

Natural Chlorine Updates – No. 7

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- I. Introduction
- II. New Natural Organohalogens
- III. Biohalogenation
- IV. Other Natural Sources of Organohalogens
- V. Biodegradation
- VI. Function
- VII. References

I. Introduction

This literature review is the seventh in a series of periodic updates to the natural halogen literature, with a particular focus on organochlorine compounds, although all new natural organohalogen compounds that have been identified since the last *Updates* are described.

The coverage is approximately from December 1997 through March 1998, with inclusions of earlier material as appropriate.

A book on the special Colloquium on Biohalogenation, "Mechanisms of Biohalogenation and Dehalogenation," that was held in Amsterdam in September 1996 has been published (1). This author has recently had published a review of natural organohalogens (2).

II. New Natural Organohalogens

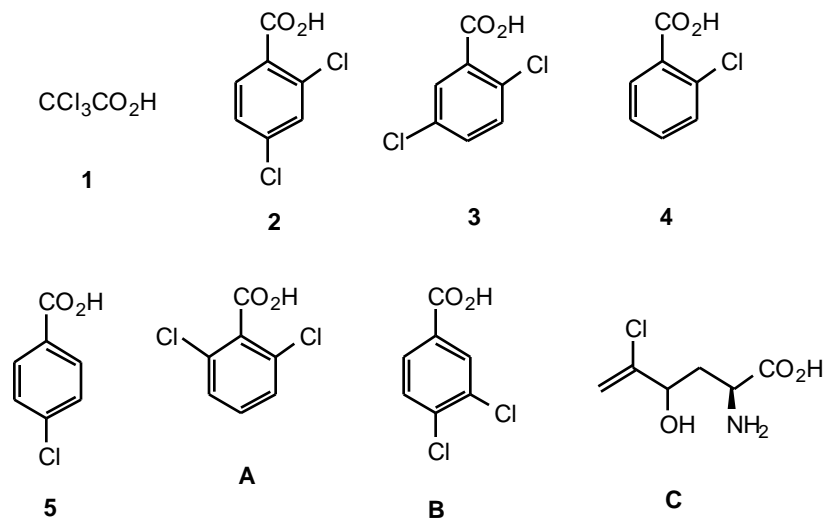
This *Updates* describes 86 new natural organohalogens, bringing the total number to 3017. Thus, the current breakdown of such naturally produced compounds reported to date is as follows:

Organochlorine:	1783
Organobromine:	1545
Organoiodine:	87
Organofluorine:	22

As in previous *Updates*, only newly discovered organohalogens are assigned explicit compound numbers (in bold), for ease in counting.

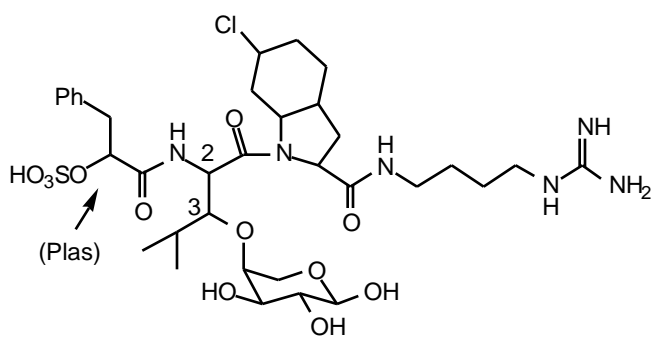
Trichloroacetic acid (**1**), which has not been previously classified as being natural by this author, has now been found in bog water, glacier ice, rain, spring water and in soil lysimeters (3). These authors also demonstrated the formation of trichloroacetic acid from acetic acid, chloroperoxidase, which is a ubiquitous soil enzyme, sodium chloride, and hydrogen peroxide. Other naturally occurring carboxylic acids (malic, fumaric, malonic, citric and acetonedicarboxylic) as well as humic acid yielded **1** under these laboratory conditions. In addition, a sample of 100 year old glacier ice was found to contain trichloroacetic acid. This same research group from Heidelberg has also found 2,4-dichlorobenzoic acid (**2**), 2,5-dichlorobenzoic acid (**3**), 2- (or 3-) chlorobenzoic acid (**4**), and 4-chlorobenzoic acid (**5**) in samples of remote bog water and sediments (4). The highest concentration was always **2**. In addition, bank-infiltrated water of the River Rhine and in

water of Hohes-Venn bog contained 2,6-dichlorobenzoic acid (**A**) and 3,4-dichlorobenzoic acid (**B**). However, these latter chlorine-containing benzoic acids are not counted as being natural at the present time.

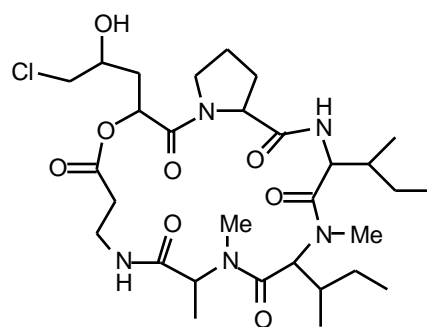


A full report has appeared on the isolation of (2*S*)-2-amino-5-chloro-4-hydroxy-5-hexenoic acid (**C**) from the mushroom *Amanita gymnopus* (**5**). This compound is also found in the fruit bodies of an unknown member of *Amanita* belonging to the section *Roanokenses*, subsection *Solitariae*.

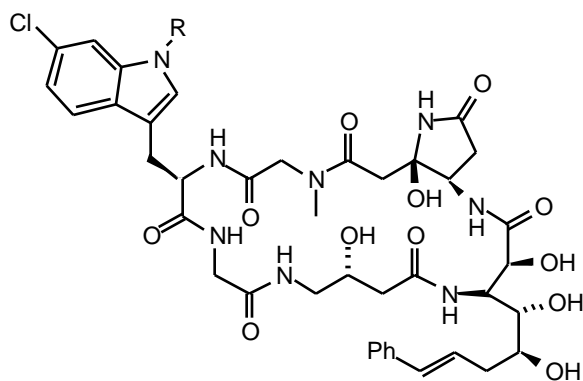
The blue-green alga *Oscillatoria agardhii* has yielded the isomeric aeruginosins 205A (**6**) and 205B (**7**), which are related to aeruginosin 98-A (**21** in *Updates #2*). These new compounds are potent inhibitors of trypsin and thrombin (**6**). The fungus OS-F68576 produces the cyclic peptide destruxin-A4 chlorohydrin (**8**) (**7**). This compound is an inducer of erythropoietin and is obtained with or without the use of chloroform in the isolation procedure. The lithistid marine sponge *Theonella* sp. contains microsclerodermins C (**9**) and D (**10**), and the related sponge *Microscleroderma* sp. contains **10** (**8**). These cyclic peptides feature three unprecedented amino acids. Filamentous bacteria associated with the lithistid sponge *Theonella swinhoei* from both Palau and Mozambique produce the novel bicyclic glycopeptide theopalauamide (**11**) (**9**).



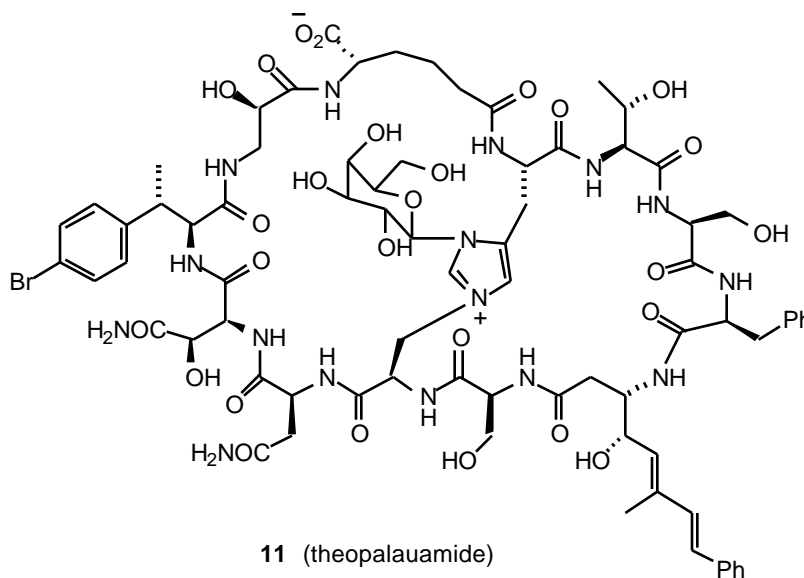
6 2R, 3S L-Plas (aeruginosin 205A)
7 2S, 3R D-Plas (aeruginosin 205B)



8 (destruxin-A4)



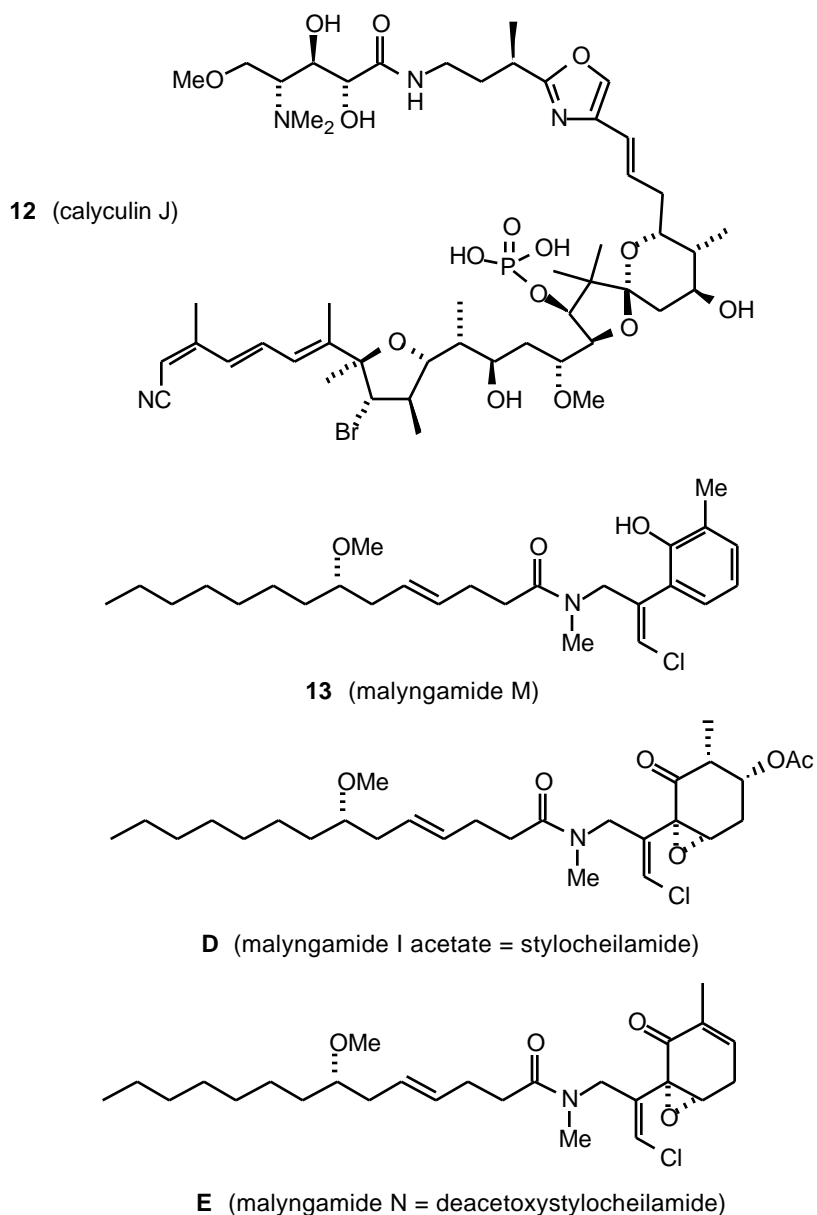
9 R = CONH₂ (microsclerdermin C)
10 R = H (microsclerdermin D)



11 (theopalauamide)

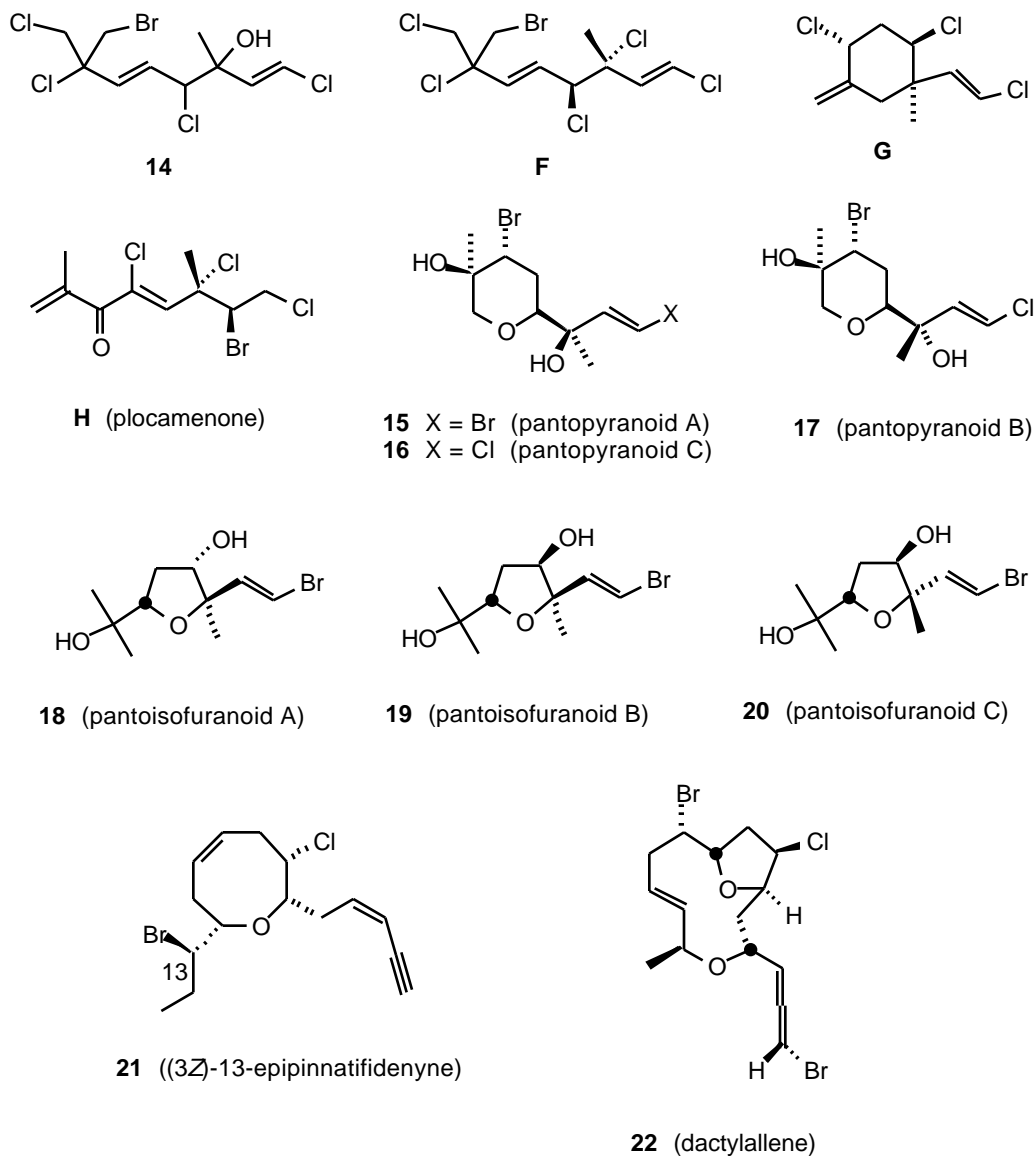
The marine sponge *Discodermia calyx* has yielded four new calyculins, one of which, calyculin J (**12**), contains bromine (10). A reinvestigation of the red alga *Gracilaria coronopifolia* from Hawai'i has led to the new malyngamide M (**13**) and revised structures for stylocheilamide (=malyngamide I acetate) (**D**) and deacetoxystylocheilamide (=malyngamide N) (**E**) (11). The authors suggest that these metabolites are actually produced by a blue-green alga growing on this

red seaweed.



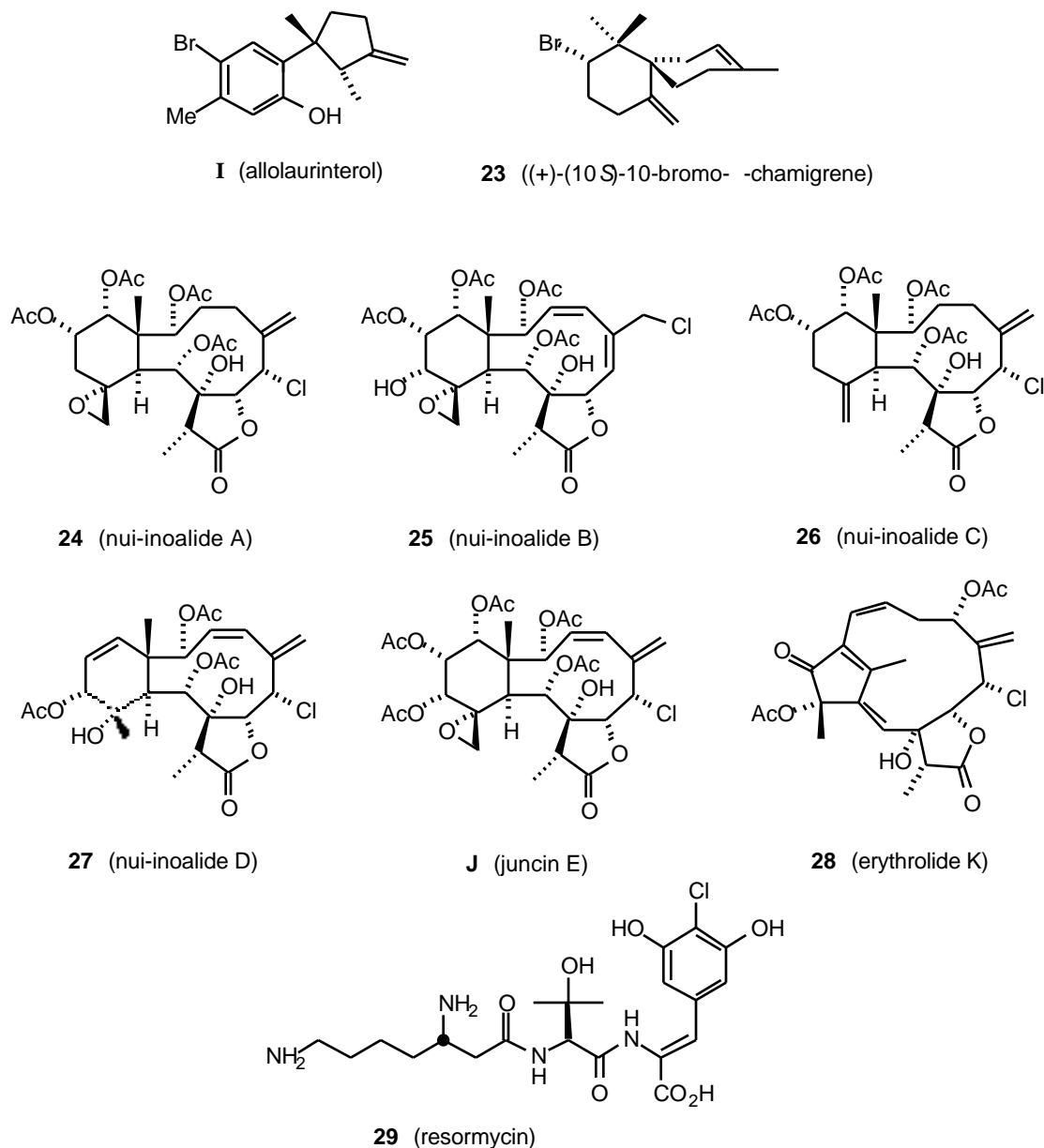
The Antarctic red alga *Plocamium cartilagineum* has afforded the new monoterpene **14** in addition to the previously known monoterpenes **F** and **G** (=epi-plocamene D), also isolated from this seaweed in the Antarctic (12). The structure of plocamenone, previously isolated from a *Plocamium* sp., has been reassigned as **H** (13). The Antarctic alga *Pantoneura plocamioides* has yielded six new halogenated monoterpenes, pantopyranoids A-C (**15-17**) and pantoisofuranoids A-C (**18-20**) (14). These novel cyclic ethers are structurally related to pantofuranoids A-F reported in *Updates #4* and isolated from the same red seaweed. The red alga *Laurencia claviformis* from Easter Island has yielded the new C₁₅ acetogenin (3*Z*)-13-epipinnatifidenyne (**21**) (15). The sea hare *Aplysia dactylomela* contains in the digestive gland the novel dietary C₁₅ bromoallene

dactylallene (**22**) (*16*). This compound, which is a diastereomer of obtusallene II previously found in the red alga *Laurencia obtusa* that is part of the diet of *Aplysia dactylomela*, is a potent ichthyotoxin and antifeedant. The absolute configuration of **22** was determined as shown.



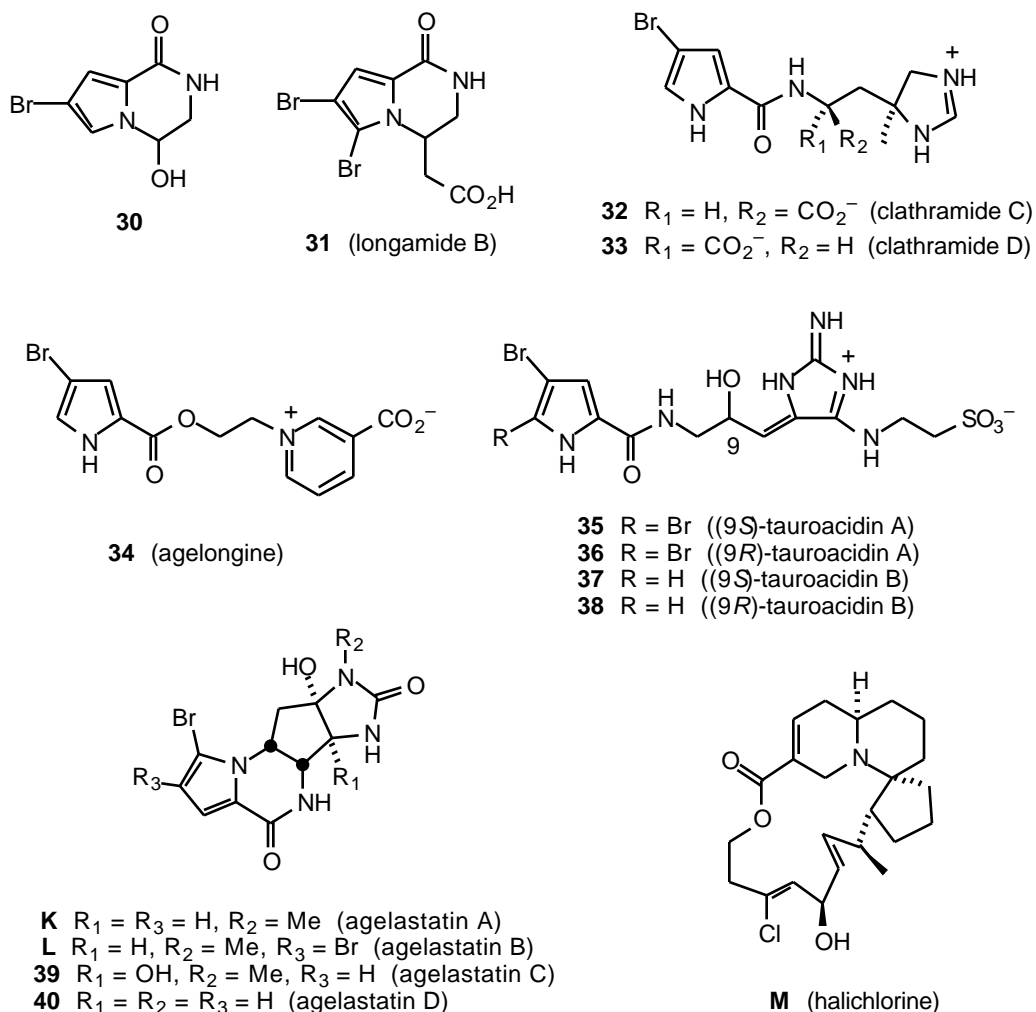
The previously known sesquiterpene allolaurinterol (**I**) has been found for the first time in *Laurencia obtusa* (*17*), and *L. rigida* has yielded the new (+)-(10*S*)-10-bromo- β -chamigrene (**23**) (absolute configuration) (*18*). Four new chlorine-containing briarane diterpenes have been isolated from Micronesian gorgonians (*19*). These are nui-inoalides A-C (**24-26**) from Pohnpei and nui-inoalide D (**27**) from Ant atoll. In addition, the known gemmacolides A, B, and D, and juncin E (**J**) were isolated. The absolute configuration of the latter compound was determined as shown. The Caribbean gorgonian octocoral *Erythropodium caribaeorum* has yielded the novel erythrolide K

(**28**), which contains the unusual bicyclo[9.2.1]tetradecane skeleton and the structure of which was confirmed by synthesis from erythrolide A and by X-ray analysis (20). The novel herbicidal and antifungal antibiotic resormycin (**29**) is produced by *Streptomyces platensis* (21).



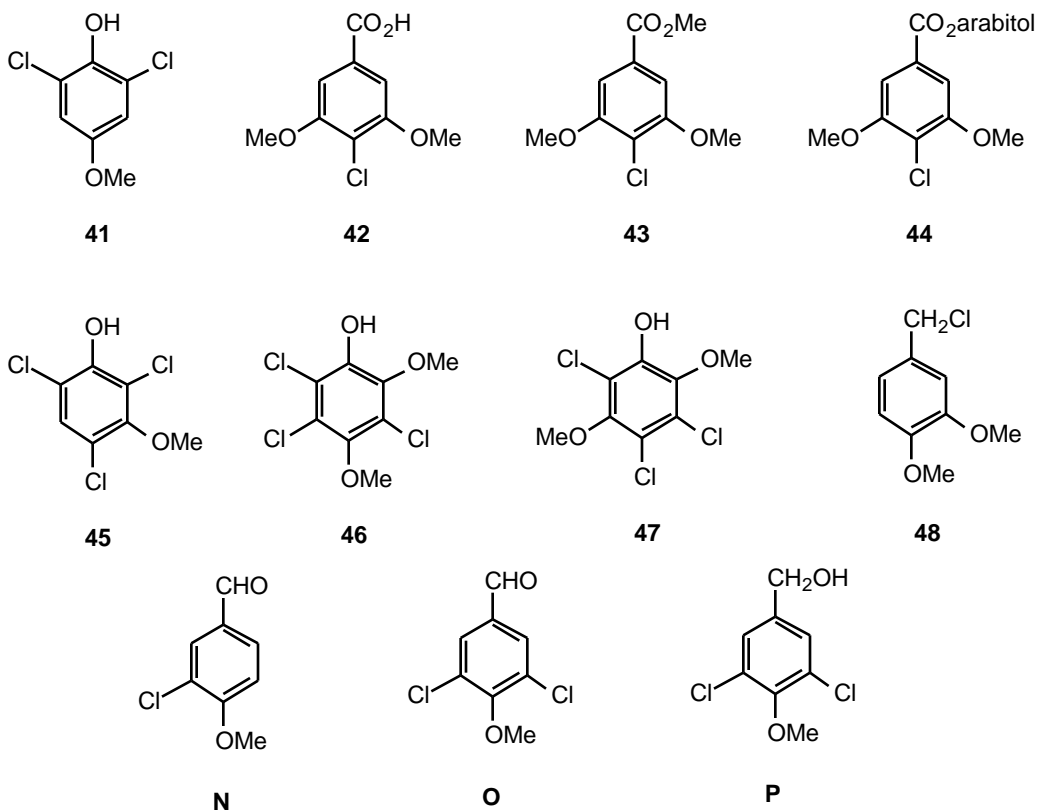
Novel bromine-containing pyrroles continue to be discovered in marine sponges. The novel 3-bromopyrrole **30** along with the previously known 2-bromoaldisin were isolated from the marine sponge *Axinella carteri* (22). Metabolite **30** is the bromo analog of longamide. The new longamide B (**31**) and clathramides C (**32**) and D (**33**), along with the known keramadine, were found in the Bahamaian sponge *Agelas dispar* (23). Agelongine (**34**), which has antiserotonergic activity, has been isolated from the sponge *Agelas longissima* (24). The Okinawan sponge

Hymeniacidon sp. has furnished the taurine-containing tauroacidins A (**35**), A' (**36**), B (**37**), and B' (**38**) (25). Since each is a mixture of two enantiomers in the ratios indicated they are counted as a total of four compounds. The previously known agelastatins A (**K**) and B (**L**) from the sponge *Agelas dendromorpha* have had their absolute configurations reversed as shown (26). Several derivatives of agelastatin A have been synthesized in a structure-activity study of the cytotoxicity of this compound (27). The sponge *Cymbastela* sp. has yielded the related new agelastatins C (**39**) and D (**40**) in addition to A and B (28). Interestingly, this study found that agelastatin A (**K**) has potent insecticidal activity against the beet army worm and the corn root worm. The absolute configuration of halichlorine, which is a potent inhibitor of the vascular cell adhesion molecule-1 (VCAM-1) and which was previously isolated from the sponge *Halichondria okadai* (Updates #4), has been determined as **M** (29).

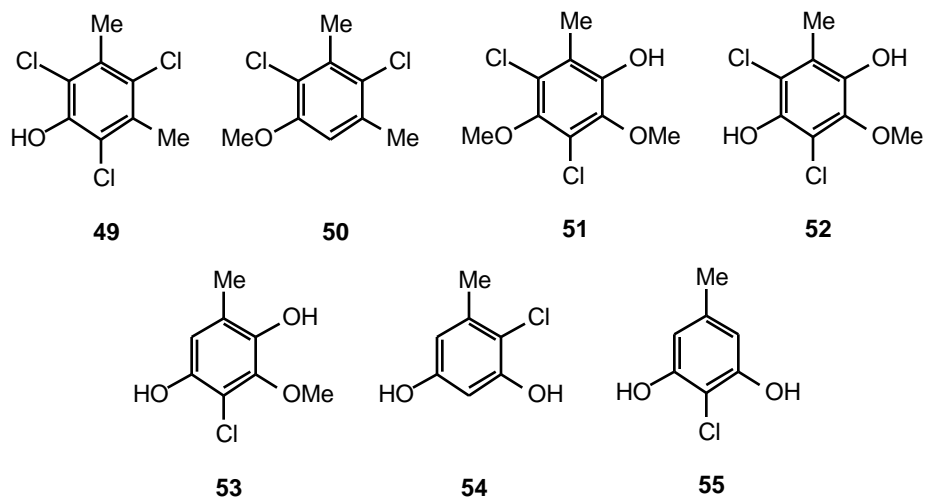


Novel chlorinated phenols continue to be isolated and characterized from fungi. The simple

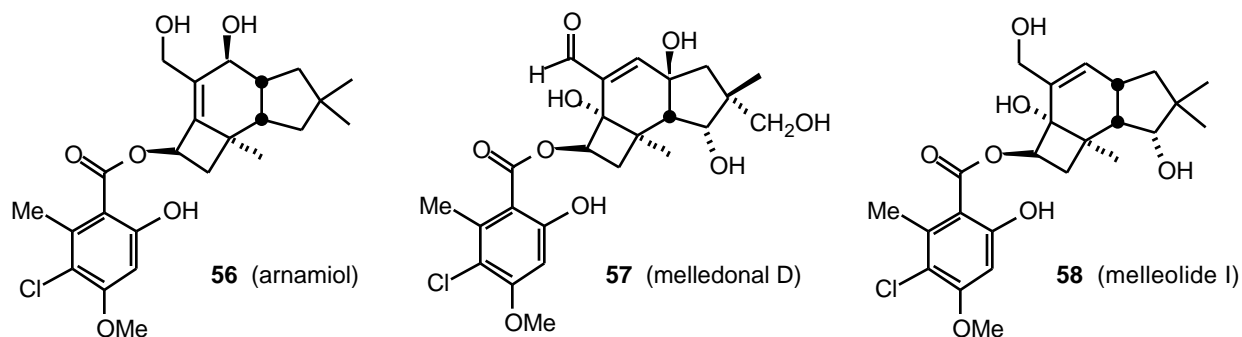
dichlorohydroquinone monomethyl ether **41** has been found in the mushroom *Russula subnigricans* (30). Cultures of the fungus *Hericium erinaceus* have produced the new 4-chloro-3,5-dimethoxybenzoic acid (**42**) and esters **43**, **44** (31), in addition to the three related compounds previously found in this fungus (*Updates #4*). The new trichloro derivatives **45-47** have been isolated from the moss inhabiting fungus *Hypholoma elongatum* (32). The white-rot fungus *Bjerkandera* sp. has yielded the first example of a naturally occurring benzyl halide, veratryl chloride (**48**) (33). The *de novo* production of this highly reactive compound (both S_N1 and S_N2 reactions are expected to be rapid) was established by feeding deuterated benzoic acid to the culture. Interestingly, benzyl chloride itself is a carcinogen. The previously known 3-chloro-*p*-anisaldehyde (**N**), 3,5-dichloro-*p*-anisaldehyde (**O**), and 3,5-dichloro-*p*-anisyl alcohol (**P**) (*Updates #1*) have now been found for the first time in these basidiomycete genera *Mycena*, *Peniophora*, *Phellinus*, and *Phylloporia*, and by these three new species *Bjerkandera fumosa*, *Hypholoma elongatum*, and *Pholiota adiposa* (34). The high production of **P** by *Hypholoma elongatum* results in the highest concentration (108 mg/L) of a chlorinated anisyl metabolite by basidiomycetes thus far reported. These dichloro compounds are known to be inhibitors of chitin synthase and seed germination.

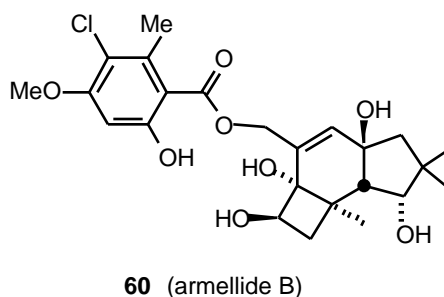
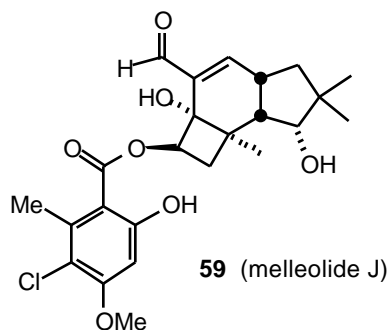


A very significant discovery is the observation that the edible lily *Lilium maximowiczii* produces seven new chlorine-containing antifungal orcinol derivatives **49-55** in direct response to attack by the pathogenic fungus *Fusarium oxysporum* (35). Chlorophenols have been found only rarely in terrestrial higher plants. This important study also demonstrated the role of chloroperoxidase in the production of **49-55** in the lily plant. Moreover, the production of hydrogen peroxide was also documented and measured.

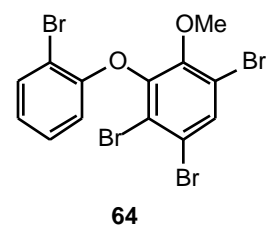
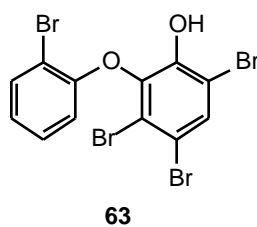
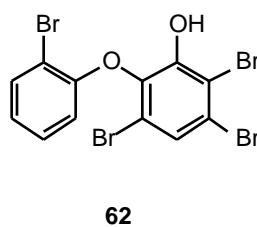
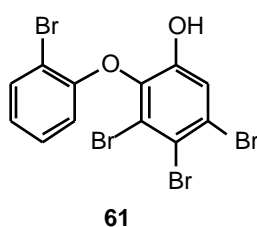


Several new sesquiterpene aryl esters from the fungus *Armillaria mellea* and related fungi have been described. Thus, arnamiol (**56**) has been found in cultures of *Armillaria mellea* (36), *A. ostoyae* (37), and *A. tabescens*, *A. monadelphae*, *A. gallica*, and *A. cepestipes* (38). Melledonal D (**57**) is produced by *Clitocybe elegans* (39), and melleolides I (**58**), J (**59**), and armellide B (**60**) were isolated from *Armillaria novae-zelandiae* (40). In these studies several previously isolated related chlorinated compounds were also found.

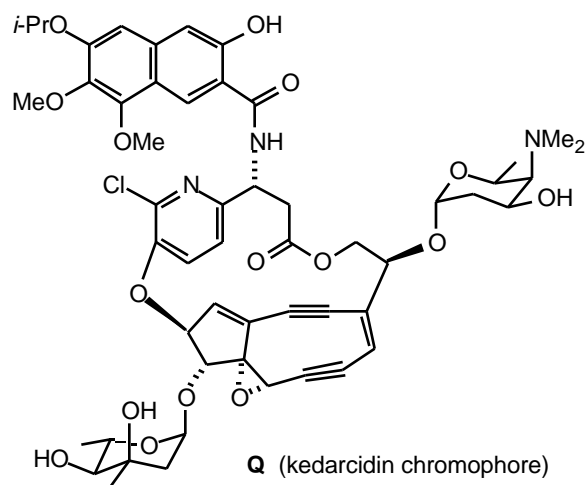




Four new polybrominated diphenyl ethers ("predioxins") **61-64** have been characterized from the sponge *Dysidea herbacea* from West Sumatra, Indonesia (41). In addition, three known brominated diphenyl ethers were also isolated in this study.

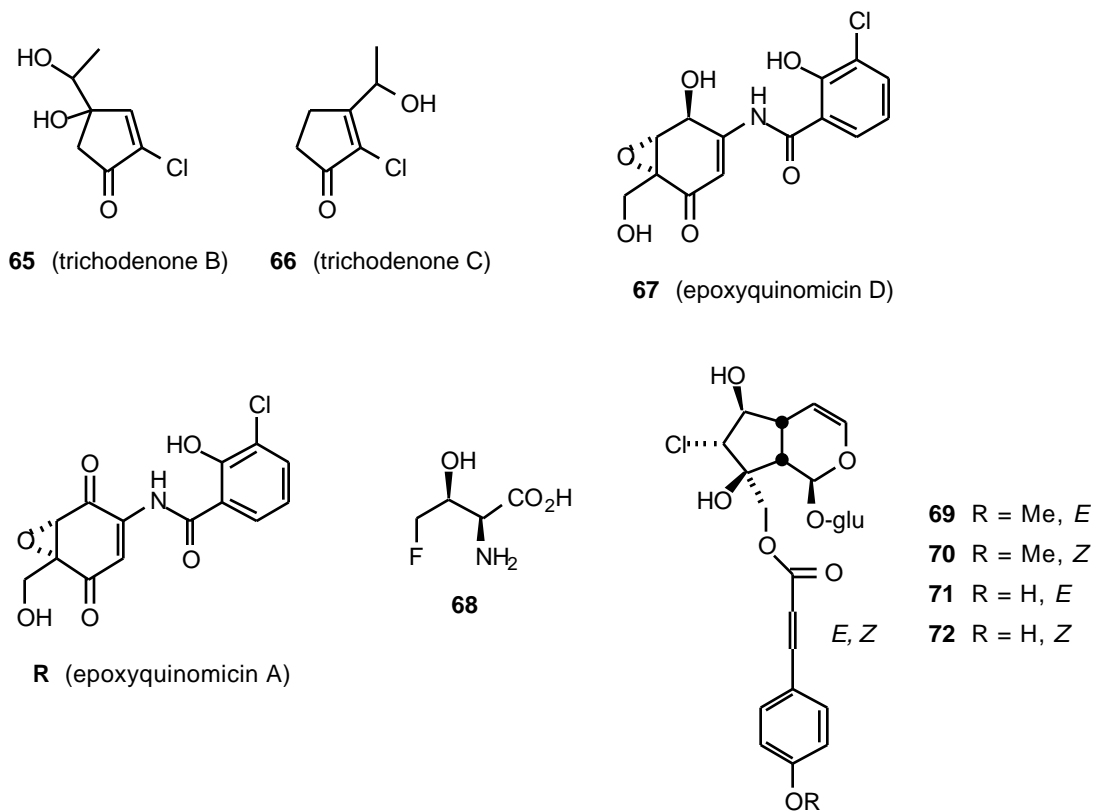


A synthetic study of the enediyne antitumor antibiotic kedarcidin has led to the revised structure **Q** (42).

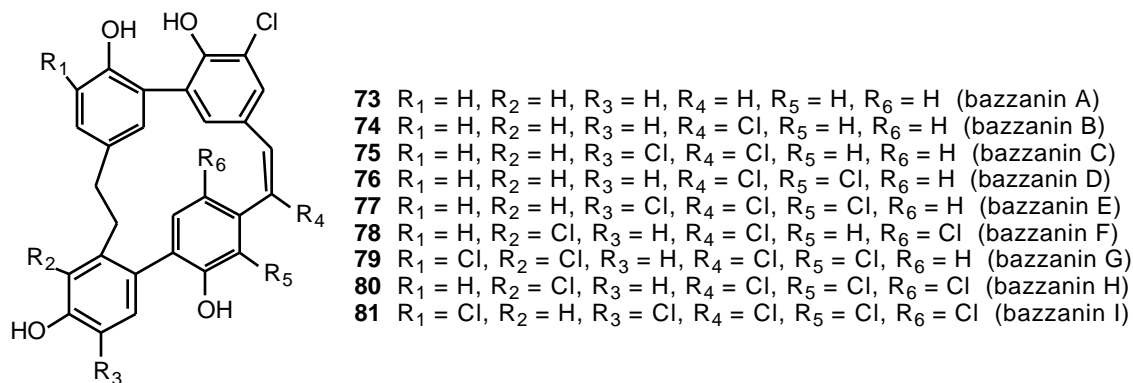


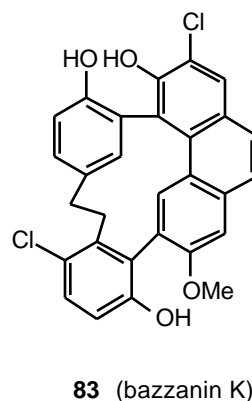
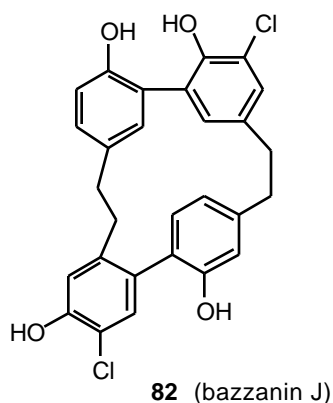
The fungus *Trichoderma harzianum*, which was found on the sponge *Halichondria okadai*, has yielded the potent cytotoxic trichodenones B (**65**) and C (**66**) (43), and *Amycolatopsis* sp. has furnished the new epoxyquinomicin D (**67**) in addition to the previously isolated A (**R**) (44). The *Streptomyces cattleya* metabolite 4-fluorothreonine (**68**), which was previously not classified as being natural by this author, is now counted as such since it is produced in cultures of this microbe containing natural levels of fluoride (45, 46). Extensive biosynthetic studies of **68** and

fluoroacetate, which is also produced by *Streptomyces cattleya*, have been reported (46). The plant *Premna subscandens* has provided the novel 10-*O*-acylated derivatives **69-72** of the previously known asystasioside E (47).

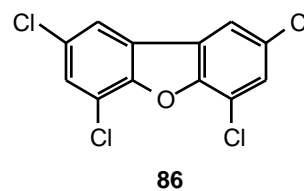
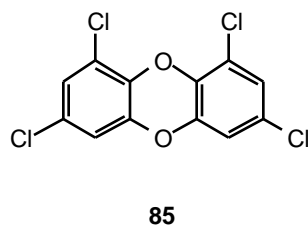
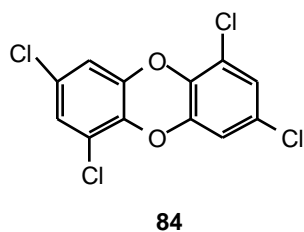


In an isolation and characterization tour de force, a research group has isolated ten chlorinated bridged biphenyls, bassanins A-J (**73-82**), and the novel, related bridged phenanthrene bassanin K (**83**) from the liverwort *Bazzania trilobata* (48).





Perhaps the most exciting and significant development since the last *Updates* is the discovery of 1,3,6,8-tetrachlorodibenzo-*p*-dioxin (**84**), 1,3,7,9-tetrachlorodibenzo-*p*-dioxin (**85**), and 2,4,6,8-tetrachlorodibenzofuran (**86**) in six different Canadian peat bogs (49). These chlorine substitution patterns are different from that of atmospheric deposition or known sources of dioxins and furans. Moreover, these authors found that the patterns are replicated with the *in vitro* oxidative coupling of 2,4-dichlorophenol and chloroperoxidase, both of which occur naturally. In addition, incorporation of added $^{36}\text{Cl}^-$ occurs in the peat. Although many other isomers were encountered in the peat, these three compounds (**84-86**) predominated and only these are counted for now as being natural. For example, the peat from one bog revealed the presence of four possible chlorodibenzofurans, nine possible dichlorobenzofurans, and six possible trichlorobenzofurans. Also identified in this study are chlorophenols, a chlorocresol, chloromethoxybenzoic acids, and chlorocinnamic acids, but exact structural characterization has not been done. Chloroform (1-2 ppm) was also detected.

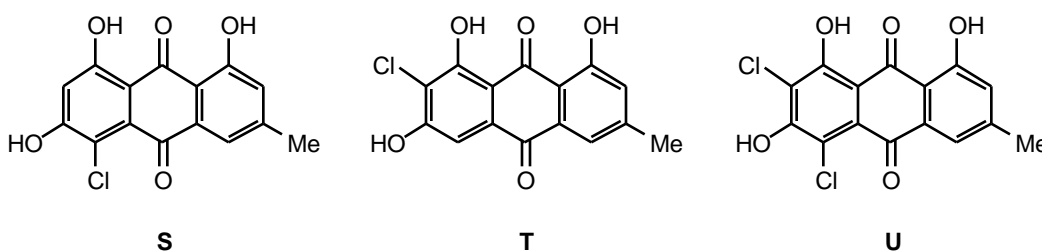


III. Biohalogenation

Several important developments have been reported since the last *Updates*.

The formation of at least two natural tetrachlorinated dioxins (**84, 85**) and at least one tetrachlorinated dibenzofuran (**86**) in peat bogs has been described (47). The biosynthesis of

chlorinated phenols **49-55** by an edible lily in response to attack by a *Fusarium* fungus is quite fantastic (35) and represents one of the few documentations of the function of naturally occurring terrestrial organochlorines, in this case acting as fungicides. The chlorination of the natural anthraquinone emodin by lichen enzymes from *Nephroma laevigatum* and commercial (fungal) chloroperoxidase (CPO) into the naturally occurring 5-chloro-(**S**), 7-chloro-(**T**), and 5,7-dichloroemodin (**U**) fungal metabolites has been observed (50). It is interesting to note that whereas the former conditions afford only 7-chloroemodin (**T**), the latter conditions give all three of these compounds (**S-U**).



The haloperoxidases continue to find utility in organic synthesis. Thus, CPO has been employed in enantioselective epoxidation to synthesize (*R*)-(-)-mevalonolactone (51), and a vanadium-containing bromoperoxidase (BPO) oxidizes sulfoxides to sulfoxides with high enantioselectivity (up to 93% ee) (52). Interestingly, CPO gives the opposite stereochemistry in the latter reaction. Reactive aldehydes, which have been implicated in promoting tissue injury at sites of inflammation, are produced by human neutrophils and the myeloperoxidase/hydrogen peroxide/chloride system (53). These reactive aldehydes include glycolaldehyde, 2-hydroxypropanal, and acrolein. Previous *Updates* have discussed the role of the MPO-H₂O₂-Cl⁻ system in the production of chlorine/hypochlorite and its apparent role in killing foreign pathogens.

IV. Other Natural Sources of Organohalogens

Further evidence has been advanced for the generation of molecular chlorine from the photolysis of ozone in the presence of sea-salt particles (54). This process may also occur in the ocean surface layer. In view of the global distribution of ozone, this chemical process may provide a general source of free chlorine, and, by further reaction with volatile organic substrates, organochlorines.

V. Biodegradation

A recent study has shown that photodegradation is an important process in the fate of dioxins and polychlorodibenzofurans on vegetation (55). The latter compounds are slightly less stable than the polychlorodibenzo-*p*-dioxins, and the higher chlorinated compounds in both series are more sensitive to photolysis in real and artificial sunlight than the lower chlorinated compounds. The authors of this study conclude that photochemical degradation of chlorine-containing dioxins and furans is a major process involved in the environmental transfer and fate of these compounds. Thus, the levels of dioxins and furans on plant surfaces may not necessarily be a good indication of the level of contamination of an area, since exposure of these compounds to sunlight, or lack thereof, must now be taken into consideration.

A new *Pseudomonas* sp. D8 strain of bacteria has been isolated that has the ability to degrade monochlorophenols, in addition to other aromatic hydrocarbons (benzene, toluene) (56). Degradation rates decrease in the order toluene > 3-chlorophenol > 4-chlorophenol > 2-chlorophenol.

A detailed study of the photodegradation of polychlorinated biphenyls (PCBs) under laboratory conditions (isopropanol, 254 nm) has revealed that photodechlorination occurs primarily in the more highly chlorinated ring, that dechlorination occurs preferentially so as to produce a symmetrical compound, and that unsymmetrical PCBs are more readily dechlorinated than symmetrical PCBs (57).

VI. Function

The mode of action of the important glycopeptide antibiotics, such as vancomycin, continues to be of intense interest (58). For example, the mode of action of the semisynthetic glycopeptide biphenylchloroeremomycin (=LY307599), which is active against vancomycin-resistant bacteria, involves dimerization and membrane anchoring, leading to an increase in biological activity over vancomycin of some 500 times.

Finally, it is of interest to make note of the recent study regarding human plasma organochlorine levels and the risk of breast cancer (59). Quite simply, the authors conclude that

their "data do not support the hypothesis that exposure to DDT and PCBs increases the risk of breast cancer." An accompanying editorial summarizes the situation regarding estrogens, breast cancer, and "chemophobia", and concludes with the statement "it is incumbent on scientists, the media, legislators, and regulators to distinguish between scientific evidence and hypothesis, and not to allow a "paparazzi science" approach to these problems" (60).

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