

## Naturally Occurring Organohalogen Compounds--A Survey

Gordon W. Gribble

*J. Nat. Prod.*, **1992**, 55 (10), 1353-1395 • DOI:  
10.1021/np50088a001 • Publication Date (Web): 01 July 2004

Downloaded from <http://pubs.acs.org> on April 4, 2009

### More About This Article

---

The permalink <http://dx.doi.org/10.1021/np50088a001> provides access to:

- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article



**ACS Publications**  
High quality. High impact.

Journal of Natural Products is published by the American  
Chemical Society, 1155 Sixteenth Street N.W., Washington,  
DC 20036

## NATURALLY OCCURRING ORGANOHALOGEN COMPOUNDS— A SURVEY

GORDON W. GRIBBLE<sup>1</sup>

*Department of Chemistry, University of Hawaii at Manoa, Honolulu, Hawaii 96822*

**ABSTRACT.**—More than 1500 different halogenated chemicals are produced and discharged into our biosphere by plants, marine organisms, insects, bacteria, fungi, and other natural processes. In a few cases, the quantities of these naturally occurring halogenated compounds far exceed the amounts of the same chemicals from anthropogenic sources. Furthermore, the evidence is overwhelming that natural enzymatic, thermal, and other processes are constantly occurring in the oceans, in the atmosphere, and in the soil that lead to the formation of chlorinated and brominated phenols and many other halogenated chemicals, including dioxins, that previously were thought only to result from the actions of man. Moreover, it is clear that these natural processes have been producing halogenated compounds and have been an important component of our ecosystem for eons.

It is sometimes assumed by the lay press, environmental activists, politicians, and others, that organohalogen compounds—organic chemicals containing one or more carbon-chlorine, carbon-bromine, carbon-iodine, or carbon-fluorine bond—are generally not found in nature. One purpose of the present review is to document that not only are naturally occurring organohalogen compounds ubiquitous in our environment, but concentrations of some of these chemicals exceed their anthropogenic levels. In addition, previously unknown naturally occurring organohalogen compounds are continually being isolated and characterized from a variety of marine and terrestrial plant and animal sources.

The Science Advisory Board to the International Joint Commission on the Great Lakes stated recently: "There is something nonbiological about halogenated organics (excluding iodinated compounds). ...Chemicals [that] do not occur naturally...are often persistent, since there are often no natural biological processes to metabolize or deactivate them" (1). Not only are these statements incorrect, but, coming from a "Science Advisory Board," they reflect a disturbing ignorance of the chemical composition of our environment and of biochemical processes therein. Similarly, in a 1990 *Science* article, a well-known cancer researcher was quoted as saying: "...some types of synthetic compounds, including halogenated hydrocarbons such as PCB, are not found in nature" (2). To the contrary, the sheer number of known naturally occurring halogen-containing chemicals is so vast (approximately 1500 according to Professor J.F. Siuda, University of Pittsburgh, private communication, October 16, 1991) that it would be unrealistic to list and discuss them all in the present review. Furthermore, numerous excellent reviews of various aspects of this topic have appeared over the past twenty years. Therefore, present coverage is detailed only from 1980 through 1991, with selective inclusions of significant earlier material. In addition, Table 4 lists the organisms that have yielded new halogenated compounds since 1980.

In 1968, the first review of organohalogen compounds stated that there existed more than 30 organochlorine natural products, along with only a few such compounds containing bromine, iodine, and fluorine (3). In 1971, Turner reported that the number of fungal metabolites containing chlorine was about 70, including one brominated compound (4). A sequel in 1983 described an additional 80 new organochlorine compounds isolated from fungi (5). An exhaustive review published in 1973 documented more than 200 organohalogen compounds (150 organochlorine and 50 organobromine) from all natural sources (6). A 1986 review, covering only organochlorine compounds in higher plants and ferns, reported that more than 130 such compounds have been isolated and characterized from these sources (7).

As will be seen, marine life is the largest source of naturally occurring organohalogen compounds. Indeed, after a very slow start, this area of natural product chemistry has received intense study over the past twenty years. In 1961, no halogenated organic compounds had been reported from marine sources, except for iodinated tyrosine derivatives. By 1973, 50 such

<sup>1</sup>Present address: Department of Chemistry, Dartmouth College, Hanover, New Hampshire 03755. The author regrets that reprints of this article are unavailable.

compounds had been discovered. In 1976, this number had grown to 140, and, two years later, it had risen to about 300. In 1982, the number stood at 700 (8). Presently, the number of halogenated organic compounds found in marine organisms is at least 1500 and growing monthly. For comprehensive reviews of marine metabolites, see Faulkner (9,10), Scheuer (11), and Fenical (12).

### HALOGENATED ORGANIC COMPOUNDS IN NATURE

**SIMPLE ALKANES.**—The simplest of naturally occurring organohalogen compounds are halogenated alkanes, and these are enormously abundant on our planet.

Chloromethane ( $\text{CH}_3\text{Cl}$ ) is produced by marine algae (*Endocladia muricata*) (13) and giant kelp (*Macrocystis pyrifera*) (14), wood-rotting fungus (*Phellinus pomaceus*) (15,16), the ice plant (*Mesembryanthemum crystallinum*) (13), cultivated mushrooms (*Agaricus bisporus*) (17), the pencil cedar (18), the evergreen cypress (18), several species of *Fomes* fungi (19), and phytoplankton (20). Chloride ion is normally present in plants, wood, soil and minerals (15,18), and the combustion of these materials leads to the formation of organochlorine compounds. Thus, forest fires (21), brush and vegetation burning (22), and volcanoes (18,23,24), including the recent eruptions of Mt. St. Helens and Mt. Kilauea, all produce significant and, in some cases, large quantities of  $\text{CH}_3\text{Cl}$ . Not surprisingly,  $\text{CH}_3\text{Cl}$  is also found in tobacco smoke (25,26). In 1976, the production of  $\text{CH}_3\text{Cl}$  from the burning of all cellulose (wood, etc.) and polyvinylchloride was estimated to be 210,000 tons in the U.S. (21). By comparison, the global emission rate of  $\text{CH}_3\text{Cl}$ , which is mainly from the marine and terrestrial biomass, as delineated above, is 5 million tons per year (27), whereas the level of man-made  $\text{CH}_3\text{Cl}$  emissions is only 26,000 tons per year (15).

In addition to  $\text{CH}_3\text{Cl}$ , bromomethane ( $\text{CH}_3\text{Br}$ ) and iodomethane ( $\text{CH}_3\text{I}$ ) have been detected in the oceans and in the air over oceans (27–32). Measurements indicate that the oceans are the major source of  $\text{CH}_3\text{I}$  (4 million metric tons/year) (30), and it has been observed that the concentration of  $\text{CH}_3\text{I}$  is 1000 times higher in water near kelp (*Laminaria digitata*) beds than in the open ocean (22).  $\text{CH}_3\text{I}$  and  $\text{CH}_3\text{Br}$  are also produced by the giant kelp *Macrocystis pyrifera* (14) and marine algae *Asparagopsis taxiformis* (33–35), *Asparagopsis armata* (36), and Fucales sargassum (37). It had been proposed that, based on the concentrations of  $\text{CH}_3\text{Cl}$  and  $\text{CH}_3\text{Br}$  in different localities, these two compounds have a common biogenic source (31). This study also found no evidence for the theory (30) that  $\text{CH}_3\text{Cl}$  arises from  $\text{CH}_3\text{I}$  by a nucleophilic substitution reaction with chloride ion (31). It has been suggested that the role of  $\text{CH}_3\text{Cl}$  and  $\text{CH}_3\text{I}$  might be to cycle chloride ion and iodide ion, respectively, between land and sea (27–29).

Several other simple haloalkanes, identified in and above oceans, are implicated as having a natural source. In some cases, these compounds have been isolated from specific sources. A summary of these observations is shown in Table 1.

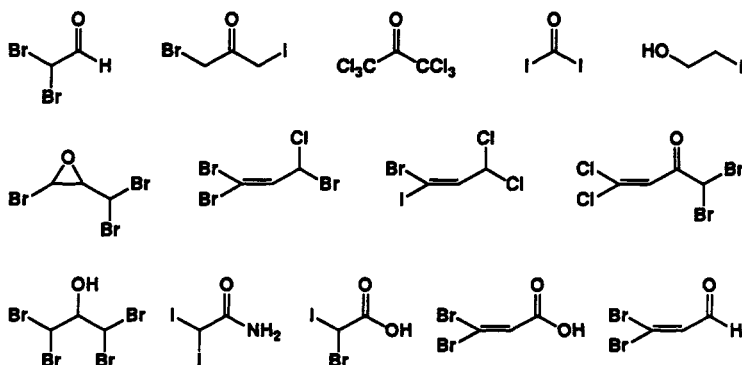
Although many of the compounds listed in Table 1 (e.g.,  $\text{CHCl}_3$ ,  $\text{CCl}_4$ , tetrachloroethylene) have an anthropogenic component as well (18,44,46), this has been taken into account and corrected for in the investigations cited. However, in some cases, the natural source has yet to be identified. Thus, although two reports indicate that the atmospheric concentration of tetrafluoromethane is too large to arise from anthropogenic sources alone, a natural source has yet to be identified for the estimated 650,000 tons of naturally occurring tetrafluoromethane in the atmosphere (47,48). Also, it is not clear what fractions of the relatively large concentrations of methylchloroform, difluorodichloromethane, and fluorotrichloromethane that are found high over eastern Washington are biogenic in origin (49,50).

In addition to the simple one- and two-carbon halogens found in *Asp. taxiformis* (33–35, 51) and *Asp. armata* (36) (Table 1), numerous halogenated alcohols, ketones, carboxylic acids and amides, aldehydes, epoxides, and alkenes have also been isolated and characterized from these species of marine algae (33–35, 51, 52). Indeed, nearly 100 different halogenated compounds have been found in *Asp. taxiformis*, the favorite edible seaweed of most Hawaiians (35). A selection of these compounds is shown in Figure 1.

Marine algae have been intensively examined for their chemical content. For example, through 1978, more than 250 halogenated compounds have been identified from red algae (Rhodophyta) (53). An array of halogenated ketones, alcohols, carboxylic acids and other simple derivatives of the alkanes have been isolated from the red algae *Bonnemaisonia nootkana*, *Bonnemaisonia*

TABLE 1. Biogenic Sources of Simple Haloalkanes.

Compound	Source(s)	Reference(s)
CH <sub>2</sub> Cl	marine algae, giant kelp, wood-rotting fungus, ice plant, cultivated mushrooms, white cedar, pencil cedar, evergreen cypress, fungi, phytoplankton, forest fires, bush-burning, volcanoes, tobacco smoke	13-26
CH <sub>2</sub> Br	oceans, marine algae, giant kelp, volcanoes	14,20,22,24,31,32
CH <sub>2</sub> I	oceans, marine algae, volcanoes	14,18,20,22,24,29-31,37,38
CHCl <sub>3</sub>	marine algae, white cedar, lemon, orange, moss, barley, volcanoes, drill wells	18,36,44
CHBr <sub>3</sub>	marine algae, oceans	32-37,39,41,42
CCl <sub>4</sub>	marine algae, oceans, volcanoes, drill wells	18,29,36,39,40,43,44
CH <sub>2</sub> Cl <sub>2</sub>	volcanoes, barley	18
CBr <sub>4</sub>	marine algae	33-36
CH <sub>2</sub> CIBr	marine algae	37
CH <sub>2</sub> CI	marine algae	36
CHBrCl <sub>2</sub>	marine algae, oceans	36,37
CHBr <sub>2</sub> Cl	marine algae, oceans	33-37,41
CH <sub>2</sub> Br <sub>2</sub> I	marine algae	33-36
CH <sub>2</sub> I <sub>2</sub>	marine algae, oceans	37
CHI <sub>3</sub>	marine algae	33-35
CH <sub>2</sub> Br <sub>2</sub>	marine algae, oceans	33-35,37,41
CH <sub>2</sub> CH <sub>2</sub> Br	marine algae	37
CH <sub>2</sub> CH <sub>2</sub> I	marine algae	37
BrCH <sub>2</sub> CH <sub>2</sub> I	marine algae	33-35
CH <sub>2</sub> BrI	marine algae	33-35
CHBrCl	marine algae	33-35
CHBrI <sub>2</sub>	marine algae	33-35
Cl <sub>2</sub> C=CHCl	oceans, volcanoes	23,44
Cl <sub>2</sub> C=CCl <sub>2</sub>	oceans, volcanoes	18,39,44
CH <sub>2</sub> CCl <sub>3</sub>	oceans	39
CHFCl <sub>2</sub>	volcanoes	18
CFCl <sub>3</sub>	volcanoes, drill wells	18,23
CF <sub>2</sub> Cl <sub>2</sub>	volcanoes	18
CHF <sub>2</sub> Cl	volcanoes	23
CHFCl <sub>3</sub>	volcanoes	23
F <sub>2</sub> C=CF <sub>2</sub>	volcanoes	23
FCIC=CF <sub>2</sub>	volcanoes	23
CCl <sub>2</sub> FCCIF <sub>2</sub>	volcanoes	23

FIGURE 1. Representative compounds produced by the marine alga *Asparagopsis taxiformis* (35).

*asparagoides*, *Bonnemaisonia hamifera*, and *Traiilliella intricata* (54,55). A selection of these compounds is shown in Figure 2, the major metabolite from *B. hamifera* being a tetrabromo ketone, a compound possessing antimicrobial activity (55).

The Australian red alga *Ptilonia australasica* produces an entirely different set of polybrominated ketones (Figure 3) (56).

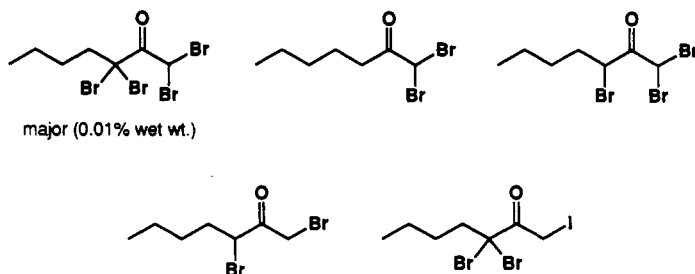


FIGURE 2. Halogenated ketones from the red alga *Bonnemaisonia bamifera* (55).

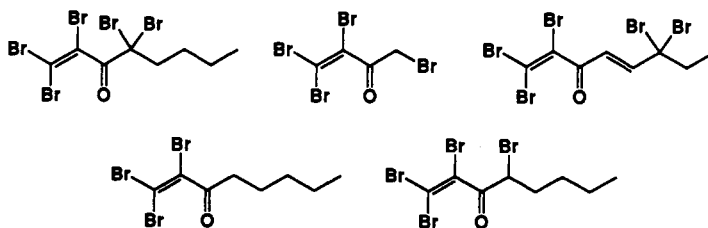
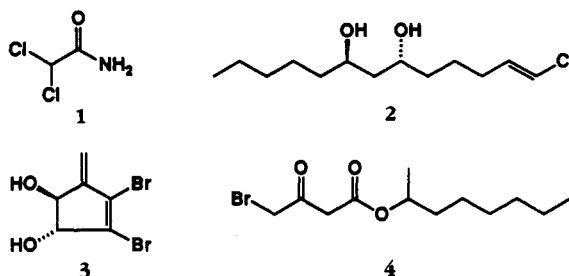


FIGURE 3. Brominated ketones from the red alga *Ptilonia australasica* (56).

The red alga *Marginisporum aberrans* produces the simple dichlorooctamide **1** (57), the first report of this compound as a natural product, while the blue-green alga *Schizothrix calcicola* and *Oscillatoria nigroviridis* produce vinyl chloride derivative **2** (58). The Western Australian red alga *Vidalia spiralis* secretes the interesting fulvene derivative **3** (59). A spectacular development is the isolation of bromo ketoester **4** from the cerebrospinal fluid of normal patients (60). This extraordinary find is the first example of a naturally occurring halogenated compound to be isolated from humans, other than thyroxine and related iodinated hormones. Compound **4** is biologically active and is postulated to have a physiological function in humans.



It has been proposed with some supporting chemical evidence, that the simple haloalkanes, such as  $\text{CHBr}_3$ ,  $\text{CHCl}_3$ , etc., may arise from in vivo Haloform reactions, and that this mechanism enables organisms such as algae to secrete continuously these "anti-predator" chemicals (35,54). More on the role and function of marine halogen compounds will be presented in a later section.

**TERPENES.**—Monoterpenes, sesquiterpenes, diterpenes, and triterpenes are ubiquitous in terrestrial organisms and play an essential role in life as we know it. Although the study of terrestrial terpenes dates back to the last century, marine terpenes were not discovered until 1955 and halogenated marine terpenes were first isolated only in 1963 (61). Reviews of terpenes have been published (62–64,6,9,11,53) Examples of halogenated (chlorinated) terrestrial terpenes first appeared in 1969 (65). Since then, there has been a veritable explosion of activity and many new halogenated terpenes—from land and sea—have been isolated and identified (62–64). Therefore, the present review will cover only recent developments in this area. A more complete tabulation of halogenated terpenes appears in Table 4.

Red algae, particularly species of *Laurencia* and *Plocamium*, have provided a rich and diverse collection of halogenated terpenes over the past 25 years. The first examples of iodinated terpenes, **5** and **6**, were found in *Laurencia nana* (66), and *Laurencia nipponica* has recently yielded the new compounds **7–9** (67,68) (Figure 4). A California species, *Laurencia pacifica*, has yielded kylinone [**10**] (69), which is a new ring system, in addition to three previously known halogen metabolites. *Laurencia obtusa* produces a different collection of halogenated terpenes, depending on where it grows. Thus, the Jamaican variety contains **11** and **12** (70), the Japanese variety contains parguerol triacetate [**13**] (71), the Canary Islands species contains **14** along with two other new halogen terpenes (72), and the Red Sea variety of *Laur. obtusa* contains hurgadol [**15**], along with several other new and old halogenated compounds (73) (Scheme 4). Yet other collections of *Laur. obtusa* have yielded the structurally novel thyransferyl 23-acetate [**16**] (74) and **17**, which is highly cytotoxic (75). Finally, *Laur. obtusa* from the Atlantic Ocean affords two other new compounds (76).

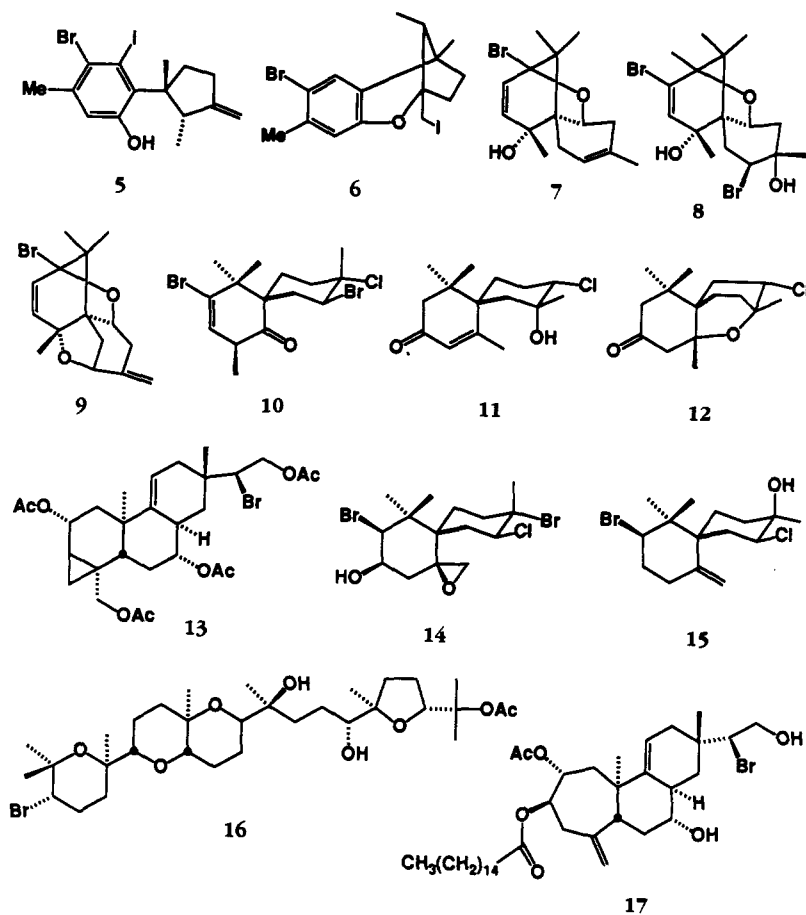
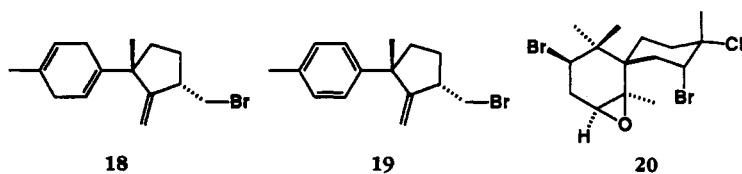


FIGURE 4. Halogenated terpenes from *Laurencia* red algae.

The Atlantic red alga *Laurencia pinnatifida* contains the sesquiterpenes **18** and **19**, in addition to a dehydrothyransferol related to **16** (77), while another collection of this same red alga from a different location has yielded the chamigrene epoxide **20** (78). Likewise, an array of new and unusual halogenated terpenes have been isolated and characterized from *Laurencia perforata* (79), *Laurencia venusta* (80,81), *Laurencia majuscula* (82), *Laurencia tenera* (83), and an unidentified *Laurencia* species (84). Since 1983, about 100 new compounds, mostly halogenated, have been found in *Laurencia* red alga (83).



Although the red seaweed *Plocamium* has been investigated for its chemical content for many years, several new compounds have been identified recently from these species. For example, *Plocamium mertensii* and another *Plocamium* sp. found in the ocean off Western Australia produce monoterpenes **21** and **22**, respectively (85), and *Plocamium telfairiae* yields telfairine [**23**] and **24** (86), the former of which has very potent insecticidal activity (Figure 5). Of the four halogen compounds isolated from *Plocamium cartilagineum*, only **25** is new (87). Two different studies of *Plocamium coccineum* (= *Ploc. cartilagineum*), one from the northwest Spanish coast (88) and one from Senegal (89), have identified new metabolites coccinene [**26**] and **27**, respectively. Crews *et al.* (90) have reported metabolites of *Ploc. cartilagineum*, *Plocamium violaceum*, and the red alga *Ochtodes secundiramea*.

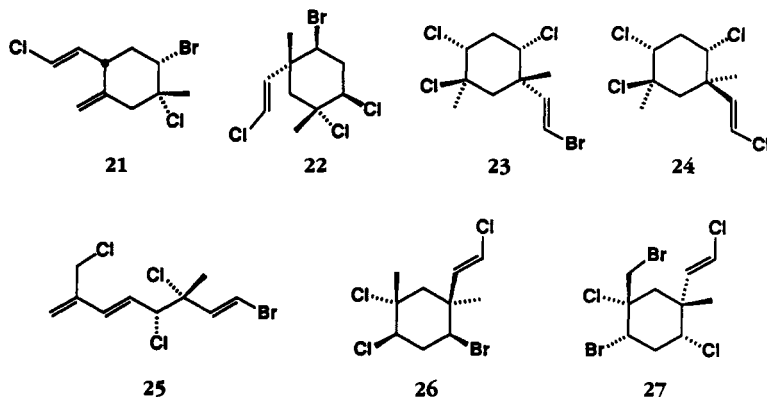
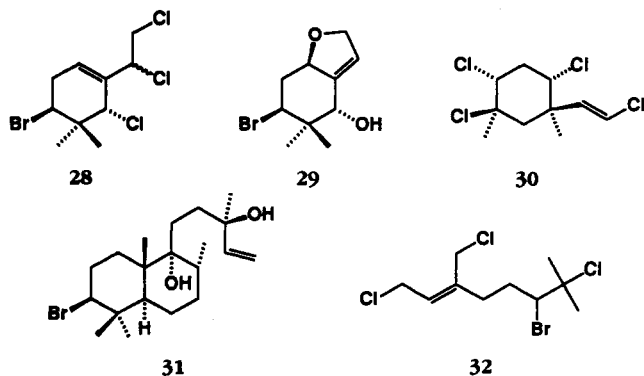
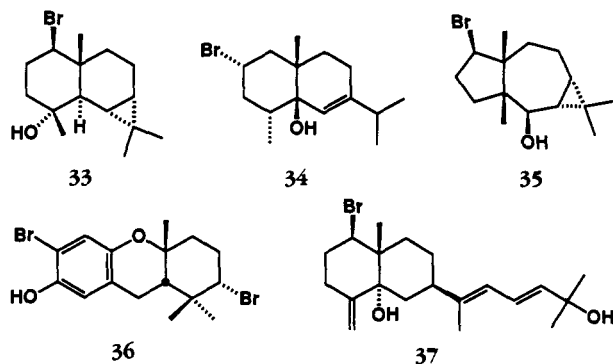


FIGURE 5. Halogenated monoterpenes from *Plocamium* red algae.

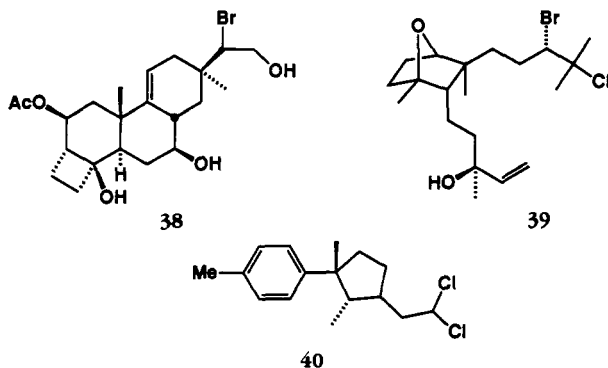
Several other red algae have been investigated in recent years. *Chondrococcus bornemanni* from Tahitian waters has yielded the new ochtodane derivative **28** (91), while *Ochtodes crockeri* contains eight new halogenated metabolites (e.g., **29**) (92). The edible Morocco red alga *Gelidium sesquipedale* produces gelidene (**30**=**24**) (93), and *Chondria tenuissima* from the Marmara Sea contains the diterpene **31** (94). Very recently, *Portieria bornemanni* (= *Chondrococcus bornemanni*) has been found to contain four new halogenated monoterpenes (e.g., **32**) (95).



Green algae are beginning to receive attention from natural products chemists. The first report of halogenated terpenes from a green alga (*Neomeris annulata*) described the isolation of the novel compounds **33–35** (96). Interestingly, these chemicals have herbicidal activity. The green alga *Cymopolia barbata* contains the highly antimutagenic cymobarbatol [**36**] and an epimer, both new compounds (97).



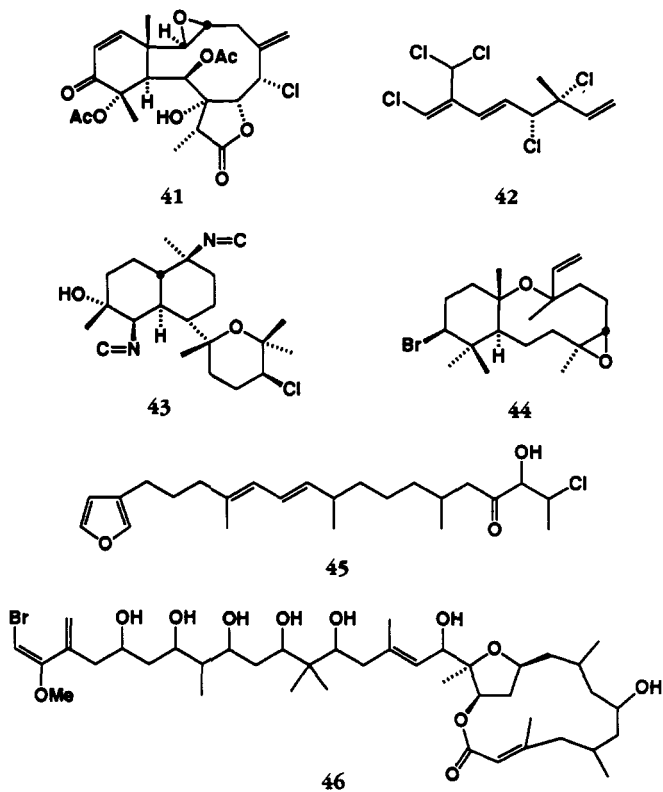
Species of sea hares, a marine mollusk, have also provided a rich source of halogenated terpenes (62). In many cases, these compounds are derived from the sea hare's algal diet (98,99). For example, a multitude of halogenated terpenes have been isolated from the sea hare *Aplysia kurodai* since 1963 (61,100–106), the most recent being aplysiadiol [**37**] (106). *Aplysia dactylomela*, which has also been extensively examined (107–111), contains the novel compounds deoxyparguerol [**38**] (108), dactylomelol [**39**] (111), and dichloro compound **40** (110), among other compounds (Table 4). The Arabian Ocean *Aplysia juliana* produces a new diterpene called angasiol acetate (112).



Nearly twenty halogenated diterpenes and one tetraterpene have been isolated from soft corals [*Briareum polyanthes* (113,114), *Erythropodium caribaeorum* (115,118), *Minabea* sp. (116), *Briareum* sp. (117,118), and *Sarcophyton glaucum* (119)]. Interestingly, all of these compounds contain only chlorine and no bromine. An example of the structural complexity of these compounds is erythrolide C [**41**] (118). Five new and structurally related chlorinated diterpenes have been isolated from the gorgonian *Solenopodium* sp. (120), and three new chlorinated diterpenes are produced by the white sea whip (*Juncella fragilis*), a Chinese gorgonian (121). Two species of sea pen, *Pteroides laboutei* (122) and *Ptilosarcus gurneyi* (123), have been found to contain a total of seven new chlorinated diterpenes, all of which are similar to **41**. A set of four polychlorinated monoterpene (e.g., **42**) were found in four species of marine hydroids (e.g., *Aglaophenia pluma*) (124). As will be seen in later sections also, marine sponges synthesize an



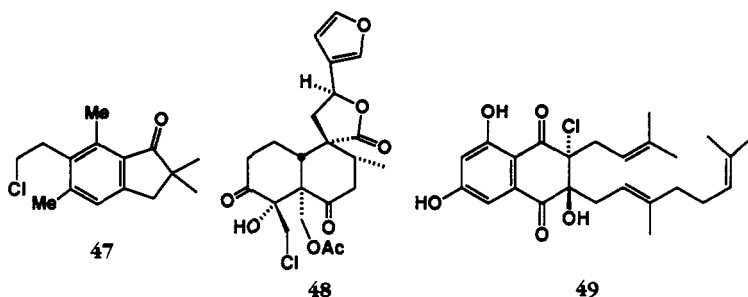
amazingly varied collection of halogenated chemicals. For example, two *Acanthella* spp. of sponges found on Guam and Fiji produce eight different chlorinated diterpenes, each of which contains the rare isonitrile functionality, e.g., kalihinol A [43] (125). The Thailand variety *Acanthella cavernosa* contains two new chlorinated diterpenes, in addition to two that were isolated earlier from the Fiji sponge (126), but *Acanthella klethra* has another new chlorinated diterpene isonitrile (127). In contrast, the sponge *Spongia zimocca* produces rogiolol acetate, a chamigrane-type sesquiterpene (128), and the sponge *Mycale rotalis* has been found to contain rotalin B [44] (129), both of which are new halogenated natural products. An unidentified sponge produces konakhin [45] (130), and the interestingly terpene macrolide 46 was isolated from the blue-green alga *Oscillatoria* sp. (131).



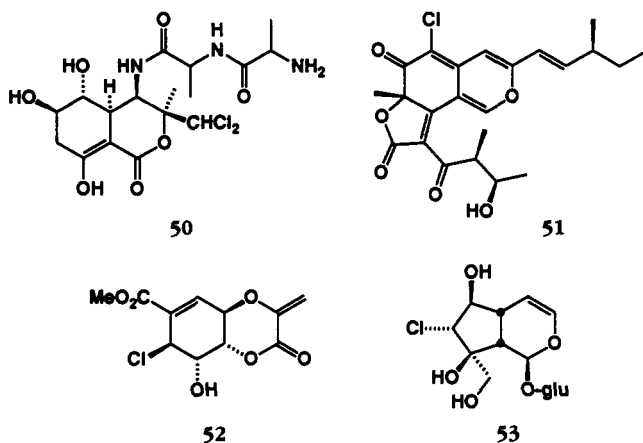
Although marine organisms far outweigh their terrestrial counterparts in the production of different halogenated terpenes, several examples of terrestrial plant halogenated terpenes have been reported in the past decade. A series of about ten chlorinated sesquiterpene indanones have been found to occur in species of ferns and related plants. For example, pterosin H [47] is found in several *Microlepia* (132), *Dennstaedtia* (133), *Myriopteris* (133), and *Pteridium* sp. (134). The South African bush *Teucrium africanum* contains the two new chlorinated diterpenes tafricanins A [48] and B (135), while *Teucrium polium* from Portugal produces teuvincentin A, a different chlorinated diterpene (136). The chlorinated naphthalenequinone 49 is produced by an Australian *Streptomyces* sp. (137).

**NONTERPENES.**—Another very large group of halogenated organic compounds are the "nonterpenes," compounds which may or may not arise from a terpenoid pathway but which are not obviously terpene-derived. The very large number of these compounds precludes a complete discussion here, although all such compounds reported from 1980 to the present are tabulated in Table 4.

A *Pseudomonas* sp. produces bactobolin B [50] and a related compound (138,139). A species



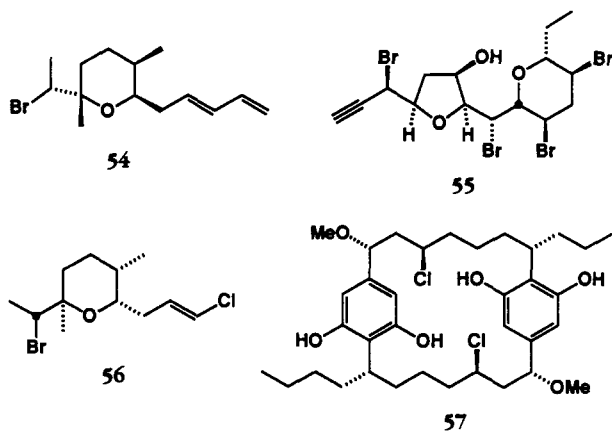
of *Gluconobacter* produces enacyloxin II, a novel dichloropolyenic antibiotic that is active against Gram-positive and Gram-negative bacteria (140). Four novel fungal metabolites, e.g., chaetovirdin A [51], have been extracted from *Chaetomium globosum* (141), and an unidentified fungus produces the unique chlorinated shikimate derivative 52 (142). Approximately ten new chlorinated iridoids, e.g., asystasioside E [53] (*Arystasia bella*) (143), have been isolated from several terrestrial plant species. The Chinese folk medicine plant *Rehmannia glutinosa*, which is still used in China, contains five different chlorinated iridoids (144–146).



Marine organisms biosynthesize a multitude of fascinating halogenated nonterpenes, as was the case with terpenes. The sponge *Haliclona* sp. contains two novel bromotetrahydropyrans (e.g., 54) (147), and the sponge *Mycale rotalis* also produces two novel brominated metabolites (e.g., 55) (148). The Guam "bubble shell" (*Haminoea cymbalum*) contains kumepaloxane [56] (149), a chemical which is discharged when this mollusk is disturbed, and which is a feeding deterrent to carnivorous fishes.

*Nostoc* blue-green algae are recognized as a threat to humans when they infest drinking water sources (150,151), and this may be the cause of the reported outbreaks of some illnesses in China (Professor R.E. Moore, University of Hawaii, private communication). Cultivation and extraction of *Nostoc linckia* has yielded four unusual chlorinated paracyclophanes (e.g., nostocyclophane D [57]) (152). Blue-green algae are obviously important organisms for future research.

Marine red algae, especially *Laurencia*, are a source of fantastically complex nonterpenoid chemicals (Figure 6). In addition to containing several known halogen metabolites, *Laur. implicata* has recently yielded to isolation and characterization six new cyclic ethers, some of which are allenes (e.g., 58) (153,154). *Laur. intricata* contains the unique okamurallene [59] in addition to several other related novel compounds (155,156). *Laur. pinnatifida* produces three new halogenated nonterpenes, two of which are shown, 60 and *cis*-pinnatifidenyne [61] (157). The heavily studied *Laur. nipponica* contains ten new halogenated nonterpenes (since 1980) (158–



163), the latest example of which is notoryne [62] (163). Similarly, *Laur. obtusa* has been found in the past decade to contain ten new nonterpenoid organohalogens (164–170), the latest example of which is cyclic ether 63 (170). The red alga *Laur. microcladia* contains rogiolenyne A, and the sponge *Spongia zimocca*, which is found in the same region of the Mediterranean Sea as *Laur. microcladia*, contains the closely related rogiolenyne B (171).

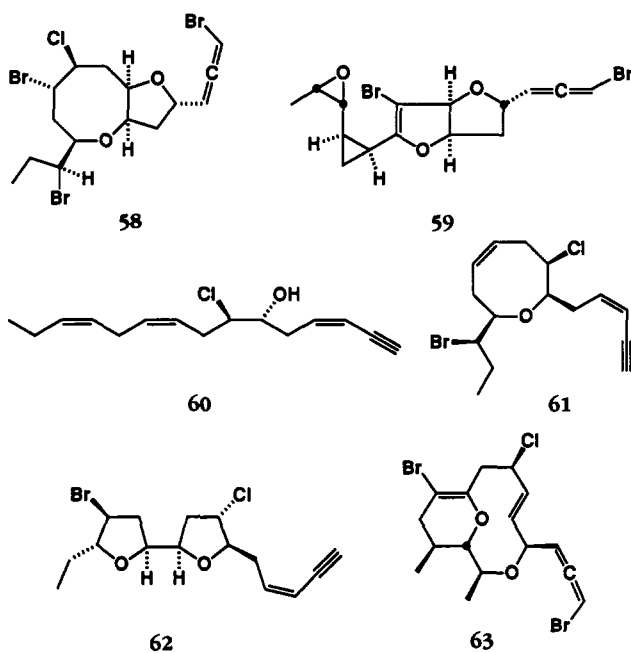
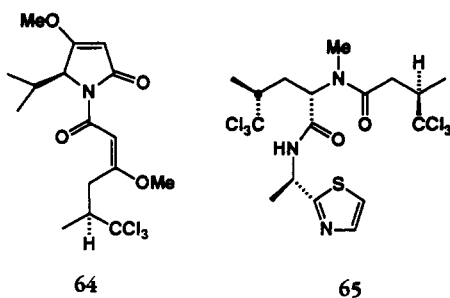


FIGURE 6. Representative halogenated nonterpenes from *Laurencia* red algae.

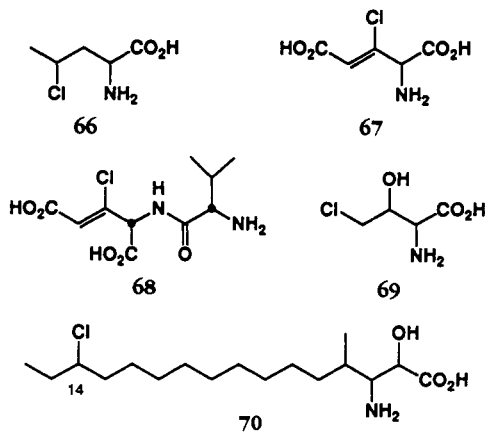
AMINO ACIDS AND PEPTIDES.—With the exception of the naturally occurring iodinated tyrosines such as thyroxine, which will be discussed later, there are relatively few examples of halogenated amino acids and peptides.

The marine sponge *Dysidea herbacea* contains four novel trichloromethyl metabolites, e.g., dysidin [64] and dysidenin [65] (172–176). It seems likely that these compounds could produce  $\text{CHCl}_3$  by an elimination reaction, a process which appears feasible from a chemical standpoint.

Several *Streptomyces* and *Pseudomonas* spp. produce chlorinated amino acids and/or peptides (177–183), many of which have potent antibacterial activity. For example, *Streptomyces griseosporus*

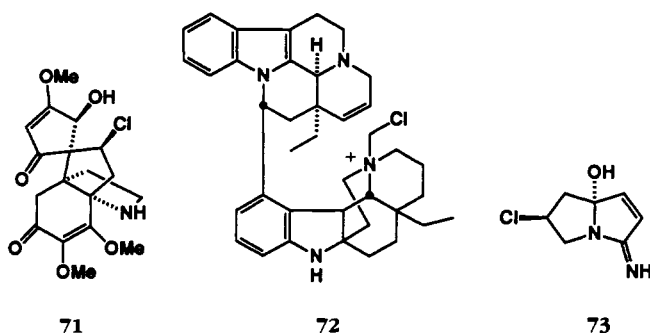


produces  $\gamma$ -chloronorvaline [66] (179) and *Streptomyces viridogenes* produces 67 (180), two novel amino acids, while *Streptomyces xanthocidicus* produces "FR900148" (178,181), which has the revised peptide structure 68 (181). *Pseudomonas syringae*, a bacterial pathogen of plants, produces several cyclic peptides, some of which contain the novel amino acid 4-chlorothreonine [69] (182,183). The terrestrial blue-green alga *Anabaena* sp. produces the most unusual puwainaphycin C, a cardioactive cyclic peptide containing the unique amino acid 3-amino-14-chloro-2-hydroxy-4-methylpalmitic acid [70] (184).

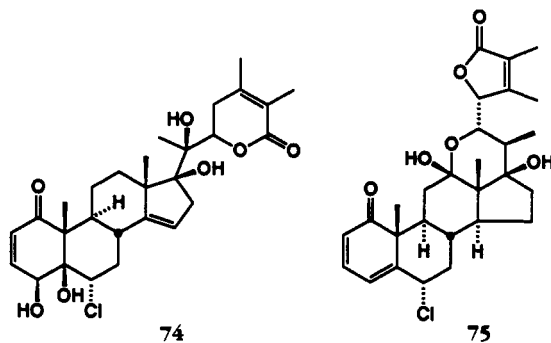


ALKALOIDS.—Although terrestrial plant alkaloids are ubiquitous and have been the object of the attention of natural product chemists for more than 100 years, very few of these nitrogen compounds contain halogen.

The first such examples appear to be acutumine and acutumidine [71], isolated from the plant *Sinomenium acutum* in 1967 (185). Very recently, two chlorinated bis-indole alkaloids were isolated from *Melodinus celastroides* (e.g., 72) (186). Likewise, only two microbial alkaloids containing halogen are known. *Streptomyces* sp. produces clazamycins A [73] and B (187–189).



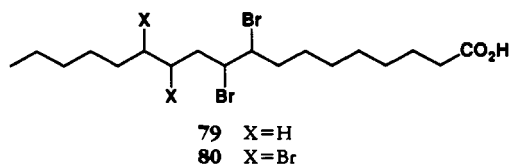
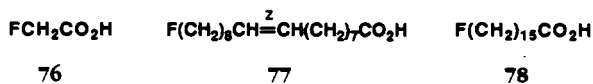
STERIODS.—As is the situation with alkaloids, steroids rarely contain halogen. However, a few notable examples are found in the plant kingdom. For example, the plants *Withania somnifera*, *Acnistus brevisflorus*, *Physalis peruviana*, and *Jaborosa magellanica* contain withanolides (190–192) (e.g., phyalolactone C [74]) (192) and related compounds (e.g., jaborochlorodiol [75]) (193). It is important to note that these chlorohydrins are not isolation artifacts, although the plant may biosynthesize them from the corresponding epoxides.



FATTY ACIDS, PROSTAGLANDINS, AND LIPIDS.—Although fluorine is the most abundant halogen in the earth's crust, ranking 13th in abundance of all elements (194), and is more abundant than iodide in sea water (1.4 vs. 0.05 ppm) (195), nature has chosen not to make use of fluorine in organic natural products, with one major exception.

The one remarkable exception is the prevalence of fluoroacetic acid and fluorofatty acids in certain terrestrial plants (196,197). Remarkably, these plants do not grow in fluoride-rich soil but, rather have the ability to sequester and concentrate fluoride. The resulting fluorinated acids are highly toxic to livestock and other mammals (198,199), by blocking a step in the Krebs cycle. In addition to fluoroacetic acid [76], which was first isolated in 1944 from the South African plant *Dichapetalum cymosum* (200), 18-fluorooleic acid [77] and 16-fluoropalmitic acid [78] are produced by *Dichapetalum toxicarium* (201–204). These two fatty acids are converted in vivo to fluoroacetic acid [76] and, hence, are equally toxic as 76.

In an important development, two brominated fatty acids have been isolated from seeds of *Eremostachys molucelloides*: 9,10-dibromo- [79] and 9,10,12,13-tetrabromostearic acids [80] (205).

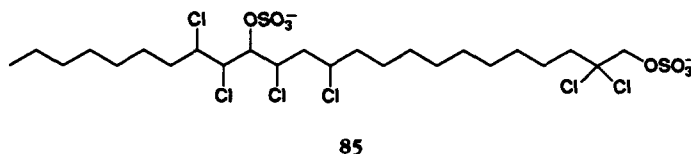
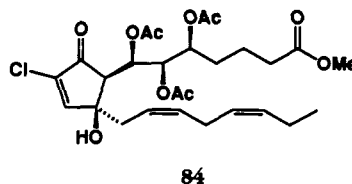
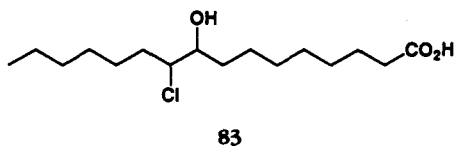
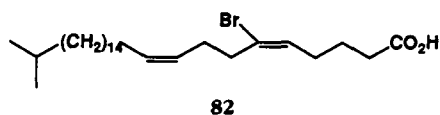
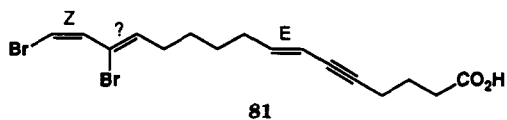


The marine sponges *Xestospongia muta* (206), *Petrosia ficiformis* (207), and *Petrosia bebes* (207) contain a series of novel bromo acids (e.g., 81, 82). The edible jelly fish and the white sea jelly fish (*Auritia aurita*) contain six fatty acid chlorohydrins (e.g., 83) (208).

Mammalian (unhalogenated) prostaglandins are of enormous importance in the biochemical regulation of physiological processes. Therefore, it was of more than just academic interest when chlorinated prostaglandins were discovered in the octocoral *Telesto riisei* (209) and in the stolonifer *Clavularia viridis* (210), a marine animal. Thus, a total of eight novel chlorinated prostaglandins

have been identified (e.g., punaglandin 1 [**84**] (209). Some of these metabolites have potent antitumor activity (210).

Of some 22 fresh water algae species that were examined for chlorosulfolipids, all but one contained quantities of these novel lipids (211,212). For example, the phytoflagellate *Ochromonas danica* produces 12 such compounds, some of which contain six chlorines, e.g., **85** (211). The exact function of these interesting naturally occurring "detergents" is unknown. Marine algae apparently do not contain these metabolites (eight species examined) (212).

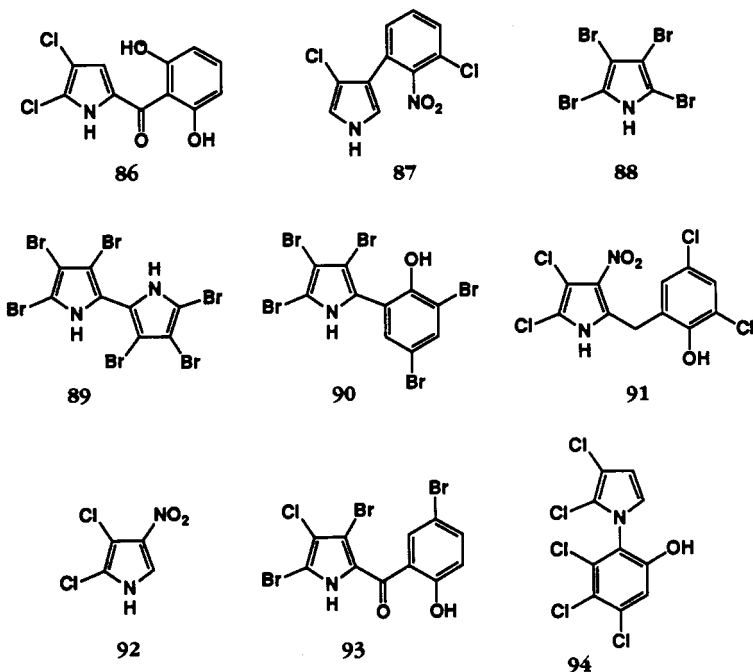


Not surprisingly, but still of tremendous significance, is the discovery of brominated lipids in salmon, halibut, sole, crab, oysters, cod, hake, seals, sea lion, walrus, dolphin, and the gray whale, at a level of 10–900 ppm (213). Thus, for the first time, it is established that larger marine creatures contain halogenated compounds.

**PYRROLES.**—The enormous reactivity of pyrroles in electrophilic substitution reactions, comparable to that of phenol, makes it not surprising that halogenated pyrroles are found widely in nature.

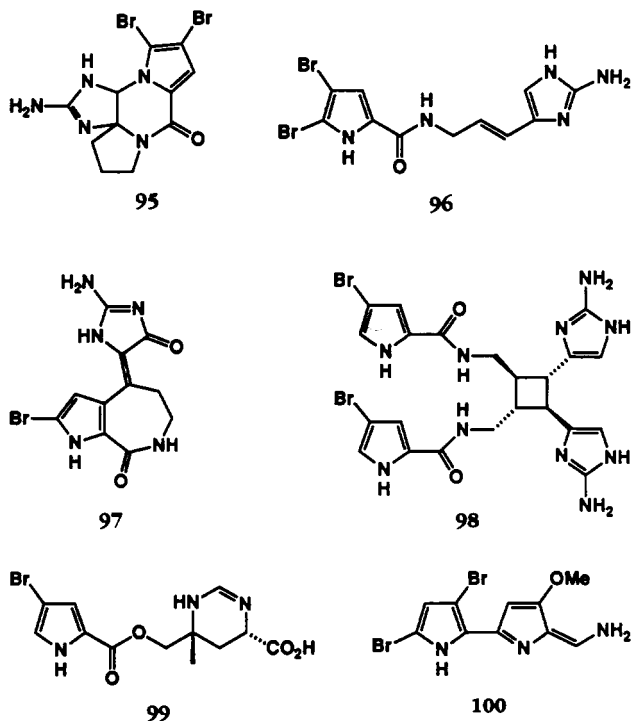
Following the isolation in 1958 of pyoluteorin [**86**], a new antibiotic from *Pseudomonas aeruginosa* (214), and in 1965 of pyrrolnitrin [**87**] from *Pseudomonas pyrrocinia* (215), there have been discovered a number of halogenated pyrroles in nature. For example, the marine bacterium *Chromobacterium* sp. produces the polybrominated pyrroles **88–90** (216), the soil microbe *Streptomyces* sp. produces pyrrolomycin B [**91**] (217), and *Actinomyces* sp. produces pyrrolomycin A [**92**] (218,219). The latter material has broad antibacterial activity. Ten related pyrrolomycins are synthesized by the microbe *Actinosporangium vitaminophilum* (220–222) (e.g., pyrrolomycin F<sub>2a</sub> [**93**], when bromide is present in the culture broth) (221). A soil *Streptomyces* sp. produces the novel neopyrrolomycin [**94**], a metabolite which is optically active (223). Many of the pyrrolomycins have strong antibiotic activity, and a clinical drug from this structural type seems to be a real possibility.

Several sponges produce brominated pyrroles. For example, *Phakellia flabellata* from the Great Barrier reef contains mono- and dibromophakellin [**95**] (224), while *Agelas oroides* from the Bay of Naples produces oroidin [**96**] and three simple dibromopyrroles (225,226). Several species of sponges contain hymenialdisine [**97**] and closely related compounds (227–229), and *Agelas sceptrum* sponge produces the antimicrobial sceptrin [**98**] (230), one of nature's uncommon



cyclobutane-containing compounds. *Agelas* also has been found to contain several other biologically active metabolites having bis-bromopyrrole structures (231–234). The marine sponge *Hymeniacidon* sp. produces three bromopyrrolopyrimidines (e.g., manzacidin A [99]) (235), and the carnivorous nudibranch *Roboastra tigris* secretes tambjamine B [100] as one of two brominated bis-pyrroles (236).

INDOLES.—The indole ring system has the distinction of being embodied in the indigo



derivative Tyrian Purple [101] (Figure 7), the ancient Egyptian dye extracted from mollusk shells and the focus of a significant industry in Mediterranean countries. For a wonderful (and colorful) review, see Baker (237). The mechanism for the formation of 101 in mollusks (e.g., *Dicathais* and *Murex* sp.) has been extensively investigated, and several Tyrian Purple precursors have been isolated from these mollusks (e.g., tyrindoxyl sulfate [102]) (238–241). The marine acorn worm *Ptychodera flava laysanica* has been found to contain 101, in addition to three new brominated indoles and indigos (242). This interesting marine animal also produces the unstable 3-chloro- [103] and 3-bromoindole and 3-chloro-6-bromoindole, compounds that are responsible for the peculiar "iodoform"-like odor of this animal (243). The acorn worm *Glossobalanus* sp. produces two novel dibromoindoles (244), and the red alga *Laurencia brongiartii* produces four new polybromoindoles (e.g., 104) (245). Even more remarkable is the red seaweed from New Zealand *Rhodophyllis membranacea*, which contains ten novel halogenated indoles (e.g., 105) (246). The marine microbe *Pseudomonas* sp. produces 6-bromoindole-3-carboxaldehyde (247), and the sponge *Pleroma menoui* yields the corresponding bromoester 106, as well as a related hydroxyketone (248). The sponge *Iotrochota* sp. produces the indole acrylate 107 (249), and the corresponding carboxylic acid, which is found in the Okinawan sponge *Penares* sp., is a potent calcium inducer (250). The 4-chloroindole ester 108 as well as the carboxylic acid are found in *Pisum sativum* and several other terrestrial plants (lentil, sweet pea, sea pea, vetch) (251–253).

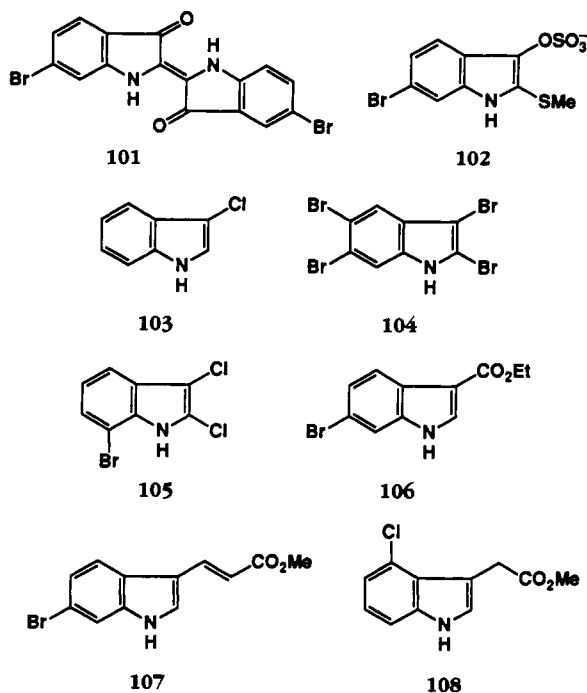
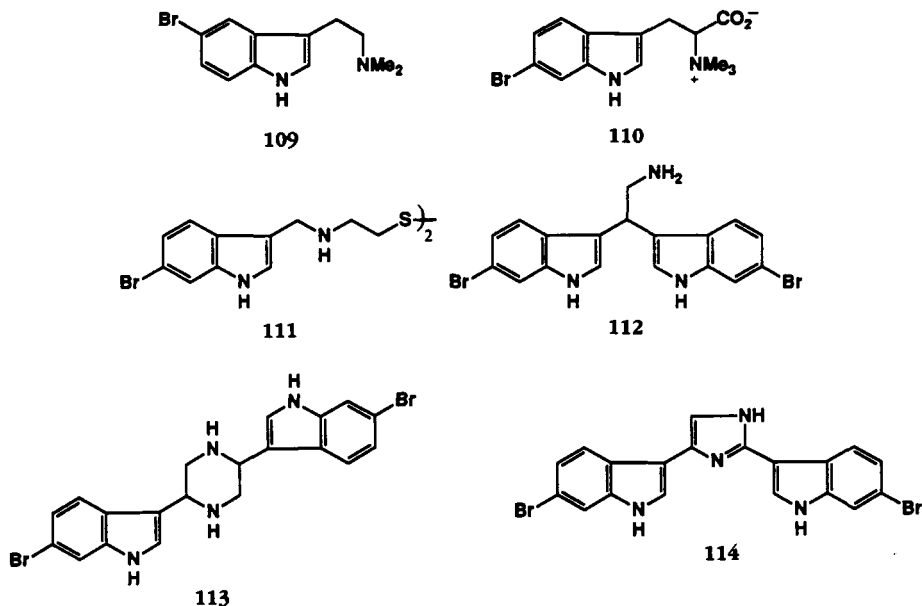


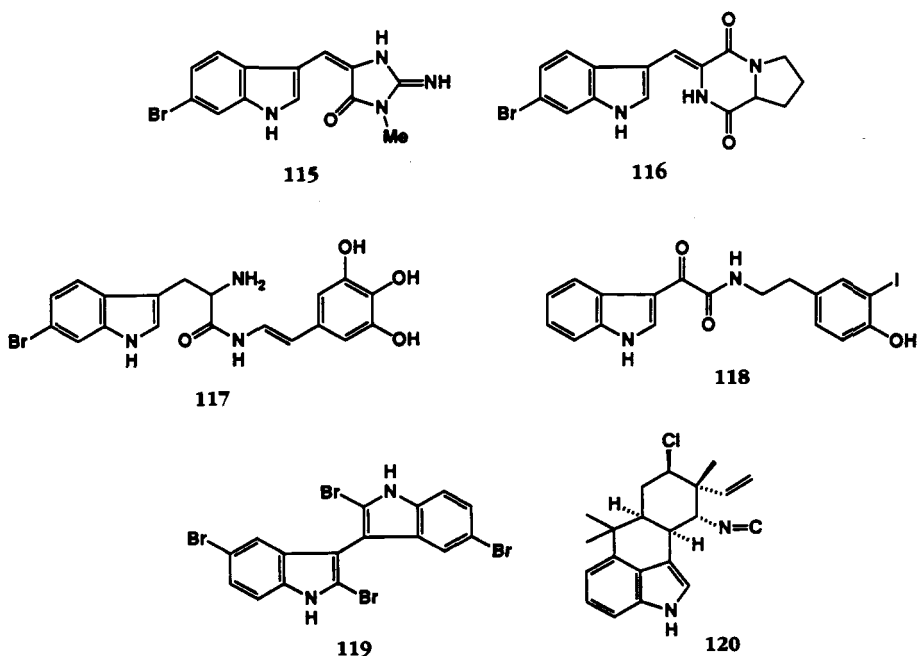
FIGURE 7. Simple naturally occurring halogenated indoles.

Many halogenated tryptamines and tryptophans are also found in nature. Several sponges and a tunicate produce 5- and 6-bromo- and 5,6-dibromotryptamines (e.g., 109) (254–257), and the novel amino acid 6-bromohypaphorine [110] is contained in the large British sponge *Pachymatisma johnstoni* (258). The Fijian tunicate *Polycitorella mariae* produces citroellamine [111], a potent antimicrobial agent (259,260). Commonly found with brominated tryptamines (i.e., 109) are dimeric compounds. For example, the grey tunicate *Didemnum candidum* produces 112 and 113 (257), and the deep-sea (460 m) Caribbean sponge *Spongosorites ruetzleri* produces nortropsetin A [114], along with two related compounds, all of which have cytotoxic and antifungal activity (261). Similar brominated bis-indoles are found in several other sponges (262–265).



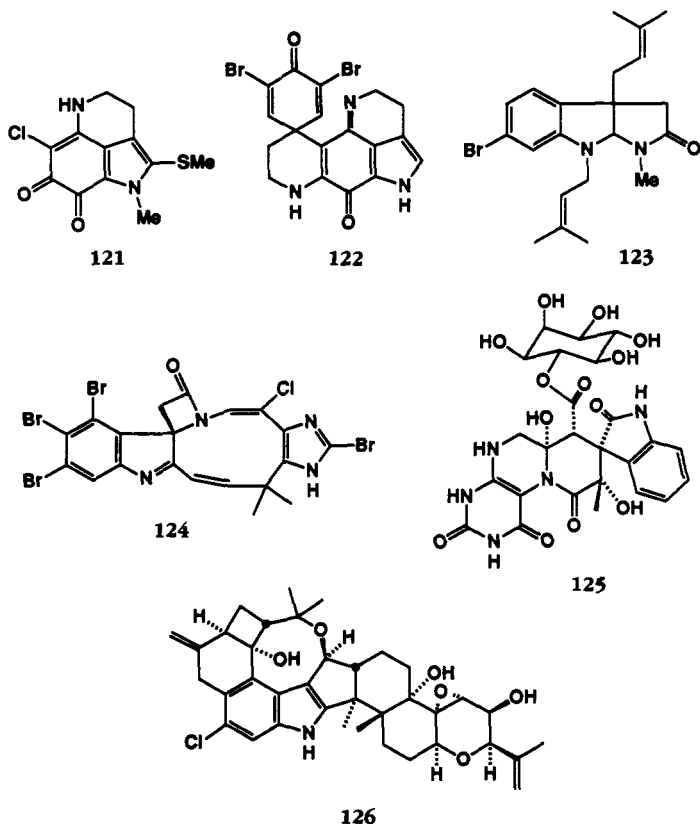


Several brominated indole hydantoin (e.g., **115**) (255,256,266–270) and related compounds (e.g., baretin [**116**]) (271,272) have been isolated over the past ten years from sponges, corals, and anthozoans, sometimes in very high concentrations. For example, indole **115** is present in the sponge *Dercitus* sp. to the extent of 1% (dry wt) (266). The marine burrowing sponge *Cliona celata* contains three novel brominated tryptophan amides, one of which is clionamide [**117**] (273,274), and the Philippine marine ascidan *Polyandrocarpa* sp. produces the halogenated polyandrocarpamides A and B [**118**], the latter of which is a rare example of an iodinated metabolite (275). Two cyclic peptides that incorporate 2-bromotryptophan have been isolated from marine sponges (276–278), and two cyclic peptides that incorporate both 2-chloroindole



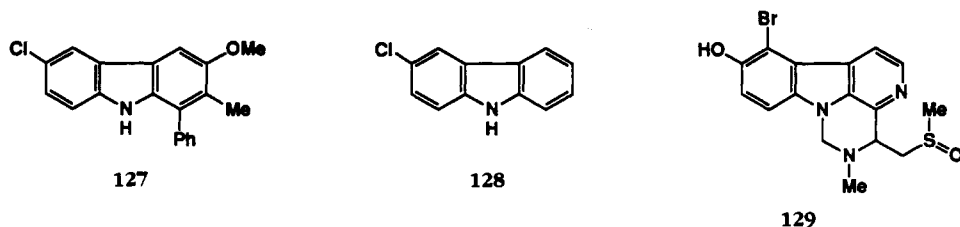
and 4-chlorooxazole have been extracted from the marine ascidian *Diazona chinensis* (279). The blue-green alga *Rivularia firma* produces six novel polybrominated diindoles (e.g., **119**), each of which is optically active (hindered rotation) (280). Another blue-green alga, *Hapalosiphon fontinalis*, contains twelve chlorinated isonitriles, one of which is hapalindole A [**120**] (281). The cyanobacterium *Fischerella* sp. produces a similar chlorinated isonitrile (282).

A number of biogenetically interesting halogenated marine metabolites in which the basic tryptamine nitrogen is attached to the C-4 indole position have been discovered in the past few years. For example, the deep water Bahamas sponge *Batzella* sp. produces six chlorinated compounds, e.g., batzelline A [**121**] (283,284), and the sponge *Latrunculia* sp. and *Prianos melanos* contain a number of structurally related compounds, e.g., discorhabdinc [**122**], which have potent antitumor activity (285–288). The marine bryozoan *Flustia foliacea*, a moss animal, produces five novel brominated indoles (289–293), some of which, such as flustramide B [**123**] (291), resemble the terrestrial plant alkaloid physostigmine, which is important in treating Alzheimer's disease. Even more illustrative of nature's virtuosity in organic synthesis is the ability of the marine bryozoan *Chartella papyracea* to construct its own complement of five brominated indoles, e.g., chartelline A [**124**] (293,294–296). It is interesting to note that only six of the estimated 4000 extant species of bryozoans have been examined for their chemical content! Another incredibly complex natural chemical is surugatoxin [**125**], the highly toxic compound produced by *Babylonia japonica* (the Japanese ivory shell). This metabolite, along with the even more toxic neosurugatoxin and prosurugatoxin, both of which are also bromoindoles, has been implicated in human poisoning (297–301). The microbe *Penicillium crustosum* produces the three 6-chloroindole metabolites penitrems A [**126**], C, and F, of almost unbelievable molecular complexity (302). Unlike the penicillins, the penitrems are highly poisonous, especially to farm animals.



CARBAZOLES.—Halogenated carbazoles, in contrast to pyrroles and indoles, are apparently rare in nature, despite the fact that (unhalogenated) carbazoles are widely dispersed throughout the terrestrial plant kingdom.

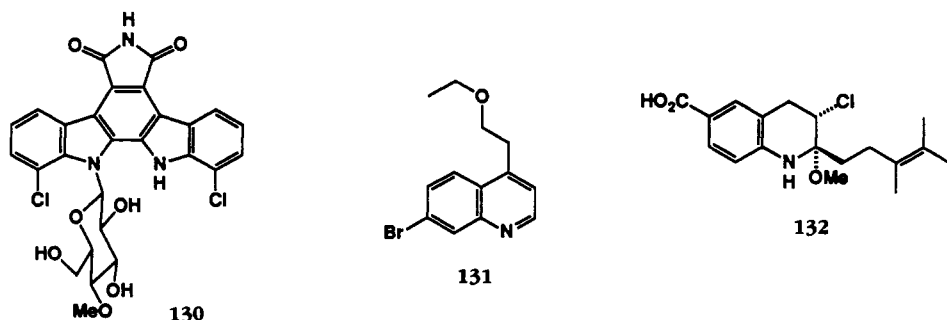
Chlorohyellazole [**127**] is produced by the blue-green alga *Hyella caespitosa* (303), and 3-chlorocarbazole [**128**], which has potent biological activity, has been isolated from bovine urine (304). This is the first carbazole to be isolated from mammals and is likely to be the compound discussed by Dewar *et al.* (305).



CARBOLINES.—In recent years, a large number of halogenated  $\beta$ -carbolines have been discovered in marine life. Notably, the tunicates *Eudistoma glaucus* (Okinawa) (306–308) and *Eudistoma olivaceum* (Bermuda) (309,310), and the ascidan *Ritterella sigillinoides* (New Zealand) (311–314) produce nearly 25 different brominated  $\beta$ -carbolines, e.g., eudistomidin E [**129**] (308). These compounds have a range of antiviral, antimicrobial, and other biological activities, including activity against Polio virus and Herpes simplex virus (312).

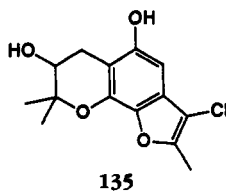
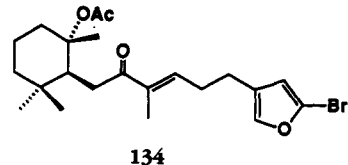
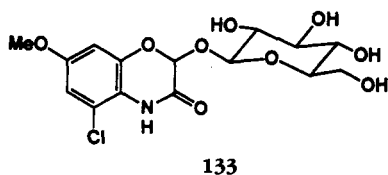
INDOLOCARBAZOLES.—Virtually unknown a decade ago, examples of the indolo[2,3-*a*]carbazole ring system have been discovered in a number of microbes and fermentation broths, and natural products of this type possess a range of biological activities. The five halogenated examples of indolo[2,3-*a*]carbazoles are rebeccamycin [**130**] (*Nocardia aerocolonigenes*, from a Panamanian soil sample) (315,316), monochlororebeccamycin (*Noc. aerocolonigenes*) (317), bromorebeccamycin (*Saccharothrix aerocolnigenes*) (318), and AT2433-A1 and -A2 (*Actinomadura mellioura*) (319). These compounds, or derivatives, may eventually have clinically useful anticancer activity.

QUINOLINES.—The first naturally occurring bromoquinoline **131** was isolated from the marine bryozoan *Flustra foliacea* (320). Although the details of its stereochemistry have been controversial, virantmycin [**132**] is produced by *Streptomyces nitrosporeus*, which was isolated from a spoiled pumpkin (321–323). Young corn roots (*Zea mays*) produce the interesting metabolite **133** (324).



FURANS AND BENZOFURANS.—Although furans are ubiquitous in the plant kingdom, halogenated examples are rare. The sponge *Dendrilla* sp. produces 2-bromofuran **134** (325), and the plant *Gilmaniella humicola* contains the benzofuran mycorrhizolin [**135**] (326).

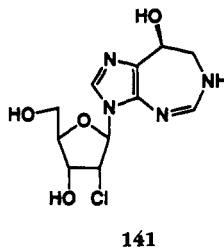
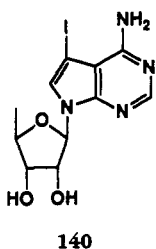
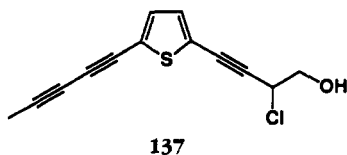
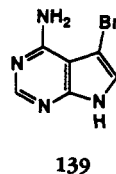
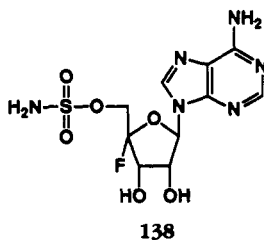
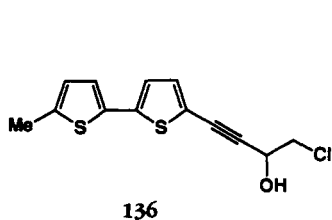
THIOPHENES.—Although sparse in nature, some very interesting halogenated thiophenes are



found in certain plants. For example, *Pterocaulon virgatum* contains five chlorinated thiophenes, three of which are new (e.g., **136**) (327), while six species of *Echinops* are found to contain **137** (328).

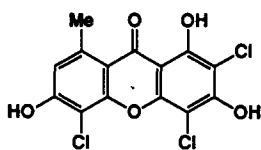
NUCLEIC ACIDS.—Literally and figuratively, nucleic acids are the backbone of our genetic material. It was, therefore, of great interest to discover that examples of all four types of halogenated nucleic acid bases exist naturally.

The antibiotic nucleocidin [**138**] from the Indian soil microbe *Streptomyces calvus*, which is very active against trypanosomes, contains fluorine (329,330). The sponge *Echinodictyum* sp. contains the new brominated purine **139** (331), and the same paper reports the isolation of iodinated nucleoside **140** from red alga *Hypnea valendiae* (331). An *Actinomyces* sp. produces 2'-chloropentostatin [**141**] (332,333).

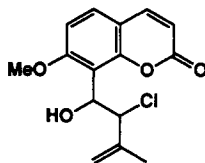


MISCELLANEOUS HETEROCYCLES.—Numerous halogenated (mainly chlorinated) oxygen heterocycles have been found in nature over the past decade, mainly from terrestrial plants and fungi. According to a 1984 review, some seven new natural chlorinated xanthenes have been characterized in the "past decade" (334). Even more recent is the isolation of arthothelin [**142**] from the Australian lichen *Lecanora broccha* and *Buellia* sp. (335). Chlorinated isocoumarins are in several plant species (336,337), and the coumarin chloculol [**143**] was recently extracted from *Murraya paniculata* (338). That **143** is not an artifact produced from the corresponding epoxide during extraction and workup was confirmed by subjecting the epoxide to the complete isolation and

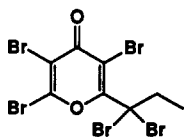
purification protocol (338). The red alga *Ptilonia australasica* produces two new and unusual polybrominated pyrones (e.g., **144**) (56). The marine sponge *Pseudaxinyssa cantharella* contains the simple imidazole chlorohydrin girolline [**145**], which is known to possess antitumor activity (339).



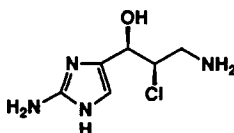
142



143



144

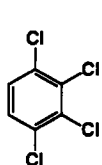


145

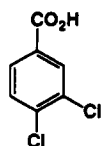
AROMATIC COMPOUNDS.—Because electrophilic halogenation in the laboratory on an unactivated benzene ring requires a degree of external vigor (heat, catalyst), it is not surprising that most of nature's halogenated aromatic rings are activated (e.g., phenolic). However, a few very interesting examples of simple halogenated aromatics do exist.

It has been reported that 1,2,3,4-tetrachlorobenzene [**146**] is contained in the Mississippi salt marsh "needlerush" (*Juncus roemerianus*) (340), a most extraordinary find. This compound represents 1.2% of the total organic oil extracted from this plant. A careful study of the ash from the 1980 eruption of Mt. St. Helens has revealed the presence of chloroaromatics **147** and **148**, and, even more noteworthy, three isomers of pentachlorobiphenyls (PCBs) **149**. Not only do control studies eliminate anthropogenic sources for these compounds, but the nature of the PCB isomers is not what would be expected from industrial PCBs (341). This landmark observation represents the first discovery of a natural source of PCBs. The authors surmised that rapid, incomplete high temperature combustion of chloride-containing plant material in the eruption zone led to these chlorinated aromatics, as well as to  $\text{CH}_3\text{Cl}$  (vide supra). Plants typically contain 200–10,000 ppm of chloride ion (15). More recently, two new glycopeptide antibiotics from *Amycolatopsis* sp., each of which contains five chlorines, were found to have a chlorinated biphenyl subunit (342).

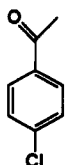
Another remarkable discovery is that an unidentified deep sea gorgonian, collected at a depth of 350 m, produces two halogenated azulenes, ehuazulene [**150**] and **151** (343).



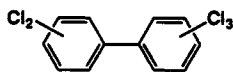
146



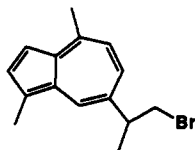
147



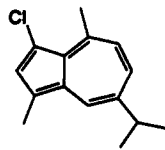
148



149



150



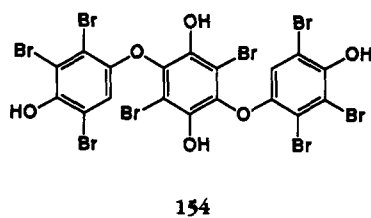
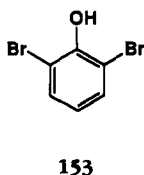
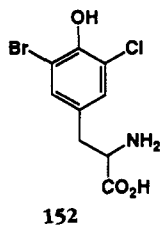
151

PHENOLS AND PHENOLIC ETHERS.—Although iodinated natural products are rarer than chlorinated or brominated natural products, nature's organic iodides have the distinction of being

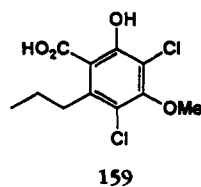
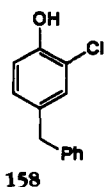
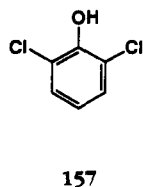
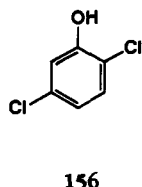
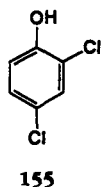
the earliest organohalides to be discovered and studied in depth. Thus, iodinated tyrosines have been known for nearly 100 years, having been isolated from the marine gorgonian *Gorgonia cavolinii* (344,345). Later, it was found that the essential thyroid gland hormone thyroxine is a tetraiodotyrosine derivative (346–348). For a review, see Roche and Michel (349).

Since then, a number of reports on the isolation of halogenated tyrosine derivatives from marine sponges, sea fans, and other gorgonians have appeared (350–352). It appears that these amino acids, when incorporated into structural proteins, may play a role in stabilizing the proteins in the organism by improving the adhesion between protein fibers or sheets (352). The mollusk *Buccinum undatum* utilizes 3-chloro-5-bromotyrosine [**152**] in its structural proteins (352). Even more interesting are the isolations of 3,4-dichlorotyrosine, as well as **152** and other brominated tyrosines, from the crustacean *Limulus polyphemus* (353), and 3-chlorotyrosine from the cuticle of locusts (*Schistocerca gregaria*) (354). Neither tyrosine derivative had been found previously in nature.

Simple halogenated phenols have been known for many years. In 1967, it was suggested that 2,6-dibromophenol [**153**], which is present to the extent of 10–15 mg per acorn worm *Balanoglossus biminensis*, may function in chemical defense to deter potential predators (355). Moreover, it is known that 2,4,6-tribromophenol, which is present in the acorn worm *Glossobalanus* sp., is toxic to mollusks (356). A detailed study of four species of acorn worms reveals the presence of a total of six brominated phenols, including the triphenyl ether **154**, the major metabolite of *Ptychodera flava* (356). A review indicates that some 220 phenolic substances, mostly halogenated, have been isolated from marine organisms up to 1980 (357).



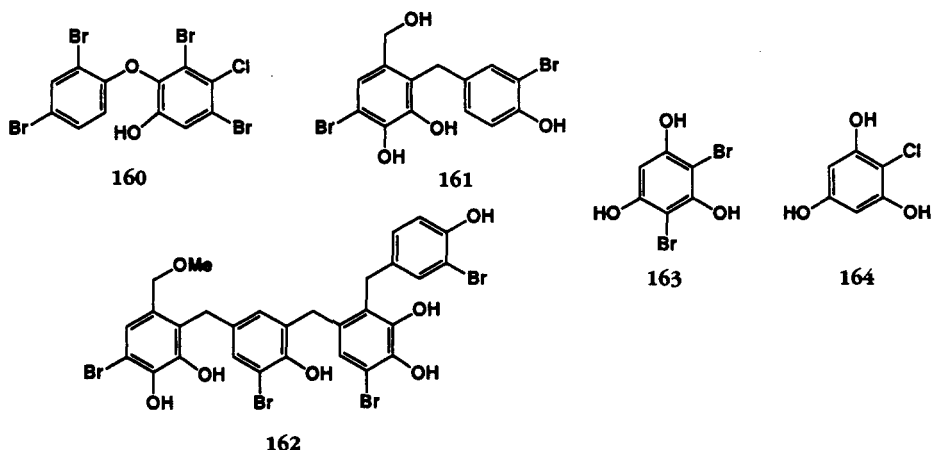
Because chlorophenols are used industrially on a large scale (200,000 tons manufactured annually) (358) and have been classified by the Environmental Protection Agency (EPA) as Priority Pollutants (359), it was an enormous surprise that several different chlorophenols are produced naturally. The soil fungus *Penicillium* sp. produces 2,4-dichlorophenol [**155**] (360), an industrial chemical used to synthesize the commonly used herbicide 2,4-D. Grasshoppers (*Romalea microptera*) secrete 2,5-dichlorophenol [**156**], which is repellent to ants (361), and the sex pheromone of the female Lone Star tick (*Amblyomma americanum*), as well as several other hard ticks, is 2,6-dichlorophenol [**157**] (362–365). Careful studies in the first and last of these investigations rule out the possibility that these compounds are artifacts (360,362–365). The blue-green alga *Anacystis marina* contains chlorophenol **158** (53), and a soil microbe (*Chaetomium* sp.) produces differanisole A [**159**], a 2,4-dichlorophenol derivative (366). *Pseudonocardia compacta* produces the new glycopeptide antibiotics helvecardins A and B, both of which contain a 2-chlorophenolic ether moiety (367).



Unfortunately, space does not permit a full presentation of the vast number of brominated phenols, phenolic ethers, and tyrosines that are found in marine organisms. Therefore, in this

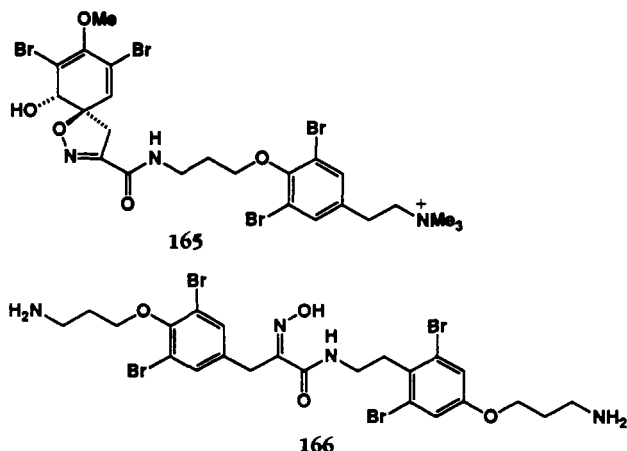
section, only a representative sampling will be given. However, a full listing of these natural products from 1980 to the present appears in Table 4.

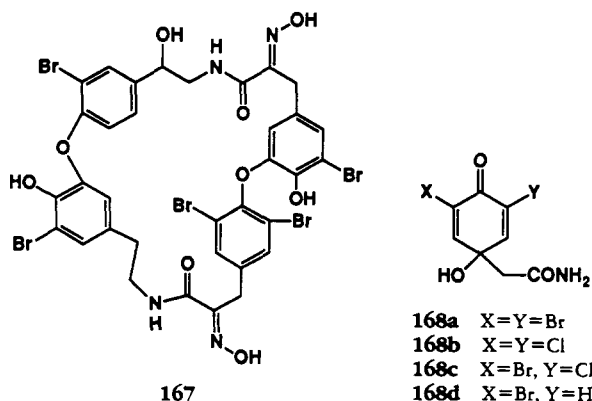
The "mixed" bromochlorodiphenyl ether **160** is produced by a marine sponge and accounts for 1.3% of the dry wt (368). It is interesting to note that this compound is a "pre-dioxin" intermediate. Another study of three Palau sponge species reveals the presence of seven different polybrominated diphenyl ethers (369). Avrainvilleol [**161**], a novel dibromodiphenylmethane, was isolated from the tropical green alga *Avrainvillea longicaulis* and found to be a powerful feeding deterrent and toxic to herbivorous reef fish (370). The related *Avrainvillea rawsoni* produces the labile rawsonol [**162**], an HMG-CoA reductase inhibitor, having a unique structure (371). The red alga *Rhabdonia verticillata* produces six bromo/chloro phloroglucinols (e.g., **163**, **164**) (372).



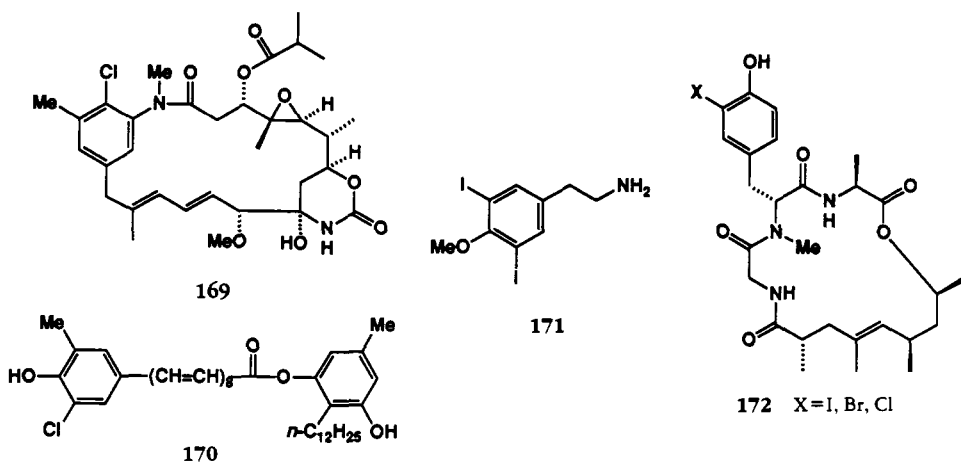
Representative of the large number of sponge metabolites that are derived from a brominated tyrosine are purealidins B [**165**] and C [**166**], isolated recently from the Okinawan sponge *Psammaphysilla purea* (373). The sponge *Ianthella basta*, collected off Guam, contains many brominated phenolic derivatives, one of which is bastadin 8 [**167**] (374). In contrast, the sponge *Aplysina cavernicola* produces the relatively simple halogenated quinols **168** (375).

Two Oregon forest mosses have yielded ansamitocin P-3 [**169**], a novel chlorinated phenolic ether which has potent activity against solid tumors (376). A dozen flexirubin pigments (e.g., chloroflexirubin [**170**]) have been extracted from several Flexibacteria (377). Although iodinated metabolites are rare compared to bromo and chloro natural products, the tunicate *Didemnum* sp.





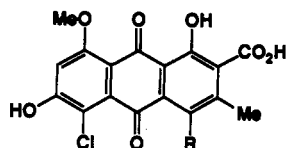
produces diiodide **171** to the extent of 0.4% dry wt (378). The marine sponge *Geodia* sp. contains the 2-iodophenol ring system as part of a cyclic peptide (379), and the sponge *Pseudaxinysa* sp. from New Guinea contains as part of a cyclic peptide, 2-iodo-2-bromo-, and 2-chlorophenol (i.e., **172**) (380). The exciting new class of powerful antitumor agents, the calicheamicins, contain an iodo- or bromo-substituted phenolic ether ring (381). These incredibly complicated natural products are produced by *Micromonospora echinospora*.



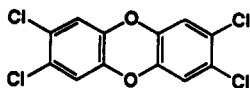
**ANTHRAQUINONES.**—Several species of *Dermocybe* fungus produce 5-chlorodermolutein [**173**] and 5-chlorodermorubin [**174**] (382–384). Otherwise, halogenated anthraquinones are relatively rare, and only these two examples have been described in the past decade.

**DIOXINS AND RELATED COMPOUNDS.**—“Dioxin,” 2,3,7,8-tetrachlorodibenzo-*p*-dioxin [**175**], was once generally thought to be the most toxic man-made chemical known (385–387). However, extensive research with dioxins over the past ten years and evaluations by epidemiologists of people exposed to dioxin [Vietnam Veterans (388,389), Seveso inhabitants (390), and industrial plant workers (391,392)] has revealed that dioxin is not the “doomsday chemical” once believed (392–394). For an excellent recent summary see Gough (394). There is no scientific evidence that dioxin causes any serious health effects in humans apart from the skin disease chloracne and some reversible liver dysfunction (394). Nevertheless, the extraordinary toxicity of some polychlorinated dioxins (PCDDs) and related compounds, such as the polychlorinated dibenzofurans (PCDFs) (e.g., **176**), in some animals is reason enough for the continued study of these compounds, especially since it is now recognized that PCDDs and PCDFs are, in fact, natural products.

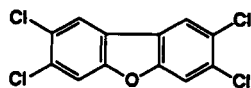




173 R=H  
174 R=OH



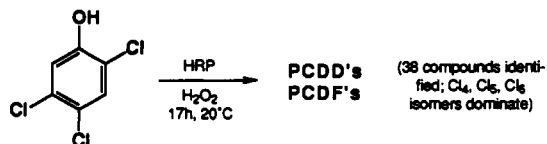
175



176

The fact that simple chlorinated organic compounds, e.g.,  $\text{CH}_3\text{Cl}$ , are produced when organic material is burned in the presence of the ubiquitous chloride ion (or organochlorine compounds) (vide supra) led to the belief, now supported by fact, that PCDDs, could form during combustion processes (395,396). Indeed, numerous studies have revealed that PCDDs, including **175**, and PCDFs form in parts-per-billion (ppb) amounts during the combustion of wood (treated or untreated) (397–400) and municipal waste (401–403). Automobiles and trucks are a significant source of these pollutants (404–406), and it is found that the emissions of PCDDs and PCDFs from high temperature industrial processing plants (e.g., steel mills, copper smelting plants) is of the same magnitude as that produced by municipal waste incinerators (407). It has been concluded that all combustion sources, except coal burning, produce PCDDs and PCDFs (402). Indeed, at least two groups conclude that forest and brush fires are the major source of PCDDs and PCDFs in the environment (397,408). In the words of one author, “based on available information, forest fires are estimated to be the largest source of PCDD release to the environment” (408). The relatively poor efficiency and incomplete oxidation when damp vegetation and wood are burned in the presence of high chloride concentrations (70–2100 ppm in wood pulp) (18) are conditions conducive to PCDD formation. It is estimated that some 130 pounds of PCDDs are produced in Canadian forest fires annually (408). This is ten times more than formed in the 1976 Seveso plant accident. Since most forest fires are lightning-caused, and there are 200,000 forest fires annually worldwide, burning 27,000 square miles (18), it is logical to assume that PCDDs have been present in the environment for many centuries. Therefore, it is not surprising that an 1877 soil sample was found to contain PCDDs and PCDFs (403).

A greater surprise than the discovery of PCDDs in combustion gases and residues is the observation that several chlorophenols are converted enzymatically into both PCDDs and PCDFs in the ppm range by horseradish peroxidase enzyme (HRP) (Scheme 1) (409). This extraordinary finding opens the door to the possibility that a source of environmental PCDDs and PCDFs may be their formation from ubiquitous chlorophenols by soil and water microbes.



SCHEME 1

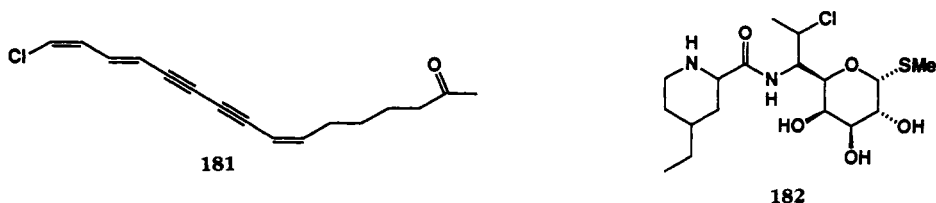
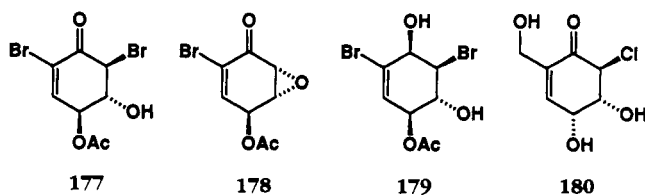
The wide distribution of bromophenols and related brominated phenolic ethers, particularly in marine life, would seem to indicate a need to search for the presence of polybrominated dibenzo-*p*-dioxins (PBDDs) and dibenzofurans in the environment, since it is known that the former can be as toxic to some laboratory animals as the corresponding PCDD analogues (387,410–412).

As a final note to this section on dioxins, the U.S. chemist who first synthesized several polychloro-, polybromo-, and polyiododibenzo-*p*-dioxins (413), before their toxicity was recognized, is alive and in good health today, thirty-five years later, although he suffered severely from chloracne following his initial exposure (Dr. J.J. Dietrich, private communication, October 29, 1991). Finally, a recent U.S. patent reports that 1,3,6,8-tetrachlorodibenzo-*p*-dioxin (a PCDD

isomer of "dioxin" [175]), as well as a trichloro PCDF derivative, have demonstrable activity against human breast cancer (414).

MISCELLANEOUS COMPOUNDS.—The acorn worm *Ptychodera* sp., a rich source of brominated phenols and indoles, also contains several brominated cyclitols, e.g., 177–179 (415). Metabolites 177 and an epimer represent more than 10% of the animal's dry weight, and epoxide 178 has excellent antitumor activity. The microorganism *Phyllosticta* sp. produces two chlorinated cyclitols (e.g., 180) (416).

The nudibranch *Diaulula sandiegensis* contains nine different chloroacetylenes (e.g., 181) (417). These chemicals are apparently stored in the animal's skin and appear to be used for defense against predators. The deactivation of pirlimycin [182], a recently isolated peptide sugar, has been studied (418).



Although this review is only concerned with organic halogen compounds, it is necessary to cite one intriguing exception. The sponge *Halichondria moorei* contains inorganic fluoride to the extent of 10% (dry wt) in the form of potassium fluorosilicate ( $K_2SiF_6$ ) (419). There are no fluoride sources available to this sponge, apart from the 1.3 ppm in ocean water, and another sponge species from the same taxonomic order and in a nearby location contains no fluoride. *Hal. moorei* is able to sequester and concentrate fluoride in the form of  $K_2SiF_6$ , which, in fact, is a potent anti-inflammatory agent.

Volcanoes also produce large quantities of HCl and HF (18,420). This is relevant to the present discussion since it has been proposed that HCl and HF can react with organic compounds to produce organohalogenes (420).

Finally, the discovery of the first chlorine-containing molecule, HCl, in interstellar space has been reported (421). It remains to be seen whether or not this exciting observation will be followed by discoveries of organochlorine molecules and other organohalogenes outside of our solar system, since nearly 100 stable organic molecules (alkynes, alcohols, amines, amides, alkenes, aldehydes) have been detected in interstellar space (422,423).

#### MECHANISMS OF BIOGENIC HALOGENATION

Two clear and distinct pathways exist for the formation of naturally occurring organohalogen compounds: (1) biosynthesis by an organism, and (2) combustion of organic matter in the presence of halide ion or other halogen source. Only the former has been studied in depth.

Because life began in the ocean, it is hardly surprising that marine organisms have not only adapted to the high salt concentrations in the ocean but have incorporated halogens into their chemical constitutions. Some marine bacteria need high salt concentrations (3% NaCl) to live, while some need exceptionally high concentrations (15–30% NaCl) for growth (424).

It is now well established that marine organisms contain haloperoxidase enzymes that can chlorinate, brominate, or iodinate organic compounds in the presence of chloride, bromide, or

iodide ions, respectively (8,425–428). For example, of 33 species of Phaeophyceae algae from the Atlantic Coast, 22 displayed peroxidase enzymatic activity (429). Evidence exists for the presence of peroxidases in the thyroid gland of mammals (430). Chloroperoxidase, which occurs in the mold *Caldariomyces fumago*, has been extensively studied (431–433), and bromoperoxidase from both green and red algae has been isolated, purified, and shown to be an efficient biogenic brominating agent (434–436). Soil extracts have been shown to have chlorinating ability (8,437), and more than 80 species of Death Valley fungi displayed chloroperoxidase activity (8). Lactoperoxidase, an enzyme present in mammalian milk (438), is capable of chlorinating organic substrates (425,438). For example, it is found that the enzymes lactoperoxidase, chloroperoxidase, HRP, or vanadium peroxidase are capable of chlorinating or brominating phenols and phenol ethers (anisole) in the presence of chloride or bromide, respectively (425,427). Some examples and chemical yields are shown in Figure 8.

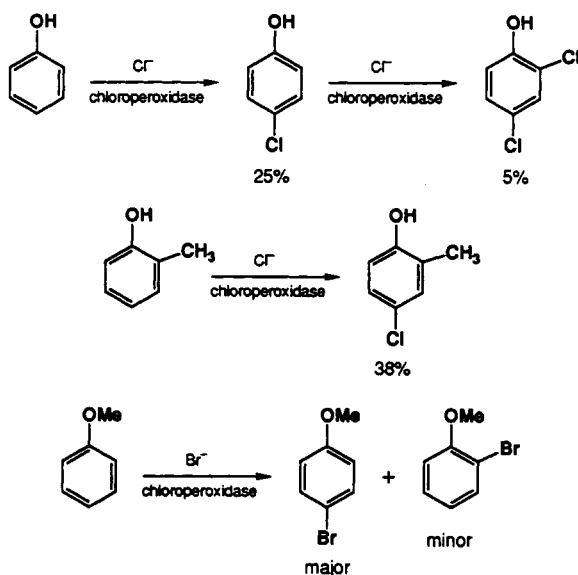


FIGURE 8. Examples of enzymatic halogenation of phenols and phenolic ethers.

These studies clearly show that the EPA Priority Pollutants such as various chlorinated phenols, cresols, and dioxins form enzymatically and, therefore, quite possibly in living organisms.

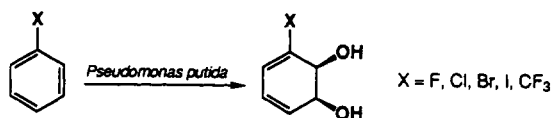
A different enzymatic mechanism, involving *S*-adenosyl methionine transferase, is involved in the biosynthesis of halogenated methanes in marine algae, fungi, and the ice plant (13).

### METABOLISM AND BIODEGRADATION

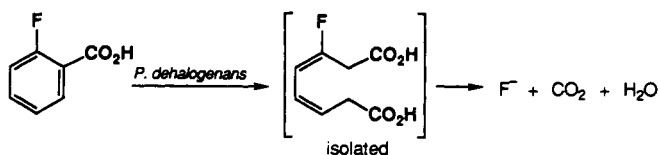
As it is with the other elements in our biosphere, the halogens, in the form of recyclable halide ions, must be recovered from plants and animals when they die, so that succeeding generations will have access to halide and other elements prerequisite for life. Thus, contrary to common perception, organohalogen compounds, both natural and unnatural, are readily metabolized and biodegraded to halide ion by a myriad of microorganisms.

The simple organohalogenes  $\text{CH}_2\text{Cl}_2$ ,  $\text{CHCl}_3$ ,  $\text{CCl}_4$ ,  $\text{BrCH}_2\text{CH}_2\text{Br}$ ,  $\text{CHBr}_3$ ,  $\text{Cl}_2\text{C}=\text{CCl}_2$ , and others can be degraded to  $\text{CO}_2$  (or other simple organics) and halide ion by soil bacteria (439–441). Aromatic halogen compounds are also metabolized by a number of different organisms. The soil bacterium *Pseudomonas putida* oxidizes halobenzenes to the cis-diol (Scheme 2) (442–444). This is a remarkably general reaction, very useful in organic synthesis (445,446), and even succeeds with fluorobenzene. Polychlorobenzenes are similarly oxidized by *Ps. putida* (447,448),

and *Pseudomonas desmolyticum* oxidizes chloro- and bromonaphthalene (449). Second-stage microbes would complete the loss of halide from these diols. For example, *Pseudomonas dehalogenans* oxidizes 2-fluorobenzoic acid completely to fluoride ion (Scheme 3) (450), and *Nocardia erythropolis* degrades aromatic fluorides (451). A review of the biotransformations of fluoroaromatics has appeared (452).



SCHEME 2



SCHEME 3

The biodegradation of chlorophenols has been widely studied. For example, 2,4-dichlorophenol is rapidly metabolized in soils (453), and an exhaustive mechanistic study of the degradation of this compound to chloride ion and CO<sub>2</sub> by the white-rot fungus *Phanerochaete chrysosporium* has been reported (454). This amazing fungus is capable of degrading other chlorinated phenols (455), DDT (456), and even pentachlorophenol (457). In the latter case, 97% of the phenol is degraded in 28 h at a concentration of 1 ppm. PCBs are also degraded by this fungus (458) as well as by a *Pseudomonas* sp. (459), and an excellent recent review of the biodegradation of PCBs is available (460). Another fungus, *Rhizoctonia praticola*, has the ability to polymerize halogenated phenols and form humic-like products (461,462).

Thus, it can be seen that organohalogen compounds not only have a natural beginning, but, in the scheme of things, they have a natural ending as well. The commonly held belief that organohalogen compounds are impervious to biodegradation is erroneous.

#### NATURAL VS. ANTHROPOGENIC ORGANOHALOGEN COMPOUNDS

We have already seen that CH<sub>3</sub>Cl is overwhelmingly biogenic in origin. But what about the relative quantities of the many other natural organohalogens vis-à-vis the approximately 20 million tons/year of 150 industrial organohalogens currently in use worldwide (8,45) and those other organohalogens formed as a result of human activity?

While a vast number of halogenated compounds have been isolated from natural sources (vide supra and Table 4), only a relatively few organisms have been examined for their chemical content, especially organisms in the oceans. For example, whereas some 12,000 natural products of all types have been isolated from terrestrial plants, only 500 had been isolated from marine plants (algae) up to 1987 (463). This contrasts with the fact that there are known some 500,000 species of marine animals, plants, and bacteria (464). For example, there are 80,000 living species of mollusks (465), 5000 species of sponges (466), and 4000 species of bryozoans (moss animals) (467), but only six of the latter have been examined (294). Of more than 90 known species of deep-sea gorgonians in the Hawaiian Islands, only 20 have been investigated for their chemical content (468), and of 13 *Mycale* sponges living in the Mediterranean Sea, only one has been investigated (129).

Since most marine organisms have been found to contain halogenated compounds, there are certainly thousands of different, new organohalogenated chemicals in marine organisms awaiting discovery. An early study of 46 marine sponge species revealed that all but one contained bromine (0.16–2.66%) and all contained iodine (0.12–1.21%) in the form of organic compounds (469). Marine algae such as *Asparagopsis taxiformis* (0.22% total halogen dry wt), *Bonnemaisonia hamifera*

(0.12%), *Laurencia pacifica* (0.29%), and *Plocamium pacificum* (0.64%) are found in all the world's oceans, and, in some cases, at depths from intertidal to >35 m (53). Moreover, not only do the oceans cover 70% of the earth's surface, they provide 99% of our living space since the total volume is occupied (470).

The diversity of marine life and, hence, of potential new organohalogen compounds, is illustrated by the Great Barrier Reef. This 100,000-square-mile area consists of 2500 separate small 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 shells, and other mollusks (471). In summary, it is clear that a very large number of marine organohalogen compounds will be discovered, to say nothing about the new halogenated compounds that have yet to be discovered in terrestrial plants, animals, bacteria, and fungi.

What are the quantities of naturally occurring organohalogen compounds? Apart from the CH<sub>3</sub>Cl estimate cited above, only a few attempts have been made to estimate the global contribution of organohalogens from natural sources. Table 2 summarizes these estimates. An inherent difficulty in making these estimates is the variability between samples of the same species. For example, the tropical green alga *Avrainvillea nigricans* from Puerto Rico contains at least two brominated metabolites, whereas the same species found in the western Caribbean is devoid of halogenated metabolites (472).

TABLE 2. Estimates of Naturally Occurring Organohalogens from Marine Sources.

Compound	Source(s)	Tons per Year	Reference
CH <sub>3</sub> Cl .....	giant kelp (macroalgae)	2,000	14
CH <sub>3</sub> Br .....	giant kelp (macroalgae)	100	14
CH <sub>3</sub> I .....	giant kelp (macroalgae)	200	14
CH <sub>3</sub> I .....	all biological sources	1,300,000	18
CH <sub>3</sub> I .....	oceans	300,000–500,000	18
CH <sub>3</sub> I .....	oceans	4,000,000	30
CH <sub>3</sub> Br .....	oceans	300,000	18
CH <sub>3</sub> Cl .....	oceans	4,900,000	18,27
"volatile organic bromine" .....	oceans	10,000	20
"volatile organic iodine" .....	oceans	100	20

Global estimates of the organohalogen content of animals are more difficult than are those of plants. However, a detailed study of the acorn worm *Ptychodera flava* has revealed that a known population of these animals (64 million) excrete in their fecal matter 95 pounds of organohalogens daily in a one square kilometer habitat on Okinawa (473). Obviously, many more studies of a similar nature are needed in order to estimate the global quantities of organohalogens from animal species.

Several researchers have reported the identification of halogenated phenolic compounds in ocean waters and in soil extracts (425,474–477). These studies conclude that the major source of most of these compounds, such as 2,4,6-trichlorophenol, is biogenic and from natural halogenation processes such as can occur between humic acid and soil microbes. Humic acids are not only present in soil but also in rivers, lakes, and the ocean (478). For a recent study of the release of humic acid from cordgrass, see Filip and Alberts (479). The yearly net production of environmental humic acid from the decomposition of organic material has been estimated at 63 billion tons (478), added to the estimated existing global 1.0–1.5 trillion tons of soil humic acids and one trillion tons of ocean humic acid (478). Numerous studies have demonstrated the ease with which humic acid model compounds (phenolics) react with halogens (478,480–482). Furthermore, chloride ion is ubiquitous in soil, plants (200–10,000 ppm) (15), in rivers (average 8 ppm) (483), lakes (483), and, of course, oceans (478,483). These ingredients, in combination with natural chloroperoxidase and other enzymes, provide a plausible rationale for the natural formation of chlorinated phenols.

The positive correlation between the level of halogenated anisoles detected in marine air and their occurrence in algae in coastal areas supports the assumption of a biogenic source for these

compounds (425). Several studies have demonstrated that the natural production of chlorinated phenols and anisole outweighs the anthropogenic sources (474–477). For example, the total pool of adsorbable halogenated organic compounds in peat in Sweden is 300,000–400,000 tons, whereas the largest industrial emissions are from paper pulp industries and are 10,000 tons per year (474). Since in this area of Sweden the topography excludes leaching from surrounding areas into the bogs under study, these organic halogen compounds must be of natural origin. Moreover, the peat bogs contain but a fraction of the total naturally occurring halogenated organic chemicals.

### SUMMARY

The field of organohalogen natural products has truly blossomed into an enormous scientific arena in the interval since 1968, when Fowden stated: "...our present information suggests that organic compounds containing covalently bound halogens are found only infrequently in living organisms" (3).

Ironically, evidence is now available to indicate that organohalogen compounds have been present on earth for centuries. For example, organohalogen compounds in fulvic acids have been isolated from groundwater samples that date back 1300, 4600, and 5200 years (474). Another study has identified organohalogen material in sediments dating back to the 13th century (484). Perhaps even more remarkable is the fact that microfossils present in Precambrian rocks, which are a billion years old, are identical to the blue-green alga *Nostoc*, and other microfossils are morphologically indistinguishable from *Oscillatoria*, two present-day species rich in organohalogen compounds (485). It would be foolish to believe that organohalogen compounds have not been with us for as long as any other organic chemicals.

A difficult question to answer is one often posed by environmental skeptics: "Why would nature create organohalogen compounds?" There is convincing evidence that, in many marine organisms, organohalogen compounds serve in chemical defense, as either feeding deterrents, irritants, or poisons (486–488). For example, a recent careful study of the sea hare *Stylocheilus longicauda* clearly indicates a feeding deterrent role for its organohalogen compounds (489,490), and the sea hare *Aplysia brasiliana* is distasteful to fish and rejected by sharks due, in part, to panacene, a brominated allene (490). There is evidence that marine algae store organohalogen compounds in the vesicular cells for facile secretion to discourage predators (34,54).

A direct correlation has been observed between the presence of organohalogen metabolites and antimicrobial activity in some 1200 marine organisms (491). In addition to the widespread antibiotic activity of many organohalogen compounds (492), antitumor, antifungal, insecticidal, herbicidal, and other potentially valuable biological activity has been observed (486–488,493–495). Telfairine [23] is 100% lethal to mosquito larvae at 10 ppm (86), and plocamene B is three times more effective than the commercial pesticide lindane against mosquito larvae (91). The aromatic iodophenolic ether calicheamicin  $\gamma_1^1$  is 1,000 times more potent than the clinical anticancer drug adriamycin (381). It seems certain that the near future will see the development of medicinally important organohalogen compounds (496).

### FUTURE OUTLOOK

The explosion of activity in the area of organohalogen natural product chemistry is certain to continue. The continued improvements in isolation, analytical, and spectroscopic techniques over the past few years ensure the fact that even the most structurally complex organohalogen natural products can and will be identified. As our understanding of natural enzymatic halogenation reactions continues to increase, it will be possible to separate more accurately natural from anthropogenic sources of halogenated chemicals.

Table 3 summarizes the present state of knowledge regarding natural sources of organohalogenated compounds. It is apparent that two-thirds of the possible sources have been realized.

Table 4 summarizes the new organohalogen compounds reported from natural sources during the period 1980–1991.

TABLE 3. Sources of Naturally Occurring Organic Compounds<sup>a</sup> [adapted from Neidleman and Geigert (8)].

Source	RCl	RBr	RI	RF
Bacteria .....	+	+	-	+
Fungi .....	+	+	-	-
Algae .....	+	+	+	-
Higher plants .....	+	+	-	+
Higher animals .....	+	+	+	-
Humans .....	-	+	+	-

<sup>a</sup> + = present in the indicated source; - = not found in the indicated source.

TABLE 4. Summary of Naturally Occurring Organohalogens Reported During the Period 1980-1991.<sup>a</sup>

Organism	Number of New Halogenated Metabolites	Reference(s)
<b>Red Algae</b>		
<i>Chondria tenuissima</i> .....	1	94
<i>Gelidium sesquipedale</i> .....	1	93
<i>Hypnea valendiae</i> .....	1	331
<i>Laurencia brongniartii</i> .....	6	556
<i>Laurencia implicata</i> .....	6	153,154
<i>Laurencia intricata</i> .....	5	155,156
<i>Laurencia majuscula</i> .....	3	82
<i>Laurencia microcladia</i> .....	1	171
<i>Laurencia nipponica</i> .....	14	67,68,158-163,497
<i>Laurencia obtusa</i> .....	31	70-76,164-170,498,499
<i>Laurencia pacifica</i> .....	1	69
<i>Laurencia perforata</i> .....	3	79
<i>Laurencia pinnatifida</i> .....	6	77,78,157
<i>Laurencia scoparia</i> .....	1	499
<i>Laurencia snyderae</i> .....	1	500
<i>Laurencia tenera</i> .....	2	83
<i>Laurencia venusta</i> .....	2	80,81
<i>Laurencia</i> sp. ....	4	84,501
<i>Ochtodes crockeri</i> .....	8	92
<i>Ochtodes secundiramea</i> .....	1	90
<i>Plocamium cartilagineum</i> (= <i>P. coccineum</i> ) .....	4	87-90,502
<i>Plocamium mertensii</i> .....	1	85
<i>Plocamium telfairiae</i> .....	1	86
<i>Plocamium violaceum</i> .....	1	90
<i>Plocamium</i> sp. ....	1	85
<i>Portieria bornemannii</i> .....	6	91,95
<i>Rhabdonia verticillata</i> .....	1	372
<i>Vidalis spiralis</i> .....	1	59
Sub-total	114	
<b>Blue-Green Algae and Cyanobacteria</b>		
<i>Anabaena</i> sp. ....	2	184
<i>Fischerella</i> sp. ....	3	282,503
<i>Hapalosiphon fontinalis</i> .....	12	281
<i>Lyngbya majuscula</i> .....	9	504
<i>Nostoc linckia</i> .....	4	152
<i>Nostoc</i> sp. ....	1	503
<i>Oscillatoria</i> sp. ....	1	131
<i>Rivularia firma</i> .....	6	280
<i>Scytonema hofmanni</i> .....	1	505
<i>Tolypothrix tjipanansensis</i> .....	13	506
Sub-total	52	
<b>Green Algae</b>		
<i>Avrainvillea longicaulis</i> .....	1	370
<i>Avrainvillea nigricans</i> .....	1	472
<i>Avrainvillea rausoni</i> .....	1	371

TABLE 4. Continued.

Organism	Number of New Halogenated Metabolites	Reference(s)
<i>Cymopolia barbata</i> .....	6	97,507
<i>Neomeris annulata</i> .....	3	96
Sub-total	12	
Brown Algae		
Fucales sargassum .....	2	37
Sub-total	2	
Sponges		
<i>Acanthella cavernosa</i> .....	2	126
<i>Acanthella klethra</i> .....	1	127
<i>Acanthella</i> sp. ....	8	125
<i>Agelas sceptrum</i> .....	1	230
<i>Agelas conifera</i> .....	8	232-234,508,518
<i>Aplysina cauliformis</i> .....	1	509
<i>Aplysina cavernicola</i> .....	13	375,510-512
<i>Aplysina lacunosa</i> .....	1	509
<i>Aplysina thiona</i> .....	4	513
<i>Aplysina</i> sp. ....	2	514
<i>Axinella verrucosa</i> , others .....	1	227,228
<i>Axinella</i> sp. ....	1	229
<i>Batzella</i> sp. ....	6	283,284
<i>Cliona celata</i> .....	2	274
<i>Dendrilla</i> sp. ....	1	325
<i>Dercitus</i> sp. ....	1	266
<i>Discodermia polydiscus</i> .....	1	270
<i>Dragmacidon</i> sp. ....	1	263
<i>Druinella purpurea</i> .....	2	515
<i>Dysidea herbacea</i> .....	7	369,516
<i>Dysidea chlorea</i> .....	1	369
<i>Echinodictyum</i> sp. ....	1	331
<i>Geodia baretii</i> .....	1	271,272
<i>Geodia</i> sp. ....	2	379
<i>Haliclona</i> sp. ....	2	147
<i>Hexadella</i> sp. ....	5	265,517
<i>Hymeniacion</i> sp. ....	3	235
<i>Ianthella ardis</i> .....	1	519
<i>Ianthella basta</i> .....	14	374,520,552
<i>Iotrocota</i> sp. ....	1	249
<i>Jaspis</i> sp. ....	1	276,277
<i>Latrunculia</i> sp. ....	3	285,287
<i>Mycale rotalis</i> .....	3	129,148
<i>Penares</i> sp. ....	1	250
<i>Petrosia ficiformis</i> .....	4	207
<i>Phyllospongia foliascens</i> .....	3	369
<i>Pleronia menoui</i> .....	2	248
<i>Prianos melanos</i> .....	2	286,288
<i>Psammaphysilla arabica</i> .....	2	521
<i>Psammaphysilla purea</i> .....	7	373,522-524
<i>Psammaphysilla purpurea</i> .....	7	525-527
<i>Pseudaxinysa cantharella</i> .....	1	339
<i>Pseudaxinysa</i> sp. ....	4	380
<i>Smenospongia aurea</i> .....	5	255,256
<i>Spongia zinocca</i> .....	3	128,171
<i>Spongosorites ruetzleri</i> .....	3	261
<i>Tbeonella</i> sp. ....	1	278
<i>Thoretopsamma xana</i> .....	1	528
<i>Topsentia genitrix</i> .....	1	262
<i>Verongula aerophoba</i> .....	3	529
<i>Verongula rigida</i> .....	1	530
Unidentified .....	5	130,264,368,531
Sub-total	158	



TABLE 4. Continued.

Organism	Number of New Halogenated Metabolites	Reference(s)
<b>Gorgonians and Octocorals</b>		
<i>Briareum polyanthes</i> .....	6	113,114
<i>Briareum</i> sp. ....	3	117,553
<i>Clavularia viridis</i> .....	4	210
<i>Dendrophyllia</i> sp. ....	1	269
<i>Erythropodium caribaeorum</i> .....	8	115,118
<i>Junceella fragilis</i> .....	5	121
<i>Minabea</i> sp. ....	5	116
<i>Ptilosarcus gurneyi</i> .....	5	123
<i>Sarcophyton glaucum</i> .....	1	119
<i>Solenopodium</i> sp. ....	5	120
<i>Teleso riisei</i> .....	4	209
<i>Tubastraea</i> sp. ....	1	268
Deep sea gorgonian .....	2	343
Sub-total	50	
<b>Marine Animals</b>		
<i>Aplysia dactylomela</i> .....	9	107-111
<i>Aplysia juliana</i> .....	1	112
<i>Aplysia kurodai</i> .....	12	102,104-106,532
<i>Astroides calycularis</i> .....	1	267
<i>Babylonia japonica</i> .....	2	298,300,301
<i>Balanoglossus carnosus</i> .....	2	356
<i>Chartella papyracea</i> .....	5	294-296
<i>Diadula sandiegensis</i> .....	9	417
<i>Diazona chinensis</i> .....	2	279
<i>Didemnum candidum</i> .....	3	257
<i>Didemnum</i> sp. ....	2	378
<i>Endistoma glaucus</i> .....	6	306-308
<i>Endistoma olivaceum</i> .....	16	309,310
<i>Flustra foliacea</i> .....	7	289-291,320,533
<i>Glossobalanus</i> sp. ....	4	244,356
<i>Gymnocrinus ricberi</i> .....	5	534
<i>Haminoea cymbalum</i> .....	1	149
<i>Hincksinoflustra denticulata</i> .....	1	535
<i>Polyandrocarpa</i> sp. ....	2	275
<i>Polycitorella mariae</i> .....	1	259,260
<i>Pteroides laboutei</i> .....	2	122
<i>Ptychodera flava</i> .....	2	356
<i>Ptychodera</i> sp. ....	6	415
<i>Ritterella sigillinoides</i> .....	3	312,314
<i>Roboastra tigris</i> .....	2	236
<i>Zoobotryon verticillatum</i> .....	2	536
Sub-total	108	
<b>Microorganisms</b>		
<i>Actinomadura mellianra</i> .....	2	319
<i>Actinomyces</i> sp. ....	4	218,219,332,333
<i>Actinoplanes</i> sp. ....	1	537
<i>Actinosporangium vitaminophilum</i> .....	7	220,221
<i>Actinosporangium</i> sp. ....	3	222
<i>Amycolatopsis</i> sp. ....	2	342
<i>Chaetomium</i> sp. ....	1	366
<i>Flavobacterium</i> sp. ....	2	538
<i>Gluconobacter</i> sp. ....	1	140
<i>Micromonospora echinospora</i> .....	7	381
<i>Nocardia aerocolonigenes</i> .....	2	315-317
<i>Penicillium crustosum</i> .....	3	302
<i>Pseudomonas syringae</i> .....	6	182,183
<i>Pseudomonas yoshitomiensis</i> .....	1	138
<i>Pseudomonas</i> sp. ....	1	139
<i>Pseudonocardia compacta</i> .....	2	367
<i>Saccharothrix aerocolonigenes</i> .....	1	318

TABLE 4. Continued.

Organism	Number of New Halogenated Metabolites	Reference(s)
<i>Streptomyces griseosporus</i> .....	1	179
<i>Streptomyces nitrosporeus</i> .....	1	321-323
<i>Streptomyces puniceus</i> spp. <i>doliceus</i> .....	1	189
<i>Streptomyces viridogenes</i> .....	1	180
<i>Streptomyces xanthocidicus</i> .....	1	178
<i>Streptomyces</i> sp. ....	4	137,217,223,554
Sub-total	55	
<b>Fungi</b>		
<i>Aspergillus terreus</i> .....	1	539
<i>Buellia canescens</i> .....	3	540,541
<i>Buellia</i> sp. ....	2	335
<i>Chaetomium globosum</i> .....	4	141
<i>Claopodium crispifolium</i> .....	1	376
<i>Mollisia ventosa</i> .....	4	555
<i>Monocillium nordinii</i> .....	1	542
<i>Pulveroboletus auriflammeus</i> .....	3	543
Unidentified .....	1	142
Sub-total	20	
<b>Higher Plants</b>		
<i>Acroptilon repens</i> .....	2	544
<i>Asystasia bella</i> .....	1	143
<i>Cibotium barometz</i> .....	1	545
<i>Cistanche salsa</i> .....	1	546
<i>Echinops</i> spp. ....	2	328
<i>Histopteris incisa</i> .....	1	133
<i>Jaborosa magellanica</i> .....	2	193
<i>Lasiolaena santosii</i> .....	3	547
<i>Ligusticum wallichii</i> .....	1	548
<i>Melodinus celastroides</i> .....	2	186
<i>Mentzelia decapetala</i> .....	1	549
<i>Murraya paniculata</i> .....	1	338
<i>Physalis peruviana</i> .....	2	191,192
<i>Pteris podophylla</i> .....	1	550
<i>Pteridium aquilinum</i> ssp. <i>uigbtianum</i> .....	1	134
<i>Pterocaulon virgatum</i> .....	3	327
<i>Rehmannia glutinosa</i> .....	5	144-146
<i>Suartzia laevicarpa</i> .....	2	336
<i>Teucrium africanum</i> .....	2	135
<i>Teucrium polium</i> ssp. <i>vincentinum</i> .....	1	136
<i>Thunbergia fragrans</i> .....	1	551
<i>Tovomita brasiliensis</i> .....	1	337
<i>Witbania somnifera</i> .....	1	190
<i>Zea mays</i> .....	1	324
Sub-total	39	
<b>Mammals</b>		
bovine .....	1	304
Sub-total	1	
<b>TOTAL</b>	<b>611</b>	

\*Although several of these compounds were isolated from more than one source, they are counted only once. Previously known compounds are not listed. Many of the organisms listed contain compounds other than the ones reported here, but only newly discovered natural products are listed.

#### ACKNOWLEDGMENTS

The author is indebted to Professor Marcus Tius and his colleagues and staff of the Department of Chemistry at the University of Hawaii at Manoa for their warm hospitality, excellent facilities, and Aloha spirit during a sabbatical stay, 1991-1992, which made the completion of this review possible. We thank Professor Richard Moore for reading and commenting on this manuscript, and also thank American Cyanamid Company for an Academic Achievement Award, Dartmouth College for a Senior Faculty Grant in support of this sabbatical, and a referee for valuable comments.

## LITERATURE CITED

1. Science Advisory Board of the International Joint Commission on the Great Lakes, "1989 Report," International Joint Commission, Hamilton, Ontario, October, 1989.
2. J. Marx, "News and Comment," *Science*, **250**, 743 (1990).
3. L. Fowden, *Proc. R. Soc. B*, **171**, 5 (1968).
4. W.B. Turner, "Fungal Metabolites," Academic Press, New York, 1971.
5. W.B. Turner and D.C. Aldridge, "Fungal Metabolites," 2nd ed., Academic Press, New York, 1983.
6. J.F. Siuda and J.F. DeBernardis, *Lloydia*, **36**, 107 (1973).
7. K.C. Engvild, *Phytochemistry*, **25**, 781 (1986).
8. S.L. Neidleman and J. Geigert, "Biohalogenation: Principles, Basic Roles and Applications," Halsted Press, New York, 1986.
9. D.J. Faulkner, *Tetrahedron*, **33**, 1421 (1977).
10. D.J. Faulkner, *Nat. Prod. Rep.*, **8**, 97 (1991), and previous papers in this series.
11. P.J. Scheuer, "Marine Natural Products," Academic Press, New York, 1978-1983, Vols. I-V.
12. W. Fenical, in: "Marine Organic Chemistry." Ed. by E.K. Duursma and R. Dawson, Elsevier Scientific Publishing Co., Amsterdam, 1981, Chapter 12.
13. A.M. Wuosmaa and L.P. Hager, *Science*, **249**, 160 (1990).
14. S.L. Manley and M.N. Dastoor, *Limnol. Oceanogr.*, **32**, 709 (1987).
15. D.B. Harper, *Nature*, **315**, 55 (1985).
16. R.H. White, *Arch. Microbiol.*, **132**, 100 (1982).
17. E.M. Turner, M. Wright, T. Ward, D.J. Osborne, and R. Self, *J. Gen. Microbiol.*, **91**, 167 (1975).
18. V.A. Isidorov, "Organic Chemistry of the Earth's Atmosphere," Springer-Verlag, Berlin, 1990.
19. M.I. Cowan, A.T. Glen, S.A. Hutchinson, M.E. MacCartney, J.M. Mackintosh, and A.M. Moss, *Trans. Br. Mycol. Soc.*, **60**, 347 (1973).
20. P.M. Gschwend, J.K. MacFarland, and K.A. Newman, *Science*, **227**, 1033 (1985).
21. T.Y. Palmer, *Nature*, **263**, 44 (1976).
22. J.E. Lovelock, *Nature*, **256**, 193 (1975).
23. R.E. Stoiber, D.C. Leggett, T.F. Jenkins, R.P. Murrmann, and W.I. Rose, *Geol. Soc. Am. Bull.*, **82**, 2299 (1971).
24. R.A. Rasmussen, M.A.K. Khalil, R.W. Dalluge, S.A. Penkett, and B. Jones, *Science*, **215**, 665 (1982).
25. P.R. Edwards, I. Campbell, and G.S. Milne, *Chem. Ind.*, 619 (1982).
26. M.R. Guerin, in: "Organic Chemistry of the Atmosphere." Ed. by L.D. Hansen and D.J. Eatough, CRC Press, Boca Raton, FL, 1991, Chapter 3.
27. R.A. Rasmussen, L.E. Rasmussen, M.A.K. Khalil, and R.W. Dalluge, *J. Geophys. Res.*, **85**, 7350 (1980).
28. H.B. Singh, L.J. Salas, H. Shigeishi, and E. Scribner, *Science*, **203**, 899 (1979).
29. J.E. Lovelock, R.J. Maggs, and R.J. Wade, *Nature*, **241**, 194 (1973).
30. O.C. Zafriou, *J. Mar. Res.*, **33**, 75 (1975).
31. H.B. Singh, L.J. Salas, and R.E. Stiles, *J. Geophys. Res.*, **88**, 3684 (1983).
32. R.J. Cicerone, L.E. Heidt, and W.H. Pollock, *J. Geophys. Res.*, **93**, 3745 (1988).
33. B.J. Bureson, R.E. Moore, and P. Roller, *Tetrahedron Lett.*, 473 (1975).
34. B.J. Bureson, R.E. Moore, and P. Roller, *J. Agric. Food Chem.*, **24**, 856 (1976).
35. R.E. Moore, *Acc. Chem. Res.*, **10**, 40 (1977).
36. O. McConnell and W. Fenical, *Phytochemistry*, **16**, 367 (1977).
37. T. Class, R. Kohnle, and K. Ballschmiter, *Chemosphere*, **15**, 429 (1986).
38. R.A. Rasmussen, M.A.K. Khalil, R. Gunawardena, and S.D. Hoyt, *J. Geophys. Res.*, **87**, 3086 (1982).
39. E. Fogelqvist, *J. Geophys. Res.*, **90**, 9181 (1985).
40. M. Krysell and D.W.R. Wallace, *Science*, **242**, 746 (1988).
41. P.M. Gschwend and J.K. MacFarlane, in "Organic Marine Geochemistry." Ed. by M.L. Sohn, American Chemical Society, Washington, DC, 1986, Chapter 18.
42. W.W. Berg, P.D. Sperry, K.A. Rahn, and E.S. Gladney, *J. Geophys. Res.*, **88**, 6719 (1983).
43. J.E. Lovelock, *Nature*, **252**, 292 (1974).
44. B. Fleming, *Pulp and Paper*, April, 115 (1991).
45. T. Leisinger, *Experientia*, **39**, 1183 (1983).
46. P. Herbert, P. Charbonnier, L. Rivolta, M. Servais, F. van Mensch, and I. Campbell, *Chem. Ind.*, 861 (1986).
47. R.J. Cicerone, *Science*, **206**, 59 (1979).
48. P. Fabian R. Borchers, B.C. Krüger, and S. Lai, *J. Geophys. Res.*, **92**, 9831 (1987).
49. E.P. Grimsrud and R.A. Rasmussen, *Atmos. Environ.*, **9**, 1010 (1975).
50. E.P. Grimsrud and R.A. Rasmussen, *Atmos. Environ.*, **9**, 1014 (1975).
51. F.X. Woolard, R.E. Moore, and P.P. Roller, *Tetrahedron*, **32**, 2843 (1976).
52. W. Fenical, *Tetrahedron Lett.*, 4463 (1974).
53. D.J. Faulkner, in: "The Handbook of Environmental Chemistry." Ed. by O. Hutzinger, Springer-Verlag, Berlin, 1980, Vol. 1, Part A.
54. O.J. McConnell and W. Fenical, *Phytochemistry*, **19**, 233 (1980).
55. J.F. Siuda, G.R. VanBlaricom, P.D. Shaw, R.D. Johnson, R.H. White, L.P. Hager, and K.L. Rinehart Jr., *J. Am. Chem. Soc.*, **97**, 937 (1975).
56. R. Kazlauskas, R.O. Lidgard, and R.J. Wells, *Tetrahedron Lett.*, 3165 (1978).
57. K. Ohta and M. Takagi, *Phytochemistry*, **16**, 1085 (1977).
58. J.S. Mynderse and R.E. Moore, *Phytochemistry*, **17**, 1325 (1978).

59. R. Kazlauskas, P.T. Murphy, and R.J. Wells, *Aust. J. Chem.*, **35**, 219 (1982).
60. I. Yanagisawa and H. Yoshikawa, *Biochim. Biophys. Acta.* **329**, 283 (1973).
61. S. Yamamura and Y. Hirata, *Tetrahedron.* **19**, 1485 (1963).
62. S. Naylor, F.J. Hanke, L.V. Manes, and P. Crews, *Prog. Chem. Org. Nat. Prod.* **44**, 189 (1983).
63. K.L. Erickson, in: "Marine Natural Products." Ed. by P.J. Scheuer, Academic Press, New York, 1983, Vol. V, Chapter 4.
64. W. Fenical, *J. Physiol.* **11**, 245 (1975).
65. S.M. Kupchan, J.E. Kelsey, M. Maruyama, J.M. Cassidy, J.C. Hemingway, and J.R. Knox, *J. Org. Chem.* **34**, 3876 (1969).
66. R.R. Izak and J.J. Sims, *J. Am. Chem. Soc.* **101**, 6136 (1979).
67. T. Suzuki, *Chem. Lett.* 541 (1980).
68. H. Kikuchi, T. Suzuki, M. Suzuki, and E. Kurosawa, *Bull. Chem. Soc. Jpn.* **58**, 2437 (1985).
69. S.J. Selover and P. Crews, *J. Org. Chem.* **45**, 69 (1980).
70. M.R. Brennan, K.L. Erickson, D.A. Minott, and K.O. Pascoe, *Phytochemistry.* **26**, 1053 (1987).
71. T. Suzuki, S. Takeda, H. Hayama, I. Tanaka, and K. Komiyama, *Chem. Lett.* 969 (1989).
72. J.D. Martin, P. Caballero, J.J. Fernandez, M. Norte, R. Perez, and M.L. Rodriguez, *Phytochemistry.* **28**, 3365 (1989).
73. S.E.N. Ayyad, A.A.M. Dawidar, H.W. Dias, R.A. Howie, J. Jakupovic, and R.H. Thomson, *Phytochemistry.* **29**, 3193 (1990).
74. T. Suzuki, M. Suzuki, A. Furusaki, T. Matsumoto, A. Kato, Y. Imanaka, and E. Kurosawa, *Tetrahedron Lett.* **26**, 1329 (1985).
75. S. Takeda, T. Matsumoto, K. Komiyama, E. Kurosawa, and T. Suzuki, *Chem. Lett.* 277 (1990).
76. A.G. González, J.D. Martín, M. Norte, R. Pérez, P. Rivera, J.Z. Ruano, M.L. Rodríguez, J. Fayos, and A. Perales, *Tetrahedron Lett.* **24**, 4143 (1983).
77. A.G. Gonzalez, J.M. Artega, J.J. Fernandez, J.D. Martin, M. Norte, and J.Z. Ruano, *Tetrahedron.* **40**, 2751 (1984).
78. S. Bano, M.S. Ali, and V.U. Ahmad, *Planta Med.* **53**, 508 (1987).
79. A.G. González, J.F. Ciccio, A.P. Rivera, and J.D. Martin, *J. Org. Chem.* **50**, 1261 (1985).
80. S. Sakemi, T. Higa, C.W. Jefford, and G. Bernardinelli, *Tetrahedron Lett.* **27**, 4287 (1986).
81. M. Suzuki, E. Kurosawa, and K. Kurata, *Phytochemistry.* **27**, 1209 (1988).
82. J.C. Coll and A.D. Wright, *Aust. J. Chem.* **42**, 1591 (1989).
83. J.C. Coll, B.W. Skelton, A.H. White, and A.D. Wright, *Aust. J. Chem.* **42**, 1695 (1989).
84. A.G. González, J.D. Martín, V.S. Martín, R. Pérez, B. Tagle, and J. Clardy, *J. Chem. Soc. Chem. Commun.* 260 (1985).
85. R.J. Capon, L.M. Engelhardt, E.L. Ghisalberti, P.R. Jefferies, V.A. Patrick, and A.H. White, *Aust. J. Chem.* **37**, 537 (1984).
86. K. Watanabe, M. Miyakado, N. Ohno, A. Okada, K. Yanagi, and K. Moriguchi, *Phytochemistry.* **28**, 77 (1988).
87. G.M. König, A.D. Wright, and O. Sticher, *J. Nat. Prod.* **53**, 1615 (1990).
88. F.J. Sardina, E. Quinoá, L. Castedo, and R. Riguera, *Chem. Lett.* 697 (1985).
89. G. Combaut, J.-M. Kornprobst, and J. Mollion, *Chem. Abstr.* **97**, 69273 (1982).
90. P. Crews, S. Naylor, F.J. Hanke, E.R. Hogue, E. Kho, and R. Braslau, *J. Org. Chem.* **49**, 1371 (1984).
91. P. Crews, B.L. Myers, S. Naylor, E.L. Clason, R.S. Jacobs, and G.B. Staal, *Phytochemistry.* **23**, 1449 (1984).
92. V.J. Paul, O.J. McConnell, and W. Fenical, *J. Org. Chem.* **45**, 3401 (1980).
93. M.A. Aazizi, G.M. Assef, and R. Faure, *J. Nat. Prod.* **52**, 829 (1989).
94. A. Oztunc, S. Imre, H. Lotter, and H. Wagner, *Phytochemistry.* **28**, 3403 (1989).
95. A.D. Wright, *Tetrahedron.* **47**, 5717 (1991).
96. D.E. Barnekow, J.H. Cardellina, A.S. Zektzer, and G.E. Martin, *J. Am. Chem. Soc.* **111**, 3511 (1989).
97. M.E. Wall, M.C. Wani, G. Manikumar, H. Taylor, T.J. Hughes, K. Gaetano, W.H. Gerwick, A.T. McPhail, and D.R. McPhail, *J. Nat. Prod.* **52**, 1092 (1989).
98. D.J. Faulkner, M.O. Stallard, J. Fayos, and J. Clardy, *J. Am. Chem. Soc.* **95**, 3413 (1973).
99. M.O. Stallard and D.J. Faulkner, *Comp. Biochem. Physiol.* **B49**, 25 (1974).
100. S. Yamamura and Y. Hirata, *Bull. Chem. Soc. Jpn.* **44**, 2560 (1971).
101. S. Yamamura and Y. Terada, *Tetrahedron Lett.* 2171 (1977).
102. A. Katayama, K. Ina, H. Nozaki, and M. Nakayama, *Agric. Biol. Chem.* **46**, 859 (1982).
103. T. Miyamoto, R. Higuchi, T. Komori, T. Fujioka, and K. Mihashi, *Chem. Abstr.* **104**, 183529 (1986).
104. T. Kusumi, H. Uchida, Y. Inouye, M. Ishitsuka, H. Yamamoto, and H. Kakisawa, *J. Org. Chem.* **52**, 4597 (1987).
105. T. Miyamoto, R. Higuchi, N. Marubayashi, and T. Komori, *Liebigs Ann. Chem.* 1191 (1988).
106. M. Ojika, Y. Yoshida, M. Okumura, S. Ieda, and K. Yamada, *J. Nat. Prod.* **53**, 1619 (1990).
107. F.J. Schmitz, D.P. Michaud, and K.H. Hollenbeak, *J. Org. Chem.* **45**, 1525 (1980).
108. F.J. Schmitz, D.P. Michaud, and P.G. Schmidt, *J. Am. Chem. Soc.* **104**, 6415 (1982).
109. M.L. Rodríguez, J.D. Martín, and D. Estrada, *Acta Crystallogr.* **C45**, 306 (1989).
110. C.B. Rao, C. Saryanarayana, D.V. Rao, E. Fahy, and D.J. Faulkner, *Indian J. Chem. B.* **28**, 322 (1989).
111. D.M. Estrada, J.L. Ravelo, C. Ruiz-Pérez, J.D. Martín, and X. Solans, *Tetrahedron Lett.* **30**, 6219 (1989).
112. A. Rahman, K.A. Alvi, S.A. Abbas, T. Sultana, M. Shameel, M.I. Choudhary, and J.C. Clardy, *J. Nat. Prod.* **54**, 886 (1991).
113. S.H. Grode, T.R. James, J.H. Cardellina, and K.D. Onan, *J. Org. Chem.* **48**, 5203 (1983).
114. S.H. Grode, T.R. James, and J.H. Cardellina, *Tetrahedron Lett.* **24**, 691 (1983).

115. S.A. Look, W. Fenical, D. Van Engen, and J. Clardy, *J. Am. Chem. Soc.* **106**, 5026 (1984).
116. M.B. Ksebati and F.J. Schmitz, *Bull. Soc. Chim. Belg.* **95**, 835 (1986).
117. B.F. Bowden, J.C. Coll, I.M. Vasilescu, and P.N. Alderslade, *Aust. J. Chem.* **42**, 1727 (1989).
118. E.O. Pordesimo, F.J. Schmitz, L.S. Ciereszko, M.B. Hossain, and D. van der Helm, *J. Org. Chem.* **56**, 2344 (1991).
119. T. Kusumi, M. Igari, M.O. Ishitsuka, A. Ichikawa, Y. Iteazono, N. Nakayama, and H. Kakisawa, *J. Org. Chem.* **55**, 6286 (1990).
120. A. Groweiss, S.A. Look, and W. Fenical, *J. Org. Chem.* **53**, 2401 (1988).
121. J. Shin, M. Park, and W. Fenical, *Tetrahedron* **45**, 1633 (1989).
122. A. Clastres, A. Ahond, C. Poupat, P. Potier, and S.K. Kan, *J. Nat. Prod.* **47**, 155 (1984).
123. R.L. Hendrickson and J.H. Cardellina, *Tetrahedron* **42**, 6565 (1986).
124. L. de Napoli, E. Fattorusso, S. Magno, and L. Mayol, *Biochem. Syst. Ecol.* **12**, 321 (1984).
125. C.W.J. Chang, A. Patra, J.A. Baker, and P.J. Scheuer, *J. Am. Chem. Soc.* **109**, 6119 (1987).
126. K.A. Alvi, L. Tenenbaum, and P. Crews, *J. Nat. Prod.* **54**, 71 (1991).
127. N. Fusetani, K. Yasumuro, H. Kawai, T. Natori, L. Brinen, and J. Clardy, *Tetrahedron Lett.* 3599 (1990).
128. G. Guella, I. Mancini, G. Chiasera, and F. Pietra, *Helv. Chim. Acta.* **73**, 1612 (1990).
129. G. Corriero, A. Madaio, L. Mayol, V. Piccialli, and D. Sica, *Tetrahedron* **45**, 277 (1989).
130. I. N'Diaye, G. Guella, I. Mancini, J.-M. Kornprobst, and F. Pietra, *J. Chem. Soc., Chem. Commun.* 97 (1991).
131. M. Murakami, H. Matsuda, K. Makabe, and K. Yamaguchi, *Tetrahedron Lett.* **32**, 2391 (1991).
132. T. Kuraishi, T. Murakami, T. Taniguchi, Y. Kobuki, H. Maehashi, N. Tanaka, Y. Saiki, and C.-M. Chen, *Chem. Pharm. Bull.* **33**, 2305 (1985).
133. T. Murakami and N. Tanaka, *Prog. Chem. Org. Nat. Prod.* **54**, 1 (1988).
134. N. Tanaka, T. Satake, A. Takahashi, M. Mochizuki, T. Murakami, Y. Saiki, J.-Z. Yang, and C.-M. Chen, *Chem. Pharm. Bull.* **30**, 3640 (1982).
135. J.R. Hanson, D.E.A. Rivett, S.V. Ley, and D.J. Williams, *J. Chem. Soc., Perkin Trans. 1.* 1005 (1982).
136. M.C. Carreiras, B. Rodríguez, F. Piozzi, G. Savona, M.R. Torres, and A. Perales, *Phytochemistry* **28**, 1453 (1989).
137. H. Henkel and A. Zeeck, *J. Antibiot.* **44**, 665 (1991).
138. I. Ueda, T. Munakata, and J. Sakai, *Acta Crystallogr.* **B36**, 3128 (1980).
139. T. Munakata, *Chem. Abstr.* **95**, 42826 (1981).
140. T. Watanabe, T. Sugiyama, M. Takahashi, J. Shima, K. Yamashita, K. Izaki, K. Furihata, and H. Seto, *Agric. Biol. Chem.* **54**, 259 (1990).
141. M. Takahashi, K. Koyama, and S. Natori, *Chem. Pharm. Bull.* **38**, 625 (1990).
142. E. Kitamura, A. Hirota, M. Nakagawa, M. Nakayama, H. Nozaki, T. Tada, M. Nukina, and H. Hirota, *Tetrahedron Lett.* **31**, 4605 (1990).
143. H. Demuth, S.R. Jensen, and B.J. Nielsen, *Phytochemistry* **28**, 3361 (1989).
144. I. Kitagawa, Y. Fukuda, T. Taniyama, and M. Yoshikawa, *Chem. Pharm. Bull.* **34**, 1399 (1986).
145. M. Yoshikawa, Y. Fukuda, T. Taniyama, and I. Kitagawa, *Chem. Pharm. Bull.* **34**, 1403 (1986).
146. I. Kitagawa, Y. Fukuda, T. Taniyama, and M. Yoshikawa, *Chem. Pharm. Bull.* **39**, 1171 (1991).
147. R.J. Capon, E.L. Ghisalberti, and P.R. Jefferies, *Tetrahedron* **38**, 1699 (1982).
148. F. Giordano, L. Mayol, G. Notaro, V. Piccialli, and D. Sica, *J. Chem. Soc., Chem. Commun.* 1559 (1990).
149. A. Poiner, V.J. Paul, and P.J. Scheuer, *Tetrahedron* **45**, 617 (1989).
150. P.R. Gorham and W.W. Carmichael, *Pure Appl. Chem.* **52**, 165 (1980).
151. R.E. Moore, *Bioscience* **27**, 797 (1977).
152. J.L. Chen, R.E. Moore, and G.M.L. Patterson, *J. Org. Chem.* **56**, 4360 (1991).
153. J.C. Coll and A.D. Wright, *Aust. J. Chem.* **42**, 1685 (1989).
154. A.D. Wright, G.M. König, and O. Sticher, *J. Nat. Prod.* **54**, 1025 (1991).
155. M. Suzuki, Y. Sasage, M. Ikura, K. Hikichi, and E. Kurosawa, *Phytochemistry* **28**, 2145 (1989).
156. M. Suzuki, H. Kondo, and I. Tanaka, *Chem. Lett.* 33 (1991).
157. A.G. González, J.D. Martín, V.S. Martín, M. Norte, R. Pérez, J.Z. Ruano, S.A. Drexler, and J. Clardy, *Tetrahedron* **38**, 1009 (1982).
158. A. Fukuzawa and E. Kurosawa, *Tetrahedron Lett.* **21**, 1471 (1980).
159. T. Suzuki, K. Koizumi, M. Suzuki, and E. Kurosawa, *Chem. Lett.* 1639 (1983).
160. T. Suzuki, K. Koizumi, M. Suzuki, and E. Kurosawa, *Chem. Lett.* 1643 (1983).
161. M. Suzuki, K. Kurata, T. Suzuki, and E. Kurosawa, *Bull. Chem. Soc. Jpn.* **59**, 2953 (1986).
162. A. Fukuzawa, M. Aye, M. Nakamura, M. Tamura, and A. Murai, *Tetrahedron Lett.* **31**, 4895 (1990).
163. H. Kikuchi, T. Suzuki, E. Kurosawa, and M. Suzuki, *Bull. Chem. Soc. Jpn.* **64**, 1763 (1991).
164. S. Caccamese, R. Azzolina, E.N. Duesler, I.C. Paul, and K.L. Rinehart, *Tetrahedron Lett.* **21**, 2299 (1980).
165. E.N. Duesler, K.L. Rinehart, I.C. Paul, S. Caccamese, and R. Azzolina, *Cryst. Struct. Commun.* **9**, 777 (1980).
166. C.P. Falshaw, T.J. King, S. Imre, S. Islimyeli, and R.H. Thomson, *Tetrahedron Lett.* **21**, 4951 (1980).
167. P.J. Cox, S. Imre, S. Islimyeli, and R.H. Thomson, *Tetrahedron Lett.* **23**, 579 (1982).
168. M. Norte, J.J. Fernández, and J.Z. Ruano, *Tetrahedron* **45**, 5987 (1989).
169. A. Oztunc, S. Imre, H. Lotter, and H. Wagner, *Phytochemistry* **30**, 255 (1991).
170. A. Oztunc, S. Imre, H. Wagner, M. Norte, J.J. Fernández, and R. González, *Tetrahedron* **47**, 2273 (1991).
171. G. Guella and F. Pietra, *Helv. Chim. Acta.* **74**, 47 (1991).
172. W. Hofheinz and W.E. Oberhänsli, *Helv. Chim. Acta.* **60**, 660 (1977).
173. R. Kazlauskas, P.T. Murphy, and R.J. Wells, *Tetrahedron Lett.* 4945 (1978).
174. R. Kazlauskas, R.O. Lidgard, R.J. Wells, and W. Vetter, *Tetrahedron Lett.* 3183 (1977).
175. C. Charles, J.C. Braekman, D. Daloz, B. Tursch, and R. Karlsson, *Tetrahedron Lett.* 1519 (1978).

176. J.E. Biskupiak and C.M. Ireland, *Tetrahedron Lett.*, **25**, 2935 (1984).
177. J.P. Scannell, D.L. Pruess, J.F. Blount, H.A. Ax, M. Kelleff, F. Weiss, T.C. Demny, T.H. Williams, and A. Stempel, *J. Antibiot.*, **28**, 1 (1975).
178. Y. Kuroda, M. Okuhara, T. Goto, M. Yamashita, E. Iguchi, M. Kohsaka, H. Aoki, and H. Imanaka, *J. Antibiot.*, **33**, 259 (1980).
179. S. Narayanan, M.R.S. Iyengar, P.L. Ganju, S. Rengaraju, T. Shomura, T. Tsuruoka, S. Inouye, and T. Niida, *J. Antibiot.*, **33**, 1249 (1980).
180. L. Chalet, B.H. Arison, R.L. Monaghan, J.P. Springer, J.L. Smith, and S.B. Zimmerman, *J. Antibiot.*, **37**, 207 (1984).
181. N. Yasuda and K. Sakane, *J. Antibiot.*, **44**, 801 (1991).
182. A. Segre, R.C. Bachmann, A. Ballio, F. Bossa, I. Grgurina, N.S. Jacobellis, G. Marino, P. Pucci, M. Simmaco, and J.Y. Takemoto, *FEBS Lett.*, **255**, 27 (1989).
183. N. Fukuchi, A. Isogai, S. Yamashita, K. Suyama, J.Y. Takemoto, and A. Suzuki, *Tetrahedron Lett.*, **31**, 695, 1589 (1990).
184. R.E. Moore, V. Bornemann, W.P. Niemczura, J.M. Gregson, J.-L. Chen, T.R. Norton, G.M.L. Patterson, and G.L. Helms, *J. Am. Chem. Soc.*, **111**, 6128 (1989).
185. M. Tomita, Y. Okamoto, T. Kikuchi, K. Osaki, M. Nishikawa, K. Kamiya, Y. Sasaki, K. Matoba, and K. Goto, *Tetrahedron Lett.*, 2421, 2425 (1967).
186. H. Mehri, S. Baassou, and M. Plat, *J. Nat. Prod.*, **54**, 372 (1991).
187. Y. Horiuchi, S. Kondo, T. Ikeda, D. Ikeda, K. Miura, M. Hamada, T. Takeuchi, and H. Umezawa, *J. Antibiot.*, **32**, 762 (1979).
188. H. Nakamura, Y. Iitaka, and H. Umezawa, *J. Antibiot.*, **32**, 765 (1979).
189. L.A. Dolak and C. DeBoer, *J. Antibiot.*, **33**, 83 (1980).
190. S.S. Nittala, V.V. Velde, F. Frolow, and D. Lavie, *Phytochemistry*, **20**, 2547 (1981).
191. F. Frolow, A.B. Ray, M. Sahai, E. Glotter, H.E. Gottlieb, and I. Kirson, *J. Chem. Soc., Perkin Trans. 1*, 1029 (1981).
192. A. Ali, M. Sahai, A.B. Ray, and D.J. Slatkin, *J. Nat. Prod.*, **47**, 648 (1984).
193. V. Fajardo, F. Podesta, M. Shamma, and A.J. Freyer, *J. Nat. Prod.*, **54**, 554 (1991).
194. O. Hutzinger, Ed., "Handbook of Environmental Chemistry," Springer-Verlag, Berlin, 1980, Vol. 1, Part A.
195. H. Friedrich, "Marine Biology," University of Washington Press, Seattle, WA, 1969.
196. R.J. Hall, *New Phytol.*, **71**, 855 (1972).
197. R.J. Hall and R.B. Cain, *New Phytol.*, **71**, 839 (1972).
198. T. McEwan, *Nature*, **201**, 827 (1964).
199. M.M. de Oliveira, *Experientia*, **19**, 586 (1963).
200. J.S.C. Marais, *Onderstepoort J. Vet. Sci.*, **20**, 67 (1944).
201. R.A. Peters and R.J. Hall, *Biochem. Pharmacol.*, **2**, 25 (1959).
202. R. Peters and R.J. Hall, *Nature*, **187**, 573 (1960).
203. R.A. Peters, R.J. Hall, P.F.V. Ward, and N. Sheppard, *Biochem. J.*, **77**, 17 (1960).
204. P.F.V. Ward, R.J. Hall, and R.A. Peters, *Nature*, **201**, 611 (1964).
205. S.D. Gusakova and A.U. Umarov, *Khimi. Prir. Soedin.*, 717 (1976); *Chem. Abstr.*, **86**, 103053 (1977).
206. F.J. Schmitz and Y. Gopichand, *Tetrahedron Lett.*, 3637 (1978).
207. W.M.D. Wijekoon, E. Ayanoglu, and C. Djerassi, *Tetrahedron Lett.*, **25**, 3285 (1984).
208. R.H. White and L.P. Hager, *Biochemistry*, **16**, 4944 (1977).
209. B.J. Baker, R.K. Okuda, P.T.K. Yu, and P.J. Scheuer, *J. Am. Chem. Soc.*, **107**, 2976 (1985).
210. K. Iguchi, S. Kaneta, K. Mori, Y. Yamada, A. Honda, and Y. Mori, *Tetrahedron Lett.*, **26**, 5787 (1985).
211. T.H. Haines, *Ann. Rev. Microbiol.*, **27**, 403 (1973).
212. E.I. Mercer and C.L. Davies, *Phytochemistry*, **18**, 457 (1979).
213. I.J. Tinsley and R.R. Lowry, *J. Am. Oil Chem. Soc.*, **57**, 31 (1980).
214. R. Takeda, *J. Am. Chem. Soc.*, **80**, 4749 (1958).
215. H. Imanaka, M. Kousaka, G. Tamura, and K. Arima, *J. Antibiot.*, **18**, 207 (1965).
216. R.J. Anderson, M.S. Wolfe, and D.J. Faulkner, *Mar. Biol.*, **27**, 281 (1974).
217. M. Kaneda, S. Nakamura, N. Ezaki, and Y. Iitaka, *J. Antibiot.*, **34**, 1366 (1981).
218. M. Koyama, Y. Kodama, T. Tsuruoka, N. Ezaki, T. Niwa, and S. Inouye, *J. Antibiot.*, **34**, 1569 (1981).
219. N. Ezaki, T. Shomura, M. Koyama, T. Niwa, M. Kojima, S. Inouye, T. Ito, and T. Niida, *J. Antibiot.*, **34**, 1363 (1981).
220. N. Ezaki, M. Koyama, T. Shomura, T. Tsuruoka, and S. Inouye, *J. Antibiot.*, **36**, 1263 (1983).
221. N. Ezaki, M. Koyama, Y. Kodama, T. Shomura, K. Tashiro, T. Tsuruoka, S. Inouye, and S. Sakai, *J. Antibiot.*, **36**, 1431 (1983).
222. M. Koyama, N. Ezaki, T. Tsuruoka, and S. Inouye, **36**, 1483 (1983).
223. T. Nogami, Y. Shigihara, N. Matsuda, Y. Takahashi, H. Naganawa, H. Nakamura, M. Hamada, Y. Muraoka, T. Takita, Y. Iitaka, and T. Takeuchi, *J. Antibiot.*, **43**, 1192 (1990).
224. G. Sharma and B. Magdoff-Fairchild, *J. Org. Chem.*, **42**, 4118 (1977).
225. S. Forenza, L. Minale, R. Riccio, and E. Fattorusso, *J. Chem. Soc., Chem. Commun.*, 1129 (1971).
226. E.E. Garcia, L.E. Benjamin, and R.I. Fryer, *J. Chem. Soc., Chem. Commun.*, 78 (1973).
227. G. Cimino, S. De Rosa, S. De Stefano, L. Mazzarella, R. Puliti, and G. Sodano, *Tetrahedron Lett.*, **23**, 767 (1982).
228. I. Kitagawa, M. Kobayashi, K. Kitanaka, M. Kido, and Y. Kyogoku, *Chem. Pharm. Bull.*, **31**, 2321 (1983).
229. G.R. Pettit, C.L. Herald, J.E. Leer, R. Gupta, D.E. Schaufelberger, R.B. Bates, P.J. Clewlow, D.L. Doubek, K.P. Manfredi, K. Rützel, J.M. Schmidt, L.P. Tackett, F.B. Ward, M. Bruck, and F. Camou, *Can. J. Chem.*, **68**, 1621 (1990).

230. R.P. Walker, D.J. Faulkner, D.V. Engen, and J. Clardy, *J. Am. Chem. Soc.*, **103**, 6772 (1981).
231. K.L. Rinehart, *Pure Appl. Chem.*, **61**, 525 (1989).
232. K.L. Rinehart, T.G. Holt, N.L. Fregeau, P.A. Keifer, G.R. Wilson, T.J. Perun, Jr., R. Sakai, A.G. Thompson, J.G. Stroh, L.S. Shield, D.S. Seigler, L.H. Li, D.G. Martin, C.J.P. Grimmelikhuijzen, and G. Gäde, *J. Nat. Prod.*, **53**, 771 (1990).
233. J. Kobayashi, M. Tsuda, T. Murayama, H. Nakamura, Y. Ohizumi, M. Ishibashi, M. Iwamura, T. Ohta, and S. Nozoe, *Tetrahedron*, **46**, 5579 (1990).
234. J. Kobayashi, M. Tsuda, and Y. Ohizumi, *Experientia*, **47**, 301 (1991).
235. J. Kobayashi, F. Kanada, M. Ishibashi, and H. Shigemori, *J. Org. Chem.*, **56**, 4574 (1991).
236. B. Carté and D.J. Faulkner, *J. Chem. Ecol.*, **12**, 795 (1986).
237. J.T. Baker, *Endeavour*, **33**, 11 (1974).
238. H. Fouquet and H.-J. Bielig, *Angew. Chem. Int. Ed. Engl.*, **10**, 816 (1971).
239. J.T. Baker and C.C. Duke, *Aust. J. Chem.*, **26**, 2153 (1973).
240. J.T. Baker and C.C. Duke, *Tetrahedron Lett.*, **24**, 1233 (1976).
241. C. Christophersen, F. Wätjen, O. Buchardt, and U. Anthoni, *Tetrahedron*, **34**, 2779 (1978).
242. T. Higa and P.J. Scheuer, *Heterocycles*, **4**, 227 (1976).
243. T. Higa and P.J. Scheuer, *Naturwissenschaften*, **62**, 395 (1975).
244. T. Higa, T. Ichiba, and R.K. Okuda, *Experientia*, **41**, 1487 (1985).
245. G.T. Carter, K.L. Rinehart, L.H. Li, S.L. Kuentzel, and J.L. Connor, *Tetrahedron Lett.*, 4479 (1978).
246. M.R. Brennan and K.L. Erickson, *Tetrahedron Lett.*, 1637 (1978).
247. S.J. Wratten, M.S. Wolfe, R.J. Andersen, and D.J. Faulkner, *Antimicrob. Agents Chemother.*, **11**, 411 (1977).
248. G. Guella, I. Mancini, D. Duher, B. Richer de Forges, and F. Pietra, *Z. Naturforsch., Teil C*, **44**, 914 (1989).
249. G. Dellar, P. Djura, and M.V. Sargent, *J. Chem. Soc., Perkin Trans. 1*, 1679 (1981).
250. J. Kobayashi, J. Cheng, S. Yamamura, T. Sasaki, and Y. Ohizumi, *Heterocycles*, **31**, 2205 (1990).
251. S. Marumo, H. Abe, H. Hattori, and K. Munakata, *Agric. Biol. Chem.*, **32**, 117 (1968).
252. S. Marumo, H. Hattori, H. Abe, and K. Munakata, *Nature*, **219**, 959 (1968).
253. K.C. Engvild, H. Egsgaard, and E. Larsen, *Physiol. Plant.*, **53**, 79 (1981).
254. G.E. Van Lear, G.O. Morton, and W. Fulmor, *Tetrahedron Lett.*, 299 (1973).
255. P. Djura, D.B. Stierle, B. Sullivan, D.J. Faulkner, E. Arnold, and J. Clardy, *J. Org. Chem.*, **45**, 1435 (1980).
256. A.A. Tyimiak, K.L. Rinehart, and G.J. Bakus, *Tetrahedron*, **41**, 1039 (1985).
257. E. Fahy, B.C.M. Potts, D.J. Faulkner, and K. Smith, *J. Nat. Prod.*, **54**, 564 (1991).
258. W.D. Raverty, R.H. Thomson, and T.J. King, *J. Chem. Soc., Perkin Trans. 1*, 1204 (1977).
259. D.M. Roll and C.M. Ireland, *Tetrahedron Lett.*, **26**, 4303 (1985).
260. R.M. Moriarty, D.M. Roll, Y.-Y. Ku, C. Nelson, and C.M. Ireland, *Tetrahedron Lett.*, **28**, 749 (1987).
261. S. Sakemi and H.H. Sun, *J. Org. Chem.*, **56**, 4304 (1991).
262. K. Barrek, J.-C. Braekman, D. Daloz, C. Stoller, J. Huysecom, G. Vandevyver, and R. Ottinger, *Can. J. Chem.*, **65**, 2118 (1987).
263. S. Kohmoto, Y. Kashman, O.J. McConnell, K.L. Rinehart, A. Wright, and F. Koehn, *J. Org. Chem.*, **53**, 3116 (1988).
264. S. Tsuji, K.L. Rinehart, S.P. Gunasekera, Y. Kashman, S.S. Cross, M.S. Liu, S.A. Pomponi, and M.C. Diaz, *J. Org. Chem.*, **53**, 5446 (1988).
265. S.A. Morris and R.J. Andersen, *Tetrahedron*, **46**, 715 (1990).
266. P. Djura and D.J. Faulkner, *J. Org. Chem.*, **45**, 735 (1980).
267. E. Fattorusso, V. Lanzotti, S. Magno, and E. Novellino, *J. Nat. Prod.*, **48**, 924 (1985).
268. G. Guella, I. Mancini, H. Zibrowius, and F. Pietra, *Helv. Chim. Acta*, **71**, 773 (1988).
269. G. Guella, I. Mancini, H. Zibrowius, and F. Pietra, *Helv. Chim. Acta*, **72**, 1444 (1989).
270. H.H. Sun and S. Sakemi, *J. Org. Chem.*, **56**, 4307 (1991).
271. G. Lidgren, L. Bohlin, and J. Bergman, *Tetrahedron Lett.*, **27**, 3283 (1986).
272. A. Lieberknecht and H. Griesser, *Tetrahedron Lett.*, **28**, 4275 (1987).
273. R.J. Andersen and R.J. Stonard, *Can. J. Chem.*, **57**, 2325 (1979).
274. R.J. Stonard and R.J. Andersen, *J. Org. Chem.*, **45**, 3687 (1980).
275. N. Lindquist and W. Fenical, *Tetrahedron Lett.*, **31**, 2521 (1990).
276. P. Crews, L.V. Manes, and M. Boehler, *Tetrahedron Lett.*, **27**, 2797 (1986).
277. T.M. Zabriskie, J.A. Klocke, C.M. Ireland, A.H. Marcus, T.F. Molinski, D.J. Faulkner, C. Xu, and J.C. Clardy, *J. Am. Chem. Soc.*, **108**, 3123 (1986).
278. J. Kobayashi, M. Sato, T. Murayama, M. Ishibashi, M.R. Wälchi, M. Kanai, J. Shoji, and Y. Ohizumi, *J. Chem. Soc., Chem. Commun.*, 1050 (1991).
279. N. Lindquist, W. Fenical, G.D. Van Duyn, and J. Clardy, *J. Am. Chem. Soc.*, **113**, 2303 (1991).
280. R.S. Norton and R.J. Wells, *J. Am. Chem. Soc.*, **104**, 3628 (1982).
281. R.E. Moore, C. Cheuk, X.-Q.G. Yang, G.M.L. Patterson, R. Bonjouklian, T.A. Smitka, J.S. Mynderse, R.S. Foster, N.D. Jones, J.K. Swartzendruber, and J.B. Deeter, *J. Org. Chem.*, **52**, 1036 (1987).
282. R.E. Schwartz, C.F. Hirsch, J.P. Springer, D.J. Pettibone, and D.L. Zink, *J. Org. Chem.*, **52**, 3704 (1987).
283. S. Sakemi, H.H. Sun, C.W. Jefford, and G. Bernardinelli, *Tetrahedron Lett.*, **30**, 2517 (1989).
284. H.H. Sun, S. Sakemi, N. Burres, and P. McCarthy, *J. Org. Chem.*, **55**, 4964 (1990).
285. N.G. Perry, J.W. Blunt, J.D. McCombs, and M.H.G. Munro, *J. Org. Chem.*, **51**, 5476 (1986).
286. J. Kobayashi, J. Cheng, M. Ishibashi, H. Nakamura, Y. Ohizumi, Y. Hirata, T. Sasaki, H. Lu, and J. Clardy, *Tetrahedron Lett.*, **28**, 4939 (1987).

287. N.B. Perry, J.W. Blunt, and M.H.G. Munro, *Tetrahedron*, **44**, 1727 (1988).
288. J. Cheng, Y. Ohizumi, M.R. Wälchli, H. Nakamura, Y. Hirata, T. Sasaki, and J. Kobayashi, *J. Org. Chem.*, **53**, 4621 (1988).
289. P. Wulff, J.S. Carlé, and C. Christophersen, *J. Chem. Soc., Perkin Trans. 1*, 2895 (1981).
290. P. Wulff, J.S. Carlé, and C. Christophersen, *Comp. Biochem. Physiol.*, **71B**, 523 (1982).
291. P. Keil, E.G. Nielsen, U. Anthoni, and C. Christophersen, *Acta Chem. Scand.*, **B40**, 555 (1986).
292. C. Christophersen, *Acta Chem. Scand.*, **B39**, 517 (1985).
293. U. Anthoni, P.H. Nielsen, M. Pereira, and C. Christophersen, *Comp. Biochem. Physiol.*, **96B**, 431 (1990).
294. L. Chevolut, A.-M. Chevolut, M. Gajhede, C. Larsen, U. Anthoni, and C. Christophersen, *J. Am. Chem. Soc.*, **107**, 4542 (1985).
295. U. Anthoni, L. Chevolut, C. Larsen, P.H. Nielsen, and C. Christophersen, *J. Org. Chem.*, **52**, 4709 (1987).
296. U. Anthoni, K. Bock, L. Chevolut, C. Larsen, P.H. Nielsen, and C. Christophersen, *J. Org. Chem.*, **52**, 5638 (1987).
297. T. Kosuge, H. Zenda, A. Ochiai, N. Masaki, M. Noguchi, S. Kimura, and H. Narita, *Tetrahedron Lett.*, 2545 (1972).
298. T. Kosuge, K. Tsuji, and K. Hirai, *Tetrahedron Lett.*, **22**, 3417 (1981).
299. T. Kosuge, K. Tsuji, and K. Hirai, *Chem. Pharm. Bull.*, **30**, 3255 (1982).
300. T. Kosuge, K. Tsuji, K. Hirai, T. Fukuyama, H. Nukaya, and H. Ishida, *Chem. Pharm. Bull.*, **33**, 2890 (1985).
301. T. Kosuge, K. Tsuji, K. Hirai, and T. Fukuyama, *Chem. Pharm. Bull.*, **33**, 3059 (1985).
302. A.E. de Jesus, P.S. Strey, F.R. van Heerden, R. Vleggaer, P.L. Wessels, and W.E. Hull, *J. Chem. Soc., Perkin Trans. 1*, 1847, 1857 (1983).
303. J.H. Cardellina, M.P. Kirkup, R.E. Moore, J.S. Mynderse, K. Seff, and C.J. Simmons, *Tetrahedron Lett.*, 4915 (1979).
304. K.-C. Luk, L. Stern, M. Weigele, R.A. O'Brien, and N. Spirt, *J. Nat. Prod.*, **46**, 852 (1983).
305. D. Dewar, V. Glover, J. Elsworth, and M. Sandler, *J. Neural Transm.*, **65**, 147 (1986).
306. J. Kobayashi, H. Nakamura, Y. Ohizumi, and Y. Hirata, *Tetrahedron Lett.*, **27**, 1191 (1986).
307. J. Kobayashi, J. Cheng, T. Ohta, S. Nozoe, Y. Ohizumi, and T. Sasaki, *J. Org. Chem.*, **55**, 3666 (1990).
308. O. Murata, H. Shigemori, M. Ishibashi, K. Sugama, K. Hayashi, and J. Kobayashi, *Tetrahedron Lett.*, **32**, 3539 (1991).
309. K.F. Kinzer and J.H. Cardellina, *Tetrahedron Lett.*, **28**, 925 (1987).
310. K.L. Rinehart Jr., J. Kobayashi, G.C. Harbour, J. Gilmore, M. Mascal, T.G. Holt, L.S. Shield, and F. Lafargue, *J. Am. Chem. Soc.*, **109**, 3378 (1987).
311. J.W. Blunt, R.J. Lake, M.H.G. Munro, and T. Toyokuni, *Tetrahedron Lett.*, **28**, 1825 (1987).
312. R.J. Lake, M.M. Brennan, J.W. Blunt, H.H.G. Munro, and L.K. Pannell, *Tetrahedron Lett.*, **29**, 2255 (1988).
313. R.J. Lake, J.D. McCombs, J.W. Blunt, M.H.G. Munro, and W.T. Robinson, *Tetrahedron Lett.*, **29**, 4971 (1988).
314. R.J. Lake, J.W. Blunt, and M.H.G. Munro, *Aust. J. Chem.*, **42**, 1201 (1989).
315. J.A. Bush, B.H. Long, J.J. Catino, W.T. Bradner, and K. Tomita, *J. Antibiot.*, **40**, 668 (1987).
316. D.E. Nettleton, T.W. Doyle, B. Krishnan, G.K. Matsumoto, and J. Clardy, *Tetrahedron Lett.*, **26**, 4011 (1985).
317. J.A. Matson, *Chem. Abstr.*, **103**, 159104 (1985).
318. K.S. Lam, D.R. Schroeder, J.M. Veitch, J.A. Matson, and S. Forenza, *J. Antibiot.*, **44**, 934 (1991).
319. J.A. Matson, C. Claridge, J.A. Bush, J. Titus, W.T. Bradner, T.W. Doyle, A.C. Horan, and M. Patel, *J. Antibiot.*, **42**, 1547, 1784 (1989).
320. P. Wulff, J.S. Carlé, and C. Christophersen, *Comp. Biochem. Physiol.*, **71B**, 525 (1982).
321. A. Nakagawa, Y. Iwai, H. Hashimoto, N. Miyazaki, R. Oiwa, Y. Takahashi, A. Hirano, N. Shibukawa, Y. Kojima, and S. Omura, *J. Antibiot.*, **34**, 1408 (1981).
322. Y. Morimoto, K. Oda, H. Shirahama, T. Matsumoto, and S. Omura, *Chem. Lett.*, 909 (1988).
323. C.M. Pearce and J.K.M. Sanders, *J. Chem. Soc., Perkin Trans. 1*, 409 (1990).
324. N. Le-Van and S.J. Wratten, *Tetrahedron Lett.*, **25**, 145 (1984).
325. B. Sullivan and D.J. Faulkner, *J. Org. Chem.*, **49**, 3204 (1984).
326. K.K. Chexal, C. Tamm, J. Clardy, and K. Hirotsu, *Helv. Chim. Acta*, **62**, 1129 (1979).
327. F. Bohlmann, W.-R. Abraham, R.M. King, and H. Robinson, *Phytochemistry*, **20**, 825 (1981).
328. B.M. Abegaz, M. Tadesse, and R. Majinda, *Biochem. Syst. Ecol.*, **19**, 323 (1991).
329. G.O. Morton, J.E. Lancaster, G.E. Van Lear, W. Fulmor, and W.E. Meyer, *J. Am. Chem. Soc.*, **91**, 1535 (1969).
330. I.D. Jenkins, J.P.H. Verheyden, and J.G. Moffatt, *J. Am. Chem. Soc.*, **98**, 3346 (1976).
331. R. Kazlauskas, P.T. Murphy, R.J. Wells, J. A. Baird-Lambert, and D.D. Jamieson, *Aust. J. Chem.*, **36**, 165 (1983).
332. E. Smal and D.C. Baker, in: "Abstracts." Division of Carbohydrate Chemistry, 188th American Chemical Society Meeting, Philadelphia, PA, 26-31 August 1984, Abstract 8.
333. J.P. Schaumberg, G.C. Hokanson, and J.C. French, in: "Abstracts." Division of Carbohydrate Chemistry, 188th American Chemical Society Meeting, Philadelphia, PA, 26-31 August 1984, Abstract 7.
334. J.A. Elix, A.A. Whitton, and M.V. Sargent, *Prog. Chem. Org. Nat. Prod.*, **45**, 101 (1984).
335. J.A. Elix, H. Jiang, and V.J. Portelli, *Aust. J. Chem.*, **43**, 1291 (1990).
336. R. Braz Filho, M.P.L. De Moraes, and O.R. Gottlieb, *Phytochemistry*, **19**, 2003 (1980).
337. R. Braz Filho, C.A.S. Miranda, O.R. Gottlieb, and M.T. Magalhaes, *Chem. Abstr.*, **99**, 155230 (1983).
338. C. Ito, H. Furukawa, H. Ishii, I. Ishikawa, and J. Haginiwa, *J. Chem. Soc., Perkin Trans. 1*, 2047 (1990).
339. A. Ahond, M. Bedoya Zurita, M. Colin, C. Fizames, P. Laboute, F. Lavelle, D. Laurent, C. Poupat, J. Pusset, M. Pusset, O. Thoison, and P. Potier, *C.R. Séances Acad. Sci. Paris, Ser. 2*, **307**, 145 (1988).
340. D.H. Miles, N.V. Mody, J.P. Minyard, and P.A. Hedin, *Phytochemistry*, **12**, 1399 (1973).
341. W.E. Pereira, C.E. Rostad, and H.E. Taylor, *Geophys. Res. Lett.*, **7**, 953 (1980).



342. S.J. Box, N.J. Coates, C.J. Davis, M.L. Gilpin, C.S.V. Houge-Frydrych, and P.H. Milner, *J. Antibiot.* **44**, 807 (1991).
343. M.K.W. Li and P.J. Scheuer, *Tetrahedron Lett.* **25**, 587 (1984).
344. E. Drechsel, *Z. Biol.* **33**, 85 (1896).
345. M. Henze, *Z. Physiol. Chem.* **51**, 64 (1907).
346. C.R. Harington, *Biochem. J.* **20**, 293, 300 (1926).
347. C.R. Harington and S.S. Randall, *J. Soc. Chem. Ind. London* **48**, 296 (1929).
348. C.R. Harington and S.S. Randall, *Biochem. J.* **25**, 1032 (1931).
349. J. Roche and R. Michel, *Physiol. Rev.* **35**, 583 (1955).
350. J. Roche, *Experientia* **8**, 45 (1952).
351. J. Roche, S. André, and G. Salvatore, *Comp. Biochem. Physiol.* **1**, 286 (1960).
352. S. Hunt and S.W. Breuer, *Biochim. Biophys. Acta* **252**, 401 (1971).
353. B.S. Welinder, *Biochim. Biophys. Acta* **279**, 491 (1972).
354. S.O. Andersen, *Acta Chem. Scand.* **26**, 3097 (1972).
355. R.B. Ashworth and M.J. Cormier, *Science* **155**, 1558 (1967).
356. T. Higa, T. Fujiyama, and P.J. Scheuer, *Comp. Biochem. Physiol.* **65B**, 525 (1980).
357. T. Higa in: "Marine Natural Products." Ed. by P.J. Scheuer, Academic Press, New York, 1981, Vol. IV.
358. J.-O. Levin and C.-A. Nilsson, *Chemosphere* **6**, 443 (1977).
359. L.H. Keith and W.A. Telliard, *Environ. Sci. Technol.* **13**, 416 (1979).
360. K. Ando, A. Kato, and S. Suzuki, *Biochem. Biophys. Res. Commun.* **39**, 1104 (1970).
361. T. Eisner, L.B. Hendry, D.B. Peakall, and J. Meinwald, *Science* **172**, 277 (1971).
362. R.S. Berger, *Science* **177**, 704 (1972).
363. R.S. Berger, *Ann. Ent. Soc. Am.* **67**, 961 (1974).
364. D. Kellum and R.S. Berger, *J. Med. Entomol.* **13**, 701 (1977).
365. R.S. Berger, *J. Med. Entomol.* **20**, 103 (1983).
366. H. Oka, K. Asahi, H. Morishima, M. Sanada, K. Shiratori, Y. Iimura, T. Sakurai, J. Uzawa, S. Iwadare, and N. Takahashi, *J. Antibiot.* **38**, 1100 (1985).
367. M. Takeuchi, S. Takahashi, M. Inukai, T. Nakamura, and T. Kinoshita, *J. Antibiot.* **44**, 271 (1991).
368. R. Capon, E.L. Ghisalberti, P.R. Jefferies, B.W. Skelton, and A.H. White, *J. Chem. Soc., Perkin Trans. 1* **2464** (1981).
369. B. Carré and D.J. Faulkner, *Tetrahedron* **37**, 2335 (1981).
370. H.H. Sun, V.J. Paul, and W. Fenical, *Phytochemistry* **22**, 743 (1983).
371. B.K. Carte, N. Troupe, J.A. Chan, J.W. Westley, and D.J. Faulkner, *Phytochemistry* **28**, 2917 (1989).
372. A.J. Blackman and D.J. Matthews, *Phytochemistry* **21**, 2141 (1982).
373. J. Kobayashi, M. Tsuda, K. Agemi, H. Shigemori, M. Ishibashi, T. Sasaki, and Y. Mikami, *Tetrahedron* **47**, 6617 (1991).
374. E.O. Pordesimo and F.S. Schmitz, *J. Org. Chem.* **55**, 4704 (1990).
375. M. D'Ambrosio, A. Guerriero, and F. Pietra, *Helv. Chim. Acta* **67**, 1484 (1984).
376. K. Suwanborirux, C.-J. Chang, R.W. Spjut, and J.M. Cassady, *Experientia* **46**, 117 (1990).
377. H. Achenbach, *Prog. Chem. Org. Nat. Prod.* **52**, 73 (1987).
378. D.F. Sesin and C.M. Ireland, *Tetrahedron Lett.* **25**, 403 (1984).
379. W.R. Chan, W.F. Tinto, P.S. Manchand, and L.J. Todaro, *J. Org. Chem.* **52**, 3091 (1987).
380. E.D. de Silva, R.J. Andersen, and T.M. Allen, *Tetrahedron Lett.* **31**, 489 (1990).
381. M.D. Lee, G.A. Ellestad, and D.B. Borders, *Acc. Chem. Res.* **24**, 235 (1991).
382. W. Steglich, W. Lösel, and V. Austel, *Chem. Ber.* **102**, 4104 (1969).
383. G. Keller, *Sydowia* **35**, 110 (1982).
384. G. Keller and J.F. Ammirati, *Mycotaxon* **18**, 357 (1983).
385. G.W. Gribble, *Chemistry* **47**(2), 15 (1974).
386. A. Poland and J.C. Knutson, *Ann. Rev. Pharmacol. Toxicol.* **22**, 517 (1982).
387. A. Poland and E. Glover, *Science* **179**, 476 (1973).
388. W.H. Wolfe, J.E. Michalek, J.C. Miner, A. Rahe, J. Silva, W.F. Thomas, W.D. Grubbs, M.B. Lustik, T.G. Karrison, R.H. Roegner, and D.E. Williams, *J. Am. Med. Assoc.* **264**, 1824, 1832 (1990).
389. M. Gough, *Am. J. Public Health* **81**, 289 (1991).
390. P. Bertazzi, *Sci. Total Environ.* **106**, 5 (1991).
391. J.A. Zack and R.R. Suskind, *J. Occup. Med.* **22**, 11 (1980).
392. F.H. Tschirley, *Sci. Amer.* **254**(2), 29 (1986).
393. G.H. Eduljee, *Chem. Brit.* **24**, 1223 (1988).
394. M. Gough, *Sci. Total Environ.* **104**, 129 (1991).
395. R.R. Bumb, *Science* **210**, 385 (1980).
396. C.C. Travis and H.A. Hattemer-Frey, *Risk Anal.* **9**, 91 (1989).
397. T.J. Nestruck and L.L. Lamparski, *Anal. Chem.* **54**, 2292 (1982).
398. R.E. Clement, H.M. Tosine, and B. Ali, *Chemosphere* **14**, 815 (1985).
399. K. Olie, M.v.d. Berg, and O. Hutzinger, *Chemosphere* **12**, 627 (1983).
400. R.E. Clement, H.M. Tosine, and B. Ali, *Chemosphere* **14**, 815 (1985).
401. T.O. Tiernan, M.L. Taylor, J.H. Garrett, G.F. VanNess, J.G. Solch, D.A. Deis, and D.J. Wagel, *Chemosphere* **12**, 595 (1983).
402. C. Chiu, R.S. Thomas, J. Lockwood, K. Li, R. Halman, and R.C.C. Lao, *Chemosphere* **12**, 607 (1983).

403. G.H. Eduljee, D.H.F. Atkins, and A.E. Eggleton, *Chemosphere*. **15**, 1577 (1986).
404. K. Ballschmiter, H. Buchert, R. Niemczyk, A. Munder, and M. Swerev, *Chemosphere*. **15**, 901 (1986).
405. S. Marklund, C. Rappe, M. Tysklind, and K.E. Egeback, *Chemosphere*. **16**, 29 (1987).
406. C. Rappe, L.-O. Kjeller, P. Bruckmann, and K.-H. Hackhe, *Chemosphere*. **17**, 3 (1988).
407. C. Rappe, R. Anderson, P.A. Bergqvist, C. Brohede, M. Hansson, L.O. Kjeller, G. Lindstroem, S. Marklund, and M. Nygren, *Chemosphere*. **16**, 1603 (1987).
408. A. Sheffield, *Chemosphere*. **14**, 811 (1985).
409. A. Svenson, L.-O. Kjeller, and C. Rappe, *Environ. Sci. Technol.*. **23**, 900 (1989).
410. A. Poland and E. Glover, *Mol. Pharm.*. **9**, 736 (1973).
411. A. Poland and E. Glover, *Environ. Health Perspect.*. **5**, 245 (1973).
412. E. Löser and I. Ivens, *Chemosphere*. **19**, 759 (1989).
413. H. Gilman and J.J. Dietrich, *J. Am. Chem. Soc.*. **79**, 1439 (1957).
414. S.H. Safe, *Chem. Abstr.*. **114**, 61914 (1991).
415. T. Higa, R.K. Okuda, R.M. Severns, P.J. Scheuer, C.-H. He, X. Changfu, and J. Clardy, *Tetrahedron*. **43**, 1063 (1987).
416. S. Sakamura, K. Nabeta, S. Yamada, and A. Ichihara, *Agric. Biol. Chem.*. **39**, 403 (1975).
417. R.P. Walker and D.J. Faulkner, *J. Org. Chem.*. **46**, 1475 (1981).
418. V.P. Marshall, J.E. McGee, J.I. Cialdella, L. Baczynskyj, D.J. Chirby, D.A. Yurek, W.F. Liggett, and M.S. Kuo, *J. Antibiot.*. **44**, 895 (1991).
419. R.P. Gregson, B.A. Baldo, P.G. Thomas, R.J. Quinn, P.R. Bergquist, J.F. Stephens, and A.R. Horne, *Science*. **206**, 1108 (1979).
420. R.D. Cadle, A.L. Lazrus, B.J. Huebert, L.E. Heidt, W.I. Rose, Jr., D.C. Woods, R.L. Chuan, R.E. Stoiber, D.B. Smith, and R.A. Zielinski, *J. Geophys. Res.*. **84**, 6961 (1979).
421. G.A. Blake, J. Keene, and T.G. Phillips, *Astrophys. J.*. **295**, 501 (1985).
422. G. Winnewisser and E. Herbst, *Top. Curr. Chem.*. **139**, 119 (1987).
423. E. Herbst, *Angew. Chem. Int. Ed. Engl.*. **29**, 595 (1990).
424. D.J. Kushner, in: "Chemical Evolution and the Origin of Life." Ed. by R. Buvet and C. Ponnampuruma, North-Holland, Amsterdam, 1971, p. 488.
425. B. Walter and K. Ballschmiter, *Chemosphere*. **22**, 557 (1991).
426. R. Wever, M.G.M. Tromp, B.E. Krenn, A. Marjani, and M.V. Tol, *Environ. Sci. Technol.*. **25**, 446 (1991).
427. C. Wannstedt, D. Rotella, and J.F. Siuda, *Bull. Environ. Contam. Toxicol.*. **44**, 282 (1990).
428. M. Morrison and G.R. Schonbaum, *Ann. Rev. Biochem.*. **45**, 861 (1976).
429. H. Vilter, K.-W. Glombitza, and A. Grawe, *Bot. Mar.*. **26**, 331 (1983).
430. A. Taurgo, and E.M. Howells, *J. Biol. Chem.*. **241**, 1329 (1966).
431. P.D. Shaw and L.P. Hager, *J. Biol. Chem.*. **236**, 1626 (1961).
432. J.A. Thomas, D.R. Morris, and L.P. Hager, *J. Biol. Chem.*. **245**, 3129, 3135 (1970).
433. R.D. Libby, J.A. Thomas, L.W. Kaiser, and L.P. Hager, *J. Biol. Chem.*. **257**, 5030 (1982).
434. D.G. Baden and M.D. Corbett, *Biochem. J.*. **187**, 205 (1980).
435. R.S. Beissner, W.J. Guilford, R.M. Coates, and L.P. Hager, *Biochemistry*. **20**, 3724 (1981).
436. R. Theiler, J.C. Cook, L.P. Hager, and J.F. Siuda, *Science*. **202**, 1094 (1981).
437. S.L. Neidleman and J. Geigert, *Endeavor. New Series*. **11**, 5 (1986).
438. J. Geigert, S.L. Neidleman, D.J. Dalietos, and S.K. DeWitt, *Appl. Environ. Microbiol.*. **45**, 366 (1983).
439. C.E. Castro and N.O. Belser, *Environ. Sci. Technol.*. **2**, 779 (1968).
440. W. Brunner, D. Straub, and T. Leisinger, *Appl. Environ. Microbiol.*. **40**, 950 (1980).
441. E.J. Bouwer and P.L. McCarty, *Appl. Environ. Microbiol.*. **45**, 1286 (1983).
442. D.T. Gibson, J.R. Koch, C.L. Schuld, and R.E. Kallio, *Biochemistry*. **7**, 3795 (1968).
443. H. Ziffer, K. Kabuto, D.T. Gibson, V.M. Kobal, and D.M. Jerina, *Tetrahedron*. **33**, 2491 (1977).
444. D.R. Boyd, M.R.J. Dorrity, M.V. Hand, J.F. Malone, N.D. Sharma, H. Dalton, D.J. Gray, and G.N. Sheldrake, *J. Am. Chem. Soc.*. **113**, 666 (1991).
445. H.A.J. Carless and O.Z. Oak, *J. Chem. Soc. Chem. Commun.*. 61 (1991).
446. T. Hudlicky, J.D. Price, and H.F. Olivo, *Synlett*. 645 (1991).
447. K. Ballschmiter, C. Unglert, and P. Heinzmann, *Angew. Chem. Int. Ed. Engl.*. **16**, 645 (1977).
448. K. Ballschmiter and Ch. Scholz, *Chemosphere*. **9**, 457 (1980).
449. N. Walker and G.H. Wiltshire, *J. Gen. Microbiol.*. **12**, 478 (1955).
450. P. Goldman, G.W.A. Milner, and M.T. Pignataro, *Arch. Biochem. Biophys.*. **118**, 178 (1967).
451. R.B. Cain, E.K. Tranter, and J.A. Darrah, *Biochem. J.*. **106**, 211 (1968).
452. D.W. Ribbons, A.E.G. Cass, J.T. Rossiter, S.J.C. Taylor, M.P. Woodland, D.A. Widdowson, S.R. Williams, P.B. Baker, and R.E. Martin, *J. Fluorine Chem.*. **37**, 299 (1987).
453. A.E. Smith and A.J. Aubin, *J. Agric. Food Chem.*. **39**, 801 (1991).
454. K. Valli and M.H. Gold, *J. Bacteriol.*. **173**, 345 (1991).
455. K.E. Hammell and P.J. Tardone, *Biochemistry*. **27**, 6563 (1988).
456. J.A. Bumpus and S.D. Aust, *Appl. Environ. Microbiol.*. **53**, 2001 (1987).
457. G.J. Mileski, J.A. Bumpus, M.A. Jurek, and S.D. Aust, *Appl. Environ. Microbiol.*. **54**, 2885 (1988).
458. J.A. Bumpus, M. Tien, D. Wright, and S.D. Aust, *Science*. **228**, 1434 (1985).
459. L.H. Bopp, *J. Ind. Microbiol.*. **1**, 23 (1986).
460. D.A. Abramowicz, *Crit. Rev. Biotech.*. **10**, 241 (1990).
461. R.D. Sjoblad and J.-M. Bollag, *Appl. Environ. Microbiol.*. **33**, 906 (1977).

462. J.-M. Bollag, R.D. Sjoblad, and R.D. Minard, *Experientia*, **33**, 1564 (1977).
463. V.J. Paul, *Bull. Mar. Sci.*, **41**, 514 (1987).
464. M. Barbier, in: "Marine Natural Products." Ed. by P.J. Scheuer, Academic Press, New York, 1981, Vol. IV, Chap. 4.
465. P.J. Scheuer, *Isr. J. Chem.*, **16**, 52 (1977).
466. L. Minale, in: "Marine Natural Products." Ed. by P.J. Scheuer, Academic Press, New York, 1978, Vol. I.
467. C. Christophersen, in: "The Alkaloids." Ed. by A. Brossi, Academic Press, New York, 1985, Vol. 24, Chapter 2.
468. R.K. Okuda, D. Klein, R.B. Kinnel, M. Li, and P.J. Scheuer, *Pure Appl. Chem.*, **54**, 1907 (1982).
469. E.M. Low, *J. Mar. Res.*, **8**, 97 (1949).
470. R.S.K. Barnes and R.N. Hughes, "An Introduction to Marine Ecology," 2nd ed., Blackwell, Oxford, 1988.
471. R. Boye, "Underwater Paradise," Abrams, New York, 1989.
472. M. Colon, P. Guevara, W.H. Gerwick, and D. Ballantine, *J. Nat. Prod.*, **50**, 368 (1987).
473. T. Higa and S. Sakemi, *J. Chem. Ecol.*, **9**, 495 (1983).
474. G. Asplund, A. Grimvall, and C. Pettersson, *Sci. Total Environ.*, **81/82**, 239 (1989).
475. B. Wigilius, B. Allard, H. Borén, and A. Grimvall, *Cbemosphere*, **17**, 1985 (1988).
476. B. Wigilius, H. Boren, A. Grimvall, G.E. Carlberg, I. Hagen, and A. Brögger, *Sci. Total Environ.*, **74**, 75 (1988).
477. G. Asplund and A. Grimvall, *Environ. Sci. Technol.*, **25**, 1347 (1991).
478. M.H.B. Hayes, P. MacCarthy, R.L. Malcolm, R.W. Swift, Eds., "Humic Substances II, In Search of Structure," Wiley-Interscience, New York, 1989.
479. Z. Filip and J.J. Alberts, *Sci. Total Environ.*, **73**, 143 (1988); **83**, 273 (1989).
480. J.J. Rook, *Water Treat. Exam.*, **23**, 234 (1974).
481. J.J. Rook, *Environ. Sci. Technol.*, **11**, 478 (1977).
482. A.G. Howard, R.A. Pizzie, and J.W. Whitehouse, *Water Res.*, **18**, 735 (1984).
483. H.D. Holland, "The Chemistry of the Atmosphere and Oceans," Wiley-Interscience, New York, 1978.
484. J. Paasivirta, J. Knuutinen, P. Maatela, R. Paukku, J. Soikkeli, and J. Särkkä, *Cbemosphere*, **17**, 137 (1988).
485. S.W. Fox and K. Dose, "Molecular Evolution and the Origin of Life," Marcel Dekker, New York, 1977.
486. P.J. Scheuer, *Science*, **248**, 173 (1990).
487. W. Fenical, *Science*, **215**, 923 (1982).
488. G.R. Schulte and P.J. Scheuer, *Tetrahedron*, **38**, 1857 (1982).
489. V.J. Paul and S.C. Pennings, *J. Exp. Mar. Biol. Ecol.*, **151**, 227 (1991).
490. R. Kinnel, A.J. Duggan, T. Eisner, and J. Meinwald, *Tetrahedron Lett.*, 3913 (1977).
491. L.P. Hagar, *Basic Life Sci.*, **19**, 415 (1982).
492. D.J. Faulkner, *Top. Antibiot. Chem.*, **2**, 9 (1978).
493. P.N. Kaul, *Pure Appl. Chem.*, **54**, 1963 (1982).
494. J.H. Cardellina, *Pure Appl. Chem.*, **58**, 365 (1986).
495. A.G. González, V. Darrías, and E. Estévez, *Planta Med.*, **44**, 44 (1982).
496. P.J. Scheuer, *Chem. Ind.*, 276 (1991).
497. A. Fukuzawa, Y. Takasugi, and A. Murai, *Tetrahedron Lett.*, **32**, 5597 (1991).
498. W.H. Gerwick, A. Lopez, R. Davila, and R. Albers, *J. Nat. Prod.*, **50**, 1131 (1987).
499. D.J. Kennedy, I.A. Selby, and R.H. Thomson, *Phytochemistry*, **27**, 1761 (1988).
500. B.M. Howard and W. Fenical, *Phytochemistry*, **19**, 2774 (1980).
501. M.L. Bittner, M. Silva, V.J. Paul, and W. Fenical, *Phytochemistry*, **24**, 987 (1985).
502. L. Castedo, M.L. Garcia, E. Quinoa, and R. Riguera, *J. Nat. Prod.*, **47**, 724 (1984).
503. R.E. Schwartz, C.F. Hirsch, D.F. Sesin, J.E. Flor, M. Chartrain, R.E. Fromtling, G.H. Harris, M.J. Salvatore, J.M. Liesch, and K. Yudin, *J. Ind. Microbiol.*, **5**, 113 (1990).
504. R.E. Moore, A.J. Blackman, C.E. Cheuk, J.S. Mynderse, G.K. Matsumoto, J. Clardy, R.W. Woodard, and J.C. Craig, *J. Org. Chem.*, **49**, 2484 (1984).
505. C.P. Mason, K.R. Edwards, R.E. Carlson, J. Pignatello, F.K. Gleason, and J.M. Wood, *Science*, **215**, 400 (1982).
506. R. Bonjouklian, T.A. Smitka, L.E. Doolin, R.M. Molloy, M. Debono, S.A. Shaffer, R.E. Moore, J.B. Stewart, and G.M.L. Patterson, *Tetrahedron*, **47**, 7739 (1991).
507. O.J. McConnell, P.A. Hughes, and N.M. Targett, *Phytochemistry*, **21**, 2139 (1982).
508. S.A. Fedoreyev, S.G. Ilyin, N.K. Utkina, O.B. Maximov, M.V. Reshetnyak, M. Yu. Antipin, and Yu. T. Struchkov, *Tetrahedron*, **45**, 3487 (1989).
509. T.N. Makarieva, V.A. Stonik, P. Alcolado, and V.B. Elyakov, *Comp. Biochem. Physiol.*, **68B**, 481 (1981).
510. M. D'Ambrosio, A. Guerriero, P. Traldi, and F. Pietra, *Tetrahedron Lett.*, **23**, 4403 (1982).
511. M. D'Ambrosio, A. Guerriero, R. De Clauser, G. De Stanchina, and F. Pietra, *Experientia*, **39**, 1091 (1983).
512. M. D'Ambrosio, C. Mealli, A. Guerriero, and F. Pietra, *Helv. Chim. Acta*, **68**, 1453 (1985).
513. F. Cruz, L. Quijano, F. Gomez-Garibay, and T. Rios, *J. Nat. Prod.*, **53**, 543 (1990).
514. R. Xynas and R.J. Capon, *Aust. J. Chem.*, **42**, 1427 (1989).
515. D.M. James, H.B. Kunze, and D.J. Faulkner, *J. Nat. Prod.*, **54**, 1137 (1991).
516. K.L. Erickson and R.J. Wells, *Aust. J. Chem.*, **35**, 31 (1982).
517. S.A. Morris and R.J. Andersen, *Can. J. Chem.*, **67**, 677 (1989).
518. P.A. Kiefer, R.E. Schwartz, M.E.S. Koker, R.G. Hughes, D. Rittschof, and K.L. Rinehart, *J. Org. Chem.*, **56**, 2965 (1991).
519. M. Litaudon and M. Guyot, *Tetrahedron Lett.*, **27**, 4455 (1986).
520. R. Kazlauskas, R.O. Lidgard, P.T. Murphy, R.J. Wells, and J.F. Blount, *Aust. J. Chem.*, **34**, 765 (1981).
521. A. Longeon, M. Guyot, and J. Vacelet, *Experientia*, **46**, 548 (1990).

522. H. Wu, H. Nakamura, J. Kobayashi, Y. Ohizumi, and Y. Hirata, *Experientia*. **42**, 855 (1986).
523. M. Ishibashi, M. Tsuda, Y. Ohizumi, T. Sasaki, and J. Kobayashi, *Experientia*. **47**, 299 (1991).
524. H. Nakamura, H. Wu, J. Kobayashi, Y. Nakamura, Y. Ohizumi, and Y. Hirata, *Tetrahedron Lett.* **26**, 4517 (1985).
525. C. Jiménez and P. Crews, *Tetrahedron*. **47**, 2097 (1991).
526. D.M. Roll, C.W.J. Chang, P.J. Scheuer, G.A. Gray, J.N. Shoolery, G.K. Matsumoto, G.D. Van Duyne, and J. Clardy, *J. Am. Chem. Soc.* **107**, 2916 (1985).
527. M. Rotem, S. Carmely, Y. Kashman, and Y. Loya, *Tetrahedron*. **39**, 667 (1983).
528. A.D. Rodriguez, R.K. Akee, and P.J. Scheuer, *Tetrahedron Lett.* **28**, 4989 (1987).
529. G. Cimino, S. De Rosa, S. De Stefano, R. Self, and G. Sodano, *Tetrahedron Lett.* **24**, 3029 (1983).
530. M. Gunasekera and S.P. Gunasekera, *J. Nat. Prod.* **52**, 753 (1989).
531. L. Arabshahi and F.J. Schmitz, *J. Org. Chem.* **52**, 3584 (1987).
532. H. Kigoshi, Y. Imamura, K. Yoshikawa, and K. Yamada, *Tetrahedron Lett.* **31**, 4911 (1990).
533. J.L.C. Wright, *J. Nat. Prod.* **47**, 893 (1984).
534. F. De Riccardis, M. Iorizzi, L. Minale, R. Riccio, B.R. de Forges, and C. Debitus, *J. Org. Chem.* **56**, 6781 (1991).
535. A.J. Blackman, T.W. Hambley, K. Picker, W.C. Taylor, and N. Thirasasana, *Tetrahedron Lett.* **28**, 5561 (1987).
536. A. Sato and W. Fenical, *Tetrahedron Lett.* **24**, 481 (1983).
537. N.J. Skelton, D.H. Williams, R.A. Monday, and J.C. Ruddock, *J. Org. Chem.* **55**, 3718 (1990).
538. H. Achenbach, W. Kohl, A. Böttger-Vetter, and H. Reichenbach, *Tetrahedron*. **37**, 559 (1981).
539. K. Nomoto, K. Mizukawa, Y. Kato, M. Kubo, T. Kamiki, and Y. Inamori, *Chem. Pharm. Bull.* **32**, 4213 (1984).
540. M.M. Mahandru and A. Tajbakhsh, *J. Chem. Soc. Perkin Trans. 1*. 413 (1983).
541. T. Sala, M.V. Sargent, and J.A. Elix, *J. Chem. Soc. Perkin Trans. 1*. 849 (1981).
542. W.A. Ayer, S.P. Lee, A. Tsuneda, and Y. Hiratsuka, *Can. J. Microbiol.* **26**, 766 (1980).
543. R. Marumoto, C. Kilpert, and W. Steglich, *Z. Naturforsch.* **41C**, 363 (1986).
544. A. Rustaiyan, L. Nazarians, and F. Bohlmann, *Phytochemistry*, **20**, 1152 (1981).
545. T. Murakami, T. Sarake, K. Ninomiya, H. Iida, K. Yamauchi, N. Tanaka, Y. Saiki, and C.-M. Chen, *Phytochemistry*. **19**, 1743 (1980).
546. H. Kobayashi, H. Karasawa, T. Miyase, and S. Fukushima, *Chem. Pharm. Bull.* **32**, 1729 (1984).
547. F. Bohlmann, J. Jakupovic, R.M. King, and H. Robinson, *Phytochemistry*. **20**, 1613 (1981).
548. M. Kobayashi and H. Mitsuhashi, *Chem. Pharm. Bull.* **35**, 4789 (1987).
549. L.J. El-Naggar, J.L. Beal, and R.W. Doskotch, *J. Nat. Prod.* **45**, 539 (1982).
550. N. Tanaka, T. Murakami, Y. Saiki, C.-M. Chen, and L.D. Gomez P, *Chem. Pharm. Bull.* **29**, 3455 (1981).
551. S.R. Jensen and B.J. Nielsen, *Phytochemistry*. **28**, 3059 (1989).
552. M.S. Butler, T.K. Lim, R.J. Capon, and L.S. Hammond, *Aust. J. Chem.* **44**, 287 (1991).
553. J. Kobayashi, J.-F. Cheng, H. Nakamura, Y. Ohizumi, Y. Tomotake, T. Matsuzaki, K.J.S. Grace, R.S. Jacobs, Y. Kato, L.S. Brinen, and J. Clardy, *Experientia*. **47**, 501 (1991).
554. G.F. Gause, M.G. Brazhnikova, N.N. Lomakina, T.F. Berdnikova, G.B. Fedorova, N.L. Tokareva, V.N. Borisova, and G.Y. Batta, *J. Antibiot.* **42**, 1790 (1989).
555. S. Nakanishi, K. Ando, I. Kawamoto, T. Yasuzawa, H. Sano, and H. Kase, *J. Antibiot.* **42**, 1775 (1989).
556. J. Tanaka, T. Higa, G. Bernardinelli, and C.W. Jefford, *Tetrahedron*. **45**, 7301 (1989).

Received 24 February 1992