

Natural Chlorine Updates – No. 15

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I. Introduction

This literature review is the fifteenth in a series of periodic updates to the natural halogen literature, with a particular focus on organochlorine compounds, although all new naturally occurring compounds that have been identified since *Updates #14* are described.

The coverage is approximately from June 2001 through July 2001, with the inclusion of several earlier reports that were not covered in the last *Updates* for reasons of time and space.

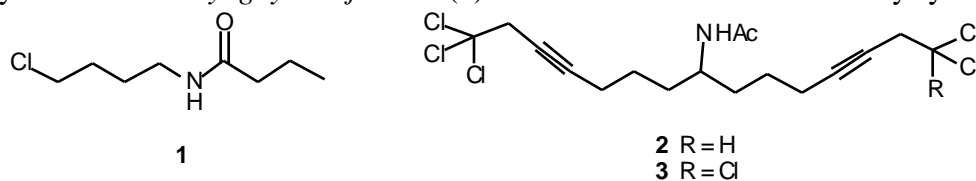
II. New Natural Organohalogens

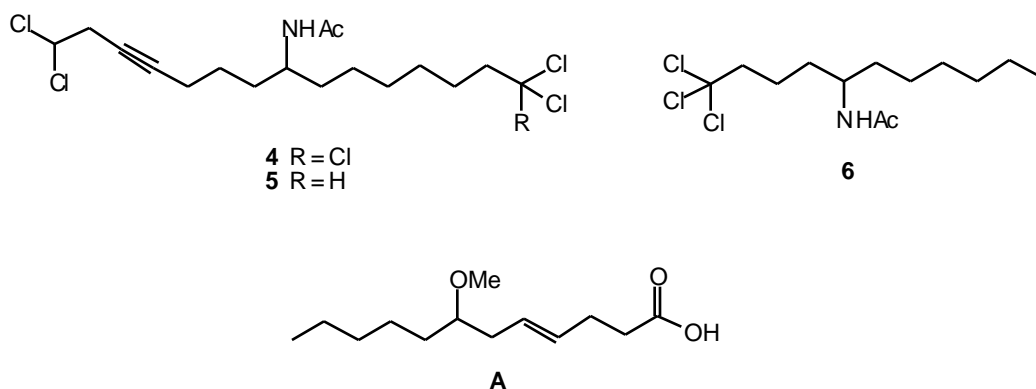
This *Updates* describes 60 new natural organohalogens, bringing the total number to 3563. Thus, the current breakdown of such naturally produced chemicals reported in the literature to date is as follows:

Organochlorine:	2084
Organobromine:	1823
Organoiodine:	95
Organofluorine:	29

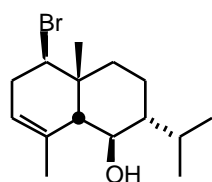
As in previous *Updates*, only newly discovered organohalogens are assigned explicit compound numbers (in **bold**), for ease in counting. Previously reported or non-halogenated compounds are indicated by name or capital letters.

The unprecedented chlorinated amide **1** has been found in *Aloe sabaea*, along with several toxic piperidine alkaloids including coniine and -coniceine (*1*). The leaves of this plant can accumulate large amounts of potassium chloride. The unusual polychlorinated acetamides **2-6** have been isolated from the cyanobacterium *Microcoleus lyngbyaceus* (*2*). The novel fatty acid **A**, which is the probable precursor of one or more of the chlorine-containing malyngamides has been isolated from the cyanobacterium *Lyngbya majuscula* (*3*). The structure was confirmed by synthesis.

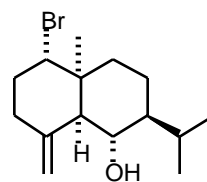




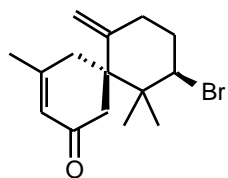
An older study, not previously catalogued in *Updates*, has revealed the presence of the *cis*-eudesmanes lankalapuol A (**7**) and B (**8**) in the sea hare *Aplysia dactylomela* (**4**). The absolute configuration of **7** was established via the corresponding acetate. Moreover, from their specific rotations, lankalapuols A and B must possess opposite absolute configurations as shown. The new chamigrane **9** has also been isolated from *Aplysia dactylomela* and determined to have the absolute configuration shown below (**5**). The sponge *Stylotella aurantium* has yielded an additional set of five novel sesquiterpene carbonimidic dichlorides **10-14**, in addition to seven known related compounds (**6**). Furthermore, this study included a determination of the absolute configuration of reticulidin A (**B**).



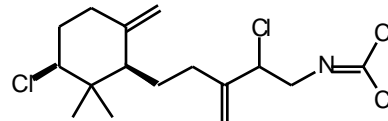
7 (lankalapuol A)



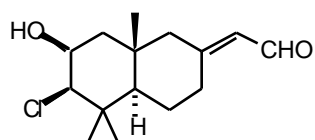
8 (lankalapuol B)



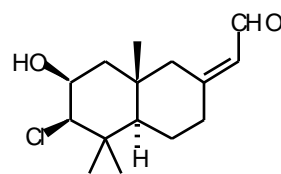
9 (10-bromo-11-chamigren-4-one)



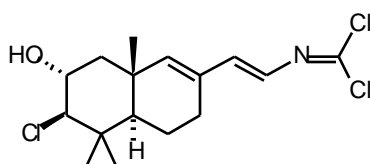
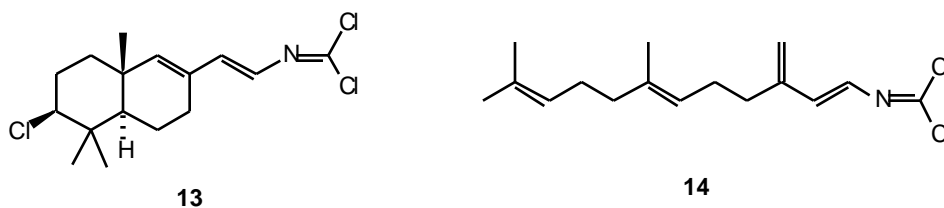
10



11

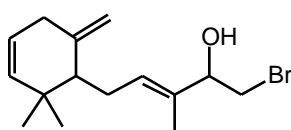


12

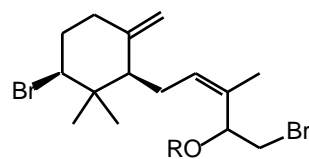


B (reticulidin A)

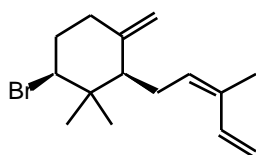
The red alga *Laurencia luzonensis* has furnished an array of sesquiterpenes including the novel isopalisol (**15**), luzonensol (**16**), luzonensol acetate (**17**), luzonensin (**18**), and **19** (7). This paper also reports the absolute configuration of 3-bromobarekoxide (**C**), which was isolated previously by these authors from this alga (*Updates #14*). The novel tricyclic cedrene-type sesquiterpene majusin (**20**) was found in *Laurencia majuscula* from the South China Sea (8). The first isolation of several known brominated chamigrene-type sesquiterpenes (prepacifenol epoxide, johnstonol, pacifidiene) from Brazilian waters in the sea hare *Aplysia dactylomela* has been described (9).



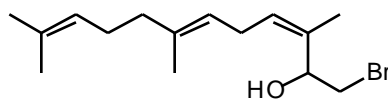
15 (isopalisol)



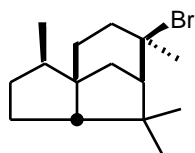
16 R = H (luzonensol)
17 R = Ac (luzonensol acetate)



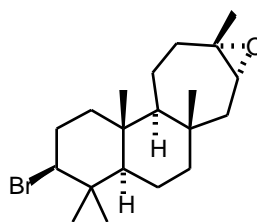
18 (luzonensin)



19

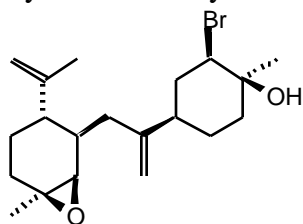


20 (majusin)

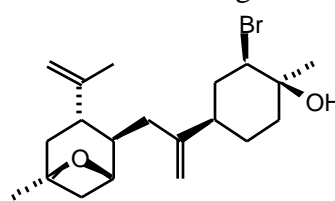


C (3-bromobarekoxide)

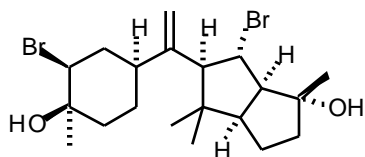
The new brominated diterpenes prevezol A (**21**) and B (**22**) have been characterized from the often examined *Laurencia obtusa* collected in the Ionean Sea, Greece (10). A novel diterpenoid tricyclic skeleton has been discovered with the isolation of neorogioldiol (**23**), along with the new rogioldiol D (**24**) and **25** (11). Their putative biogenetic precursor geranylinalool **D** was also isolated in this study from a colony of *Laurencia microcladia* found along the coast of Tuscany.



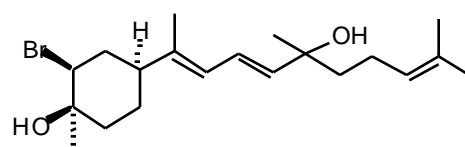
21 (prevezol A)



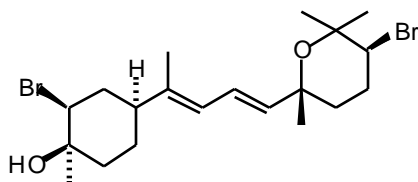
22 (prevezol B)



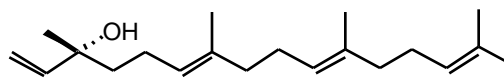
23 (neorogioldiol)



24 (rogioldiol D)

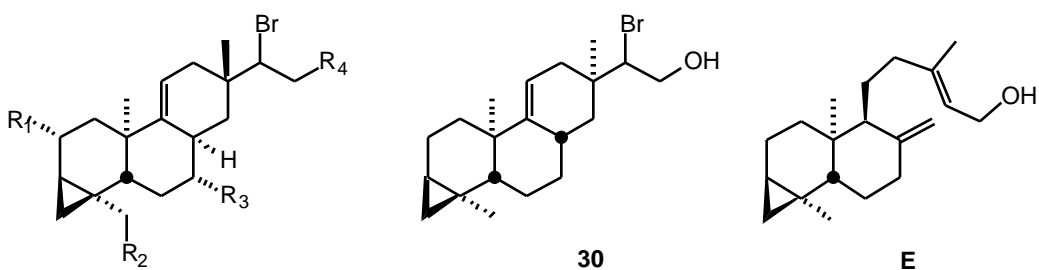


25



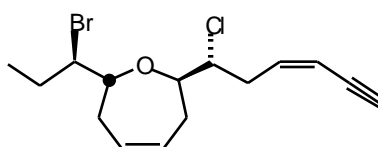
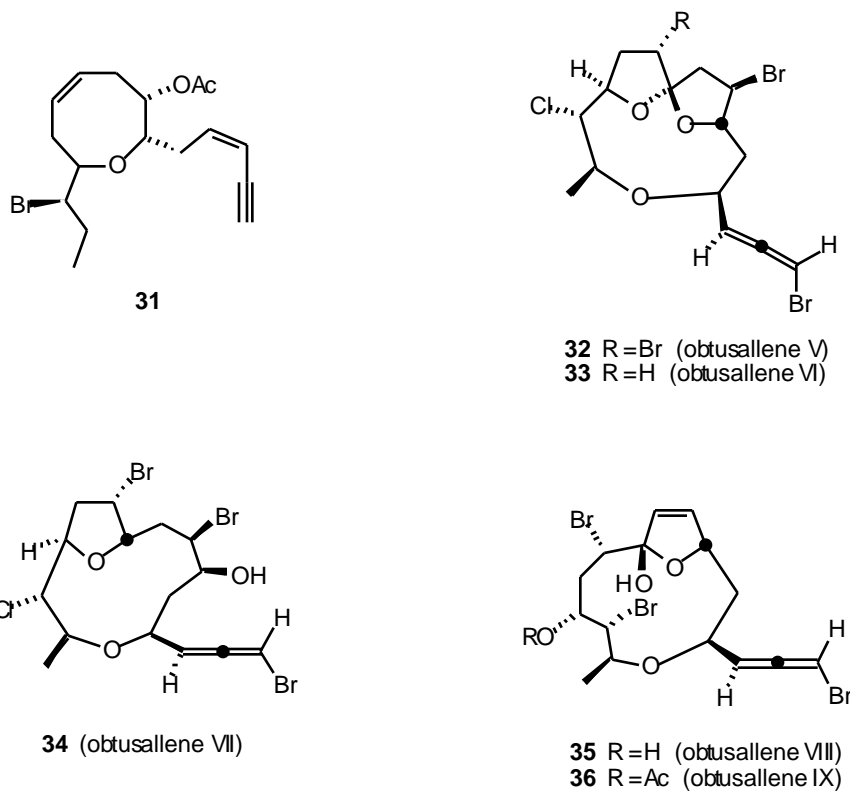
D

An Australian collection of *Laurencia filiformis* has furnished the new parguerenes **26-30** along with the plausible biogenetic precursor **E** (12). Metabolite **26** had been previously synthesized but this is the first report of it as naturally occurring. The squalene-derived thyriferyl 23-acetate and its derivatives have been found to induce apoptosis in various T- and B-leukemia cells (13).



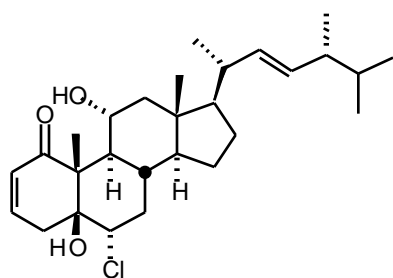
- 26** $R_1 = R_3 = R_4 = \text{OAc}$, $R_2 = \text{H}$
27 $R_1 = R_3 = \text{OAc}$, $R_2 = \text{H}$, $R_4 = \text{OH}$
28 $R_1 = \text{OAc}$, $R_2 = R_3 = \text{H}$, $R_4 = \text{OH}$
29 $R_1 = R_2 = R_3 = \text{H}$, $R_4 = \text{OH}$

The prolific *Laurencia obtusa*, which is widely abundant in Turkish waters, has yielded the C_{15} nonterpenoid acetylene **31** (14). Several new obtusallenes, **32-36**, have also been isolated from *Laurencia obtusa* living in the Turkish Mediterranean Sea (15). An elegant total synthesis of the known (+)-rogioioxepane A (**F**) has confirmed its absolute configuration (16).

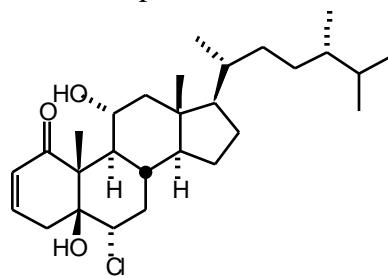


F (+)-rogioioxepane A

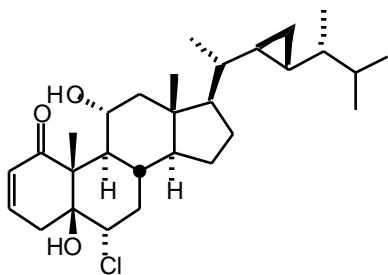
Although halogenated steroids are extremely rare in nature, the Okinawan soft coral *Clavularia viridis* has produced three chlorinated sterols, yonarasterols G-I (**37-39**) (17). The absolute configurations were established by chemical conversion with hydrochloric acid from stoloniferone-c (**G**), which is the epoxide corresponding to **38**. Interestingly, heating this epoxide in methanol for three days containing sodium chloride with and without silica gel showed no reaction, and the authors conclude that **37-39** are indeed natural products and not isolation artifacts.



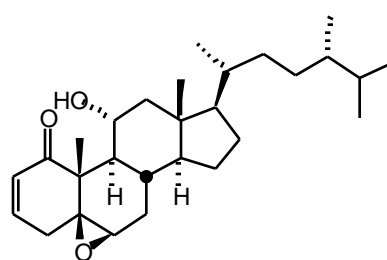
37 (yonarasterol G)



38 (yonarasterol H)

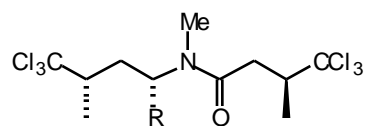
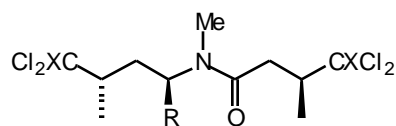
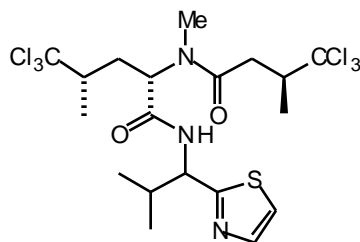


39 (yonarasterol I)

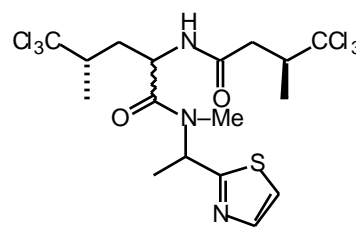


G (stoloniferone-c)

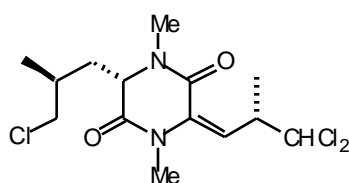
Sponges of genus *Dysidea* continue to be a rich source of chlorinated peptides. Several collections of *Dysidea herbacea* and *Dysidea* sp. from the Great Barrier Reef have led to five new metabolites **40-44**, whose absolute configurations are shown (18). Likewise, one of these collections of *Dysidea herbacea* provided the novel thiazoles **45** and **46** (19). A Chinese group has also found a novel trichlorinated diketopiperazine in a Yap collection of *Dysidea* sp., namely dysamide U (**47**) (20). This same research group has isolated the unusual 10-membered ring cyclic *N*-bromoimide-urea **48** from the sponge *Rhaphisia pallida* (21). Interestingly, a related *N*-bromo-*N*-chlorohydantoin **G** is used to disinfect swimming pools (including this author's).

40 R = CO₂Me41 R = CO₂H42 X = Cl, R = CO₂Me43 X = H, R = CO₂Me44 X = Cl, R = CO₂H

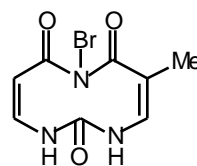
45



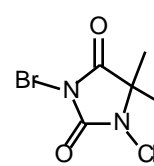
46



47 (dysamide U)

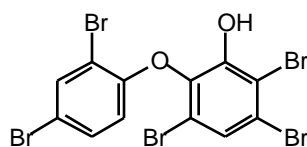


48

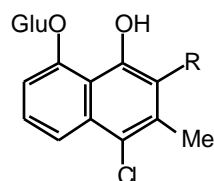


G

Despite the existence of many natural brominated diphenyl ethers, new examples continue to be uncovered. The sponge *Dysidea herbacea* has afforded the novel **49** (22). The terrestrial plant *Rumex patientia* from Turkey, which is used in traditional medicine, contains the novel naphthalene glycosides patientoside A (**50**) and B (**51**) (23). The new chlorinated bis-bibenzyl **52** has been isolated from the liverwort *Plagiochila* sp. (24), and polysiphenol (**53**) is the first example of a 9,10-dihydrophenanthrene from a marine organism, the Senegalese red alga *Polysiphonia ferulacea* (25). This hindered biphenyl analogue is optically active and the absolute configuration was determined from its CD spectrum.

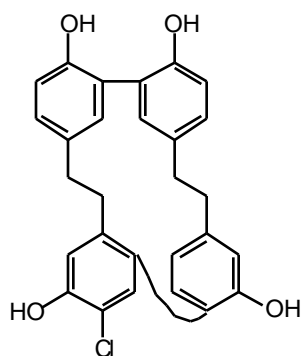


49

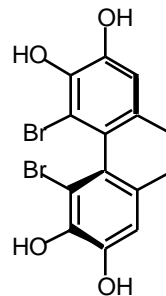


50 R = Ac (patientoside A)

51 R = Cl (patientoside B)

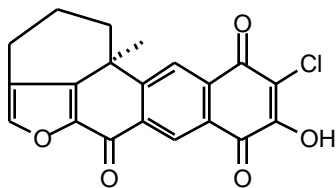


52

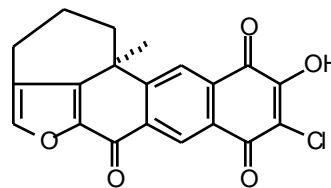


53

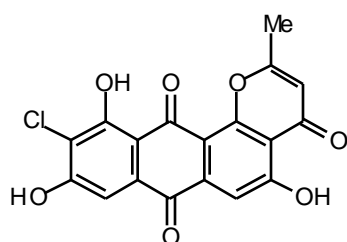
The isomeric estoquinones **54** and **55**, which are topoisomerase II active, have been characterized from the Philippine sponge *Xestospongia* sp. (26). A screening of the fungi *Phoma* sp. and *Penicillium* sp. has revealed the identity of the novel topoisomerase I inhibitors topopyrone A (**56**) and B (**57**) (27,28). The activity and selectivity of **57** is comparable to those of camptothecin. This metabolite is also potent against the herpes virus VZV. Even more remarkable is the report of the first naturally occurring chlorinated dibenzofuran, AB0022A (**58**), from the cellular slime mold *Dictyostelium purpureum* (29). The structure was confirmed by synthesis.



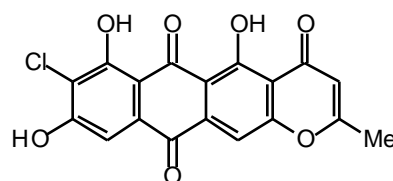
54



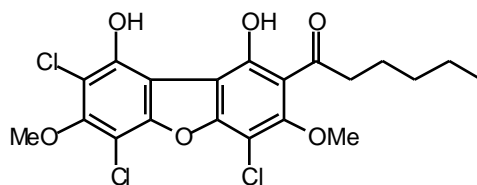
55



56 (topopyrone A)



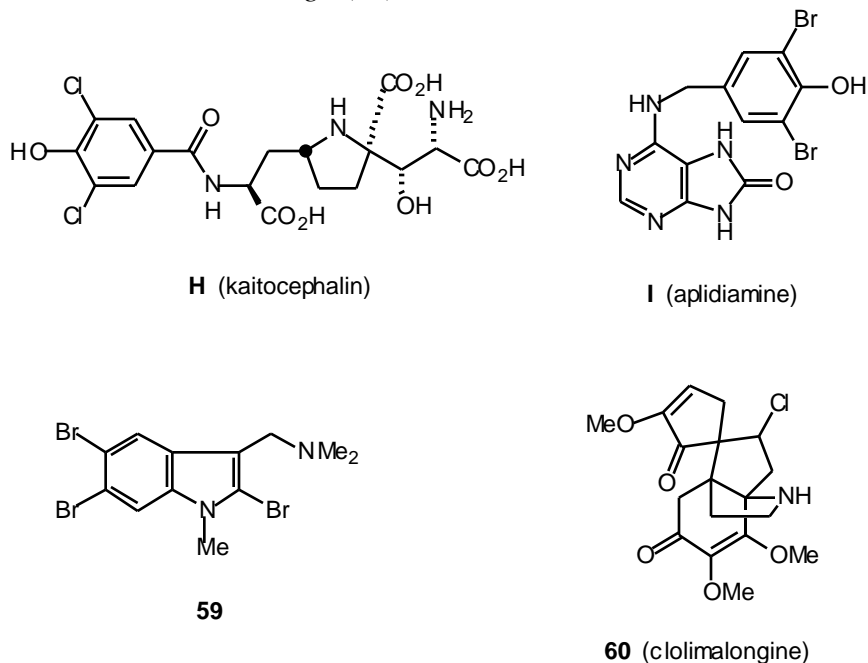
57 (topopyrone B)



58 (AB0022A)

The absolute configuration of kaitocephalin (**H**), a compound that was presented in *Updates*

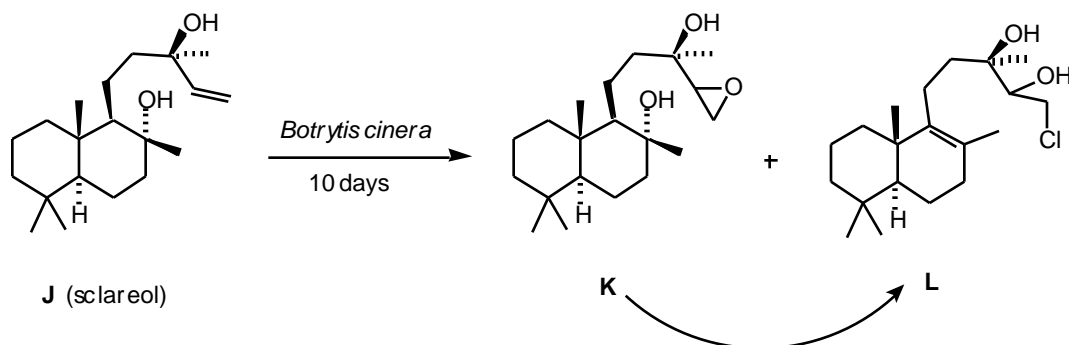
#6, has now been determined as shown (30). The structure of the novel marine ascidian metabolite, aplidiamine (**I**), has been revised to that shown (**I**), based on a synthesis (3,32). Previously (*Updates #5*), this compound was assigned a zwitterionic structure. The tribromogramine **59**, which was isolated from the bryozoan *Zoobotryon pellucidum* (33), is a potent inhibitor of larval settlement by the barnacle *Balanus amphitrite* (34). This biological effect is not a toxic one, but rather a repellent one. The hasubanan chlorine-containing alkaloid (+)-clolimalongine (**60**) has been characterized from *Limacia oblonga* (35).



III. Biohalogenation

Peroxidase activity is present in extracts of the alga *Ascophyllum nodosum*, as judged by the iodination and bromination, but not chlorination, of various compounds (36). Similarly, cell-free extracts of three species of marine microalgae (*Porphyridium purpureum*, *Phaeodactylum tricorutum*, and *Dunaliella tertiolecta*) exhibit peroxidase activity (37). However, this heme-containing enzyme is not a chloro- or bromoperoxidase as judged from the standard 2-chlorodimedon assay, although iodide is oxidized by this enzyme. Vanadium bromoperoxidase from *Ascophyllum nodosum* and *Corallina officinalis* oxidizes 1,3-di-*tert*-butylindole to the corresponding 2-indolinone, in stark contrast to the reactions of this indole with bromine (38). An isotopic labeling study using $\text{NaH}^{13}\text{CO}_3$ has shown incorporation of the label into chloromethane, bromomethane, iodomethane, and chloroform, which are produced by the marine microalgae

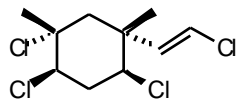
Porphyridium purpureum and *Dunaliella tertiolecta* (39). In the case of chloroform, only *Porphyridium purpureum* is a producer. The first enzymatic synthesis of carbon-fluorine bonds by nucleophilic fluorination has been uncovered in the action of two glycosidase mutants (40). The metabolism of sclareol (**J**) by the plant pathogenic fungus *Botrytis cinerea* affords epoxysclareol (**K**) and chloro compound (**L**), the latter representing a rare example of microbial halogenation (41).



A study of North American coastal air has revealed the daily production of high (up to 330 ppt) concentrations of gaseous chlorine from a previously unrecognized night-time source (42).

IV. Function

Several known bromoditerpenes were isolated from *Laurencia saitoi* and found to have significant feeding-deterrent activity against young abalone (*Haliotis discus hannai*) and young sea urchins (*Strongylocentrotus nudus* and *S. intermedius*) (43). Another study has revealed that the red alga *Plocamium hamatum* has a deleterious effect on the soft coral *Sinularia cruciata* by direct contact (44). This allelopathic effect (tissue necrosis) is caused by chloromertensene (**M**), which is produced by this alga. This is the first clear evidence of allelopathy between an alga and another marine organism.



M (chloromertensene)

V. References

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