105	stecholide F (R_1 = COC_2H_5, R_2 = H)		32
	**106**	3-acetoxystecholide E		32
	**107**	11,12-deoxy-12-acetoxystecholide E acetate		32
	**108**	stecholide G		32
	**109**	stecholide H	ED_{50} (P-388) = 10 μg/mL	32
	**110**	milolide A (R = H)		33
	111	16-acetoxymilolide A (R = OAc)		33
	112	16-hydroxymilolide A (R = OH)		33
	**113**	milolide B (R = H)		33
	114	16-chloromilolide B (R = Cl)		33
	115	16-acetoxymilolide B (R = OAc)		33
	**116**	milolide C		33

Structure	No.	Name	Biological activity	Ref.
	**117**	4-hydroxymilolide C		33
	**118**	milolide D (R_1 = H, R_2 = COC_3H_7)		33
	119	milolide E (R_1 = Ac, R_2 = COC_5H_{11})		33
	**120**	milolide F		33

[a](1*R**,2*S**,3*R**,5*Z*,7*S**,8(17)*Z*,10*R**,11*R**,12*S**,14*S**)-3,14-diacetoxy-11,12-epoxy-18-oxobriara-5,8(17)-dien-2-yl butanoate
[b](1*R**,2*R**,5*Z*,7*S**,8(17)*Z*,10*R**,11*R**,12*S**,14*S**)-14-acetoxy-11,12-epoxy-18-oxobriara-5,8(17)-dien-2-yl butanoate
[c](1*R**,2*R**,4*R**,5*Z*,7*S**,8(17)*Z*,10*R**,11*R**,12*S**,14*S**)-4,14-diacetoxy-11,12-epoxy-18-oxobriara-5,8(17)-dien-2-yl butanoate
[d](1*R**,2*R**,4*R**,5*Z*,7*S**,8(17)*Z*,10*R**,11*R**,12*S**,14*S**)-4,14-diacetoxy-11,12-epoxy-18-oxobriara-5,8(17)-dien-2-yl propanoate

E. *Briareum* spp.

Based on the classic taxonomic analyses, gorgonian coral of the genus *Briareum* is recognized as a transitional species between the Alcyonacea and Gorgonacea, the two major orders of Octocorallia.[34] In some cases of the previous studies, the *Briareum* gorgonian corals were even identified as a soft coral of the order Stolonifera, *Pachyclavularia violacea,* on the basis of their similarity in colonial morphology.[30,35,36] Besides, the *Briareum stechei* was collected as a *Parerythropodium* species (order Alcyonacea, family Alcyoniidae).[31] However, the specimen identification were subsequently revised on the basis of their chemical constituents.

Six new diterpenoids, solenolides A–F (**121**–**126**), were isolated from a gorgonian, *Briareum* sp. collected in the Western Caroline Islands of Palau. The structures of briaranes (**121**–**126**) were assigned by spectroscopic (IR, UV, MS, ^{1}H and ^{13}C NMR) and chemical methods.[37] However, the stereochemistry of solenolides C (**123**) and D (**124**) is revised by detailed spectral analyses (^{1}H NMR) and by the interpretations of MM2 molecular mechanics calculations, respectively.[33,38] Under the revisions, solenolide D (**124**) and briaexcavatolide E (**64**) were proved to be the same metabolite. Due to the potential biological activities, some research groups start to synthesize the solenolide derivatives.[39,40]

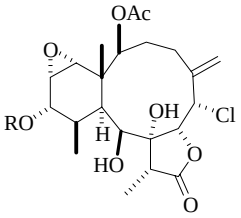
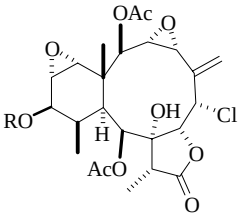
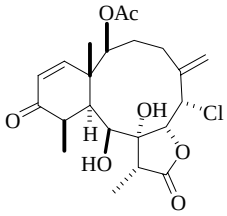
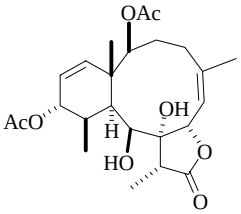
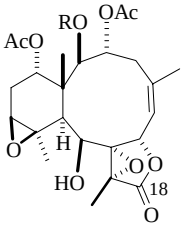
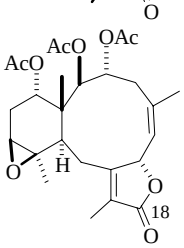
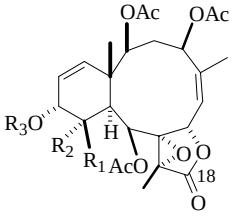
Eleven new metabolites (**127**–**137**) possessing the briarane carbon skeleton, were isolated from the dichloromethane extracts of the Australian gorgonians, *Briareum* spp. The structures of metabolites

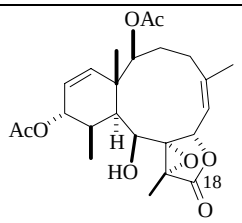
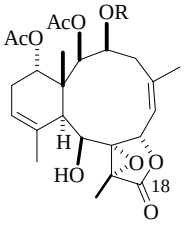
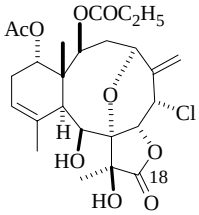
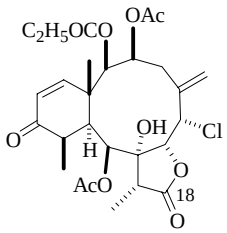
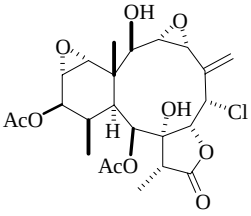
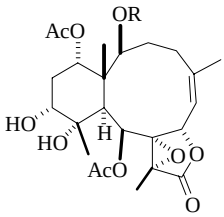
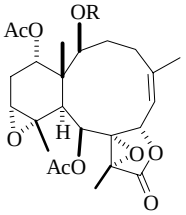
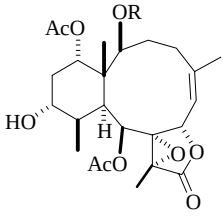
(**127**–**137**) were elucidated by NMR (1D and 2D) and chemical methods.[34,35] Metabolite (**136**) is the first briarane possessing a 17-hydroxyl group. Briarane (**133**) was also obtained from the Taiwanese gorgonian coral, *B. excavatum*.[18]

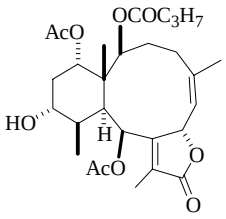
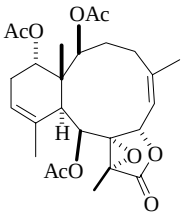
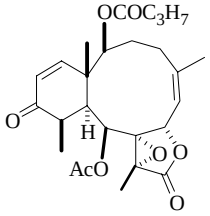
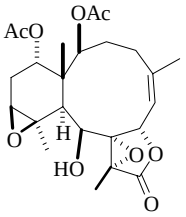
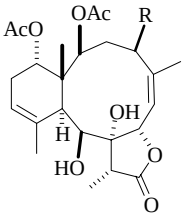
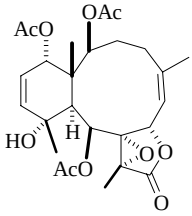
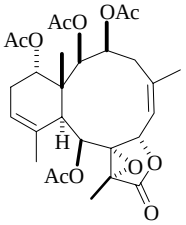
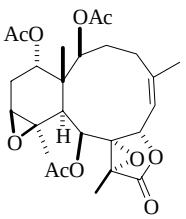
Brianolide (**138**), a new antiinflammatory diterpenoid of the briarane class, was isolated from an Okinawa gorgonian, *Briareum* sp. The structure, including the absolute stereochemistry of **138** was determined on the basis of single-crystal X-Ray analyses of the monoacetate (**138**) prepared by acetylation of **138** with Ac_2O/pyridine.[41] A gorgonian coral, *Briareum* sp. (identified as either *B. asbestinum* or *B. polyanthes*), from Puerto Rico contained nine new briarane derivatives (**139**–**147**), which have been named briareolides A–I, respectively. The structures of briaranes (**139**–**147**) were determined by spectroscopic methods (IR, UV, MS, ^{1}H and ^{13}C NMR), including 2D NMR spectral analyses. The structure and absolute stereochemistry of briareolide B (**140**) were further confirmed by X-Ray crystallographic analyses. Briareolides A–E (**139**–**143**) have displayed antiinflammatory activity.[42] Collections of the gorgonian *Briareum* sp. from the coast of Taiwan yielded three new briaranes, 2β-acetoxy-2-debutyryloxystecholide E (**148**), 9-deacetylstylatulide lactone (**149**), and 4β-acetoxy-9-deacetylstylatulide lactone (**150**). The structures and relative stereochemistry of these metabolites were determined by the combination of spectroscopic (IR, MS, ^{1}H and ^{13}C NMR) and chemical methods.[30] In addition, the ^{13}C NMR spectral data of brianthein W (**81**) was revised in this study. In 1998, an Indonesian gorgonian, *Briareum* sp., has afforded two new stecholide metabolites, 2,9-diacetyl-2-debutyrylstecholide H (**151**) and 13-dehydroxystecholide J (**152**), along with the semisynthetic product, 2β-acetoxy-2- debutyryloxystecholide E acetate (**153**), which was isolated as a natural product for the first time.[21,43] The structures of metabolites (**151**–**153**) were deduced by extensive NMR studies, and by comparison the spectral and physical data with those of the other known briarane-type metabolites, and the relative configuration of briarane (**152**) was further confirmed by MMX energy minimization calculations.[21]

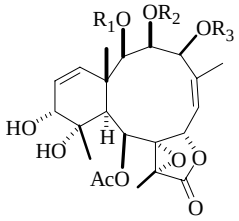
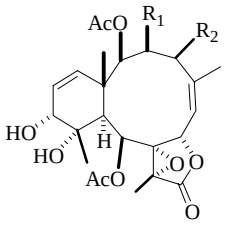
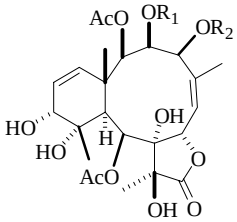
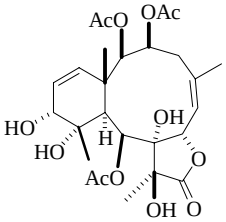
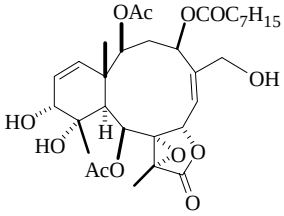
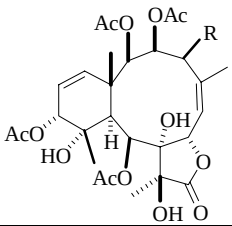
The organic extracts of a gorgonian, *Briareum* sp., collected in the area of Bonotsu, Kagoshima Prefecture, Japan, which show ichthyotoxicity against Japanese killifish, *Orzia latipes*. Bioassay guided fractionation of the extracts, sixteen novel polyoxygenated briaranes, violides A–P (**154**–**169**), were obtained from this organism.[36,44–46] The structures of compounds (**154**–**169**) were elucidated by the interpretations of spectral analyses (IR, MS, ^{1}H and ^{13}C NMR) and chemical methods. The structures and relative configurations of violides A (**154**) and J (**163**) were further confirmed by X-Ray diffraction analyses.[36,45] The violides A–F (**154**–**159**), J–L (**163**–**165**), and O (**168**) were found to contain independent oxygenated functional groups at C-2, C-3, and C-4 positions.[36,44–46] Compounds of this type are rarely found in related studies.[15,19] Furthermore, violides K (**164**) and L (**165**), the only briarane-type metabolites were found to exist pentahydroxyl groups in structures.[45] Violides B (**155**), E (**158**), G (**160**), and H (**161**) were also isolated from a Japanese gorgonian, *Briareum* sp., collected in the sea near Satsuma Peninsula, Japan.[47]

Table 5. The Briarane-Type Metabolites from *Briareum* spp.

Structure	No.	Name	Biological activity	Ref.
	**121**	solenolide A (R = COC_5H_{11})	excess of 70% reduction of edema at concentration in the range of 15 μg; inhibit the arachidonic acid pathway enzyme 5-lipoxygenase; IC_{50} (Rhinovirus) = 0.39 μg/mL; ihhibit Polio III, Herpes, Ann Arbor, and Maryland viruses.	37
	122	solenolide B (R = Ac)		37
	**123**	solenolide C (R = H)[a]		33,37,38
	124	solenolide D (R = Ac)[a]	excess of 70% reduction of edema at concentration in the range of 15 μg; ihhibits Semiliki Forest and Ann Arbor viruses.	37,38
	**125**	solenolide E	excess of 70% reduction of edema at concentration in the range of 15 μg; inhibitor of the arachidonic acid pathway enzyme cyclooxygenase; IC_{50} (Rhinovirus) = 12.5 μg/mL; ihhibit Herpes and Ann Arbor viruses.	37
	**126**	solenolide F	excess of 70% reduction of edema at concentration in the range of 15 μg. solenolides A–F (**121**–**126**) show activity against Blowfly larvae at 30–35 ppm.	37
	**127**	(R = Ac)[b]		34
	128	($R = COC_3H_7$)[c]		34
	**129**[d]			34
	**130**	(R_1 = OH, R_2 = CH_3, R_3 = Ac)[e]		34
	131	(R_1 = CH_3, R_2 = OH, R_3 = H)[f]		34
	132	(R_1 = CH_3, R_2 = OH, R_3 = Ac)[g]		34

Structure	No.	Name	Biological activity	Ref.
	**133**[h]		ED_{50} (P-388, HT-29) = 0.4, 1.1 μg/mL[i]	18,34
	**134**	(R = COC_3H_7)[j]		34
	135	(R = Ac)[k]		34
	**136**[l]			35
	**137**[m]			35
	**138**	brianolide	37% reduction of edema at concentration in the range of 25 μg (mouse ear assay).	41
	**139**	briareolide A (R = COC_3H_7)	Briareolides A–E (**139**–**143**) show 71, 55, 75, 85, and 46% inhibition of inflammation in the mouse ear assay, respectively (50 μg/mL).	42
	140	briareolide B (R = Ac)		42
	**141**	briareolide C (R = COC_3H_7)		42
	142	briareolide D (R = Ac)		42
	**143**	briareolide E (R = COC_3H_7)		42
	144	briareolide F (R = Ac)		42

Structure	No.	Name	Biological activity	Ref.
	**145**	briareolide G		42
	**146**	briareolide H		42
	**147**	briareolide I		42
	**148**	2β-acetoxy-2-debutyryloxy-stecholide E	ED_{50} (P-388, KB, A-549, HT-29) = 0.61, >50, >50, 6.96 μg/mL	30
	**149**	9-deacetylstylatulide lactone (R = H)	ED_{50} (P-388, KB, A-549, HT-29) = 1.12, >50, >50, 1.79 μg/mL	30
	150	4β-acetoxy-9-deacetylstylatulide lactone (R = OAc)	ED_{50} (P-388, KB, A-549, HT-29) = >50, >50, >50, >50 μg/mL	30
	**151**	2,9-diacetyl-2-debutyryl-stecholide H		21
	**152**	13-dehydroxystecholide J		21
	**153**	2β-acetoxy-2-debutyryloxy-stecholide E acetate	ED_{50} (P-388, KB, A-549, HT-29) = 1.59, 24.45, 17.39, 10.07 μg/mL^n	21,30

Structure	No.	Name	Biological activity	Ref.
	154	violide A (R_1 = Ac, R_2 = H, R_3 = COC_7H_{15})	CC_{50} (Vero, MDCK) = 1.90, 1.90 μg/mL	36,44,45
	155	violide B (R_1 = R_2 = R_3 = Ac)		36,44
	**156**	violide C (R_1 = R_2 = Ac, R_3 = COC_7H_{15})	CC_{50} (Vero, MDCK) = 1.69, 1.67 μg/mL	44,45
	157	violide D (R_1 = R_2 = Ac, R_3 = COC_5H_{11})	CC_{50} (Vero, MDCK) = 2.53, 3.57 μg/mL	44,45
	158	violide E (R_1 = R_2 = Ac, R_3 = COC_3H_7)	CC_{50} (Vero, MDCK) = 3.65, 4.69 μg/mL	44,45
	159	violide F (R_1 = R_2 = H, R_3 = COC_7H_{15})	CC_{50} (Vero, MDCK) = 3.93, 4.03 μg/mL	44,45
	**160**	violide G (R_1 = OAc, R_2 = H)	CC_{50} (Vero, MDCK) = 9.37, 11.7 μg/mL	44,45
	161	violide H (R_1 = H, R_2 = $OCOC_7H_{15}$)	CC_{50} (Vero, MDCK) = 0.85, 0.85 μg/mL	44,45
	162	violide I (R_1 = H, R_2 = $OCOC_5H_{11}$)	CC_{50} (Vero, MDCK) = 1.41, 1.30 μg/mL	44,45
	**163**	violide J (R_1 = R_2 = Ac)	CC_{50} (Vero, MDCK) = >100, >100 μg/mL	45
	164	violide K (R_1 = H, R_2 = COC_7H_{15})	CC_{50} (Vero, MDCK) = >100, >100 μg/mL	45
	165	violide L (R_1 = H, R_2 = COC_5H_{11})	CC_{50} (Vero, MDCK) = >100, >100 μg/mL	45
	**166**	violide M	CC_{50} (Vero, MDCK) = >100, >100 μg/mL	45
	**167**	violide N	CC_{50} (Vero, MDCK) = 3.3, 3.2 μg/mL	46
	**168**	violide O (R = OAc)	CC_{50} (Vero, MDCK) = >100, >100 μg/mL	46
	169	violide P (R = H)	CC_{50} (Vero, MDCK) = >100, >100 μg/mL	46

[a]The structures of solenolides C (**123**) and D (**124**) have been revised. See ref. 33 and 38.
[b](1*R**,2*R**,3*R**,5*Z*,7*S**,8*S**,9*S**,10*S**,11*R**,12*S**,14*S**,17*R**)-2,3,14-triacetoxy-8,17:11,12-bisepoxy-9-hydroxybriara-5-en-18-one
[c](1*R**,2*R**,3*R**,5*Z*,7*S**,8*S**,9*S**,10*S**,11*R**,12*S**,14*S**,17*R**)-3,14-diacetoxy-2-butyryloxy-8,17:11,12-bisepoxy-9-hydroxy-

briara-5-en-18-one
[d](1*R**,2*R**,3*R**,5*Z*,7*S**,8(17)*Z*,10*R**,11*R**,12*S**,14*S**)-2,3,14-triacetoxy-11,12-epoxybriara-5,8(17)-dien-18-one
[e](1*S**,2*S**,4*R**,5*Z*,7*S**,8*S**,9*S**,10*S**,11*R**,12*R**,13*Z*,17*R**)-2,4,9,12-tetraacetoxy-8,17-epoxy-11-hydroxybriara-5,13-dien-18-one
[f](1*S**,2*S**,4*R**,5*Z*,7*S**,8*S**,9*S**,10*S**,11*S**,12*R**,13*Z*,17*R**)-2,4,9-triacetoxy-8,17-epoxy-11,12-dihydroxybriara-5,13-dien-18-one
[g](1*S**,2*S**,4*R**,5*Z*,7*S**,8*S**,9*S**,10*S**,11*S**,12*R**,13*Z*,17*R**)-2,4,9,12-tetraacetoxy-8,17-epoxy-11-hydroxybriara-5,13-dien-18-one
[h](1*S**,2*S**,5*Z*,7*S**,8*S**,9*S**,10*S**,11*R**,12*R**,13*Z*,17*R**)-2,12-diacetoxy-8,17-epoxy-9-hydroxybriara-5,13-dien-18-one
[i]These cytotoxic data were reported by Sung *et al*. See ref. 18.
[j](1*R**,2*R**,3*S**,5*Z*,7*S**,8*S**,9*S**,10*S**,11*Z*,14*S**,17*R**)-2,14-diacetoxy-3-butyryloxy-8,17-epoxy-9-hydroxybriara-5,11-dien-18-one
[k](1*R**,2*R**,3*S**,5*Z*,7*S**,8*S**,9*S**,10*S**,11*Z*,14*S**,17*R**)-2,3,14-triacetoxy-8,17-epoxy-9-hydroxybriara-5,11-dien-18-one
[l](1*R**,2*S**,4*S**,6*S**,7*R**,8*R**,9*S**,10*S**,11*Z*,14*S**,17*S**)-14-acetoxy-6-chloro-4,8-epoxy-9,17-dihydroxy-2-propionyloxybriara-5(16),11-dien-18-one
[m](1*R**,2*R**,3*S**,6*S**,7*R**,8*R**,9*S**,10*S**,11*R**,13*Z*)-3,9-diacetoxy-6-chloro-8-hydroxy-2-propionyloxybriara-5(16),13-diene-12,18-dione
[n]These cytotoxic data were reported by Sheu *et al*. See ref. 30.

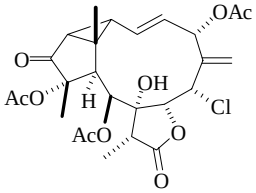
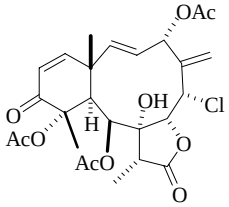
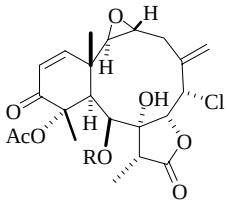
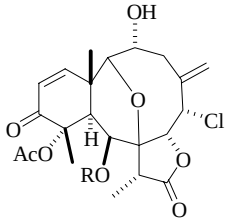
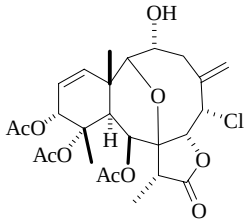
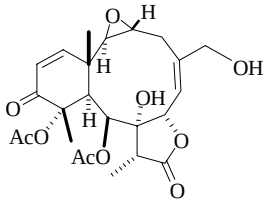
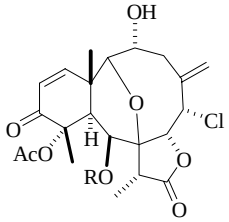
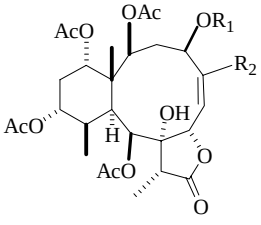
2.2 *Erythropodium* (family Spongiodermatinae)

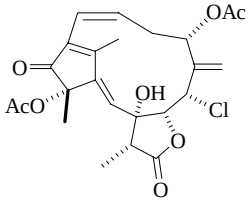
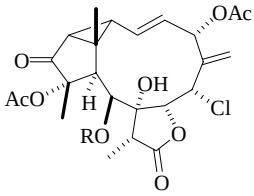
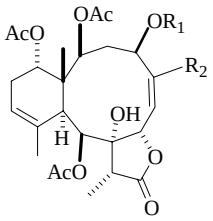
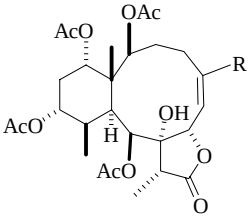
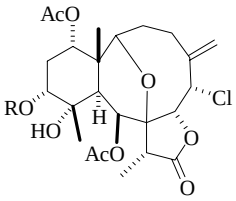
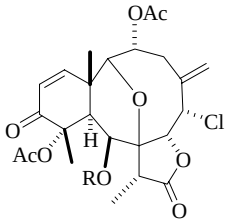
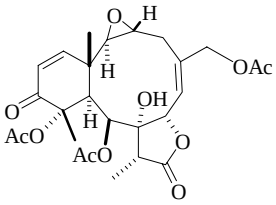
A. *Erythropodium caribaeorum*

Relatively uncommon, the only documented species of the genus, *E. caribaeorum*, can be found in the Caribbean water. *E. caribaeorum* produces a series of diterpenoids of the briarane skeleton class. Erythrolides A (**170**) and B (**171**) were isolated from the $CHCl_3$ extract of *E. caribaeorum*, that was collected at Carrie Bow Cay, Belize. The structure, including the absolute stereochemistry of erythrolide A (**170**) was elucidated by X-Ray crystallographic methods, and the structure of erythrolide B (**172**) was determined by the interpretations of spectral analyses (^{1}H and ^{13}C NMR) and chemical methods.[48] It is noted that erythrolide A (**170**) appeared to be produced in nature from erythrolide B (**171**) by a di-π-methane rearrangement. In the continuing researches for *E. caribaeorum*, fifteen novel diterpenoids, erythrolides C–Q (**172**–**186**),[42,49–51] and three unnamed new erythrolide derivatives (**187**–**189**),[52] have been isolated from the gorgonian coral, *E. caribaeorum*, collected in the West Indian Islands. The structures and relative configurations of erythrolides (**172**–**189**) were elucidated by extensive spectral analyses (IR, UV, MS, ^{1}H and ^{13}C NMR), including 1D and 2D NMR studies. In addition, the structures and absolute stereochemistry of erythrolides K (**180**) and P (**185**) were confirmed by X-Ray crystallographic methods.[50,51] The diterpenoids from *E. caribaeorum* possess certain structural features not found so far in the literatures for compounds of briarane-type. Erythrolides A (**170**) and L (**181**) possess di-π-methane rearrangement carbon skeletons. Erythrolides C (**172**), D (**173**), H (**177**), and metabolite (**189**) have 2*R**,3*R**-epoxy groups in the ten-membered rings while erythrolides E–G (**174**–**176**), I (**178**), P (**185**), Q (**186**), and metabolites (**187** and **188**) have ether bridges across the ten-membered rings between C-2 and C-8. Erythrolides D (**173**), F (**175**), L (**181**), and compound (**188**) contain unusual acetoxyacetate groups attaching at C-9. Erythrolides J (**179**), M (**182**), and N (**183**) contain 4-acetoxybutanoyl groups. Erythrolide K (**180**) possesses an unusual bicyclo[9.2.1] tetradecane skeleton. On basis of the special structural features, erythrolide derivatives may well be chemotaxonomic markers for *E. caribaeorum*. Erythrolides B (**171**)

and D (**173**) were found to show feeding deterrent effect to inhibit fish feeding behavior in field assays.[53]

Table 6. The Briarane-Type Metabolites from *E. caribaeorum*

Structure	No.	Name	Biological activity	Ref.
	**170**	erythrolide A		48
	**171**	rythrolide B	show feeding deterrent effect to inhibit fish feeding behavior in field assays.	48,53
	**172**	erythrolide C (R = Ac)		42
	173	erythrolide D (R = $COCH_2OAc$)	show feeding deterrent effect to inhibit fish feeding behavior in field assays.	42,53
	**174**	erythrolide E (R = Ac)		42
	175	erythrolide F (R = $COCH_2OAc$)		42
	**176**	erythrolide G		42
	**177**	erythrolide H		42
	**178**	erythrolide I (R = $COCH_2OH$)		42
	**179**	erythrolide J (R_1 = $COCH_2CHCH_3(OAc)$, R_2 = $COOCH_3$)		49

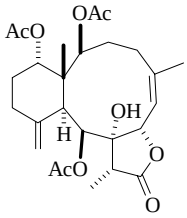
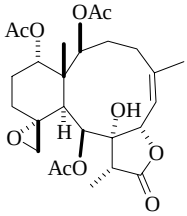
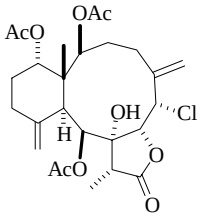
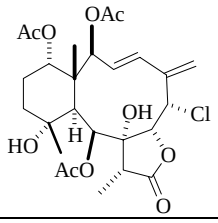
Structure	No.	Name	Biological activity	Ref.
	**180**	erythrolide K		50
	**181**	erythrolide L (R = $COCH_2OAc$)		51
	**182**	erythrolide M (R_1 = $COCH_2CH(CH_3)OAc$, R_2 = CH_3)		51
	183	erythrolide N (R_1 = $COCH_2CH(CH_3)OAc$, R_2 = CH_2OH)		51
	**184**	erythrolide O (R = $COOCH_3$)		51
	**185**	erythrolide P (R = H)		51
	186	erythrolide Q (R = Ac)		51
	**187**	(R = Ac)		52
	188	(R = $COCH_2OAc$)		52
	**189**			52

2.3 *Gorgonella* (family Ellisellidae)

A. *Gorgonella umbraculum*

Four new briarane-type diterpenoids, umbraculolides A–D (**190**–**193**), were isolated from the Indian Ocean gorgonian coral, *G. umbraculum*, collected from Tuticorin area of the Bay of Bengal and Vallinukum coast, Tamil Nadu, India, respectively, and their structures were established by extensive spectroscopic methods (IR, UV, MS, ^{1}H and ^{13}C NMR).[54,55] Umbraculolide A (**190**) showed antibacterial activity.[54]

Table 7. The Briarane-Type Metabolites from *G. umbraculum*

Structure	No.	Name	Biological activity	Ref.
	**190**	umbraculolide A	antibacterial activity against *Bacillus pumilus* at 500 μg/mL.	54,55
	**191**	umbraculolide B		55
	**192**	umbraculolide C		55
	**193**	umbraculolide D		55

2.4 *Junceella* (family Ellisellidae)

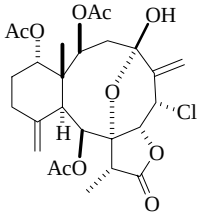
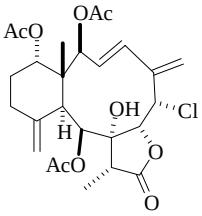
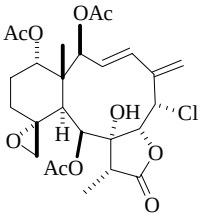
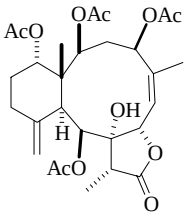
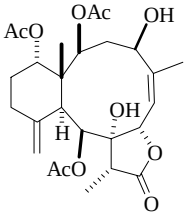
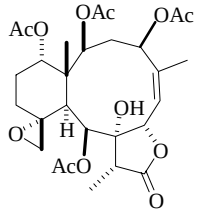
A. *Junceella fragilis*

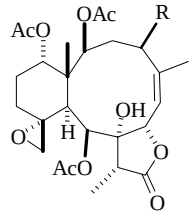
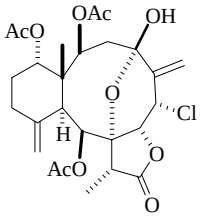
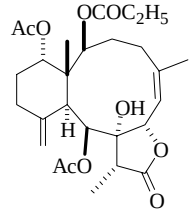
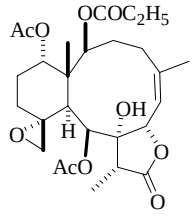
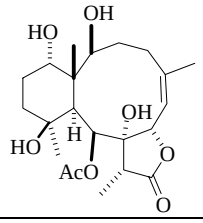
In 1989, Shin *et al*. reported the occurrence of four novel briarane derivatives, which were named junceellolides A–D (**194**–**197**), in the South China Sea gorgonian coral, *J. fragilis*, collected from coastal water off the Sanya Bay, Hainan Island, People's Republic of China. The structure determination works of junceellolides A–D (**194**–**197**) were based on spectral analyses (IR, UV, MS, ^{1}H and ^{13}C NMR).[56] In the biological activity testing, junceellolide B (**195**) showed antiviral activities against Herpes simplex viruses I and II. As antiinflammatory agents, junceellolides A–D (**194**–**197**) have displayed antiinflammtory activity, and junceellolides B (**195**) and C (**196**) were found to inhibit bee venom-derived phospholipase A_2 *in vitro* testing.[56] Four new diterpenoids with briarane skeleton, (–)-4-deacetyljunceellolide D (**198**), (+)-11α,20α-epoxyjunceellolide D (**199**), (–)-11α,20α-epoxy-4-deacetyljunceellolide D (**200**), and (–)-11α,20α-epoxy-4-deacetoxyjunceellolide D (**201**), were isolated from the Indonesian gorgonian coral *J. fragilis*. The structures of the new metabolites (**198**–**201**) were established on the basis of extensive NMR studies and by comparison the spectral data (^{1}H and ^{13}C NMR) with those of the other known briarane compounds. The absolute configurations for briaranes (**198**–**201**) were determined by the modified Mosher's method and by unambiguous chemical interconversions.[57] Besides, a solid, (+)-junceellolide A

(**202**) ($[\alpha]_D$ +3.1°; *c* 0.6, $CHCl_3$), which was proven as the antipodal derivative of (–)-junceellolide A (**194**) ($[\alpha]_D$ –7.9°; *c* 0.6, $CHCl_3$) by the rotation value.[56,57]

A species of *J. fragilis*, collected in the Taiwanese tropical water, yielded three new briaranes, junceellolides E–G (**203**–**205**). The structures, including the relative stereochemistry of metabolites (**203**–**205**) were elucidated from extensive NMR experiments, and the structure of **203** was further confirmed by X-Ray crystallography.[58] The six-membered rings in junceellolides E (**203**) and F (**204**) were found to exist in boat conformations.[58]

Table 8. The Briarane-Type Metabolites from *J. fragilis*

Structure	No.	Name	Biological activity	Ref.
	**194**	junceellolide A	reduction in edema of 88.4 %	56
	**195**	junceellolide B	antiviral activities against Herpes simplex viruses I and II within concentration ranges of 27 to 52 μg/mL; reduction in edema of 70.2%; inhibit bee venom-derived phospholipase A_2 in *in vitro* testing.	56
	**196**	junceellolide C	reduction in edema of 80.0 %; inhibit bee venom-derived phospholipase A_2 in *in vitro* testing.	56
	**197**	junceellolide D	reduction in edema of 82.3 %	56
	**198**	(–)-4-deacetyljunceellolide D		57
	**199**	(+)-11α,20α-epoxyjunceellolide D		57

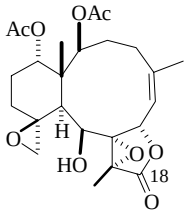
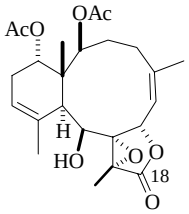
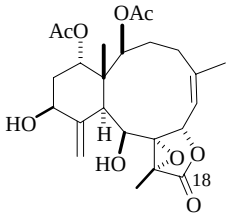
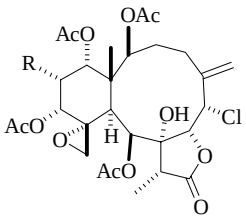
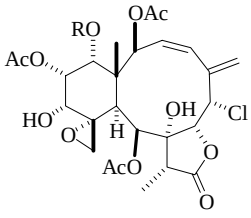
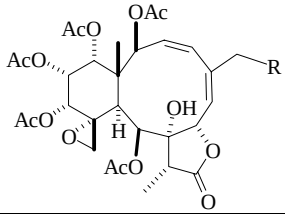
Structure	No.	Name	Biological activity	Ref.
	**200**	(–)-11α,20α-epoxy-4-deacetyl-junceellolide D (R = OH)		57
	201	(–)-11α,20α-epoxy-4-deacetoxy-junceellolide D (R = H)		57
	**202**	(+)-junceellolide A		57
	**203**	junceellolide E		58
	**204**	junceellolide F		58
	**205**	junceellolide G		58

B. *Junceella gemmacea*

Three new briaranes (**206**–**208**) were isolated from the gorgonian coral, *J. gemmacea*, collected at Broadhurst Reef, Australia. The structures, including the absolute sterechemistry of compounds (**206**–**208**) were deduced on the basis of extensive 1D and 2D NMR and Horeau kinetic resolution experiments.[59] Compound (**207**) was also isolated from a Taiwanese gorgonian coral, *Briareum* sp., and designated as 9-deacetylbriareolide H.[30] In addition, six new highly oxidized diterpenoids, gemmacolides A–F (**209**–**214**), were isolated from the gorgonian coral, *J. gemmacea*, collected at Jokaj Pass, Kolonia, Pohnpei, Micronesia. The structures and relative configurations of gemmacolides A–F (**209**–**214**) were assigned on the basis of extensive NMR studies.[60] Gemmacolide E (**213**) is the first 14-hydroxylbriarane-type metabolite. In the insecticidal activity testing, gemmacolide A (**209**) showed activity against the newly hatched larvae of the southern corn rootworm, *Diabrotica undecimpunctata howardi* and the tobacco budworm, *Heliothis virescens*, respectively.[61] Gemmacolides A (**209**), B (**210**), and D (**212**) exhibited selective immunomodulatory activity with MLR (mixed lymphocyte reaction) to LcV (lymphocyte viability) in

ratios of 23, 23, and 11, respectively. The ratios indicate immunosuppressive activity at concentrations significantly lower than the cytotoxicity levels.[62]

Table 9. The Briarane-Type Metabolites from *J. gemmacea*

Structure	No.	Name	Biological activity	Ref.
	**206**[a]			59
	**207**	9-deacetylbriareolide H[b]	ED_{50} (P-388, KB, A-549, HT-29) = 0.28, 0.27, 10.35, 8.27 μg/mL[c]	30,59
	**208**[d]			59
	**209**	gemmacolide A (R = OAc)	insecticidal activity against the newly hatched larvae of the southern corn rootworm, *D. undecimpunctata howardi* and the tobacco budworm, *H. virescens*; selective immunomodulatory activity with MLR to LcV in ratio of 23.	60–62
	210	gemmacolide B (R = $OCOCH_2CH(CH_3)_2$)	selective immunomodulatory activity with MLR to LcV in ratio of 23.	60,62
	211	gemmacolide C (R = H)		60
	**212**	gemmacolide D (R = Ac)	selective immunomodulatory activity with MLR to LcV in ratio of 11.	60–62
	213	gemmacolide E (R = H)		60
	**214**	gemmacolide F (R = OAc)		60

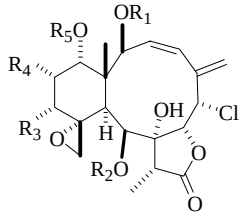
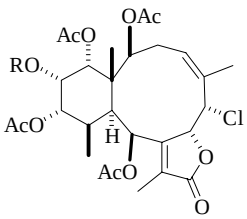
[a](1*R*,2*R*,5*Z*,7*R*,8*S*,9*R*,10*R*,11*R*,14*R*,17*S*)-2,14-diacetoxy-8,17:11,20-bisepoxy-9-hydroxybriara-5-en-18-one
[b](1*R*,2*R*,5*Z*,7*R*,8*S*,9*R*,10*R*,11*Z*,14*R*,17*S*)-2,14-diacetoxy-8,17-epoxy-9-hydroxybriara-5,11-dien-18-one
[c]The cytotoxic data of briarane (**207**) were reported by Sheu *et al*. See ref. 30.
[d](1*R*,2*R*,5*Z*,7*R*,8*S*,9*R*,10*R*,12*R*,14*R*,17*S*)-2,14-diacetoxy-8,17-epoxy-9,12-dihydroxybriara-5,11(20)-dien-18-one

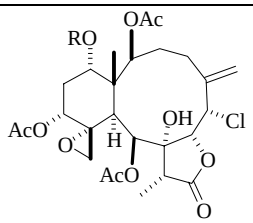
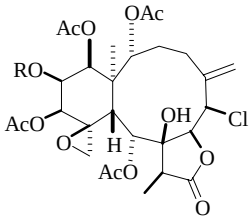
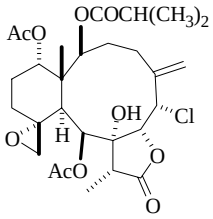
C. *Junceella juncea*

Isaacs *et al*. have isolated six new diterpenoids, denoted as juncins A–F (**215**–**220**) from *J. juncea*. The organisms were collected from sites in the entrances to the Gulf of Eilat and Gulf of Suez, Red Sea. Their structures and relative configurations were determined through a combination of 1D and 2D NMR spectral analyses, and the absolute stereochemistry of juncin E (**219**) was established by X-Ray analyses.[62,63] However, the locations of acyl groups in juncins C (**217**) and F (**220**) were not determined completely.[63] Juncin E (**219**) showed insecticidal activity against the newly hatched larvae of the southern corn rootworm, *Diabrotica undecimpunctata howardi*, and the tobacco budworm, *Heliothis virescens*, respectively.[61]

Two new briarane-type metabolites, juncins G (**221**) and H (**222**), along with the antipodal derivatives of known gemmacolides A (**223**) and B (**224**) were isolated from the gorgonian coral *J. juncea* collected in the Indian Ocean.[64] The NMR spectral data (^{1}H and ^{13}C) of metabolites (**223**) and (**224**) were identical with those of gemmacolides A (**209**) and B (**210**), respectively. However, they differed in their physical state and sign of specific rotation, and the structures of briaranes (**223**) and (**224**) could then regarded as (+)-gemmacolide A and (+)-gemmacolide B, respectively.[60,64] In addition, a new cytotoxic briarane, juncenolide A (**225**), was isolated from the Taiwanese gorgonian coral, *J. juncea*. The structure of **225** was established by 2D NMR studies, and further confirmed by X-Ray crystallographic analyses.[65]

Table 10. The Briarane-Type Metabolites from *J. juncea*

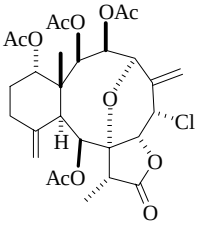
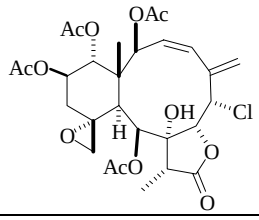
Structure	No.	Name	Biological activity	Ref.
	215	juncin A ($R_1 = R_2 = R_5 = Ac$, $R_3 = R_4 = H$)		63
	216	juncin B ($R_1 = R_2 = R_5 = Ac$, $R_3 = R_4 = H$, 11,20-deoxy)		63
	**217**	juncin C (R_1, OR_3, R_5, = 2Ac + isovalerate, $R_2 = Ac$, $R_4 = H$)		63
	218	juncin D ($R_1 = R_2 = R_5 = Ac$, $R_3 = OAc$, $R_4 = H$)		63
	219	juncin E ($R_1 = R_2 = R_5 = Ac$, $R_3 = R_4 = OAc$)	insecticidal activity against the newly hatched larvae of the southern corn rootworm, *D. undecimpunctata howardi*, and the tobacco budworm, *H. virescens*.	61–63
	220	juncin F (R_1, R_2, OR_3, R_5, = 3Ac + isobutyrate, R_4 = H, 3,4-dihydro)		63
	**221**	juncin G ($R = COCH_2CH(CH_3)_2$)		64

Structure	No.	Name	Biological activity	Ref.
	**222**	juncin H (R = $COCH_2CH(CH_3)_2$)		64
	**223**	(+)-gemmacolide A (R = Ac)		64
	224	(+)-gemmacolide B ($R = COCH_2CH(CH_3)_2$)		64
	**225**	juncenolide A	cytotoxic toward the human colon adenocarcinoma (DLD) and oral epidermoid carcinoma (KB-16) cells at a concentration of 3.4 and 5.9 μg/mL, respectively.	65

D. *Junceella squmata*

The South China Sea gorgonian coral, *J. squmata*, was found to contain two new briarane-type metabolites, junceellins A (**226**) and B (**227**).[66,67] The structures of briaranes (**226**) and (**227**) were elucidated by spectral analyses (IR, UV, MS, ^1H and ^{13}C NMR). Furthermore, the structure and absolute stereochemistry of junceellin A (**226**) were determined by crystallographic method.[68] Junceellin A (**226**) was also isolated from the gorgonian corals *Junceella fragilis* and *Gorgonella umbraculum*,[54,56,57] and its hydrolytic products exhibited cytotoxicity toward the A-549 tumor cells.[69]

Table 11. The Briarane-Type Metabolites from *J. squmata*

Structure	No.	Name	Biological activity	Ref.
	**226**	junceellin A		54,56,57, 66,68,69
	**227**	junceellin B		67

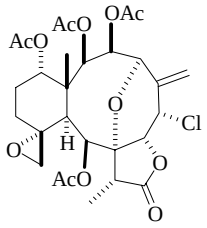
2.5 *Plexaureides* (family Plexauridae)

A. *Plexaureides praelonga*

Praelolide (**228**) is a new compound that was isolated from the South China Sea gorgonian coral, *P.*

praelonga. The structure, including the absolute stereochemistry of praelolide (**228**) was elucidated by a combination of spectral and X-Ray single-crystal diffraction analyses.[70,71] This metabolite was also isolated from both the gorgonian corals *Gorgonella umbraculum* and *Junceella fragilis*, and exhibited antiviral activity.[54,56,57]

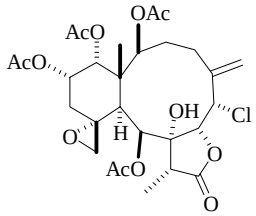
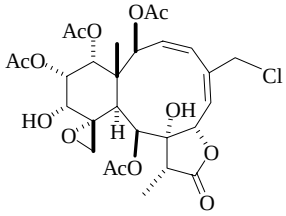
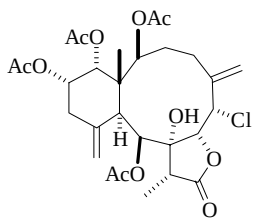
Table 12. The Briarane-Type Metabolite from *P. praelonga*

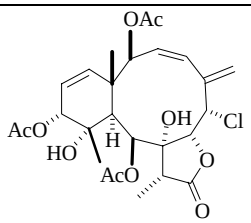
Structure	No.	Name	Biological activity	Ref.
	**228**	praelolide	antiviral activities against Herpes simplex viruses I and II within concentration ranges 27 to 52 μg/mL.	54,56,57, 70,71

2.6 Unidentified Gorgonian Corals

Four new briaranes, nui-inoalides A–D (**229**–**232**), were isolated from the undescribed gorgonian corals collected in Pohnpei and Ant atoll, Micronesia.[62] The structures of the new briaranes (**229**–**232**) were determined by spectral analyses. The authors supposed that nui-inoalide B (**230**) might have arisen from an allylic rearrangement of the corresponding 6-chlorobriarane, gemmacolide D (**212**). Nui-inoalide A (**229**) exhibited selective immunomodulatory activity with mixed lymphocyte reaction (MLR) to lymphocyte viability (LcV) in ratio of 15.[62]

Table 13. The Briarane-type Metabolites from the Unidentified Gorgonian Corals

Structure	No.	Name	Biological activity	Ref.
	**229**	nui-inoalide A	selective immunomodulatory activity with MLR to LcV in ratio 15.	62
	**230**	nui-inoalide B		62
	**231**	nui-inoalide C		62

Structure	No.	Name	Biological activity	Ref.
	**232**	nui-inoalide D		62

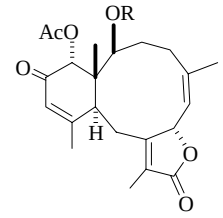
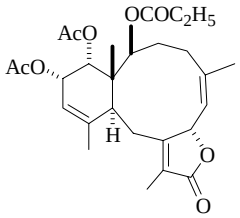
3. PENNATULACEA

3.1 *Anthoptilum* (family Anthoptilidae)

A. *Anthoptilum* cf. *kukenthali*

Marine coelenterates of the order Pennatulacea have been proven to be rich sources of diterpenoids featuring the skeletal class of briarane. The Australian sea pen coral, *A. kukenthali*, has afforded five new briarane-type diterpenoids, which designated as anthoptilides A–E (**233**–**237**). The structures of briaranes (**233**–**237**) were determined on the basis of their spectral data (IR, UV, MS, ^{1}H and ^{13}C NMR). Single-crystal X-Ray determination was performed on anthoptilide A (**233**). The senecioate and benzoate substituents in the C-2 positions of anthoptilides A (**233**) and D (**236**), respectively, both of which are rare among briarane-type metabolites. Briaranes (**233**–**237**) showed activity to inhibit [^{3}H]DPCPX binding to rat-brain adenosine A_1 receptors.[72]

Table 14. The Briarane-type Metabolites from *A. kukenthali*

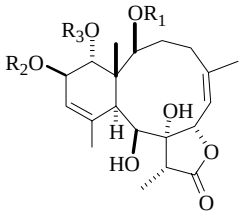
Structure	No.	Name	Biological activity	Ref.
	**233**	anthoptilide A (R = $COC(CH_3)$=$CHCH_3$)	anthoptilides A–E (**233**–**237**) inhibit [^{3}H]DPCPX binding to rat-brain adenosine A_1 receptors, IC_{50} = 420, 45, 3.1, 500, and 490 μM, respectively.	72
	234	anthoptilide B (R = $COCH(CH_3)_2$)		72
	235	anthoptilide C (R = COC_2H_5)		72
	236	anthoptilide D (R = COC_6H_5)		72
	**237**	anthoptilide E		72

3.2 *Cavernulina* (family Veretillidae)

A. *Cavernulina grandiflora*

Three new diterpenoids, cavernuline (**238**), *O*-deacetylpropionyl cavernuline (**239**), and cavernulinine (**240**), were isolated from a new species of sea pen coral, *C. grandiflora*. The structures of metabolites (**238**–**240**) were elucidated on the basis of spectral evidence (UV, IR, MS, ^{1}H and ^{13}C NMR).[73]

Table 15. The Briarane-Type Metabolites from *C. grandiflora*

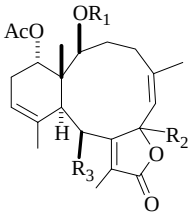
Structure	No.	Name	Biological activity	Ref.
	**238**	cavernuline (R_1 = COC_5H_{11}, R_2 = R_3 = Ac)		73
	239	*O*-deacetylpropionyl cavernuline (R_1 = COC_5H_{11}, R_2 = Ac, R_3 = COC_2H_5)		73
	240	cavernulinine (R_1 = R_3 = COC_3H_7, R_2 = COC_2H_5)		73

3.3 *Funiculina* (family Funiculinidae)

A. *Funiculina quadrangularis*

Six new briarane-type metabolites, funicolides A–E (**241**–**245**) and 7-epifunicolide A (**246**), along with a known metabolite, brianthein W (**81**),[23] were isolated from the luminescent sea pen coral, *F. quadrangularis*, collected in the Vada and Capraia Islands in the Tuscan archipelago, Ligurian Sea. The structures and relative configurations of briaranes (**241**–**246**) were established by extensive spectroscopic (IR, UV, MS, ^{1}H and ^{13}C NMR) and chemical methods.[74] Due to the slow flipping rotation in the ten-membered ring, the kinetic and equilibrium NMR spectral studies were performed on funicolides A (**241**), D (**244**), brianthein W (**81**), and a chemical derivative of brianthein W, 7-epibrianthein W. These kinetic and equilibrium NMR spectral observations and molecular mechanics calculations for briaranes (**81**, **241**, and **244**), and 7-epibrianthein W, led to general views on the conformational preferences of diterpenoids of this class.[75]

Table 16. The Briarane-Type Metabolites from *F. quadrangularis*

Structure	No.	Name	Biological activity	Ref.
	**241**	funicolide A (R_1 = COC_2H_5, R_2 = H_β, R_3 = H)		74,75
	242	funicolide B (R_1 = COC_2H_5, R_2 = α-OH, R_3 = H)		74
	243	funicolide C (R_1 = COC_2H_5, R_2 = H_β, R_3 = OAc)		74
	244	funicolide D (R_1 = COC_3H_7, R_2 = H_β, R_3 = H)		74,75
	245	funicolide E (R_1 = Ac, R_2 = α-OH, R_3 = H)		74
	246	7-epifunicolide A (R_1 = COC_2H_5, R_2 = H_α, R_3 = H)		74

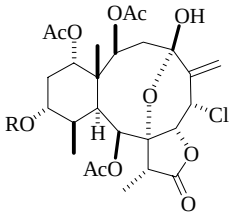
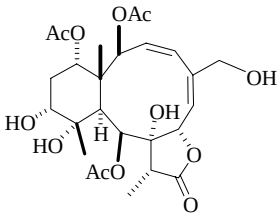
3.4 *Pteroeides* (family Pteroeididae)

A. *Pteroeides laboutei*

P. laboutei, a sea pen coral collected in the Mediterranean Sea, was studied for its chemical constituents.

Three novel highly oxidized metabolites, featuring the briarane skeleton, were designated as pteroidine (**247**), 12-*O*-deacetyl-12-*O*-benzoylpteroidine (**248**), and labouteine (**249**). Briarane (**248**) is the first briarane-type metabolite possessing a benzoate functional group, and briarane (**249**) is also the first briarane compound existing tetrahydroxyl groups.[76]

Table 17. The Briarane-Type Metabolites from *P. laboutei*

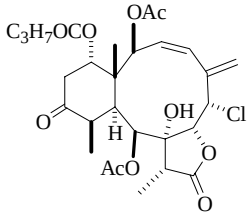
Structure	No.	Name	Biological activity	Ref.
	**247**	pteroidine (R = Ac)		76
	248	12-*O*-deacetyl-12-*O*-benzoyl-pteroidine (R = COC_6H_5)		76
	**249**	labouteine		76

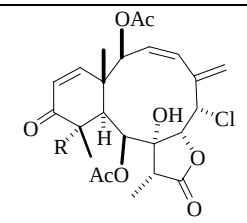
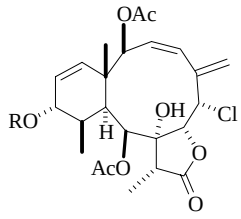
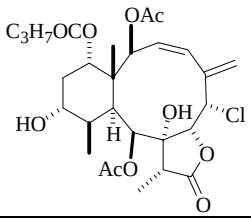
3.5 *Ptilosarcus* (family Pennatulidae)

A. *Ptilosarcus gurneyi*

A toxic briarane, ptilosarcone (**250**), and its decomposition product, ptilosarcenone (**251**), were isolated from a North Pacific Ocean sea pen coral, *P. gurneyi*. The gross structures of briaranes (**250**) and (**251**) were elucidated by NMR data (^{1}H and ^{13}C) and by comparison with those of a known metabolite, briarein A (**1**).[77] In the later studies for this marine organism, the samples were collected from sites near Sidney, British Columbia, and Seattle, Washington, and afforded the compounds ptilosarcone (**250**) and ptilosarcenone (**251**), along with five new briaranes, 11-hydroxyptilosarcenone (**252**), ptilosarcen-12-ol (**253**), ptilosarcen-12-acetate (**254**), ptilosarcen-12-propionate (**255**), and ptilosarcol (**256**) were isolated, and their (briaranes **250**–**256**) complete structures and stereochemistry were elucidated by detailed spectral analyses (IR, UV, MS, ^{1}H and ^{13}C NMR).[78] Briarane (**251**) (showed potential insecticidal activity toward the larvae of the tobacco hornworm, *Manduca sexta*.[78]

Table 18. The Briarane-type Metabolites from *P. gurneyi*

Structure	No.	Name	Biological activity	Ref.
	**250**	ptilosarcone	toxic to mice (LD_{50} = 7.4 mg/Kg)	77,78

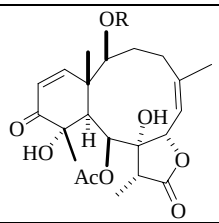
Structure	No.	Name	Biological activity	Ref.
	**251**	ptilosarcenone (R = H)	toxic to the larvae of the tobacco hornworm, *M. sexta* at 250 ppm.	77,78
	252	11-hydroxyptilosarcenone (R = OH)		78
	**253**	ptilosarcen-12-ol (R = H)		78
	254	ptilosarcen-12-acetate (R = Ac)		78
	255	ptilosarcen-12-propionate ($R = COC_2H_5$)		78
	**256**	ptilosarcol		78

3.6 *Renilla* (family Renillidae)

A. *Renilla reniformis*

Benethic marine organisms such as invertebrates also produce natural products to deter the settlement of fouling organisms. Much of the researches in this field have focused on the development of commercial alternatives to current commercial antifouling paints. Based on above request, the extracts of the Atlantic sea pansy, *R. reniformis*, which inhibit the settlement of barnacle larvae, have been found to contain three new metabolites, renillafoulins A–C (**257**–**259**).[79] The structures of metabolites (**257**–**259**) were established by using 1D and 2D NMR spectral data and by comparison with those of the other known briarane metabolites. The structure and relative configuration of briarane (**259**) were further confirmed by single-crystal X-Ray diffraction data analyses. Renillafoulins A–C (**257**–**259**) show antifouling activity toward the barnacle larvae.[79–83]

Table 19. The Briarane-Type Metabolites from *R. reniformis*

Structure	No.	Name	Biological activity	Ref.
	**257**	renillafoulin A (R = Ac)	renillafoulins A–C (**257**–**259**) inhibit the settlement of barnacle larvae, EC_{50} = 0.02–0.2 μg/mL.	79–83
	258	renillafoulin B ($R = COC_2H_5$)		79–81
	259	renillafoulin C ($R = COC_3H_7$)		79–81

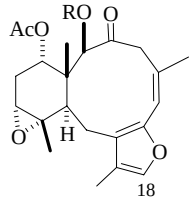
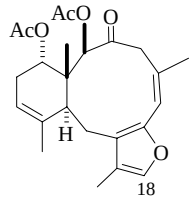
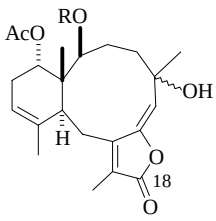
3.7 *Scytalium* (family Virgulariidae)

A. *Scytalium tentaculatum*

The sea pen octocoral, *S. tentaculatum*, collected by trawling, near Port Douglas, Queensland, Australia,

was found to contain three novel diterpenoids (**260**–**262**), related to briarane-type metabolites. The structures and relative configurations of briaranes (**260**–**262**) were determined by NMR spectral analyses (^{1}H and ^{13}C) and chemical methods. However, in briarane (**262**), the stereochemistry of C-5 hydroxyl group was not determined. Unlike the most briarane-type metabolites, the γ-lactone in briaranes (**261**) and (**262**) were disappeared and replaced by furan groups, respectively.[84] The 3-keto group in briaranes (**261**) and (**262**), and the 5-hydroxyl group in (**263**) are never found in other briarane class compounds.

Table 20. The Briarane-Type Metabolites from *S. tentaculatum*

Structure	No.	Name	Biological activity	Ref.
	**260**[a]	R = $COCH_2CH(CH_3)_2$		84
	**261**[b]			84
	**262**[c]	R = $COCH_2CH(CH_3)_2$		84

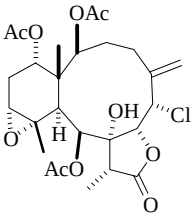
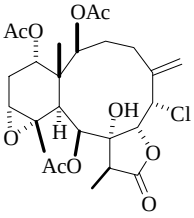
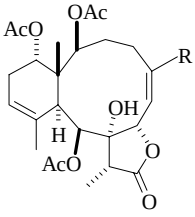
[a](1*R**,2*R**,5*Z*,10*R**,11*S**,12*R**,14*S**)-14-acetoxy-11,12-epoxy-3-oxobriara-5,7,17-trien-2-yl 3-methylbutanoate
[b](1*R**,2*R**,5*Z*,10*S**,11*Z*,14*S**)-2,14-diacetoxybriara-5,7,11,17-tetraen-3-one
[c](1*R**,2*R**,6*E*,10*S**,11*Z*,14*S**)-14-acetoxy-5-hydroxy-18-oxobriara-6,8(17),11-trien-2-yl 3-methylbutanoate

3.8 *Stylatula* (family Virgulariidae)

A. *Stylatula* sp.

Stylatulide (**263**) is the first briarane-type metabolite with toxicity originally isolated from the sea pen coral, *Stylatula* sp., collected in the intertidal zone at Isla Partida, Gulf of California. This metabolite crystallized from 1:1 hexane:dichloromethane solution, and its structure, including the absolute configuration was determined by single-crystal X-Ray diffraction analyses.[85] In the later study, a new metabolite, 17-epistylatulide (**264**) and three unnamed new briaranes (**265**–**267**), along with stylatulide (**263**) have been isolated from this organism. The structures of **264**–**267** were elucidated by spectral analyses (UV, IR, MS, ^{1}H and ^{13}C NMR) and chemical methods. Moreover, the complete NMR data (^{1}H and ^{13}C) of stylatulide (**263**) were assigned.[86] Stylatulide (**263**) was found to be toxic to the larvae of the copepod *Tisbe furcata johnsonii*.[85]

Table 21. The Briarane-Type Metabolites from *Stylatula* sp.

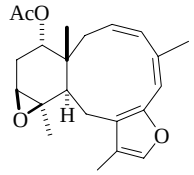
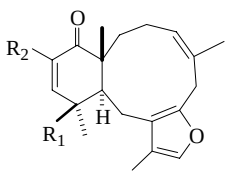
Structure	No.	Name	Biological activity	Ref.
	**263**	stylatulide	toxic to copepodite larvae of *T. furcata johnsonii* at concentration greater than 0.5 ppm (LD_{100}).	85,86
	**264**	17-epistylatulide		86
	**265**	(R = CH_3)		86
	266	(R = CH_2OH)		86
	267	(R = $COOCH_3$)		86

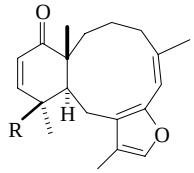
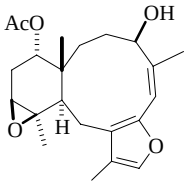
3.9 *Veretillum* (family Veretillidae)

A. *Veretillum cynomorium*

Seven novel briaranes, verecynarmins A–G (**268**–**274**), were isolated from both the Mediterranean nudibranch mollusk, *Armina maculata* (family Arminidae) and its prey, the sea pen coral, *V. cynomorium*.[87–89] Verecynarmin A (**268**) also is the first briarane-type metabolite from a Mediterranean marine organism.[87] The structures of briaranes (**268**–**274**) were elucidated by extensive spectral studies, including 1D and 2D NMR experiments, and by chemical methods. The absolute configuration of verecynarmin A (**268**) has been elucidated by chemical methods.[87] Verecynarmins B–D (**269**–**271**) are proven that they are single compounds existing in slowly interconverting forms by NMR spectral and chemical techniques.[88] The 14-keto groups in metabolites (**269**–**273**),[88,89] and the 13-chloro group in (**271**),[88] are never found in other briarane-type compounds.

Table 22. The Briarane-Type Metabolites from *V. cynomorium*

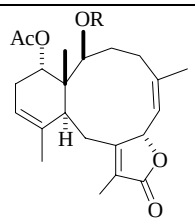
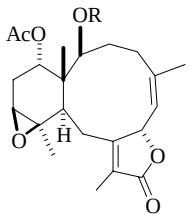
Structure	No.	Name	Biological activity	Ref.
	**268**	verecynarmin A		87
	**269**	verecynarmin B (R_1 = R_2 = H)		88
	270	verecynarmin C (R_1 = OH, R_2 = H)		88
	271	verecynarmin D (R_1 = OH, R_2 = Cl)		88

Structure	No.	Name	Biological activity	Ref.
	**272**	verecynarmin E (R = OH)		89
	273	verecynarmin F (R = H)		89
	**274**	verecynarmin G		89

B. *Veretillum malayense*

The malayenolides A–D (**275**–**278**), which are biologically active diterpenoids of the briarane class, have been isolated from the sea pen coral, *V. malayense*, collected near Monado, Sulawesi, Indonesia. The structures of metabolites (**275**–**278**) were elucidated on the basis of detailed spectral analyses (UV, IR, MS, ^{1}H and ^{13}C NMR).[90] The benzoate groups in briaranes (**275**) and (**276**), and the senecioate groups in briaranes (**277**) and (**278**) are rare among marine natural products.[72,76] Malayenolides A–D (**275**–**278**) showed toxicity in the brine shrimp assay.

Table 23. The Briarane-Type Metabolites from *V. malayense*

Structure	No.	Name	Biological activity	Ref.
	**275**	malayenolide A (R = COC_6H_5)	LC_{50} (brine shrimp) = 100 μg/mL	90
	277	malayenolide C (R = $COCH{=}C(CH_3)_2$)	LC_{50} (brine shrimp) = 20 μg/mL	90
	**276**	malayenolide B (R = COC_6H_5)	LC_{50} (brine shrimp) = < 2 μg/mL	90
	278	malayenolide D (R = $COCH{=}C(CH_3)_2$)	LC_{50} (brine shrimp) = 20 μg/mL	90

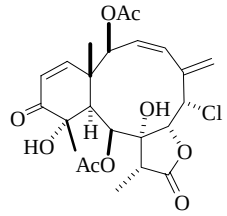
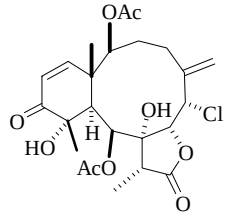
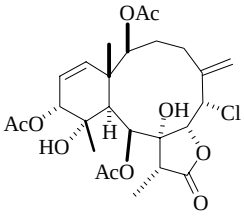
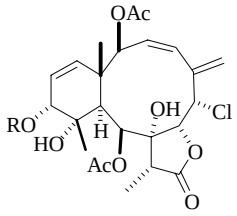
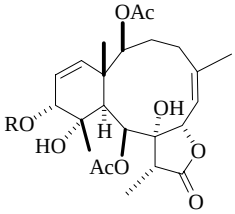
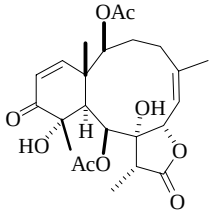
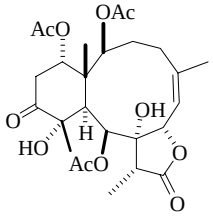
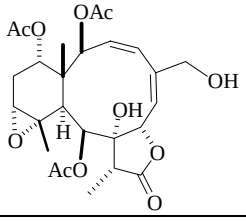
4. ALCYONACEA

4.1 *Minabea* (family Alcyoniidae)

A. *Minabea* sp.

Ten new representatives of the briarane skeleton class, namely minabeins 1–10 (**279**–**288**), were isolated from the soft coral, *Minabea* sp., collected in Truk Lagoon, Eastern Caroline Islands. The structures of metabolites (**279**–**288**) were established on the basis of spectral analyses (IR, UV, MS, ^{1}H and ^{13}C NMR). This is the first observation of the occurrence of briarane-type compounds in the soft corals of order Alcyonacea.[91]

Table 24. The Briarane-Type Metabolites from *Minabea* sp.

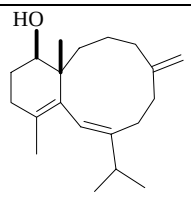
Structure	No.	Name	Biological activity	Ref.
	**279**	minabein-1		91
	**280**	minabein-2		91
	**281**	minabein-3		91
	**282**	minabein-4 (R = Ac)		91
	283	minabein-5 (R = H)		91
	**284**	minabein-6 (R = Ac)		91
	285	minabein-7 (R = H)		91
	**286**	minabein-8		91
	**287**	minabein-9		91
	**288**	minabein-10		91

4.2 *Nephthea* (family Nephtheidae)

A. *Nephthea* sp.

Chemical examination of a soft coral species of the *Nephthea* genus, collected from the Hutbay Island of the Andaman and Nicobar group of Islands of the Indian Ocean, has afforded an unnamed novel briarane-type metabolite (**289**). The structure, including the relative configuration of **289**, was elucidated by spectral analyses (IR, UV, MS, ^{1}H and ^{13}C NMR). Unlike the structure of the briaranes that have been reported, there are no complex functional groups, but there is a bicyclo[8.4.0] system in the carbon skeleton of **289**. However, this is the first briarane containing a 14β-hydroxyl group. Briarane possessing a double bond between C-10 and C-11 is also never found previously.

Table 25. The Briarane-Type Metabolite from *Nephthea* sp.

Structure	No.	Name	Biological activity	Ref.
	**289**			92

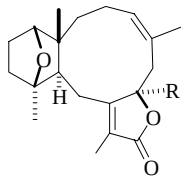
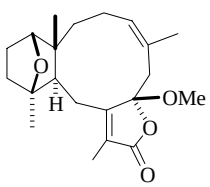
5. STOLONIFERA

5.1 *Pachyclavularia* (family Tubiporidae)

A. *Pachyclavularia violacea*

The investigation on the chemical constituents of *P. violacea*, collected in the shallow reefs near Sek point off Madang, Paupa New Guinea, has afforded four novel briaranes, pachyclavulariolides A–D (**290**–**293**). The structures of **290**–**293** were elucidated by analyses of spectroscopic data (IR, UV, MS, ^{1}H and ^{13}C NMR). The structure and relative configuration of pachyclavulariolide B (**291**) were further confirmed by single X-Ray diffraction analyses.[93] Briaranes (**290**–**293**) are the first briarane-type metabolites possessing ether linkage between C-11 and C-14, in the six-membered ring. Furthermore, in the structures of briaranes (**291**) and (**292**), the C-7 α-oriented oxygen-bearing functional groups were rarely found previously.[74]

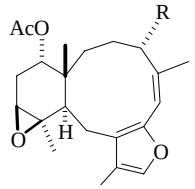
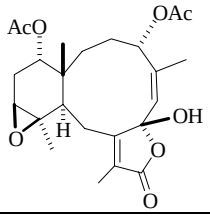
Table 26. The Briarane-Type Metabolites from *P. violacea*

Structure	No.	Name	Biological activity	Ref.
	**290**	pachyclavulariolide A (R = H)		93
	291	pachyclavulariolide B (R = OH)		93
	292	pachyclavulariolide C (R = OMe)		93
	**293**	pachyclavulariolide D		93

B. *Pachyclavularia* sp.

Extraction of an octocoral, *Pachyclavularia* sp., collected in the Great Barrier Reef, Australia, led to the isolation of three new unnamed briaranes (**294**–**296**). The structures of diterpenoids (**294**–**296**) were determined by spectral analyses (UV, IR, MS, ^{1}H and ^{13}C NMR). Briarane (**294**) exhibited ichthyotoxicity toward the mosquito fish, *Gambusia affinis*.[94]

Table 27. The Briarane-Type Metabolites from *Pachyclavularia* sp.

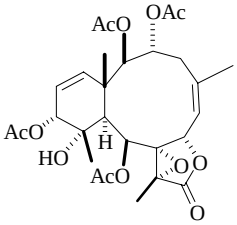
Structure	No.	Name	Biological activity	Ref.
	**294**	R = OAc	ichthyotoxic to the mosquito fish, *G. affinis* at concentrations 2–5 ppm.	94
	295	R = H		94
	**296**			94

5.2 *Tubipora* (family Tubiporidae)

A. *Tubipora* sp.

In 1990, a soft coral of the genus *Tubipora*, collected at Kuchino-shima Island of the Satsunan archipelago, whose organic extract exhibited cytotoxicity toward the B-16 mouse melanoma tumor cells, was studied for discovering potential antitumor agents. A new diterpenoid of the briarane ring system, tubiporein (**297**), was isolated from this organism. The gross structure was determined by ^{1}H and ^{13}C NMR-based spectral analyses. Moreover, the relative configuration was elucidated by the interpretations of NOE experiments and the coupling constant calculations. Tubiporein (**297**) exhibited cytotoxicity toward the B-16 tumor cells.[95]

Table 28. The Briarane-type Metabolite from *Tubipora* sp.

Structure	No.	Name	Biological activity	Ref.
	**297**	tubiporein	IC_{50} (B-16) = 2.0 μg/mL	95

6. NUDIBRANCH

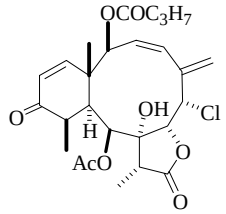
6.1 *Tochuina* (family Tritoniidae)

A. *Tochuina tetraquetra*

T. tetraquetra is a common nudibranch that appeared in the North Pacific Ocean coast. The chemical

constituents of *T. tetraquetra*, collected at Bamfield, British Columbia, Canada, has been studied. A known toxic briarane-type metabolite, ptilosarcenone (**251**), which was found from a North Pacific Ocean sea pen coral, *Ptilosarcus gurneyi*, previously.[77,78] along with an unnamed new briarane (**298**), were obtained from the skin extracts of *T. tetraquetra*.[96] Based on detailed spectral analyses (UV, IR, MS, ^{1}H and ^{13}C NMR), the structure of briarane (**298**) was elucidated as a butanoate analogue of **251**. The sea pen coral and soft coral were proven to be the diets of nudibranch, *T. tetraquetra*.[97] However, an exhaustive study of the chemical constituents of *P. gurneyi*, collected at Seattle, Washington, and Sidney, B. C. failed to obtain briarane (**298**) or any metabolite that could be viewed as precursor to briarane (**298**).[77,78] Therefore, there is no obvious evidence to indicate that briarane (**298**) was originally from *P. gurneyi*, however, the authors suggested probably the chemistry of the Bamfield population of *P. gurneyi*, differs slightly from the Strait of Georgia and Puget Sound populations.[96,97]

Table 29. The Briarane-Type Metabolite from *T. tetraquetra*

Structure	No.	Name	Biological activity	Ref.
	**298**			96

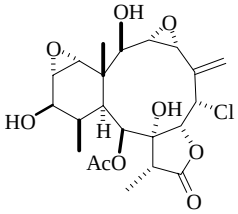
7. SPONGE

7.1 *Psammaplysilla* (family Verongiidae)

A. *Psammaplysilla purpurea*

A new diterpenoid, bis(deacetyl)solenolide D (**299**) was isolated from the marine sponge, *P. purpurea*, collected on the coast of Ie island, Okinawa Prefecture, Japan. The structure of metabolite (**299**) was established by NMR spectral analyses (1D and 2D) and chemical methods, and by comparison the spectral data with those of a known metabolite, solenolide D (**124**).[37] However, because of the stereochemistry of solenolide D (**124**) has been revised,[32,38] therefore, the hydroxyl group attaching at the C-12 position in briarane (**299**) should be β-oriented. In the antifouling activity assay, bis(deacetyl)solenolide D (**299**) exhibited activity to regulate the biofilm formation.[98] Briarane (**299**) is the only briarane-type metabolite from sponge. The origin of this compound is still uncertain.

Table 30. The Briarane-Type Metabolite from *P. purpurea*

Structure	No.	Name	Biological activity	Ref.
	**299**	bis(deacetyl)solenolide D	exhibit activity to regulate the biofilm formation.	98

8. CONCLUSION

Terpenoid compounds are often present in large amounts in marine invertebrates, and as a major class, represent the largest percentage of natural products isolated from marine organisms.[99] Furthermore, marine invertebrates were proven to possess the ability to synthesize the terpenoid metabolites.[100] Up to date, Two hundred ninety-nine briarane-type diterpenoids have been isolated from numerous of marine organisms, including soft corals (Gorgonacea, Pennatulacea, Alcyonacea, and Stolonifera), a nudibranch and a sponge. The structures, names, biological activities, and related references of these metabolites have been presented in this review article. These compounds exhibited potential activities in the applications for ecological, agrochemical, and pharmaceutical researches in future.

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REFERENCES AND NOTES

1. J. E. Burks, D. van der Helm, C. Y. Chang, and L. S. Ciereszko, *Acta Cryst.*, 1977, **B33**, 704.
2. F. M. Bayer, *Proc. Biol. Soc. Wash.*, 1981, **94**, 902.
3. D. J. Faulkner, *Nat. Prod. Rep.*, 2001, **18**, 1, and previous reports in this series.
4. J. R. Hanson, *Nat. Prod. Rep.*, 2001, **18**, 88, and previous reports in this series.
5. D. B. Stierle, B. Carté, D. J. Faulkner, B. Tagle, and J. Clardy, *J. Am. Chem. Soc.*, 1980, **102**, 5088.
6. S. J. Selover, P. Crews, B. Tagle, and J. Clardy, *J. Org. Chem.*, 1981, **46**, 964.
7. A. D. Rodríguez, C. Ramírez, and O. M. Cóbar, *J. Nat. Prod.*, 1996, **59**, 15.
8. S. J. Coval, S. Cross, G. Bernardinelli, and C. W. Jefford, *J. Nat. Prod.*, 1988, **51**, 981.
9. D. Maharaj, B. S. Mootoo, A. J. Lough, S. McLean, W. F. Reynolds, and W. F. Tinto, *Tetrahedron Lett.*, 1992, **33**, 7761.
10. R. Dookran, D. Maharaj, B. S. Mootoo, R. Ramsewak, S. McLean, W. F. Reynolds, and W. F. Tinto, *Tetrahedron*, 1994, **50**, 1983.
11. B. S. Mootoo, R. Ramsewak, R. Sharma, W. F. Tinto, A. J. Lough, S. McLean, W. F. Reynolds, J.-P. Yang, and M. Yu, *Tetrahedron*, 1996, **52**, 9953.
12. F. J. Schmitz, M. M. Schulz, J. Siripitayananon, M. B. Hossain, and D. van der Helm, *J. Nat. Prod.*, 1993, **56**, 1339.
13. J.-H. Sheu, P.-J. Sung, M.-C. Cheng, H.-Y. Liu, L.-S. Fang, C.-Y. Duh, and M. Y. Chiang, *J. Nat. Prod.*, 1998, **61**, 602.
14. P.-J. Sung, J.-H. Su, G.-H. Wang, S.-F. Lin, C.-Y. Duh, and J.-H. Sheu, *J. Nat. Prod.*, 1999, **62**, 457.

15. J. E. Neve, B. J. McCool, and B. F. Bowden, *Aust. J. Chem.*, 1999, **52**, 359.
16. J.-H. Sheu, P.-J. Sung, J.-H. Su, G.-H. Wang, C.-Y. Duh, Y.-C. Shen, M. Y. Chiang, and I.-T. Chen, *J. Nat. Prod.*, 1999, **62**, 1415.
17. J.-H. Sheu, P.-J. Sung, J.-H. Su, H.-Y. Liu, C.-Y. Duh, and M. Y. Chiang, *Tetrahedron*, 1999, **55**, 14555.
18. P.-J. Sung, J.-H. Su, C.-Y. Duh, M. Y. Chiang, and J.-H. Sheu, *J. Nat. Prod.*, 2001, **64**, 318.
19. S.-L. Wu, P.-J. Sung, M. Y. Chiang, J.-Y. Wu, and J.-H. Sheu, *J. Nat. Prod.*, 2001, **64**, 1415.
20. S. Aoki, M. Okano, K. Matsui, T. Itoh, R. Satari, S. Akiyama, and M. Kobayashi, *Tetrahedron*, 2001, **57**, 8951.
21. J. Rodríguez, R. M. Nieto, and C. Jiménez, *J. Nat. Prod.*, 1998, **61**, 313.
22. R. I. Geran, N. H. Greenberg, M. M. MacDonald, A. M. Schumacher, and B. J. Abbott, *Cancer Chemother. Rep.*, 1972, 1.
23. J. H. Cardellina II, T. R. James Jr, M. H. M. Chen, and J. Clardy, *J. Org. Chem.*, 1984, **49**, 3398.
24. S. H. Grode, T. R. James Jr, J. H. Cardellina II, and K. D. Onan, *J. Org. Chem.*, 1983, **48**, 5203.
25. S. H. Grode, T. R. James, and J. H. Cardellina II, *Tetrahedron Lett.*, 1983, **24**, 691.
26. J. H. Cardellina II, *Pure & Appl. Chem.*, 1986, **58**, 365.
27. G. S. Linz, M. J. Musmar, A. J. Weinheimer, G. E. Martin, and J. A. Matson, *Spectrosc. Lett.*, 1986, **19**, 545.
28. D. E. Barnekow and J. H. Cardellina II, *Tetrahedron Lett.*, 1989, **30**, 3629.
29. D. van der Helm, R. A. Loghry, J. A. Matson, and A. J. Weinheimer, *J. Crystallogr. Spectrosc. Res.*, 1986, **16**, 713.
30. J.-H. Sheu, P.-J. Sung, L.-H. Huang, S.-F. Lee, T. Wu, B.-Y. Chang, C.-Y. Duh, L.-S. Fang, K. Soong, and T.-J. Lee, *J. Nat. Prod.*, 1996, **59**, 935.
31. B. F. Bowden, J. C. Coll, W. Patalinghug, B. W. Skelton, I. Vasilescu, and A. H. White, *Aust. J. Chem.*, 1987, **40**, 2085.
32. S. J. Bloor, F. J. Schmitz, M. B. Hossain, and D. van der Helm, *J. Org. Chem.*, 1992, **57**, 1205.
33. J. H. Kwak, F. J. Schmitz, and G. C. Williams, *J. Nat. Prod.*, 2001, **64**, 754.
34. B. F. Bowden, J. C. Coll, and I. M. Vasilescu, *Aust. J. Chem.*, 1989, **42**, 1705.
35. B. F. Bowden, J. C. Coll, I. M. Vasilescu, and P. N. Alderslade, *Aust. J. Chem.*, 1989, **42**, 1727.
36. T. Iwagawa, N. Takenoshita, H. Okamura, M. Nakatani, M. Doye, K. Shibata, and M. Shiro, *Heterocycles*, 1998, **48**, 123.
37. A. Groweiss, S. A. Look, and W. Fenical, *J. Org. Chem.*, 1988, **53**, 2401.
38. J.-F. Cheng, S. Yamamura, and Y. Terada, *Tetrahedron Lett.*, 1992, **33**, 101.
39. M. B. Roe, M. Whittaker, and G. Procter, *Tetrahedron Lett.*, 1995, **36**, 8103.

40. R. P. Balasubramaniam, D. K. Moss, J. K. Wyatt, J. D. Spence, A. Gee, and M. H. Nantz, *Tetrahedron*, 1997, **53**, 7429.
41. J. Kobayashi, J.-F. Cheng, H. Nakamura, Y. Ohizumi, Y. Tomotake, T. Matsuzaki, K. J. S. Grace, R. S. Jacobs, Y. Kato, L. S. Brinen, and J. Clardy, *Experientia*, 1991, **47**, 501.
42. E. O. Pordesimo, F. J. Schmitz, L. S. Ciereszko, M. B. Hossain, and D. van der Helm, *J. Org. Chem.*, 1991, **56**, 2344.
43. The artificial derivative, 2β-acetoxy-2-debutyryloxystecholide E acetate (**154**) was obtained by the acetylation of 2β-acetoxy-2-debutyryloxystecholide E (**149**) in 1996. See ref. 30.
44. T. Iwagawa, K. Takayama, H. Okamura, M. Nakatani, and M. Doe, *Heterocycles*, 1999, **51**, 1653.
45. T. Iwagawa, K. Takayama, H. Okamura, M. Nakatani, M. Doe, K. Takemura, and M. Shiro, *Heterocycles*, 1999, **51**, 2619.
46. T. Iwagawa, T. Hirose, K. Takayama, H. Okamura, M. Nakatani, M. Doe, and K. Takemura, *Heterocycles*, 2000, **53**, 1789.
47. Y. Uchio, T. Haino, S. Usui, and Y. Fukazawa, *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu* (39th Symposium on The Chemistry of Natural Products, Symposium Paper, Sapporo, Japan), 1997, **39th**, p. 625, (*Chem. Abstr.*, 1999, **131**, 100029h).
48. S. A. Look, W. Fenical, D. Van Engen, and J. Clardy, *J. Am. Chem. Soc.*, 1984, **106**, 5026.
49. R. Dookran, D. Maharaj, B. S. Mootoo, R. Ramsewak, S. McLean, W. F. Reynolds, and W. F. Tinto, *J. Nat. Prod.*, 1993, **56**, 1051.
50. D. Banjoo, A. R. Maxwell, B. S. Mootoo, A. J. Lough, S. McLean, and W. F. Reynolds, *Tetrahedron Lett.*, 1998, **39**, 1469.
51. B. S. Mootoo, D. Banjoo, R. S. Ramsewak, R. Sharma, A. J. Lough, S. McLean, and W. F. Reynolds, 10th International Symposium on Marine Natural Products, Symposium Paper, Okinawa, Japan, 2001, p.133.
52. D. Maharaj, K. O. Pascoe, and W. F. Tinto, *J. Nat. Prod.*, 1999, **62**, 313.
53. W. Fenical and J. R. Pawlik, *Mar. Ecol. Prog. Ser.*, 1991, **75**, 1.
54. C. Subrahmanyam, R. Kulatheeswaran, and R. S. Ward, *J. Nat. Prod.*, 1998, **61**, 1120.
55. C. Subrahmanyam, S. Ratnakumar, and R. S. Ward, *Tetrahedron*, 2000, **56**, 4585.
56. J. Shin, M. Park, and W. Fenical, *Tetrahedron*, 1989, **45**, 1633.
57. M. García, J. Rodríguez, and C. Jiménez, *J. Nat. Prod.*, 1999, **62**, 257.
58. P.-J. Sung, S.-L. Wu, H.-J. Fang, M. Y. Chiang, J.-Y. Wu, L.-S. Fang, and J.-H. Sheu, *J. Nat. Prod.*, 2000, **63**, 1483.
59. B. F. Bowden, J. C. Coll, and G. M. König, *Aust. J. Chem.*, 1990, **43**, 151.
60. H.-Y. He and D. J. Faulkner, *Tetrahedron*, 1991, **47**, 3271.

61. K. A. El Sayed, D. C. Dunbar, T. L. Perry, S. P. Wilkins, M. T. Hamann, J. T. Greenplate, and M. A. Wideman, *J. Agric. Food Chem.*, 1997, **45**, 2735.
62. M. T. Hamann, K. N. Harrison, A. R. Carroll, and P. J. Scheuer, *Heterocycles*, 1996, **42**, 325.
63. S. Isaacs, S. Carmely, and Y. Kashman, *J. Nat. Prod.*, 1990, **53**, 596.
64. A. S. R. Anjaneyulu and N. S. K. Rao, *J. Chem. Soc., Perkin Trans. 1*, 1997, 959.
65. Y.-C. Shen, Y.-C. Lin, and M. Y. Chiang, *J. Nat. Prod.*, 2002, **65**, 54.
66. Y. Lin and K. Long, *Zhongshan Daxue Xuebao, Ziran Kexueban*, 1982, 46.
67. K. Long, Y. Lin, and W. Huang, *Zhongshan Daxue Xuebao, Ziran Kexueban*, 1987, 15.
68. J. Yao, J. Qian, H. Fan, K. Shih, S. Huang, Y. Lin, and K. Long, *Zhongshan Daxue Xuebao, Ziran Kexueban*, 1984, 83.
69. Y. Lin, T. Jin, K. Long, and Z. Wu, *Zhongguo Haiyang Yaowu*, 1995, **14**, 1.
70. Y. Luo, K. Long, and Z. Fang, *Zhongshan Daxue Xuebao, Ziran Kexueban*, 1983, 83.
71. J. Dai, Z. Wan, Z, Rao, D. Liang, Z. Fang, Y. Luo, and K. Long, *Sci. Sinica Ser. B*, 1985, **28**, 1132.
72. N. B. Pham, M. S. Butler, P. C. Healy, and R. J. Quinn, *J. Nat. Prod.*, 2000, **63**, 318.
73. A. Clastres, P. Laboute, A. Ahond, C. Poupat, and P. Potier, *J. Nat. Prod.*, 1984, **47**, 162.
74. A. Guerriero, M. D'Ambrosio, and F. Pietra, *Helv. Chim. Acta*, 1995, **78**, 1465.
75. G. Chiasera, A. Guerriero, M. D'Ambrosio, and F. Pietra, *Helv. Chim. Acta*, 1995, **78**, 1479.
76. A. Clastres, A. Ahond, C. Poupat, P. Potier, and S. K. Kan, *J. Nat. Prod.*, 1984, **47**, 155.
77. S. J. Wratten, W. Fenical, D. J. Faulkner, and J. C. Wekell, *Tetrahedron Lett.*, 1977, 1559.
78. R. L. Hendrickson and J. H. Cardellina II, *Tetrahedron*, 1986, **42**, 6565.
79. P. A. Keifer, K. L. Rinehart Jr., and I. R. Hooper, *J. Org. Chem.*, 1986, **51**, 4450.
80. K. L. Rinehart, *Pure & Appl. Chem.*, 1989, **61**, 525.
81. D. Rittschof, N. Sasikumar, D. Murlless, A. S. Clare, D. Gerbart, and J. Bonaventura, *Recent Dev. Biofouling Control*, 1994, 269.
82. K. Tsurumi and N. Fusetani, *Baiosaiensu to Indasutori*, 1995, **53**, 328.
83. A. S. Clare, D. Rittschof, D. J. Gerhart, I. R. Hooper, and J. Bonaventura, *Mar. Biotechnol.*, 1999, **1**, 427.
84. B. N. Ravi, J. F. Marwood, and R. J. Wells, *Aust. J. Chem.*, 1980, **33**, 2307.
85. S. J. Wratten, D. J. Faulkner, K. Hirotsu, and J. Clardy, *J. Am. Chem. Soc.*, 1977, **99**, 2824.
86. S. J. Wratten and D. J. Faulkner, *Tetrahedron*, 1979, **35**, 1907.
87. A. Guerriero, M. D'Ambrosio, and F. Pietra, *Helv. Chim. Acta*, 1987, **70**, 984.
88. A. Guerriero, M. D'Ambrosio, and F. Pietra, *Helv. Chim. Acta*, 1988, **71**, 472.
89. A. Guerriero, M. D'Ambrosio, and F. Pietra, *Helv. Chim. Acta*, 1990, **73**, 277.
90. X. Fu, F. J. Schmitz, and G. C. Williams, *J. Nat. Prod.*, 1999, **62**, 584.

91. M. B. Ksebati and F. J. Schmitz, *Bull. Soc. Chim. Belg.*, 1986, **95**, 835.
92. A. S. R. Anjaneyulu and M. V. R. Krishna Murthy, *Indian J. Chem.*, 2000, **B39**, 42.
93. L. Xu, B. O. Patrick, M. Roberge, T. Allen, L. van Ofwegen, and R. J. Andersen, *Tetrahedron*, 2000, **56**, 9031.
94. Y. Uchio, Y. Fukazawa, B. F. Bowden, and J. C. Coll, *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu* (31th Symposium on The Chemistry of Natural Products, Symposium Paper, Nagoya, Japan), 1989, **31th**, p. 548, (*Chem. Abstr.*, 1990, **112**, 175870s).
95. T. Natori, H. Kawai, and N. Fusetani, *Tetrahedron Lett.*, 1990, **31**, 689.
96. D. E. Williams and R. J. Andersen, *Can. J. Chem.*, 1987, **65**, 2244.
97. D. J. Faulkner, T. F. Molinski, R. J. Andersen, E. J. Dumdei, and E. D. de Silva, *Comp. Biochem. Physiol.*, 1990, **C97**, 233.
98. A. Yamada, H. Kitamura, K. Yamaguchi, S. Fukuzawa, C. Kamijima, K. Yazawa, M. Kuramoto, G.-Y.-S. Wang, Y. Fujitani, and D. Uemura, *Bull. Chem. Soc. Jpn.*, 1997, **70**, 3061.
99. M. K. Harper, T. S. Bugni, B. R. Copp, R. D. James, B. S. Lindsay, A. D. Richardson, P. C. Schnabel, D. Tasdemir, R. M. VanWagoner, S. M. Verbitski, and C. M. Ireland, “Introduction to the Chemical Ecology of Marine Natural Products” In “Marine Chemical Ecology” ed. by J. B. McClintock and B. J. Baker, CRC Press, LLC., Washington, D. C., 2001, pp. 3–69.
100. W. C. M. C. Kokke, S. Epstein, S. A. Look, G. H. Rau, W. Fenical, and C. Djerassi, *J. Biol. Chem.*, 1984, **259**, 8168.