Natural Chlorine Updates – No. 16

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Dr. Gordon W. Gribble
Department of Chemistry
Dartmouth College
Hanover, New Hampshire 03755 USA
FAX: 603-646-3946
Phone: 603-646-3118
e-mail: grib@Dartmouth.edu

I. Introduction

This literature review is the sixteenth in a series of periodic updates to the natural halogen literature, with a particular focus on organochlorine compounds, although all new naturally occurring organohalogens that have been identified since *Updates #15* are described.

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

The 2nd International Conference on Naturally Produced Organohalogens was held in Heidelberg, Germany, from September 30–October 3, 2001. Some of the papers presented at this Conference will be discussed in *Updates #17* and a special issue of *Chemosphere* will be devoted to this Conference.

II. New Natural Organohalogens

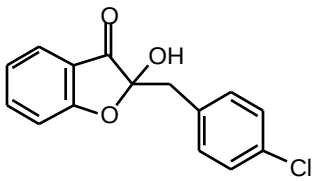
This *Updates* describes 70 new natural organohalogens, bringing the total number to 3633. Thus, the current breakdown of such naturally produced chemicals reported in the literature to date is as follows:

Organochlorine:	2137
Organobromine:	1849
Organoiodine:	95
Organofluorine:	29

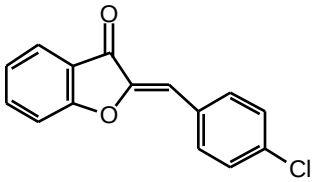
As in previous *Updates*, only newly discovered organohalogens are assigned explicit compound numbers (in **bold**), for ease in counting. Previously reported or non-halogenated compounds are indicated by name or capital letters.

The two new chlorine-containing aurones, **1** and **2**, have been isolated from the brown alga *Spatoglossum variabile*, found along the Pakistan coast (*1*). The authors propose that the *Z* isomer of **2** is more stable than the *E* isomer (1.98 kcal/mole difference by AM1 calculations). Interestingly, the chlorine in these metabolites is on an unactivated benzene ring, one of the few such examples known to occur naturally. The plant *Harbouria trachypleura*, commonly called whiskbroom parsley, has yielded several coumarins and furanocoumarins including the new (±)-trachypleuranin-B (**3**) (*2*). The corresponding epoxide, which is also found in this higher plant, is

not converted to **3** under the isolation conditions. The novel angucyclinone-type antibiotic simocyclinone D8 (**4**) is produced by *Streptomyces antibioticus* (*3*). This compound displays pronounced cytostatic activity against some human cancer cell lines (MCF 7, HMO 2). The absolute configuration of several positions of the previously reported enacyloxins has been determined as shown for ENX IIa (*4*). A combination of degradation and synthesis was used. The paper describing the novel polychlorinated acetamides from the cyanobacterium *Microcoleus lyngbyaceus* (*Updates #15*) has now appeared (*5*). A review of marine cyanobacteria, which are a rich source of chlorinated natural products, has been published (*6*).



1



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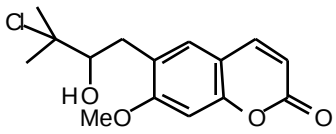
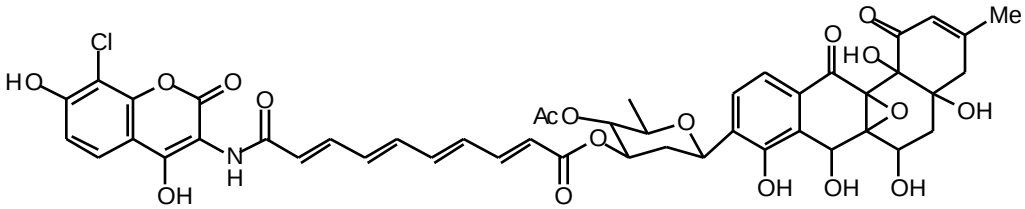
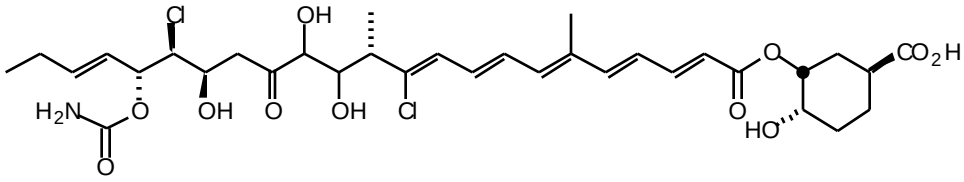


3 ((±)-trachypleuranin-B)



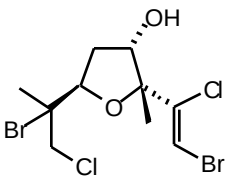
4 (simocyclinone D 8)



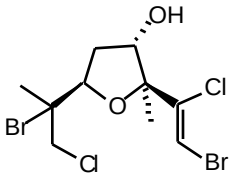
ENX IIa

New halogenated terpenes continue to be discovered, particularly from marine organisms. The red alga *Plocamium cartilagineum* has furnished the novel furoplocamioids A-C (**5**-**7**) (*7*), which are related structurally to the previously isolated pantofuranoids from the antarctic *Pantoneura plocamioides* (*Updates #4*). Notably, the chlorobromo vinyl moiety in these furoplocamioids is unusual. The report of several brominated sesquiterpenes in the red alga *Laurencia luzonensis* (*Updates #15*) has now appeared in print (*8*). This paper also reports the absolute configuration of 3-bromobarekoxide, which was previously isolated by these authors

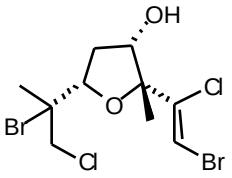
(*Updates #14*). The Australian sponge *Ulosa spongia* has yielded several sesquiterpene carbonimide dichlorides, one of which, ulosin B (**8**), is new (*9*). Ulosin A was independently isolated by a different group from the sponge *Stylotella aurantium* as reported in *Updates #15*. This latter sponge has also recently yielded five previously known sesquiterpene carbonimidic dichlorides (*10*). This study presents revised NMR assignments for three cyclic metabolites. An unidentified species of *Laurencia* sp. red alga from the Philippines has afforded ma'iliohydrin (**9**), a cytotoxic chamigrene sesquiterpene (*11*). Complete proton and carbon NMR assignments and stereochemical evaluations are reported for the well-known chamigrenes johnstonol, pacifenediol, pacifidiene, and pacifenol as isolated in this study from the sea hare *Aplysia dactilomela* (*12*). A collection of the red alga *Laurencia pannosa* from Malaysia has identified pannosanol (**10**), pannosane (**11**), and the C_{15}-acetogenin (3*Z*)-chlorofucin (**12**) (*13*). An examination of *Laurencia pinnatifida* from the Canary Islands has uncovered the presence of *E*-dihydrorhodophytin (**13**) (*14*). The previsouly known *Z* isomer was also found in this seaweed.



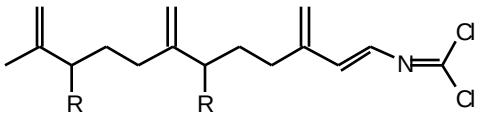
5 (furoplocamioid A)



6 (furoplocamioid B)

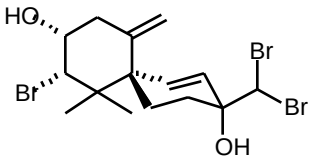


7 (furoplocamioid C)

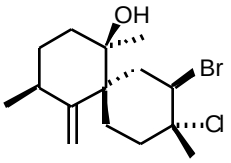


8 R = OH (ulosin B)

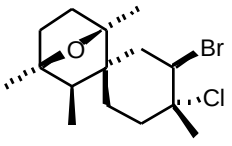
[R = H, ulosin A]



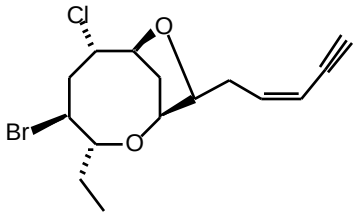
9 (ma'iliohydrin)



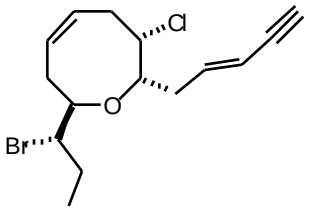
10 (pannosanol)



11 (pannosane)

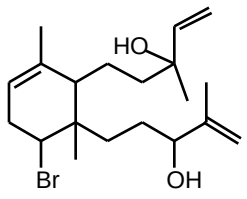


12 ((3*Z*)-chlorofucin)

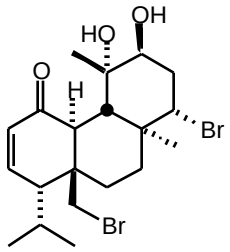


13 (*E*-dihydrorhodophytin)

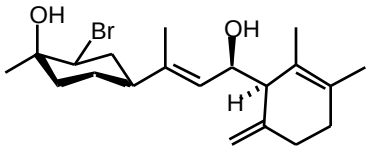
In addition to containing two known bromoditerpenes, the red alga *Sphaerococcus coronopifolius* has yielded the new sphaerolabdadiene-3,14-diol (**14**) and bromosphaerone (**15**) (*15*). A collection of *Laurencia microcladia* from the Tuscany coast has led to the discovery of rogioldiol B (**16**) and rogioldiol C (**17**) (*16*). These are the first examples of 15,14-friedoobtusane diterpenes. The mangrove plant *Excoecaria agallocha* Linn has yielded several novel diterpenoids, three of which, agallochins A-C (**18**-**20**), contain chlorine (*17*).



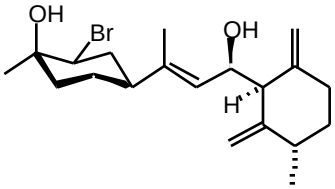
14



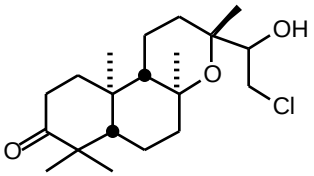
15



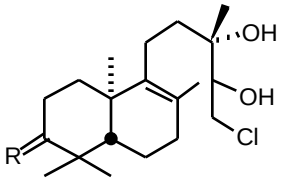
16 (rogioldiol B)



17 (rogioldiol C)

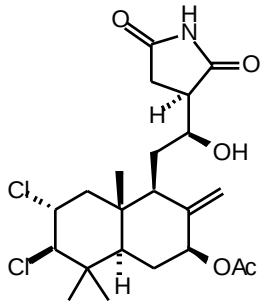


18 (agallochin A)

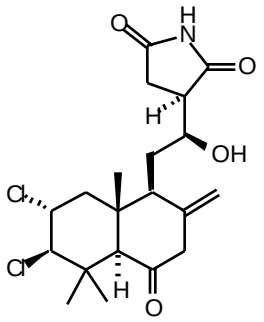


19 R = O (agallochin B)
20 R = •···OH (agallochin C)

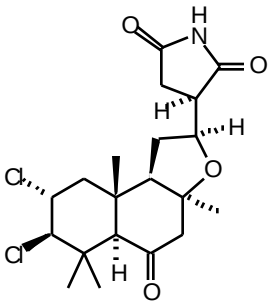
The ascidian species *Lissoclinum* sp. has yielded an array of chlorinated diterpenoids, haterumaimides A-I (**21**-**29**), in addition to the known dichlorolissoclimide and chlorolissoclimide (*18*,*19*).



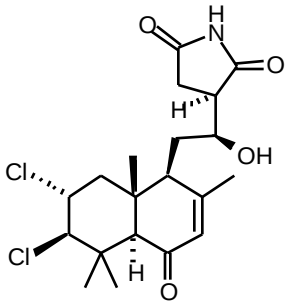
21 (haterumaimide A)



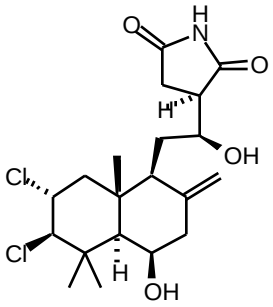
22 (haterumaimide B)



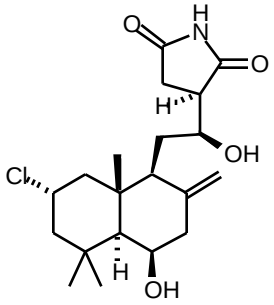
23 (haterumaimide C)



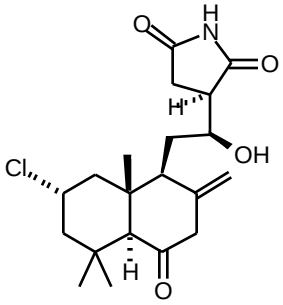
24 (haterumaimide D)



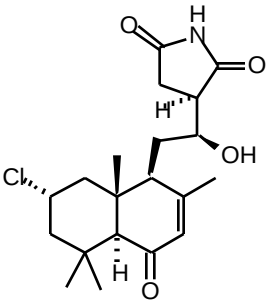
25 (haterumaimide E)



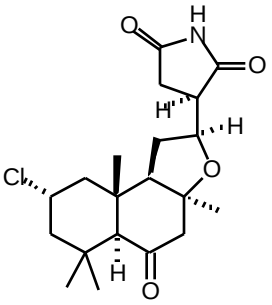
26 (haterumaimide F)



27 (haterumaimide G)

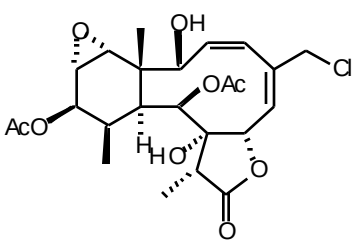


28 (haterumaimide H)

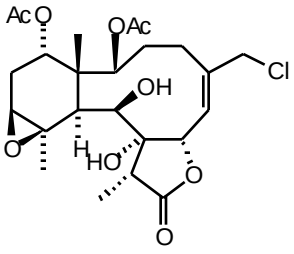


29 (haterumaimide I)

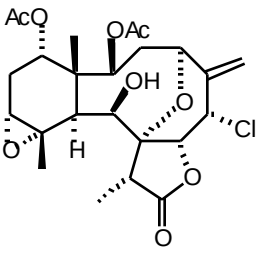
Gorgonians continue to provide a source of new chlorinated diterpenes. Thus, the Taiwanese gorgonian *Briareum excavatum* has yielded the chlorine-containing briaexcavatolide M (**30**) in addition to several non-chlorinated metabolites (*20*). The Western Pacific *Briareum stechei* has furnished several new briaranes, five of which contain chlorine, milolides **31**-**35** (*21*).



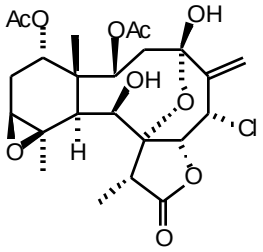
30 (briaexcavatolide M)



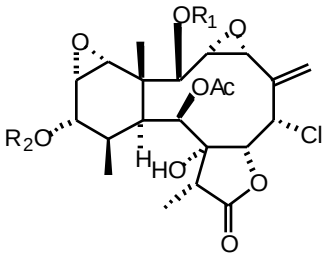
31 (16-chloromilolide B)



32 (milolide C)



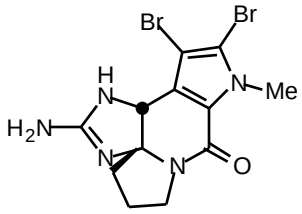
33 (4-hydroxymilolide C)



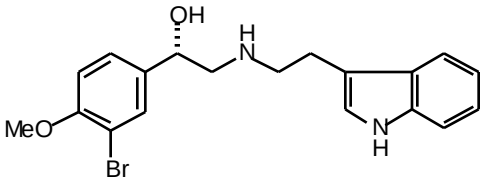
34 R_1 = H, R_2 = COC_3H_7 (milolide D)

35 R_1 = Ac, R_2 = COC_5H_{11} (milolide E)

The first chemical study of the sponge *Stylissa caribica* has yielded the reef fish feeding deterrent *N*-methyldibromoisophakellin (**36**) along with the known dibromoisophakellin and ageliferin (*22*). In this regard a universal biogenic pathway has been proposed for the formation of more than 60 pyrrole-imidazole sponge metabolites, many of which contain bromine or chlorine (*23*). There has been renewed interest in the ancient royal dye Tyrian Purple, both with regard to the biology behind this fascinating and historically important mollusc brominated indole metabolite (*24*,*25*) and its synthesis (*26*). The absolute configuration of the previously known chelonin B (**A**) has been determined through an asymmetric synthesis (*27*). A recent examination of the red alga *Laurencia similis* from Borneo, Malaysia, has yielded the known 1-methyl-2,3,5,6-tetrabromoindole and 2,3,5,6-tetrabromoindole (*28*).

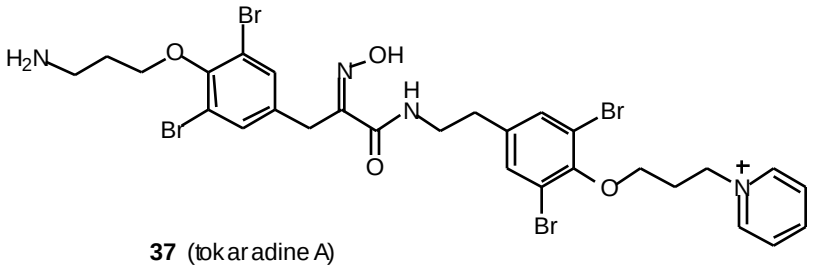


36 (*N*-methyldibromoisophakellin)

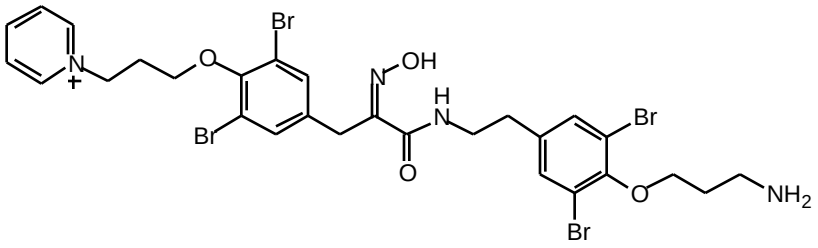


A (chelonin B)

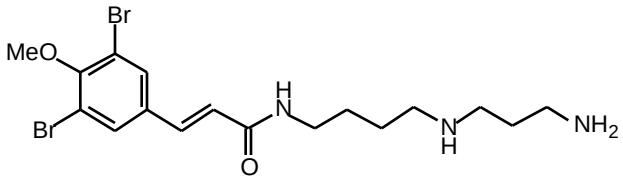
Marine sponges continue to yield an array of novel brominated tyrosine derivatives, which are often potent feeding deterrents. The sponge *Pseudoceratina purpurea* contains tokaradines A-C (**37**-**39**), which are lethal to the crab *Hemigrapsus sanguineus* (*29*). The Okinawan sponge *Subera* sp. has afforded suberediamines A (**40**) and B (**41**) (*30*). The Caribbean sponge *Aplysina archeri* contains the novel archerine (**42**) (*31*). This metabolite exhibits antihistamine activity at concentrations as low as 1 μM.



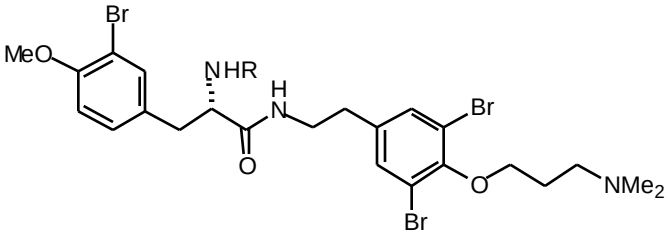
37 (tokaradine A)



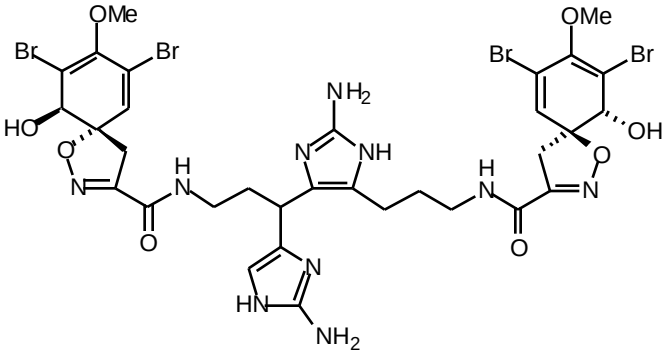
38 (tokaradine B)



39 (tokaradine C)

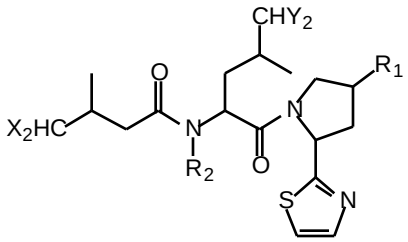


40 R = H (suberedamine A)
41 R = Me (suberedamine B)

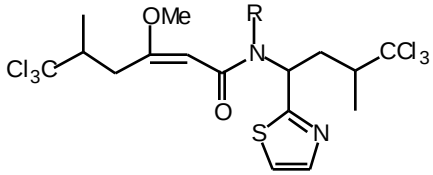


42 (archerine)

A study of the sponge *Dysidea* sp., collected at Bararin Island, Philippines, has identified the novel dysideaprolines A-F (**43**-**48**), which are related to the known dysidenin, and also the barbamide analogs barbaleucamides A (**49**) and B (**50**) (*32*). The report of two related novel thiazoles from *Dysidea herbacea* (*Updates #15*) has now appeared in print (*33*).

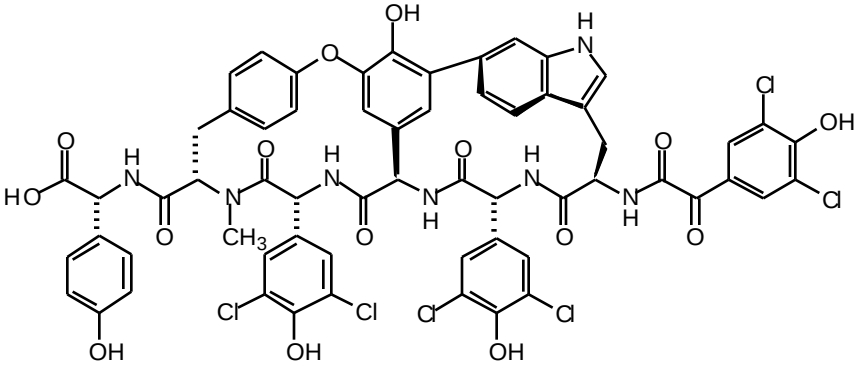


43 R_1 = H, R_2 = Me, X = Y = Cl (dysideaproline A)
44 R_1 = R_2 = Me, X = Y = Cl (dysideaproline B)
45 R_1 = R_2 = H, X = Y = Cl (dysideaproline C)
46 R_1 = H, R_2 = Me, X = H, Y = Cl (dysideaproline D)
47 R_1 = H, R_2 = Me, X = Cl, Y = H (dysideaproline E)
48 R_1 = H, R_2 = Me, X = Cl, Y_2 = ClH (dysideaproline F)

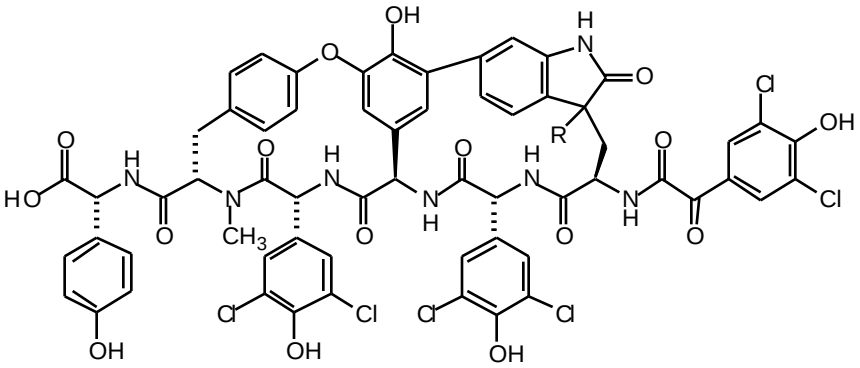


49 R = H (barbaleucamide A)
50 R = Me (barbaleucamide B)

Further investigation of the *Streptomyces* sp. that previously afforded complestatin, which is related to vancomycin, has now been found to produce isocomplestatin (**51**) and complestatins A (**52**) and B (**53**) (*34*). These compounds possess HIV-1 integrase activity. Isocomplestatin is an axial-chiral isomer of complestatin that is not convertible into the latter, even at high temperatures.

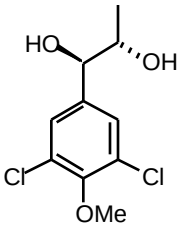


51 (isocomplestatin)

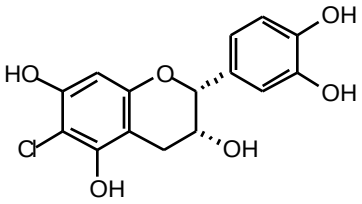


52 R = H (complestatin A)
53 R = OH (complestatin B)

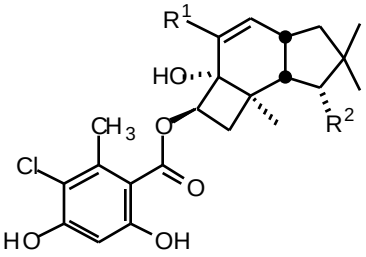
One of the most abundant classes of natural organohalogen compounds are chlorophenols, and several examples of complex chlorophenols have already been presented (*vide supra*). The white rot fungus *Bjerkandera adusta* has yielded the new metabolite bjerkanderol B (**54**) (*35*). Experiments with $Na^{37}Cl$ supplied to the culture reveal incorporation of ^{37}Cl in all of the chlorophenol metabolites. The Turkish folk medicine plant "Turnagagasi" (*Geranium pratense*) contains 6-chloroepicatechin (**55**) (*36*), and the paper describing the two novel chlorinated naphthalene glycosides from *Rumex patientia*, which were cited in *Updates #15*, has now been published (*37*). The three new melleolides K-M (**56**-**58**) have been characterized from the cultured mycelia of *Armillariella mellea* (*38*).



54 (bjerkanderol B)

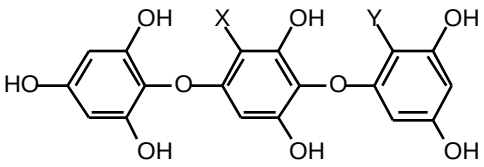


55 (6-chloroepicatechin)

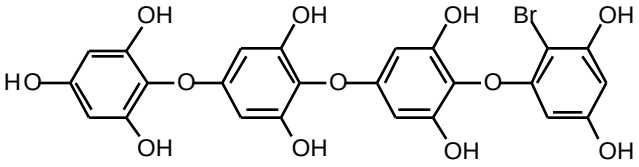


56 R^1 = CHO, R^2 = H (melleolide K)
57 R^1 = CHO, R^2 = OH (melleolide L)
58 R^1 = CH_2OH, R^2 = OH (melleolide M)

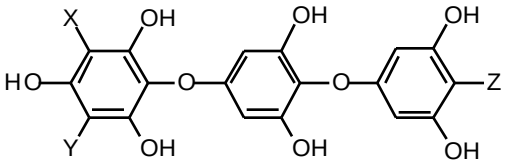
A detailed study of the brown alga *Cystophora retroflexa* has uncovered the presence of 17 halogenated derivatives of phlorethol and fucophlorethol, isolated as peracetates (*39*). Of these 17, 12 are the new compounds **59**-**70**.



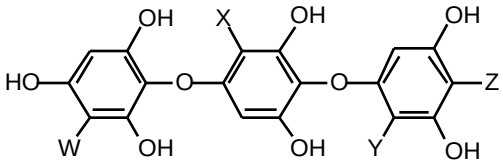
59 X = Br, Y = H
60 X = H, Y = Br
61 X = Y = Br



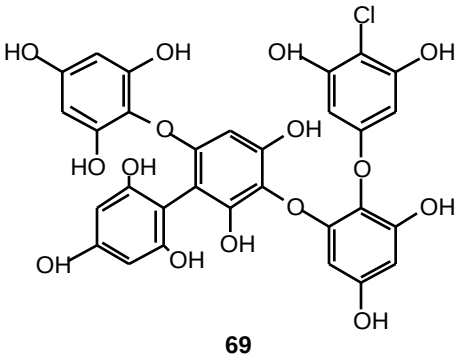
62



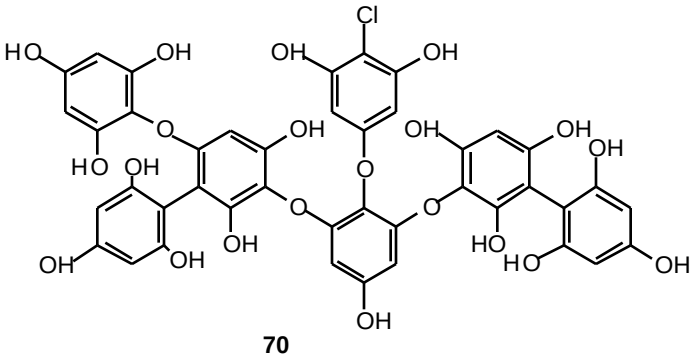
63 X = Y = Cl, Z = H
64 X = H, Y = Z = Cl
65 X = H, Y = Cl, Z = Br



66 W = Y = H, X = Z = Cl
67 W = Y = Br, X = Z = H
68 W = Br, Y = Cl, X = Z = H

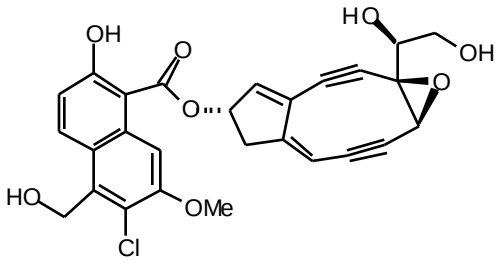


69



70

The first total synthesis of N1999-A2 has established its absolute configuration as shown (*40*). This enediyne antibiotic was disclosed in *Updates #14*.



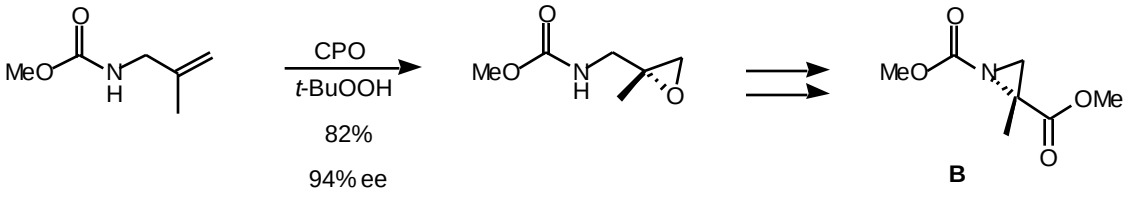
N1999-A2

III. Biohalogenation and Biosynthesis

The complestatin biosynthetic and regulatory gene cluster has been cloned and sequenced from *Streptomyces lavendulae* (*41*). Biosynthetic studies on the vancomycin group of glycopeptides continue to be reported. Thus, a hydroxymandelate oxidase that is involved in the biosynthesis of (*S*)-4-hydroxyphenylglycine and (*S*)-3,5-dihydroxyphenylglycine, which are two amino acids present in the backbone of the vancomycin family, has been characterized from the chloroeremomycin gene cluster using genetic engineering techniques (*42*). This same research group has also characterized a type III polyketide synthase from the vancomycin-chloroeremomycin producing bacterial strain *Amycolatopsis orientalis* (*43*). This enzyme is involved in the biosynthesis of 3,5-dihydroxyphenylacetate, a proposed precursor for 3,5-dihydroxyphenylglycine. Nitrogen-15 dynamic NMR has been used to probe amide proton exchange rates at the two sides of the eremomycin dimer (*44*).

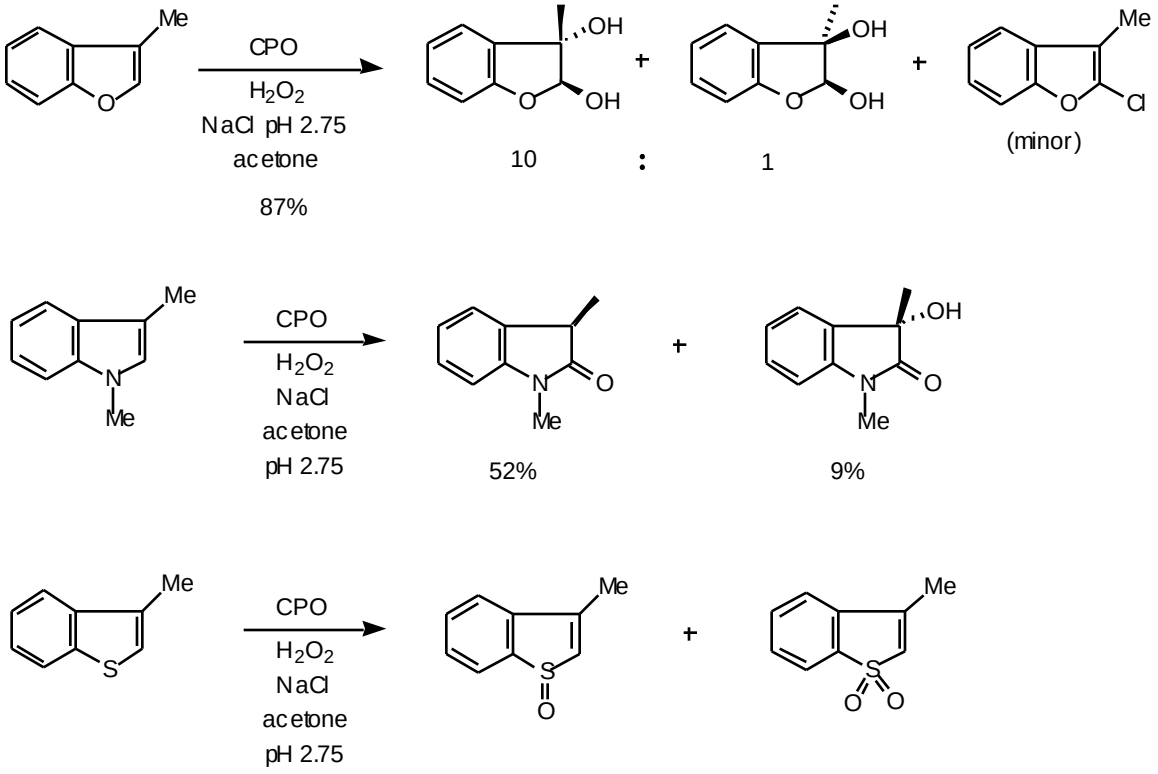
The ubiquitous enzyme chloroperoxidase (CPO) continues to find use in organic synthesis. Thus, CPO-mediated asymmetric epoxidation has led to a useful synthesis of the α-methylamino acid synthon (*R*)-dimethyl 2-methylaziridine-1,2-dicarboxylate (**B**), as summarized in Scheme 1 (*45*).

Scheme 1



An investigation of the CPO oxidation of benzofurans, indoles, and a benzothiophene has been described and a selection of these results is summarized in Scheme 2 (*46*).

Scheme 2


Me
O
CPO
H_2O_2
NaCl pH 2.75
acetone
87%
OH
OH
10
:
1
(minor)
Cl
N
Me
52%
9%
S
O

IV. References

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