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SURVEY OF BRIARANE-TYPE DITERPENOIDS–PART III

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Abstract – The structures, names, biological activities, and references of 137 briarane-type diterpenoids are summarized. All briaranes mentioned in this review article were obtained from various octocorals including the specimens belonging to the genus *Briareum*, *Ellisella*, *Gorgonella*, *Junceella*, *Subergorgia*, *Renilla*, and *Pachyclavularia*.

1. INTRODUCTION

This review is of the literature from Oct. 2004 to July 2008 and describes 137 briarane-related diterpenoids, which contained a bicyclo[8.4.0] carbon skeleton and most possessed a γ-lactone in structures (Figure 1). As in our previous reviews,[1,2] we show the structures, names, biological activities, and references for new briaranes, or for previously reported briaranes where there has been a structural revision or a newly established stereochemistry (including X-ray structure). All briaranes mentioned in this article were isolated from the soft corals belonging to the order Gorgonacea, including *Briareum excavatum*, *Briareum polyanthes*, *Briareum* sp., *Ellisella robusta*, *Gorgonella umbraculum*, *Junceella fragilis*, *Junceella juncea*, *Subergorgia reticulata*; the order Pennatulacea, including *Renilla reniformis*; and the order Stolonifera, including *Pachyclavularia violacea*, *Pachyclavularia* sp. This survey of briarane-type compounds will be presented taxonomically according to genus and species.

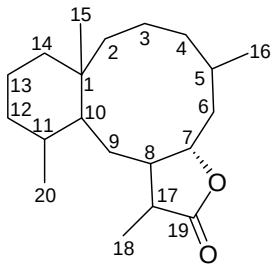


Figure 1. The carbon skeleton of briarane-type compounds

2. GORGONACEA

2.1. *Briareum* (family Briareidae)

A. *Briareum excavatum*

The octocorals belonging to the genus *Briareum* played the major sources of briarane-type natural products. In the continuing studies on Taiwanese gorgonian corals, *B. excavatum* was further studied for their interesting and complex chemical constituents. 19 briarane derivatives, including 16 new compounds, briaexcavatins A–P (**1**–**16**),[3–7] and three known briaranes, excavatolides B (**17**), C (**18**), and E (**19**),[8] were isolated from *B. excavatum* (Table 1). The structures of **1**–**16** were determined by spectroscopic methods and chemical conversion; and the configurations of **1**, **3**, and **8** were further supported by minimum molecular mechanics calculations.[3–5] The absolute configurations for **7**, **8**, and **17**–**19** were determined by modified Mosher's method and chemical conversion.[3,5,6] The X-ray structures for **18** and **19** were also reported for the first time.[6] It has to be noted that briaexcavatin A (**1**) is the first 11,12-secobriarane possessing an ε-lactone moiety.[3] Furthermore, the structures for two known compounds, briaexcavatolides X (**20**) and Y (**21**),[9] had been revised and reported in a later study, and these two metabolites should be recognized as the first briarane derivatives containing a 5,6-epoxide group (Table 1).[4]

In the biological activity testing, briaexcavatin C (**3**) exhibited mild cytotoxicity toward MDA-MB-231 human breast tumor cells and briaexcavatins E (**5**), G (**7**), P (**16**), and excavatolide C (**18**) showed inhibitory effects on superoxide anion generation or elastase release by human neutrophils.[4–7]

Table 1. The Briarane-Type Diterpenoids from *B. excavatum*

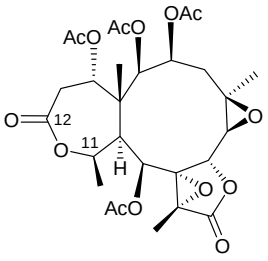
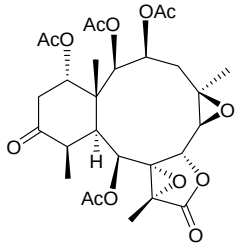
Structure	No.	Name	Biological Activity	Ref.
	**1**	briaexcavatin A	n.r.[a]	3
	**2**	briaexcavatin B	n.r.	3

Table 1. The Briarane-Type Diterpenoids from *B. excavatum*

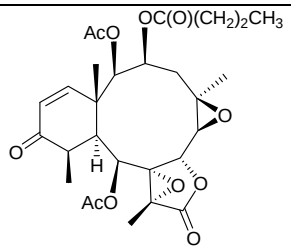
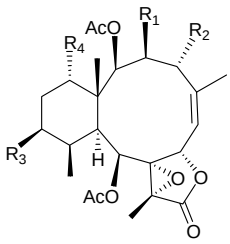
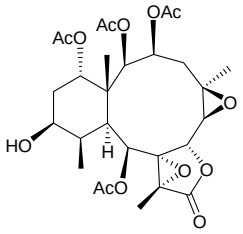
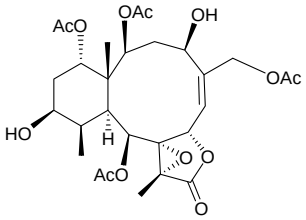
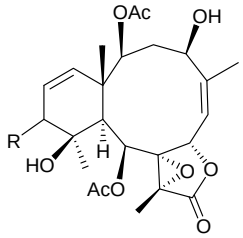
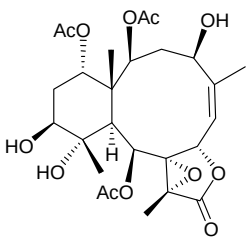
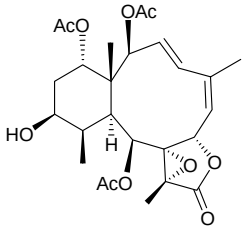
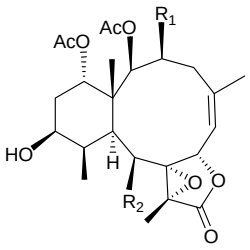
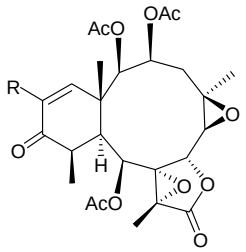
Structure	No.	Name	Biological Activity	Ref.
	**3**	briaexcavatin C	IC_{50} (MDA-MB-231) = 17.50 μg/mL	4
	**4**	briaexcavatin D ($R_1 = R_4 = OAc$, $R_2 = H$, $R_3 = OC(O)(CH_2)_2CH{=}CH_2$)	n.r.	4
	5	briaexcavatin E ($R_1 = R_4 = OAc$, $R_2 = H$, $R_3 = OC(O)CH_2CH(CH_3)_2$)	showed inhibitory effects on superoxide anion generation (101.19%, conc. 10 μM) and elastase release (87.77, 65.96, 37.89% at conc. 3, 5, 10 μM)	4
	6	briaexcavatin F ($R_1 = OC(O)(CH_2)_2CH_3$, $R_2 = H$, $R_3 = OC(O)(CH_2)_2CH{=}CH_2$, $R_4 = OAc$)	n.r.	4
	7	briaexcavatin G ($R_1 = OC(O)(CH_2)_2CH_3$, $R_2 = H$, $R_3 = OC(O)CH_2CH(CH_3)_2$, $R_4 = OAc$)	showed inhibitory effects on elastase release (36.44%), but not active in inhibition of superoxide anion generation (–8.49%) at 10 μg/mL	5
	9	briaexcavatin I ($R_1 = R_2 = H$, $R_3 = OH$, $R_4 = OAc$)	not active in inhibition of superoxide anion generation (2.38%) at 10 μg/mL	6
	15	briaexcavatin O ($R_1 = OC(O)(CH_2)_2CH_3$, $R_2 = OAc$, $R_3 = R_4 = OH$)	n.r.	7
	16	briaexcavatin P ($R_1 = R_3 = OH$, $R_2 = R_4 = OAc$)	showed weak inhibitory effects on superoxide anion generation (14.99%) at 10 μg/mL	7
	**8**	briaexcavatin H	not active in inhibition of superoxide anion generation (9.02%) and elastase release (5.19%) at 10 μg/mL	5
	**10**	briaexcavatin J	n.r.	6
	**11**	briaexcavatin K (R = α-OH)	n.r.	6
	14	briaexcavatin N (R = β-OAc)	n.r.	7
	**12**	briaexcavatin L	not active in inhibition of superoxide anion generation (3.04%) at 10 μg/mL	6

Table 1. The Briarane-Type Diterpenoids from *B. excavatum*

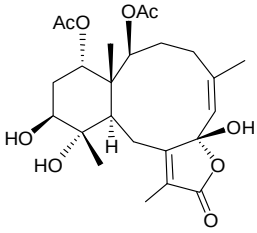
Structure	No.	Name	Biological Activity	Ref.
	**13**	briaexcavatin M	n.r.	7
	**17**[b]	excavatolide B (R_1 = $OC(O)(CH_2)_2CH_3$, R_2 = OAc)		3,5,8
	18[b]	excavatolide C (R_1 = R_2 = OAc)	showed weak inhibitory effects on superoxide anion generation (15.47%) at 10 μg/mL	3,5,6,8
	19[b]	excavatolide E (R_1 = H, R_2 = OH)	not active in inhibition of superoxide anion generation (4.88%) at 10 μg/mL	6,8
	**20**	briaexcavatolide X (R = OH) (revised)	IC_{50} (P-388D1, DLD-1, IMR-32, RPMI-7951, CCRF-CEM)[c] = > 20 μg/mL	4,9
	21	briaexcavatolide Y (R = H) (revised)	IC_{50} (P-388D1, DLD-1, IMR-32, RPMI-7951, CCRF-CEM)[c] = > 20 μg/mL	4,9

[a]n.r. = not reported. [b]The cytotoxicity of compounds (**17**–**19**) had been reported and reviewed, please see ref. 1 and 8. [c]P-388D1 (mouse lymphoid neoplasm), DLD-1 (human colon adenocarcinoma), IMR-32 (human neuroblastoma), RPMI-7951 (human malignant melanoma), and CCRF-CEM (human T-cell acute lymphoblastic leukemia).

B. *Briareum polyanthes*

A new 7β-hydroxybriarane (**22**) was obtained from the Caribbean gorgonian coral *B. polyanthes*, collected at the coral reef of Cabo Rojo, Puerto Rico (Table 2).[10] The structure of **22** was established by spectroscopic methods and this compound was found to show antiplasmodial activity.[10]

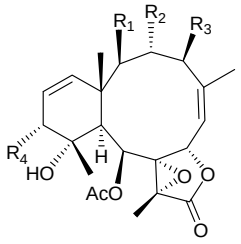
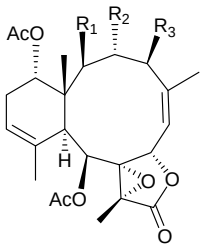
Table 2. The Briarane-Type Diterpdnoid from *B. polyanthes*

Structure	No.	Name	Biological Activity	Ref.
	**22**	unnamed	IC_{50} (*Plasmodium falciparum* W2) = 8 μg/mL	10

C. *Briareum* sp.

In the continuing studies on the chemical constituents of a gorgonian identified as *Briareum* sp., collected at Amami Island, Kagoshima Prefecture, Japan, 10 new briarane derivatives, briarlides I–R (**23**–**32**) (Table 3-1), were obtained and their structures were determined by spectral data analysis.[11,12]

Table 3-1. The Briarane-Type Diterpenoids from *Briareum* sp.

Structure	No.	Name	Biological Activity	Ref.
	**23**	briarlide I ($R_1 = R_2 = R_4 = OAc$, $R_3 = OC(O)(CH_2)_6CH_3$)	n.r.	11,12
	24	briarlide J ($R_1 = R_3 = OAc$, $R_2 = R_4 = OH$)	n.r.	11,12
	25	briarlide K ($R_1 = R_2 = OH$, $R_3 = OC(O)(CH_2)_2CH_3$, $R_4 = OAc$)	n.r.	11,12
	26	briarlide L ($R_1 = R_4 = OAc$, $R_2 = H$, $R_3 = OC(O)(CH_2)_6CH_3$)	n.r.	11,12
	27	briarlide M ($R_1 = OAc$, $R_2 = H$, $R_3 = OC(O)(CH_2)_4CH_3$, $R_4 = OH$)	n.r.	11,12
	28	briarlide N ($R_1 = R_3 = R_4 = OAc$, $R_2 = H$)	n.r.	11,12
	**29**	briarlide O ($R_1 = OAc$, $R_2 = OH$, $R_3 = OC(O)(CH_2)_6CH_3$)	n.r.	11,12
	30	briarlide P ($R_1 = R_3 = OAc$, $R_2 = OH$)	n.r.	11,12
	31	briarlide Q ($R_1 = OH$, $R_2 = OAc$, $R_3 = OC(O)(CH_2)_6CH_3$)	n.r.	11,12
	32	briarlide R ($R_1 = OH$, $R_2 = OAc$, $R_3 = H$)	n.r.	11,12

In addition, 24 new briaranes, including, violides Q–U (**33**–**37**) and their six unnamed derivatives (**38**–**43**);[13] briviolides A–D (**44**–**47**), 12-*O*-acetylbriviolide D (**48**), 9-deacetoxybriviolide D (**49**), 4-acetoxybriviolide D (**50**), and briviolides E–J (**51**–**56**) (Table 3-2),[14] were isolated from the gorgonian *Briareum* sp., collected in the area of Bonotsu, Kagoshima Prefecture, Japan. The structures of **33**–**56** were elucidated by spectroscopic methods and the structure of briviolide C (**46**) was further confirmed by X-ray diffraction analysis.[14] Briaranes (**36**, **37**, and **39**–**43**) contained unusual 17-hydroxy or 17-acyloxy groups.[13] Unlike the structures of briaranes that had been reported, there are no functional group was found to attach at C-2, -3, -4, and C-9 in briviolides G–I (**53**–**55**), and the compounds of this type were rarely found in briarane derivatives.[14] Briviolide I (**55**) is the first briarane containing a 7-keto group.[14]

Several of above briaranes were found to show cytotoxicity toward African Green Monkey Kidney (Vero) and Madin-Daby Canine Kidney (MDCK) cells.[13,14]

Table 3-2. The Briarane-Type Diterpenoids from *Briareum* sp.

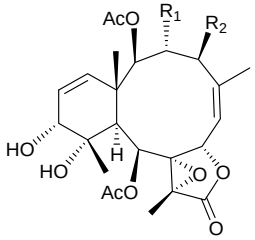
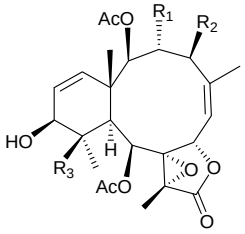
Structure	No.	Name	Biological Activity	Ref.
	**33**	violide Q ($R_1 = OC(O)(CH_2)_6CH_3$, $R_2 = OH$)	CC_{50} (Vero, DMCK) = 5.09, 4.88 μg/mL	13
	38	unnamed ($R_1 = OH$, $R_2 = OC(O)(CH_2)_4CH_3$)	n.r.	13
	**34**	violide R ($R_1 = H$, $R_2 = OC(O)(CH_2)_6CH_3$, $R_3 = OH$)	CC_{50} (Vero, DMCK) = 2.57, 3.96 μg/mL	13
	35	violide S ($R_1 = R_2 = OAc$, $R_3 = H$)	CC_{50} (Vero, DMCK) = >100, >100 μg/mL	13

Table 3-2. The Briarane-Type Diterpenoids from *Briareum* sp.

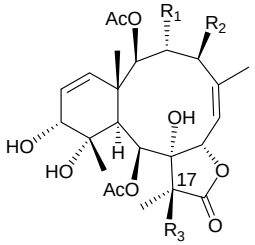
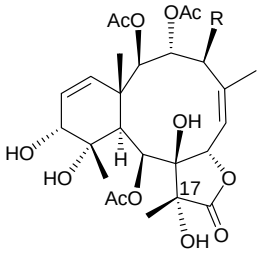
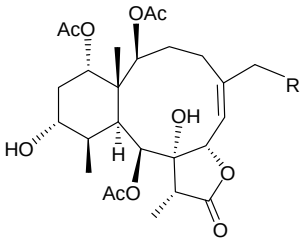
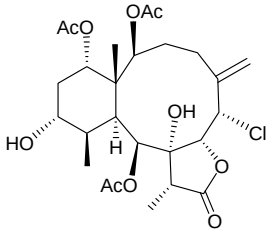
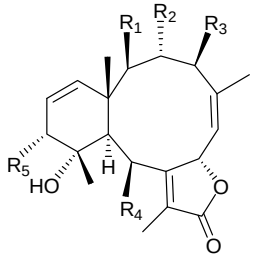
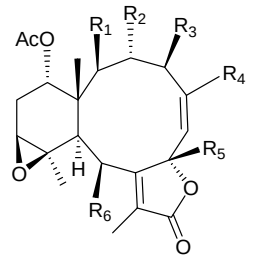
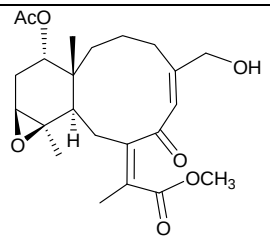
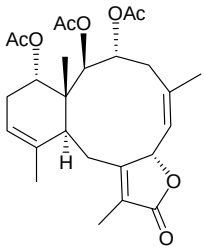
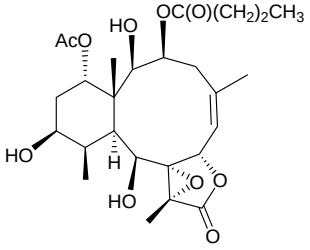
Structure	No.	Name	Biological Activity	Ref.
	**36**	violide T (R_1 = OAc, R_2 = $OC(O)(CH_2)_6CH_3$, R_3 = OH)	CC_{50} (Vero, DMCK) = 39.5, 55.3 μg/mL	13
	37	violide U (R_1 = $OC(O)(CH_2)_2CH_3$, R_2 = OAc, R_3 = OH)	CC_{50} (Vero, DMCK) = >100, >100 μg/mL	13
	39	unnamed (R_1 = H, R_2 = $OC(O)(CH_2)_6CH_3$, R_3 =OH)	CC_{50} (Vero, DMCK) = 32.5, 19.1 μg/mL	13
	40	unnamed (R_1 = H, R_2 = $OC(O)(CH_2)_2CH_3$, R_3 = OH)	CC_{50} (Vero, DMCK) = >100, >100 μg/mL	13
	41	unnamed (R_1 = OH, R_2 = $OC(O)(CH_2)_6CH_3$, R_3 = OAc)	n.r.	13
	42	unnamed (R_1 = OH, R_2 = $OC(O)(CH_2)_6CH_3$, R_3 = $OC(O)CH_2CH_3$)	n.r.	13
	**43**	unnamed (R = $OC(O)(CH_2)_6CH_3$)	n.r.	13
	**44**	briviolide A (R = OH)	not cytotoxic toward Vero and MDCK cells	14
	45	briviolide B (R = Cl)	CC_{50} (Vero) = 91.5 μg/mL, not cytotoxic against MDCK cells	14
	**46**	briviolide C	n.r.	14
	**47**	briviolide D (R_1 = R_2 = R_4 = OAc, R_3 = H, R_5 = OH)	CC_{50} (Vero) = 87.6 μg/mL, not cytotoxic against MDCK cells	14
	48	12-*O*-acetylbriviolide D (R_1 = R_2 = R_4 = R_5 = OAc, R_3 = H)	CC_{50} (Vero) = 45.3 μg/mL, not cytotoxic against MDCK cells	14
	49	9-deacetoxybriviolide D (R_1 = R_2 = OAc, R_3 = R_4 = H, R_5 = OH)	CC_{50} (Vero, MDCK) = 69.0, 82.1 μg/mL	14
	50	4-acetoxybriviolide D (R_1 = R_2 = R_3 = R_4 = OAc, R_5 = OH)	not cytotoxic against Vero and MDCK cells	14
	51	briviolide E (R_1 = R_2 = R_5 = OH, R_3 = $OC(O)(CH_2)_6CH_3$, R_4 = OAc)	n.r.	14
	**52**	briviolide F (R_1 = R_6 = OAc, R_2 = OH, R_3 = $OC(O)(CH_2)_6CH_3$, R_4 = CH_3, R_5 = H)	CC_{50} (Vero, MDCK) = 31.9, 42.2 μg/mL	14
	53	briviolide G (R_1 = R_2 = R_3 = R_5 = R_6 = H, R_4 = CH_3)	n.r.	14
	54	briviolide H (R_1 = R_2 = R_3 = R_6 = H, R_4 = CH_2OH, R_5 = OCH_3)	not cytotoxic against Vero and MDCK cells	14

Table 3-2. The Briarane-Type Diterpenoids from *Briareum* sp.

Structure	No.	Name	Biological Activity	Ref.
	**55**	briviolide I	n.r.	14
	**56**	briviolide J	n.r.	14

A new trihydroxybriarane, briarenol A (**57**) (Table 3-3), was isolated from a Taiwanese gorgonian identified as *Briareum* sp. The structure of **57** was established by spectral data analysis and further supported by molecular mechanics calculations.[15]

Table 3-3. The Briarane-Type Diterpenoid from *Briareum* sp.

Structure	No.	Name	Biological Activity	Ref.
	**57**	briarenol A	n.r.	15

10 new 8,17-epoxybriaranes, briaranolides A–J (**58**–**67**) (Table 3-4), were isolated from the gorgonian specimens of *Briareum* sp., collected off the coral reef of Hatoma Island, Okinawa, Japan.[16] The structures of **58**–**67** were elucidated by spectroscopic and chemical methods and the absolute configurations of **58**–**67** were determined by the combination of chemical conversion and X-ray diffraction analysis.[16]

Table 3-4. The Briarane-Type Diterpenoids from *Briareum* sp.

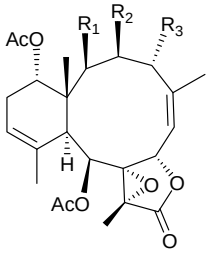
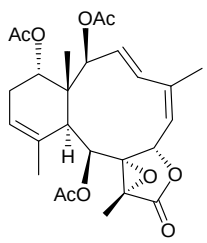
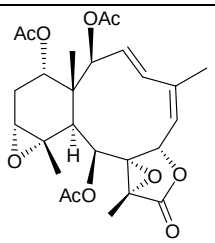
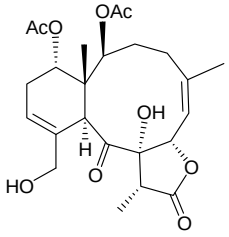
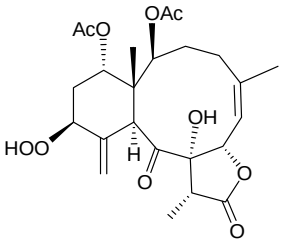
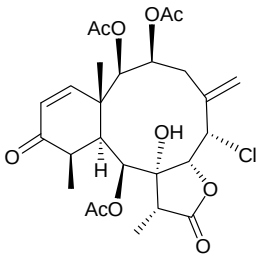
Structure	No.	Name	Biological Activity	Ref.
	**58**	briaranolide A ($R_1 = R_2 = R_3 = OAc$)	n.r.	16
	59	briaranolide B ($R_1 = R_2 = OAc$, $R_3 = OC(O)(CH_2)_2CH_3$)	n.r.	16
	60	briaranolide C ($R_1 = OAc$, $R_2 = R_3 = OC(O)(CH_2)_2CH_3$)	n.r.	16
	61	briaranolide D ($R_1 = OAc$, $R_2 = OH$, $R_3 = OC(O)(CH_2)_2CH_3$)	n.r.	16
	62	briaranolide E ($R_1 = R_2 = OAc$, $R_3 = H$)	n.r.	16
	63	briaranolide F ($R_1 =$ OAc $R_2 = OC(O)(CH_2)_2CH_3$, $R_3 = H$)	n.r.	16
	64	briaranolide G ($R_1 =$ OAc $R_2 = OH$, $R_3 = H$)	n.r.	16
	65	briaranolide H ($R_1 = OC(O)CH_2CH_3$, $R_2 = OC(O)(CH_2)_2CH_3$, $R_3 = H$)	n.r.	16
	**66**	briaranolide I	n.r.	16

Table 3-4. The Briarane-Type Diterpenoids from *Briareum* sp.

Structure	No.	Name	Biological Activity	Ref.
	**67**	briaranolide J	n.r.	16

Chemical investigation on a Taiwanese gorgonian *Briareum* sp., has led to the isolation of three new natural products, including two 9-ketobriaranes, briarenolides A (**68**) and B (**69**), and a 6-chlorinated compound, briarenolide C (**70**) (Table 3-5).[17] The structures of **68**–**70** were determined on basis of spectral data analysis. Briarenolide A (**68**) is the first briarane possessing a 20-hydroxy group. The 9-keto group in compounds (**68** and **69**) and the hydroperoxy group in **69** are rarely found in briarane derivatives.

Table 3-5. The Briarane-Type Diterpenoids from *Briareum* sp.

Structure	No.	Name	Biological Activity	Ref.
	**68**	briarenolide A	ED_{50} (Hela, Hepa59T/VGH, Med, KB)[a] = >20, >20, >20 μg/mL	17
	**69**	briarenolide B	ED_{50} (Hela, Hepa59T/VGH, Med, KB)[a] = >20, >20, >20 μg/mL	17
	**70**	briaraenolide C	ED_{50} (Hela, Hepa59T/VGH, Med, KB)[a] = >20, >20, >20 μg/mL	17

[a]Hela (human cervical epitheloid carcinoma), Hepa59T/VGH (human liver carcinoma), Med (human medulloblastoma), KB (human oral epidermoid carcinoma).

2.2. *Ellisella* (family Ellisellidae)

A. *Ellisella robusta*

Three new briaranes, robustolides A–C (**71**–**73**), were isolated from the Formosan gorgonian *E. robusta* (Table 4). The structures of **71**–**73** were elucidated by spectral data analysis and the structure of **71** was further confirmed by a single-crystal X-ray diffraction analysis.[18] In a previous study, the structure of **71** had been reported and named as umbraculolide C.[19] However, by comparison of the NMR data of **71** with

those of umbraculolide C, the NMR data for **71** differ significantly from those of umbraculolide C. Because of the structure of **71** (robustolide A) had been established by X-ray analysis.[18] The structure for the reported compound, umbraculolide C, should be re-examined.[19] Compounds (**71** and **72**) showed weak antibacterial activity.[18] Furthermore, six chlorinated briaranes, robustolides D–I (**74**–**79**), were isolated from *E. robusta* (Table 4).[20,21] The structures of **74**–**79** were determined by spectroscopic methods and the absolute configurations of robustolides D (**74**), F (**76**), G (**77**), and I (**79**) were established by X-ray diffraction analysis for the first time.[20,21] Compounds **76**, **77**, and **79** had been isolated from a Japanese gorgonian *Ellisella* sp.[22] Based on X-ray diffraction data, the $\Delta^{3,5(16)}$-butadiene systems in robustolides G (**77**) and I (**79**) existed in an *s-cis* conjugated system and the structures for these two compounds reported previously should be re-examined.[20–22] It is noteworthy to mention that robustolide D (**74**) represents the first example of a briarane possessing two halogen atoms.[20]

Table 4. The Briarane-Type Diterpenoids from *E. robusta*

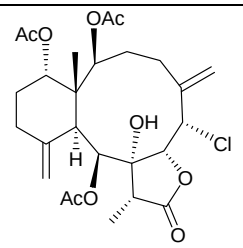
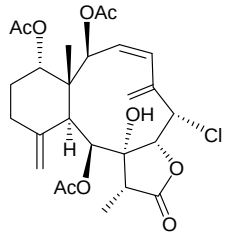
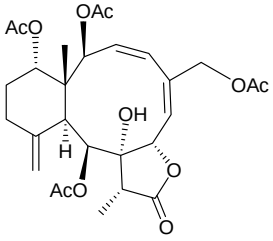
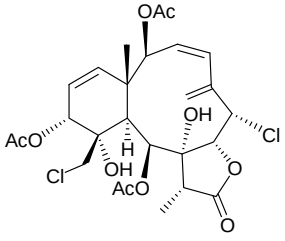
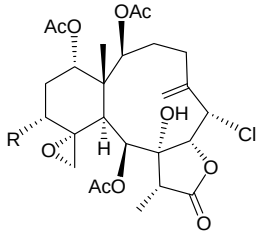
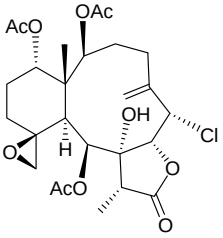
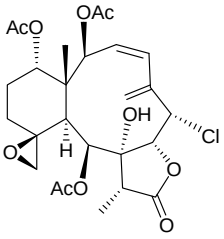
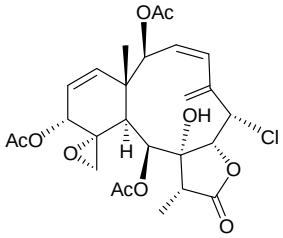
Structure	No.	Name	Biological Activity	Ref.
	**71**	robustolide A	showed weak activity toward the bacteria *Pseudomonas aeruginosa* (0.5 mm, 200 μg/mL) and *Staphylococcus aureus* (0.5 mm, 200 μg/mL)	18
	**72**	robustolide B	showed weak activity toward the bacterium *Pseudomonas aeruginosa* (0.5 mm, 200 μg/mL)	18
	**73**	robustolide C	not active toward the bacteria *Pseudomonas aeruginosa* and *Staphylococcus aureus*	18
	**74**	robustolide D	not cytotoxic toward the HepG2, Hep3B, MDA-MB-231, MCF7, A549, and Ca9-22 cells (IC_{50} > 20 μg/mL)[a]	20
	**75**	robustolide E (R = H)	not cytotoxic toward the HepG2, Hep3B, MDA-MB-231, MCF7, A549, and Ca9-22 cells (IC_{50} > 20 μg/mL)[a]	20
	78	robustolide H (R = OAc)	n.r.	21

Table 4. The Briarane-Type Diterpenoids from *E. robusta*

Structure	No.	Name	Biological Activity	Ref.
	**76**	robustolide F	not cytotoxic toward the HepG2, Hep3B, MDA-MB-231, MCF7, A549, and Ca9-22 cells (IC_{50} > 20 μg/mL)[a]	20,22
	**77**	robustolide G	not cytotoxic toward the HepG2, Hep3B, MDA-MB-231, MCF7, A549, and Ca9-22 cells (IC_{50} > 20 μg/mL)[a]	20,22
	**79**	robustolide I	n.r.	21,22

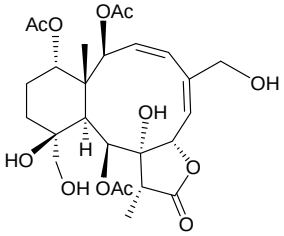
[a]HepG2 and Hep3B (human hepatocellular carcinoma), MDA-MB-231 (human breast carcinoma), MCF7 (human breast carcinoma), A549 (human lung adenocarcinoma), Ca9-22 (oral squamous cell carcinoma).

2.3. *Gorgonella* (Ellisellidae)

A. *Gorgonella umbraculum*

Umbraculolide E (**80**) is a new tetrahydroxybriarane that was isolated from an Indian gorgonian coral *G. umbraculum* and its structure was elucidated by spectral data analysis (Table 5).[23] The 20-hydroxy group in **80** was rarely found in briarane derivatives.

Table 5. The Briarane-Type Diterpenoid from *G. umbraculum*

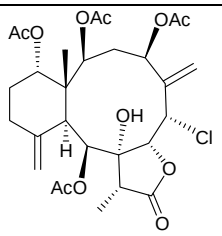
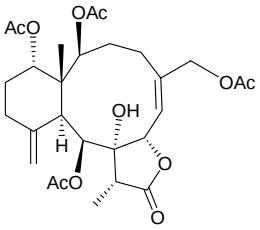
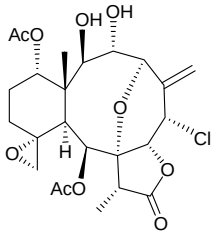
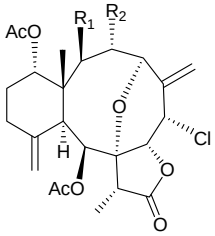
Structure	No.	Name	Biological Activity	Ref.
	**80**	umbraculolide E	n.r.	23

2.4. *Junceella* (Ellisellidae)

A. *Junceella fragilis*

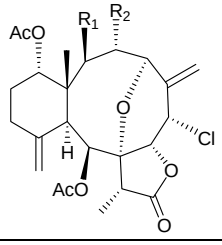
The gorgonian corals belonging to the genus *Junceella* also played major sources of briarane-related natural products.[24] The South China Sea gorgonian, *J. fragilis*, was found to contain five new briarane derivatives, junceellonoids A–E (**81**–**85**) (Table 6-1). The structures of **81**–**85** were established by spectroscopic methods.[25,26] Junceellonoids C (**83**) and D (**84**) were found to exhibit mild cytotoxicity against human breast carcinoma MDA-MB-231 and MCF7 cells.[26]

Table 6-1. The Briarane-Type Diterpenoids from *J. fragilis*

Structure	No.	Name	Biological Activity	Ref.
	**81**	junceellonoid A	n.r.	25
	**82**	junceellonoid B	n.r.	25
	**83**	junceellonoid C	showed mild cytotoxicity against MDA-MB-231 and MCF cell lines at a concentration of 100 μM, but not active at a concentration of 33.3 μM (IC_{50} values for this metabolite were not calculated)	26
	**84**	junceellonoid D (R_1 = R_2 = OH)	showed mild cytotoxicity against MDA-MB-231 and MCF cell lines at a concentration of 100 μM, but not active at a concentration of 33.3 μM (IC_{50} values for this metabolite were not calculated)	26
	85	junceellonoid E (R_1 = R_2 = OAc)	n.r.	26

Two new chlorinated briaranes, (–)-2-deacetyljunceellin (**86**) and (–)-3-deacetyljunceellin (**87**), were isolated from *J. fragilis*, collected at the Pass Reef of Madang, Papua New Guinea (Table 6-2).[27] The structures of **86** and **87** were determined by NMR experiments, and these two compounds were proven to be existed in host coral and are not artifacts. The absolute configuration of **87** was determined by the application of a method using the combination of chemical shifts simulation and molecular dynamic (MD) calculations.

Table 6-2. The Briarane-Type Diterpenoids from *J. fragilis*

Structure	No.	Name	Biological Activity	Ref.
	**86**	(–)-2-deacetyljunceellin (R_1 = OH, R_2 = OAc)	n.r.	27
	87	(–)-3-deacetyljunceellin (R_1 = OAc, R_2 = OH)	n.r.	27

Chemical investigation on the gorgonian *J. fragilis*, collected in the Taiwanese tropical waters have yielded 11 new briaranes, including junceellolides I–L (**88**–**91**),[28,29] fragilides B–D (**92**–**94**),[6,30,31] and frajunolides A–D (**95**–**98**) (Table 6-3).[32] The structures of compounds (**88**–**98**) were determined by spectroscopic

methods and the structure of junceellolide J (**89**) was further confirmed by a single-crystal X-ray diffraction analysis.[29] The absolute configuration of **89** was determined by chemical conversion of a known briarane (–)-11β,20β-epoxy-4-deacetoxyjunceellolide D (**99**) (Table 6-3).[29,33,34]

For determining the stereochemistry of briaranes possessed an exocyclic 11,20-epoxy group, the ^{13}C NMR chemical shifts of exocyclic 11,20-epoxy groups have been summarized; these appear at δ 62–63 and 58–60 ppm, respectively, while the epoxy group existed in 11*S** form and led the cyclohexane rings to show a boat conformation. If the epoxy group was found to exist in 11*R** configuration, the ^{13}C NMR data for C-11 and C-20 were appeared at δ 55–61 and 47–52 ppm, respectively, and the cyclohexane rings were found to exist in chair conformation.[29] Due to above observation, the stereochemistry of 11,20-epoxy group in several known briaranes such as (+)-11α,20α-epoxyjunceellolide D,[33] (–)-11α,20α-epoxy-4-deacetyljunceellolide D,[33] (–)-11α,20α-epoxy-4-deacetoxyjunceellolide D,[33,34] and junceellolide F[35] should be revised as having a β-orientation. In addition, the geometry for the $\Delta^{3,5(16)}$-butadiene in briaranes such as junceellolides B and C,[36] umbraculolide D,[19] juncin O,[37] and an unnamed briarane isolated from a Japanese octocoral *Pteroeides* sp.,[22,38] should be revised as the *s-cis* form by NMR data analysis.[30]

A briarane diterpene containing a 2-(3-methylbutanoyloxy)acetate ester substituent, like as fragilide D (**94**), was observed for the first time.[31] The 11,20-epoxybriarane derivatives were also proven to be a chemical marker for the gorgonian corals belong to family Ellisellidae.[39] Several briaranes from Taiwanese *J. fragilis* showed inhibitory effects on superoxide anion generation and elastase release by human neutrophils.

Table 6-3. The Briarane-Type Diterpenoids from *J. fragilis*

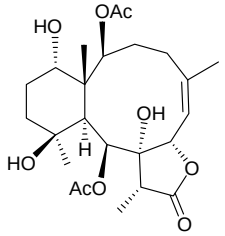
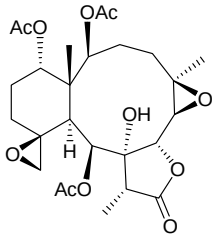
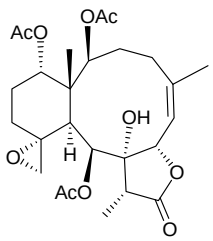
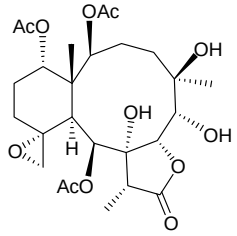
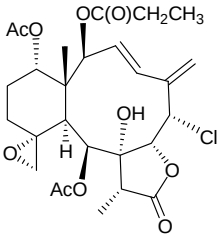
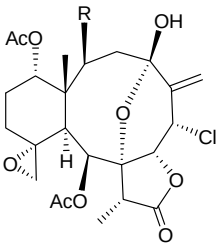
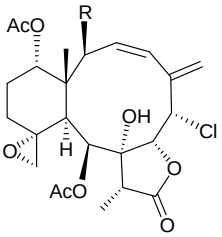
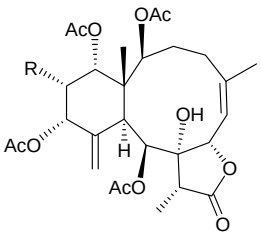
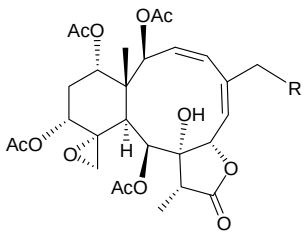
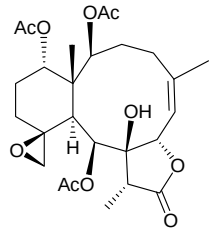
Structure	No.	Name	Biological Activity	Ref.
	**88**	junceellolide I	n.r.	28
	**89**	junceellolide J	not active in inhibition of superoxide anion generation (7.66%) and elastase release (5.17%) at 10 μg/mL	29
	**90**	junceellolide K	showed weak inhibitory effects on superoxide anion generation (13.89%) and elastase release (15.04%) at 10 μg/mL	29

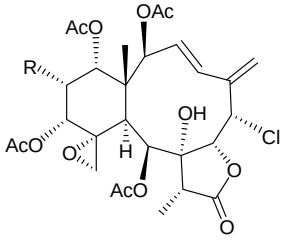
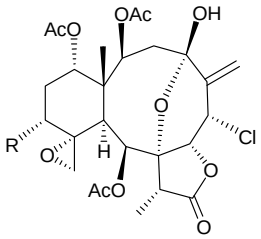
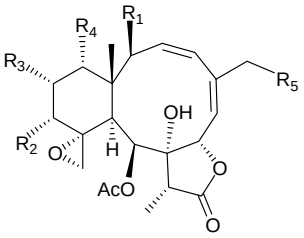
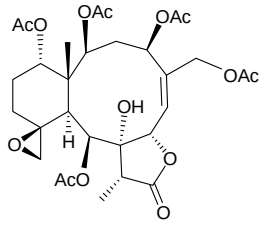
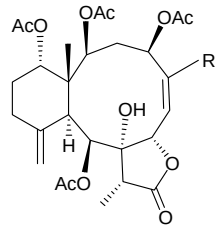
Table 6-3. The Briarane-Type Diterpenoids from *J. fragilis*

Structure	No.	Name	Biological Activity	Ref.
	**91**	junceellolide L	not active in inhibition of superoxide anion generation (5.55%) and elastase release (5.52%) at 10 μg/mL	29
	**92**	fragilide B	showed weak inhibitory effects on superoxide anion generation (17.55%) and elastase release (20.67 %) at 10 μg/mL	30
	**93**	fragilide C (R = $OCOCH_2CH_3$)	showed weak inhibitory effects on superoxide anion generation (11.61%) at 10 μg/mL	6
	**94**	fragilide D (R = $OC(O)CH_2OC(O)CH_2CH(CH_3)_2$)	n.r.	31
	**95**	frajunolide A (R = H)	showed weak inhibitory effects on superoxide anion generation (13.93%), but not active in the inhibition of elastase release (6.47%) at 10 μg/mL	32
	96	frajunolide B (R = OAc)	showed weak inhibitory effects on superoxide anion generation (14.50%), but not active in the inhibition of elastase release (5.16%) at 10 μg/mL	32
	**97**	frajunolide C (R = Cl)	showed weak inhibitory effects on superoxide anion generation (19.76%) and elastase release (14.47%) at 10 μg/mL	32
	98	frajunolide D (R = OAc)	not active in the inhibition of superoxide anion generation (5.61%) and elastase release (2.54%) at 10 μg/mL	32
	**99**	(–)-11β,20β-epoxy-4-deacetoxy-junceellolide D		29,33,34

B. *Junceella juncea*

Qi *et al.*, have isolated 13 new briaranes, juncins O–Z (**100**–**111**) and juncin ZI (**112**), from the South China Sea gorgonian *J. juncea* and their structures were determined through the combination of spectral data analysis (Table 7-1).[37,40] Briaranes (**103**–**112**) showed antifouling activity against the larval settlement of barnacle *Balanus amphitrite*.[40]

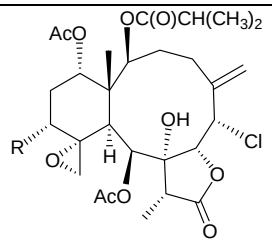
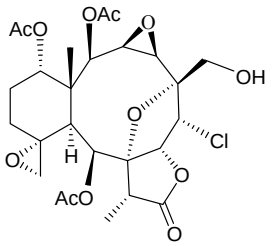
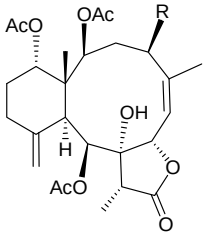
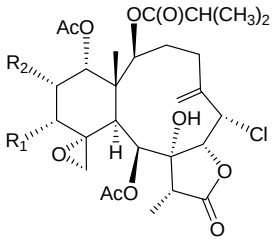
Table 7-1. The Briarane-Type Diterpenoids from *J. juncea*

Structure	No.	Name	Biological Activity	Ref.
	**100**	juncin O (R = $OC(O)CH_2CH(CH_3)_2$)[a]	n.r.	30,37
	**101**	juncin P (R = OAc)	n.r.	37
	112	juncin ZI (R = H)	EC_{50} = 0.51 μg/mL	40
	**102**	juncin Q (R_1 = R_3 = OAc, R_2 = R_4 = R_5 = OH)	n.r. briaranes **103**–**112** showed antifouling activity toward the barnacle *Balanus amphitrite* larvae	37
	103	juncin R (R_1 = R_2 = R_3 = OAc, R_4 = $OC(O)CH_2CH(CH_3)_2$, R_5 = Cl)	EC_{50} = 0.004 μg/mL	40
	104	juncin S (R_1 = R_3 = R_4 = OAc, R_2 = $OC(O)CH_2CH(CH_3)_2$, R_5 = Cl)	EC_{50} = 0.34 μg/mL	40
	105	juncin T (R_1 = $OC(O)CH_2OC(O)(CH_2)_2CH(CH_3)_2$, R_2 = R_3 = R_4 = OAc, R_5 = OH)	EC_{50} = 2.65 μg/mL	40
	106	juncin U (R_1 = R_2 = R_4 = OAc, R_3 = $OC(O)CH_2CH(CH_3)_2$, R_5 = OCH_3)	EC_{50} = 1.61 μg/mL	40
	107	juncin V (R_1 = R_3 = OAc, R_2 = R_4 = OH, R_5 = OCH_3)	EC_{50} = 3.77 μg/mL	40
	108	juncin W (R_1 = R_3 = R_5 = OAc, R_2 = R_4 = OH)	EC_{50} = 21.06 μg/mL	40
	**109**	juncin X	EC_{50} = 0.004 μg/mL	40
	**110**	juncin Y (R = CH_2OAc)	EC_{50} = 0.14 μg/mL	40
	111	juncin Z (R = $C(O)OCH_3$)	EC_{50} = 1.47 μg/mL	40

[a]The structure of juncin O (**100**) had been revised, please see ref. 30.

In the continuing researches on Taiwanese gorgonian coral *J. juncea*, five new briaranes, juncenolides F (**113**), G (**114**),[41] and junceols A–C (**115**–**117**) (Table 7-2),[31] were isolated. The structures of **113**–**117** were elucidated by spectral data analysis. **114** is the first briarane with an ether linkage between C-5 and C-8.[41] Briaranes (**115**–**117**) exhibited inhibitory effects on superoxide anion generation by human neutrophils.[31]

Table 7-2. The Briarane-Type Diterpenoids from *J. juncea*

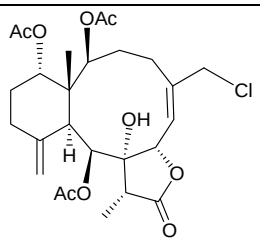
Structure	No.	Name	Biological Activity	Ref.
	**113**	juncenolide F (R = $OC(O)CH_2CH(CH_3)_2$)	n.r.	41
	**114**	juncenolide G	n.r.	41
	**115**	junceol A (R = $OC(O)CH_2CH(CH_3)_2$)	showed inhibitory effects on superoxide anion generation (45.64 %) at 10 μg/mL	31
	**116**	junceol B (R_1 = OAc, R_2 = $OC(O)CH_2CH(CH_3)_2$)	showed inhibitory effects on superoxide anion generation (159.60 %) at 10 μg/mL	31
	117	junceol C (R_1 = R_2 = $OC(O)CH_2CH(CH_3)_2$)	showed inhibitory effects on superoxide anion generation (124.14%) at 10 μg/mL	31

2.5. *Subergorgia* (Subergorgiidae)

A. *Subergorgia reticulata*

A new chlorinated briarane, reticulolide (**118**), was isolated from the gorgonian *Subergorgia reticulata*, collected at South China Sea (Table 8).[42] The structure of **118** was determined by spectroscopic methods and this compound is the first briarane derivative isolated from the gorgonians belonging to the family Subergorgiidae.

Table 8. The Briarane-Type Diterpenoid from *S. reticulata*

Structure	No.	Name	Biological Activity	Ref.
	**118**	reticulolide	n.r.	42

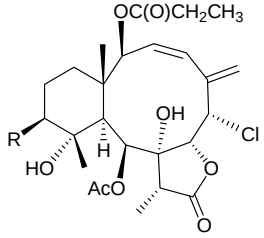
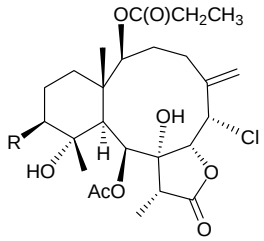
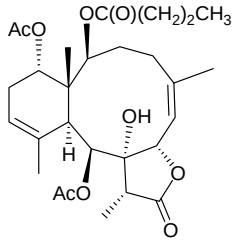
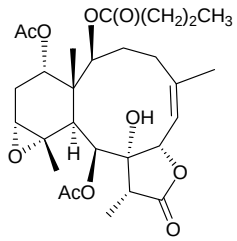
3. PENNATULACEA

3.1. *Renilla* (Renillidae)

A. *Renilla reniformis*

The sea peasy coral *R. reniformis*, collected at the sand bars off Wassaw, Little Tybee, and South Cabbage Islands, Georgia, United States, was found to contain four new briaranes, renillins A–D (**119**– **122**) (Table 9).[43] The structures of **119**–**122** were determined by spectral data analysis. Renillins A (**119**) and B (**120**) are the first briarane derivatives with fully reduced C-14 centers.[43] Briaranes (**119**–**122**) tested at natural concentrations significantly deterred feeding by the predatory lesser blue crab, *Callinectes similis*. **121** and **122** also deterred feeding by the predatory mummichog fish, *Fundulus heteroclitus*.

Table 9. The Briarane-Type Diterpenoids from *Renilla reniformis*

Structure	No.	Name	Biological Activity	Ref.
	**119**	renillin A (R = $OC(O)CH(CH_3)_2$)	deterred the lesser blue crab *Callinectes similis*, reducing food consumption by 70% at 0.060 mM.	43
	**120**	renillin B (R = $OC(O)CH(CH_3)_2$)	deterred the lesser blue crab *Callinectes similis*, reducing food consumption by 70% at 0.060 mM.	43
	**121**	renillin C	deterred the lesser blue crab *Callinectes similis*, reducing food consumption by 50% at 0.060 mM and deterred feeding by the mummichog fish *Fundulus heteroclitus* at 0.060 mM (reduced feeding 40%).	43
	**122**	renillin D	deterred the lesser blue crab *Callinectes similis*, reducing food consumption by 40% at 0.060 mM and deterred feeding by the mummichog fish *Fundulus heteroclitus* at 0.060 mM (reduced feeding 40%).	43

4. STOLONIFERA

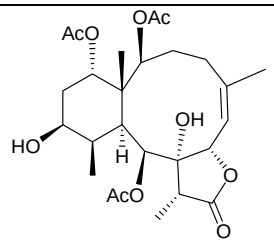
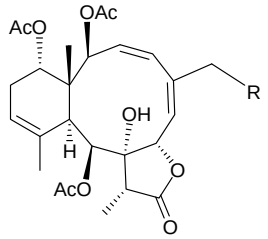
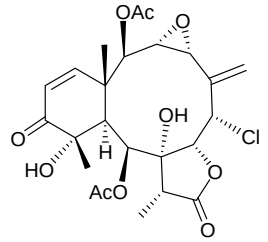
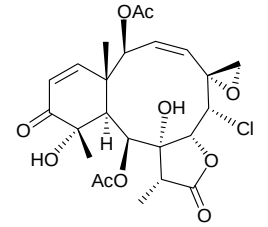
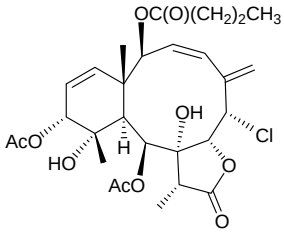
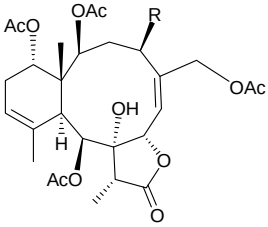
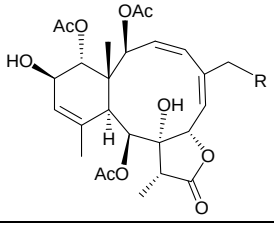
4.1. *Pachyclavularia* (Clavularidae)

A. *Pachyclavularia violacea*

Study on the octocoral *P. violacea*, collected off Ishigaki Island, Okinawa Prefecture, Japan, has afforded nine new briaranes, pachyclavulides A–I (**123**–**131**) (Table 10-1).[44,45] The structures of **123**–**131** were elucidated by spectroscopic and chemical methods and the absolute configuration of **123** was determined

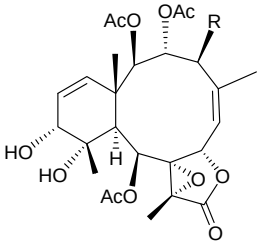
by the X-ray crystallographic analysis of its *p*-bromobenzoyl ester derivative.[44,45] Briaranes **124** and **127** showed cytotoxicity toward SNB-75 (human CNS) and A549 (human lung cancer) cell lines, respectively.[45] The enantioselective preparation of the six-membered ring of **124**, was achived.[46]

Table 10-1. The Briarane-Type Diterpenoids from *P. violacea*

Structure	No.	Name	Biological Activity	Ref.
	**123**	pachyclavulide A	not active toward the 39 cell lines was evaluated in the Jpn. Fdn.	44,45
	**124**	pachyclavulide B (R = OH)	GI_{50} (SNB75) = 5.2 μM	44,45,46
	125	pachyclavulide C (R = OAc)	not active toward the 39 cell lines were evaluated in the Jpn. Fdn.	44,45
	**126**	pachyclavulide D	n.r.	44
	**127**	pachyclavulide E	GI_{50} (A549) = 5.1 μM	45
	**128**	pachyclavulide F	not active toward the 39 cell lines were evaluated in the Jpn. Fdn.	45
	**129**	pachyclavulide G (R = OH)	n.r.	45
	130	pachyclavulide H (R = H)	n.r.	45
	**131**	pachyclavulide I (R = OCH_3)	n.r.	45

Moreover, two known briaranes, violides B (**132**)[47,48] and E (**133**)[48] were isolated from the octocoral *P. violacea*, collected in Akasaki Bay, Bonotsu, Kagoshima Prefecture, Japan (Table 10-2).[49] The structures of these two metabolites were established by the combination of NMR data analysis and further confirmed by molecular mechanics calculations, particularly with the coupling constant calculations and the calculated distances analysis between the protons having key NOE correlations. The structure of **132** (violide B) had been reconfirmed by X-ray diffraction analysis and the absolute configuration of **133** (violide E) was determined by X-ray crystallographic analysis of its bis-MTPA ester.[49]

Table 10-2. The Briarane-Type Diterpenoids from *P. violacea*

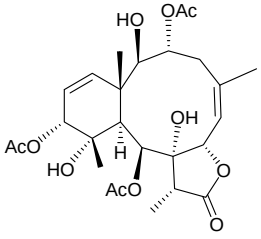
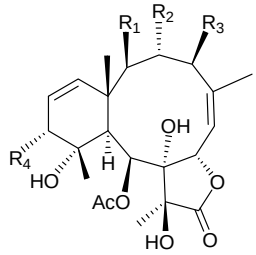
Structure	No.	Name	Biological Activity	Ref.
	**132**[a]	violide B (R = OAc)	n.r.	47,48,49
	133[a,b]	violide E (R = OC(O)$(CH_2)_2CH_3$)		48,49,50

[a]Briaranes (**132** and **133**) were named as (1*S**,2*R**,3*R**,4*S**,5*Z*,7*S**,8*S**,9*S**,10*S**,11*S**,12*R**,13*Z*,17*R**)-2,3,4,9-tetraacetoxy-8,17-epoxy-11,12-dihydroxybriara-5,13-dien-18-one and (1*S*,2*R*,3*R*,4*S*,5*Z*,7*S*,8*S*,9*S*,10*S*,11*S*,12*R*,13*Z*,17*R*)-2,3,9-triacetoxy-4-butyryloxy-8,17-epoxy-11,12-dihydroxybriara-5,13-dien-18-one, respectively, please see ref. 49. [b]The cytotoxicity for violide E (**133**) had been reported and reviewed, please see ref. 1 and 50.

B. *Pachyclavularia* sp.

In 2008, Ishiyama et al., reported the occurrence of four new briaranes, brianodins A–D (**134**–**137**), from an Okinawa octocoral *Pachyclavularia* sp. (Table 11).[51] The structure determination works of these four natural products were based on spectral data analysis and the absolute configurations of **136** and **137** were determined by chemical methods. Brianodin A (**137**) was found to show modest activity toward L1210 (murine leukemia) and KB (human oral epidermoid carcinoma) tumor cells.[51]

Table 11. The Briarane-Type Diterpenoids from *Pachyclavularia* sp.

Structure	No.	Name	Biological Activity	Ref.
	**134**	brianodin A	IC_{50} (L1210, KB) = 1.8, 4.3 μg/mL	51
	**135**	brianodin B (R_1 = R_3 = R_4 = OAc, R_2 = OH)	IC_{50} (L1210, KB) = >10, >10 μg/mL	51
	136	brianodin C (R_1 = R_3 = OAc, R_2 = R_4 = OH)	IC_{50} (L1210, KB) = >10, >10 μg/mL	51
	137	brianodin D (R_1 = R_4 = OH, R_2 = OAc, R_3 = H)	IC_{50} (L1210, KB) = >10, >10 μg/mL	51

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