

## Natural Chlorine Updates – No. 5

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## I. Introduction

This literature review is the fifth in a series of periodic updates to the natural halogen literature, with a particular focus on organochlorine compounds, although all new natural organohalogen compounds are described.

The coverage is approximately from January 1997 through September 1997, with inclusions of earlier material as appropriate.

Several reviews of various aspects of naturally occurring organohalogens have appeared in foreign languages (Spanish, Polish, Swedish, and German) (1-5). The biosynthesis of bacterial halogenated metabolites has been reviewed (6), and a "Current Issue in Carcinogenesis and Mutagenesis" presents a brief overview of the "common misconception that....organic chemicals containing a halogen atom are of purely anthropogenic origin" (7).

Other reviews will be cited in the following sections as appropriate.

## II. New Natural Organohalogens

The discovery of new natural organohalogen compounds steadily continues. This *Updates* describes 106 new natural organohalogens, bringing the total number to 2893. Thus, the current breakdown of such natural products reported to date is as follows:

Organochlorine:	1695
Organobromine:	1503
Organoiodine:	87
Organofluorine:	21

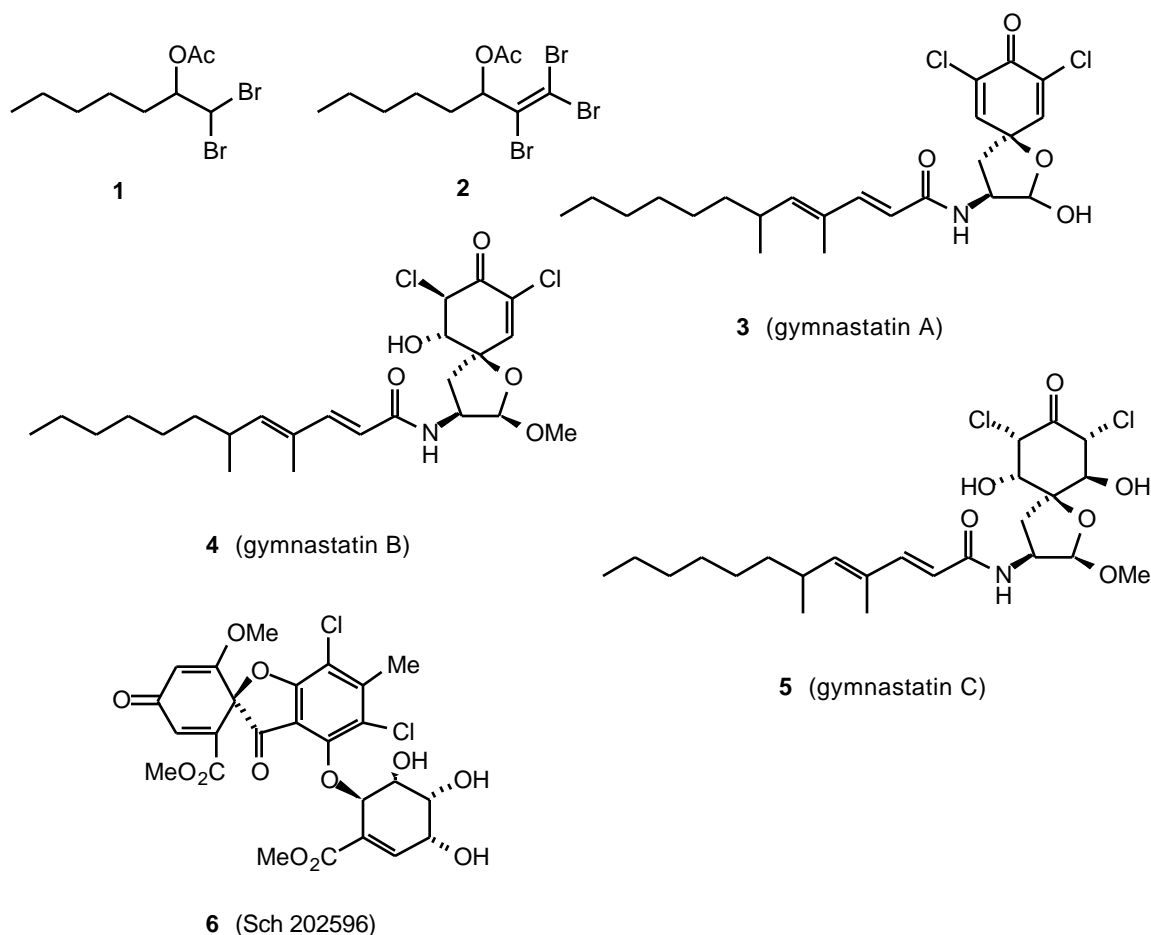
[These numbers are adjusted for previous errors or double counting.]

As in previous *Updates*, only newly discovered organohalogens are given explicit compound numbers (in bold), so as to making counting easier.

The production of CH<sub>3</sub>Cl, CH<sub>3</sub>Br, and CH<sub>3</sub>I by laboratory cultures of the marine phytoplankton *Phaeodactylum tricornutum*, *Phaeocystis* sp., and *Thalassiosira weissflogii* has been demonstrated (8), and the average annual flux of CH<sub>3</sub>I out of the southern North Sea is estimated at 8 x 10<sup>5</sup> moles per year (9), presumably from algal sources. Chlorofluorocarbons (CFCs) and simple organochlorines continue to be discovered from geological phenomena. The

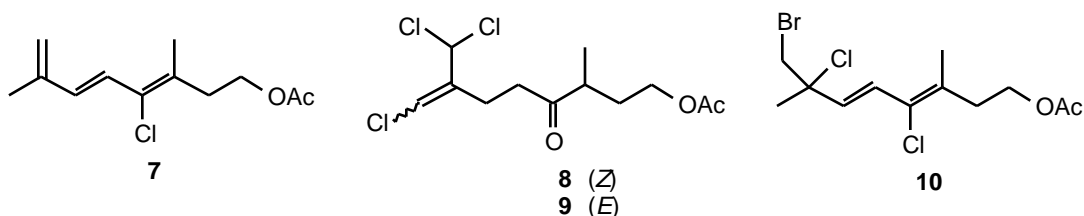
crushing of the mineral silvinites yields  $\text{CH}_2\text{Cl}_2$ ,  $\text{CHCl}_3$ ,  $\text{CCl}_4$ ,  $\text{CCl}_2=\text{CHCl}$ ,  $\text{CCl}_2=\text{CCl}_2$ , and chlorobenzene (all previously reported as naturally occurring) (10). Studies of the thermal springs and vents in the Ashkhabad region of Turkmenia and the Tskhaltubo region in Georgia have indicated the presence of  $\text{CHCl}_3$ ,  $\text{CCl}_4$ , and  $\text{CFCl}_3$  (11). Likewise, the solfataric and hydrothermal vents of the Kamchatka volcanoes produce  $\text{CFCl}_3$ ,  $\text{CF}_2\text{Cl}_2$ , and  $\text{CCl}_4$  (12). These results reinforce the notion that chloride and fluoride minerals react with organic material under conditions of high temperatures and high pressures to form CFCs and organochlorine compounds.

The Antarctic red alga *Delisea fimbriata* contains the novel bromoacetates **1** and **2**, in addition to six known organobromines (13). The fungus *Gymnasella dankaliensis*, which is associated with the sponge *Halichondria japonica*, produces gymnastatins A-C (**3-5**), which have significant cytotoxicity against cancer cells *in vitro* (14). The griseofulvin-related Sch 202596 (**6**) was found in cultures of the fungus *Aspergillus* sp. (15).

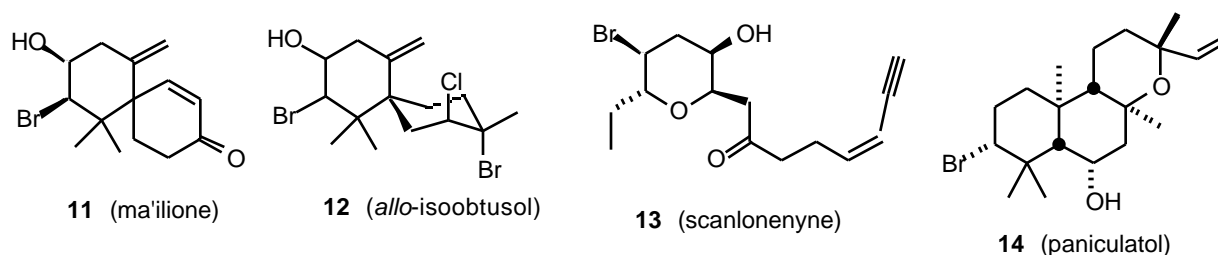


The sea hare *Aplysia punctata*, which has been a prolific source of diet-derived organohalogen compounds, has yielded the new cytotoxic monoterpenes **7-10**, in addition to four known

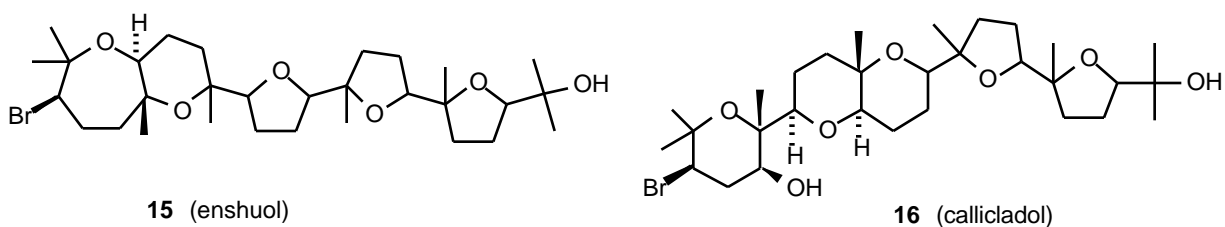
halogenated cyclohexanes (16).



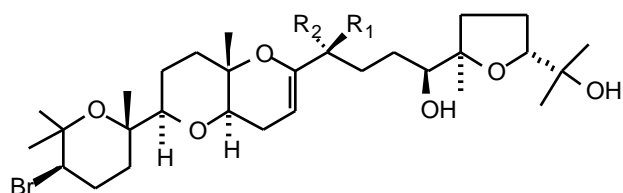
The Hawaiian red alga *Laurencia cartilaginea* has yielded two new chamigranes, ma'ilione (**11**) and *allo*-isoobtusol (**12**), in addition to four known halogenated sesquiterpenes (17). Irish waters have furnished scanlonenyne (**13**), a C<sub>15</sub> acetogenin from the red alga *Laurencia obtusa* (18), and *L. paniculata* contains the novel *ent*-labdane diterpene paniculatol (**14**), the absolute configuration of which is shown (19).



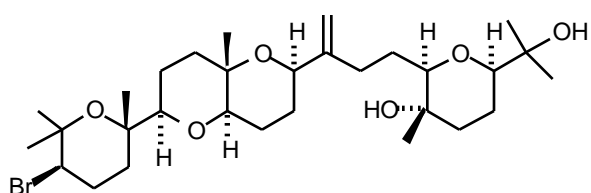
Several new squalene-derived triterpenes containing bromine have been discovered in seaweeds. Enshuol (**15**) was isolated from *Laurencia omaezakiana* (20), and the Vietnamese *L. calliclada* contains callicladol (**16**) (21).



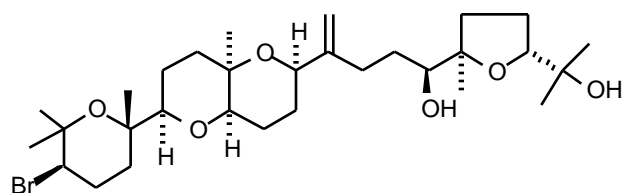
The red alga *Laurencia viridis* from the Canary Islands has yielded several new bromine-containing polyether squalene-derived metabolites. These include thyrsenol A (**17**) and B (**18**) (22), isodehydrothyrsiferol (**19**) and 10-epidehydrothyrsiferol (**20**) (23), and dehydrovenustatriol (**21**), 15,16-dehydrovenustatriol (**22**), 16-hydroxydehydrothyrsiferol (**23**), and 10-epi-15,16-dehydrothyrsiferol (**24**) (24).



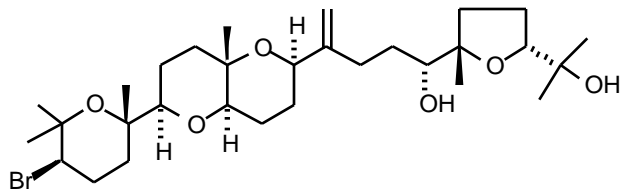
**17**  $R_1 = \text{OH}$ ,  $R_2 = \text{CH}_2\text{OH}$  (thyrnsenol A)  
**18**  $R_1 = \text{CH}_2\text{OH}$ ,  $R_2 = \text{OH}$  (thyrnsenol B)



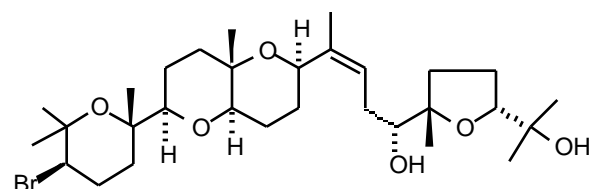
**19** (isodehydrothyrnsiferol)



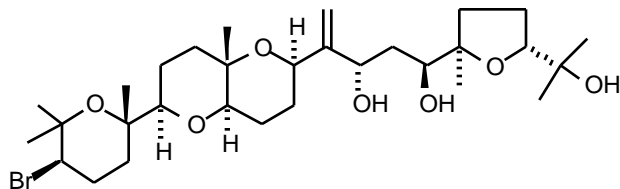
**20** (10-epidehydrothyrnsiferol)



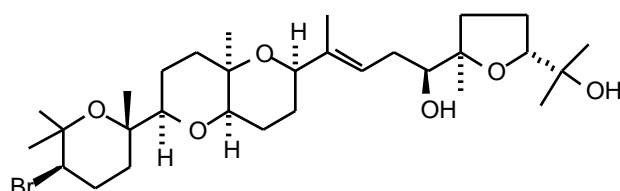
**21** (dehydrovenustatriol)



**22** (15,16-dehydrovenustatriol)

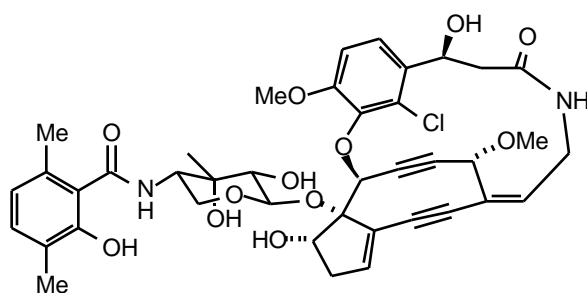


**23** (16-hydroxydehydrothyrnsiferol)

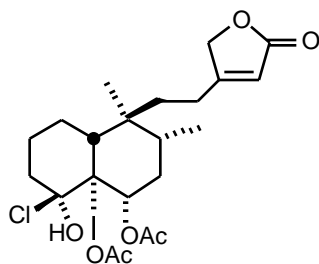


**24** (10-epi-15,16-dehydrothyrnsiferol)

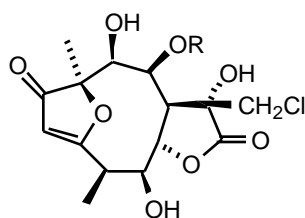
A new naturally occurring chlorine-containing enediyne antibiotic, maduropeptin, has been isolated from *Actinomadura madurae* (25). This complex chromophore, which is associated with a protein of 14 amino acids, has an unstable chromophore, the methanol adduct of which is shown as **25**. The full structure remains unknown although speculation regarding the mode of action has been advanced (25*b,c*). The neo-clerodane diterpene **26** is found in *Ajuga parviflora* and is ajugarin-I chlorohydrin (26). The South American plant *Bejaranoa balansae* has yielded the new furanoheliangolides **27-29**, while *B. semistriata* contains **30** (27).



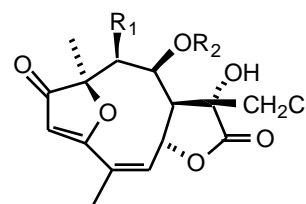
25 (maduropeptin apoprotein methanol adduct)



26

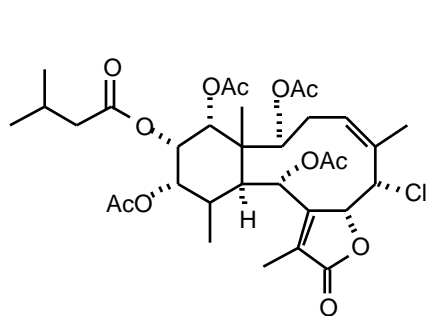


27 R = tiglyl  
28 R = angelyl

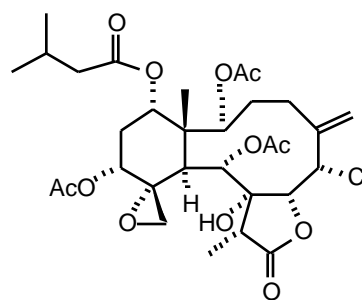


29 R<sub>1</sub> = OH, R<sub>2</sub> = tiglyl  
30 R<sub>1</sub> = H, R<sub>2</sub> = 5-OAc-tiglyl

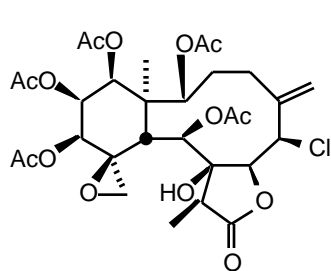
The Indian Ocean gorgonian *Junceella juncea* has been found to contain two new chlorinated briarane diterpenoids, juncin G (**31**) and H (**32**), as well as the new antipodes of gemmacolides A (**33**) and B (**34**) (28).



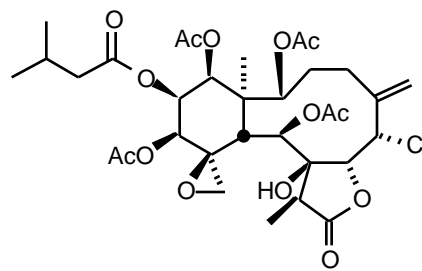
31 (juncin G)



32 (juncin H)

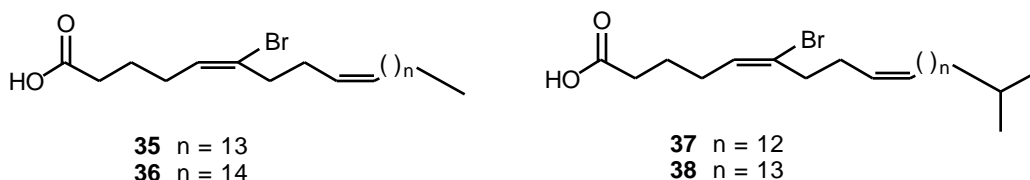


33

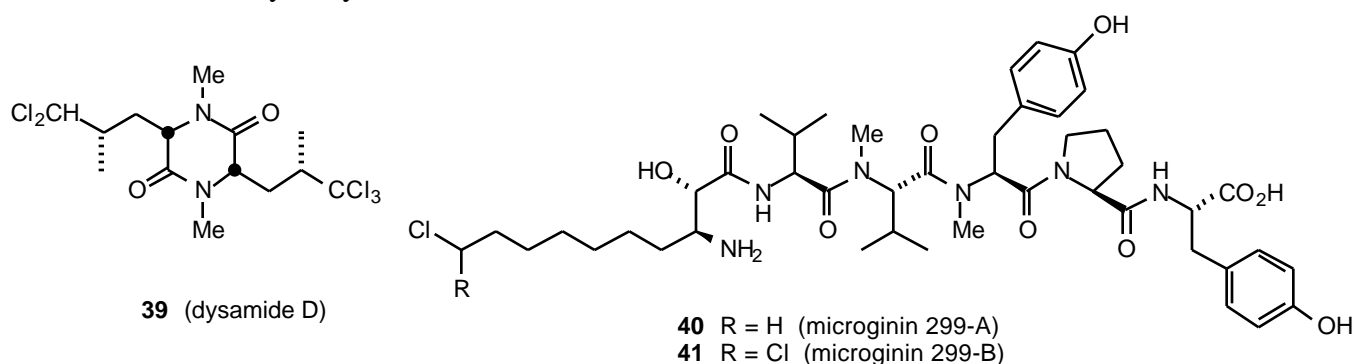


34

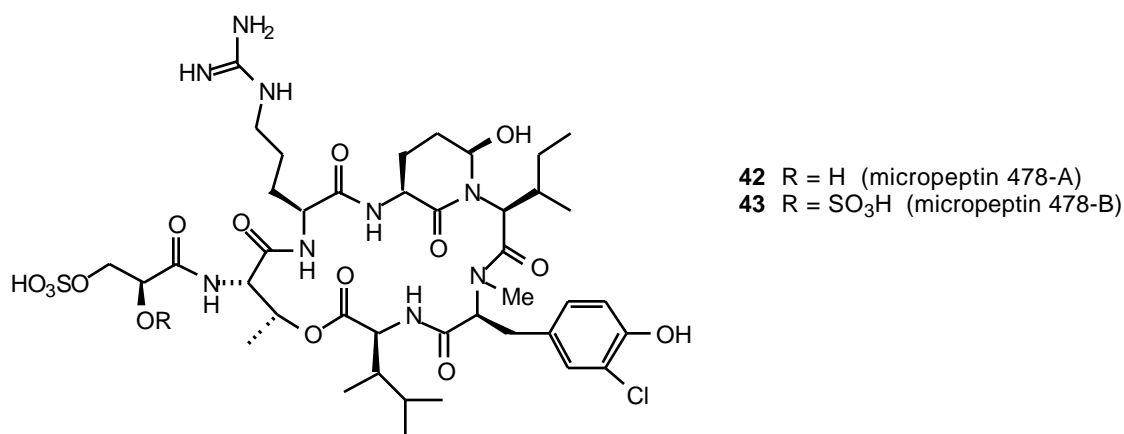
Four new brominated fatty acids **35-38** have been characterized from an *Agelas* sp. sponge (29), and the previously known aurantoside A was isolated from a theonellid sponge from Mozambique (30).



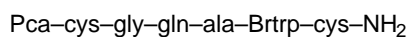
A new diketopiperazine, dysamide D (**39**), has been isolated from the South China sea sponge *Dysidea fragilis* (**31**). It is assumed that the all *S* configuration obtains as in dysamide A. The blue-green alga *Microcystis aeruginosa* has furnished microginins 299-A (**40**) and -B (**41**), which inhibit leucine aminopeptidase (**32**). The key structural features are the novel 10-chloro- and 10,10-dichloro-3-amino-2-hydroxydecanoic acid residues.



Micropeptins 478-A (**42**) and -B (**43**) are also produced by cultures of *Microcystis aeruginosa* (**33**). These cyclic peptides are inhibitors of plasmin.

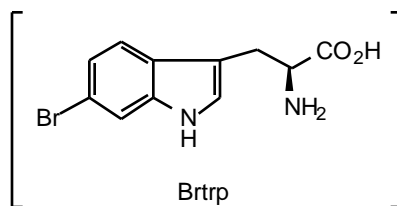


The venomous cone snail *Conus imperialis* contains the heptapeptide **44** in which a 6-bromotryptophan amino acid is present, and *Conus radiatus* produces a 33-amino acid peptide **45** (not shown) that also contains 6-bromotryptophan (**34**). The venom from this latter snail has also yielded the octapeptide bromocontryphan (**46**), which contains a 6-bromotryptophan unit.



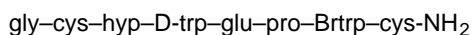
44

[Pca = pyroglutamic acid]



33-amino acid peptide

45



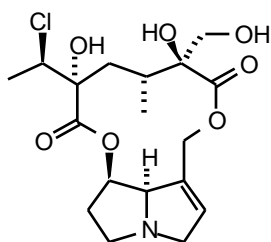
46

(bromocontryphan)

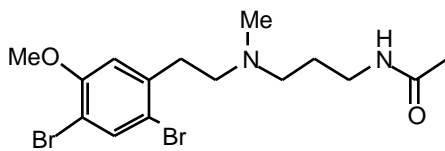
[hyp = *trans*-4-hydroxyproline]

Some synthetic correlation evidence has been advanced to indicate that the proposed structure of the 2-bromo-5-hydroxytryptophan containing konbamide is incorrect (36). Full papers have appeared describing the isolation and characterization of chloropeptins I and II (=complestatin) from *Streptomyces* sp. (37, 38), and a detailed structural study of the former compound has been described (39). These chlorine-containing glycopeptides were previously announced as natural products. The absolute configuration of the 4-fluorothreonine (*Streptomyces cattleya*) has been confirmed as 2*S*, 3*S* (40), although this compound is not counted as "natural" since the producing organism was cultured in the presence of fluoride.

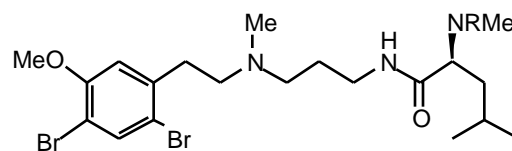
A new chlorine-containing pyrrolizidine alkaloid, 18-hydroxyjaconine (47), has been found in *Senecio selloi* from Brazil (41). The Atlantic bryozoan *Amathia convoluta* has yielded volutamides A-E (48-52) (42). These amino acid-derived alkaloids are potent feeding deterrents.



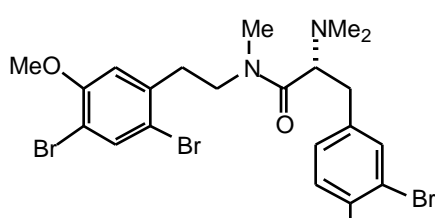
47 (18-hydroxyjaconine)



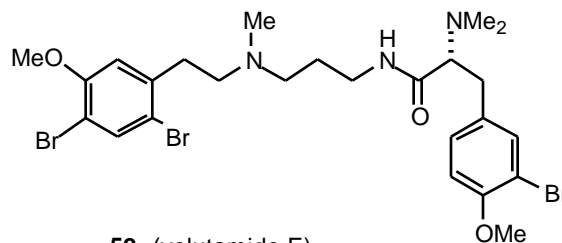
48 (volutamide A)



49 R = H (volutamide B)  
50 R = Me (volutamide C)

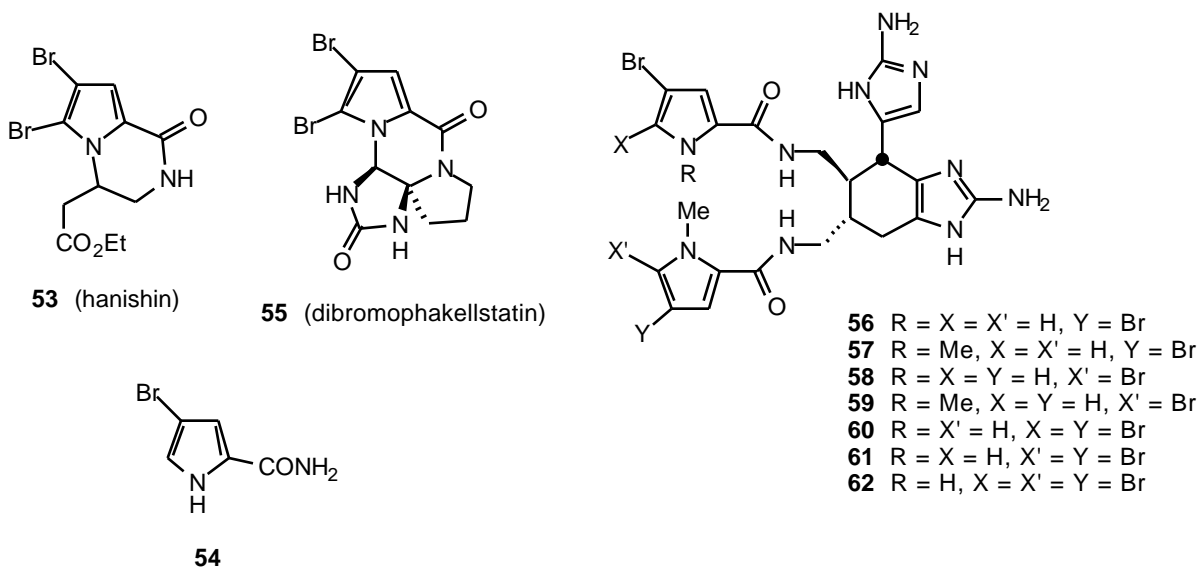


51 (volutamide D)

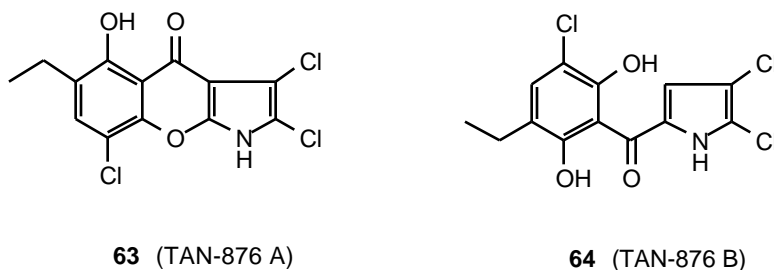


52 (volutamide E)

The pyrrole-containing alkaloid hanishin (**53**) and amide **54** have been found in the Red Sea sponge *Acanthella carteri* (**43**). Hanishin can be viewed as a shunt metabolite of the well-known oroidin, which is also present in this sponge. The Indian Ocean sponge *Phakellia mauritiana* has afforded dibromophakellstatin (**55**), which has good activity against six human cancer cell lines (**44**). The sponge *Astrosclera willeyana* has yielded seven new ageliferins (**56-62**) (**45**).



The novel chlorinated antibiotics TAN-876 A (**63**) and B (**64**) are produced by *Streptomyces* sp. (**46**). The former compound has the unique chromeno[2,3-*b*]pyrrole ring system.

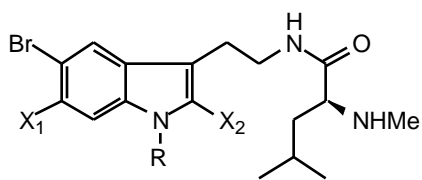


The absolute configurations of pyralomicins 1a and 1b, which were first presented in *Updates* #3, have been determined by X-ray crystallography (**47**). These interesting metabolites were isolated from *Microtetraspora spiralis* (**48, 49**). The biosynthesis of pyralomicin 1a has been studied (**50**).

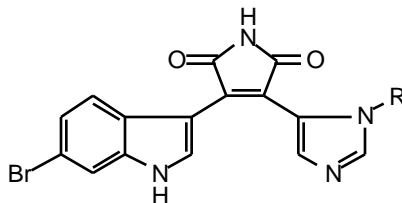
The new bromotryptamines, alternatamides A-D (**65-68**), are produced by the Atlantic bryozoan *Amathia alternata* (**51**). The Caribbean mangrove ascidian *Didemnum conchyliatum* has yielded the didemnimides B (**69**) and D (**70**), in addition to two without halogen (**52**).

Didemnimide D is a potent feeding deterrent. The previously known *E* and *Z* indoles **A** have now

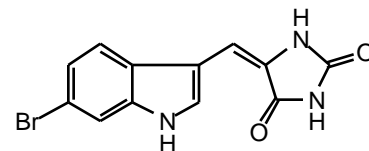
been found in the stony coral *Tubastrea faulkneri* (53).



- 65** R = Me, X<sub>1</sub> = X<sub>2</sub> = Br (alternatamide A)  
**66** R = H, X<sub>1</sub> = X<sub>2</sub> = Br (alternatamide B)  
**67** R = X<sub>1</sub> = H, X<sub>2</sub> = Br (alternatamide C)  
**68** R = X<sub>2</sub> = H, X<sub>1</sub> = Br (alternatamide D)

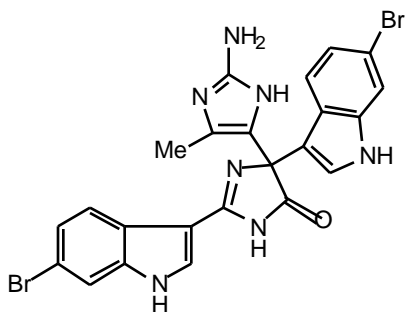


- 69** R = H (didemnimide B)  
**70** R = Me (didemnimide D)

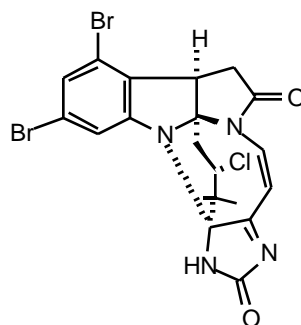


**A** (4:1 Z/E)

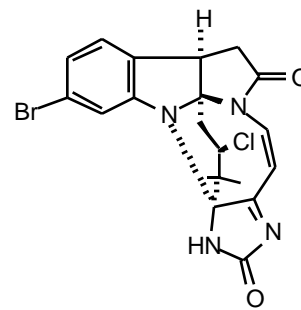
Nortopsentin D (**71**) is found in the deep water New Caledonian sponge *Drarmacidon* sp. (54). Although **71** is inactive, the synthetic permethylated analog (seven methyl groups) is highly active against KB cells. The bryozoan *Securiflustra securifrons*, which produces the securamines A-D featured in *Updates #3*, has now yielded the closely related securamines E-G (**72-74**) (55). Securamine E is a brominated analog of C, while F is an epimer of C and G is a hydrogenated derivative of C.



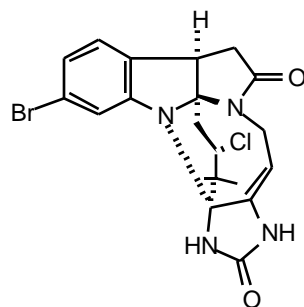
**71** (nortopsentin D)



**72** (securamine E)



**73** (securamine F)



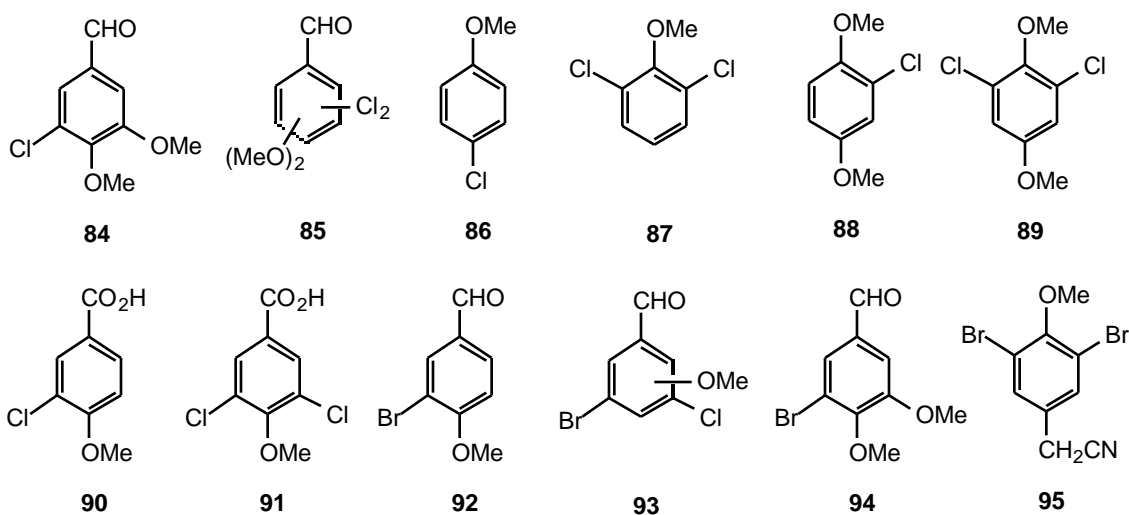
**74** (securamine G)

The Philippino sponge *Zyzzya fuliginosa* has yielded the new makaluvamine N (**75**) in addition to five known compounds (56). A deep water green demosponge from pre-Antarctic waters has yielded epinardins B-D (**76-78**) (57). The related metabolites, 14-bromodiscorhabdin C (**79**) and 14-bromodihydrodiscorhabdin C (**80**) are found in a South African *Latrunculia* sp.

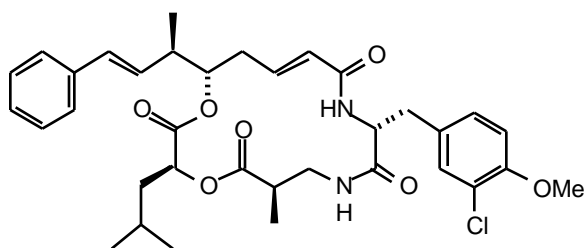


Much additional evidence has appeared to support the natural occurrence of chlorinated benzodiazepines in mammalian brains, including *in vivo* biosynthesis (65) as well as a possible dietary origin (66). One study of preserved brains, from before the first synthesis of diazepam, revealed the presence of this compound (67), and another reports the presence of diazepam and desmethyldiazepam in corn, lentils, potatoes, soybeans, rice, mushrooms, rats, cats, dogs, deer, bovine, chickens, frogs, fish, and humans at levels of 0.005-0.05 ng/g (68). Interestingly, rats with hepatic encephalopathy have 4-6 times more benzodiazepines than normal rats, and these compounds include deschlorodiazepam, deschlorolorazepam, lorazepam, oxazepam, diazepam, and *N*-desmethyldiazepam (69). Several papers have described the development of monoclonal antibodies to benzodiazepines, which have been used to identify such compounds in the brain (70-74). These studies confirm the fact that chlorinated benzodiazepines were present in human brains since at least 1940, 15 years before the first chemical synthesis of these drugs!

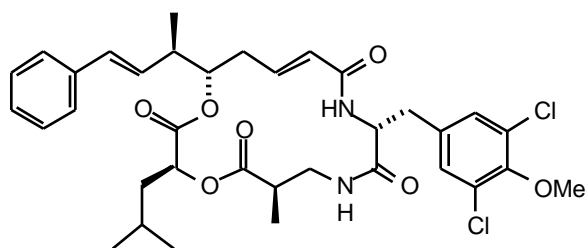
An examination of the forest soil surrounding the wood-rotting fungus *Lepista nuda* (common wood blewitt) has discovered the presence of several new naturally occurring halogenated phenols (84-95), including three bromo compounds, which represents the first time natural brominated low-molecular weight compounds have been found in soil (75). These compounds are present in concentrations up to 8.6 ppm. In addition, the previously known 4-chloro-3-methoxybenzaldehyde, 3-chloro-4-methoxybenzaldehyde, and 3,5-dichloro-4-methoxybenzaldehyde were present in 1.9 and 20 ppm, respectively. The bromotyrosine precursor 3,5-dibromo-4-methoxyphenylacetonitrile has been detected in (76).



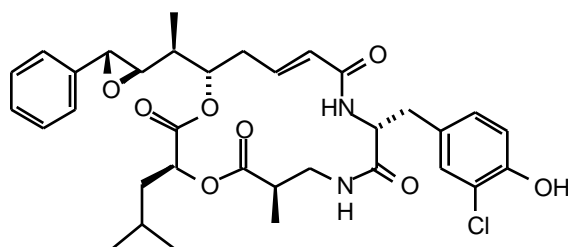
The blue-green alga *Nostoc* sp. has yielded an additional three chlorinated cryptophycins (**96-98**) (77).



**96** (cryptophycin-46)



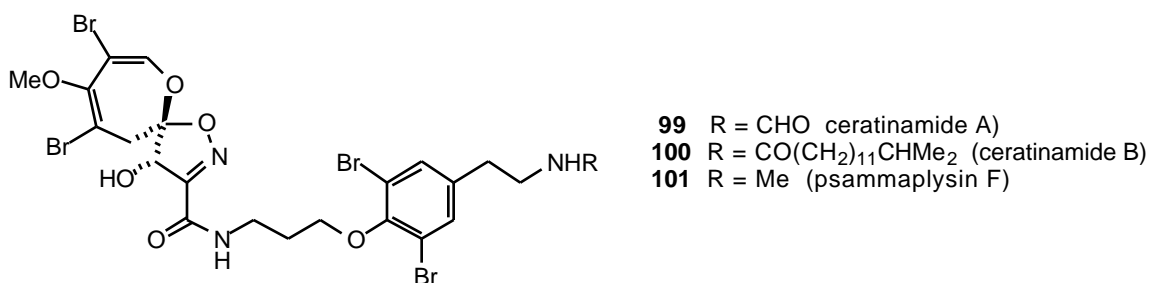
**97** (cryptophycin-175)



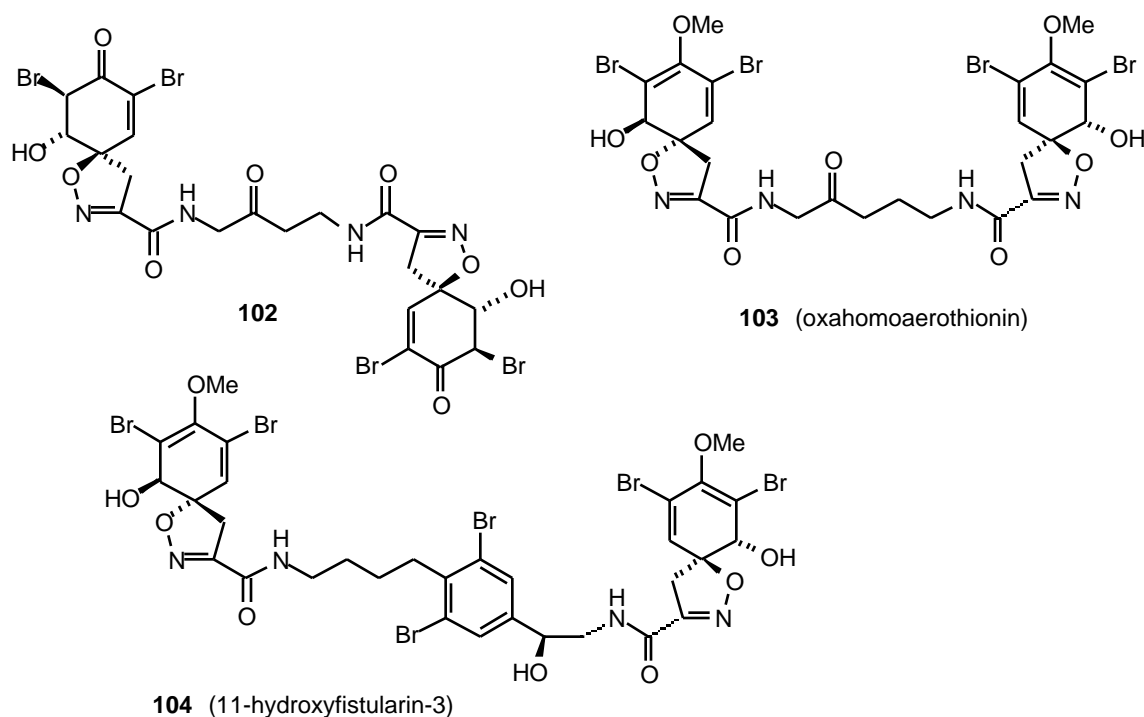
**98** (cryptophycin-176)

The total number of ticks that produce 2,6-dichlorophenol as a sex attractant now number at least 14 and several recent studies in this area have appeared (78-80), including the use of 2,6-dichlorophenol with pesticides in tick control in dogs (81a) and cattle (81b). Neurons in the legs of male ticks (*Amblyomma americanum*) have been identified that are sensitive to 2,6-dichlorophenol (82). The previously known chlorophenol differanisole A from the soil microbe *chaetomium* sp. is an inducer of the differentiation of mouse leukemia cells and of stalk cells (83). A previously known brominated diphenyl ether, 2-(2',4'-dibromophenyl)-4,6-dibromophenol, from the sponge *Dysidea herbacea* has now been shown to be produced by the symbiotic blue-green alga *Oscillatoria spongelliae* (84). Interestingly, crystals of this compound are present in the sponge tissue.

Several new brominated tyrosine sponge metabolites have been characterized during this period. Ceratinamides A and B (**99**, **100**) are antifouling compounds isolated from *Pseudoceratina purpurea*, along with six known bromo compounds, all of which inhibit larval settlement and metamorphosis of the barnacle *Balanus amphitrite* (85). The closely related psammaphysin F (**101**) is found in the sponge *Aplysinella* sp. in addition to the known psammaphysins A-C, E (86).



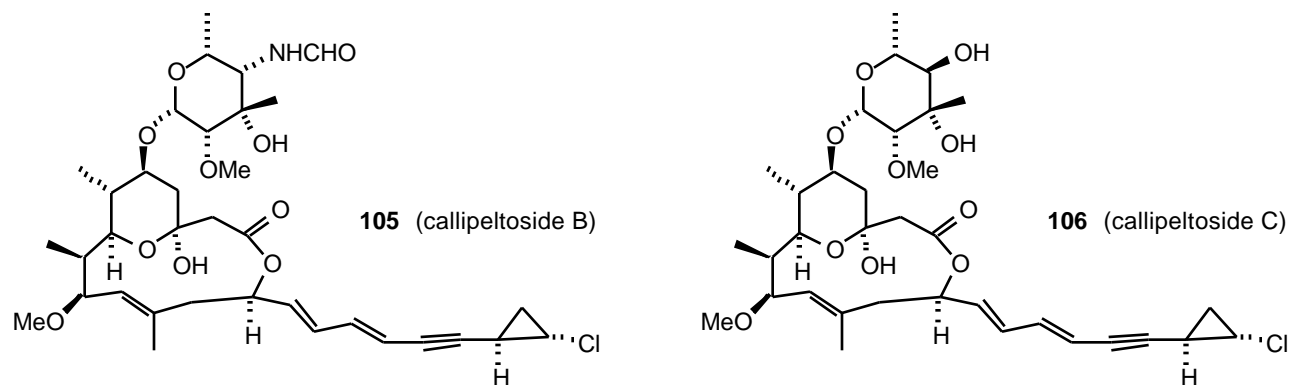
The Caribbean sponge *Aplysina archeri* has yielded the new **102**, in addition to nine known bromotyrosine derivatives (87). The Mediterranean sponge *Aplysina cavernicola* has furnished oxahomoaerothionin (**103**) and 11-hydroxyfistularin-3 (**104**) (88).



The mode of cytotoxic action of the known bromotyrosine derivatives aeroplysinin-1 and dibromoverongiaquinol has been investigated (89). The absolute configurations of the halogen-containing sponge macrolides althoyrtins A, B and desacetyl A have been determined (90). The importance of vancomycin and other glycopeptide antibiotics in the treatment of penicillin-resistant bacteria (91) continues to inspire studies of the mode of action of these drugs and the development of new agents to treat vancomycin-resistant bacteria (92, 93). The role of the chlorine atoms in the mechanism of activity of vancomycin is beginning to be understood (91), the first X-ray crystal structure of vancomycin has been achieved (94).

Two new callipeltosides, B (**105**) and C (**106**), have been characterized from the sponge

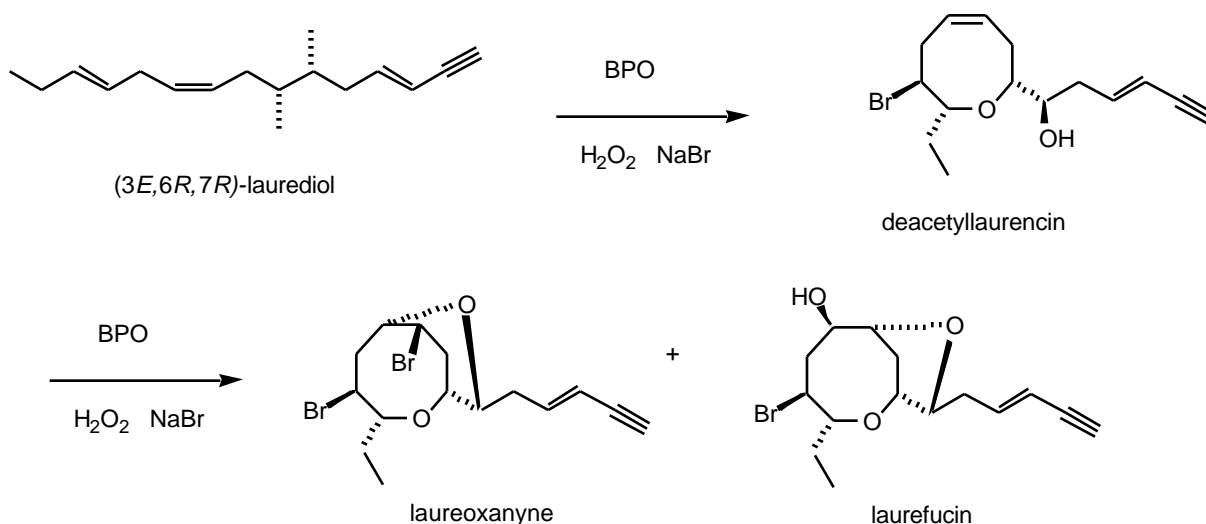
*Callipelta* sp. (95).



### III. Biohalogenation

The various aspects of biological halogenation continue to be vigorously pursued and the gene for the two bromoperoxidases (BPO-A1 and BPO-A2) found in *Streptomyces aureofaciens*, which produces 7-chlorotetracycline, have been cloned and sequenced (96, 97). Similarly, the chloroperoxidase (CPO) gene from the fungus *Caldariomyces fumago* has been isolated and sequenced (98). Synthetic analogs of the CPO active site have been designed, synthesized, and evaluated for their ability to effect catalytic chlorination reactions (99). The enantioselective epoxidation of bromoalkenes catalyzed by CPO has been described (100). A study of the amino acid composition of the active sites of vanadate-containing haloperoxidases shows conservation within families of acid phosphatases, suggesting a common evolutionary ancestor for these families of enzymes (101). The biomimetic synthesis of several *Laurencia* sp. red algae metabolites with BPO has been reported (Scheme 1) (102).

Scheme 1



Several papers describing the generation of active chlorine intermediates from the action of myeloperoxidase (MPO) and H<sub>2</sub>O<sub>2</sub> on chloride ion were not reported earlier. Thus, under these conditions the *in vitro* production of HOCl or Cl<sub>2</sub> has been demonstrated (103), and the same reaction in the presence of *E. coli* bacteria, which results in their death, forms *N*-chloro derivatives of peptides (104). It is suggested that long after the oxidation of Cl<sup>-</sup> is complete to HOCl or Cl<sub>2</sub>, the subsequently formed *N*-chloro compounds can still oxidize and kill the bacterial targets. A more recent study indicates that tyrosine may be the target in the action of MPO/Cl<sup>-</sup>/H<sub>2</sub>O<sub>2</sub> in neutrophils, and that the chlorination of the tyrosine ring is via a *N*-chloro derivative by intramolecular delivery (105). The killing of *E. coli* bacteria by human MPO under these conditions is by increased penetration of the cell wall by HOCl (106). The so generated HOCl in neutrophils is strongly selective towards nucleotides and compounds in the respiratory redox chains in bacteria (e.g., Fe-S proteins, cysteine proteins, cytochromes, adenine and nucleotides, carotene pigments) (107). The *N*-chlorination of taurine by human neutrophils *in vitro* (MPO, Cl<sup>-</sup>, H<sub>2</sub>O<sub>2</sub>) and by HOCl has been demonstrated (108).

#### IV. Other Natural Sources of Organohalogens

The importance of additional research into the possible formation of reactive chlorine gases (Cl<sub>2</sub>, HOCl, ClNO<sub>2</sub>) from sea-salt aerosol in the marine boundary layer has been stressed (109).

The *in vitro* production of organochlorines by 8 of 9 species of white-rot fungi has been

found (110), and the presence of chlorinated 4-hydroxyphenyl structures in natural aquatic fulvic acid has been reported (111). Additional evidence is presented to indicate that chlorinated dibenzo-*p*-dioxins and dibenzofurans can form during compositing of material containing chlorophenols (112). Moreover, the earlier reported formation of octachlorodibenzo-*p*-dioxin from pentachlorophenol and horseradish peroxidase was confirmed (113). Evidence is described to indicate that bonfires and/or fireworks may be a significant source (400% increase) in ambient air of dioxins (114).

## V. Biodegradation

It has been found that microbes exist in bedrock groundwaters capable of anaerobically dechlorinating tetrachloroethylene to ethane (115). The wood-rotting fungus *Phanerochaete chrysosporium* is able to degrade the highly persistent DDE to 4,4'-dichlorobenzophenone initially and then to CO<sub>2</sub> (116). The metabolism of 2,4-dichlorophenol by the human cytochrome P450 3A4 system leads to 2-chloro-1,4-hydroquinone, 2-chloro-1,4-benzoquinone, and 1,2,4-trihydroxybenzene (117). The biodegradation of 2,4-dichlorophenol by the fungi *Paxillus involutus* and *Suillus variegatus*, particularly in symbiosis with a host pine tree (*Pinus sylvestris*), has been shown (118). The new anaerobic bacterium *Desulfitobacterium dehalogenans*, which can reductively dechlorinate chlorophenols, has been isolated from a lake sediment (119).

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