

## Natural Organohalogens

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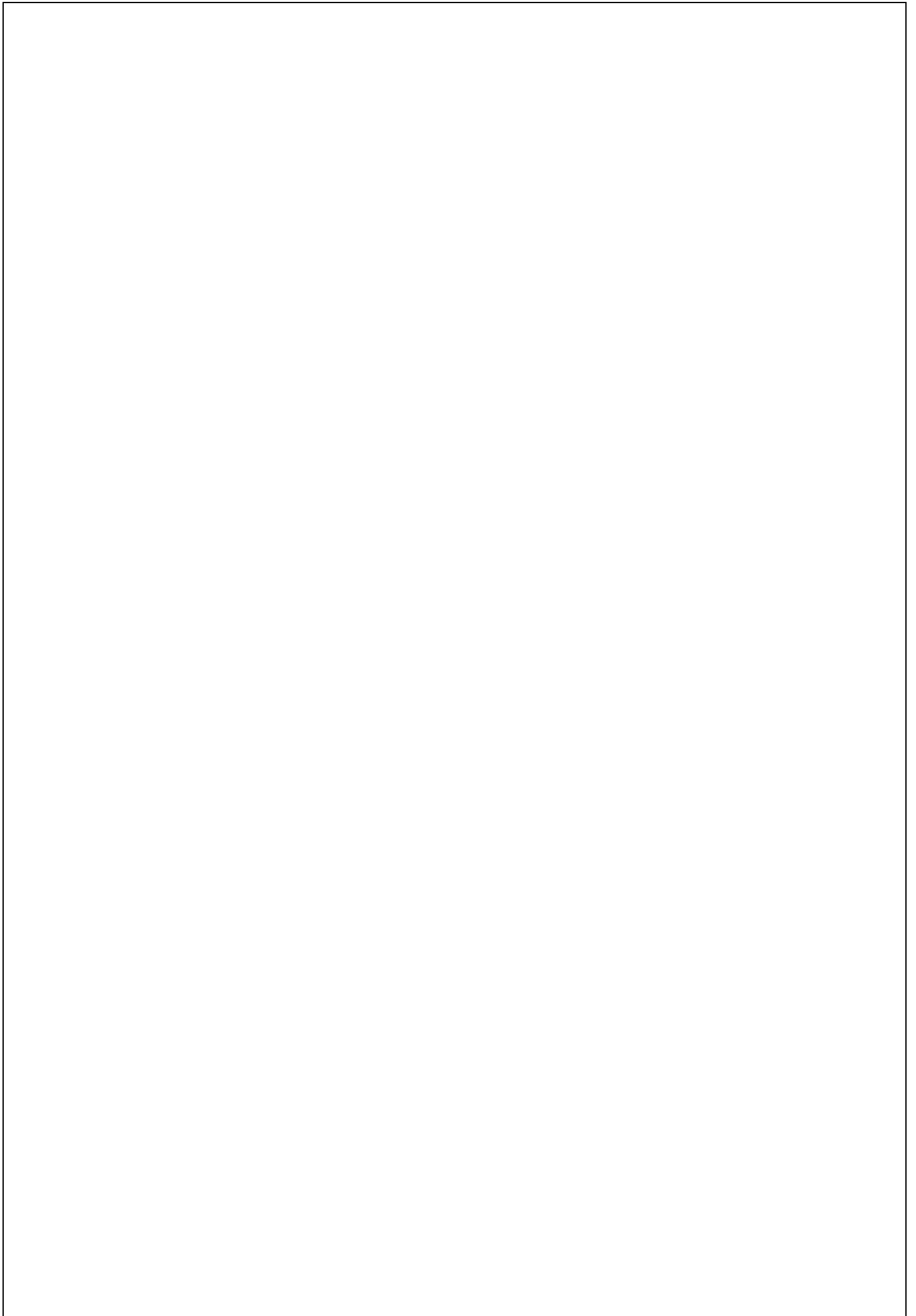
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## Foreword

The Monitoring & Environmental Chemistry Working group (MECW) is a science group of Euro Chlor, which represents the European chlor-alkali industry. The main objectives of the group are to identify both natural and anthropogenic sources of chlorinated substances, study their fate, gather information on the mechanisms of formation and degradation in the environment, and achieve a better knowledge of the persistence of such substances. The MECW often uses external specialists to assist in developing reports that review the state of existing knowledge of the different aspects mentioned.

Dr Gordon W Gribble is Professor of chemistry at Dartmouth College, Hanover, New Hampshire USA. His research interests include the synthesis and isolation of biologically active natural products, heterocyclic chemistry, synthetic methodology and environmental organic chemistry, and he has published 170 papers in these areas. For the past 25 years Professor Gribble has had a special research interest in naturally-occurring chemicals, particularly those containing chlorine and other halogens. From 1995 to 2002 he provided Euro Chlor with a series of periodic updates to the natural organohalogen literature, with a particular focus on organochlorine compounds. This dossier reviews all organohalogens that have so far been identified.

Research into the natural occurrence of organohalogens is relatively new with much attention in the past focussing on the environmental impact of anthropogenic organohalogens. *Natural Organohalogens* examines the increasing number of these substances which are being discovered at a rate of 100 to 200 per year, so far totalling more than 4,000. Whilst looking at chemicals that are new to science, Professor Gribble also shows the natural chemicals in some cases to be identical to the man-made version. A key conclusion to the study is that chlorine, along with bromine, iodine and fluorine are natural components of the biosphere and are essential for normal ecosystem functioning. Nearly all forms of life produce organohalogens with marine organisms making the greatest contribution.



## Summary

This dossier was prepared at the request of Euro Chlor and compiled from the peer reviewed and readily available scientific literature. This review has led to the following conclusions:

- Naturally occurring organochlorine, organobromine, organoiodine, and organofluorine chemical compounds are abundant on Earth, and more than 4,000 such compounds have been identified from both biogenic and abiogenic sources, being isolated at a rate of 100-200 new compounds per year.
- Although most of these compounds are new to science, a significant number are identical to man made compounds, such as methyl chloride, methyl bromide, chloroform, chlorophenols, dioxins, brominated diphenyl ethers, some CFCs, fluoroacetic acid, chlorinated acetic acids and others.
- Natural biogenic organohalogens are produced by organisms (bacteria, fungi, plants, marine organisms, higher animals) for a specific purpose usually involving the survival of the species.
- Natural abiogenic organohalogens are formed during geothermal processes from chloride, fluoride and bromide salts and organic matter.
- The quantities of some natural organohalogens greatly exceed the identical organohalogens that are produced by man.
- Like the carbon cycle, chlorine and the other halogens cycle between the ocean, atmosphere and terrestrial environments.





# 1 Introduction

Chlorine and the other halogen elements (bromine, iodine and fluorine) occur in several forms. Chloride, fluoride and bromide salts are abundant in the oceans and in the earth's crust. Both hydrogen chloride and hydrogen fluoride have been detected in interstellar space and are emitted in massive amounts by volcanoes. Synthetic organochlorines have found widespread use over the past 75 years as commercial pesticides, herbicides, drugs, plastics and other products necessary to society.

Over the past 30 years, it has become clear that nature produces organohalogens in significant numbers and, in some cases, massive quantities. Once considered to be isolation artifacts or chemical accidents of nature, the number of known natural organohalogen compounds has grown from a dozen in 1954 to more than 4,000 today. This enormous increase is both a consequence of the revitalization of natural products chemistry in the search for novel medicinal compounds and the development of new chemical isolation, separation and identification methods. Improved sample collection of previously inaccessible marine organisms includes SCUBA and remote unmanned submersible vessels. Powerful and selective bioassays allow scientists to identify biologically active compounds, and an awareness of folk medicine and ethobotany has guided chemists to new natural medicinal sources. Multidimensional nuclear magnetic resonance (NMR) and high resolution mass spectroscopy techniques, high-pressure liquid chromatography and liquid-liquid extraction allow the chemist to isolate, purify and characterize sub-milligram quantities of new natural products. A result of this exploration has been the discovery of more than 4,000 natural organohalogens. As of July 2004, the breakdown of natural organohalogens was approximately: organochlorines, 2300; organobromines, 2050; organoiodines, 110; organofluorines, 30 (Gribble, 2004). A few hundred of these compounds contain both chlorine and bromine.

Since it is obviously impractical to illustrate and discuss all known natural organohalogens, many of which have been presented in previous articles (Gribble, 1992, 1996a, 1998, 2000, 2003a, 2003b), this dossier focuses on an overview of natural organohalogens, including classic examples and recent findings, natural function and biological activity, quantities and fluxes, and a comparison of natural vs. anthropogenic organohalogens. Appendix I lists some of the most recently discovered natural organohalogens.

In addition to the references cited above, the reader is referred to several other recent review articles on various aspects of natural organohalogens (Hoekstra & De Leer, 1995; de Jong & Field, 1997; Khalil & Rasmussen, 1999; Naumann, 1999; Harper, 2000; Winterton, 2000; Dembitsky & Srebnik, 2002; Laturnus *et al.*, 2002; McCulloch, 2002; Öberg, 2002; Ballschmiter, 2003; Field & Wijnberg, 2003; Harper & Hamilton, 2003; Harper *et al.*, 2003b; Henderson & Heinecke, 2003; Jordan, 2003; McCulloch, 2003; Moore, 2003; Murphy, 2003; Neilson, 2003; Schöler & Keppler, 2003; van Pée & Unversucht, 2003; van Pée & Zehner, 2003).



## 2 Sources and Structures of Natural Organohalogens

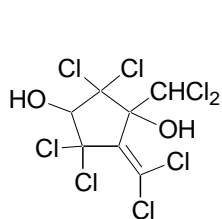
### 2.1 Biogenic Organohalogens

Since the vast number of natural organohalogen compounds cannot be covered in this *dossier*, coverage will be limited to recent examples and a few of those "classic" compounds of great biological importance. Unless otherwise indicated, cited compounds can be found in the review articles listed above.

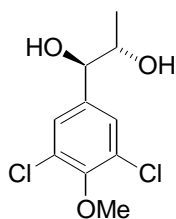
#### 2.1.1 Fungi and lichen

Fungi and lichen, the latter of which are symbionts of a fungus and an alga coexisting in a unified structure, produce an astounding array of organohalogens, from the simple chloromethane (methyl chloride) and chloroform (trichloromethane) to exceedingly complex compounds. Fungi may have evolved as much as one billion years ago and the oldest lichen fossils are 400 million years old (Pennisi, 2001). The earliest discovered biogenic organohalogen compounds are the chlorine-containing fungal metabolites griseofulvin, chloramphenicol, aureomycin, caldariomycin, sporidesmin, and ochratoxin A.

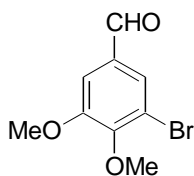
At least three fungal species (*Caldariomyces fumago*, *Mycena metata*, and *Peniophora pseudopini*) produce de novo up to 70 µg chloroform/liter of culture medium/day (Hoekstra *et al.*, 1998a). Fungi — mainly *Caldariomyces fumago* — "are important sources of elevated chloroform in soil air". Labeling experiments with <sup>37</sup>Cl- show that chloroform is produced naturally in soil top layers (Hoekstra *et al.*, 1998b). Methyl chloride is also produced by wood-rotting fungi and an estimated 160,000 tons/year is released to the atmosphere, of which 75% originates from tropical and subtropical forests and 86% of this amount is from the fungal species *Phellinus* (Watling & Harper, 1998). The fungus *Mollisia ventosa* produces four calmodulin inhibitors such as KS-504d (**1**), which contains 70% chlorine by weight, comparable to the heaviest chlorinated PCB (polychlorinated biphenyl) (Nakanishi *et al.*, 1989). The white rot fungus *Bjerkandera adusta* has furnished bjerkanoderol B (**2**), and Na<sup>37</sup>Cl in the culture medium is incorporated in **2** (Silk *et al.*, 2001). This fungus also produces 3-chloro-4-methoxybenzaldehyde, 3-chloro-4-methoxybenzyl alcohol, 3,5-dichloro-4-methoxy benzaldehyde, and 3,5-dichloro-4-benzyl alcohol (Spinnler *et al.*, 1994). These compounds are found at concentrations of 75 mg/kg of wood in the fungi and in the surrounding environment (leaves, twigs, branches, nut husks, rotting logs), but not in fresh forest litter or intact wood when fungi are not present. Indeed, rotting wood or leaf litter adjacent to the fungal fruiting bodies contains these chlorinated aromatics in "concentrations high enough to be considered hazardous according to Dutch environmental regulations concerning chlorophenols in soil (≥10 mg/kg)" (de Jong *et al.*, 1994). The white rot fungus *Hypholoma fasciculare*, which is very common in Germany and The Netherlands, produces chlorinated aromatic compounds at the rate of 0.6-3.2 mg per gram of dry fungus per day (Verhagen *et al.*, 1998), and the in vitro production of organochlorines by eight of nine white-rot fungi species has been described (Öberg *et al.*, 1997). The wood-rotting and edible fungus *Lepista nuda* produces 14 organohalogens including several brominated phenols such as **3** (Hjelm *et al.*, 1996). Another brominated metabolite, CJ-19,784 (**4**), has been isolated from the fermentation broth of the fungus *Acanthostigmella* sp. (Watanabe *et al.*, 2001). The novel chlorine-containing topoisomerase inhibitors topopyrones A (**5**) and B are produced by a *Phoma* sp. fungus (Ishiyama *et al.*, 2000), and the slime mold *Dictyostelium purpureum* has yielded AB0022A (**6**), which is the first naturally occurring chlorinated dibenzofuran to be characterized (Sawada *et al.*, 2000). Extraordinarily complex chlorinated fungal metabolites are also known, such as chlorofusin (**7**), which is a p53-MDM2 antagonist, from a *Fusarium* sp. fungus (Duncan *et al.*, 2001). And the simple chloroacetyl phosphonic acid (fosfonochlorin, ClCH<sub>2</sub>COPO<sub>3</sub>H<sub>2</sub>) is produced by four fungi (*Fusarium avenaceum*, *F. oxysporum*, *F. tricinctum*, *Talaromyces flavus*). This unusual organochlorine is an antibiotic with spheroplast-forming activity (Takeuchi *et al.*, 1989). Ectomycorrhizal fungi, which envelop plant roots and comprise as much as 15 percent of the soil organic matter, emit CH<sub>3</sub>Cl, CH<sub>3</sub>Br, and CH<sub>3</sub>I at levels of micrograms/gram of fungi (Perkins, 2001).



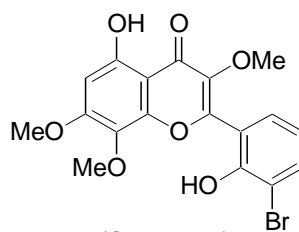
1 (KS-504d)



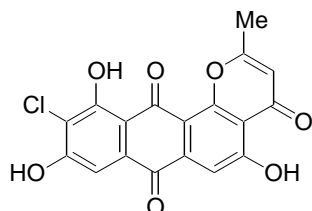
2 (bjerkanderol B)



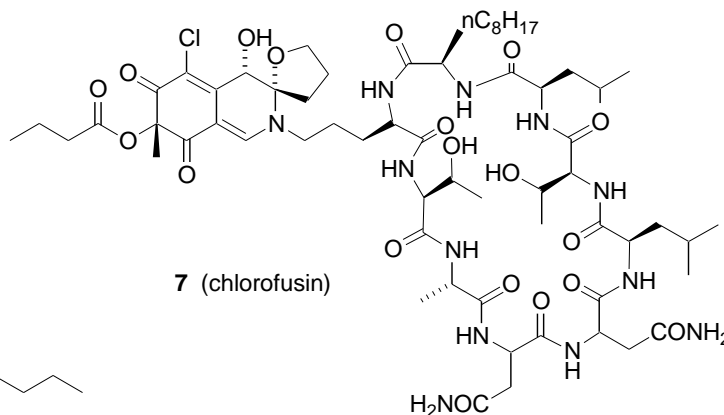
3



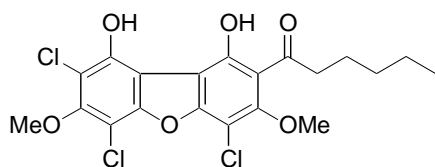
4 (CJ-19,784)



5 (topopyrone A)

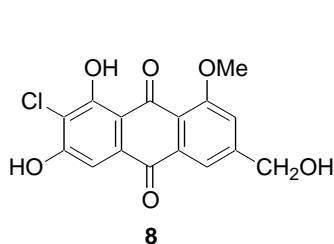


7 (chlorofusin)

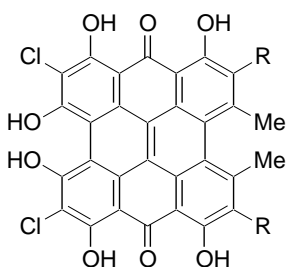


6 (AB0022A)

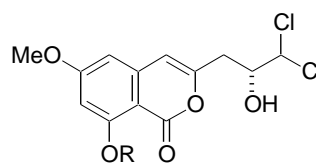
Like fungi and bacteria, lichen represent one of the earliest and most resilient forms of life. The author H.G. Wells in *The Time Machine* prophesized that in 30 million years the only remaining life forms on Earth will be lichens and liverworts. The lichen *Nephroma laevigatum* produces the novel anthraquinone **8** as well as the polycyclic metabolites **9** (Cohen & Towers, 1995). Isocoumarin **10a** is found in the lichen *Graphis* sp. growing on tree bark in the Philippines (Tanahashi *et al.*, 2000), and the related dichlorodiaportin (**10b**) is produced by the cheese mold *Penicillium malgiovense* (Larson & Breinholt, 1999). Seven novel bromine-containing fatty acids, e.g., **11**, are found in lichens growing around the Central Asian fresh water lake Issyk-Kul (Rezanka & Dembitsky, 1999, 2001). This lake has a very high salt content up to 5800 mg/liter (chloride, sulfate, and bromide salts), and only certain lichens can grow around this lake.



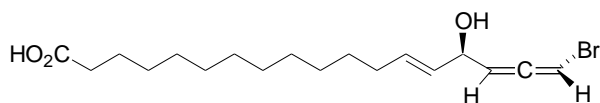
8



9a R = H  
9b R = Cl



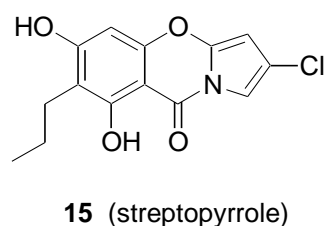
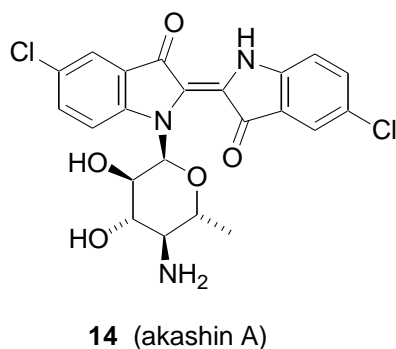
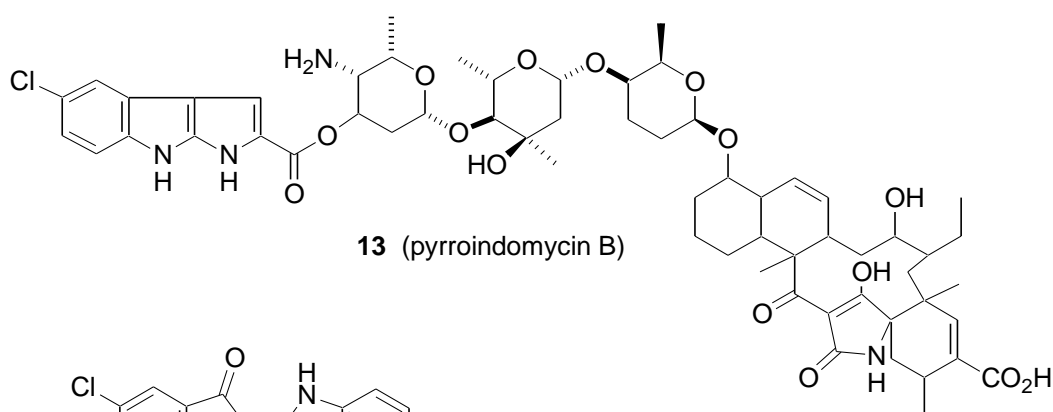
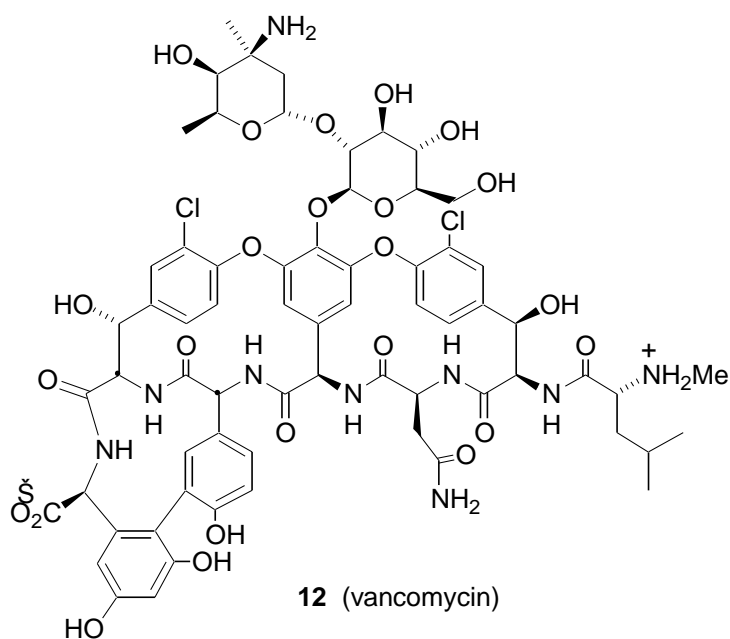
10a R = Me  
10b R = H



11

### 2.1.2 Bacteria

Despite their minuscule size relative to all other life forms, bacteria are amazing chemical factories and their metabolites often display astounding structural diversity and complexity. The fossil record reveals that bacteria date back between 3400 and 1500 million years ago (Brasier, 1979). More than 60 *Streptomyces* species produce organohalogen metabolites and *Amycolatopsis orientalis* provides the life-saving glycopeptide antibiotic vancomycin (**12**), which has been used for 50 years to treat penicillin-resistant infections (Nicolaou *et al.*, 1999; Gao, 2002). The two chlorine atoms are essential for optimal biological activity. Pyrroindomycin B (**13**), from *Streptomyces rugosporus*, is active against both penicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococci* bacteria (Ding *et al.*, 1994). Another *Streptomyces* sp. produces the novel chlorinated indigo glycoside akashin A (**14**), which possesses significant antitumor activity (Maskey *et al.*, 2002). At least seven chlorine-containing streptopyrroles, e.g., **15**, have been isolated from fermentations of *Streptomyces rimosus* (Trew *et al.*, 2000).



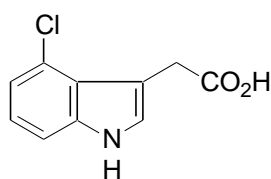
### 2.1.3 Plants

Although thousands of plant metabolites are known, including alkaloids, terpenoids, amino acids, steroids, sugars and others, relatively few contain halogen despite the ubiquitous presence of chloride in plants and wood. Nevertheless, several noteworthy organochlorines and a few other organohalogens have been isolated from plants (Engvild, 1986; Gribble, 1996a).

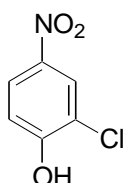
The growth hormone 4-chloroindole-3-acetic acid (**16**) and its methyl ester are produced by peas, lentil, vetch, fava bean and other Leguminosae plants (Gribble, 1998). This hormone is 100 times more potent than indole-3-acetic acid. Parsley and other plants contain the chlorine-containing saxalin, and the edible Japanese lily (*Lilium maximowiczii*) produces seven novel chlorophenol fungicides in response to attack by the pathogenic fungus *Fusarium oxysporum* at the site of infection (Monde *et al.*, 1998). The carrot truffle *Stephanospora caroticolor* affords 2-chloro-4-nitrophenol (**17**), which is a commercial fungicide, and stephanosporin (**18**) (Lang *et al.*, 2001). The liverwort *Jamesoniella colorata* contains the chlorinated bisbenzyl **19** (Hertewich *et al.*, 2003), one of several polyaromatic organochlorines isolated from liverworts (Scher *et al.*, 2003; Baek *et al.*, 2004). The aromatic Pakistanian herb *Mentha longifolia* has yielded menthone **20** (Ali *et al.*, 2002), and the Turkish folk medicine plant "Turnagagasi" (*Geranium pratense*) contains 6-chloroepicatechin (**21**) (Akdemir *et al.*, 2001). Two chlorinated dammarane triterpenoids have been isolated from the Chinese plant *Amoora yunnanensis* (Luo *et al.*, 2000).

Although organobromines are rare in terrestrial plants, a few notable examples exist. The Thai plant *Arundo donax* contains the natural weevil repellent **22** (Miles *et al.*, 1993), joining nicotine, pyrethrins, rotenone, and cocaine as natural repellents/insecticides.

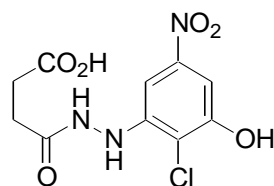
Bromobenzene is present in oakmoss and methyl bromide, a commercial fumigant and nematocide, is produced by broccoli, cabbage, radish, turnip, mustard, pak-choi, and rapeseed, at rates of 18-36 ng/g plant material per day. The global annual production of methyl bromide by rapeseed and cabbage is estimated to be 6600 and 400 tons, respectively. The authors of this study conclude that "Given the ubiquitous distribution of bromide in soil, methyl bromide production by terrestrial higher plants is likely a large source for atmospheric methyl bromide" (Gan *et al.*, 1998). Chloromethane has several terrestrial plant sources, including evergreen trees, the ice plant, and potato tubers (Harper, 2000). Chloromethane from potato tubers (61 cultivars) is produced at rates of 4-650 ng/g fresh wt/day (Harper *et al.*, 1999). The California shrubland plants, *Brassica juncea* (wild mustard), *Carpobrotus edulis* (sea fig or ice plant), and *Larrea tridentata* (creosote bush), produce both CH<sub>3</sub>Cl and CH<sub>3</sub>Br (Rhew *et al.*, 2001). Tropical plants (Yokouchi *et al.*, 2000, 2002) and ferns (Harper *et al.*, 2003a) are important CH<sub>3</sub>Cl producers. One of the most toxic organohalogens is the notorious fluoroacetic acid (**23**), which, along with equally toxic long chain ω-fluorocarboxylic acids (16-fluoropalmitoleic acid, 18-fluorostearic acid, 18-fluorolinoleic acid, 20-fluoroarachidic acid, 20-fluoroeicosenoic acid, and probably 18-fluoro-9,10-epoxystearic acid (Hamilton & Harper, 1997; Christie *et al.*, 1998), are produced by several plants indigenous to West Africa, Australia, and other countries (Hall, 1972; Gribble, 1973; Grobbelaar & Meyer, 1989; O'Hagan & Harper, 1999; Harper *et al.*, 2003b). Over many years the shrub *Dichapetalum toxicarium*, rich in these organofluorines, has killed thousands of livestock in Africa and Australia (Annisson *et al.*, 1960; McCosker, 1989). The 50% lethal dose in sheep is only 0.3 mg/kg body weight. Not surprising, fluoroacetic acid was also widely used as a pesticide, "1080", in the Western United States to kill rodents and coyotes, and the equally poisonous methyl fluoroacetate was once considered for use as a chemical warfare water poison (Gribble, 1973). Genetically modified bacteria with a gene encoding fluoroacetate dehalogenase have a protective effect for sheep from fluoroacetate poisoning (Gregg *et al.*, 1998).



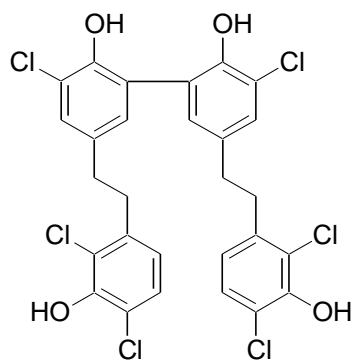
**16** (4-Cl-IAA)



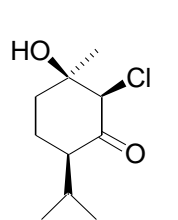
**17**



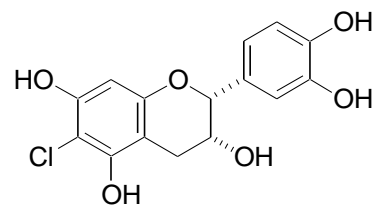
**18** (stephanosporin)



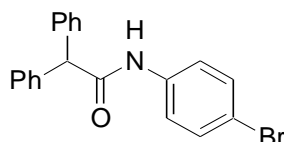
19



20 (longifone)



21 (6-chloroepicatechin)



22

FCH<sub>2</sub>CO<sub>2</sub>H

23

#### 2.1.4 Marine Organisms

Given the abundance of chloride and bromide in the oceans, it is not surprising that most natural organohalogens are of marine origin. Moreover, nearly *all* of the 2,000 natural organobromines are produced by marine organisms. Although chloride is more abundant than bromide in the oceans, marine organisms utilize (oxidize) more bromide than chloride for incorporation into organic compounds. This may reflect the wealth of bromoperoxidase (BPO) relative to chloroperoxidase (CPO) in marine life, and chloride cannot be oxidized to active chlorine by BPO (Section 3.1) (Gribble, 1996a, 1998). Nevertheless, a large number of marine organisms contain both bromine and chlorine (Gribble, 1996a). Interestingly, whereas the oceans contain only 65 mg/liter of bromide and rivers 0.005-0.15 mg/liter of bromide, the Dead Sea contains 4000 mg/liter bromide! (Song & Müller, 1993). Since coral reefs originated some 500 million years ago, the associated marine organisms have had a long time to evolve their metabolites.

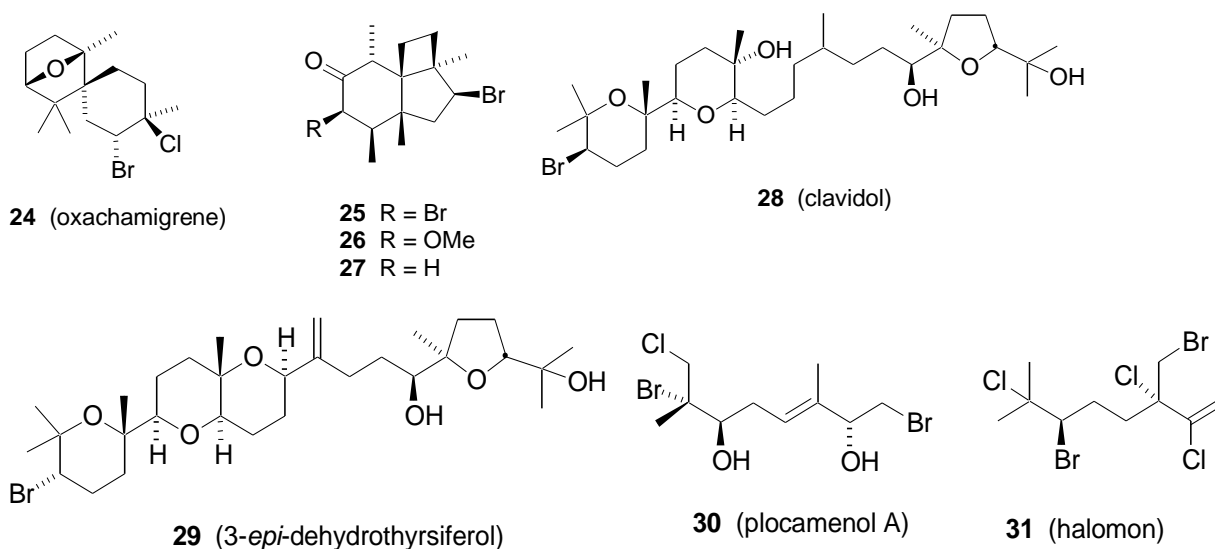
##### 2.1.4.a Plants

The vast array and incredible diversity of organohalogens from marine plants, both macro (seaweeds) and micro (phytoplankton), are truly amazing. Such compounds perhaps represent 20-25% of all known natural organohalogens. These compounds seem to serve in a chemical defensive role — antibacterials, antifeedants, antifouling agents, and repellents.

A myriad of halomethanes are produced by marine algae: CH<sub>3</sub>Cl, CH<sub>3</sub>Br, CH<sub>3</sub>I, CH<sub>2</sub>Cl<sub>2</sub>, CH<sub>2</sub>Br<sub>2</sub>, CH<sub>2</sub>I<sub>2</sub>, CHCl<sub>3</sub>, CHBr<sub>3</sub>, CHI<sub>3</sub>, CCl<sub>4</sub>, CBr<sub>4</sub>, CH<sub>2</sub>ClBr, CH<sub>2</sub>ClI, CH<sub>2</sub>BrI, CHBr<sub>2</sub>Cl, CHBrI<sub>2</sub>, CHBrClI, CHBr<sub>2</sub>I, and CHBrCl<sub>2</sub> (Gribble, 1996a; Carpenter *et al.*, 1999; Abrahamsson *et al.*, 2003). A study of 22 different species of Arctic red, brown, and green macroalgae found that all species release CHBr<sub>3</sub> in relatively large quantities, in addition to six other haloalkanes (Laturnus, 1996). Seaweeds also contain larger haloalkanes: CH<sub>3</sub>CH<sub>2</sub>Br, CH<sub>3</sub>CH<sub>2</sub>I, CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>I, CH<sub>3</sub>(CH<sub>2</sub>)<sub>3</sub>I, CH<sub>3</sub>(CH<sub>2</sub>)<sub>4</sub>Br, CH<sub>3</sub>(CH<sub>2</sub>)<sub>4</sub>I, (CH<sub>3</sub>)<sub>2</sub>CHI, CH<sub>3</sub>CH<sub>2</sub>CH(CH<sub>3</sub>)I, (CH<sub>3</sub>)<sub>2</sub>CHCH<sub>2</sub>I, BrCH<sub>2</sub>CH<sub>2</sub>Br, and ClCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>I. The latter compound is also a commercial fumigant. Laboratory cultures of marine phytoplankton yield CH<sub>3</sub>Cl, CH<sub>3</sub>Br, and CH<sub>3</sub>I (Scarratt & Moore, 1996), and (CH<sub>3</sub>)<sub>2</sub>CHCH<sub>2</sub>I has been detected in the volatile emissions of 29 macroalgae species (Laturnus, 2001; Giese *et al.*, 2001). The batch culture production of CHBr<sub>3</sub>, CHBr<sub>2</sub>Cl, CHBrCl<sub>2</sub>, CHCl<sub>3</sub>, ClCH=CCl<sub>2</sub>, CH<sub>2</sub>Br<sub>2</sub>, CH<sub>2</sub>I<sub>2</sub>, CH<sub>2</sub>ClI, CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>I, and CH<sub>3</sub>I by the red alga *Meristiella gelidium* requires both hydrogen peroxide and peroxidase (Collén *et al.*, 1994; Tokarczyk & Moore, 1994). The distinctive "smell of the ocean" is probably due in part to these volatile organohalogens. The favorite edible seaweed of native Hawaiians is "limu kohu" (*Asparagopsis taxiformis*), which is prized for its rich aroma and flavor. This alga contains nearly 100 organohalogens, most of which were previously unknown compounds. The major component is bromoform. Coastal salt marshes emit large quantities of CH<sub>3</sub>Cl and CH<sub>3</sub>Br, perhaps as much as 10 percent of

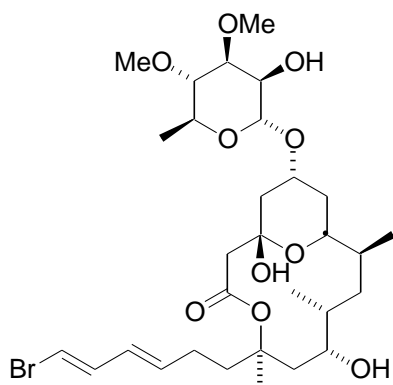
the total fluxes of these atmospheric gases; "salt marshes may constitute the largest natural terrestrial source of methyl bromide, and possibly of methyl chloride identified thus far" (Rhew *et al.*, 2000). Tropical coastal areas are also a strong source of methyl chloride (Yokouchi *et al.*, 2000).

At least 40 species of the red alga *Laurencia* have yielded organohalogen metabolites, typically terpenoids and C<sub>15</sub>-acetogenins. The prolific *Laurencia obtusa* has yielded oxachamigrene (**24**) (Brito *et al.*, 2002) and the novel sesquiterpenoids **25-27** (Iliopoulou *et al.*, 2002), and *Laurencia viridis* has furnished the squalene-derived polyethers clavidosol (**28**) and 3-*epi*-dehydrothysiferol (**29**) (Souto *et al.*, 2002). Numerous polyhalogenated linear monoterpenes have been isolated from red seaweeds, such as plocamenol A (**30**) from *Plocamium cartilagineum* collected in Chile (Díaz-Marrero *et al.*, 2002), and halomon (**31**) from *Portieria hornemannii*, which displays potent and highly differential cytotoxicity against human tumor cell lines (Fuller *et al.*, 1992). The simple tribromoacetamide is found in the Okinawan alga *Wrangelia* sp. and has activity against human leukemia P388 cells (Kigoshi *et al.*, 2004).

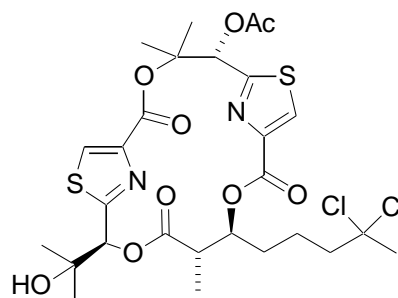


Blue-green algae (cyanobacteria) are the source of many halogenated metabolites, many of which have powerful biological activity (Namikoshi & Rinehart, 1996; Burja *et al.*, 2001; Gerwick *et al.*, 2001). It might be noted that some cyanobacteria, when they bloom in drinking water, are highly toxic, but the causative agents (anatoxin, saxitoxin, microcystin, and other cyclic heptapeptides) associated with these toxic algal blooms do not contain halogen. Cyanobacteria are perhaps 500-1000 million years older than previously believed (Brasier, 1979; Brocks *et al.*, 1999), and one might reasonably speculate that cyanobacterial organochlorines have been on Earth for this period of time. *Nostoc* blue-green alga microfossils are present in Precambrian rocks (1000 million years old) and some are morphologically indistinguishable from present day *Oscillatoria* cyanobacteria (Fox & Dose, 1977). The widespread *Lyngbya majuscula* is exceptionally prolific in this regard and some recent examples are lyngbyaloside B (**32**) (Luesch *et al.*, 2002) and hectochlorin (**33**) (Marquez *et al.*, 2002). The potent anticancer drug candidate cryptophycin 1 (**34**) was isolated along with about 30 other chlorinated analogues from a blue-green *Nostoc* sp. (Trimurtulu *et al.*, 1994; Golakoti *et al.*, 1995; Subbaraji *et al.*, 1997; Eggen & Georg, 2002). Removal of the chlorine atom from **34** results in a ten-fold decrease in activity. Cryptophycin 1 is the most potent suppressor of microtubule dynamics yet described (Panda *et al.*, 1997). The HIV reverse transcriptase inhibitor ambigol A (**35**) is found in *Fischerella ambigua* (Falch *et al.*, 1993).

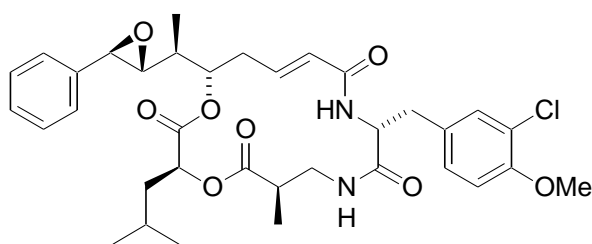




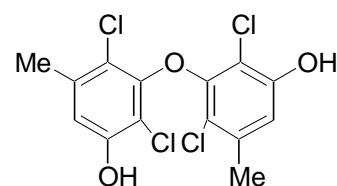
**32** (lyngbyaloside B)



**33** (hectochlorin)



**34** (cryptophycin 1)

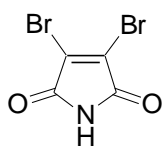


**35** (ambigol A)

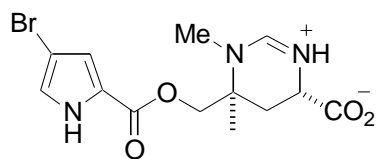
#### 2.1.4.b Sponges

Of the estimated 10,000 sponge species, which first appeared in the fossil record about 650 million years ago, the relatively small number that have been examined for their chemical content produce a mind-boggling collection of organohalogens (Gribble, 1996a, 1999). Their function is presumably to resist feeding by fish and fouling by barnacles, bacteria, and fungi. For some sponge metabolites, it is evident that bacteria or microalgae associated with the host sponge actually biosynthesize these compounds (Faulkner *et al.*, 1993, 2000). Perhaps due to their enormous reactivity towards electrophilic halogenation reactions, pyrroles, indoles, phenols, and tyrosines are commonly found to be halogenated in sponges. Pyrroles 36 and 37 are produced by the sponge *Axinella brevistyla* (Tsukamoto *et al.*, 2001), and the unusual sulfate-sulfamate indole ancorinolates A (38) and C (39) were isolated from *Ancorina* sp. (Meragelman *et al.*, 2002). The Caribbean sponge *Plakortis simplex* has yielded the first examples of iodinated indoles, plakohypaphorines A-C (40-42) (Campagnuolo *et al.*, 2003). An Okinawan sponge contains the bromotyrosine nakirodin A (43) (Tsuda *et al.*, 2002), and the dimeric caissarine B (44) was isolated from the Brazilian sponge *Aplysina caissara* (Saeki *et al.*, 2002). The macrocyclic bastadin 21 (45) was characterized from the sponge *Ianthella quadrangulata* from the Great Barrier Reef (Coll *et al.*, 2002). Given the very large number of known marine brominated diphenyl ethers (Liu *et al.*, 2004), it was only a matter of time before a natural brominated dibenzo-p-dioxin was found. Indeed, the sponge *Dysidea dendyi* has yielded six polybrominated dioxins, e.g., spongiadioxin C (46), the first examples of natural dioxins to be isolated from a living organism (Utkina *et al.*, 2002). These dioxins are potent inhibitors of cell division of fertilized sea urchin eggs and may play a defensive role for this sponge. Two other studies have found brominated dioxins in sponges. The numerous brominated diphenyl ethers found in sponges (Gribble, 1996a) bioaccumulate in large marine mammals (dolphins, seals, dugongs, whales) and the Green turtle. The highest measured concentration was 3.8 mg/kg of 4,6-dibromo-2-(2',4'-dibromo)phenoxyanisole ("BC-2") found in a pygmy sperm whale (Vetter *et al.*, 2002). This *Dysidea* sponge metabolite is found in the blubber of marine mammals from Africa and the Antarctic, suggesting a widespread distribution. The quantities of BC-2 found in marine mammals are higher than that of any anthropogenic contaminant investigated, including brominated flame retardants, PCBs, DDT, other chlorinated pesticides and their metabolites (Vetter *et al.*, 2002). Of the sponge metabolites that contain halogen, most are brominated, but a few contain chlorine and, recently, the sponge *Phakellia fusca* has yielded five 5-fluorouracil compounds, e.g., 47 (Xu *et al.*, 2003c). Interestingly, 5-fluorouracil is also a synthetic anticancer drug of enormous utility.

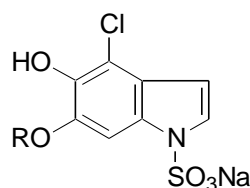
This is the first report of any natural organofluorines from a marine source. An example of sponge organochlorines is provided by the Indonesian *Theonella* cf. *Swinhoei*, which affords four chlorinated polyketides, e.g., bitungolide A (**48**) (Sirirath *et al.*, 2002).



**36**

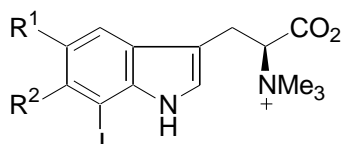


**37**



**38** R = SO<sub>3</sub>Na (ancorinolate A)

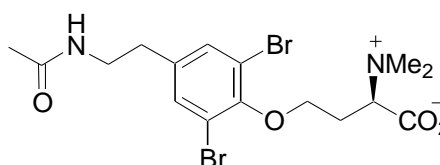
**39** R = H (ancorinolate C)



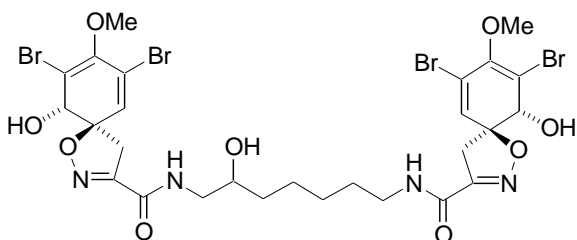
**40** R<sup>1</sup> = R<sup>2</sup> = H (plakohypaphorine A)

**41** R<sup>1</sup> = H, R<sup>2</sup> = I (plakohypaphorine B)

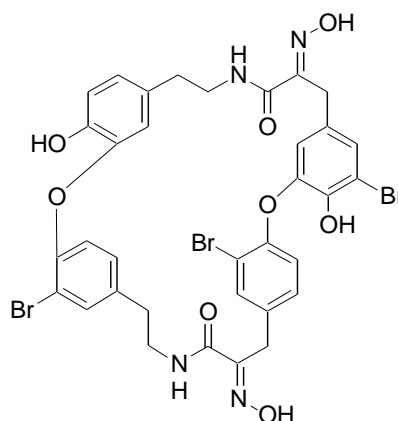
**42** R<sup>1</sup> = I, R<sup>2</sup> = H (plakohypaphorine C)



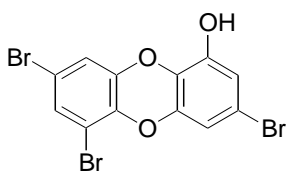
**43** (nakirodin A)



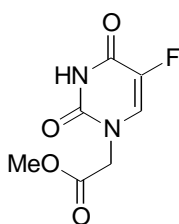
**44** (caissarine B)



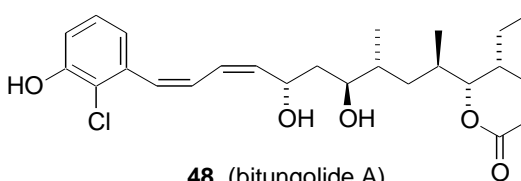
**45** (bastadin 21)



**46** (spongiadioxin C)



**47**



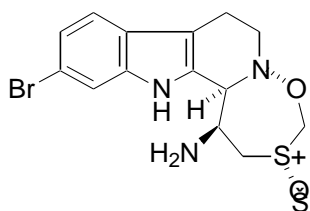
**48** (bitungolide A)

#### 2.1.4.c Other marine animals

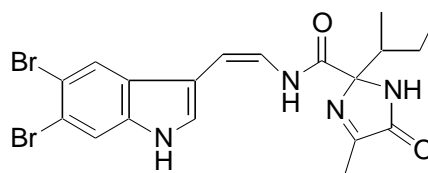
The shell-less marine animals such as ascidians (tunicates or sea squirts), nudibranchs (sea slugs), soft corals (gorgonians), bryozoans (moss animals), sea hares, and acorn worms all produce a dazzling array of metabolites.

The filter feeding ascidians may be solitary or colonial in habitat and are closer than sponges to humans on the evolution scale (Lewis, 2002; Kaiser, 2002; Dehal *et al.*, 2002). The New Zealand *Ritterella signillinoides* contains several brominated carbolines such as eudistomin K sulfoxide (**49**), which is active against both *Polio* and *Herpes simplex* viruses (Larsen *et al.*, 1994). From another New Zealand ascidian, *Pycnoclavella kottae*, has been

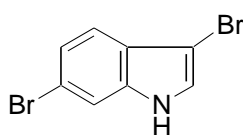
isolated four brominated kottamides such as **50**, which display antiinflammatory, antimetabolic, and antitumor activity (Appleton *et al.*, 2002b; Appleton & Copp, 2003). The Palauan *Distaplia regina* has yielded the novel 3,6-dibromoindole (**51**) (Qureshi & Faulkner, 1999), and a Far Eastern *Eudistoma* sp. contains pibocin B (**52**) (Makarieva *et al.*, 2001). The common edible oyster (*Crassostrea virginica*) contains several as yet unidentified di- and tribromoindoles (Maruya, 2003).



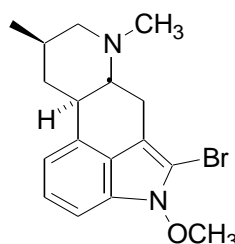
**49** (eudistomin K sulfoxide)



**50** (kottamide D)

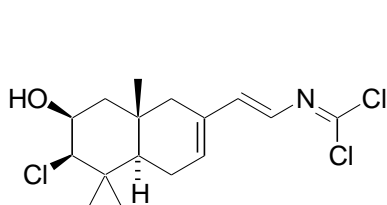


**51**

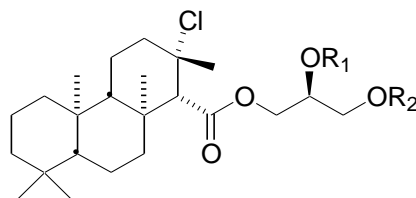


**52** (pibocin B)

The brightly colored nudibranchs, which are the largest and most varied species of opisthobranch molluscs (Gavagnin & Fontana, 2000), apparently "steal" their chemical arsenal by feeding on sponges, tunicates, or even other nudibranchs — giving new meaning to the phrase "lazy slug"! However, at least one nudibranch, *Doriopsilla areolata*, biosynthesizes terpenoid metabolites, although these particular compounds are not halogenated (Gavagnin *et al.*, 2001). The Okinawan *Reticulidia fungia* contains four novel cytotoxic carbonimidic dichlorides, e.g., **53** (Tanaka & Higa, 1999), and the Mediterranean *Doris verrucosa* has yielded nine new isocopalane diterpenes, two of which contain chlorine, e.g., verrucosins 7 (**54**) and 8 (**55**) (Gavagnin *et al.*, 1997).



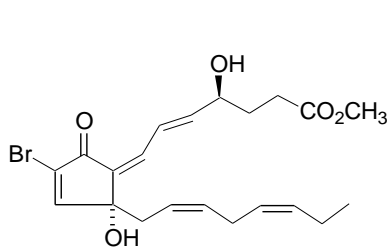
**53** (reticulidin B)



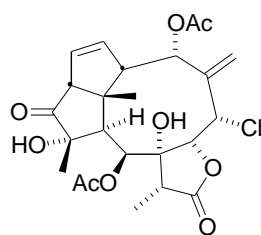
**54** R<sub>1</sub> = H, R<sub>2</sub> = Ac (verrucosin-7)

**55** R<sub>1</sub> = Ac, R<sub>2</sub> = H (verrucosin-9)

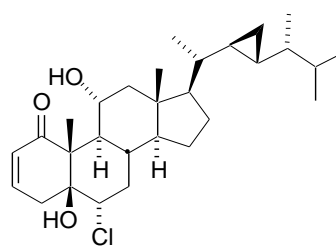
While some hard (stony) corals afford halogenated compounds, soft corals (gorgonians and octocorals) provide most examples of these compounds. For example, briarane diterpenes, many of which contain chlorine, are ubiquitous metabolites of gorgonians (Sung *et al.*, 2002, 2003, 2004; Anjaneyulu *et al.*, 2003; Shen *et al.*, 2003; Tagliatela-Scafati *et al.*, 2003). Several Red Sea soft corals contain eight novel brominated oxylipins, e.g., **56** (Rezanka & Dembitsky, 2003a), related to mammalian prostaglandins, and the Caribbean gorgonian *Erythropodium caribaeorum* has yielded aquariolide A (**57**), which shows modest activity against the MCF-7 human breast cancer cell line (Tagliatela-Scafati *et al.*, 2002). Although halogenated steroids are exceedingly rare, the Okinawan soft coral *Clavularia viridis* produces three chlorinated sterols, e.g., yonarasterol I (**58**) (Iwashima *et al.*, 2001).



56

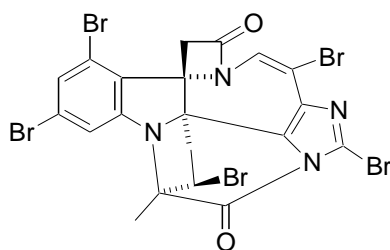


57 (aquariolide A)

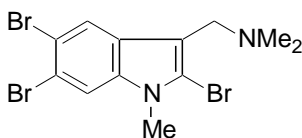


58 (yonarasterol I)

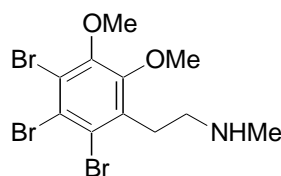
Although bryozoans may appear as nondescript clumps of ocean moss, these amazing creatures produce some of the most unique and structurally complex organohalogenes yet to be identified. Indeed, the maestro of organic synthesis in the phylum Bryozoa is clearly *Chartella papyracea*, which synthesizes an array of stunningly intricate metabolites such as chartellamide B (**59**) (Anthoni *et al.*, 1987). The bryozoan *Zoobotryon pellucidum* produces indole **60**, which is a potent inhibitor of larval settlement by the infamous ship-fouling barnacle *Balanus amphitrite* (Kon-ya *et al.*, 1994a), and convolutamine H (**61**) from *Amathia convoluta* is a powerful nematocide against *Haemonchus contortus*, a parasitic nematode of sheep and other ruminants (Narkowicz *et al.*, 2002).



59 (chartellamide B)

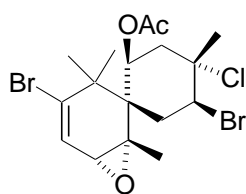


60

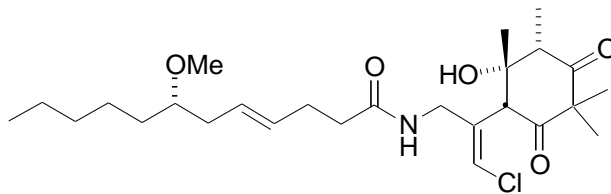


61 (convolutamine H)

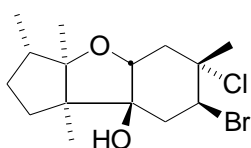
Like their smaller nudibranch cousins, sea hares apparently acquire their chemical defensive agents through their diet of seaweeds and sponges. Thus, in several cases the sea hare isolates are identical to those metabolites isolated from algae. For example, the new chamigrene **62** is found in both the sea hare *Aplysia parvula* and its diet of the red alga *Laurencia filiformis* (Jongaramruong *et al.*, 2002). The New Zealand sea hare *Bursatella leachii* contains malyngamide S (**63**), which exhibits cytotoxicity and antiinflammatory properties (Appleton *et al.*, 2002a). This compound probably originates from a blue-green alga. The ubiquitous *Aplysia dactylomela*, from South African waters, has furnished four new halogenated sesquiterpenes, e.g., ibhayinol (**64**) (McPhail *et al.*, 1999) and another collection of this animal yielded aplydactone (**65**) (Fedorov *et al.*, 2001). The promiscuous feeding sea hare *Aplysia punctata* has afforded 23 compounds including four new halogenated terpenes (Findlay & Li, 2002), all of which are presumably diet derived.



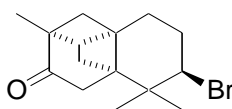
62



63 (malyngamide S)

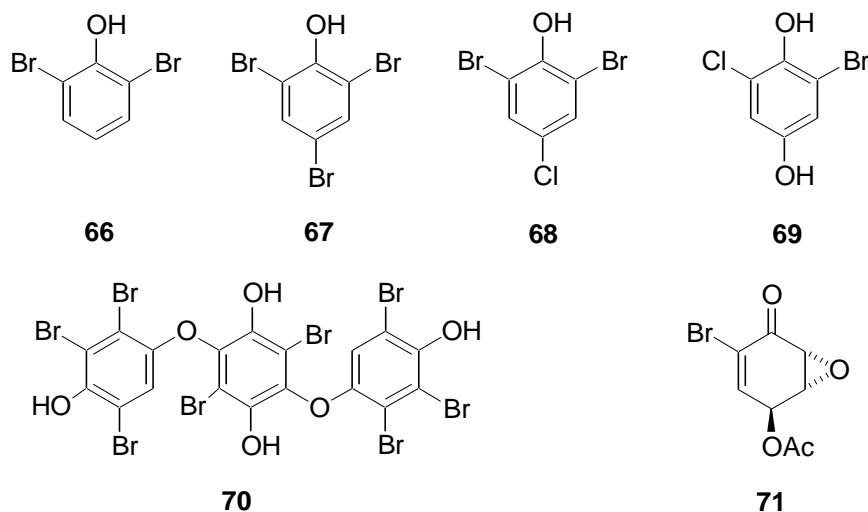


64 (ibhayinol)

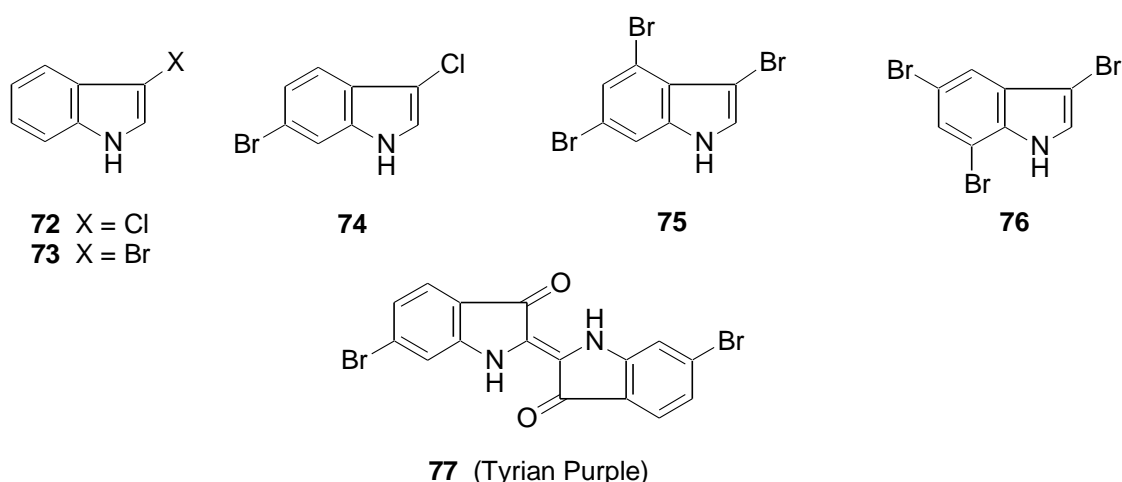


65 (aplydactone)

Unlike other marine animals, acorn worms live in burrows under the sand and are generally concealed from the diver and snorkeler. Nevertheless, these worms exude tremendous quantities of organobromines, such as brominated phenols and indoles (Gribble, 1996a). For example, *Balanoglossus biminiensis* produces up to 15 mg of 2,6-dibromophenol (**66**) per animal, and both **66** and 2,4,6-tribromophenol (**67**) are secreted by *Phoronopsis viridis*. The Florida *Ptychodera bahamensis* has yielded 12 different halogenated phenols and hydroquinones, such as **68** and **69**. The major metabolite of *Ptychodera flava* is the octabrominated ether **70** and a Maui *Ptychodera* sp. has yielded epoxide **71**, which is highly cytotoxic against P-388 cancer cells in vitro ( $IC_{50} = 10$  ng/mL). The highest levels of bromophenols are in the tail, which is the most exposed portion of this head-down, deposit-feeding worm, and is consistent with the idea that these bromophenols are defensive chemicals against predators that would encounter the tail first (Yoon *et al.*, 1994).



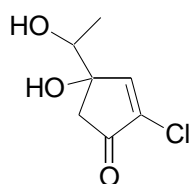
These worms also produce numerous halogenated indoles. *Ptychodera flava laysanica* contains seven chlorinated/brominated indoles, e.g., **51**, **72-76**, as well as the ancient natural dye Tyrian Purple (**77**) (McGovern & Michel, 1990; Gribble, 1996a). The novel amino acid 6-bromotryptophan is invariably found in conotoxin venoms, the peptides produced by the toxic cone snails (Walker *et al.*, 1999; Lirazan *et al.*, 1999).



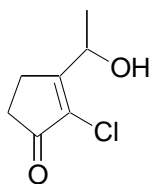
#### 2.1.4.d Fungi

A relatively new area of ocean exploration by natural products chemists involves marine fungi (Bugni & Ireland, 2004). The fungus *Trichoderma harzianum*, which was collected from the sponge *Halichondria okadae*, affords the potent cytotoxic trichodenones B (**78**) and C (**79**) (Amagata *et al.*, 1998). A *Fusarium* sp. marine fungus from the Bahamas contains the novel sesterterpenes neomangicols A (**80**) and B (**81**), which have antibacterial and antitumor activity (Renner *et al.*, 1998). A marine-derived strain of *Emericella unguis* yielded the depside guisinol (**82**) (Nielsen *et al.*, 1999), and cryptosporiopsinol (**83**) is found

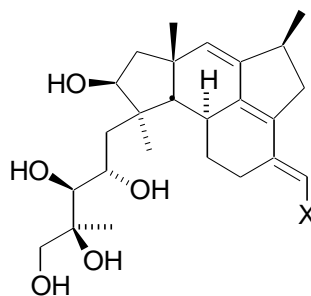
in a *Coniothyrium* sp. that is associated with the sponge *Ectyplasia perox* (Höller *et al.*, 1999). A *Pestalotia* sp. found on the surface of the brown alga *Rosenvingea* sp. in the Bahamas produces the novel antibiotic pestalone (**84**), which shows potent antibacterial activity against methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium* (Cueto *et al.*, 2001). The marine fungus FOM-8108 from beach sand in Japan has furnished the simple quinone **85**, which inhibits neutral sphingomyelinase activity of rat brain membranes (Uchida *et al.*, 2001). *Gymnasella dankaliensis*, which is associated with the sponge *Halichondria japonica*, produces three gymnastatins, e.g., **86**, all of which have significant *in vitro* activity against cancer cells (Numata *et al.*, 1997).



**78** (trichodenone B)

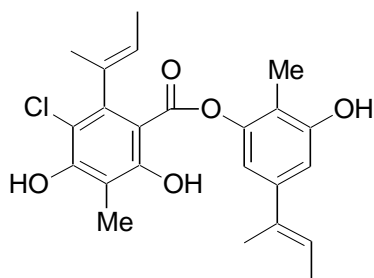


**79** (trichodenone C)

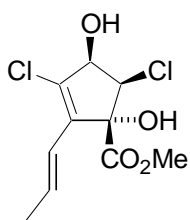


**80** X = Cl (neomangicol A)

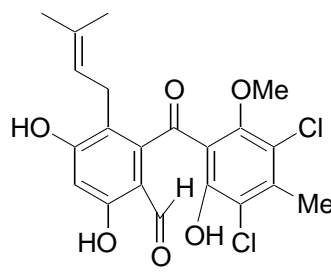
**81** X = Br (neomangicol B)



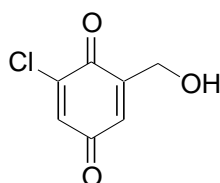
**82** (guisinol)



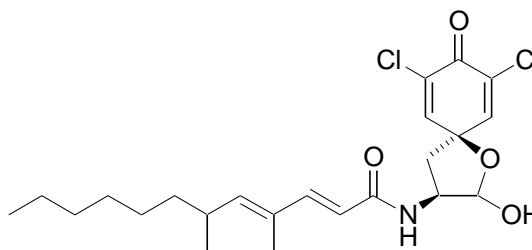
**83** (cryptosporiopsinol)



**84** (pestalone)



**85** (chlorogentisylquinone)



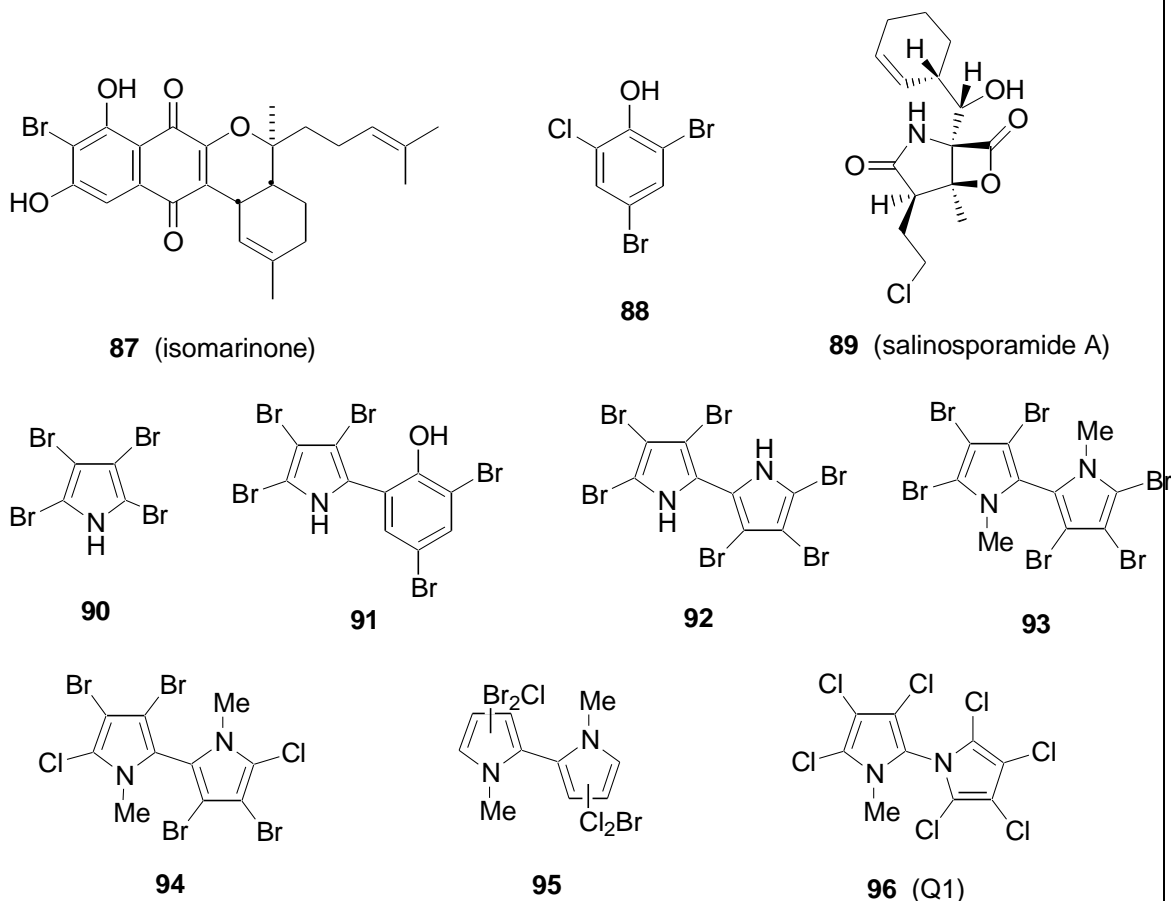
**86** (gymnastatin A)

#### 2.1.4.e Bacteria

Like marine fungi, marine bacteria have only recently been tapped for collection, identification, cultivation, and metabolite isolation (Fenical, 1993). Bacteria associated with the marine sponges *Aplysina aerophoba* and *Aplysina cavernicola* (27 distinct isolates) exhibit activity against Gram-positive and Gram-negative strains as well as against multi-resistant *Staphylococcus aureus* and *Staphylococcus epidermidis* strains from hospital patients (Hentschel *et al.*, 2001). A large fraction of these bacteria resides permanently in *Aplysina aerophoba* suggesting a symbiotic relationship (Friedrich *et al.*, 2001).

A marine filamentous bacterium has afforded isomarinone (**87**) (Hardt *et al.*, 2000), and cultures of *Pseudoalteromonas luteoviolacea* yielded 6-chloro-2,4-dibromophenol (**88**), which shows antibacterial activity against methicillin-resistant *Staphylococcus aureus* and the cystic fibrosis associated pathogen *Burkholderia cepacia* (Jiang *et al.*, 2000). A marine bacterium of the new genus *Salinospora* has yielded (**89**), which is a highly cytotoxic

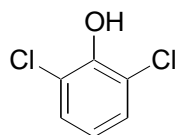
proteasome inhibitor (Feling *et al.*, 2003). An early example of a marine bacterium metabolite is 2,3,4,5-tetrabromopyrrole (**90**) from *Chromobacterium* sp. along with **91** and the polybrominated bipyrrole **92** (Anderson *et al.*, 1974). Related to **92** are the three halogenated bipyrroles **93-95**, which are the first examples of natural organohalogens to bioaccumulate in the food chain. These three compounds are present in Pacific Ocean surface-feeding seabirds (albatross, puffins, gulls, petrel) and bald eagles, but not in any Great Lakes herring gulls (Tittlemier *et al.*, 1999, 2002a; Gribble *et al.*, 1999). These halogenated bipyrroles are also present in the Arctic marine food web (plankton, fish, seabirds, seal) (Tittlemier *et al.*, 2002b, 2002c; Tittlemier, 2004). A marine bacterial food-chain origin seems likely. The related "Q1" (**96**) is present in a multitude of marine fish and mammals and even in the milk of Eskimo women who consume whale blubber (Vetter *et al.*, 2000, 2001, 2003; Jun *et al.*, 2002; Vetter, 2002; Vetter & Jun, 2002; Vetter & Stoll, 2002), thus representing the first example of a bioaccumulating natural organohalogen to be found in humans. A marine origin also seems likely for this unique compound. The resemblance of Q1 and the halogenated bipyrroles (**92-95**) to PCBs (polychlorinated biphenyls) is noteworthy and preliminary evidence reveals that the halogenated bipyrroles bind to the aryl hydrocarbon receptor, but much weaker than 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (Tittlemier *et al.*, 2003a). Likewise, the halogenated bipyrroles are not an acute threat to the reproduction or development of American kestrels (Tittlemier *et al.*, 2003b).



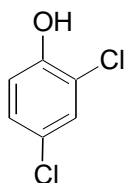
### 2.1.5 Insects

In addition to possessing the means for motion and flight, body armor and mandibles, insects rely heavily on chemicals for communication ("pheromones") and defense ("allomones"), but very few of these compounds contain a halogen. However, at least 14 species of tick employ 2,6-dichlorophenol (**97**) as a sex pheromone (Berger, 1983; Yunker *et al.*, 1992; de Bruyne & Guerin, 1994; Norval *et al.*, 1996), and this compound is used in tick control (Norval *et al.*, 1996). Radiolabeled chloride feeding studies prove that **97** is biosynthesized within the female tick. Unlike 2,4-dichlorophenol, 2,6-dichlorophenol has no industrial sources. The isomeric 2,5-dichlorophenol has been isolated from the common grasshopper and is an ant repellent, and 2,4-dichlorophenol (**98**), the precursor to the common synthetic herbicide "2,4-D" (one half of Agent Orange), is produced by a

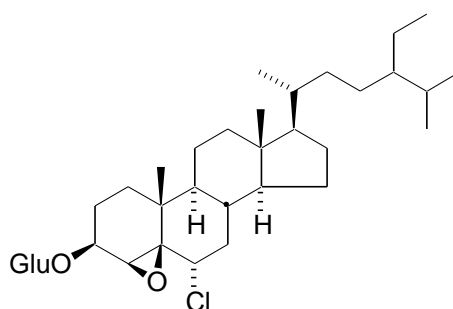
*Penicillium* sp. soil fungus (Gribble, 1996a). The German cockroach (*Blattella germanica*) employs the two chlorinated stigmastane steroids blattellastanosides A (**99**) and B as aggregation pheromones (Sakuma & Fukami, 1993).



**97**



**98**

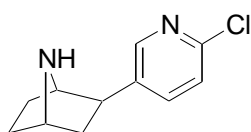


**99** (blattellastanoside A)

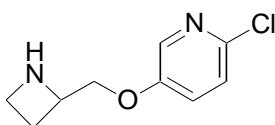
Several insects contain 2- (or 4-)iodohistidine and mono- and dibromotyrosines, and 3-chlorotyrosine occurs in the cuticle of locusts. These halogenated tyrosines are believed to improve adhesion between protein fibers and sheets (Gribble, 1996a). An extraordinary finding is that chloroform is a termite product. Six Australian termite species produce chloroform within their mounds, and up to 1000 times higher than the ambient concentration for one species (Khalil *et al.*, 1990). The authors conclude that this source may account for as much as 15% of the global emissions of chloroform, amounting to perhaps 100,000 tons per year.

#### 2.1.6 Higher animals

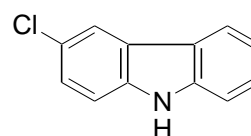
Natural organohalogens are rare in higher animals but a few notable examples exist. The Ecuadorian tree frog *Epipedobates tricolor* has yielded epibatidine (**100**), a structurally unique 2-chloropyridine 7-azanorbornane that is 500-1000 times more potent than morphine as an analgesic (Spande *et al.*, 1992; Daly *et al.*, 2000; Carroll, 2004). Although too toxic for human use, epibatidine analogues are under active investigation as new drugs. For example, the synthetic ABT-594 (**101**) lacks epibatidine-like toxicity and is in clinical trials (Bannon *et al.*, 1998; Strauss, 1998). The potent monoamine oxidase inhibitor 3-chlorocarbazole (**102**) is found in bovine urine (Luk *et al.*, 1983), and iodolactones **103** and **104** have been identified in the thyroid gland of dogs (Boeynaems *et al.*, 1981). The synthetic transformation of arachidonic acid and docosahexaenoic acid with lactoperoxidase, iodide and hydrogen peroxide into **103** and **104**, respectively, suggests that this pathway may operate *in vivo* with thyroid peroxidase. Of related interest is the reported *in vivo* conversion of pentachlorophenol in cow feces and of a nonachlorodiphenyl ether in rats to octachlorodibenzo-*p*-dioxin (**105**) (Huwe *et al.*, 2000).



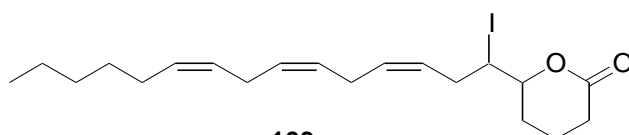
**100** (epibatidine)



**101** (ABT-594)

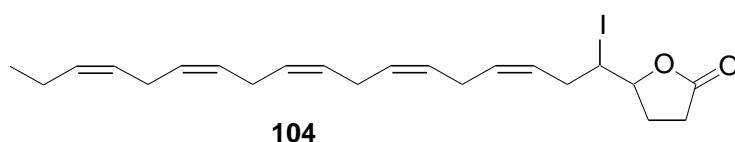


**102**

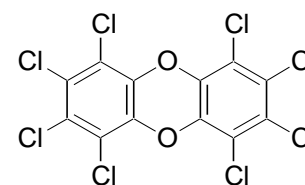


**103**





104

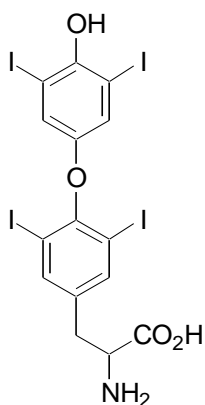


105

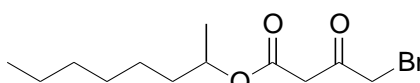
### 2.1.7 Humans

For more than 100 years, the only known natural organohalogen identified as humanoid was the thyroid hormone thyroxine (**106**) and a few related iodinated tyrosines. Since then several amazing discoveries in this area have been made. Bromo ester **107** has been isolated from mammalian cerebrospinal fluid (human, cat, rat) and is a very effective inducer of rapid-eye movement sleep (Patricelli *et al.*, 1998; Yanagisawa & Torii, 2002). This novel compound — the first natural organobromine to be found in mammals — may play a role in promoting sleep, and its concentration is 100-200 times higher in the retina, hypophysis, and cerebral cortex than in blood.

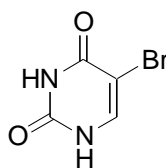
Extensive studies of the chemical artistry of the mammalian immune system reveal that free chlorine, as generated from chloride, hydrogen peroxide, and myeloperoxidase (MPO), may be employed by our white blood cells (neutrophils) to fight infection and kill invading pathogens (Hazen *et al.*, 1996a, 1996b; Kettle & Winterbourn, 1997; Winterton, 1997; Hurst & Lyman, 1999; Spickett *et al.*, 2000; Hawkins *et al.*, 2003; Henderson & Heinecke, 2003). MPO is the most abundant protein in neutrophils, amounting for up to 5% of dry weight (Suzuki *et al.*, 2002). This MPO-catalyzed halogenation activity leads to the production of 3-chlorotyrosine (**108**), 3-bromotyrosine (**109**), and 5-bromouracil (**110**) (Hazen & Heinecke, 1997; Heinecke, 2000; Henderson *et al.*, 2001a, 2001b; Gaut *et al.*, 2001), presumably as byproducts of the halogenation of the invading organism. 3-Chlorotyrosine (**108**) has also been detected in human atherosclerotic lesions, in the reaction of human serum albumin with MPO, H<sub>2</sub>O<sub>2</sub>, and chloride in neutrophils, and in high levels in cystic fibrosis patients, who contain high levels of MPO (Van Der Vliet *et al.*, 2000). MPO-deficient mice fail to generate chlorotyrosine or to kill the pathogenic fungus *Candida albicans in vivo* and display increased atherosclerosis (Brennan *et al.*, 2001; Nauseef, 2001).



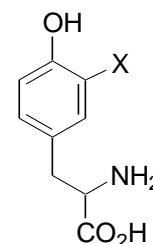
106 (thyroxine)



107



110 (5-bromouracil)

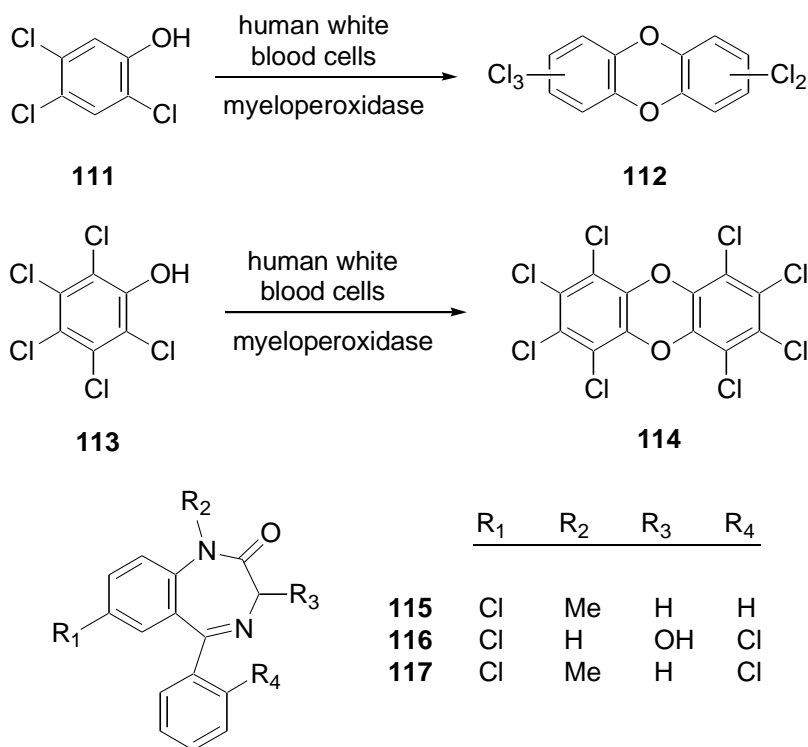


108 X = Cl (3-chlorotyrosine)  
109 X = Br (3-bromotyrosine)

An X-ray crystal structure of human MPO has identified halide-binding sites in this heme protein (Fiedler *et al.*, 2000). Twenty-eight percent of the oxygen consumed by stimulated neutrophils oxidizes chloride to chlorine or hypochlorite, and the active oxidants so produced might actually be chloramines (Gribble, 1998; Hawkins & Davies, 2001). Biochlorination is also responsible for the conversion of cholesterol in the presence of myeloperoxidase into several chlorinated sterols (Heinecke *et al.*, 1994; Hazen *et al.*, 1996a; Carr *et al.*, 1996), and for the hypochlorite-induced oxidation of amino acids, peptides, proteins (Hawkins *et al.*, 2003), and phospholipids (Albert *et al.*, 2001). Interestingly, 5-chlorocytosine was isolated from salmon sperm DNA in 1973, and was the first halogenated nucleic acid to be isolated from a natural source (Lis *et al.*, 1973). This chlorinated nucleic acid is also isolated, along with the hydrolysis product 5-chlorouracil,

when DNA is treated with HOCl and then hydrolyzed (Chen *et al.*, 2002), and 8-chloroadenine is also formed under these conditions (Whiteman *et al.*, 1999). Both of these chlorinated nucleic acids will most probably be found in humans as by-products of the inflammatory response. The reaction of 2'-deoxyguanosine with MPO, H<sub>2</sub>O<sub>2</sub>, Cl<sup>-</sup> or HOCl alone gives rise to the same suite of three novel products, 8-chloro-2'-deoxyguanosine and two ring-cleaved products (Suzuki *et al.*, 2001, 2002, 2003; Suzuki & Ohshima, 2002). Hypochlorous acid, as generated from MPO, H<sub>2</sub>O<sub>2</sub>, and Cl<sup>-</sup>, induces cross-links between DNA and protein (Kulcharyk & Heinecke, 2001), the significance of which is unknown. An intrastrand cross-link has been observed in DNA between adjacent 5-bromocytosine and guanine upon UV irradiation (Zeng & Wang, 2004), although 5-bromocytosine seems not to have been reported as a natural product.

Since human MPO converts chlorophenols to chlorinated dioxins and dibenzofurans, e.g., **111** to **112**, and **113** to **114**, a human biosynthesis of dioxins from ubiquitous chlorophenols is possible (Wittsiepe *et al.*, 2000). Seven chlorinated benzodiazepines, e.g., **115-117**, including diazepam (valium) (**115**) have been isolated from the brains of humans and other animals, including three human brains that were preserved years prior to the laboratory synthesis of diazepam! (Unselde *et al.*, 1990; Sand *et al.*, 2000). These natural compounds are biosynthesized in plants (corn, potato, lentil, rice, wheat, soybean, mushrooms) (Unselde *et al.*, 1989) and so enter the food chain. Some of these benzodiazepines may be biosynthesized by neural cells and have a biological role (Klotz, 1991; De Blas *et al.*, 1993; Medina *et al.*, 1993; Gribble, 1998).



### 2.1.8 Abiogenic organohalogenes

Although the diversity and structural complexity of abiogenically produced organohalogenes cannot rival that of their biogenic counterparts, the quantities of some abiogenic organohalogenes are truly enormous.

### 2.1.9 Geothermal processes

Natural combustion processes — volcanoes and other geothermal events — produce vast amounts of volatile chemicals including organohalogenes. The catastrophic eruption of Laki, Iceland, in 1783 released 15 million tons of HF, 7 million tons of HCl, and 122 million tons of SO<sub>2</sub>, blanketing much of Europe for six months (Oppenheimer *et al.*, 1998a). A four-year study of the Popocatepetl, Mexico, volcano revealed that hundreds of tons of HF and

thousands of tons of HCl are released per day (Love *et al.*, 1998). Similarly, Mt. Etna releases 8.6 kg/sec of HCl and 2.2 kg/sec of HF, making this volcano one of the largest known point sources of these gases (Francis *et al.*, 1998). The Soufriere Hills volcano, Montserrat, in July-August 1996 emitted HCl at a rate of 15 kg/sec (1,300 tons/day) (Oppenheimer *et al.*, 1998b). It has been estimated that the 1991 Mt. Pinatubo eruption ejected a minimum of 11-25 kilotons of bromine, comparable to the total annual influx of bromine into the stratosphere from all natural and anthropogenic sources. This single event could have been partially responsible for the massive ozone depletion observed after this eruption (Bureau *et al.*, 2000).

In addition to the enormous annual emissions of hydrogen chloride and hydrogen fluoride, volcanoes emit an array of organohalogenes, including those previously thought to be solely anthropogenic (Gribble, 1996a). The early study by Stoiber of the gases from a fumarole on the Santiaguito volcano in Guatemala revealed  $\text{CF}_2=\text{CF}_2$ ,  $\text{CF}_3\text{CF}=\text{CF}_2$ ,  $\text{CHF}_2\text{Cl}$ ,  $\text{CHFCl}_2$ ,  $\text{CClF}=\text{CF}_2$ ,  $\text{CH}_3\text{Cl}$ ,  $\text{CFCl}_3$ ,  $\text{CCl}_2=\text{CHCl}$ , and  $\text{CCl}_2\text{FCClF}_2$  among other organic compounds (Stoiber *et al.*, 1971). Other organohalogenes remained unidentified due to their complex mass spectra. Corroboration of these unprecedented and remarkable findings were reported by Isidorov with the discovery of  $\text{CF}_2\text{Cl}_2$  (CFC-12),  $\text{CHFCl}_2$ ,  $\text{CFCl}_3$  (CFC-11),  $\text{CHCl}_3$ ,  $\text{CCl}_4$ ,  $\text{CCl}_2=\text{CCl}_2$ , and  $(\text{CH}_3)_2\text{SiF}_2$  in gases from the Siberian Kamchatka volcanoes (Isidorov *et al.*, 1990; Isidorov, 1990). In some cases, the concentrations of the CFCs (chlorofluorocarbons) emerging from solfataric vents from the Kamchatka volcanoes are 400 times that of background. Chloroform,  $\text{CCl}_4$ , and CFCs are also found in the gases from hydrothermal vents and thermal springs in the Kamchatka, Ashkhabad, and Tskhaltubo regions of the former Soviet Union (Isidorov *et al.*, 1991a, 1991b, 1993a, 1993b). The Kamchatka region volcanoes, hot springs, and bacterial thermophiles are beautifully illustrated in two articles of general interest (Hoffmann 2001; Schmidt & Peter, 2001). The 1980 Mt. St. Helens eruption released  $\text{CH}_3\text{Cl}$ ,  $\text{CH}_3\text{Br}$ ,  $\text{CH}_3\text{I}$ , and other (unidentified) organohalogenes (Rasmussen *et al.*, 1982). These organohalogenes, including the CFCs, probably originate from high temperature and high-pressure reactions that occur deep in the volcano between carbon-rich sediments or fossil soils and HCl, HF, or halide minerals. A study of the Kujū, Satsuma Iwojima, Mt. Etna, and Vulcano volcanoes uncovered 100 organochlorines, 25 organobromines, five organofluorines, and four organoiodines, most of which are new natural compounds (Jordan *et al.*, 2000). A recent detailed examination of the organic gas emissions from both the flank and the crater of Vulcano on the Aeolian Islands in Italy reaffirms the emission of  $\text{CCl}_3\text{F}$  (CFC-11),  $\text{CH}_3\text{Br}$ ,  $\text{CH}_3\text{Cl}$ ,  $\text{CH}_3\text{I}$ ,  $\text{CHCl}_3$ ,  $\text{CCl}_4$ ,  $\text{CH}_2\text{Cl}_2$ ,  $\text{CH}_3\text{CH}_2\text{Br}$ , chlorobenzene, and 1,4-dichlorobenzene (Schwandner *et al.*, 2004). Isidorov estimates that 75% of the world's 2000 active volcanoes have a mineral composition and geologic configuration suitable for producing organohalogenes (Isidorov, 1990).

Haloalkanes are present in rock, minerals, and shales. Since the oldest sedimentary and igneous rocks formed 3400 and 4200 million years ago, respectively (Brasier, 1979), the organohalogenes within have been entombed for a long time! When crushed during mining operations or during weathering, these rocks release  $\text{CH}_3\text{Cl}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $\text{CHCl}_3$ ,  $\text{CCl}_4$ ,  $\text{CH}_3\text{CH}_2\text{Br}$ ,  $\text{CHF}_3$ ,  $\text{CFCl}_3$ ,  $\text{CF}_2\text{Cl}_2$ ,  $\text{CCl}_3\text{CHCl}_2$ ,  $\text{CCl}_3\text{CCl}_3$ ,  $\text{CH}_3\text{CHCl}_2$ ,  $\text{ClCH}_2\text{CH}_2\text{Cl}$ ,  $\text{CF}_3\text{CF}_2\text{CF}_2\text{H}$ ,  $\text{CHBr}_2\text{CHBr}_2$ , 1-chloronaphthalene, chlorobenzene, and 2-bromomesitylene (Isidorov, 1990; Isidorov *et al.*, 1993a,b; Buslaeva, 1994). For example, 1000 tons of silvinitic ore yields 50 g of chloroform, and the potassium salt mining industry alone accounts for the annual liberation of 10,000-15,000 tons of  $\text{CHCl}_3$  and 100-150 tons each of  $\text{CCl}_4$  and  $\text{CFCl}_3$ . Several natural fluorites contain  $\text{CF}_4$ ,  $\text{CF}_2\text{Cl}_2$ ,  $\text{CFCl}_3$ ,  $\text{CF}_3\text{Cl}$ ,  $\text{CHF}_3$ ,  $\text{SF}_6$ ,  $\text{NF}_3$ , and  $\text{CF}_2=\text{CF}_2$ , the latter of which is the chemical precursor to Teflon (Harnisch & Eisenhauer, 1998; Harnisch *et al.*, 2000). One dark purple fluorite from Bavaria exudes the unmistakable smell of fluorine gas when crushed, earning it the name of "stinkspat" among local miners.

Following an early identification of chlorobenzene, dichlorobenzene, and several chloroalkanes in carbonaceous chondrites (meteorites) (Mueller, 1953; Studier *et al.*, 1965), further examination of four meteorites (Cold Bokkeveld, Murray, Murchison, Orgueil) uncovered organohalogenes in levels up to 200 ppm, including 2-chloro-, 2,4-, and 2,6-dichlorobenzoic acid in Cold Bokkeveld (Nkusi *et al.*, 1996). It might be noted here that hydrogen chloride and hydrogen fluoride are present in interstellar space (Blake *et al.*, 1985; Neufeld *et al.*, 1997), and the eventual discovery of organohalogenes in deep space seems possible.

### 2.1.10 Biomass burning

Whether human or naturally induced, forest and brush fires are a major source of methyl chloride, methyl bromide and other chemicals. Some 200,000 lightning-triggered fires occur annually, and these natural fires must have occurred on earth since terrestrial vegetation evolved 350-400 million years ago (Gribble, 1996a; Harper, 2000; Cochrane, 2003). Recent evidence in northern Israel indicates that fires were controlled by humans at least 790,000 years ago (Balter, 2004; Goren-Inbar *et al.*, 2004). Ten thousand Canadian forest fires are reported annually, with lightning responsible for 35% of these fires but consuming 85% of the total burn area (Blake *et al.*, 1994). Fires are a significant source of CH<sub>3</sub>Cl (Reinhardt & Ward, 1995; Rudolph *et al.*, 1995) and CH<sub>3</sub>Br (Yvon-Lewis & Butler, 1997). The massive peat and forest fires in Indonesia during 1997 released between 0.8 and 2.6 gigatons of carbon to the atmosphere. This one event contributed greatly to the largest annual increase in atmospheric CO<sub>2</sub> since records began in 1957 (Page *et al.*, 2002). Undoubtedly, organohalogenes were also produced in this catastrophe.

Dioxins are certainly produced in forest fires (Bumb *et al.*, 1980; Nestruck & Lamparski, 1982; Clement *et al.*, 1985; Sheffield, 1985; Rappe, 1996) but the amounts are difficult to quantify for obvious reasons, although it has been estimated that 130 lb of dioxins are produced in Canadian forest fires annually (Sheffield, 1985). This is ten times the amount of dioxins produced in the 1976 Seveso industrial plant explosion. However, some studies of forest fires fail to reveal the formation of dioxins and chlorinated dibenzofurans (Gabos *et al.*, 2001). Biomass burning and subsequent deposition has been proposed as a source of dioxins and polychlorinated dibenzofurans in sediments and soils (Gaus *et al.*, 2001a, 2001b; Green *et al.*, 2001; Prange *et al.*, 2002), and also from the domestic burning of coastal peat, which was a household practice in the British Isles and beyond for millennia and long before the industrial revolution (Meharg & Killham, 2003). For example, the dioxin production from peat burning on the Isle of Hirta, Scotland, is estimated to be 1 kg/year. This compares with today's figure of 5.1 kg/year for the production of dioxin from coal combustion in the entire United Kingdom (Keller & Ross, 1993). Queensland soils and sediment cores indicate a continuous natural source of dioxins over a period of several centuries, perhaps from biomass burning and deposition (Gaus *et al.*, 2001a, 2001b; Prange *et al.*, 2002). It is suggested that Great Barrier Reef (Queensland) dugongs (*Dugong dugon*) may acquire relatively high levels of dioxins and chlorinated dibenzofurans by ingesting these sediments and/or seagrass during feeding (Haynes *et al.*, 1999). In particular, octachlorodibenzo-*p*-dioxin is the dominant congener. Bonfires and fireworks may be a significant source of dioxins (400% increase over background) (Dyke & Coleman, 1995; Fleischer *et al.*, 1999), and wood stoves also contribute dioxins and furans to the atmosphere, but the amounts appear to be relatively minor and depend greatly on operating conditions and wood type (Vikelsøe *et al.*, 1994).

### 2.1.11 Sediments and soil chemistry

Whether the origin is biogenic or abiogenic, organohalogenes of many types are found in sediments and soils, in some cases dating back thousands or even millions of years (Gribble, 1996a, 1998; Müller *et al.*, 1996; Winterton, 2000; Müller, 2003; Schöler *et al.*, 2003; McCulloch, 2003; Hoekstra, 2003).

Organic plant material decays to humic acids at a rate of 63 billion tons/year giving an estimated global soil humic acid concentration of 1.0-1.5 trillion tons, with another one trillion tons in the oceans. Rivers and lakes are also repositories of these highly condensed aromatic phenol polymers (Hayes *et al.*, 1989). The abiogenic and biogenic halogenation and subsequent breakdown of humic and fulvic acids leads to large quantities of organohalogenes, especially organochlorines, such as chloroform, chloroacetic acids, chlorophenols, and dioxins (Asplund *et al.*, 1989; Gribble, 1996a; Winterton, 2000). There is evidence that the white-rot fungus *Phanerochaete chrysosporium* can biochlorinate and degrade lignins, which may provide a pathway for the production of organochlorines in soil (Johansson *et al.*, 2000). Lakes and rivers that do not receive industrial discharge contain large amounts of organohalogenes (Asplund *et al.*, 1989; Dahlman *et al.*, 1993), and up to 50% of the organohalogenes in the Rhine river are of natural origin (Hoekstra & de Leer, 1994). Humic acids from forest and bog drainage water have high concentrations of organochlorines (200-400 mg/liter) and lesser amounts of organobromines (7-16 mg/liter)

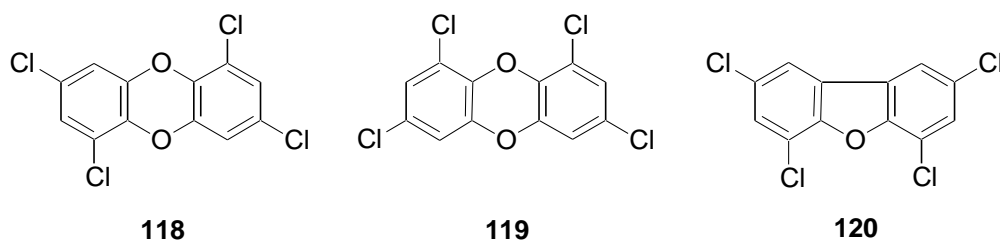
(Manninen & Lauren, 1993), and sea water iodine is found in humic acid deposits (Francois, 1987). Samples of remote bog water and sediments yielded 2,4-dichlorobenzoic acid, 2,5-dichlorobenzoic acid, 2- (or 3-) chlorobenzoic acid, and 4-chlorobenzoic acid (Niedan & Schöler, 1997). The highest concentration was invariably 2,4-dichlorobenzoic acid. Bank-infiltrated water of the Rhine river and the Hohes-Venn bog yielded 2,6-dichlorobenzoic acid and 3,4-dichlorobenzoic acid. Salt marsh cordgrass (*Spartina alterniflora*) releases annually 330 kg/hectare of humic substances into the surrounding salt water (Filip & Alberts, 1988, 1989). Organochlorines in fulvic acid samples from unpolluted waters have been found (Dahlman *et al.*, 1993), including high molecular weight aromatic organohalogens from both limnic and marine environments (Johansson *et al.*, 1993). The latter samples contain organobromines and organoiodines in addition to organochlorines, and chlorinated 4-hydroxyphenyl units are present in natural aquatic fulvic acid (Flodin *et al.*, 1997). A halogenated soil humic acid containing 0.24% halogen was isolated (Grøn & Raben-Lange, 1992). In fact, organohalogens are present in fulvic acids isolated from ancient groundwater samples dating back 1,300, 4,600, and 5,200 years (Asplund *et al.*, 1989), and aquatic sediments from the year 1900 contain 30-50 mg/kg organohalogens (Müller & Schmitz, 1985). Organohalogens are present in 13th century sediments (Paasivirta *et al.*, 1988), and pre-industrial glacial ice from Antarctica and Sweden contains 1-3 ppb organohalogens, including trichloroacetic acid. The latter compound, along with chloroform, is ubiquitous in soil, the biogenesis of which was confirmed by <sup>37</sup>Cl labeling experiments (Asplund & de Leer, 1995). The biogenic chloroform production in the upper soil layer of spruce forests in Denmark has been reported, and the authors conclude that "the terrestrial environment can be considered as an important contributor to the atmospheric chloroform input" (Haselmann *et al.*, 2000a, 2000b, 2002; Laternus *et al.*, 2000). The concentration of chloroform in soil air ranges up to 10 ng/liter (ambient air = 0.02 ng/liter) and up to 1,600 ng/liter in ground water (Haselmann *et al.*, 2002). A study of rural forests in The Netherlands revealed chloroform emission rates of up to 1000 ng/m<sup>2</sup> per hour in wood degrading areas and soils with a humic top layer or covered with wood chips (Hoekstra *et al.*, 2001). Some sites showed emission of CH<sub>3</sub>CCl<sub>3</sub>, CCl<sub>4</sub>, and Cl<sub>2</sub>C=CCl<sub>2</sub>. This is apparently the first report of the latter organochlorine from soil. Trichloroacetic acid is present in bog water, snow, rain, and soil samples from pristine areas (Haiber *et al.*, 1996). A study of snow, firn, and glacier ice hundreds of years old uncovered concentrations of mono-, di-, and trichloroacetic acids too high to be explained by anthropogenic emissions (von Sydow *et al.*, 1999). Likewise, an examination of 200-year old snow shows the presence of dibromoacetic acid, bromoacetic acid, and all three chloroacetic acids (von Sydow *et al.*, 2000).

Carbon-14 dating experiments on 35,000-year old organic matter reveals the presence of organochlorines, organobromines, and organoiodines. Organohalogens have also been found in 1,000-year old peat and 4,000-year old marine clay (Grøn, 1995), and in several thousand-year old peats from the holocene period (200-300 ppm concentrations), in two lignite samples that date from the Tertiary era, 15 million years ago (107 and 166 ppm concentrations), and in a 300-million year old bituminous coal sample from the Upper Carboniferous period (74 ppm concentration) (Müller, 1995). Whether these organohalogens result from deposition of biogenic halogenated material from plants or by the formation of organohalogens within the sediments remains to be established. However, several studies indicate that both biogenic and abiogenic processes lead to organohalogens in soils and sediments (Gribble, 1996a; Winterton, 2000; Laternus *et al.*, 2002; Öberg, 2002). Recent studies indicate that the chlorination of organic compounds during humification processes in peat is pervasive in nature and has led to the accumulation of 280-1000 million tons of organically bound chlorine in peatlands during the post glacial period worldwide (Keppler & Biester, 2003). Irish peatland ecosystems are important sources of CH<sub>3</sub>Cl, CH<sub>3</sub>Br, CH<sub>3</sub>I, and CHCl<sub>3</sub>, especially those in coastal areas and conifer plantation forests (Dimmer *et al.*, 2001). Likewise, the natural decay (weathering) of plant material leads to the formation of organochlorines (Myneni, 2002; Isidorov & Jdanova, 2002). The humification of peat also leads to the production of organoiodine compounds in a process believed to provide a major reservoir of iodine in terrestrial ecosystems, estimated to be 12-36 million tons since the last glacial period (Keppler *et al.*, 2004). Vinyl chloride, which is the monomer of the important industrial polymer polyvinylchloride (PVC), is also a natural soil product, and control experiments indicate that it is produced by the degradation of humic acid via soil processes (Keppler *et al.*, 2002).

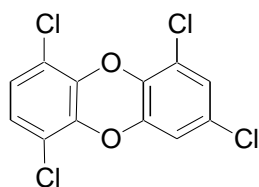
Rice paddies are significant sources of CH<sub>3</sub>Cl, CH<sub>3</sub>Br, and CH<sub>3</sub>I, and estimates are that rice fields worldwide emit 1% of atmospheric CH<sub>3</sub>Br and 5% of CH<sub>3</sub>I (Redeker *et al.*, 2000; Redeker *et al.*, 2002; Redeker *et al.*, 2004; Redeker & Cicerone, 2004). Wetlands are also a source of CH<sub>3</sub>Cl and CH<sub>3</sub>Br, perhaps from biological sources (Varner *et al.*, 1999). The amounts of these gases from wetland sites may have a significant impact on the troposphere.

Dioxins and chlorinated dibenzofurans, but not PCBs, are present in archived soil samples (1856-1938) from the U.K., U.S., and Belgian Congo (Green *et al.*, 2000, 2001), in sediments and clays, and in animal feeds that incorporate ball clay as an anti-caking additive (Fiedler *et al.*, 1996; Cooper *et al.*, 1996; Ferrario *et al.*, 1997, 1999, 2000a, 2000b; Rappe *et al.*, 1997, 1998, 2000; Hayward *et al.*, 1999; Ferrario & Byrne, 2000, 2002; Jobst & Aldag, 2000; Rappe & Andersson, 2000). The distribution of dioxin isomers is distinctly different from that typically seen with anthropogenic dioxins. The evidence for the natural formation of dioxins in mined clay products was summarized: "These recent findings of elevated dioxin levels in clay deposits millions of years old in disparate regions of the U.S. with distinct unprecedented isomer patterns that reportedly match those originating from ancient deposits in Germany argues for some natural geologic mechanism to account for their origin" (Ferrario *et al.*, 2000a, 2000b). Marine sediments also contain dioxins, mainly octachlorodibenzo-*p*-dioxin, but not chlorinated dibenzofurans and PCBs (polychlorinated biphenyls) (Hashimoto *et al.*, 1990; Hashimoto *et al.*, 1995). A remote lake in Finland yielded dioxins and polychlorinated dibenzofurans from 8,000-year old sediments (Isosaari *et al.*, 2002), and the dioxins and furans found in sediments from Hong Kong may have nonanthropogenic origins in view of the similar profiles that are observed in the ancient clays (*vide supra*) (Müller *et al.*, 2002).

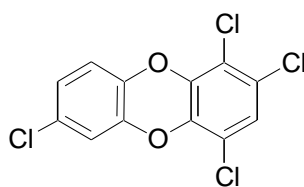
A second important development in the area of natural dioxins is the discovery of 1,3,6,8-tetrachlorodibenzo-*p*-dioxin (**118**), 1,3,7,9-tetrachlorodibenzo-*p*-dioxin (**119**), and 2,4,6,8-tetrachlorodibenzofuran (**120**) in six different Canadian peat bogs (Silk *et al.*, 1997). These dioxin chlorine substitution patterns are different from those of atmospheric deposition and other known sources of dioxins and chlorinated dibenzofurans. Furthermore, the patterns seen in **118-120** are replicated with the *in vitro* oxidative coupling of 2,4-dichlorophenol and the ubiquitous soil enzyme chloroperoxidase. Incorporation of added <sup>36</sup>Cl<sup>-</sup> occurs in the peat. Although many other isomeric dioxins and furans were detected in the peat, **118-120** predominated. Thus, the peat from one bog revealed four monochlorodibenzofurans, nine dichlorodibenzofurans, and six trichlorodibenzofurans. Also identified in this study are chlorophenols, a chlorocresol, chloromethoxybenzoic acids, and chlorocinnamic acids, in addition to chloroform (1-2 ppm).



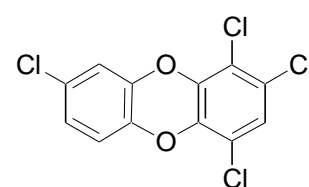
A study of the soil in a Douglas fir forest discovered several chlorophenols, dioxins, and chlorinated dibenzofurans (Hoekstra *et al.*, 1999c). The specific compounds include 4-chlorophenol, 2,4-dichlorophenol, 2,5-dichlorophenol, 2,6-dichlorophenol, 2,4,5-trichlorophenol, dioxins **121-124** and furan **125**, and the latter five compounds are shown to form naturally using <sup>37</sup>Cl<sup>-</sup> spiked soil samples and *in vivo* experiments. Also isolated in this study were 1,2,3,4,6-pentachlorodibenzo-*p*-dioxin, 1,2,3,4,6-pentachloro-, 1,2,3,4,6,7,9-heptachloro-, and 1,2,3,4,6,8,9-heptachlorodibenzofuran. These latter compounds may form from anthropogenic pentachlorophenol.



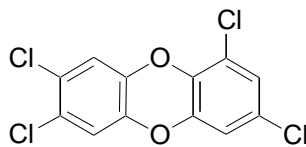
121



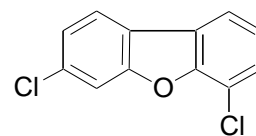
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123



124

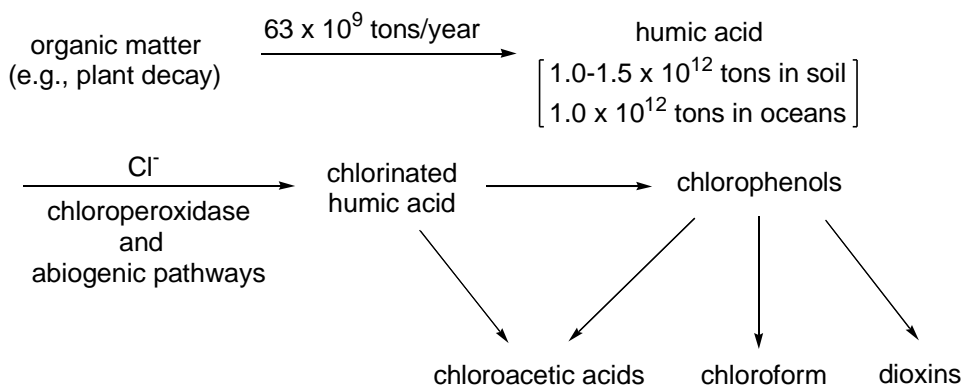


125

Two other biogenic sources of dioxins and chlorinated dibenzofurans are in fresh garden compost piles (Öberg *et al.*, 1992; Malloy *et al.*, 1993; Krauss *et al.*, 1994) and sewage sludge (Öberg *et al.*, 1993; Klimm *et al.*, 1998), presumably from chlorophenols. The enzymatic dimerization of chlorophenols to form dioxins is discussed in Section 3.1. Similarly, the enzymatic chlorination of humic acids to yield dioxins and chlorinated dibenzofurans has been reported (Hemming *et al.*, 1991; Vikelsøc *et al.*, 1994). Composting of organic household waste also yields chloromethoxybenzaldehyde (Eklind *et al.*, 2004). The photolysis of pentachlorophenol on soil surfaces affords octachlorodibenzo-*p*-dioxin and heptachlorodibenzo-*p*-dioxin (Liu *et al.*, 2002), thus presenting another natural source of dioxins.

One can summarize these results for the formation of various organochlorines from humic acids as shown in Scheme 1. Compelling laboratory experiments and field observations support each pathway.

**Scheme 1**







### 3 Formation of Natural Organohalogens

Two pathways exist for the formation of naturally occurring organohalogen compounds: (1) Enzymatic biosynthesis by living organisms; and (2) Chemical transformation, such as combustion or oxidation, of organic matter in the presence of halide salts or other halogen sources. In addition, several pathways have been identified that form free halogen.

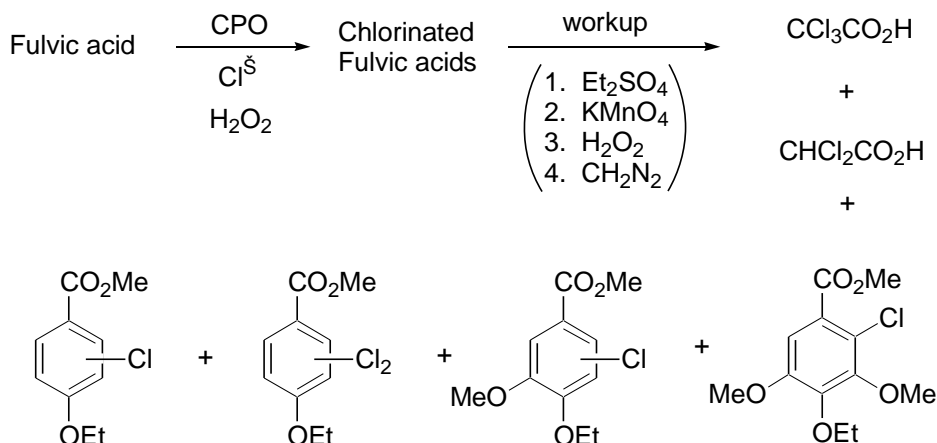
#### 3.1 Biogenic organohalogens

Since life began in the oceans, it is logical that marine organisms have not only adapted to high salt concentrations but have incorporated halogens into their chemical constitutions. Some marine bacteria need high salt concentrations (3% NaCl) to live, while others require extraordinarily high concentrations (15-30% NaCl) for growth (Kushner, 1971). The mechanisms for how living organisms incorporate halide into organic compounds, e.g., via oxidation to halogen or hypohalite, are slowly becoming understood (Neidleman & Geigert, 1986; Gribble, 1996a, 1998; Butler, 1999; Winterton, 2000; van Pée, 2001; Ballschmiter, 2003; Butler & Carter-Franklin, 2004).

Marine plants and animals, terrestrial plants, bacteria, fungi, and mammals all utilize peroxidase enzymes, usually with hydrogen peroxide to oxidize halide to halogen for the biosynthesis of organohalogen compounds. Chloroperoxidase (CPO) (Littlechild, 1999), bromoperoxidase (BPO) (Rorrer *et al.*, 2001), iodoperoxidase (Almeida *et al.*, 2000), other haloperoxidases (Almeida *et al.*, 2001), myeloperoxidase (MPO), and other halogenating enzymes (van Pée *et al.*, 2000) have been extensively characterized and shown to oxidize halide to halogen or enzyme-bound halogen. Of 33 species of *Phaeophyceae* algae from the Atlantic coast, 22 displayed peroxidase activity, 80 species of Death Valley fungi in California exhibit CPO activity, and BPO activity has been detected in 94 species of red, green and brown algae (Gribble, 1996a, 1998; Ohshiro *et al.*, 1999).

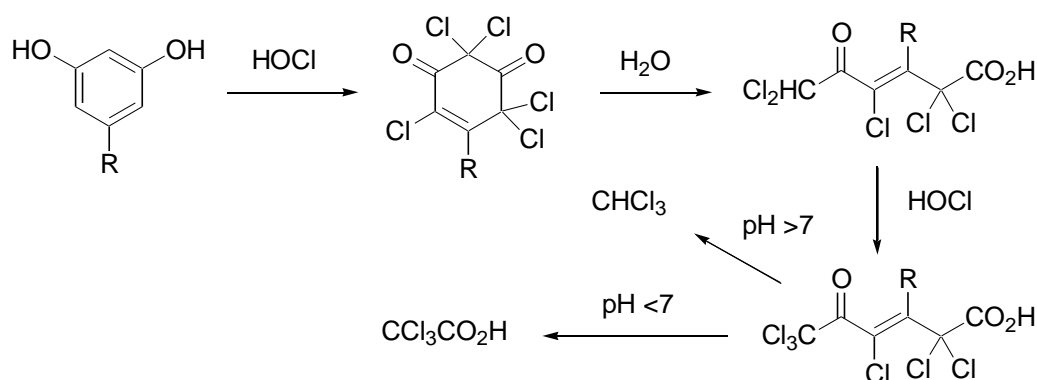
The BPO responsible for the production of  $\text{CHBr}_3$ ,  $\text{CH}_2\text{Br}_2$ ,  $\text{CH}_2\text{I}_2$ ,  $\text{CH}_2\text{ClI}$ , and  $\text{CH}_2\text{BrI}$  by marine phytoplankton has been isolated, and BPO in the green alga *Ulvella lens* is shown to produce  $\text{CH}_2\text{Br}_2$  and  $\text{CHBr}_3$  from oxaloacetate, bromide, and hydrogen peroxide (Ohshiro *et al.*, 1999). A labeling study using  $\text{NaH}^{13}\text{CO}_3$  shows incorporation of carbon into  $\text{CH}_3\text{Cl}$ ,  $\text{CHCl}_3$ ,  $\text{CH}_3\text{Br}$ , and  $\text{CH}_3\text{I}$ , which are produced by the marine microalgae *Porphyridium purpureum* and *Dunaliella tertiolecta* (Murphy *et al.*, 2000). BPO is also present in terrestrial lichen, bacteria, and acorn worms, and the BPO genes from *Streptomyces aureofaciens* have been cloned and sequenced (Gribble, 2000). The CPO gene from the fungus *Caldariomyces fumago* has been isolated and sequenced, and CPO activity is found in many soil extracts (Gribble, 1996a, 1998), and in a liverwort (Speicher *et al.*, 2003). CPO is able to convert acetic acid, NaCl, and  $\text{H}_2\text{O}_2$  to trichloroacetic acid in the laboratory (Haiber *et al.*, 1996). Likewise, other naturally occurring carboxylic acids (malic, fumaric, malonic, citric, acetonedicarboxylic acid, and humic) give trichloroacetic acid under these conditions. Other studies support a CPO mediated formation of trichloroacetic acid (Juuti & Hoekstra, 1998; Hoekstra *et al.*, 1999a, 1999b). The CPO-induced chlorination of fulvic acid affords a series of chlorophenols and chloroacetic acids (Scheme 2) (Niedan *et al.*, 2000).

## Scheme 2



Model chlorination studies with 1,3-dihydroxybenzenes and other phenolic compounds reveal how the formation of chloroform and trichloroacetic might occur from humic acid (Scheme 3) (Boyce & Hornig, 1983a, 1983b; de Leer *et al.*, 1985; Haselmann *et al.*, 2000b). This chemistry has been developed into an undergraduate laboratory experiment (Olson *et al.*, 2001).

## Scheme 3

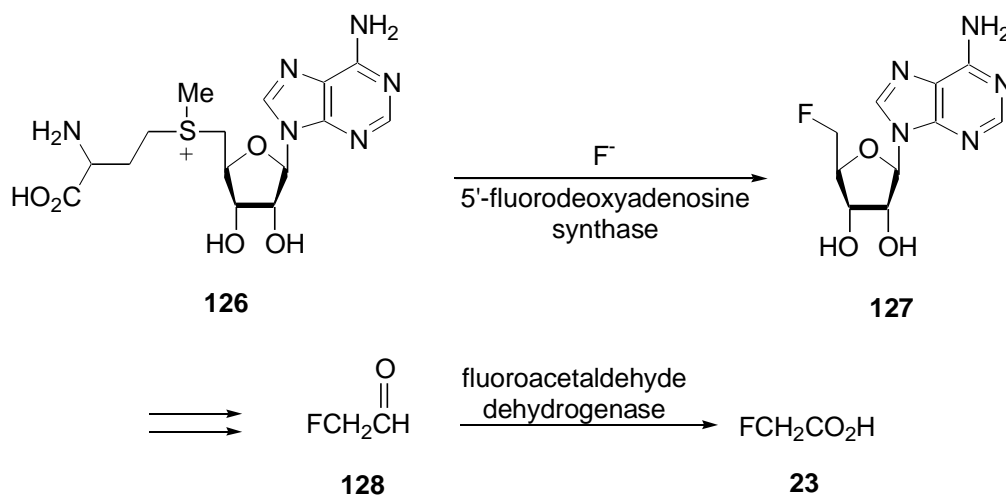


The biosynthesis of chloroarylpropane diols that are produced by the white-rot fungus *Bjerkandera adusta* has been extensively investigated using isotopically labeled substrates (Silk & Macaulay, 2003). This process does not appear to involve CPO, and the metabolic role of these chlorinated diols, e.g., 2, remains to be established.

A newly discovered group of enzymes capable of halogenation are the halogenases, which function by generating peracetic acid that oxidizes halide to hypohalite (van Pée *et al.*, 2000), and a heme-based haloperoxidase has been discovered in the fresh water alga *Cladophora glomerata* (Verdel *et al.*, 2000). Haloperoxidase activity is found in spruce forest soil (Laternus *et al.*, 1995).

The first enzymes to be identified that are directly involved in organofluorine biosynthesis are fluoroacetaldehyde dehydrogenase, from *Streptomyces cattleya*, that mediates the oxidation of fluoroacetaldehyde (128) to fluoroacetic acid (23) (Murphy *et al.*, 2001a, 2003), and 5'-fluorodeoxyadenosine synthase that is involved in the prior C-F bond formation, 126 to 127 (O'Hagan *et al.*, 2002; Schaffrath *et al.*, 2002, 2003; Cobb *et al.*, 2004) (Scheme 4). Another enzyme, threonine transaldose, that uses fluoroacetaldehyde (128) and threonine to generate 4-fluorothreonine has also been found in *Streptomyces cattleya* (Murphy *et al.*, 2001b; Schaffrath *et al.*, 2001). Enzymatic catalyzed carbon-fluorine bond formation by nucleophilic substitution has also been seen in the action of two glycosidase mutants (Zechel *et al.*, 2001).

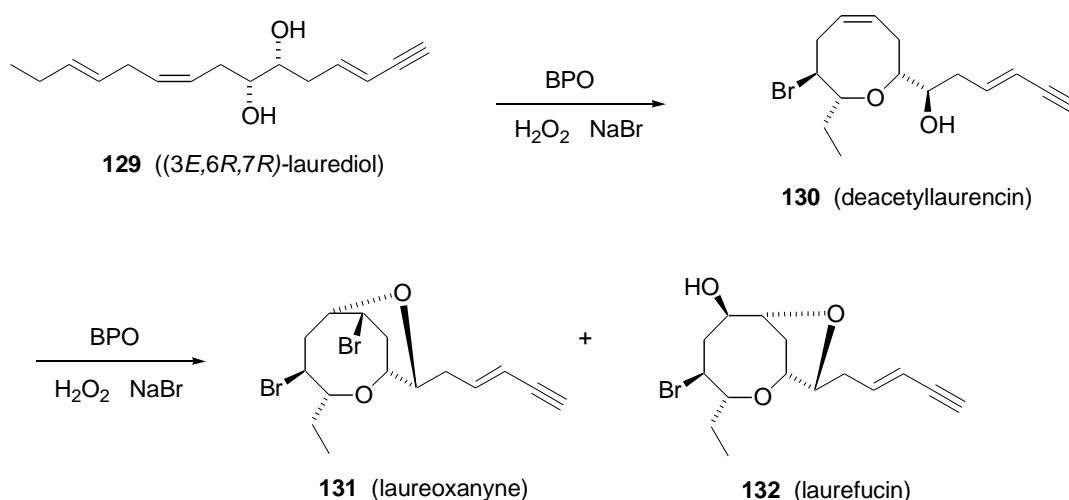
#### Scheme 4



Haloperoxidases and other peroxidases are extremely useful in organic synthesis and many applications have been reported (Neidleman & Geigert, 1986; Hager *et al.*, 1998; Littlechild, 1999; Dembitsky, 2003; Murphy, 2003). The "directed evolution" of CPO has led to improved oxidation and chlorination catalysts for organic synthesis (Rai *et al.*, 2001).

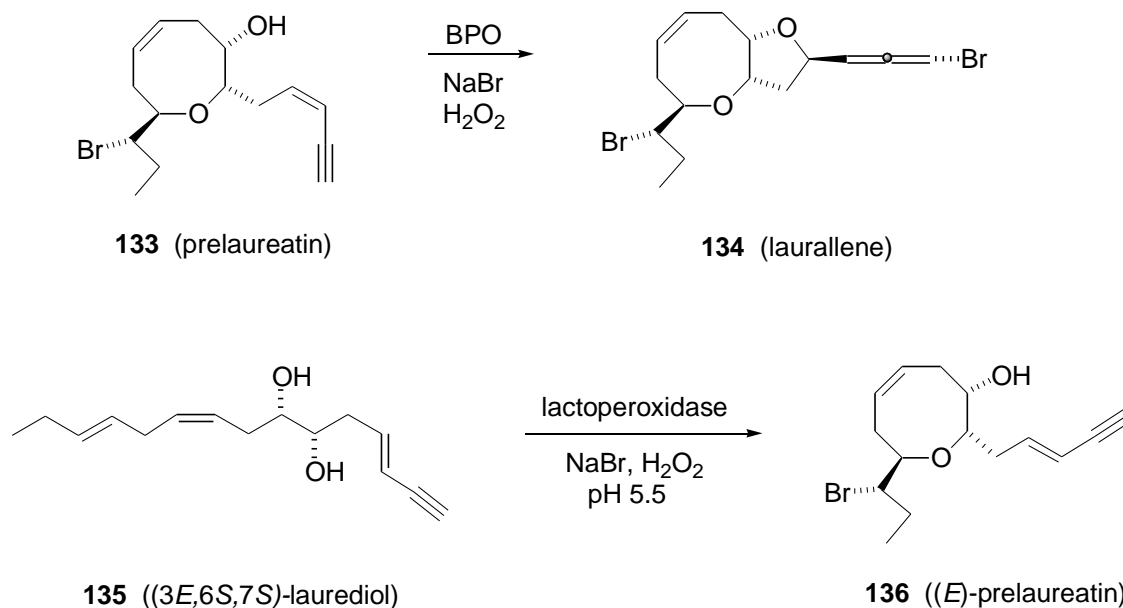
Despite the thousands of biogenically produced organohalogens, only a very few have been synthesized in the laboratory under biomimetic enzymatic conditions, although early model experiments supported the formation of halonium ions as logical intermediates in the biohalogenation of alkenes and alkynes (Faulkner, 1976; Wolinsky & Faulkner, 1976; Geigert *et al.*, 1984; Butler & Carter-Franklin, 2004). Laurediol (**129**), which is found in *Laurencia* red algae, is converted in the laboratory with BPO, bromide, and  $H_2O_2$  to the naturally occurring *Laurencia* metabolites deacetyl-laurencin (**130**), laureoxanyne (**131**), and laurefucin (**132**) (Scheme 5) (Fukuzawa *et al.*, 1994), a process that may mimic nature.

#### Scheme 5



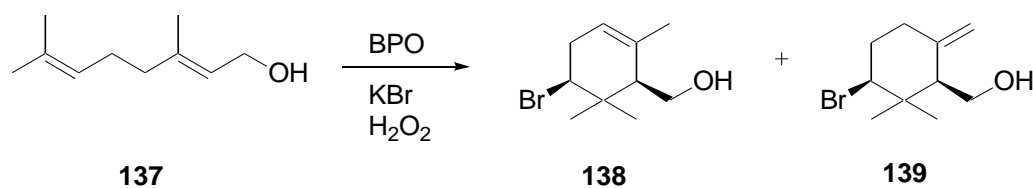
Under similar conditions, another *Laurencia* metabolite prelaureatin (**133**) is converted to laurallene (**134**) (Scheme 6) (Ishihara *et al.*, 1997), one of many bromoallene natural products unique to marine life. The isomeric laurediol **135** affords (*E*)-prelaureatin (**136**) under these biomimetic conditions (Ishihara *et al.*, 1995).

### Scheme 6



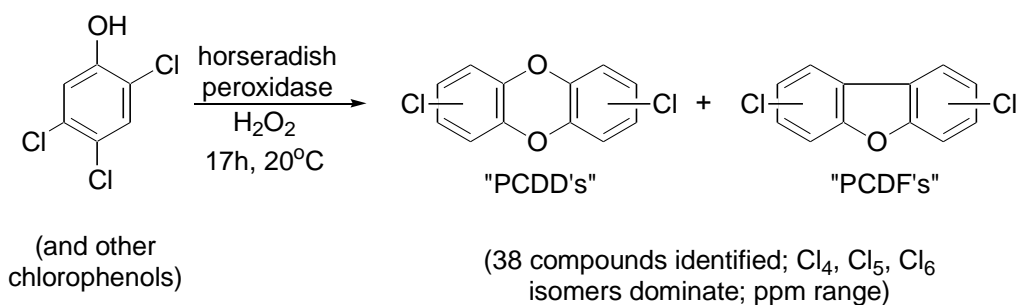
A vanadium BPO that is found in all classes of marine algae converts the monoterpene geraniol (**137**) to **138** and **139**, which are related to the natural  $\alpha$ - and  $\beta$ -snyderols, along with non-cyclized products (Scheme 7) (Carter-Franklin *et al.*, 2003).

### Scheme 7



Electron-rich organic substrates like phenols, pyrroles, indoles, tyrosine, and  $\beta$ -keto carboxylic acids are readily chlorinated and brominated with CPO and BPO, respectively (Gribble, 1996a). Moreover, chlorophenols are converted into both dioxins and chlorinated dibenzofurans in the ppm range (Scheme 8) (Svenson *et al.*, 1989; Wagner *et al.*, 1990; Öberg & Rappe, 1992; Gribble, 1996a; Morimoto & Tatsumi, 1997) by the well-known enzyme horseradish peroxidase (HRP) (Veitch, 2004). Nearly 40 different dioxins and furans were identified, with tetra-, penta-, and hexachloro congeners predominating. Subsequent work confirmed the formation of octachlorodibenzo-*p*-dioxin from pentachlorophenol and HRP (Morimoto & Kenji, 1995).

### Scheme 8



The detailed biochemical steps involved in the formation of naturally occurring organohalogens have been elucidated in a few cases. For example, the biosyntheses of vancomycin (**12**) (Hubbard & Walsh, 2003), pyrrolnitrin and other phenylpyrrole antibiotics (van Pée & Ligon, 2000), marine alga bromophenols (Flodin & Whitfield, 1999), fluoroacetic

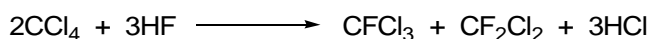
acid (**23**) (Schaffrath *et al.*, 2001; Murphy *et al.*, 2003; Cobb *et al.*, 2004), the dichloroimine-containing stylotellanes (Brust & Garson, 2003), and the *Lyngbya majuscula* cyanobacterium barbamide (Gerwick *et al.*, 2003) are becoming well understood.

### 3.2 Abiogenic organohalogens

Despite the overwhelming evidence for the biological formation of organohalogens in soils (Section 3.1), recent studies indicate that pure abiogenic chemical processes also occur in the soil to give organohalogen compounds. Thus, phenolic structures, as found in humic acids, are oxidized by iron(III) in both dissolved form and as the mineral phase ferrihydrite (Pracht *et al.*, 2001), leading to the production of organohalogens (e.g., CH<sub>3</sub>Cl, CH<sub>3</sub>Br, CH<sub>3</sub>I, C<sub>2</sub>H<sub>5</sub>Cl, C<sub>3</sub>H<sub>7</sub>Cl, C<sub>4</sub>H<sub>9</sub>Cl) (Keppler *et al.*, 2000). The authors suggest that "such abiotic processes could make a significant contribution to the budget of the important atmospheric compounds CH<sub>3</sub>Cl, CH<sub>3</sub>Br, and CH<sub>3</sub>I". The three chloroacetic acids also have an abiogenic source from the oxidative degradation of humic acid (Fahimi *et al.*, 2003). Likewise, six organoiodides (CH<sub>3</sub>I, CH<sub>3</sub>CH<sub>2</sub>I, CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>I, (CH<sub>3</sub>)<sub>2</sub>CHI, CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>I, CH<sub>3</sub>CH<sub>2</sub>CH(CH<sub>3</sub>)I) are produced abiogenically from humic acid and iron (III) (Keppler *et al.*, 2003), a soil source of naturally occurring organoiodides that may contribute significantly to tropospheric iodine.

One of the more interesting organohalogen-forming mechanisms is that of volcanic organohalogens. How do CFCs form in volcanic emissions? Isidorov has proposed the mechanism shown in Scheme 9 for the formation of CFCl<sub>3</sub> (CFC-11) and CF<sub>2</sub>Cl<sub>2</sub> (CFC-12), which is similar to the industrial production of these CFCs (Isidorov, 1990).

#### Scheme 9

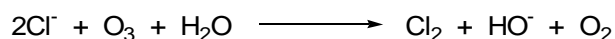


### 3.3 Production of free halogen

Although most naturally occurring organohalogens are produced from halide salts, either biogenically or abiogenically (previous two sections), there are processes, such as sea salt volatilization, marine algae, volcanoes, and coal combustion that generate free halogen (chlorine, bromine) or equivalent species (bromine oxide) that may react with organic compounds or materials to produce organohalogens (Graedel & Keene, 1995).

While extremely complicated, the oxidation of sea salt spray by ozone leads to the formation of chlorine and bromine atom precursors that photolyze to give reactive chlorine and bromine atoms, an observation supported by several studies (e.g., Scheme 10) (Keene, 1995; Maben *et al.*, 1995; Graedel & Keene, 1996; Oum *et al.*, 1998; Foster *et al.*, 2001; Moldanová & Ljungström, 2001; Finlayson-Pitts, 2003; Herrmann *et al.*, 2003; Knipping & Dabdub, 2003; Platt & Hönninger, 2003).

#### Scheme 10



Subsequent reactions of chlorine atoms with alkanes, for example, will form HCl and alkyl radicals. The reaction of bromine atoms with alkanes is much slower. The important reaction of bromine atoms is the destruction of ozone in the troposphere, particularly in the Arctic at polar sunrise. Many studies have noticed this phenomenon (Foster *et al.*, 2001; Finlayson-Pitts, 2003; Platt & Hönninger, 2003). The dominant form of chlorine during the polar sunrise is thought to be BrCl (Foster *et al.*, 2001). A source of iodine atoms and iodine oxide species in the atmosphere is photolysis of biogenic alkyl iodides (O'Dowd *et al.*, 2002; Carpenter, 2003), and the Soufrière Hills volcano (Montserrat) was a source of bromine oxide during May 2002 volcanic activity (Bobrowski *et al.*, 2003). Reactive chlorine (e.g., ClO) and bromine (e.g., BrO) species are present over the Great Salt Lake, Utah (Stutz *et al.*, 2002) and over the Dead Sea, Israel (Matveev *et al.*, 2001). Both studies reveal a negative correlation of BrO with ozone levels. Concentrations of ozone over the Dead Sea decreased from noontime levels of 50-80 ppb down to an occasional low of 2 ppb. A study of North American coastal air revealed the daily production of high

concentrations of gaseous chlorine (up to 330 ppt) from a previously unrecognized night-time source (Spicer *et al.*, 1998). The global quantities of these reactive halogens and their effect and role in the production of organohalogen compounds are unknown.

## 4 Quantities and Fluxes of Natural Organohalogens

Before one can assess the relative contributions of natural and anthropogenic organohalogens to the global environment, the quantities and fluxes of these chemicals need to be estimated. Most of these estimates have been made for the simple gaseous haloalkanes. Table 1 lists the ranges of estimated quantities of these haloalkanes, with the anthropogenic quantities listed where known. For a listing of earlier estimates see Gribble, 1996a.

**Table 1: Average estimates of emissions of naturally occurring haloalkanes from various sources (and selected anthropogenic estimates)<sup>a</sup>**

Compound	Source	Tons per Year	Reference
CH <sub>3</sub> Cl	all sources	3,500,000	(1)
CH <sub>3</sub> Cl	tropical plants	8,200,000	(2)
CH <sub>3</sub> Cl	biomass burning	910,000	(3)
CH <sub>3</sub> Cl	oceans	650,000	(4)
CH <sub>3</sub> Cl	oceans	600,000	(1)
CH <sub>3</sub> Cl	oceans	400,000	(5)
CH <sub>3</sub> Cl	salt marshes		(6)
		170,000	
CH <sub>3</sub> Cl	Wood rotting fungi		(7)
		160,000	
CH <sub>3</sub> Cl	Terrestrial	140,000	(4)
CH <sub>3</sub> Cl	Coal combustion	107,000	(8)
CH <sub>3</sub> Cl	Forests	85,000	(9)
CH <sub>3</sub> Cl	Wetlands	48,000	(10)
CH <sub>3</sub> Cl	Incineration	46,000	(8)
CH <sub>3</sub> Cl	Shrublands	15,000	(11)
CH <sub>3</sub> Cl	Industry	10,000	(8)
CH <sub>3</sub> Cl	Peatlands	5,500	(12)
CH <sub>3</sub> Cl	Rice paddies	5,300	(13)
CH <sub>3</sub> Cl	Macroalgae	2,000	(14)
CH <sub>3</sub> Cl	Macroalgae	140	(1)
CH <sub>3</sub> Cl	volcanoes	78	(15)
CH <sub>3</sub> Br	All sources	122,000	(1)
CH <sub>3</sub> Br	Oceans	56,000	(16)
CH <sub>3</sub> Br	Anthropogenic	46,000	(16)
CH <sub>3</sub> Br	Salt marshes	14,000	(6)
CH <sub>3</sub> Br	Biomass burning	20,000	(16)
CH <sub>3</sub> Br	Wetlands	4,600	(10)
CH <sub>3</sub> Br	Rice paddies	3,500	(13)
CH <sub>3</sub> Br	Wood rotting fungi	1,700	(17)
CH <sub>3</sub> Br	Peatlands	900	(12)
CH <sub>3</sub> Br	Shrublands	700	(11)
CH <sub>3</sub> Br	Macroalgae	100	(14)
CH <sub>3</sub> Br	Macroalgae	56	(1)
CH <sub>3</sub> Br	volcanoes	1	(15)
CHBr <sub>3</sub>	All sources	220,000	(18)
CHBr <sub>3</sub>	macroalgae	200,000	(20)
CHBr <sub>3</sub>	Antarctic microalgae	53,000-80,000	(19)
CHBr <sub>3</sub>	Antarctic microalgae	4,700-70,000	(19)
CHBr <sub>3</sub>	Macroalgae	4,000-40,000	(19)
CHBr <sub>3</sub>	Macroalgae	400	(21)
CHCl <sub>3</sub>	All sources	660,000	(22)
CHCl <sub>3</sub>	All sources	470,000	(1)
CHCl <sub>3</sub>	Oceans	450,000	(1)

CHCl <sub>3</sub>	Oceans	360,000	(4)
CHCl <sub>3</sub>	Terrestrial	220,000	(22)
CHCl <sub>3</sub>	Terrestrial	200,000	(4)
CHCl <sub>3</sub>	Termites	100,000	(23)
CHCl <sub>3</sub>	Industrial	67,000	(4)
CHCl <sub>3</sub>	Rice paddies	23,000	(24)
CHCl <sub>3</sub>	Volcanic, geologic	<20,000	(22)
CHCl <sub>3</sub>	Peatlands	4,700	(9)
CHCl <sub>3</sub>	Biomass burning	2,000	(3)
CHCl <sub>3</sub>	Microalgae	250	(1)
CHCl <sub>3</sub>	volcanoes	95	(15)
CH <sub>3</sub> I	All sources	40,000,000	(25)
CH <sub>3</sub> I	All sources	2,100,000	(1)
CH <sub>3</sub> I	Rice paddies	72,000	(13)
CH <sub>3</sub> I	Peatlands	1,400	(9)
CH <sub>3</sub> I	Macroalgae	280	(1)
CH <sub>3</sub> I	Volcanoes	1.4	(15)
CH <sub>3</sub> I	macroalgae	0.9	(21)
CH <sub>2</sub> Cl <sub>2</sub>	All sources	6,000,000	(1)
CH <sub>2</sub> Cl <sub>2</sub>	Oceans	200,000	(1)
CH <sub>2</sub> Cl <sub>2</sub>	Oceans	190,000	(4)
CH <sub>2</sub> Cl <sub>2</sub>	Biomass burning	59,000	(3)
CH <sub>2</sub> Cl <sub>2</sub>	Macroalgae	320	(1)
CH <sub>2</sub> Cl <sub>2</sub>	volcanoes	21	(15)
CCl <sub>4</sub>	All sources	1,900,000	(25)
CCl <sub>4</sub>	volcanoes	3.4	(15)
CCl <sub>2</sub> CCl <sub>2</sub>	Oceans	19,000	(4)
CH <sub>3</sub> CCl <sub>3</sub>	Biomass burning	16,000	(3)
CH <sub>2</sub> ClI	All sources	4,800,000	(1)
CH <sub>2</sub> ClI	macroalgae	240	(1)
CH <sub>3</sub> CH <sub>2</sub> I	All sources	230,000	(1)
CH <sub>3</sub> CH <sub>2</sub> I	macroalgae	38	(1)
C <sub>6</sub> H <sub>5</sub> Cl	volcanoes	12.7	(15)
CFCl <sub>3</sub>	volcanoes	8.6	(15)
CH <sub>2</sub> Br <sub>2</sub>	macroalgae	12	(21)
CH <sub>2</sub> I <sub>2</sub>	macroalgae	39	(21)

<sup>a</sup> Since literature values are usually given in grams (Tg, Gg, Mg), for convenience, we used the conversion factor of 1 ton  $\cong$  10<sup>6</sup> grams.

(1) Baker *et al.*, 2001; (2) Yokouchi *et al.*, 2002; (3) Lobert *et al.*, 1999; (4) Khalil *et al.*, 1999; (5) Moore *et al.*, 1996b; (6) Rhew *et al.*, 2000; (7) Wating & Harper, 1998; (8) Keene *et al.*, 1999; (9) Dimmer *et al.*, 2000; (10) Varner *et al.*, 1999; (11) Rhew *et al.*, 2001; (12) Dimmer *et al.*, 2001; (13) Redeker & Cicerone, 2004; (14) Manley & Dastoor, 1987; (15) Schwandner *et al.*, 2004; (16) Yvon-Lewis & Butler, 1997; (17) Lee-Taylor & Holland, 2000; (18) Carpenter & Liss, 2000; (19) Sturges *et al.*, 1992; (20) Manley *et al.*, 1992; (21) Giese *et al.*, 1999; (22) McCulloch, 2003; (23) Khalil *et al.*, 1990; (24) Khalil *et al.*, 1998; (25) Lovelock *et al.*, 1973

Although some of the estimates in Table 1 are wildly discrepant, certain facts emerge from the data. Macroalgae produce about 70% of the world's bromoform (Carpenter & Liss, 2000). Biomass burning seems to be the single largest source of methyl chloride and a significant source of dichloromethane (Lobert *et al.*, 1999). In fact, 85% of methyl chloride emissions originate in the tropical and subtropical zones between 30°S and 30°N (Khalil & Rasmussen, 1999). The largest natural terrestrial source of methyl bromide, and possibly of



methyl chloride, appears to be salt marshes (Rhew *et al.*, 2000). Marine sources account for 25% of the emissions of dichloromethane (Keene *et al.*, 1999). More than 100 tons of methyl iodide is released out of the southern North Sea annually (Campos *et al.*, 1996), and methyl bromide is supersaturated over a large region of the northeast Atlantic Ocean (Baker *et al.*, 1999). Despite the wealth of research on the fluxes of the methyl halides, there are undiscovered sources of methyl chloride and methyl bromide, and perhaps other haloalkanes (Harper, 2000; Redeker & Cicerone, 2004). It has been estimated that 268 million tons of trifluoroacetic acid is present in the oceans (Frank *et al.*, 2002).

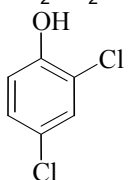
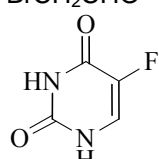
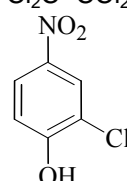
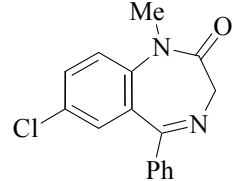
A quantitative study of the acorn worm *Ptychodera flava* living in Okinawa estimates that the approximate 64 million worms living in a one-square kilometer habitat excretes 95 pounds of organohalogens (mainly bromophenols) daily, or 35,000 pounds (17 tons) annually. This amount represents one-half of the annual US anthropogenic production of 2,4,6-tribromophenol (Higa & Sakemi, 1983). A similar study of the Floridian *Ptychodera bahamensis* estimates an annual output of 0.5-1.3 tons of organohalogens per kilometer of coastline (Corgiat *et al.*, 1993), and investigation of the brown alga *Ascophyllum nodosum* has determined that some two tons of HOBr is produced annually by this seaweed along a 30 kilometer stretch of dike in the Netherlands (Wever *et al.*, 1991). Many more studies of these kinds need to be performed to determine biogenic organohalogen outputs.



## 5 Comparison of Natural versus Anthropogenic Organohalogens

As seen in the previous sections, a significant number of organohalogens are both natural and man-made. A summary of these compounds is listed in Table 2.

**Table 2: Organohalogens that have natural and anthropogenic origins**

Organohalogen	Natural Source	Anthropogenic
CHCl <sub>3</sub>	Algae, volcanoes, termites, plants	Solvent, water chlorination byproduct
CH <sub>3</sub> Br	Vegetables, algae	Fumigant, pesticide
CH <sub>3</sub> I	Algae	Industrial chemical
BrCH <sub>2</sub> CH <sub>2</sub> Br	Algae	Industrial fumigant
	<i>Penicillium</i> sp. hormone	Industrial chemical 2,4-D herbicide precursor
CH <sub>2</sub> =CHCl	Abiogenic soil product	Polyvinylchloride precursor
Dioxins (several)	Natural combustion biogenic soil product	Industrial byproduct Incineration product
CFCs (CFCl <sub>3</sub> , CF <sub>2</sub> Cl <sub>2</sub> )	Volcanoes, minerals	refrigerants
CH <sub>3</sub> Cl	Volcanoes Biomasa combustión Biogenic soil product	Industrial chemical
ClCH <sub>2</sub> CO <sub>2</sub> H	Biogenic soil product	Industrial soil product
Cl <sub>2</sub> CHCO <sub>2</sub> H	Biogenic soil product	Lactic acidosis drug
Cl <sub>3</sub> CCO <sub>2</sub> H	Biogenic soil product	Herbicide
FCH <sub>2</sub> CO <sub>2</sub> H	Terrestrial plants	Pesticida ("1080")
CHBr <sub>2</sub>	Algae	Industrial chemical
CHBr <sub>2</sub>	Minerals, algae?	Teflón precursor
ClCH <sub>2</sub> COCH <sub>2</sub> Cl	Algae	Water chlorination byproduct
BrCH <sub>2</sub> CHO	Algae	Industrial chemical
	Marine sponge	Antidepressant (valium)
Cl <sub>2</sub> C=CCl <sub>2</sub>	Volcanoes, algae, minerals	Dry clearing agent
	Carrot truffle	Fungicide
	Vegetables, mammals	Antidepressant (valium)

Another group of natural organohalogens have very similar structures to anthropogenic industrial chemicals (Table 3).

**Table 3: Anthropogenic and natural organohalogens that are structurally closely related**

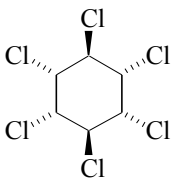
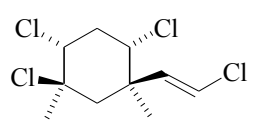
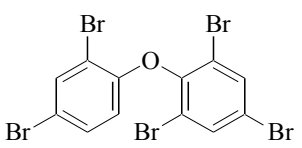
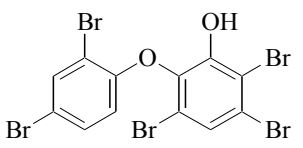
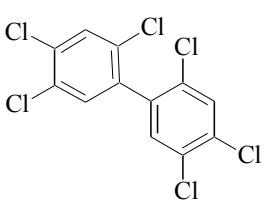
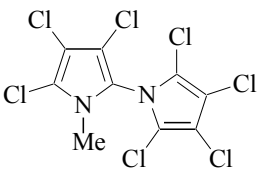
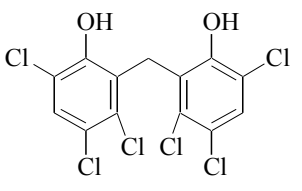
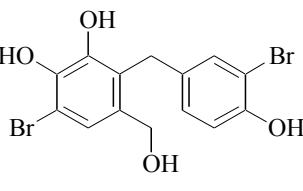
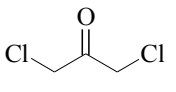
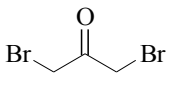
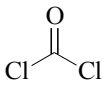
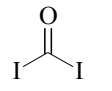
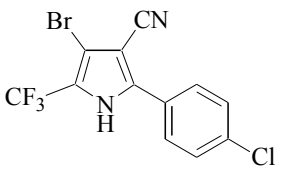
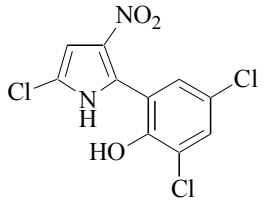
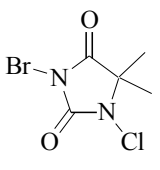
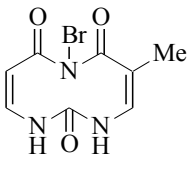
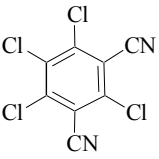
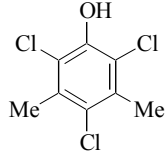
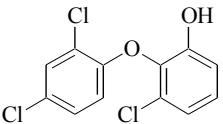
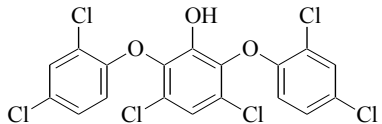
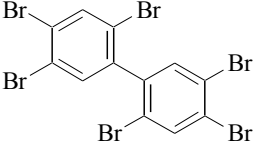
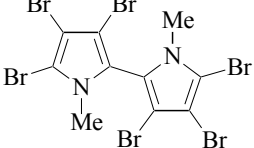
Anthropogenic Organohalogen	Anthropogenic Source	Natural Organohalogen	Natural Function
	insecticide		algae metabolite; antifeedant?
<b>lindane</b>		<b>gelidene</b>	
	fire retardant		sponge metabolite; function unknown
	industrial chemical		marine metabolite?
<b>a PCB</b>		<b>Q1</b>	
	antiseptic soap ("PhisoHex")		marine alga antifeedant
<b>hexachlorophene</b>			
	water chlorination byproduct		marine alga metabolite
	war gas; industrial chemical		marine alga metabolite
	insecticide		soil microbe antibiotic
		<b>pyrrolomycin E</b>	
	swimming pool disinfectant		sponge metabolite; function unknown

Table 3 (cont'd)

Anthropogenic Organohalogen	Anthropogenic Source	Natural Organohalogen	Natural Function
 <p>daconil</p>	fungicide	 <p>Japanese lily fungicide</p>	Japanese lily fungicide
	anti-plaque oral formulation	 <p>ambigol B</p>	cyanobacterial metabolite
 <p>a PBB</p>	fire retardant	 <p>marine bacterial metabolite</p>	marine bacterial metabolite



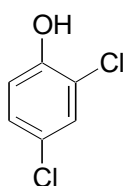
## 6 Natural Function of Organohalogens

Why do living organisms biosynthesize secondary metabolites, which, in some cases, are molecules of incredible complexity? It is unreasonable to believe that these unique molecules, representing an enormous investment in the organisms' gene inventory, are synthesized without a specific function. The biosyntheses of some organohalogens presented thus far require multiple enzymatic steps. Each enzyme of 300-600 amino acids occupies 900-1800 nucleic acid base pairs on the gene. For example, chloroperoxidase (CPO) from *Caldariomyces fumago* has a molecular weight of 42,000 (Morris & Hager, 1966), and bromoperoxidase (BPO) monomer from *Ascophyllum nodosum* has a molecular weight of 60,000 (Weyand *et al.*, 1999). Both of these enzymes consist of about 560 amino acids.

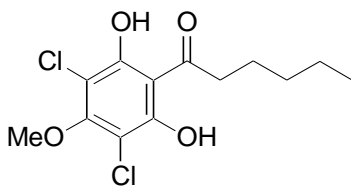
The preceding sections have cited numerous examples of natural organohalogens with antibacterial, antifungal, antitumor, antiviral, and antifeedant activity. However, these activities may not necessarily be related to the natural function of the metabolites. The benefits of these biologically active organohalogens are discussed in Section 7. Several studies provide compelling evidence for the role that organohalogens play in their natural setting. For general reviews on the function of metabolites in nature, see (Williams *et al.*, 1989; Christophersen, 1991).

Insect pheromones and allomones have been utilized for many years as a means with which to monitor and control insects. The few examples of halogenated insect pheromones are 2,6-dichlorophenol, a sex pheromone of several species of tick, the two chlorine-containing blattellastanosides, which are aggregation pheromones of the German cockroach, and halogenated tyrosine-containing proteins in locusts (*Schistocerca gregaria*) that apparently strengthen cuticle and improve adhesion between protein sheets (Hunt & Breuer, 1971; Welinder *et al.*, 1976). These proteins are also present in molluscs, such as 2-bromo-6-chlorotyrosine that is present in *Buccinum undatum*.

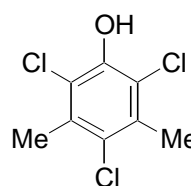
It is thought that the frog secretion epibatidine (**100**) is toxic to birds, and 2,4-dichlorophenol (**140**) is a growth hormone produced by a *Penicillium* sp. (Ando *et al.*, 1970). The related chlorinated phenolic slime mold (*Dictyostelium discoideum*) metabolite **141** is a hormone that triggers the transformation of undifferentiated cells into fruiting bodies (Morris *et al.*, 1988). The plant growth hormone 4-chloro-3-indoleacetic acid (**16**) is biosynthesized and utilized by peas, beans, lentils, vetch and other members of the Leguminosae family. The Japanese lily *Lilium maximowiczii* produces seven novel chlorinated fungicidal phenols (e.g., **142-143**) in response to attack by a pathogenic *Fusarium* fungus at the site of infection (Monde *et al.*, 1998). Terrestrial plants also produce a myriad of natural pesticides, such as the familiar examples of nicotine, rotenone, and pyrethrins. A few halogenated examples are known. The Thai plant *Arundo donax* contains the weevil repellent **22**. The chlorine-containing tafricanins A and B, which are found in the South African bush *Teucrium africanum* are insect antifeedants (Hanson *et al.*, 1982). The lichen *Lethariella canariensis* produces a series of allelochemicals, including five chlorinated metabolites (e.g., **144-146**), that are phytotoxic and apparently prevent the germination and subsequent development of seeds from potentially competitive lichens and plants (Marante *et al.*, 2003).



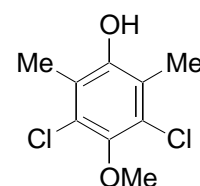
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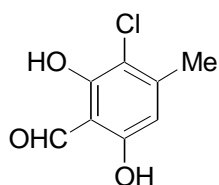
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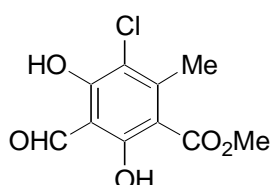
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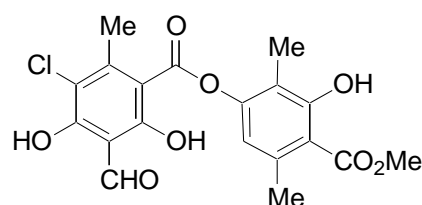
**143**



**144** (chloroatranol)



**145** (methyl chlorohematommate)

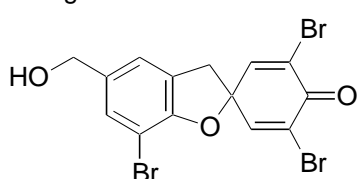


**146** (chloroatranorin)

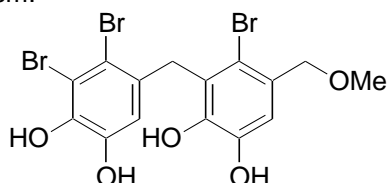
Most examples of clearly defined functions ascribed to organohalogens are from marine organisms, both in the laboratory and in the ocean environment. These marine metabolites usually play a defensive role and numerous organohalogen (and nonhalogenated) metabolites from sponges, sea hares, ascidians, gorgonians, nudibranchs, and marine algae are repellents, antifeedants, antifoulants and antibacterial compounds. Lacking mobility or a protective covering, these marine animals and plants employ chemical warfare for survival (Pawlik, 1993). The erythrolides of the gorgonian coral *Erythropodium caribaeorum* have pronounced antifeedant activity against reef fishes at the natural concentrations of these metabolites found in the gorgonian (Fenical & Pawlik, 1991). The bromopyrroles present in *Agelas wiedenmayeri* and *Agelas conifera* Caribbean sponges are potent feeding deterrents (Assmann *et al.*, 2000), and bromine substitution enhances the activity. The *Thelepus* sp. acorn worm metabolite thelepin (**147**) protects the mucous cocoon of this animal and may be an antiseptic in wound healing since it occurs in highest amounts in the tentacles and the end of the abdomen, those parts that protrude into the environment (Goerke *et al.*, 1991).

The prevention of larval settlement, barnacle fouling, and bacterial overgrowth is essential for the survival of marine organisms and many organohalogen metabolites have this function. For example, the function of BPO in the red alga *Corallina pilulifera* is to generate bromoform, which serves to eliminate surface microalgae (Ohsawa *et al.*, 2001). Tribromogramine **60** from the bryozoan *Zoobotryon pellucidum* is a potent inhibitor of larval settlement by the barnacle *Balanus amphitrite* (Kon-ya *et al.*, 1994a, 1994b). The powerful antifouling activity of isocyanoterpenoids, like kalihinol A, against larvae of the barnacle *Balanus amphitrite* has been reviewed (Fusetani *et al.*, 1996). These sponge and nudibranch metabolites have low toxicity to other organisms unlike the commercial antifouling organotin compounds. Many other marine metabolites exhibit antifouling properties (Fusetani, 2004), and there is general interest in the development of tin-free antifouling paints (Omae, 2003). Natural brominated indole-3-carbaldehydes from the ascidian *Stomozoa murrayi*, and related synthetic derivatives, prevent the development of sea urchin eggs (Moubax *et al.*, 2001). Maximum activity is observed with C-2 brominated indoles. Natural concentrations of the crude organic extracts from 21 of 26 species of Caribbean sponges inhibited bacterial attachment, which is the first step in bacterial infection and colonization (Kelly *et al.*, 2003). In particular, the three brominated pyrroles isolated from *Agelas* sponges, oroidin, 4,5-dibromopyrrole-2-carboxylic acid, and sceptrin, are highly active at natural concentrations. Four new brominated diphenyl ethers from the Palauan sponge *Phyllospongia dendyi* exhibit antimacroalgal activity with IC<sub>50</sub> values of 0.02-0.05 ppm, and antimicroalgal values of 0.5-5.0 ppm (Hattori *et al.*, 2001).

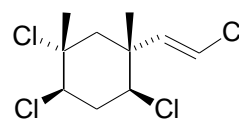
The diphenylmethane **148** from the red alga *Odonthalia corymbifera* is a potent antifeedant against abalone and sea urchin (Kurata *et al.*, 1997). Several brominated diterpenes from *Laurencia saitoi* are feeding deterrents towards young abalone (*Haliotis discus hannai*) and young sea urchins (*Strongylocentrotus nudus* and *S. intermedius*) (Kurata *et al.*, 1998). The red alga *Plocamium hamatum* has a direct contact deleterious effect on the soft coral *Sinularia cruciata* (de Nys *et al.*, 1991). This tissue necrosis is caused by chloromertensene (**149**), a metabolite of this seaweed. This is the first clear evidence of allelopathy between an alga and another marine organism.



**147** (thelepin)



**148**

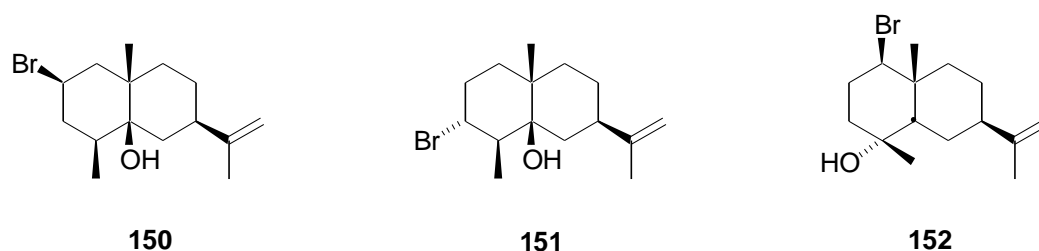


**149** (chloromertensene)

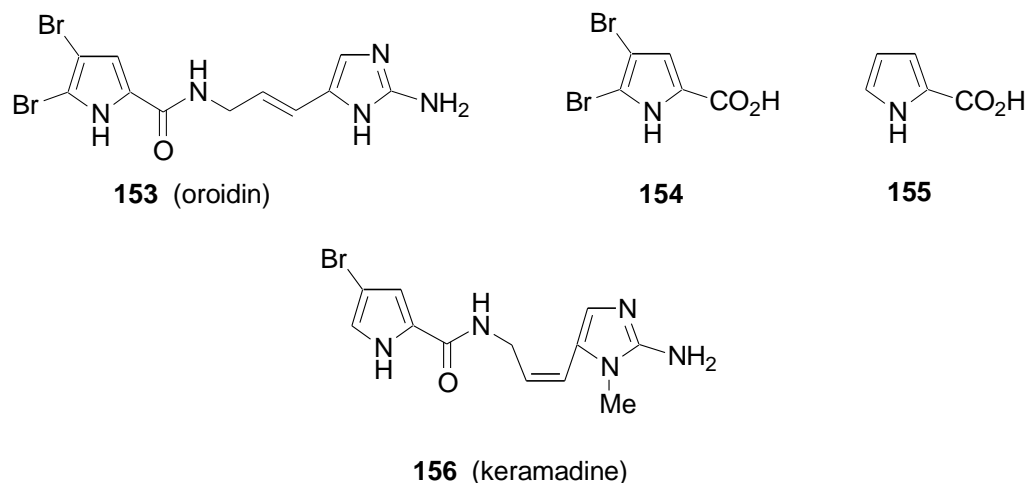


Marine algae also produce HOBr as a potential antimicrobial agent (Wever *et al.*, 1991), and the *Laurencia intermedia* red seaweed brominated terpene laurinterol and related algal metabolites have antimicrobial activity approaching that of streptomycin (Paul, 1987). In some cases, marine bacteria that are associated with host organisms (e.g., sponges, tunicates, algae) produce antifouling compounds. For example, ten marine *Pseudoalteromonas* bacteria species, which are common on marine living surfaces, express antibacterial, antifungal, anti-algal and antilarval activities (Holmström *et al.*, 2002). These results lend support to the hypothesis that marine bacteria may regulate biofouling events on marine organisms.

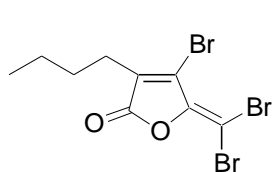
Marine organism metabolites also act as fish antifeedants and numerous halogenated and nonhalogenated compounds have this property. For example, the algal metabolites vidalol A, avrainvilleol, and debromoisocymbobarbatol are either feeding deterrents or highly toxic to reef fish (Gribble, 1996a). Several common brominated algal metabolites (cymopol, isolaurinterol, elatol and aplysin) show antifeeding activity at natural concentrations towards reef fishes and the herbivorous sea urchin *Diadema antillarum* (Hay *et al.*, 1987). The tropical green alga *Neomaeris annulata* contains the novel brominated sesquiterpenes **150-152** that deter feeding by reef fishes (Paul *et al.*, 1993).



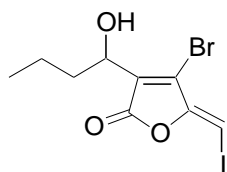
Sponges are also prolific producers of fish antifeedants. The bromine-containing stevensine from the sponge *Axinella corrugata* deters feeding of reef fish in the laboratory and on the reef (Wilson *et al.*, 1999). Several other natural (and unnatural) brominated pyrroles from sponges of the genus *Agelas* exhibit antifeedant activity, especially oroidin (**153**) and dispacamide A (Lindel *et al.*, 2000). Bromine substitution leads to increased efficacy; thus **154** is more active than **155**, and oroidin (**153**) is more active than keramidine (**156**).



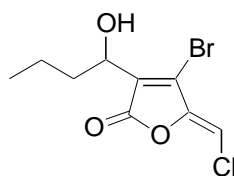
The antarctic sponge *Latrunculia apicalis* produces the bromine-containing discorhabdin G, which is structurally similar to discorhabdin S (see Appendix 1), that effectively repels the predatory sea star *Perknaster fuscus* (Furrow *et al.*, 2003). Most of this metabolite is concentrated within 2 mm of the sponge surface. Nudibranchs and sea hares also rely heavily on chemicals for defense (Cimino & Ghiselin, 1999; de Nys *et al.*, 1996), some of which are halogenated, e.g., furanones **157-159** from the sea hare *Aplysia parvula* and its host plant *Delisea pulchra*, and panacene (**160**) from the sea hare *Aplysia brasiliensis*, an animal rejected by sharks (Kinnel *et al.*, 1977). The toxicity of sea hare extracts was known since pre-Christian times when they were used as poisons (Pettit *et al.*, 1976).



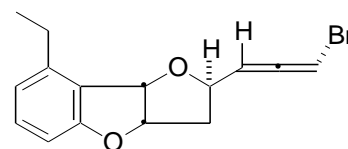
157



158



159



160 (panacene)

Most chemical defensive compounds are not lethal to the target organism. Notable exceptions are the toxic *Conus* snail toxins. These highly toxic peptides, which typically contain 6-bromotryptophan, are used by the snail to paralyze and eat fish, molluscs and worms (Myers *et al.*, 1993; Nelson, 2004). The function of the bromine in these *Conus* peptides, which are also found in the hagfish, may be to make the peptides less susceptible to detoxifying proteolysis by the prey due to the size of the bromine and the poor fit in the active site of chymotrypsin (Shinnar *et al.*, 2003).

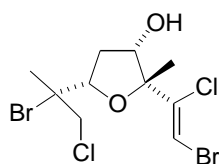
Less well understood are the natural functions of the simple biogenic haloalkanes. One suggested role of the halomethanes is to recycle halogen/halide between oceans, atmosphere and land. Methyl iodide may be a natural carrier of iodine (Lovelock *et al.*, 1973), bromoform and/or methyl bromide may be carriers of bromine (Manley *et al.*, 1992; Sturges *et al.*, 1992), and methyl chloride may be a natural regulator of the ozone layer. A more secure role for biogenic methyl chloride is in the degradation of lignin by wood-rotting fungi, by regenerating veratryl alcohol degraded by the attack of lignin peroxidase (Harper, 2000; Hamilton *et al.*, 2003). Since methyl chloride is also emitted by the potato, cypress, cedar, and other higher plants, it may play a biosynthetic role here as well. The role of methyl chloride as a methyl donor in the biosynthesis of veratryl alcohol has been further investigated and labeling studies indicate that methyl chloride in these fungi is derived from methionine and not *S*-adenosylmethionine (Harper *et al.*, 1996).

## 7 Benefits of Natural Organohalogens

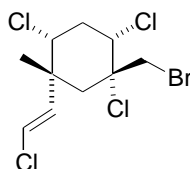
Like penicillin, morphine, vincristine, digitalis, quinine, aspirin, taxol, colchicine and other natural products that are drugs or have been developed into drugs, several natural organohalogens have important medicinal value (Laus, 2001; Gribble, 2003c).

Vancomycin (**12**) has found commercial use as an antibiotic for more than 50 years (Loll & Axelsen, 2000; Hubbard & Walsh, 2003). It is active against penicillin-resistant bacterial infections, especially the *Staph* infections that occur in hospital patients. Vancomycin derivatives are being developed to overcome vancomycin-resistant germs that have developed in recent years (Süssmuth, 2002; Ahrendt *et al.*, 2003; Mu, *et al.*, 2004). Other halogenated natural products that are in clinical development as new anticancer agents include rebeccamycin (Bailly *et al.*, 1997), cryptophycins (**34**) (Menon *et al.*, 2000; Wagner *et al.*, 1999), and punaglandins, which are similar to the *Clavularia viridis* metabolites (Appendix I) (Fukushima & Kato, 1985).

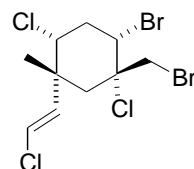
The marine monoterpenes furoplocamioid C (**161**) and cyclohexanes **162** and **163** are very efficient aphid repellents and antifeedants (Argandoña *et al.*, 2002), and agelastatin A (**164**) has potent insecticidal activity against the beet army worm and the corn root worm (Hong *et al.*, 1998). Compounds **161-163** have low mammalian toxicity and no phytotoxicity.



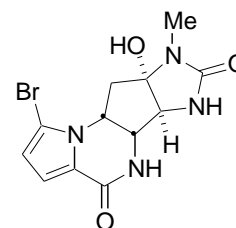
**161** (furoplocamioid C)



**162**

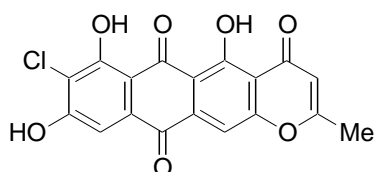


**163**

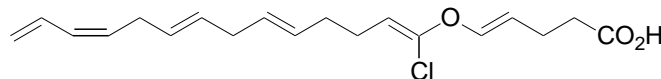


**164** (agelastatin A)

The topoisomerase I inhibitor topopyrone B (**165**) is potent against the herpes virus VZV and is comparable to camptothecin in topo I activity (Kanai *et al.*, 2000; Ishiyama *et al.*, 2000). The maracens (e.g., **166**) have activity against mycobacteria, which is the cause of tuberculosis (Herrmann *et al.*, 1998).



**165** (topopyrone B)



**166** (maracen A)

The bromine-containing cyclic depsipeptide microspinosamide, from the sponge *Sidonops microspinosus*, shows strong anti-HIV activity (Rashid *et al.*, 2001). This metabolite contains the novel  $\beta$ -hydroxy-*p*-bromophenylalanine amino acid. Hymenialdisine, a marine sponge brominated pyrrole, is a potent and selective inhibitor of the kinases that appear to play a role in the hyperphosphorylation of substrates involved in Alzheimer's disease (Meijer *et al.*, 2000). This pyrrole is also a G<sub>2</sub> checkpoint inhibitor, a property that may be used to sensitize cancer cells to DNA-damaging therapies (Curman *et al.*, 2001). The bromotryptophan *Conus* toxins have clinical analgesic activity and a drug (ziconotide) has been developed (Alonso *et al.*, 2003; Staats *et al.*, 2004).

Other recently discovered biologically active organohalogens, particularly from marine sources, are potential insecticides (El Sayed *et al.*, 1997; González *et al.*, 2003; Peng *et al.*, 2003), general agrochemical agents (Peng *et al.*, 2003), cytotoxic agents (Gribble, 2003c), HIV active agents (Loya *et al.*, 1999), antifungal agents (Ligon *et al.*, 2000), antiinflammatory agents (Amagata *et al.*, 2003), antibacterials (Nicholas *et al.*, 2002),

antioxidants (Takamatsu *et al.*, 2003), and protein kinase inhibitors (Tasdemir *et al.*, 2002a; Gompel *et al.*, 2004). Several marine seaweed extracts (e.g., *Rhodomela confervoides*, *Symphyocladia latiuscula*, *Laminaria japonica*) show powerful antioxidant activity comparable to BHT (Huang & Wang, 2004).

Although marine organisms are a relatively unexplored frontier in the search for new medicines, several reviews of this area are available (Cardellina, 1986; Carté, 1996; Scheuer, 1999; Capon, 2001; Kubanek *et al.*, 2003; Donia & Hamann, 2003; Krajick, 2004). The search for new antitumor drugs from cyanobacteria has been reviewed (Moore *et al.*, 1996a), and the importance of natural products in drug discovery has been emphasized (Cragg *et al.*, 1997).

## 8 Latest Findings

The most exciting development in the field of naturally occurring organohalogens — and one of monumental importance — is the work of Reddy that provides for the first time direct determination as to whether an organohalogen compound is natural or anthropogenic! The method relies on the fact that natural compounds have more carbon-14 than anthropogenic compounds, the latter which are derived from petroleum for which the carbon-14 content has been depleted over the eons (Reddy *et al.*, 2002a, 2002b, 2004; Drenzek *et al.*, 2002). Although the method requires substantial material for analysis, this radiocarbon method, like DNA forensic evidence, can provide absolute proof of origin. Chlorine isotope effects for biogenic chlorination also provide a means to distinguish natural from nonnatural chlorination (Reddy *et al.*, 2000, 2002c; Harper *et al.*, 2003a).

Other significant recent findings are the formation in soil of organochlorines by an abiogenic mechanism involving iron-catalyzed oxidation of humic acid leading to, for example, vinyl chloride; the discovery of the bioaccumulative Q1 (**96**) in humans; a polychlorinated bipyrrrole that presumably has a marine origin; and the natural formation of dioxins in pristine soils. Each of these findings was presented earlier.

## 9 Future Outlook

To combat antibiotic-resistant germs and emerging third-world diseases, and to discover new drugs against cancer and HIV, scientists continue to explore nature as a source of new drugs. The chemical entities that nature provides surpass the inventiveness of synthetic chemists and offer the best hope of novel drug discovery. After a period of stagnation in the 1980s, the pursuit of natural products has been revitalized. New and improved techniques for compound characterization (multidimensional nuclear magnetic resonance spectroscopy, high resolution mass spectroscopy), compound purification (high pressure liquid chromatography, counter current separation), and organism collection (SCUBA and remote submersibles for marine organism collection) have greatly facilitated natural product discovery. Powerful, selective bioassays combined with folk medicine and ethnobotany have guided the scientist to biologically important organisms. Illustrative of the increase in natural products discovery is that in 2002, some 756 new marine natural products were reported, 14% of which contain halogen. Table 4 summarizes these data for the years 1998-2002. It is interesting to note that most marine natural products are **not** halogenated. Of 4145 marine natural products described in this five year period, 697 (17%) are halogenated.

**Table 4: Marine natural products described during 1998-2002**

Year	Marine Natural Products			Reference
	Total Number	Organohalogens	% Organohalogens	
1998	841	140	17	Faulkner, 2000
1999	886	163	18	Faulkner, 2001
2000	869	126	14	Faulkner, 2002
2001	793	162	20	Blunt <i>et al.</i> , 2003
2002	756	106	14	Blunt <i>et al.</i> , 2004

Given the fact that only a small percentage of terrestrial plants, marine organisms, fungi, and microbes have been investigated for their chemical content, new natural products of all types are certain to be discovered in the years ahead, and a percentage of these natural products will inevitably contain halogen. With its largely unexplored 500,000 species in 30 phyla of plants, animals, bacteria, unicellular algae and fungi, the marine world offers the greatest source of new medicines. Fewer than 10% of the 4,000 species of bryozoans have been investigated for their chemical makeup, and only 20 of the 90 Hawaiian deep-sea gorgonians described thus far have been examined (Okuda *et al.*, 1982). The 80,000 species of molluscs remain substantially untapped for their metabolites. One promising relatively new area of marine exploration are deep water sponges. A study of a small area of the north Jamaican coast at depths between 70-90 meters revealed the presence of 27 sponge species, 10 of which are new to science (Lehnert & van Soest, 1996).

The incredible diversity of marine life is epitomized by the Great Barrier Reef in Australia. This 100,000-square mile habitat consists of 2,500 individual small coral reefs. Around one of these, of less than 14 square miles, there have been identified 930 species of fish, 107 corals, and 154 urchins, cone snails, and other molluscs, to say nothing of sponges, tunicates, and seaweeds (Gribble, 1992). Of the 2,500 recorded nudibranch species, 400-500 live on the Great Barrier Reef, and 20 unique species of Staghorn coral are found living together on this reef. It seems clear that a very large number of marine metabolites, halogenated and not, are awaiting discovery. A similar treasure trove will greet the natural products chemist who pursues the thousands of unexplored terrestrial plants, bacteria, fungi and higher animals for novel natural chemicals.



## 10 Conclusion

- Natural organohalogens continue to be discovered at a frequency of 100-200 per year, and now number in excess of 4,000.
- Chlorine, bromine, iodine and fluorine are natural components of the biosphere, and join the list of carbon, hydrogen, nitrogen, oxygen, sulfur, phosphorus, iron, and the other elements of life.
- Nearly all forms of life produce organohalogens, and marine organisms furnish most of the known examples.
- Some simple haloalkanes function as natural recyclers of halogen between oceanic, atmospheric and terrestrial environments.
- Some natural organohalogens are used in chemical defense (repellents, antifeedants) whereas others serve as hormones or pheromones.
- Many organohalogens have powerful beneficial biological activity and are, or will become, medicines.
- Volcanoes and other natural geothermal processes produce organohalogens, most notably simple haloalkanes including some chlorofluorocarbons (CFCs).
- Several natural organohalogens that undoubtedly have been on earth since its birth have been "rediscovered" by man in the search for novel industrial chemicals.





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