CHEMICAL REVIEWS

REVIEW

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Disulfide- and Multisulfide-Containing Metabolites from Marine Organisms

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1. INTRODUCTION

The special living environment in the oceans, including high concentration of salts, high pressure, low concentration of oxygen, and dark conditions, has made marine organisms evolve unique metabolic pathways. It is well-known that marine invertebrates such as sponges, bryozoans, and tunicates are rich sources of a variety of secondary metabolites possessing novel structures and bioactivities, which is not surprising given the environment that these organisms inhabit. Most marine invertebrates lack physical protection in the form of an exoskeleton, e.g., spines, stings, or shells. Despite this, their own unique chemical protection strategy provides them successful survival and evolution. The capability to produce highly potent and structurally interesting metabolites by marine invertebrates has attracted much interest of chemists and pharmacologists in order to discover marine natural products with pharmaceutical application potential.[1]

Marine disulfide- and multisulfide-containing metabolites are a special and important class of natural products. It was found that many marine disulfides and multisulfides exhibit promising bioactivities including antitumor, antibiotic, anti-inflammatorym and enzyme-inhibitory activities. In particular, the disulfide or multisulfide moieties played important roles for their bioactivities.[2] The pharmacological value of these compounds resides on the fact that disulfide or even multisulfide chemical bonds can be broken only by highly specifically acting enzymes, namely, disulfidases, that are only rarely found in vertebrates.

The fact that these compounds are abundantly present in marine organisms is not surprising in view of the fact that sulfur is the fourth most common element in seawater after chlorine, sodium, and magnesium. However, the biosynthetic pathways of most of these compounds are unknown. Two book chapters that cover the literature dealing with the natural sulfur-containing marine metabolites before 2002 are available,[1,3] but none of them has provided a comprehensive review on all marine disulfide- and multisulfide-containing metabolites. Because of the rapid development in the area of research on marine disulfide- and multisulfide-containing metabolites, it appears that an updated and state-of-the-art overview is required. The present review covers isolation, structural elucidation, synthetic progress, and bioactivities of this intriguing class of secondary metabolites from diverse marine organisms. It includes 175 metabolites that have appeared in the published literature between the years 1971 and 2010.

2. TUNICATES (ASCIDIANS)

Tunicates or ascidians belong to the phylum Chordata. Ascidiacea is a class of the subphylum Urochordata (Tunicata), and members belonging to this taxon are often referred to as tunicates or sea squirts, because their bodies are covered with a sack or tunic and many species can expel water through a siphon when they are disturbed.[4]

2.1. Dopamine Alkaloids

The tropical ascidians belonging to the genus *Lissoclimun* have turned out to be an exceptional source of structurally interesting

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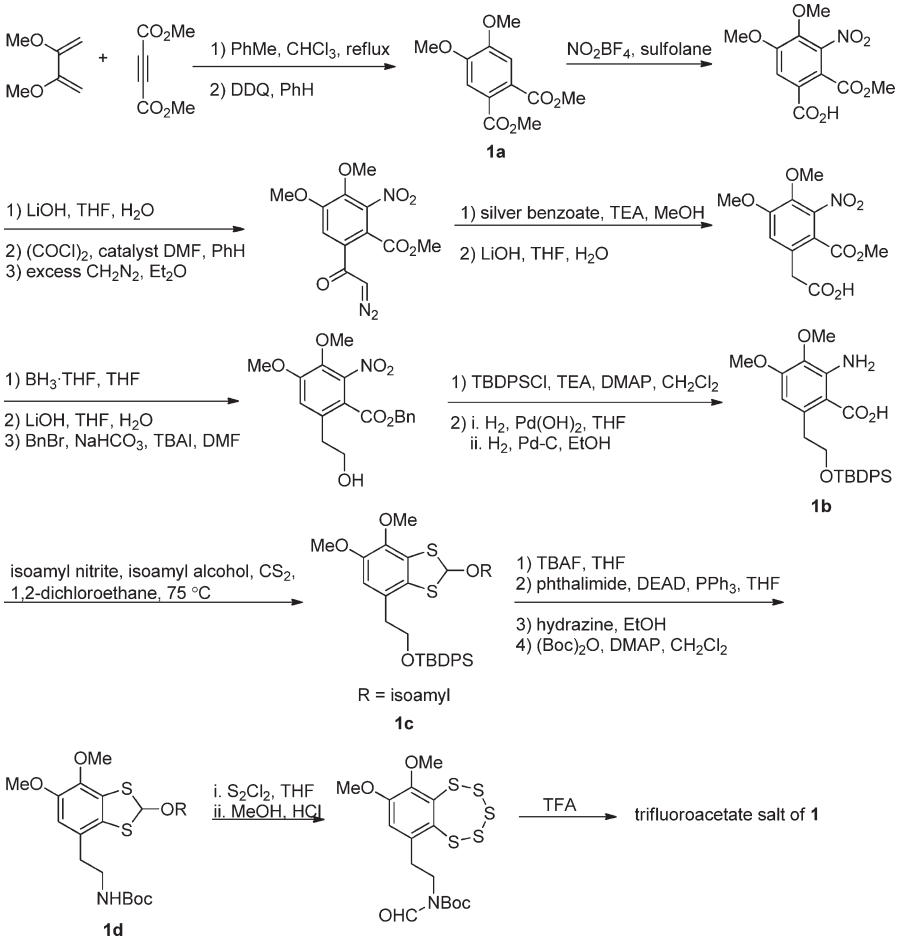
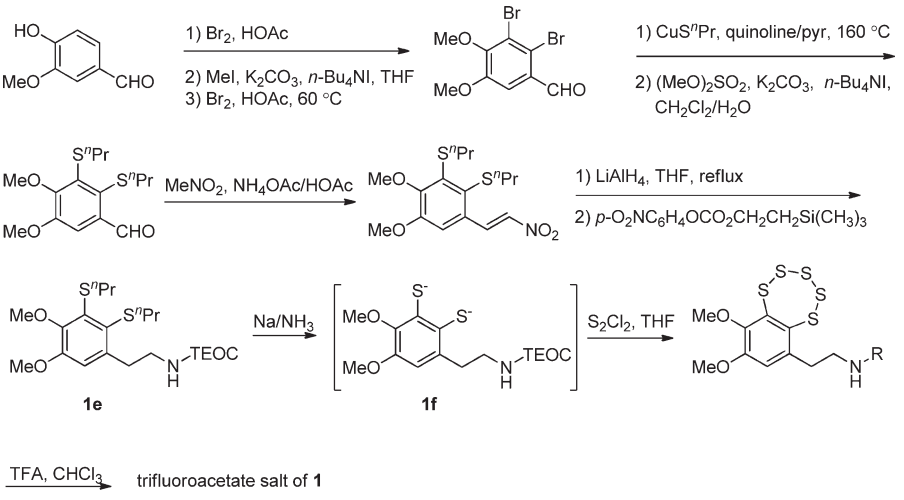
Scheme 1. Studies toward Total Synthesis of Varacin (1) by Behar and Danishefsky[10]



Scheme 2. Studies toward Total Synthesis of Varacin (1) by Ford and Davidson[11]



and biologically active natural products. Many metabolites produced by these animals are derived from amino acids. Varacin (**1**), a cytotoxic dopamine derivative, was isolated as trifluoroacetate salt from the ascidian *L. vareau*. Varacin (**1**) is not only the first naturally occurring polysulfide bearing a modified amino acid but also the first naturally occurring benzopentathiepin. The benzopentathiepin structure of **1** was proposed on the basis of spectroscopic data. **1** exhibited potent antifungal activity against fungus *Candida albicans* and strong antitumor activity against human colon tumor cell line HCT-116 (IC_{90} = 0.05 μg/mL),

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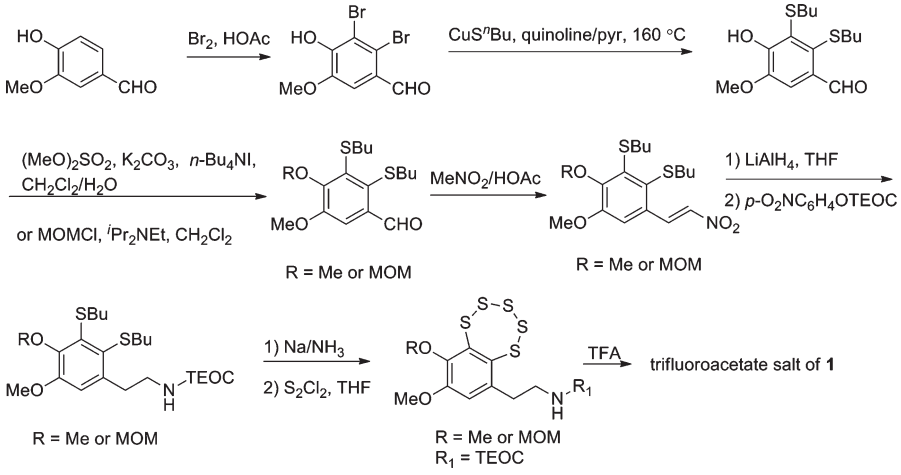
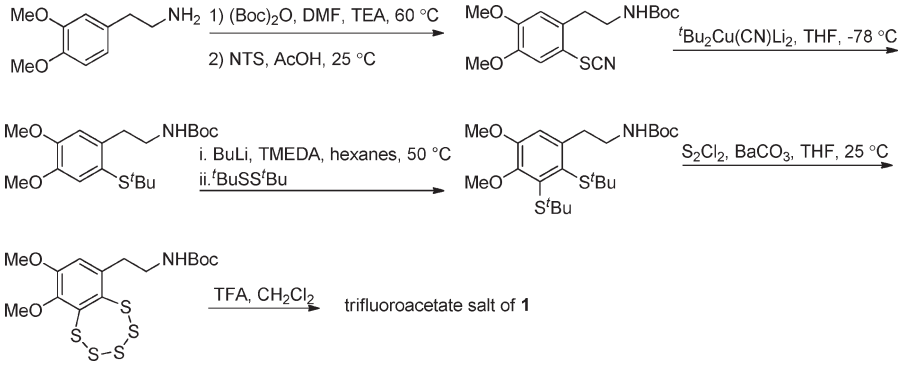
Scheme 3. Studies toward Total Synthesis of Varacin (1) by Ford et al.[12]



Scheme 4. Studies toward Total Synthesis of Varacin (1) from Toste and Still[13]



which is 100-fold more potent than 5-fluorouracil (5-FU).[5] A preliminary mechanism study suggested that **1** acts through DNA damaging. The antitumor activity of varacin has been extensively studied, and its mode of action was reviewed by Lee.[2] Although many studies toward the syntheses of cyclic polysulfides containing three,[6] five,[7] seven,[8] and nine[9] contiguous sulfur atoms have been reported before the discovery of **1**, the accommodation of the potentially incompatible primary amine and pentathiepin moieties, and the incorporation of a pentathiepin in a pentasubstituted aromatic ring, make the total syntheses of **1** difficult to realize. In 1993, the total syntheses of **1** were accomplished by Behar and Danishefsky[10] (Scheme 1) and Ford and Davidson[11] (Scheme 2), respectively, and later further syntheses in more concise routes were described by Ford et al.[12] (Scheme 3) and Toste and Still[13] (Scheme 4). As outlined in Scheme 1[10] Behar and Danishefsky started the synthesis of **1** with a Diels–Alder reaction of 2,3-dimethoxy-1,3-butadiene and dimethylacetylene dicarboxylate followed by an oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to generate the dimethyl phthalate **1a**. The step for the introduction of the sulfur atoms was realized by reacting anthranilic acid **1b** with isoamyl nitrite in the presence of carbon disulfide to afford **1c**. The key step for introduction of the pentathiepin array proved to be difficult by using the previously reported methods. To solve this problem, Behar and Danishefsky designed a method by treatment of **1d** with S_2Cl_2, allowing one to effectively remove the *ortho*-ester and install the pentathiepin moiety. Ford's synthetic strategy[11,12] was quite different from that of Behar's. He developed two almost identical synthetic routes as described in Schemes 2 and 3 by the treatment of 2,3-dibromoveratraldehyde with cuprous *n*-propylmercaptide or cuprous *n*-butylmercaptide for the introduction of the sulfur atom. The intermediate **1e** derived by the above-mentioned reactions was treated with Na/NH_3, which led to the removal of the *n*-propyl or *n*-butyl groups, yielding the key dithiolate **1f**; the subsequent addition of S_2Cl_2 to react with **1f** provides pentathiepin. The synthetic route reported by Toste and Still[13] is similar to that of Ford, but they used two steps for the introduction of the sulfur atoms. It is worth pointing out that varacin could only be obtained as its trifluoroacetate (TFA) salt form through all the above-mentioned synthetic methods. The efforts to obtain free amine **1** from its trifluoroacetate salt under various desalting conditions have resulted in a rapid decomposition of **1**. It is suspected that at physiological pH varacin (**1**) may exist in the protonated form, and it is only in this state that the amino and pentathiepin functional group could coexist.[10]

Varacins A–C (**2**–**4**) with benzotrithiane structures have been isolated as their respective acetates from an unidentified species of Far Eastern ascidian *Polycitor* sp. collected in the Sea of Japan. Their structures were elucidated by spectroscopic methods and chemical transformations.[14] It has been reported that some aromatic fused benzopentathiepins are capable of decomposing into sulfur and the corresponding benzotrithiols in solution.[7]

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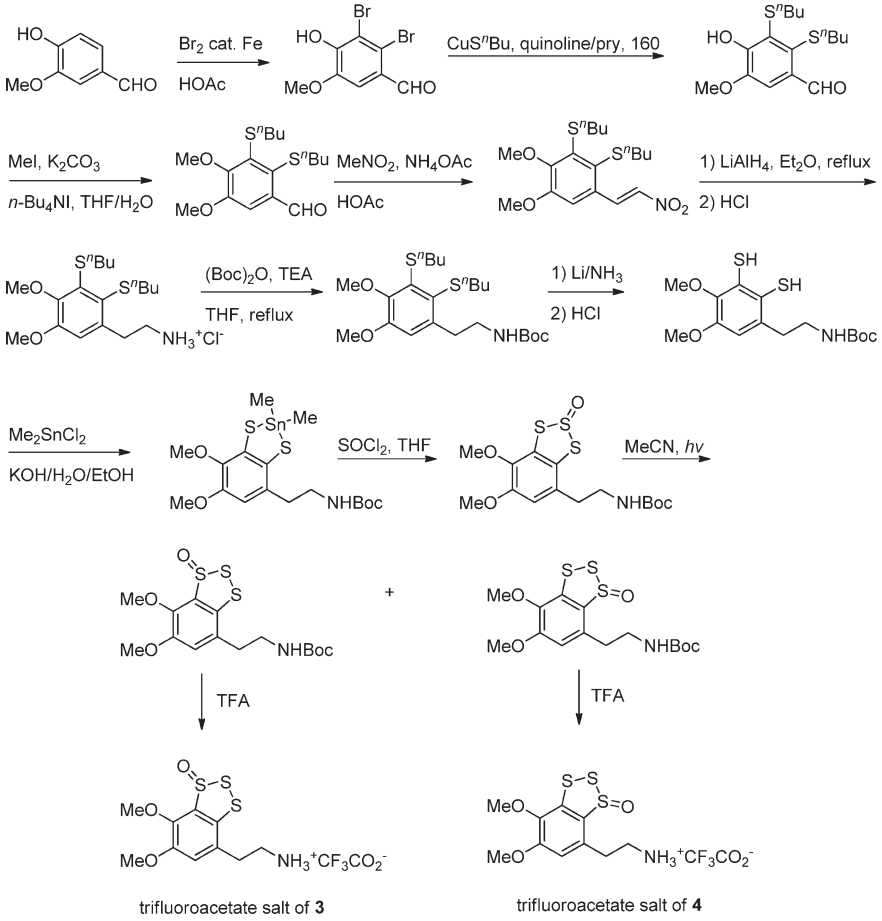
Scheme 5. Studies toward Total Syntheses of Varacins B (3) and C (4) by Lee[15] and Li and Co-workers,[16] Respectively



The same phenomena that varacin (**1**) or varacin acetate and varacin A (**2**) or varacin A acetate can interconvert each other (**1** ↔ **2** + S_8 or varacin acetate ↔ varacin A acetate + S_8) were observed in $CHCl_3$, MeOH, or pyridine solution. However, the fact that the acetate of **2** did not change into the acetate of *S*-oxides **3** or **4** at room temperature in MeOH solution after standing for 1 year indicates that both **3** or **4** are natural products. In the bioassays, varacin (**1**), varacin acetate, and varacin A−C acetates were all found to exhibite potent antifungal and antimicrobial activities against fungus *C. albicans* and bacteria *Bacillus subtilus*. These results suggested that antibiotic activities of this series of compounds did not depend upon the presence of a free amino group in their side-chains. The mechanism study performed by Lee et al.[16] demonstrated that 1′-*S*-oxides **4** are capable of effectively causing DNA cleavage that explains the observed potent cytotoxicities against a series of cancer cell lines and the antibiotic activities of **4**. Most importantly, Lee's work revealed that the rate of DNA cleavage caused by **4** can be promoted by an intrinsic lower pH environment possessed by tumor cells, providing the strategies for designing new acid-activated and tumor-activated prodrugs. The total syntheses of **3** and **4** were accomplished by applying an identical method (Scheme 5),[15,16] but only the trifluoroacetate salts of **3** and **4** were obtained. The dithiolate was formed used a similar method reported by Ford and Davidson,[11] which reacted with dimethyltin dichloride and subsequently $SOCl_2$ to provide the benzotrithiole 2-oxide. The oxygen atom of benzotrithiole 2-oxide can conduct rearrangement to afford benzotrithiole 1-oxide and benzotrithiole 3-oxide under photolysis conditions.

Faulkner and co-workers isolated and identified five additional antimicrobial polysufides of the varacin family, namely, *N,N*-dimethyl-5-(methylthio)varacin (**5**) and its corresponding trithiane **6** as trifluoroacetate salt, from *L. japonicum* collected from Palau; 3,4-desmethylvaracin (**7**) as trifluoroacetate salt from an unidentified species of *Eudistoma* sp. collected from Pohnpei; an inseparable 2:3 mixture of 5-(methylthio)varacin (**8**); and the corresponding trithiane **9** from an unidentified species of *Lissoclimun* sp. collected from Pohnpei. It was believed that trithiane **6** is a natural product because the ratio of **5** and **6** did not change during the isolation procedure. All of these five compounds selectively inhibit protein kinase C, a drug target for the treatment of cardiovascular, inflammatory, central nervous system (CNS), and neoplastic diseases.[17] Among the tested varacins, the mixture of **8** and **9** was the most active, and **7** showed comparable activity. The dimethylamino compounds **5** and **6** were less active, but it is significant that the trithiane **6** was twice as active as the pentathinpin **5**, possibly due to the evolution of a sulfur atom in the molecule. Both compounds **5** and **6** also showed mild antimicrobial activity against bacteria *B. subtilis* and *Staphylococcus aureus* and fungus *C. albicans*.

Two pentathiepin derivatives, lissoclinotoxins A (**10**)[18,19] and B (**11**),[19] were identified from *L. perforatum*. Lissoclinotoxin A (**10**) was originally reported to have the cyclic trithiane structure[18] but was subsequently revised to be a pentathiepin.[19]

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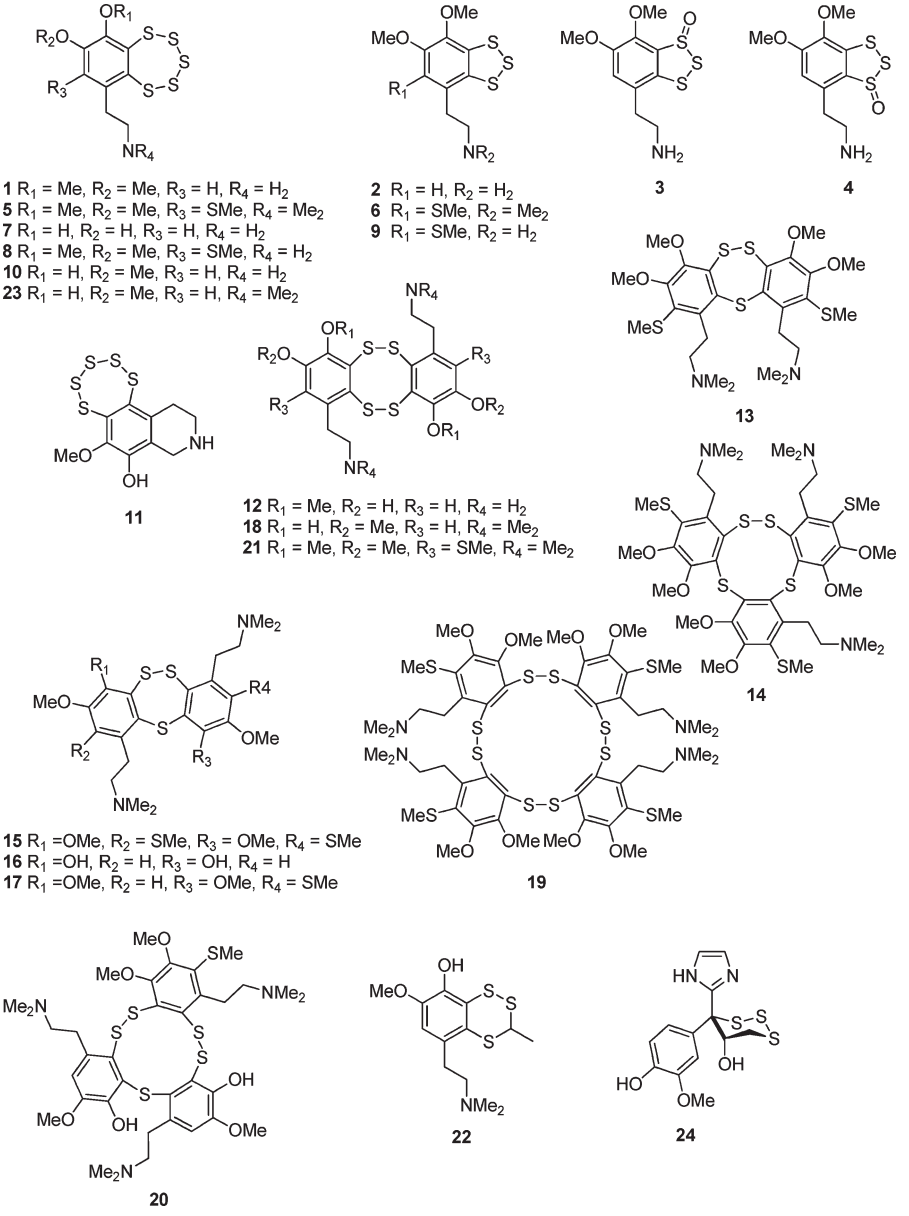
Chart 1. Structures of 1−24



Both compounds **10** and **11** are weakly soluble in most organic solvents. Pentathiepin **10** exhibited potent antibiotic activities in vitro against a series of bacteria and fungi, a moderate cytotoxicity toward leukemia cells (ID_{50} = 4 μg/mL), and toxicity in vivo for mice (ID_{50} < 50 μg/mL).[18] The dimeric lissoclinotoxin D (**12**) was isolated as a trifluoroacetate salt along with its formal precursor lissoclinotoxin A (**10**) from an unidentified species of *Lissoclimun* sp. collected from the Great Barrier Reef, Australia, by Molinski's group.[20] The structure of lissoclinotoxin A (**10**) was unambiguously characterized as a racemic chiral pentathiepin for the first time by Molinski's group. The structure of **12** was tentatively assigned as a "head-to-tail" dimer because the C_{20v} dimeric head-to-tail structure connected through two disulfide bonds to **12** is energetically more favorable. However, the alternative "head-to-head" dimer structure for **12** could not be excluded. To confirm the proposed structure of **12**, the trifluoroacetate salt of **12** was treated with CH_2N_2; unfortunately, only a complex mixture was obtained. The scarcity of **12** prevented their further effort to confidently characterize the structure of **12**. Polysulfides **10** and **12** were both found to exhibit antifungal activity against fungus *C. albicans*.[20] The dimeric lissoclinototxin F (**13**) was isolated as a trifluoroacetate salt from a MeOH extract of a Philippine didemnid ascidian. The gross structure for **13** was determined by interpretation/comparison of spectroscopic data and chemical degradation methods. Compound **13** also possesses a dimeric structure characterized by two identical dopamine-derived units as that of **5** connected together through sulfide and disulfide bonds, respectively. There are three possible geometric isomers that exist (two cis and one trans) for **13**. The depicted structure of **13** was determined based on the computational modeling studies by comparison of global energy minima values that suggest that the two *N*-alkyl chains had cis orientations (as shown in Chart 1) with respect to the tricyclic system of **13**. Compound **13** displayed cytotoxicity toward the phosphatase

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and tensin homologue deleted on chromosome 10 (PTEN)-deficient human breast carcinoma cell line MDA-MB-468 with an IC_{50} value of 1.5 μg/mL.[21]

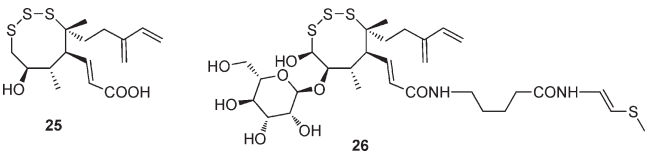
Lissoclibadins **14**−**23** were isolated as their trifluoroacetate salts from ascidian cf. *L. badium* by Namikoshi and co-workers, and the structures of these compounds were assigned on the basis of spectroscopic data and computational modeling studies mentioned above.[22−25] Lissoclibadin 1 (**14**) has a trimeric structure characterized by three dopamine-like units as that of **5** connected together through two sulfides and one disulfide bond, whereas lissoclibadin 2 (**15**) was simply a geometric isomer of **13**. Both compounds **14** and **15** inhibited the growth of the marine bacterium *Ruegeria atlantica* (15.2 mm at 20 μg/disk and 12.2 mm at 5 μg/disk, respectively) and showed in vitro cytotoxicity against HL-60 cells (IC_{50} = 0.37 and 0.21 μM, respectively), and **14** also showed antifungal activity against fungus *Mucor hiemalis* (13.8 mm at 50 μg/disk).[22,23] Lissoclibadins 4 (**16**) and 5 (**17**) are analogues of **13**, whereas lissoclibadin 7 (**18**) is an analogue of **12**. Lissoclibadins **16**−**18** inhibited colony formation of Chinese hamster V79 cells with EC_{50} values ranging from 0.06 to 0.71 μM and also showed weak antimicrobial activity against bacteria *Stapylococcus aureus* and *Escherichia coli* and fungus *Saccharomyces cerevisiae*.[24] Lissoclibadin 8 (**19**), which consists of four identical dopamine-derived units as that of **5** linking together through four disulfides bonds, is the first example of a tetramer. Lissoclibadin 9 (**20**) represents the second example of trimeric polysufides like **14**. Lissoclibadin 10 (**21**) is a symmetric dimer, and lissoclibadin 13 (**22**) is a dopamine and ethyl units connected by sulfide and disulfide bonds. Lissoclibadin 14 (**23**) is a varacin-type monomer. Lissoclibadins **19**−**23** all exhibited inhibitition effects on the colony formation of Chinese hamster V79 cells and proliferation of murine leukemia L1210 cells.[25]

cis-5-Hydroxy-4-(4′-hydroxy-3′-methoxyphenyl)-4-(2″-imidazolyl)-1,2,3-trithiane (**24**), an imidazole alkaloid different from the polysulfides mentioned above, was isolated from an unidentified species of New Zealand ascidians *Aplidium* sp.[26] Interestingly, in neutral or slightly basic solution, **24**[26] could interconvert to the trans isomer, which was later isolated from the New Zealand ascidian *Hypsistozoa fasmeriana*.[27] Both trithiane enantiomers exhibited identical bioactivities in a range of bioassays, including cytotoxic and antimicrobial properties.[26,27]

Until now about 24 polysulfides containing dopamine-derived units have been isolated from different species of ascidians. Although these metabolites formally display an obvious structural and biosynthetic relationship to dopamine, the real biosynthetic origin of them is still unclear, and the report about their biosynthesis is very rare. The fact that the majority of these metabolites were isolated or synthesized in their trifluoroacetate salt or acetates strongly indicates that most of them can only stably exist in the specific physiological environment in the body of ascidian. The structures of some polysulfides were mainly assigned on the basis of spectroscopic data, with the aid of chemical degradation or computational modeling studies as well. Because only limited amounts of these metabolites are available for chemical degradation, to confirm the correctness of their structures is still a challengeable task. Attempts to obtain crystalline material suitable for X-ray diffraction analysis should be one solution to confirm their structures. Unfortunately, until now there is no report in the literature about the crystallographic study of this unique type of natural product.

The promising bioactivities of these polysulfide metabolites caused great interest of chemists and pharmacologists.

Chart 2. Structures of 25 and 26



In particular, the action mechanisms of varacin (**1**) have received more attention. Substantial related studies provided evidence that varacin (**1**) plays its pharmacological role through DNA damage.[5,28−33] The DNA cleavage by **1** was observed in the presence of thiols, and the cleaving activity was enhanced when increasing thiol concentration and decreasing the pH.[30] In these studies, the polysulfur ring is found to be important for the activity of damaging DNA. Recently, the function of the primary amine group at the end of the alkyl chain of polysulfides also drew attention based on the observation that all natural pentathiepins isolated to date contain an amino group. Through computational and experimental studies, Brzostowska et al. suggested that the primary or secondary amine attacks S(1) by intramolecular nucleophilic addition, leading to the loss of S_3 to confer an enhanced reactivity in varacin (**1**) and lissoclinotoxin A (**10**). These results may provide a novel strategy to design new antitumor or antibiotic agents containing a polysulfur ring.

2.2. Trithiocane Derivatives

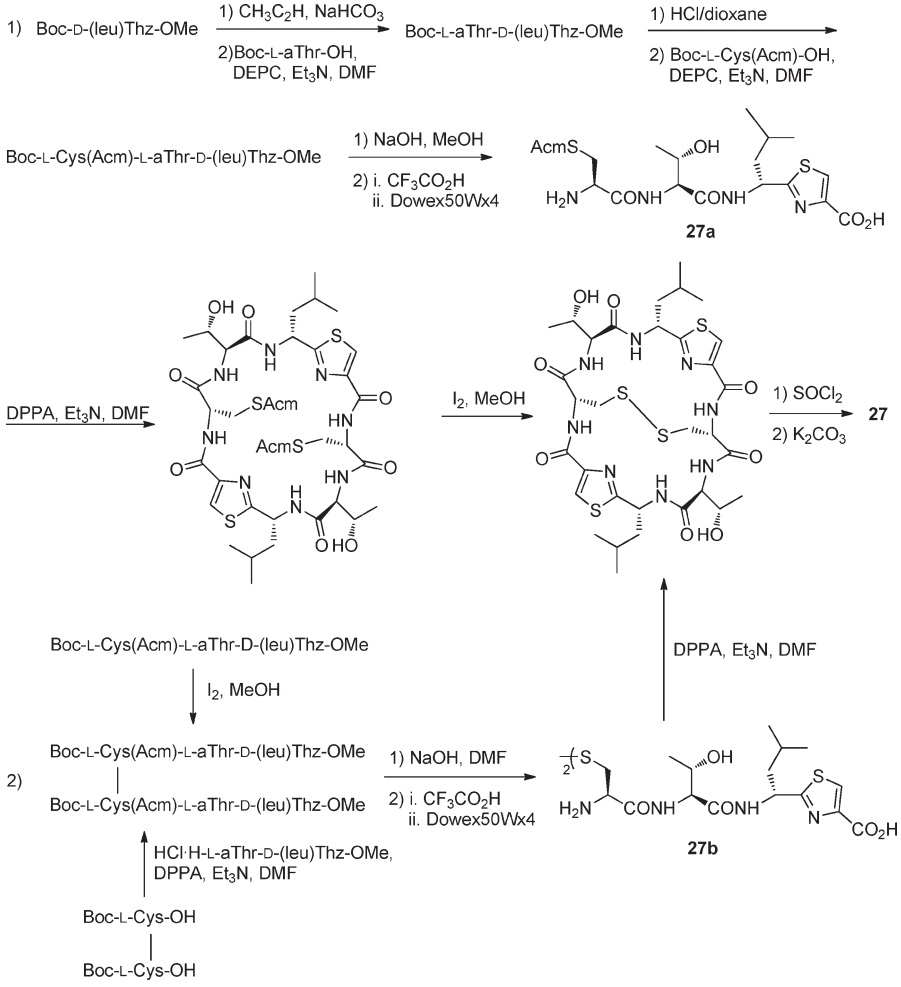
Two unusual eight-membered cyclic 1,2,3-trithiocane derivatives **25** and **26**, one of them a glycoside, were isolated from tunicate *Perophora viridis* collected from the Atlantic coast of North Carolina.[34] Their structures including relative stereochemistries were deduced from analyses of their 2D NMR spectra (COSY, HMQC, HMBC, and NOESY), while methylthiopropionate (MTPA) derivation of the hydroxyl groups on their eight-membered rings helped to secure their absolute configurations. Compounds **25** and **26** are the first two examples of naturally occurring 1,2,3-trithiocane from ascidians. Both compounds exhibited mild antibacterial activity as well as toxicity toward brine shrimp.

2.3. Cyclic Peptides

Cycle peptides are a group of important marine natural products. Ascidians are a rich source of biologically active cycle peptides. Among the cyclic peptides isolated from ascidians, didemnin B, which was isolated from the Caribbean tunicate *Tridemnum solidum*,[35] is probably the most known one because it was the first marine natural product to be permitted for clinical trials as a potential anticaner drug. The phase II human clinical trials against adenocarcinoma of the kidney,[36] advanced epithelial ovarian cancer,[37] and metastatic breast cancer of didemnin B have been completed.[38] Unfortunately, because of the low activity and severe drug-related toxicities, further clinical trials with didemnin B were ceased.[39] Apart from didemnin B, several novel cyclic peptides characterized by unusual amino acids containing thiazole, oxazoline functions, and disulfide bonds have been isolated from the ascidian *Lissoclinum patella*, and some of them also exhibit strong in vitro cytotoxicity.

Ulithiacyclamide (**27**), a symmetric cyclopeptide with strong cytotoxicity, was isolated from *L. patella* collected from the Palau Islands by Ireland and Scheuer.[40,41] Ulithiacyclamide (**27**) formally could be biosynthesized from two leucines, two threonines, and four cysteines. Ireland and co-workers developed a method,

Scheme 6. Total Synthesis of Ulithiacyclamide (27) by Kato et al.[43]



based on the reaction of thiazoles with ozone, to determine the absolute configuration of **27**.[42] The structure of **27** was unambiguously confirmed by the total synthesis (Schemes 6[43] and 7[44]). For the construction of **27**, Kato's group[43] developed two different cyclization processes: (1) the cyclodimerization of the key intermediate *S*-acetamidomethyl tripeptide **27a** and (2) the double cyclization of the key intermediate hexapeptide **27b**, building a disulfide bond bridge. The unstable oxazoline moieties were constructed from L-allothreonine residues in the final step. The later cyclization process is similar to that developed by Schmidt's group.[44] Among the cyclopeptides isolated from *L. patella*, **27** showed the most potent in vitro antitumor activity against L1210 murine leukemia cells (IC_{50} = 0.35 μg/mL) and the human ALL cell line (T cell acute leukemia) CEM with an ID_{50} values of 0.01 μg/mL.[41] The structure−activity relationship (SAR) studies of **27** and its related analogues[45] indicated that the oxazoline function is essential for its high cytotoxicity, whereas the cyclic skeleton of peptides might not be important for cytotoxicity. In addition, the disulfide bridge could assist to fix the conformation of the macrocyclic molecule. The observation that treatment of **27** with dithiothreitol, a reagent to cleave the disulfide bond, led to a decrease in the cytotoxicity suggested that the fixed conformation and/or disulfide bridge may be necessary to improve cytotoxic activity. Ulithiacyclamide B (**28**), an analogue of **27** isolated from *L. patella* from Pohnpei, was highly cytotoxic against the human oral carcinoma cell line KB with an IC_{50} value of 17 ng/mL.[46] The proposed structure of **28** was based on spectroscopic analysis and chemical degradation, and its absolute configuration was established using the method[42] developed by Ireland with modification. Preulithiacyclamides (**29**), along with **27** and some known lissoclinamines, were isolated from *L. patella* from Palau by Patil et al.[47] Among these isolates, compound **27** was found to be the most potent inhibitor of macrophage scavenger receptor (MSR) with an IC_{50} value of 98 nM, whereas its oxazoline ring-opening derivatives **29** and other analogues showed either weak or no activity in the same assay,[47] indicating that the oxazoline function is necessary for its promising cytotoxicity. Ulithiacyclamides E−G (**30**−**32**), containing one or two noncyclized threonines, were isolated from *L. patella* collected from Pohnpei. Their absolute stereochemistries of the amino acid units, except for cysteine, were assigned by chiral GC analysis, and the structures were confirmed by chemical conversion. Compounds **30**−**32** showed anti-MDR (multidrug resistance) activity against vinblastine-resistant CCRF-CEM human leukemic lymphoblasts with IC_{50} values of 112, 44, and 90 nM, respectively.[48]

Eudistomides A (**33**) and B (**34**) were isolated from an unidentified ascidian species of the genus *Eudistoma* collected from Fijian.[49] These five-residue cystine-linked cyclic peptides are flanked by a C-terminal methyl ester and a 12-oxo- or

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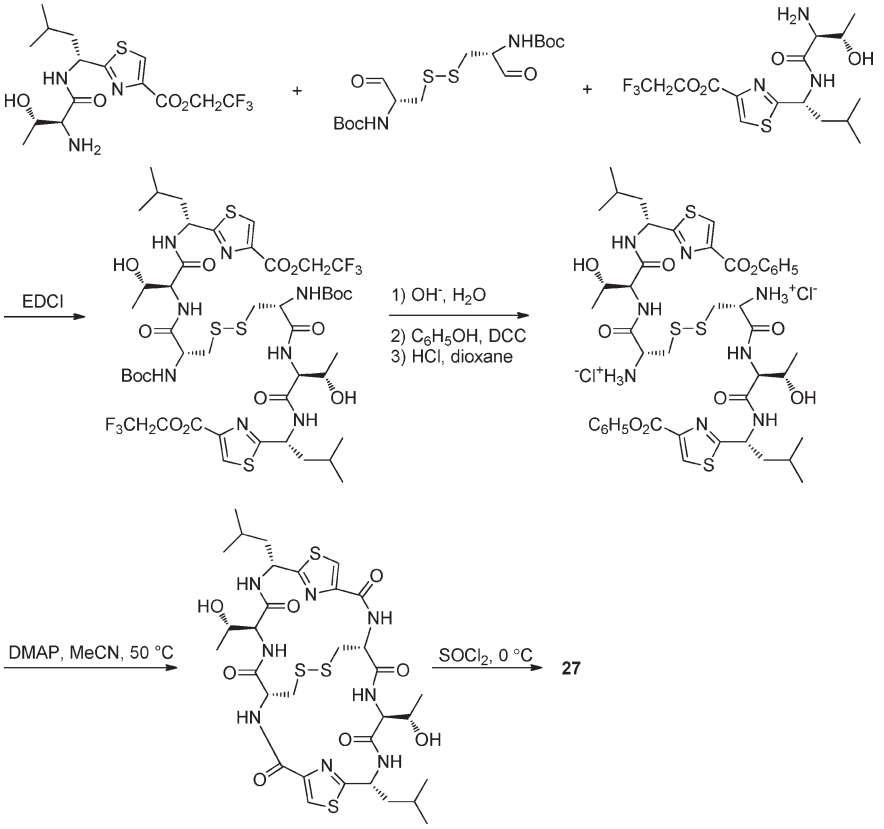
Scheme 7. Total Synthesis of Ulithiacyclamide (27) by Schmidt and Weller[44]



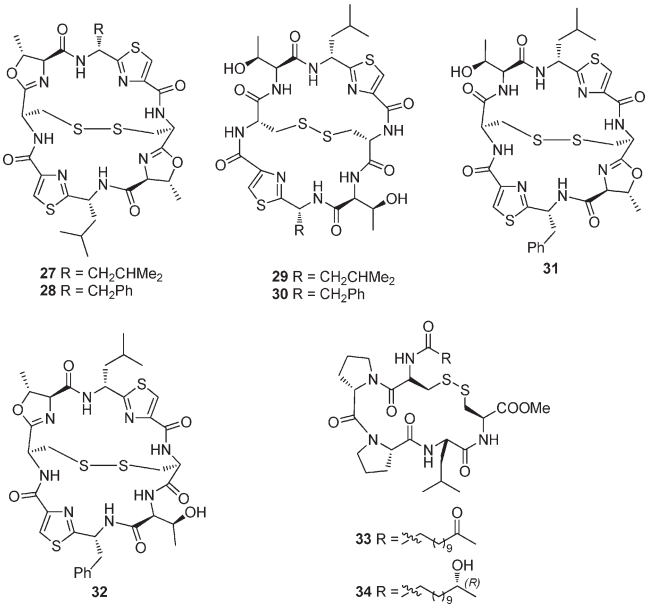
12-hydroxytetradecanoyl moiety. Their complete structures were determined using a combination of spectroscopic and chemical methods. Chiral high-performance liquid chromatography (HPLC) analysis revealed that all five amino acid residues in both compounds had the L-configuration. Determination of the configuration of the alcohol at C-35 of **34** was a challenging task. Several attempts using the Mosher method were unsuccessful. The 35*R* configuration for **34** was successfully determined by enantioselective lipase-catalyzed hydrolysis of a mixture of C-35 acetoxy epimers. Although the cyclopeptides mentioned above all contain cystine moieties, eudistomides **33** and **34** are the first two peptides cyclized solely by a disulfide bridge from an ascidian source. Total synthesis of both eudistomides as outlined in Scheme 8 confirms the proposed structures. The key raw material, cyclized pentapeptide (Cys-Pro-Pro-Leu-Cys), was synthesized using standard solid-phase peptide synthesis procedures.

2.4. Indoles

Citorellamine (**35**), a bromoindole derivative, was isolated from the Fijian tunicate *Polycitorella mariae*. It exhibits potent antimicrobial and insecticidal activity.[50] The initially assigned structure **35b**[50] was later revised and confirmed by total synthesis to be **35a**.[51] The concise synthetic strategy (shown in Scheme 9) by 6-bromoindole-3-carboxaldehyde as starting compound reacting with cystamine directly introduced the disulfide bond into the molecule.

Kottamide E (**36**), an alkaloid containing dibrominated indole enamide, oxalic acid diamide, and 4-amino-1,2-dithiolane-4-carboxamide

Chart 3. Structures of 27−34



moieties, was isolated from the New Zealand ascidian *Pycnoclavella kottae*. Its structure was determined by interpretation of spectroscopic data.[52] This is the first report that a natural product contains a 4-amino-1,2-dithiolane-4-carboxylic acid (Adt) residue.

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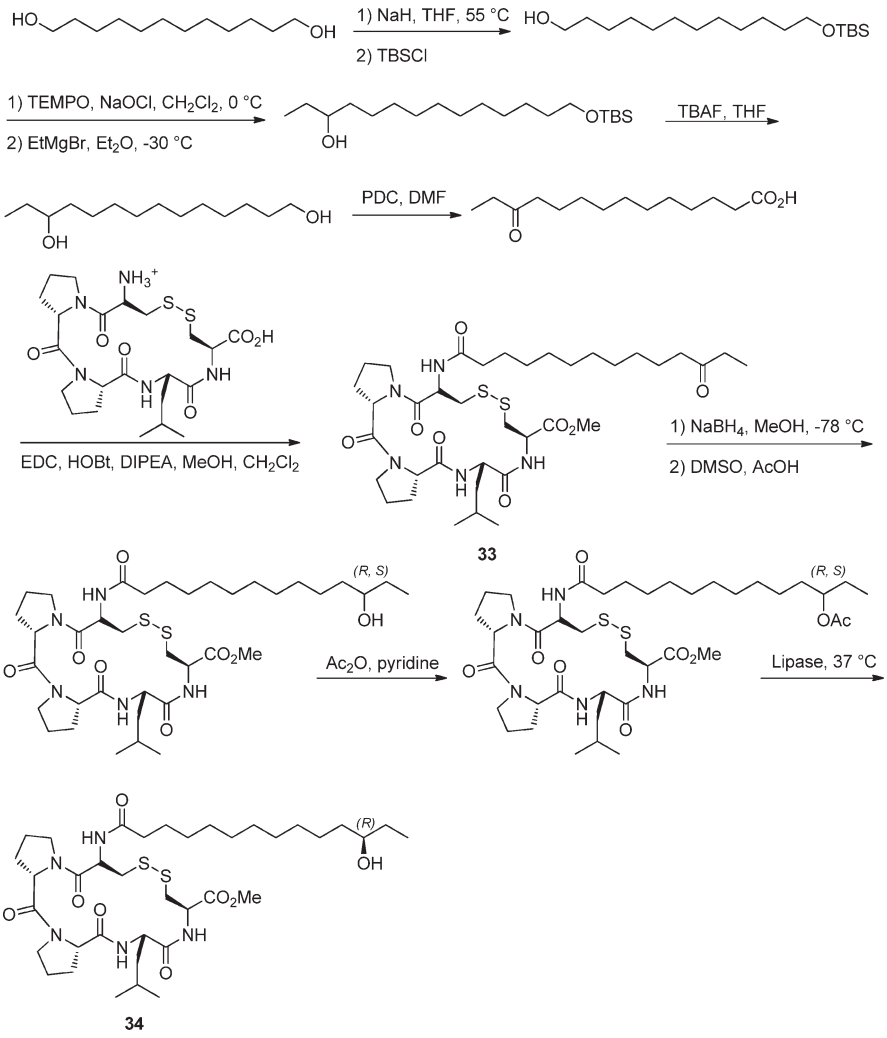
Scheme 8. Total Syntheses of Eudistomides A (33) and B (34) by Whitson et al.[49]



Scheme 9. Total Synthesis of Citorellamine (35) by Moriarty et al.[51]

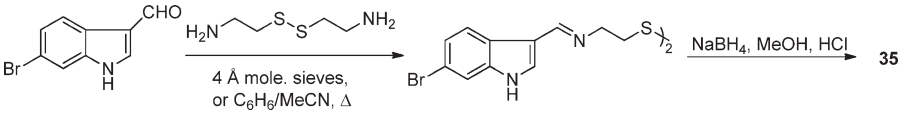
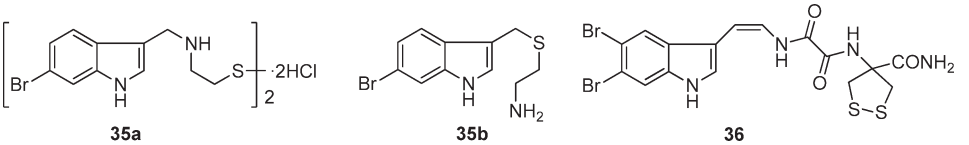


Chart 4. Structures of 35 and 36

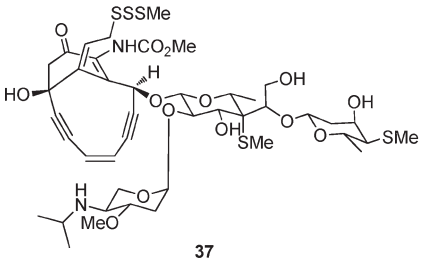


2.5. Enediynes

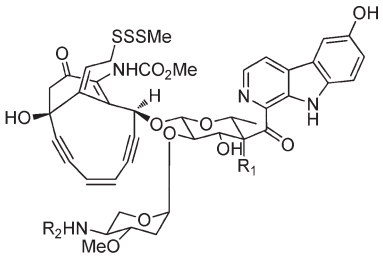
The enediyne family of antibiotics are potent antitumor agents with a unique mode of action, and clinical promise and success in cancer chemotherapy have been reported.[53] Namenamicin (**37**) was isolated from the ascidian *Polysyncraton lithostrotum* from Fiji. It contains the same "enediyne warhead" as the calicheamicins,[54,55] which are a class of antibiotics derived from the bacterium *Micromonospora echinospora* with calicheamicin γ_1^I being the most notable, and it is the first example of this enediyne family from marine source. Compound **37** is an efficient, albeit moderately site-selective, double-standard DNA-cleaving agent that exhibits high in vitro cytotoxicity with

dx.doi.org/10.1021/cr200173z |*Chem. Rev.* 2012, 112, 2179–2207

Chart 5. Structures of 37−40

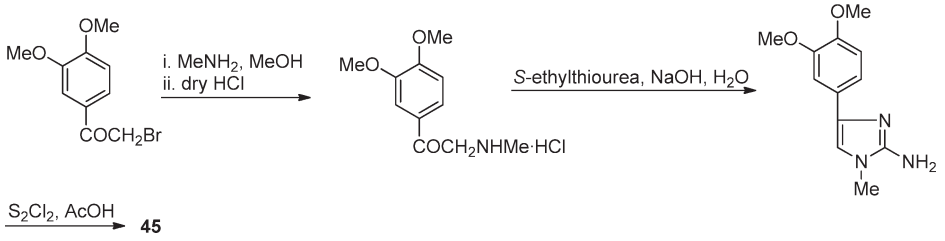


37



38 R_1 = SMe, R_2 = $CHMe_2$
39 R_1 = H, R_2 = $CHMe_2$
40 R_1 = SMe, R_2 = Et

Scheme 10. Total Synthesis of Polycarpine Dihydrochloride (45) by Radchenko et al.[63]

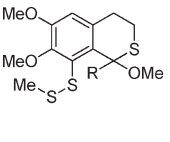


a mean IC_{50} of 3.5 ng/mL and in vivo antitumor activity in P388 leukemia model in mice, as well as shows potent antimicrobial activity.[56] DNA-cleavage experiments indicated that **37** cleaved DNA with a slightly different recognition pattern compared to calicheamicin γ_1^I. Although **37** possesses remarkable antitumor activitites and unique structure, its poor availability from the ascidian (∼1 mg from 1 kg of frozen tissue) prevents further pharmacological studies. The promising bioactivity of **37** stimulated much interest of synthetic chemists. Plenty of attempts toward the synthesis of **37** have been carried out, and the related progress was reviewed by Weinstein and Nicolaou.[57]

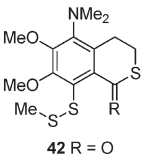
Together with the known **37**, another three enediyne type metabolites, shishijimicins A−C (**38**−**40**), all bearing unique β-carboline moieties in their molecules, were isolated from the Japanese ascidian *Didemnum proliferum*. These shishijimicins show extremely strong cytotoxicity; especially shishijimicin A (**38**) is almost 10 times more active than **37** in three tumor cell lines tested, including 3Y1, HeLa, and P388.[58] It was supposed that **38** could possibly exhibit a different pattern of DNA sequence recognition from other enediynes due to the presence of carboline moiety, because β-carboline could not only intercalate DNA[59] but also occupy the position like that of the aryl group in calicheamicin γ_1^I.

It is well-known that marine plants and animals often contain many symbiotic bacteria that are speculated to be the true producers of natural products found from those macroorganisms. Recently, much concrete evidence was disclosed giving strong support to this hypothesis. For example, the above-mentioned calicheamicins, which are analogues of these marine enediynes, are a class of antibiotics derived from the bacterium *Micromonospora echinospora*.[60] The fact that all of the enediyne antitumor antibiotics previously isolated have been produced by actinomycetes implies that to find the symbiotically coexisting microorganisms, which are responsible for producing bioactive enediynes, could be helpful for solving the poor availability of marine enediynes from the ascidian.

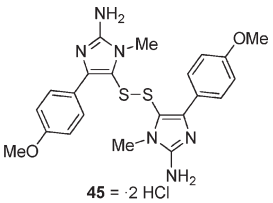
Chart 6. Structures of 41−46



41 R = H
44 R = COMe



42 R = O
43 R = S



45 = ·2 HCl
46

2.6. Polycarpamines and Polycarpines

Polycarpamines A−D (**41**−**44**) are antifungal agents isolated from the tunicate *Polycarpa auzata* collected from the Philippines. These are benzenoid compound with uncommon sulfur functionalities and were elucidated by interpretation of spectroscopic data. Of the polycarpamines, **42** was found to have the strongest antifungal activity against *S. cerevisiae* and *C. albicans*.[61] It was interesting to note that although Fenical and co-workers had collected *P. auzata* on numerous occasions from locations throughout the Philippines and Indonesia, only their initial collection at Siquijor Island, Philippines, in May 1986, yielded these polycarpamines, suggesting that the ascidian may not be the true source of these unique compounds. The authors suspected that these compounds may have been derived from some planktonic organisms or microorganism ingested by *P. auzata*.

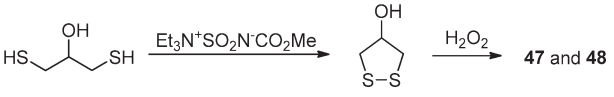
Continuing chemical study of another unidentified species of Indian Ocean ascidian *Polycarpa* sp. carried out by Fenical and co-workers led to isolation of two symmetric disulfide alkaloids, namely, polycarpine dihydrochloride (**45**) and its corresponding

free base, polycarpine (**46**). Their structures were determined by combined spectroscopic and chemical studies. Compound **45** showed significant cytotoxicity against HCT-116 cells in vitro.[62] In 1997, Novikov and co-workers reported the synthesis of **45** in three steps from *p*-methoxyphenacyl bromide in 57% overall yield (Scheme 10).[63] The key step for construction of symmetrically substituted disulfide linkage was realized through the treatment of imidazole with S_2Cl_2 in acetic acid solution. The alkaloid **46** was later also isolated from *P. aurata* collected in Chuuk, Federated States of Micronesia.[64] It was reported to inhibit the enzyme inosine monophosphate dehydrogenase, but the inhibition could be reversed by adding excess dithiothreitol, suggesting that **46** probably react with the sulfhydryl group on the enzyme.[64]

3. *BRUGUIERA*

The magrove *Bruguiera* (family Rhizophoraceae) has six species and one variety.[65] Of the genus *Bruguiera*, *B. gymnorhiza* is considered one of the most broadly distributed by longitude of any mangrove species. In China, its fruits have been used as folk medicine to treat diarrhea.[66] The first report about the chemical investigation on *Bruguiera* could be traced back to 1972, when Kato and Numata isolated brugierol (**47**) and isobrugierol (**48**) from *B. conjugate*.[67] Both disufides were characterized as *cis*- and *trans*-4-hydroxy-1,2-dithiolane-1-oxide, respectively, mainly based on the spectroscopic evidence. Brugierol (**47**) exhibits antibacterial activity against bacteria *Lactobacillus acidophilus* and *B. subtilis*[68]and termicidal activity against *Coptotermis formosanus*.[69] Isobrugierol (**48**) also has termicidal activity.[69] The total syntheses of **47** and **48** (Scheme 11), through two steps of successive oxidation of 2-hydroxy-1, 3-dimercaptopropane with methyl(carboxysulfamoyl)triethylammonium hydroxide inner salt and 30% hydrogen peroxide, was achieved by Kato and Okutani.[70] Recently, from the flowers of *B. gymnorrhiza* collected in Thailand, a new cyclic 4-hydroxyditihiosulfonate, bruguiesulfurol (**49**), has been isolated together with known **47** and **48**.[71] The structure of **49** was determined by spectroscopic data and confirmed by X-ray diffraction analysis. Disulfides **47**−**49** were found to activate luciferase via the antioxidant response element (ARE) with EC_{50} values of 3.7, 1.8, and 56.5 μM, respectively. Further, compounds **47** and **48** were reported to inhibit phorbol ester-induced NF-κB (nuclear factor-κB) luciferase activity with IC_{50} values of 85.0 and 14.5 μM, respectively. Moreover, compound **47** was also found to inhibit COX-2 activity with an IC_{50} value of 6.1 μM.[71]

Scheme 11. Total Syntheses of Brugierol (47) and Isobrugierol (48) by Kato and Okutani[70]



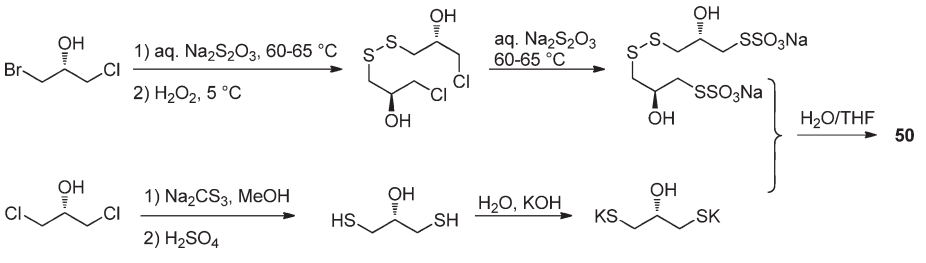
Further chemical constituent investigations on the Chinese *B. gymnorrhiza* were carried out by Guo and co-workers. Apart from the above-mentioned disulfides, four novel polysulfides, gymnorrhizol (**50**), neogymnrrhizaol (**51**), and *trans*- and *cis*-3,3′-dihydroxy-1,5,1′,5′-tertrathiacyclodecanes (**52** and **53**), have been isolated and characterized.[72,75,76] Gymnorrhizol (**50**), a novel unusual 15-membered macyrocylic polydisulfide with an unprecedented carbon skeleton composed of three repeated 1, 3-dimercaptopropan-2-ol units, was isolated from the Chinese *B. gymnorrhiza* collected at Guangxi Province.[72] Its structure was determined by extensive spectroscopic studies and further confirmed by X-ray crystallographic analysis.[73] It exhibits inhibitory activity against protein tyrosine phosphatase 1B (PTP1B) with an IC_{50} value of 14.9 μM. The total synthesis of **50** was later achieved by the same group in only three steps in 25% overall yield (Scheme 12).[74] Neogymnrrhizaol (**51**), possessing a carbon skeleton characterized by a 20-membered macrocycle with four repeated 1,3-dimercaptopropan-2-ol units, was isolated from *B. gymnrrhiza* collected from Zhanjiang, Guangdong Province, China.[75] Two further uncommon 10-membered macrocyclic polydisulfides, *trans*- and *cis*-3, 3′-dihydroxy-1,5,1′,5′-tertrathiacyclodecanes (**52** and **53**, respectively), were isolated from *B. gymnorrhiza* collected from both Guangdong and Hannan Provinces, China, together with known **49**, which was found to significantly inhibit PTP1B with an IC_{50} value of 17.5 μM.[76]

A plausible biogenetic pathway for these cyclic disulfides and polysulfides was proposed by Guo and co-workers.[75,76] The 1,3-dimercaptopropan-2-ol unit (**47a**) should be the common building block for the biosynthesis of all these cyclic difufides and polysulfides (Figure 1). Thus, the self-cyclization of **47a** via disulfide bond will yield 1,2-dithiolane (**47b**); then the oxidation of sulfur atom of **47b** will lead to isomeric compounds **47** and **48** as well as dioxide **49** by further oxidation. The dimerization of two units **47a** will generate 10-membered epimeric polydisufides **52** and **53**, whereas 15-membered polydisufide **50** and 20-membered polydisufide **51** are formally derived through the polymerization of three and four units of **47a**. In light of this observation, it is reasonable to expect the discovery also of 25-and 30-membered or even larger polydisulfides (e.g., **47c**) even though they have not been found as of now.

4. MARINE MICROORGANISMS

Marine microorganisms are an important source of disulfide and polysulfide marine metabolites, such as epipolythiopiperazine and thiomarinols.

Scheme 12. Total Synthesis of Gymnorrhizol (50) by Guo and Co-workers[74]



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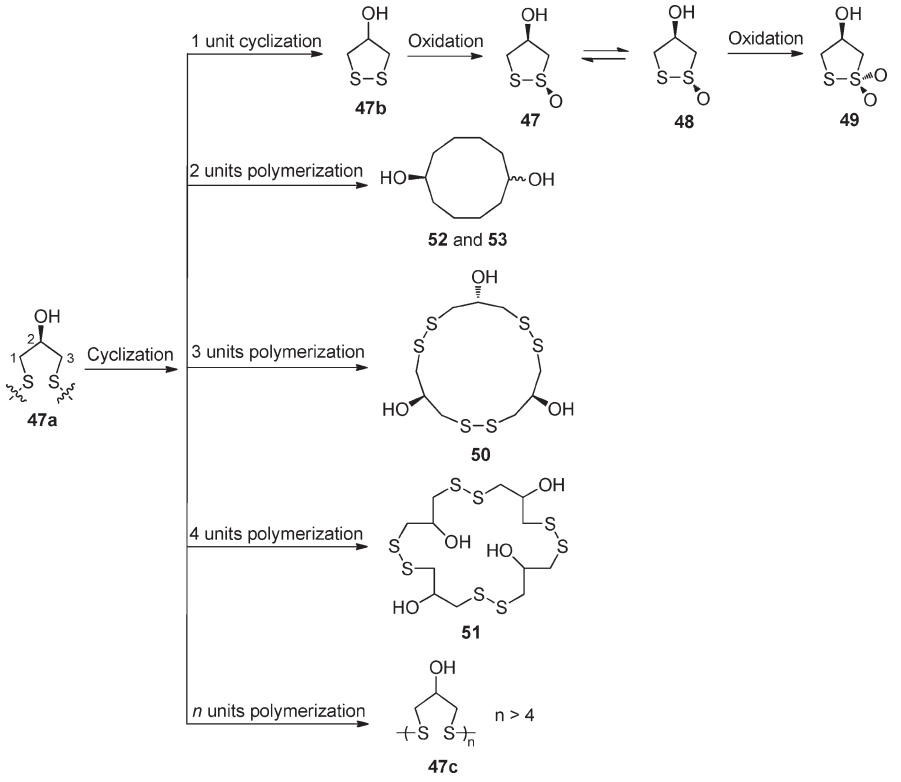
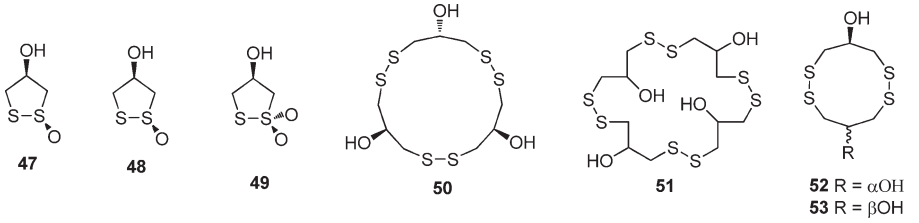


Figure 1. Possible biosynthetic pathways of disulfides or polydisulfides from *Bruguiera*.

Chart 7. Structures of 47−53



4.1. Epipolythiopiperazines

Epipolythiopiperazines (ETPs), toxic secondary metabolites that can be only synthesized by fungi, are a group of important natural products characterized by a unique bridge disulfide or polysulfide dioxopiperazine six-membered ring. The most well-known ETP is gliotoxin, which appears to be a virulence factor associated with invasive aspergillosis of immunocompromised patients. The toxicity of ETPs is due to the presence of a disulfide bridge, which can inactivate proteins via reaction with thiol groupsm and to the generation of reaction oxygen species by redox cycling.[77] Because of their broad spectra of bioactivities, ETPs have drawn wide attention in recent years. To date, more than 120 ETPs have been isolated from various natural sources, in particular, from the marine fungi.[78]

Leptosins A-G (**54**−**60**), G_1 (**61**), G_2 (**62**), H−K (**63**−**66**), K_1 (**67**), K_2 (**68**), M (**69**), M_1 (**70**), N (**71**), N_1 (**72**), O (**73**), and P (**74**) are produced by an unknown species of the fungus *Leptosphaeria* sp. isolated from the marine alga *Sargassum tortile* and were studied by Numata and co-workers.[79−84] The structures of these compounds were elucidated by spectroscopic analysis, selected chemical transformation, and X-ray diffraction analysis in the cases of **66**−**68**.[82] Leptosins A (**54**) and C (**56**) exhibited significant antitumor activity against Sarcoma-180 ascites tumor in mice.[79] Leptosins **54**−**74** showed potent cytotoxicity against cultured P388 cells.[79−84] It was found that dimeric ETPs **54**−**56** and **60**−**63** showed more potent activity than the monomeric ETPs **57**−**59** with the indole moiety, and the number of sulfur atoms in dioxopiperazine rings does not appear to influence the cytotoxiciy toward P388 cells.[79,80] Although the configuration of sulfur bridge in **66**−**68** differs from that in **54**−**56** and **60**−**63**, the cytotoxic effects (ED_{50}) of these compounds were almost identical, indicating that the configuration of the sulfur bridge may not influence the cytotoxicity in P388.[79,80,82] Compounds **71** and **72** were 10-fold more potent than **69** and **70** in the cytotoxic bioassay against P388.[83] It is worth noting that **69** showed appreciable cytotoxicities against 39 human cancer cell lines, and that evaluation of the pattern of differential cytotoxicity using the COMPARE program suggested that the mode of action for **69** might be different from that shown by any other anticancer drug developed to date. Moreover, **69** was found to selectively inhibit the protein kinases PTK and CaMKIII and in addition to have an

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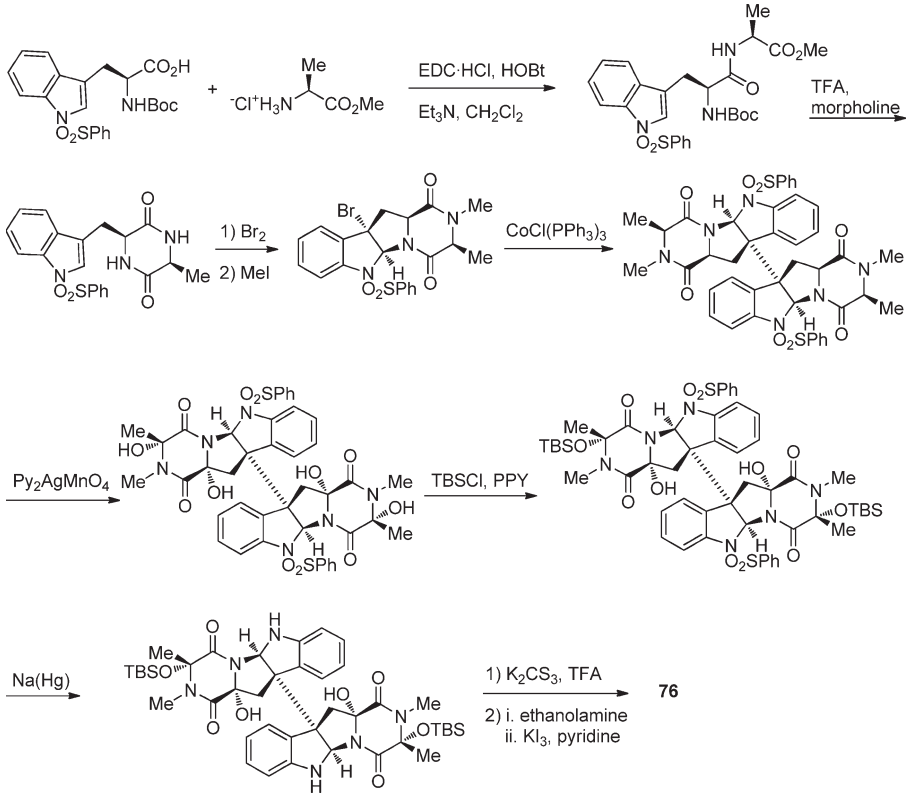
Scheme 13. Total Synthesis of 11,11′-Dideoxyverticillin A (76) by Kim et al.[86]



IC_{50} value of 59.1 μM against topoisomerase II without affecting topoisomerase I.[83]

Verticillin A (**75**), an antitumor antibiotic originally isolated from an unidentified species of fungus *Verticillium* sp.;[85] 11,11′-dideoxyverticillin A (**76**); and 11′-deoxyverticillin A (**77**) were identified in a mycelium of a marine-derived fungus of the genus *Penicillium*. The structures and absolute stereochemistries of **76** and **77** were assigned on the basis of NMR and circular dichroism (CD) experiments. Compounds **76** and **77** exhibited potent in vitro cytotoxicity against HCT-116 human colon carcinoma cells (IC_{50} = 30 ng/mL). Recently, the concise enantioselective total synthesis of **76** has been achieved in 11 steps via a strategy inspired by the biosynthetic hypothesis (Scheme 13).[86] Highly stereo- and chemoselective advanced-stage tetrahydroxylation and tetrathiolation reactions, as well as a mild strategy for the introduction of the epidithiodiketopiperazine core in the final step, were the key steps for synthesizing this highly sensitive substructure.

T988 (**78**), originally isolated from an unidentified species of fungus *Tilachlidium* sp.,[87] and plectosphaeroic acid C (**79**) bearing a cinnabarinic acid moiety were isolated from the fungus *Plectosphaerella cucumerina* obtained from marine sediments collected at −100 m in Barkley Sound, British Columbia.[88] Their absolute configurations were determined by comparison of CD spectra with the literature reported values for the structurally related leptosins[79] mentioned above. Alkaloid **79** represents a new family of complex fungal alkaloids containing both indole ring and phenoxazinone heterocycle. The phenoxazinone heterocycle has been reported to arise from oxidative coupling of two 3-hydroxyanthranilic acid units[89] that can in turn arise from catabolic degradation of tryptophan via the kynurenine pathway.[90] **79** exhibited inhibitory activity against indoleamine 2,3-dioxygenase (IDO) ($IC_{50} \approx 5$ μM), a promising target for the development of a new class therapeutic agents for treating cancer.

Rostratins A−D (**80**−**83**) were isolated from the whole broth of the marine-drived fungus *Exserohilum rostratum*, a fungal strain found to be associated with a marine cyanobacterial mat. The rostratins are pseudo-dimeric structures composed of an indole unit (probably derived from tryptophan) and a sulfur-bridged diketopiperazine, and their absolute configurations were determined by the modified Mosher's method. It is interesting to note that the stereochemistry of the C-4(4′)-9(9′) ring juncture in **80** is opposite to those of **81**−**83**. Rostratins **80**−**83** all showed in vitro cytotoxicity against human colon carcinoma HCT-116 with IC_{50} values of 8.5, 1.9, 0.76, and 16.5 μg/mL, respectively.[91] Recently, a unified synthetic strategy directed toward rostratin A (**80**) was reported by Gross et al.[92]

As mentioned above, many EPTs and related natural products exhibit remarkable antitumor activities.[78] The well-known antitumoral gliotoxin isolated from *Gliocladium fimbriatum* in 1932 is the first member of ETPs. Although almost 80 years have passed, very little is known about the biosynthesis of ETPs. Labeling and feeding experiments have been carried out, leading to the discovery that amino acids and cyclic dipeptides were the precursors or intermediates for some related ETPs, and labeling experiments suggested that the sulfur atoms in ETPs may be derived from methionine, cysteine, and sodium sulfate. However, how the sulfur atoms are introduced in their molecules is unknown. The plausible biosynthetic hypotheses of some ETPs has been summarized in our very recent review.[78] Recently, the identification of the putative ETP biosynthetic gene cluster could

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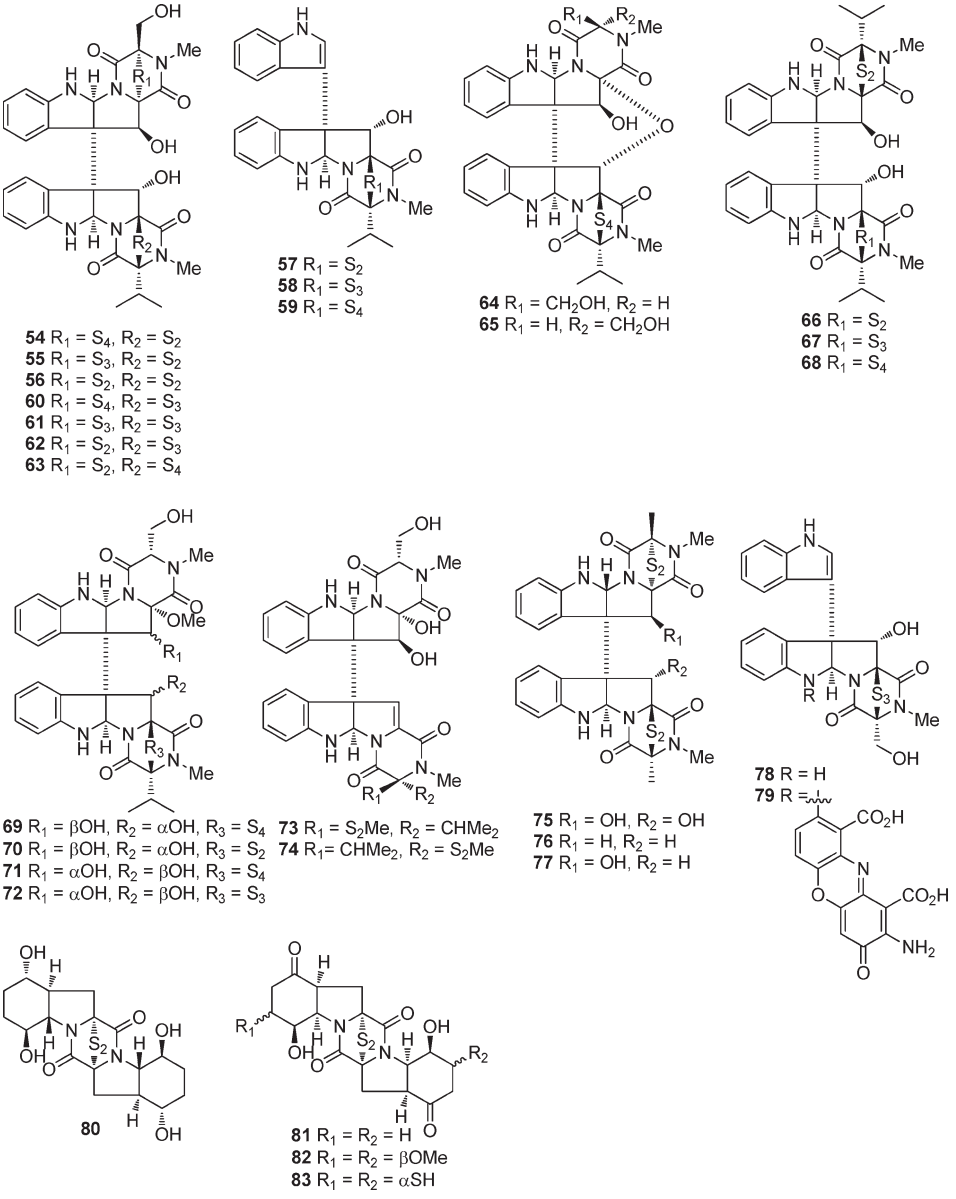
Chart 8. Structures of 54−83



be a major step forward in understanding how these molecules are produced.[93−95] Their potent activities have inspired great interest for chemists and pharmacologists, and several ETPs have been successfully totally synthesized,[86,96−98] and the efforts toward the syntheses of ETP core have also been carried out by several groups.[92,99,100] However, because of the complexity of these molecules, it is still a challenging task for synthetic chemists to totally synthesize these fascinating compounds. The elegant synthesis of **76**[86] based on the biosynthetic pathway analysis provides a helpful synthetic strategy, which can be applied to design/synthesize other bioactive ETPs and to get insight into the function of enzymes involved in the biosynthesis of these natural products.

4.2. Thiomarinols

Thiomarinols A−G (**84**−**90**) (abbreviated as TMA−G), antibiotic hybrids of two independently active species, the pseudomonic acid mixture, namely, mupirocin [used clinically against methicillin-resistant *Staphylococcus aureus* (MRSA)], and the pyrrothine core of holomycin, were isolated and characterized from the cultured broth of marine bacterium *Alteromonas rava* sp. nov. SANK 73390 by Takahashi and co-workers.[101−104] TMA−G all showed excellent in vitro antimicrobial activity against Gram-positive and Gram-negative bacteria, especially against MRSA, with **84**, **85**, and **88** being the most active. The antimicrobial spectra of thiomarinols could be attributable to both pseudomonic acids,[105] which strongly inhibited isoleucyl-tRNA synthetase in bacteria but not so strongly the mammalian enzyme,[106] and short-chain pyrrothine antibiotics,[107] which inhibited RNA synthesis.[108,109] Bioassay results indicated that thiomarinols **84**, **85**, and **87** do specifically inhibit bacterial isoleucyl-tRNA synthetase, whereas they did not inhibit leucyl, valyl, and phenylalanyl-tRNA synthetase.[104]

Recently, high-throughput DNA sequencing of the complete genome of the bacterium SANK73390 carried out by Fukuda et al. revealed a novel 97 kb plasmid, consisting almost entirely of two distinct gene clusters. Targeted gene knockouts confirmed

dx.doi.org/10.1021/cr200173z |*Chem. Rev.* 2012, 112, 2179–2207

Chart 9. Structures of 84-90

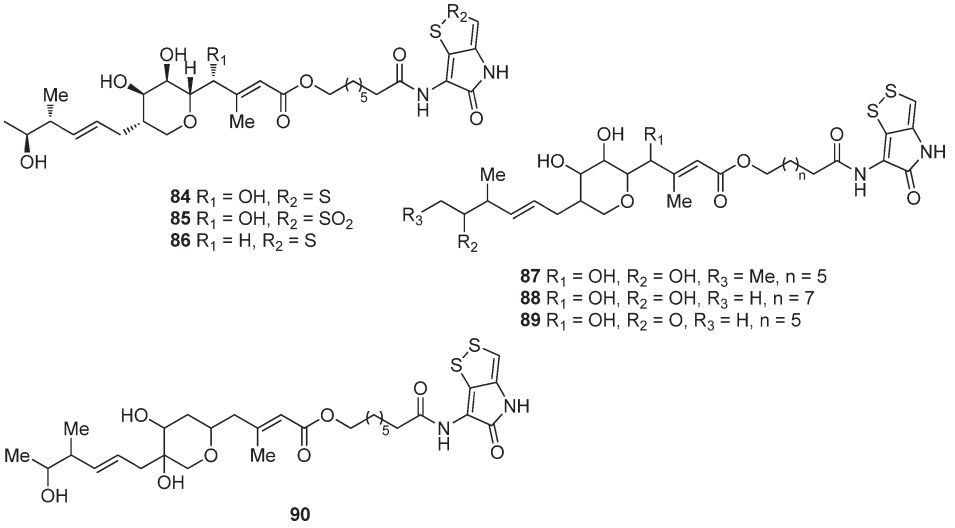
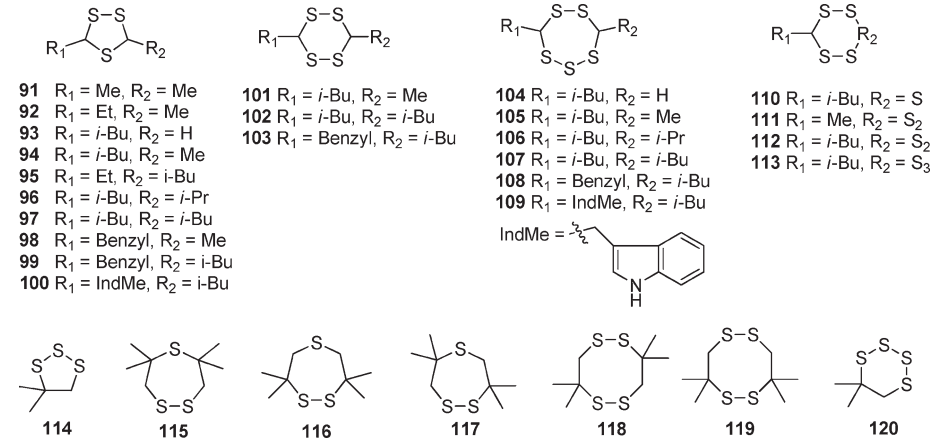
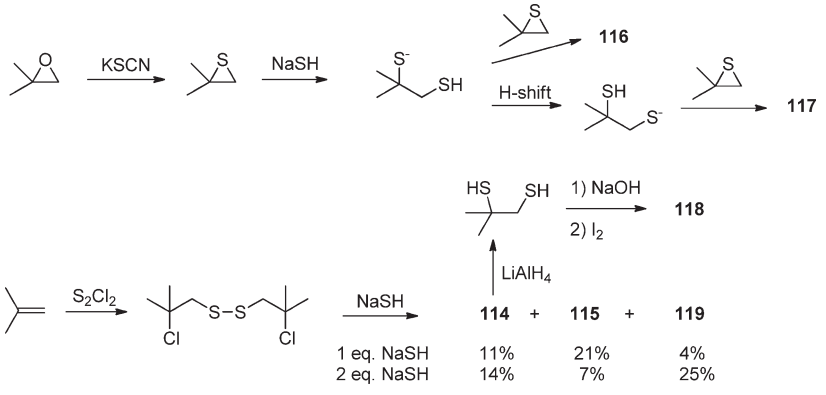


Chart 10. Structures of 91−120



Scheme 14. Total Syntheses of Cyclic Polysulfides 144−119 by Sobik et al.[112]



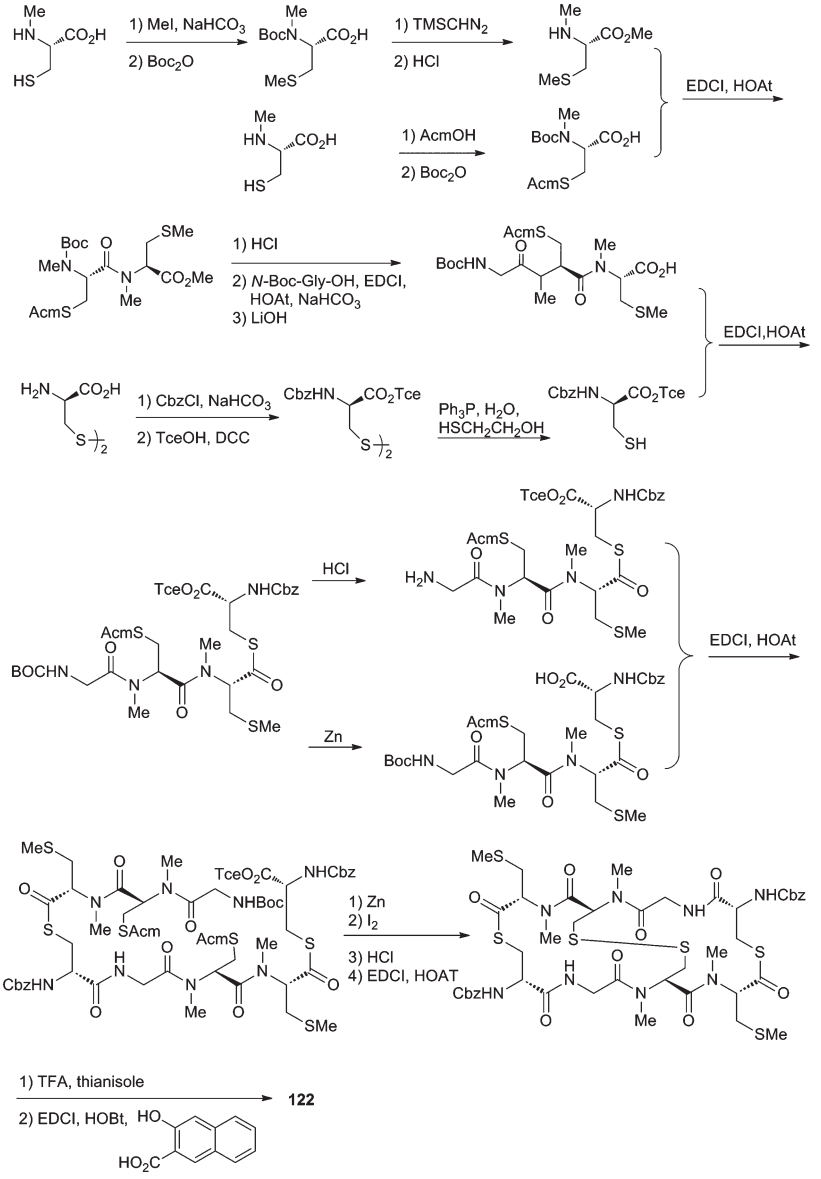
the role of these clusters in the biosynthesis of the two separate components, pseudomonic acid and the pyrrothine, and identified a putative amide synthetase that joins them together.[110]

4.3. Cyclic Polysulfides

The hyperthermophilic archaea of the genus *Thermococcus*, collected from marine hydrothermal system near Obock (Djibouti)

dx.doi.org/10.1021/cr200173z |*Chem. Rev.* 2012, 112, 2179–2207

Scheme 15. Total Synthesis of Thiocoraline (122) by Boger and Ichikawa[117]



and Vulcano (Italy), turned out to be a rich source of cyclic methylene sulfur compounds. From the intact cell of archea *T. tadjuricus* (strain Ob9) and *T. acidaminovorans* (strain Vc6bk), 23 cyclic polysulfides **91**−**113** were isolated by using chemical screening methods.[111] The structures of nine of these compounds were determined by spectroscopic methods, whereas the rest could only be established by GC-MS. Cyclic polysulfide **105** exhibited antifungal activity against *Microsporum canis*. Moreover, **105** and **107** showed moderate activity against *M. vaginalis*.

Compounds **114**−**120** were identified in extracts of two bacterial *Cytophaga* strains (CFB-phylum) isolated from biofilms from the North Sea.[112] Their structures were deduced by analysis of mass spectra and confirmed by synthesis (Scheme 14).

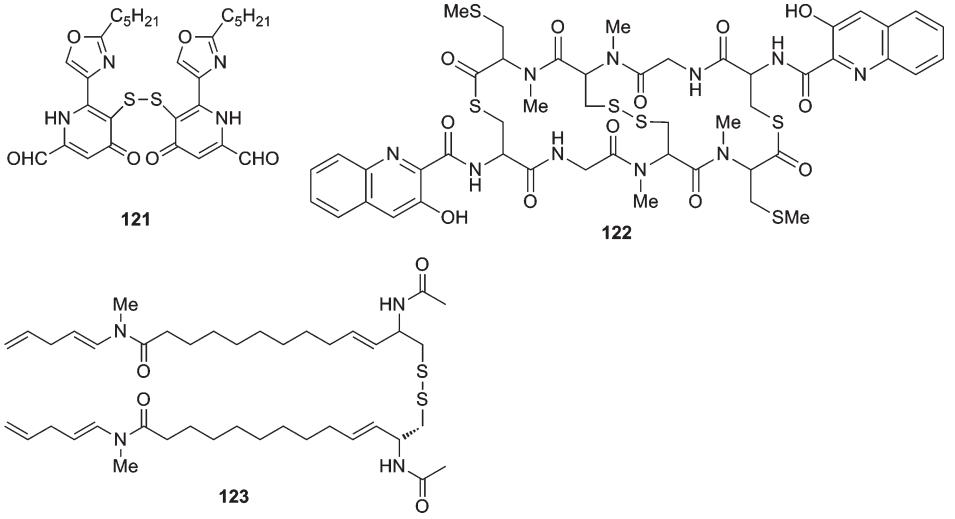
4.4. Miscellaneous

A unique pyridine oxazole B-90063 (**121**) has been isolated from the culture supernatant of the marine bacterium *Blastobacter* sp. SANK 71894.[113] On the basis of spectral analyses and chemical reactions, the structure of **121** was determined to be bis[6-formyl-4-hydroxy-2-(2′-*n*-pentyloxazol-4′-yl)-4-pyridon-3-yl]disulfide. B-90063 (**121**) inhibits human and rat endothelin-converting enzymes (ECEs) with IC_{50} values of 1.0 and 3.2 μM, respectively. ECE, the key enzyme in endothelin-1 (ET-1) generation, is unique to proendothelin processing in endothelial, smooth muscle, and other cell types.[114] Selective ECE inhibitors may be useful for the prevention and treatment of various diseases such as acute renal insufficiency, acute myocardial infraction, hypertension, arteriosclerosis, and so on. B-90063 (**121**) was also found to inhibit the binding of endothelin-1 (ET-1) to rat endothelin$_A$ and bovine endothelin$_B$ receptor.[113]

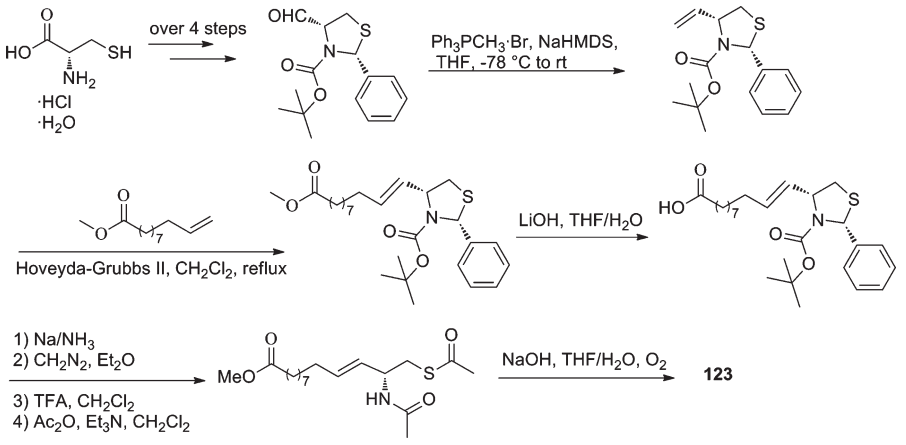
A thiodepsipeptide, thiocoraline (**122**), has been isolated from the mycelium of an unidentified species of bacterium *Micromonospora* sp. L-13-ACM2-092. Thiodepsipeptide **122** showed potent cytotoxic activity against P388, A549, and MEL28 cell lines, as well as strong antimicrobial activity against Gram-positive microorganisms, whereas its activity against Gram-negative bacteria is very weak. It was reported that this antibiotic could bind to supercoiled DNA and inhibit RNA synthesis, but it

dx.doi.org/10.1021/cr200173z |*Chem. Rev.* 2012, 112, 2179–2207

Chart 11. Structures of 121−123



Scheme 16. Total Synthesis of Somocystinamide A (123) by Suyama and Gerwich[122]



does not inhibit topoisomerases I and II.[115] The structure of **122** was deduced on the basis of spectroscopic method.[116] The total synthesis of **122** was reported by Boger and Ichikawa (14 steps, > 15% overall yield).[117] The synthetic approach is outlined in Scheme 15, and the key elements of Boger's approach include the late-stage introduction of the chromophore, symmetrical tetrapeptide coupling, macrocyclization of the 26-membered octadepsipeptide following disulfide formation, and convergent assemblage of the tetradepsipeptide with introduction of the labile thiol ester linkage in the final coupling reaction under near racemization free conditions (Scheme 15).

Somocystinamide A (**123**), a disulfide dimer of mixed polyketide synthease (PKS)/nonribosomal peptide synthetase (NRPK) biosynthetic origin, was isolated from the extract of a marine cyanobacteria *Lyngbya majuscula*/*Schizothrix* sp. assemblage collected from Somo Somo, Fiji. The absolute stereochemistry of **123** was determined by chemical degradation. Disulfide **123** exhibits significant cytotoxicity against mouse neuro-2a neuroblastoma cell with an IC_{50} value of 1.4 μg/mL.[118] In subsequent studies, **123** shows potent inhibitory activity against human umbilical vein endothelial cells with an IC_{50} value of 500 fM.[119] This in vitro activity was verified by in vivo experiment using zebrafish. Most importantly, **123** was shown to have no observable adverse effects on zebrafish even at 30 μM. In addition, **123** triggers apoptosis selectively via caspase 8.[119] Because of the promising pharmacological results described above, **123** and its analogues are intense research subjects for potential use in cancer treatment. Biosynthetically, **123** appears to be assembled through alternating NRPS−PKS elements with a unique termination of a PKS unit via decarboxylation and dehydration to furnish the terminal olefin as seen in curacin A,[120] a potent cancer cell toxin isolated from tropical marine cyanobacterium *Lyngbya majuscula*.[121] The total synthesis of **123** was accomplished in a concise and stereospecific manner (Scheme 16).[122] The key step for carbon−carbon connection at the internal olefin was achieved by olefin cross metathesis reaction using the second-generation Hoveyda−Grubbs catalyst.

5. SPONGES

The filter feeding sponge, phylum Porifera, is considered to be the most simple and evolutionarily oldest marine invertebrate.

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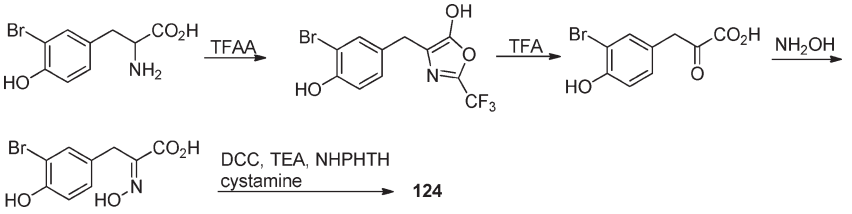
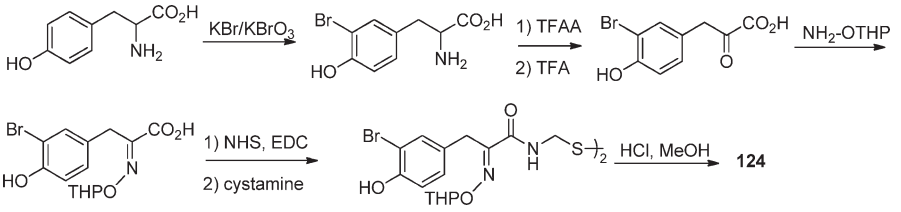
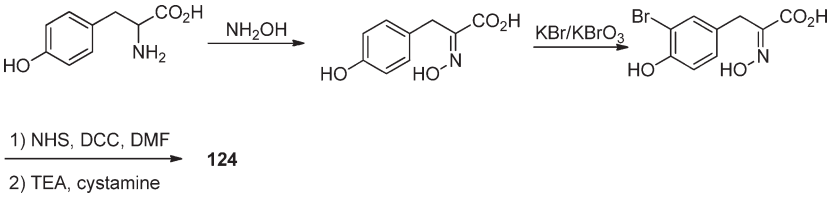
Scheme 17. Total Synthesis of Psammaplin A (124) by Hoshino et al.[126]



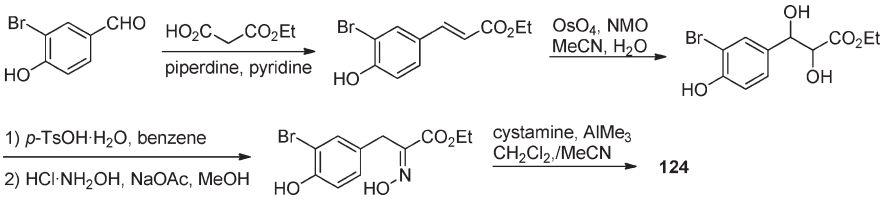
Scheme 18. Total Synthesis of Psammaplin A (124) by Nicolaou et al.[127]



Scheme 19. Total Synthesis of Psammaplin A (124) by Godert et al.[128]



Scheme 20. Total Synthesis of Psammaplin A (124) by Baud et al.[129]



Even though most of them comprise a silica-based skeleton, composed of spicules, their survival is challenged by a huge number of microorganisms which they suck in from the aqueous environment. Therefore, as filter feeders they are dependent on the production of secondary metabolites by which they protect themselves against predation, overgrowth, or fouling.[123]

5.1. Bromotyrosine Derivatives

Bromotyrosin-derived metabolites **124** and its (*E*,*Z*)-isomer **125**, as cystamine dimers, were first isolated from an unidentified sponge, probably a member of the Verongidae family, collected from Guam.[124] The structures of **124** and **125** were determined primarily from ^{1}H and ^{13}C NMR data. Compound **124** was also obtained from an unidentified species of sponge *Psammaplysilla* and was named psammaplin A.[125] The first total synthesis of **124** was completed in good yield via direct coupling of phenolic oxime acid and cystamine using a mixture of DCC and NHPHTH in the presence of Et_3N as the key step (Scheme 17).[126] Later, additional synthetic studies (Schemes 18−20) were reported by several groups.[127−129] Compound **124** was found to be a potent DNA methyltransferase inhibitor in vitro but could not alter genomic DNA methylation levels in treated human cancer cells.[128]

Psammaplin A (**124**) was also isolated from the sponge *Thorectopsamma xana* collected from Guam, together with a minor dimeric metabolite bisaprasin (**126**). Both compounds were found to inhibit growth of bacteria *B. subtilis* and *S. aureus*.[130] Bromotyrosin-derived metabolite **127**, a (*Z*,*Z*)-isomer of **124**, isolated from an unknown species of sponge *Dysidea* sp., was found to act on Ca^{2+}-induced release from the heavy fraction of skeletal muscle sarcoplasmic reticulum (HSR) of rabbit skeletal muscle,[131] which may serve as a useful biochemical tool to clarify the regulatory mechanism of Ca^{2+}-induced Ca^{2+} release in HSR.

Psammaplin D (**128**) and presammplin A (**129**) were isolated from Fijian sponge *Psammaplysilla purpurea*. Compound **128**

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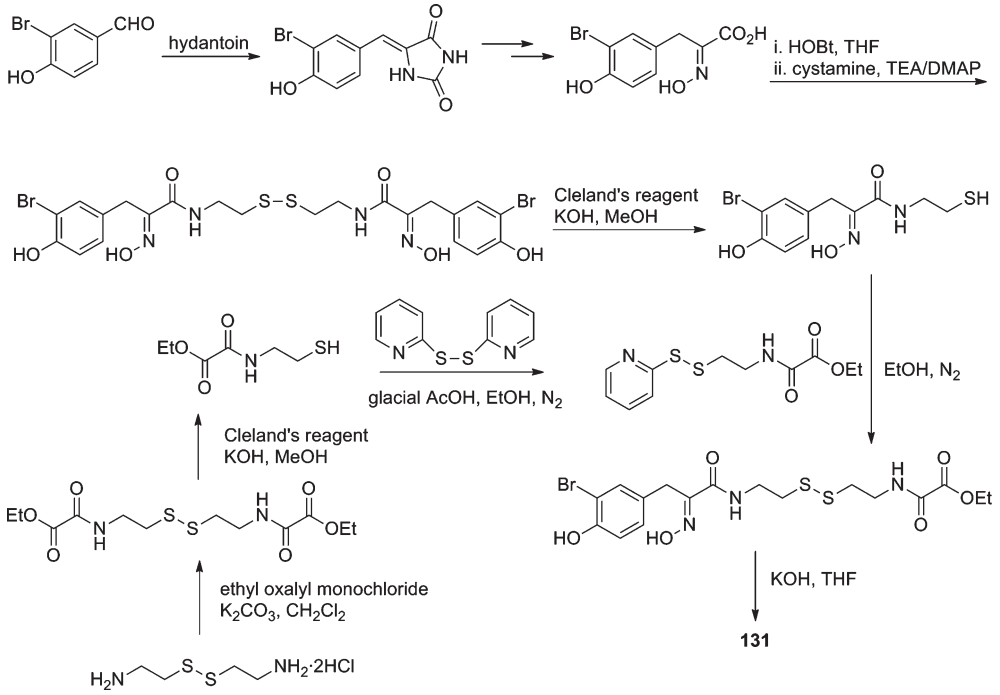
Scheme 21. Total Synthesies of Psammaplin F (131) by Zhao and Co-workers[136]



showed antimicrobial and mild tyrosine kinase inhibitory activities.[132] It is interesting to note that presammaplin A (**129**) is simply a degraded cysteine dimer without a tyrosine unit. Psammaplins E−H (**130**−**133**) and J (**134**) have been isolated from Indo-Pacific sponge *Pseudoceratina purpurea*, along with the known **124**, **126**, and **128**.[133] Compounds **124**, **126**, and **131** were found to be potent histone deacetylase (HDAC) inhibitors and also showed mild cytotoxicity, and **124**, **126**, and **132** were also found to be potent DNA methyltransferase (DNMT) inhibitors.[133] These compounds are the first examples of marine natural products acting as dual inhibitors of HDAC and DNMT, of which both are the targets for cancer chemotherapy.[134,135] The first total synthesis of psammaplin F (**131**) was achieved by Zhao's group in 12% overall yield. The key step (Scheme 21) of the synthesis is to employ Cleland's reagent for the reduction of disulfide bond.[136]

Psammaplins K (**135**) and L (**136**), together with the known **124** and **126**, were isolated from the Fijian sponge *Aplysinella rhax* during a bioassay guided isolation protocol. Their structures were determined using NMR and MS techniques.[137] Compound **124** was found to moderately and noncompetitively inhibit Chitinase B from bacterium *Serratia marcescens*. Because of the importance of chitinases in many biological processes, their inhibitors could be potential antifungal, insecticidal, and antimalarial agents.[138] The crystal complex of Chitinase B and **124** suggested that a disordered molecule **124** is bound near the active site.[137]

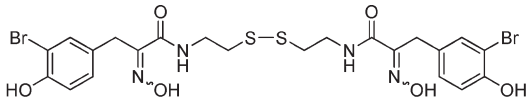
Psammaplins A_1 (**137**), A_2 (**138**), aplysinellins A (**139**), and B (**140**) were isolated from sponge *A. rhax* collected from various locations of Micronesia.[139] On the basis of the spectroscopic analysis and chemical reaction, the structures of psammaplins A_1 (**137**) and A_2 (**138**) have been determined to be a *N*,*N*-dimethylguanidium salts of psammaplin A sulfate and its bis-*N*, *N*-dimethylguanidium disulfate derivative, respectively. Aplysinellin A (**139**) possesses an additional bromotyrosine-derived C9 unit connected directly to the carbon framework of psammaplin A by a biphenylic linkage, whereas aplysinellin B (**140**) is the corresponding cyclic enol ether. These compounds exhibit moderate cytotoxicity against the K562 cell lines and also show inhibitory activities against farnesyl protein transferase (FPTase) and leucine aminopeptidase (LAP). FPTase inhibitors are developed as means of targeting oncogenic Ras for the treatment of cancer,[140] whereas LAP is of medical important because of its altered activity, observed in some diseases, such as cancer, eye lens aging, cataract, and early events of HIV infection.[141]

Psammalin A 11′-sulfate (**141**) and bisaprasin 11′-sulfate (**142**) were also isolated from sponge *A. rhax* collected from Swain Reef, Queensland, Australia, along with the known **124**. Their structures were determined on the basis of spectroscopic analysis.[142] Adenosine receptors (ARs) play an important role in a variety of diseases, such as inflammatory conditions, sepsis, heart attack, ischemia-reperfusion injury, vascular injury, spinal cord injury, chronic obstructive pulmonary disease, asthma, diabetes, obesity, inflammatory bowel disease, retinopathy. and Parkinson's Disease.[143] Bioassay indicated that psammalin (**124**) and its 11′-sulfates **141** inhibited [^3H]1,3-dipropyl-8-cyclopentylxanthine (DPCPX), an A_1 selective antagonist ligand, binding to rat-brain adenosine A_1 receptors with IC_{50} values of 20 and 90 μM, respectively, indicating that they are a new class of AR antagonists.

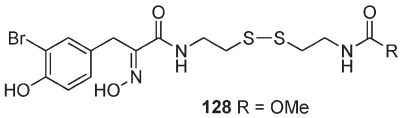
Bromotyrosine derivatives **143**, (*E*,*E*)-bromopsammaplin A (**144**), and bispsammaplin (**145**) were isolated from an association of two sponges *Jaspis wondoensis* and *Poecillastra wondoensis* collected off the coast of Gomun Island, Korea, along with the known **124**, **126**, and **128**.[144] Bromotyrosine derivatives **124**, **126**, **128**, **144**, and **145** displayed significant cytotoxicity against A549, SK-OV-3, SK-MEL-2, XF498, and HCT15 cancer cell lines. The bioassay of antibacterial activity indicated that **143** exhibited the potent antibacterial activity against several human solid tumor cells (A549, SK-OV-3, SK-MEL-2, XF498, HCT15), and the potency of **143** was stronger than that of Meropenem

dx.doi.org/10.1021/cr200173z |*Chem. Rev.* 2012, 112, 2179–2207

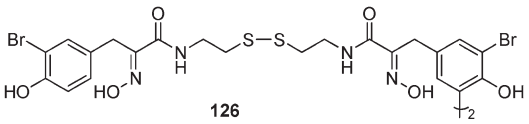
Chart 12. Structures of 124−148



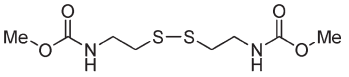
124 (*E*,*E*)
125 (*E*,*Z*)
127 (*Z*,*Z*)



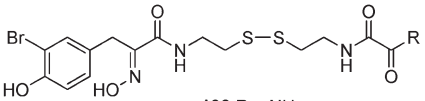
128 R = OMe
133 R = OEt



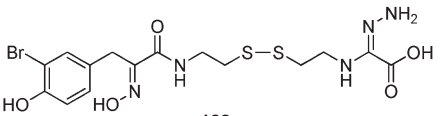
126



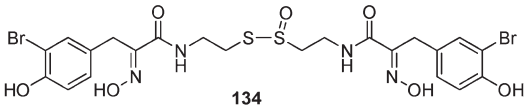
129



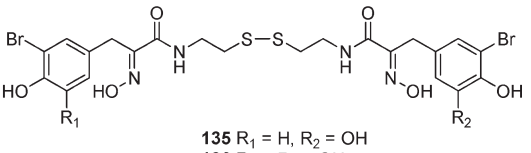
130 R = NH_2
131 R = OH



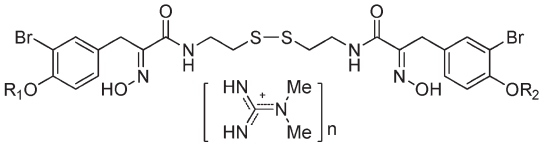
132



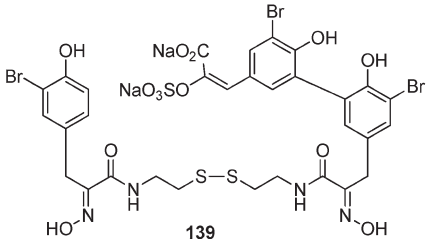
134



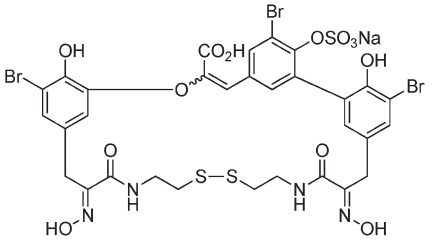
135 R_1 = H, R_2 = OH
136 R_1 = R_2 = OH



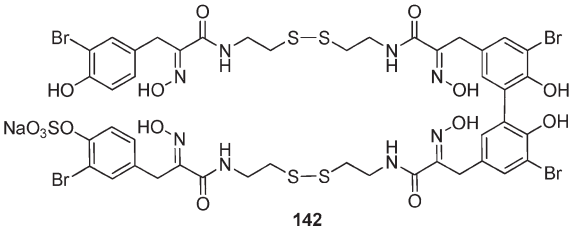
137 R_1 = H, R_2 = SO_3^-, n = 1
138 R_1 = R_2 = SO_3^-, n = 2
141 R_1 = H, R_2 = SO_3Na, n = 0



139



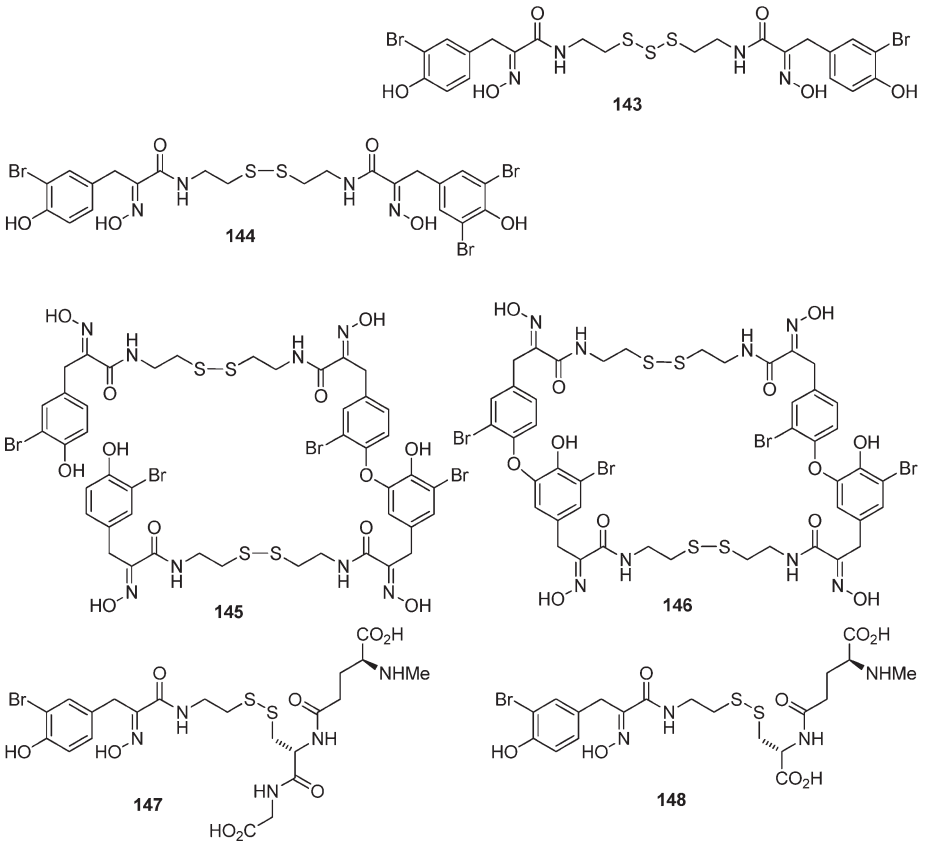
140



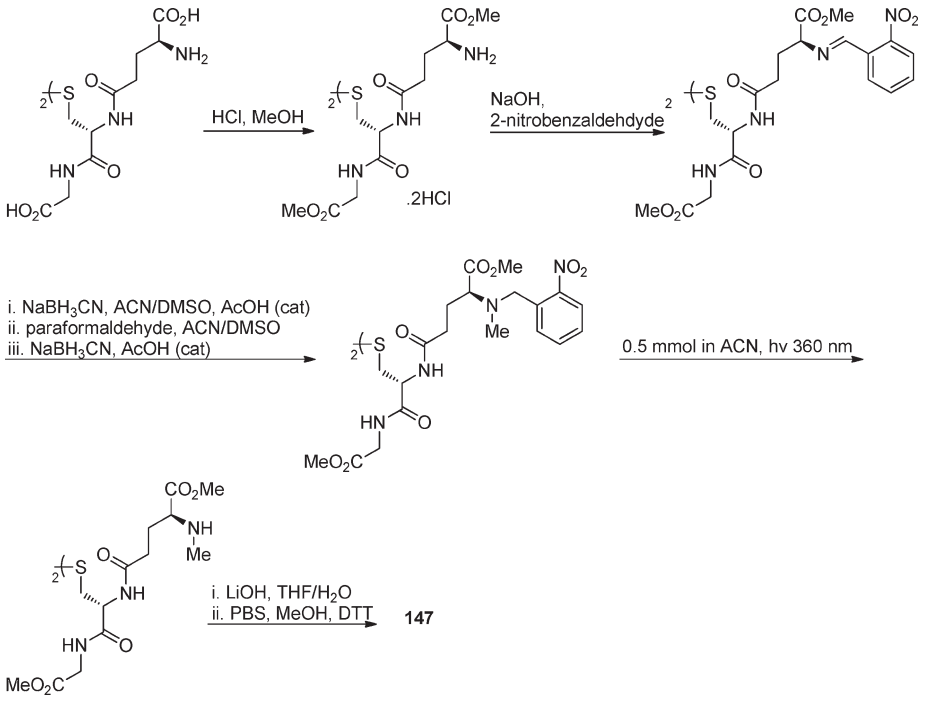
142

dx.doi.org/10.1021/cr200173z |*Chem. Rev.* 2012, 112, 2179–2207

Chart 12. Continued



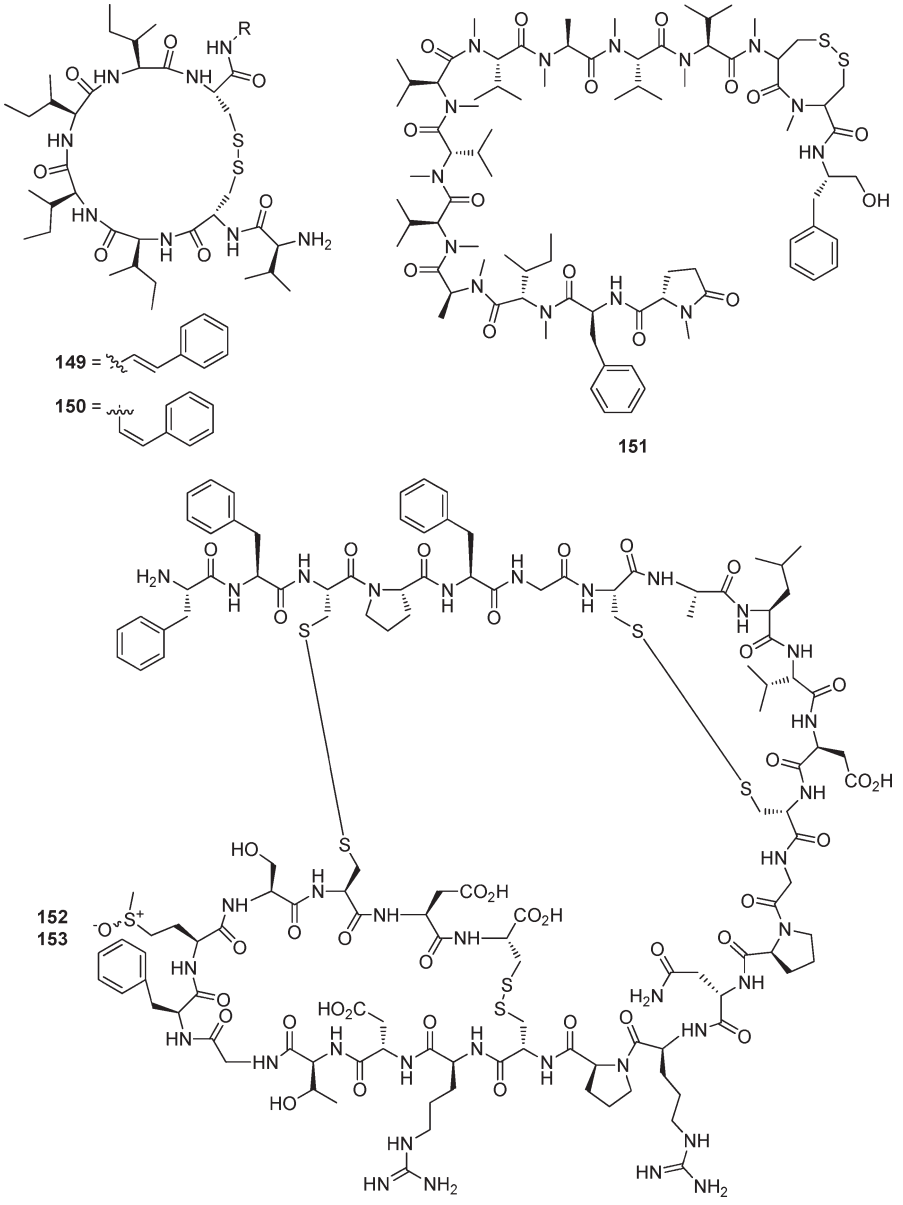
Scheme 22. Total Synthesis of Disulfides 147 by McCulloch et al.[146]



against several strains. Further chemical study on the same mixtured sponges leads to isolate cyclobispsammaplin A (**146**), a cyclic derivative of psammaplin A (**124**). The structure of **146** was elucidated by analysis of high-resolution mass spectrometry

dx.doi.org/10.1021/cr200173z |*Chem. Rev.* 2012, 112, 2179–2207

Chart 13. Structures of 148−153



(MS) and 2D NMR spectra. Cyclobispsammaplin A (**146**) exhibited significant cytotoxicity against several solid tumor cell lines including A549, SK-OV-3, SK-MEL-2, XF498, and HCT15 cell lines.[145]

The mixed disulfides **147** and **148**, together with the known **124**, were isolated from the sponge *Pseudoceratina purpurea* collected along the coast of Fiji. Compound **124** was found to be a general activator in cell-based signaling assays via HDAC inhibition.[146] The structure of **147** was confirmed by semisynthesis from **124** and *N*-methyl glutathione. The synthetic route for **147** is outlined in Scheme 22.

It is interesting that many bromotyrosine disulfides have displayed remarkable bioactivities, implying great application potential for the design and development of novel antitumor and antibiotic agents. Besides those mentioned above, plenty of their analogues have been synthesized and biologically evaluated as well. For example, using a conbinatorial scrambling strategy through catalytically induced disulfide exchange, Nicolaou et al. prepared a series of psammaplin A analogues, some of which showed more potent antibacterial activity against MRSA.[127] The various potent bioactivities displayed by these compounds are not surprising due to their unique structures, which biosynthetically appear to be derived from the union of bromotyrosine and cysteine. Although a lot of studies for understanding their biosynthetic origin have been carried out, the true biosynthetic pathways of these metabolites are still unknown.

5.2. Peptides

Macrocyclic peptides microcionamides A (**149**) and B (**150**), both formally cyclized via a cystine moiety and having their *C*-terminus blocked by a 2-phenylethyleneamine group, were isolated from the Philippine sponge *Clathria (Thalysias) abietina*. Their structures, including absolute stereochemistries, were determined by a combination of spectroscopic and chemical methods.

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Both microcionamides exhibited significant cytotoxicity against the human breast tumor cells lines MCF-7 and SKBR-3 and displayed inhibitory activity against *Mycobacterium tuberculosis* $H_{37}Ra$.[147]

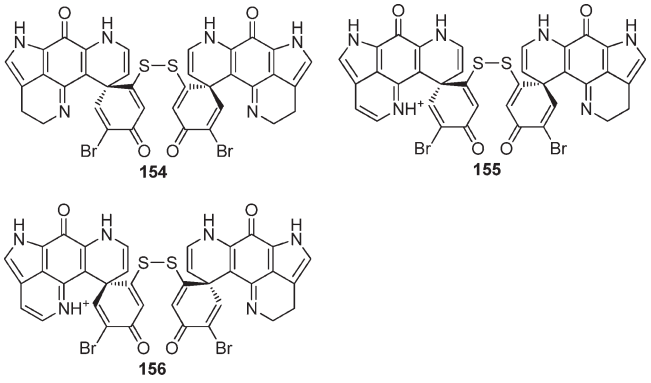
Kendarimide A (**151**), characterized by a linear peptide composed of *N*-methylpyroglutamic acid, an eight-membered disulfide containing *N*-methylcysteinyl-*N*-methylcysteine (*ox*-[MeCys-Mecys]), and many *N*-methyl amino acid residues, was isolated from an Indonesian marine sponge *Haliclona* sp. Compound **151** was found to be a modulator of MDR, which could completely reverse colchicine in KB-C2 cells mediated by P-glycoprotein (P-gp) at a 6 μM concentration. The structure of **151** was determined by 2D NMR and fast atom bombardment (FAB) MS analysis, and the absolute configuration of the amino acid residues except for the MeCys part was determined to be L-form, based on the chiral HPLC analysis and synthetic approach.[148] Later, the absolute stereostructure (L-configuration) of two MeCys parts was elucidated by comparison with synthetic model compounds.[149]

Neopetrosiamdes A (**152**) and B (**153**), two diastereomeric tricyclic peptides, were isolated from an unidentified species of sponge *Meopetrosia* sp. collected in Papua New Guinea. Their structures were elucidated by analysis of MS and NMR spectra and confirmed by chemical degradation. Bioassay indicated that both neopetrosiamides inhibit amoeboid invasion of human tumor cells at 6 μg/mL.[150]

5.3. Discorhabdins

The discorhabdins, together with the prianosins and epinardins, constitute a group of pyrroloiminoquinone alkaloids that are produced by sponges of the families Latrunculiidae and Acarnidae. The first disulfide-linked discorhabdin dimer, (+)-discorhabdin W (**154**), was isolated from a New Zealand unknown species of *Latrunculia* sp. by Munro and co-workers in 2005.[151] The structure and stereochemistry of **154** were assigned by analysis of 2D-NMR and MS spectra. (+)-Discorhabdin W (**154**) was found to exhibit potent in vitro cytotoxicity against the P388 murine leukemia cell line with an IC_{50} value of 84 nM.

Chart 14. Structures of 154−156



Recently, Grkovic and Copp also isolated another three discorhabdin W analogues, identified as (−)-(**154**), (−)-16a,17a-dehydrodiscorhabdin W (**155**), and its enantiomer **156**, from another collection of an unidentified species New Zealand sponge *Latrunculia* sp. Their absolute configurations were assigned by comparison with a data set of CD profiles of the known (+)-**154**. Both enantiomers **155** and **156** exhibited potent antiproliferative activity against murine leukemia P388 cell line (IC_{50} = 0.45 μM).[152]

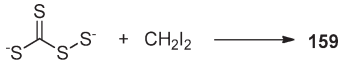
Since the first reports of discorhabdin C in 1986[153] and prianosin A/discorhabdin A (+)-1 in 1987,[154,155] close to 58 members of the natural pyrroloiminoquinone alkaloids have been reported from marine sponges, which was recently reviewed by Hu et al.[156] However, the slow growth rates, the low incorporation rates, and the presence of symbiotic microorganisms make their biosynthesis pathways difficult to be understood. In 1995, Munro and co-workers proposed a putative biogenesis of discorhabdin-type monomer based on the structural similarities.[157] In the putative biogenetic pathway outlined by Munro and co-workers, the amino tryptophan and phenylalanine (via tryptamine and tyramine) are considered to be the precursors of the discorhabdin skeleton. Labeling experiments have been also carried out by Munro co-workers that led to the discovery that L-phenylalanine (closely related to tyrosine or tyramine) is a precursor of the discorhabdin skeleton. On the basis of the above evidence, it is reasonable to suggest that the dimeric discorhabdins should be derived from the corresponding monomers.

Most of the discorhabdin-type compounds have exhibited potent cytotoxicities, and the total syntheses for some discorhabdins have been achieved by several groups.[156] However, there is still no report about the total synthesis of discorhabdin dimers (**154**−**165**), due probably to the difficulty of the formation of disulfide bond and the construction of the polycyclic ring skeleton. Moreover, further investigation on the mechanism for their antitumor activities is still required, which might be beneficial for improved activities.

6. ALGAE

The Mexican red alga *Chondria californica* has been found to possess a strong "sulfur" odor. Cyclic polysulfides, such as 1,2,4-trithiolane (**157**), 1,2,4,6-tetrathiepane (**158**), 1,2,3,5,6-pentathiepane (**159**), 1-oxo-1,2,4-trithiolane (**160**), 4-oxo-1,2,4-trithiolane (**161**), 4-dioxo-1,2,4,6-tetrathiepane (**162**), and a 12-membered heterocycle containing eight sulfur atoms **163**, were isolated from the Mexican red alga *C. californica*. Bioassay showed that these unusual cyclic polysulfides, particularly **162**,

Scheme 24. Total Synthesis of Cyclic Polysulfide 159 by Hansen et al.[160]



Scheme 23. Total Syntheses of Cyclic Polysulfides 157 and 158 by Akhmetova et al.[159]

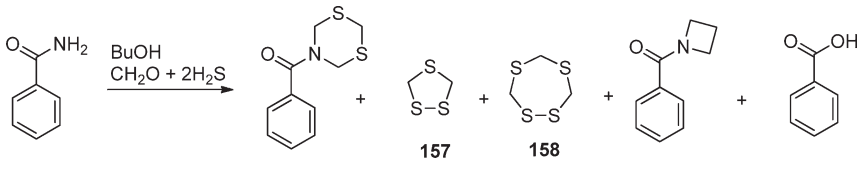


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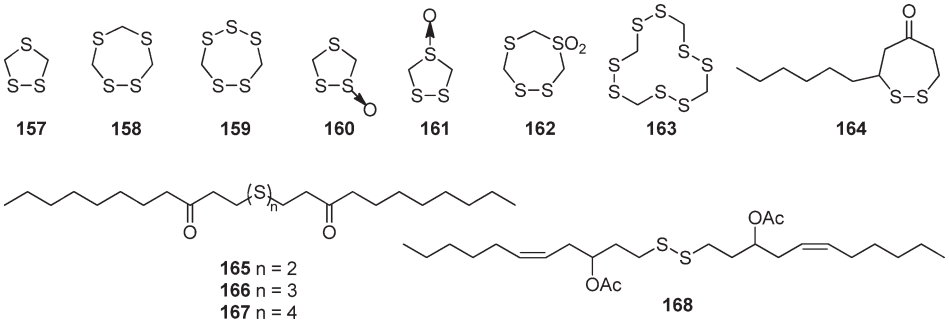
Chart 15. Structures of 157−168



Scheme 25. Total Synthesis of Bis-(3-oxoundecyl) Disulfide (165) by Schnitzler et al.[164]

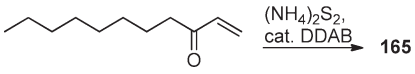
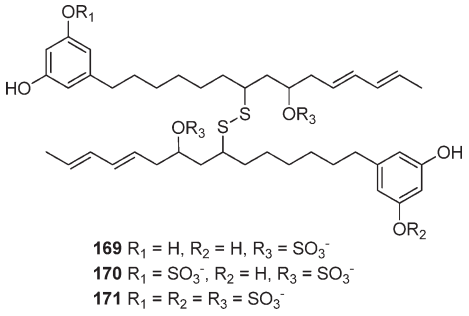


Chart 16. Structures of 169−171

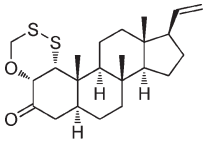


are responsible for the antibiotic activity of *C. californica*.[158] Some of them, such as **157**, **158** (Scheme 23),[159] and **159** (Scheme 24),[160] have been synthesized by a one-step simple reaction.

Further cyclic polysulfides, including (−)-3-hexyl-4,5-dithiacycloheptanone (**164**) and symmetrical long-chain disulfides, bis-(3-oxoundecyl) disulfide (**165**),[161] bis-(3-oxoundecyl) trisulfide (**166**), bis-(3-oxoundecyl) tetrasulfide (**167**),[162] and (−)-bis-(3-acetoxyundec-5-enyl) disulfide (**168**),[163] were isolated from Hawaiian algae of the genus *Dictyopteris*. Compounds **165**−**168** structurally appear to be the ring-opening dimeric derivatives of **164**. Disulfide **165** has been prepared from undec-1-en-3-one and ammonium disulfide with didecyldimethylammonium bromide as a phase-transfer catalyst (Scheme 25).[164]

It has long been recognized that algae play an important role in global biogeochemical cycles of low molecular weight and/or volatile species, such as oxygen, carbon, nitrogen, phosphorus, and sulfur.[165] Although the biosynthetic pathway of these metabolites containing sulfur is still unclear, it could be possible that the rich sulfur atoms found in their molecules may be due to their living environment near volcanic eruption zones. Fox example, it was reported that some algae living in the Mexico gulf could release an unpleasant strong sulfur odor. The fact that many sulfur-containing algae exhibit antibacterial, antifouling bioactivities suggest that algae produce these polysulfides most likely for the purpose of chemical defense themselves.

Chart 17. Structure of 172



7. BRYOZOANS

Pentaporins A−C (**169**−**171**), differing from each other in the number of sulfate ester groups, have been isolated from the Mediterranean bryozoan *Pentapora fascialis*.[166] Their structures were determined by NMR, MS spectra, and energy-dispersive X-ray (EDX) analysis. The pentaporins show in vitro anthelmintic activity against *Trichinella spiralis*, and preliminary SAR indicates the sulfate ester groups are responsible for their anthelmintic activity.

It may be worth noting that, although sulfur-containing metabolites isolated from bryozoans have been previously reported,[167−170] pentaporins A−C (**169**−**171**) are only three disulfide bond containing metabolites isolated from byrozoans.

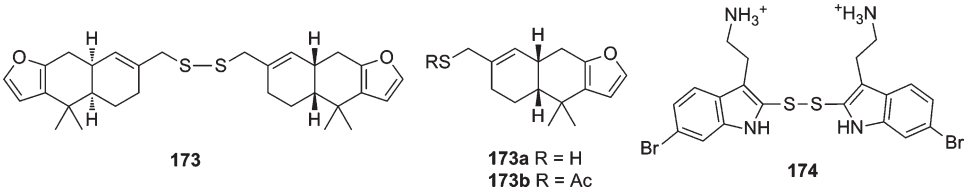
8. CORALS

Although Cnidaria are a big factory to produce various secondary metabolites, the sulfur-containing compounds are rarely reported from this phylum. To our knowledge, krempene A (**172**), isolated from the Hainan soft coral *Cladiella krempfi*, appears to be the only naturally occurring disulfide reported to date. Its structure is characterized by an unusually pregnane-type steroidal nucleus containing an unusual hexacyclic oxadithiino unit fused to ring A.[171]

9. MOLLUSCS

With respect to other marine organisms, disulfides or polysulfides are rarely encountered in mollusks. Dithiofurodysinin disulfide (**173**), a symmetrical furanosesquiterpene dimer linked by a disulfide bond, was isolated from an Australian nudibranch *Ceratosoma brevicaudatum*.[172] Its monomeric analogues such as **173a** and **173b** were earlier isolated from two *Dysidea* sponges.[173−175] Although there is no direct evidence that the nudibranchs feed on the sponges, it is believed that the sulfur-containing sesquiterpenes **173a** and **173b** were sequestered by *C. brevicaudatum* from their sponge diet as chemical defense agents. Structurally, dimer **173** might be an artifact arising from oxidative coupling of the corresponding thiol **173a** because thiols dimerize readily in air.[172]

Chart 18. Structures of 173 and 174



Scheme 26. Total Synthesis of Histidine Derivative 175 by Holler et al.[178]

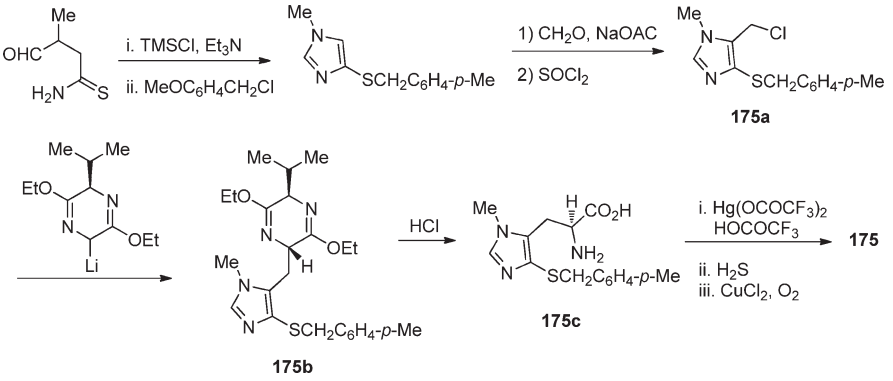
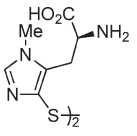


Chart 19. Structure of 175



6-Bromo-2-mercaptotrytamine (**174**), a symmetrical indole derivative linked by a disulfide bond, was isolated from the defensive mucus secreted by nudibranch *Calliostoma canaliculatum*, a marine snail found in the temperate coastal waters of the western Pacific.[176] It was found to be a new class of channel-gating antagonist of voltage-gated potassium channels.

10. ECHINODERMS

Although echinoderms (phylum Echinodermata) are a phylum of marine animals that comprises ~7000 living species and also can produce many sulfur-containing metabolites,[1] their disulfided metabolites are very rare. The histidine derivative **175** was isolated from an unfertilized egg of echinoderm *Paracentrotus lividus*.[177] Its structure was initially wrongly assigned to be 1-methyl-5-thiol-L-histidine disulfide and later revised after unambiguous synthesis.[178] The route for synthesis of **175** (shown in Scheme 26) involves using thionoamide as starting material, which was cyclized to form imidazole. The key steps involve the reaction in which **175a** was alkylated to form **175b** as a major diastereoisomer, which was later hydrolyzed to form the chiral amino acid **175c**.

11. CONCLUSION

The ocean has proven to be a rich source of sulfides. Numerous different types of polysulfides have been and continue to be isolated and identified from the various marine organisms, especially from tunicates, marine microorganisms, and sponges. Most of the polysulfides not only possess fascinating molecular architecture but also exhibit a variety of biological activities ranging from antitumor, antibiotic, to enzyme-inhibitory activities. These interesting marine natural products are a valuable treasure with great potential for leads or drug candidate discovery. However, further investigation on the mechanism of action and SAR for these metabolites is strongly requested to find more promising analogues with clinical application potential. In addition, complex structure, limited sample availability, and unstable nature of the polysulfides are long-term challenges for chemists.

Knowledge about the biogenetic origin and the real ecological role of polysulfides is still limited. More in-depth basic studies aimed at understanding/answering the above questions are needed. Even though many polysulfides show an obvious structural and biosynthetic relationship to some amino acids, such as dopamine, tryosine, cystamine, cysteine, and so on, concrete experimental evidence regarding their biosynthesis needs to be provided. The real producer of polysulfides also need to be clarified in future studies because some polysulfides isolated from marine plants or animals are structurally related to those found in their prey or strongly reminiscent of those produced by associated or symbiotic microorganisms. As to the real biological role of polysulfides to their host organisms, it is speculated that these molecules are produced for protecting their hosts from the attacks of other competitive organisms because many polysulfides have exhibited either cytotoxic or antibiotic activities in various bioassays.

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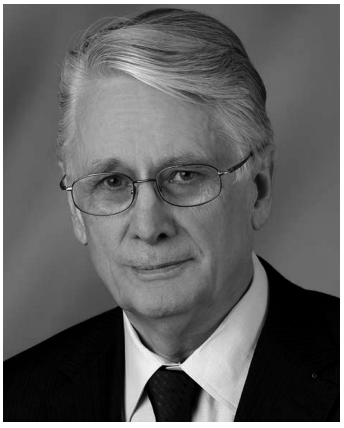
BIOGRAPHIES

Cheng-Shi Jiang was born in Shandong Province, China, in 1985. He obtained his Bachelor's degree in Department of Chemistry from Qufu Normal University, China, in 2007. In 2007, he joined the research group of Professor Yue-Wei Guo as a Ph.D. student at Shanghai Institute of Materia Medica, CAS, where he is carrying out research on isolation, synthesis, and modification of biologically active natural products isolated from Chinese marine organisms.



Werner E. G. Müller is University Professor at the Institute for Physiological Chemistry (University Medical Center) of the Johannes Gutenberg University Mainz (Germany). He is honorary professor at the Chinese Academy of Sciences. His work is focused on molecular evolution, molecular biomineralization, and deep sea biominerals. In addition his research interest includes the field of drug development. He recently has been awarded with the "ERC Advanced Investigator Grant".

Heinz C. Schröder studied Chemistry and Medicine and completed his Ph.D. and his M.D. with distinction. Since 1985 he is Professor at the University Medical Center of the University of Mainz. He has received several awards in recognition of his work and has been involved in several joint EU—Chinese projects. His research interests are focused on marine bioproducts, in particular the biosynthesis of sponge biosilica and its application in nanomedicine and nanobiotechnology.

Yue-Wei Guo received his Ph.D. degree in 1997 at University of Naples Italy. From 1997 to 2000 he worked as postdoctoral fellow in the Instituto di Chimica Biomoleculare-CNR, Italy, and Hokkaido University, Japan. He has been a Professor at Shanghai Institute of Materia Medica, CAS, since 1999. His field of research interests concern natural bioactive compounds from marine and terrestrial fauna and flora. He is an author of over 200 scientific papers and also one of the inventers of 7 patents. He received several awards including 2010 "Paul Scheuer Prize". He is a member of several editorial boards of chemical or pharmaceutical journals.

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ABBREVIATIONS

ACNacetonitrile
ALLacute lymphoblastic leukemia
Boc_2Odi-*tert*-butyldicarbonate
n-Bu_4NI (TBAI)tetra-*n*-butylammonium iodide
CbzClbenzyl chloroformate
Cleland's reagent (DTT)dithiothreitol
CNScentral nervous system
DCCdicyclohexylcarbodiimide
DDABdimethyldidodecylammonium bromide
DDQ2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEADdiethyl azodicarboxylate
DEPCdiethyl phosphorocyanidate
DIPEAdiisopropylethylamine

DMAP4-dimethylaminopyridine
DPPAdiphenyl phosphorazidate
EDC1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDCI1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
ETPsepipolythiopiperazines
Grubbs Ibenzylidene bis(tricyclohexylphosphine)dichlororuthenium
HOAT1-hydroxy-7-azabenzotriazole
HOBT1-hydroxybenzotriazole
MDRmultidrug resistance
MRSAmethicillin-resistant *Staphylococcus aureus*
NaHMDSsodium bis(trimethylsilyl)amide
NH_2—OTHP*O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine
NHPHTH*N*-hydroxyphthalimide
NHS*N*-hydroxysuccinimide
PBSphosphate-buffered saline
PDCpyridinium dichromate
PPY(*R*)-(+)-4-pyrrolidinopyridinyl-(pentamethylcyclopentadienyl) iron
PTP1Bprotein tyrosine phosphatase 1B
SARstructure—activity relationship
TBAFtetra-*n*-butylammonium fluoride
TBDPSCl*tert*-butyldiphenylchlorosilane
TBSCl*tert*-butylchlorodimethylsilane
TceOHtrichloroethanol
TEAtriethylamine
TEMPO2,2,6,6-tetramethylpiperdine-1-oxyl
TFAtrifluoroacetic acid
TFAAtrifluoroacetic anhydride
TMEDAtetramethylethylenediamine
$TMSCHN_2$trimethylsilyldiazomethane
p-TsOH*p*-toluenesulfonic acid

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