

# Natural Chlorine Updates – No. 8

September 1, 1998

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](mailto:grib@Dartmouth.edu)

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

## I. Introduction

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

The coverage is approximately from April 1998 through August 1998, with inclusions of earlier material as appropriate.

This author has had published a review of natural organochlorine compounds (1).

## II. New Natural Organohalogens

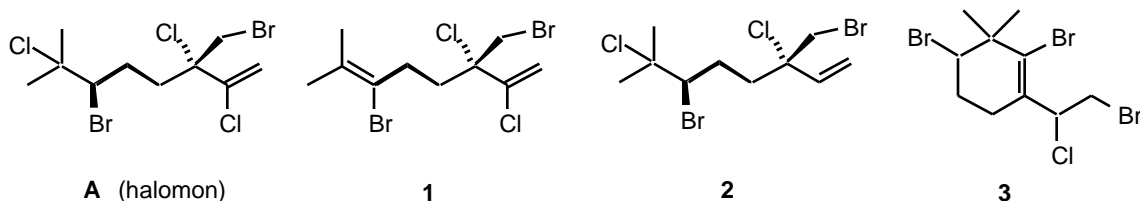
This *Updates* describes 55 new natural organohalogens, bringing the total number to 3072.

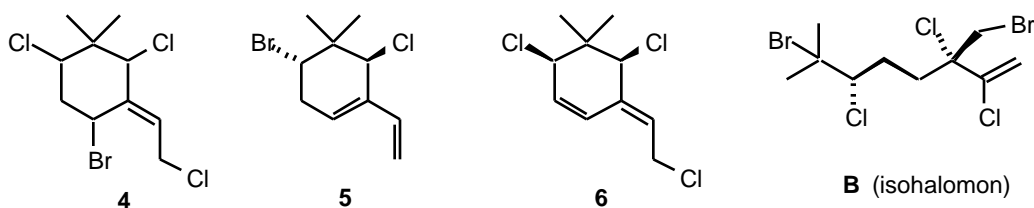
Thus, the current breakdown of such naturally produced compounds reported to date is as follows:

Organochlorine:	1814
Organobromine:	1570
Organoiodine:	88
Organofluorine:	28

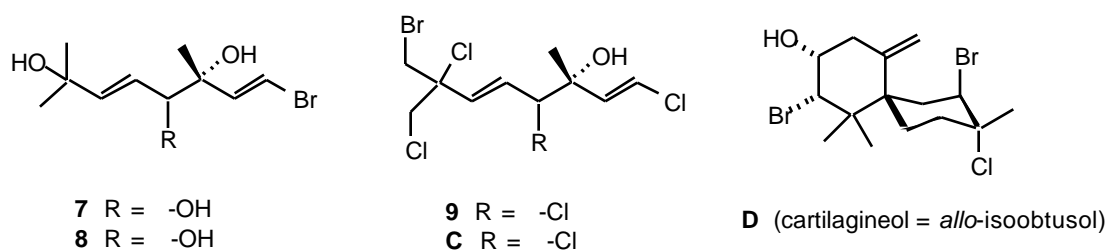
As in previous *Updates*, only newly discovered organohalogens are assigned explicit compound numbers (in bold), for ease in counting. Previously known organohalogens are indicated by capital letters (in bold).

A more complete investigation of the red alga *Portieria hornemannii* from different geographical regions (Philippines and Hawaii) has led to the isolation of several new monoterpenes **1-5** that are related to the antitumor compound halomon (**A**), which was also present (2). In addition, several other compounds were isolated, including **6**, which was missed from an earlier paper (3), and the absolute configuration of isohalomon (**B**) was established (2).



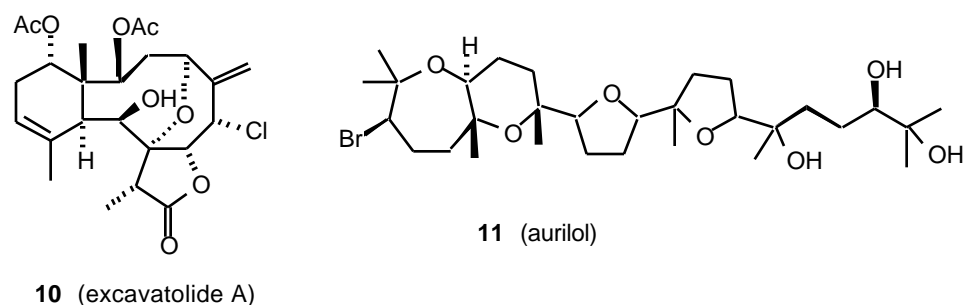


The Antarctic red alga *Pantoneura plocamioides* has yielded pantoneurotriols **7** and **8** along with compounds **9** and **C** (**4**). The former metabolites are proposed as biogenetic precursors of pantofuranoids and pantoisofuranoids, which were discussed in *Updates #4* and *#7*, respectively. Compound **C** was previously described in *Updates #7* but without stereochemistry.

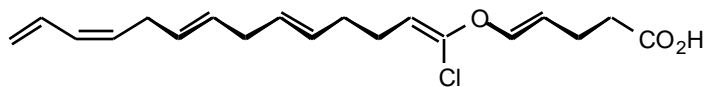
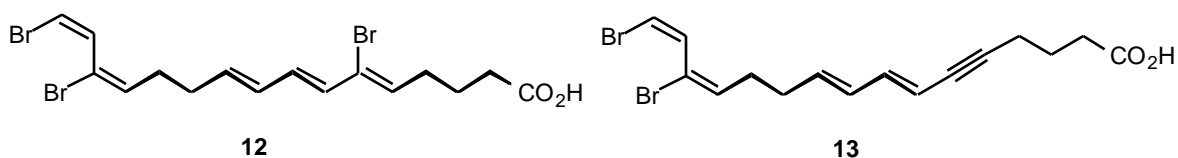
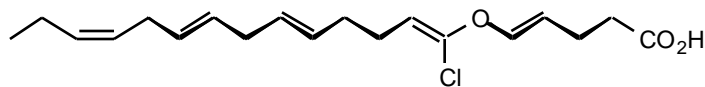
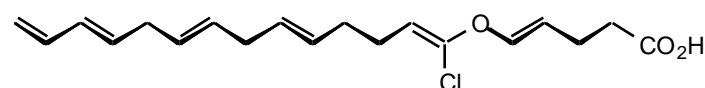
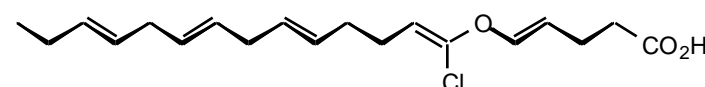
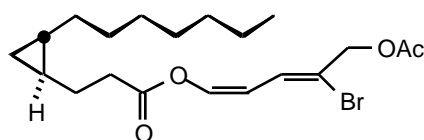


The earlier assignment for the red alga *Laurencia cartilaginea* metabolite *allo*-isooobtusol, reported in *Updates #5*, has been revised to **D** and renamed cartilagineol (**5**).

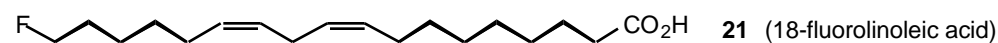
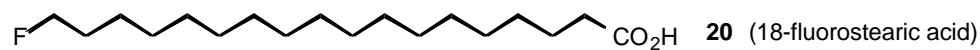
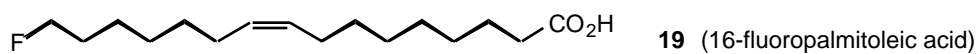
Excavatolide A (**10**) is the one chlorine-containing diterpene isolated from the Formosan gorgonian *Briareum excavatum* along with four nonhalogenated diterpenes (**6**). The cytotoxic bromotriterpene aurilol (**11**) is found in the sea hare *Dolabella auricularia* (**7**).

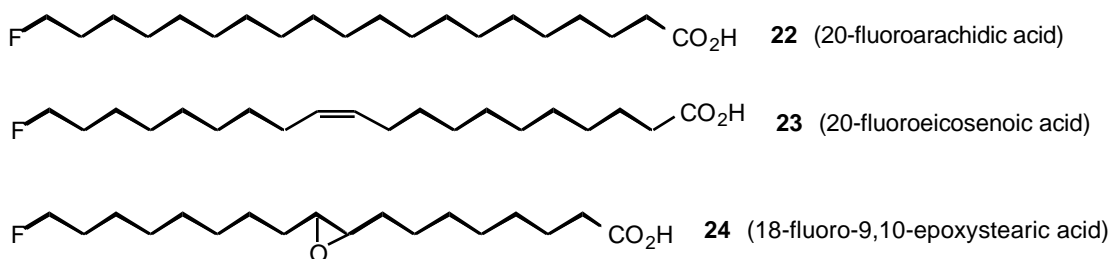


The new bromine-containing fatty acids **12** and **13** have been isolated from the sponge *Oceanapia* sp., in addition to a known fatty acid (**8**). The novel  $\gamma$ -chloro divinyl ethers maracens A (**14**), B (**15**), C (**16**), and D (**17**) are produced by *Sorangium cellulosum* (**9**). These new antibiotics have activity against mycobacteria, which is the cause of tuberculosis. The novel cyclopropyl-containing grenadadiene (**18**) has been characterized from the blue-green alga *Lyngbya majuscula* (**10**).

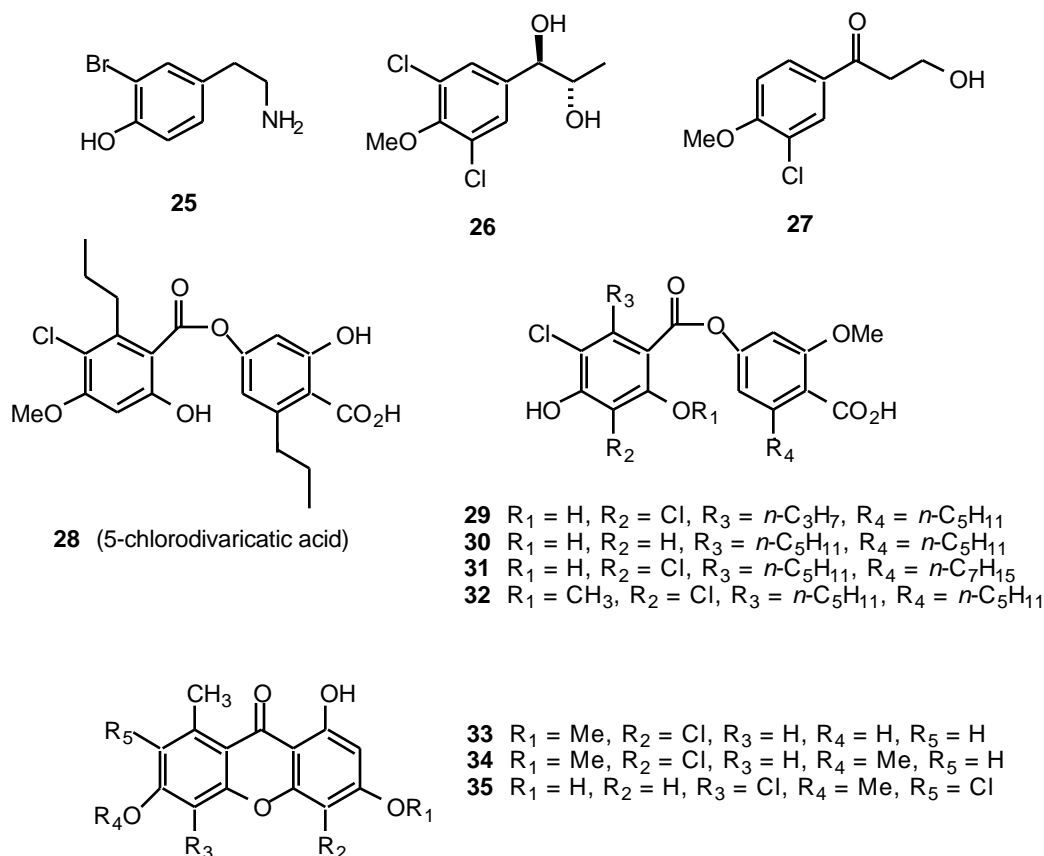
**14** (maracen A)**15** (maracen B)**16** (maracen C)**17** (maracen D)**18** (grenadadiene)

Although organofluorine compounds are the least abundant of the naturally occurring organohalogens, a recent examination of the seed oil of *Dichapetalum toxicarium* has revealed the presence of the novel  $\omega$ -fluorofatty acids **19-23** (11). In addition, strong evidence was obtained for the presence of 18-fluoro-9,10-epoxystearic acid (**24**) in this oil.



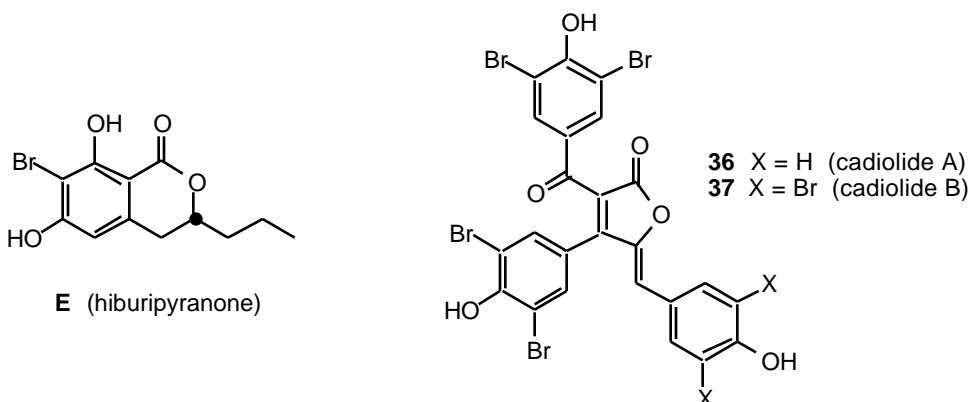


The New Zealand ascidian *Cnemidocarpa bicornuta* has yielded the simple bromine-containing phenethylamine **25** (12), and the prolific *Bjerkandera* sp. BO555 and *B. fumosa* have yielded the two new chlorinated metabolites **26** and **27** (13). The lichen *Dimelaena* cf. *radiata* contains the novel 5-chlorodivaricatic acid (**28**) (14). This depside had been previously synthesized but this is the first report of its natural occurrence. The lichen *Lecanora lividocinera* has yielded three new depsides, **29-31** (15), and *Lecanora jamesii* has furnished **32** (16). The structures of all four new compounds were confirmed by total synthesis. Lichens of the genus *Byssoloma* and *Sporopodium* have yielded the new metabolites **33-35** (16).

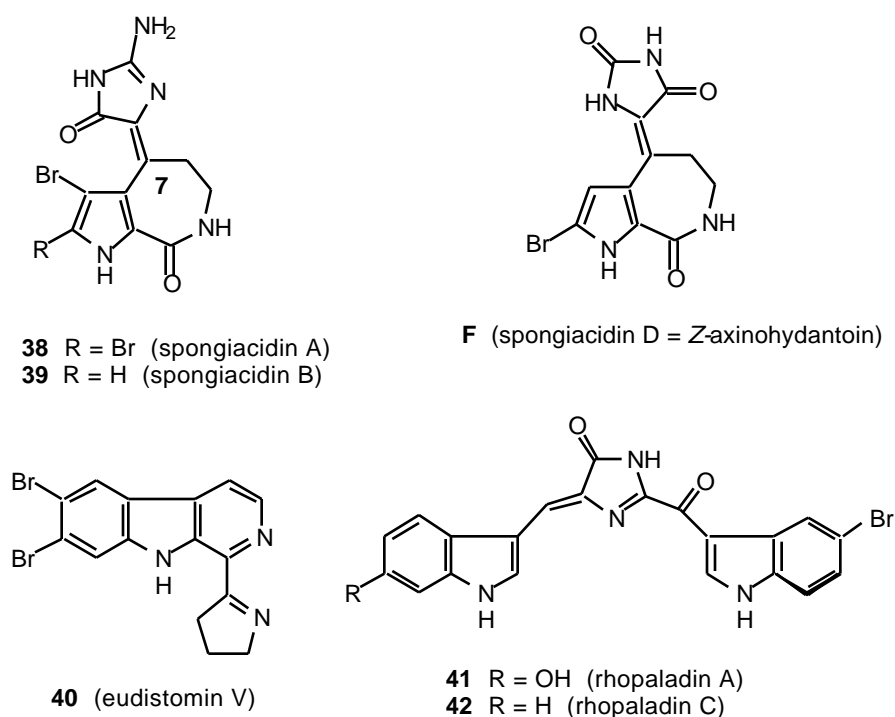


The absolute configuration of the previously described hiburipyranone (**E**) has been determined as shown to be *R* by total synthesis of both enantiomers (17). The new metabolites,

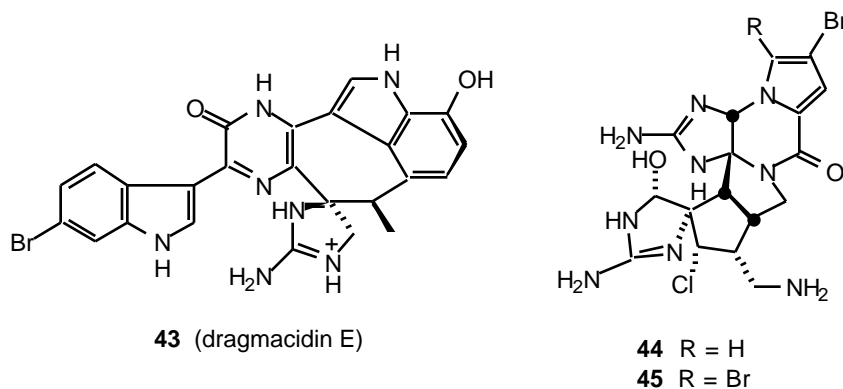
cadiolides A (**36**) and B (**37**) are found in the Indonesian ascidian *Botryllus* sp. (18). In addition, the related known rubrolide A was present in this animal.



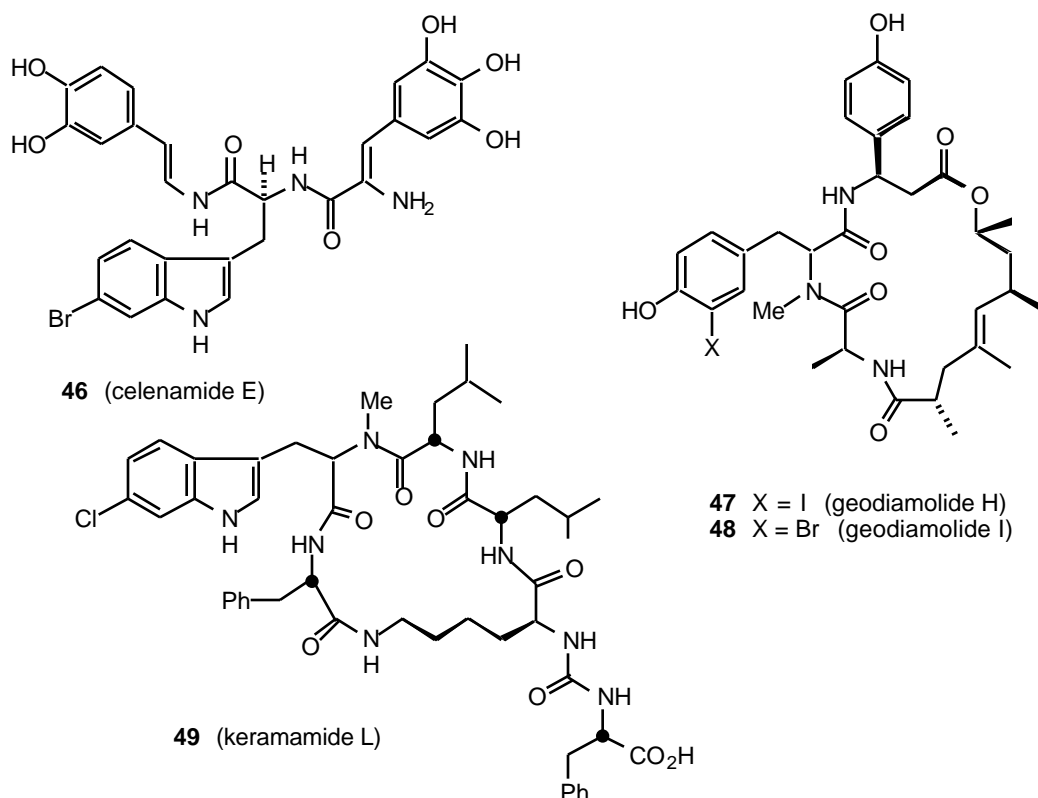
Several new bromopyrrole alkaloids, spongiacidins A (**38**), B (**39**), and D (**F**) have been isolated from a *Hymeniacidon* sponge (19). The latter was previously described in *Updates #6*. Spongiacidin A is the *7E* isomer of 3-bromohymenialdisine (*Updates #3*) and spongiacidin D is the *7Z* isomer of axinohydantoin. The Australian ascidian *Pseudodistoma aureum* has yielded the new  $\beta$ -carboline, eudistomin V (**40**) along with previously known eudistomin H and I (20). The novel bis-indole alkaloids, rhopaladin A (**41**) and C (**42**), along with two non-brominated analogues, were isolated from the marine tunicate *Rhopalaea* sp. (21). The major component is rhopaladin C. These are the first bis-indoles from a tunicate to possess an imidazolinone ring.



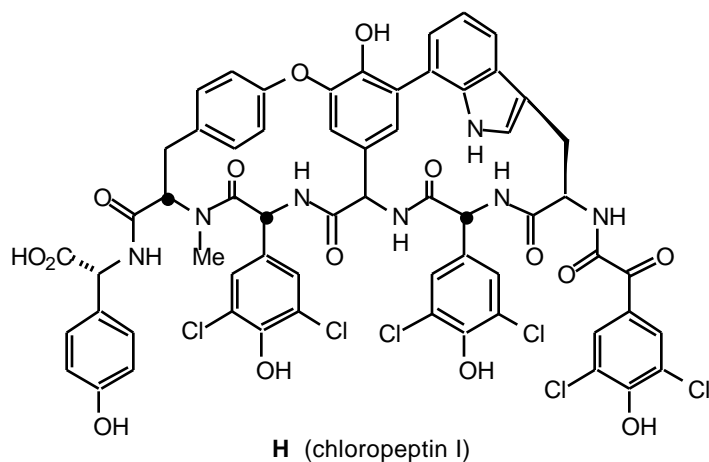
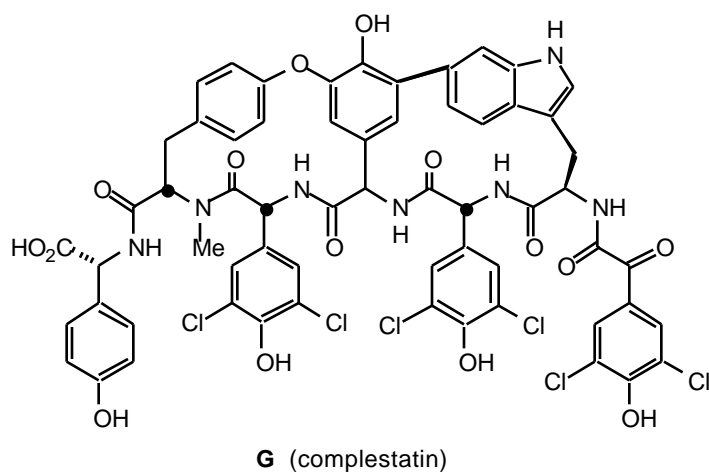
A new protein phosphatase inhibitor, dragmacidin E (**43**), along with the known dragmacidin D and isobromotopsentin, was characterized from the Southern Australian deep water sponge *Spongosorites* sp. (22). The Belau sponge *Stylotella aurantium* (formerly *S. agminata*) has yielded the two bromo derivatives, **44** and **45**, of the very complex palau'amine (23).



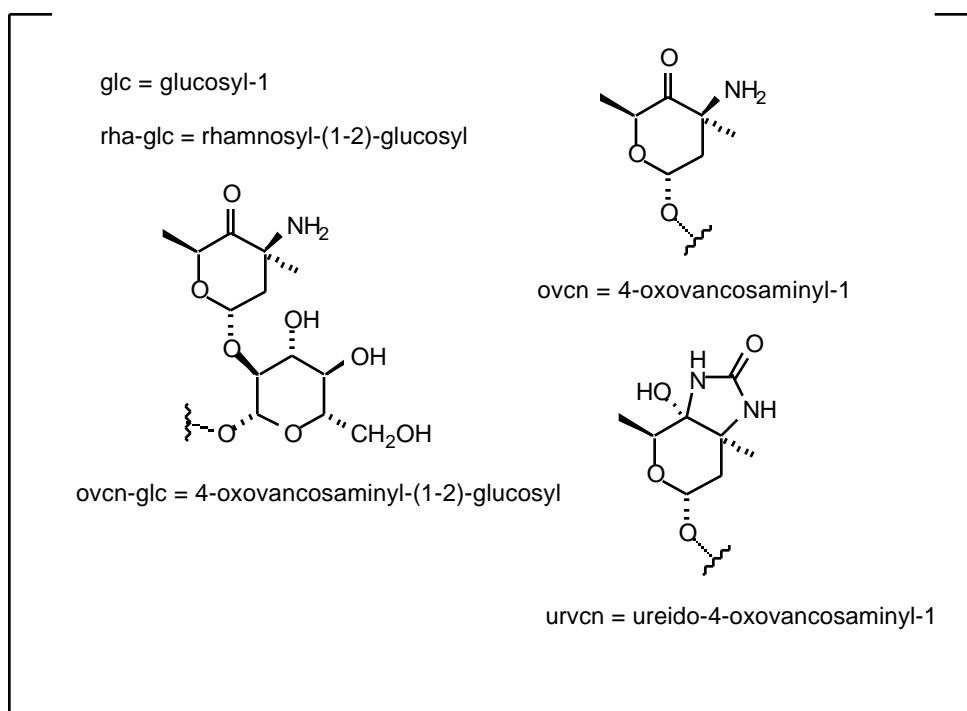
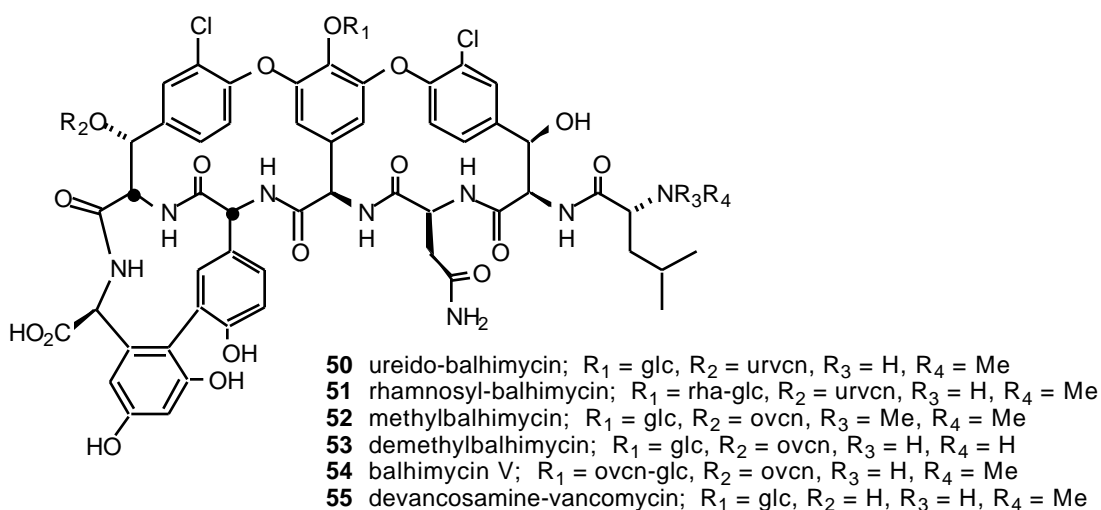
The tripeptide alkaloid celenamide E (**46**) was found in the Patagonian sponge *Cliona chilensis* (24), and the marine sponge *Geodia* sp. has yielded two new cyclodepsipeptides, geodiamolide H (**47**) and I (**48**) (25). Surprisingly, whereas **47** showed *in vitro* cytotoxicity against several human cancer cell lines, **48** was completely devoid of activity! Keramamide L (**49**) was isolated from an Okinawan *Theonella* sponge, along with the previously known keramamide A (26).



A study has shown that the previously described hexapeptide complestatin (chloropeptin II) (**G**) is converted cleanly into chloropeptin I (**H**), which was also described earlier as a natural product. In addition, this latest study has determined the absolute configuration of complestatin (27). The suggestion in this paper that chloropeptin I is an acid-catalyzed isolation artifact is refuted in a subsequent study (28).

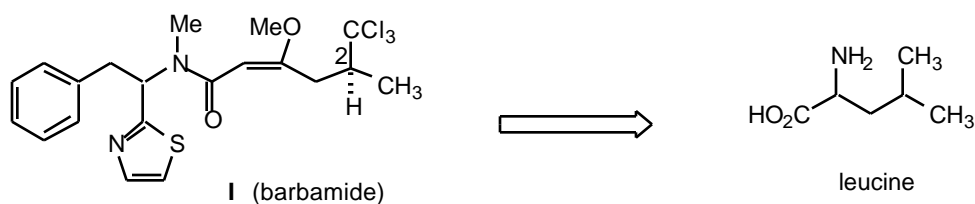


Six new 4-oxovancosamine-containing glycopeptide antibiotics, **50-55**, have been isolated from cultures of *Amycolatopsis* sp. Y-86, 21022 (29) (following page).

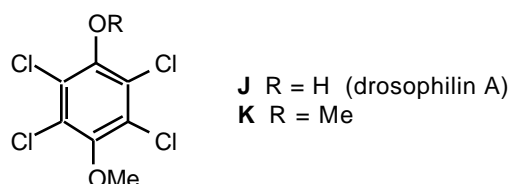


### III. Biohalogenation

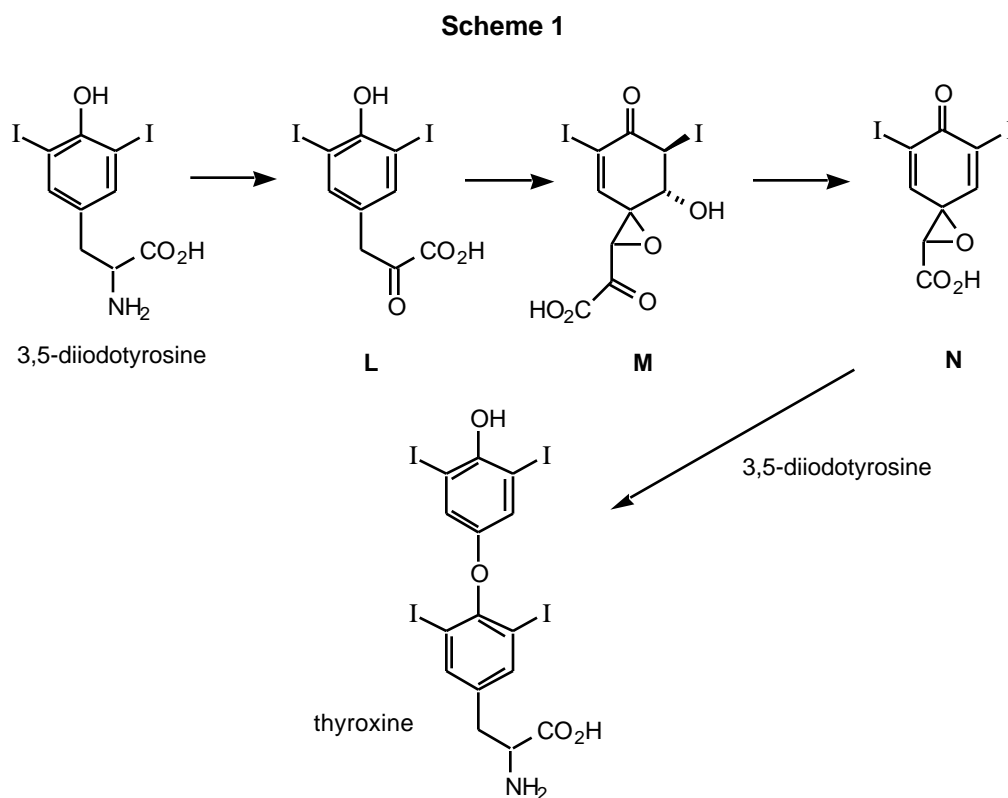
A study of the biochlorination of the blue-green alga (*Lyngbya majuscula*) metabolite barbamide (**I**) has revealed that the trichloromethyl group is derived from leucine, perhaps via a novel radical chlorination pathway (30). Using  $^{13}\text{C}$ -labeled leucines these authors determined that the stereochemistry at C-2 is (*S*) in barbamide.



A study of the *de novo* production of drosophilin A (**J**) and drosophilin A methyl ether (**K**) by basidiomycetes fungi has revealed that hydroquinone is a possible biosynthetic precursor of these metabolites (31). Moreover, these metabolites were found for the first time in strains of *Bjerkandera* and *Peniophora*, and evidence is presented that **K** has an antibiotic function in *Phellinus fastuosus*.



A study of thyroxine biosynthesis supports a pathway shown in Scheme 1 (32). Although all of the details have yet to be established, it is clear that intermediate epoxides **M** and **N** are involved, as is the pyruvic acid **L**.



The biosynthesis of fluorinated secondary metabolites by *Streptomyces cattleya*, examined using  $^{19}\text{F}$  NMR spectroscopy, shows that glycolate, or an activated derivative, may be the substrate for the biosynthesis of fluoroacetate (33). Moreover, fluoroacetate and 4-fluorothreonine are not

significantly interconverted, suggesting that one is not a biosynthetic intermediate of the other.

A study of the white rot basidiomycete fungus *Hypholoma fasciculare*, which is one of the most common higher fungi in The Netherlands and in Germany, reveals that the maximum production rate of chlorinated aromatic compounds ranges from 0.63-3.23 mg per gram of dry fungus per day (34). The major compounds are the previously known 3,5-dichloro-*p*-anisyl alcohol and 3,5-dichloro-*p*-anisic acid.

A review of the biogenesis and metabolic role of halomethanes in fungi and plants has appeared (35). This important document focuses mainly on chloromethane.

Several important advances have been made in the investigation of haloperoxidase enzymes. A thesis on the structure and function of fungal vanadium chloroperoxidase has been published (36), and the four genes necessary for the biosynthesis of pyrrolnitrin have been isolated from *Pseudomonas fluorescens* (37). Subsequent work by this same group has identified the four reaction steps that the enzymes encoded by these four genes carry out (38). A chloroperoxidase that has been isolated from the marine worm *Notomastus lobatus* is the first histidine-ligated heme-containing peroxidase capable of chlorinating substrates using chloride (39). Lignin peroxidase from the basidiomycete fungus *Phanerochaete chrysosporium*, which catalyzes the oxidation of a variety of lignin model compounds, is capable of oxidizing bromine and iodide but not chloride in the presence of hydrogen peroxide (40). This same fungus also contains a manganese peroxidase that exhibits haloperoxidase activity (41).

#### **IV. Other Natural Sources of Organohalogens**

For the first time, several fungi (*Mycena metata*, *Peniophora pseudopini*, and *Caldariomyces fumago*) have been shown to produce chloroform (42). The average production rates are 0.0007-70 µg/L culture fluid/day. The authors suggest that fungi are important sources of airborne chloroform.

An extensive review of the production of chloromethane by wood-rotting fungi has appeared (43). These authors estimate that the annual global input of chloromethane to the atmosphere from this source is 160,000 tons, of which 75% is released from tropical and subtropical forests and 86% is attributable to the fungal species *Phellinus*.

The importance of sea-salt aerosol in the marine boundary layer as a source of reactive chlorine gases ( $\text{Cl}_2$ , HOCl,  $\text{ClNO}_2$ ) has been reiterated in a brief review (44).

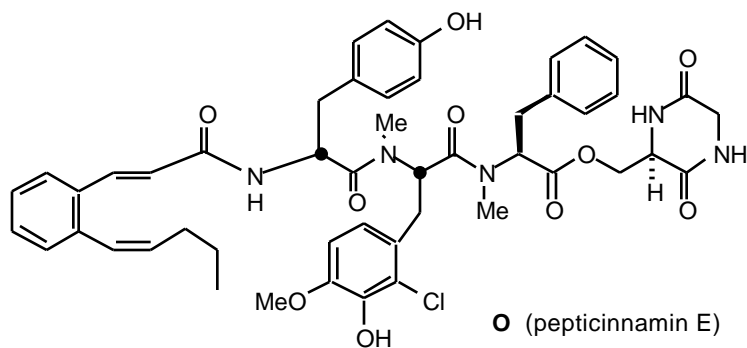
## V. Biodegradation

The chemistry and mechanism of environmental biodehalogenation has been reviewed (45), and a theoretical study of the active site of *Xanthobacter autotrophicus* haloalkane dehalogenase, with 1,2-dichloroethane as a substrate has been performed (46). The marine acorn worm *Amphitrite ornata* contains a dehaloperoxidase capable of catalyzing peroxide-dependent defluorination reactions (39, 47). One of the natural substrates of this animal is 2,4,6-tribromophenol, which is degraded initially to a dibromobenzoquinone. Thus, natural bromophenols may be biodegraded and recycled in this fashion.

## VI. Function

The extraordinary paper reported in *Updates #7* on the production of chlorophenols by the Japanese edible lily in direct response to attack by the pathogenic fungus *Fusarium oxysporum* has now been published (48).

The marine metabolite tambjamine E binds DNA very efficiently and cleaves DNA in the presence of Cu(II) and oxygen (49). The *in vitro* activity of the Ras farnesyltransferase inhibitor pepticinnamin E has been reported (50). This paper, which describes the synthesis of pepticinnamin E, also establishes the absolute configuration as shown in **O**.



The mode of action of the glycopeptide antibiotic vancomycin continues to receive intense

interest (51), and a tris-vancomycin analogue binds a peptide ligand with very high affinity (dissociation constant of  $4 \times 10^{17}$ ) (52). Similarly, a dimer of the antitumor calicheamicin binds to a DNA duplex with very high affinity (53).

The role of chloromethane as a methyl donor in the biosynthesis of veratryl alcohol biosynthesis has been probed, and labeling studies reveal that the chloromethane is derived from methionine and not *S*-adenosylmethionine (54).

Biological activities of 69 marine natural products, many of which contain halogen, have been reviewed and all but 13 possess biological activity in at least one of the three assay systems (cytotoxicity, antimalarial, antimicrobial) (55). Using the frog metabolite epibatidine as a model, Abbott Pharmaceutical Co. chemists have synthesized an analogue, ABT-594, which possesses the analgesic properties of epibatidine but not its toxicity (56). Both epibatidine and ABT-594 contain a 2-chloropyridine unit.

## VII. References

1. G.W. Gribble, "Chlorinated Compounds in the Biosphere, Natural Production," in *Encyclopedia of Environmental Analysis and Remediation*, R.A. Meyers, ed., John Wiley & Sons, Inc., New York, 1998, pp. 972-1035.
2. R.W. Fuller, *et al.*, *J. Med. Chem.* **37**, 4407-4411 (1994).
3. R.W. Fuller, J.H. Cardellina, II, Y. Kato, L.S. Brinen, J. Clardy, K.M. Snader, and M.R. Boyd, *J. Med. Chem.* **35**, 3007-3011 (1992).
4. M. Cueto, J. Darias, J. Rovirosa, and A. San-Martín, *Tetrahedron* **54**, 3575-3580 (1998).
5. M.E.Y. Francisco, M.M. Turnbull, and K.L. Erickson, *Tetrahedron Lett.* **39**, 5289-5292 (1998).
6. J.-H. Sheu, P.-J. Sung, M.-C. Cheng, H.-Y. Liu, L.-S. Fang, C.-Y. Duh, and M.Y. Chiang, *J. Nat. Prod.* **61**, 602-608 (1998).
7. K. Suenaga, T. Shibata, N. Takada, H. Kigoshi, and K. Yamada, *J. Nat. Prod.* **61**, 515-518 (1998).
8. T. Ichiba, P.J. Scheuer, and M. Kelly-Borges, *Helv. Chim. Acta* **76**, 2814-2816 (1993).
9. M. Herrmann, B. Böhlendorf, H. Irschik, H. Reichenbach, and G. Höfle, *Angew. Chem. Int. Ed.* **37**, 1253-1255 (1998).
10. N. Sitachitta and W.H. Gerwick, *J. Nat. Prod.* **61**, 681-684 (1998).
11. J.T.G. Hamilton and D.B. Harper, *Phytochemistry* **44**, 1129-1132 (1997).
12. B.S. Lindsay, C.N. Battershill, and B.R. Copp, *J. Nat. Prod.* **61**, 857-858 (1998).
13. H.J. Swarts, F.J.M. Verhagen, J.A. Field, and J.B.P.A. Wijnberg, *J. Nat. Prod.* (1998) in press.
14. J.A. Elix, H. Mayrhofer, and A. Wippel, *Aust. Lichen. News.* **36**, 25-26 (1995).
15. J.A. Elix, C.E. Barclay, H.T. Lumbsch, and J.H. Wardlaw, *Aust. J. Chem.* **50**, 971-975 (1997).
16. J.A. Elix, H.T. Lumbsch, and R. Lücking, *Bibl. Lichenol.* **58**, 81-96 (1995).
17. K. Uchida, H. Watanabe, and T. Kitahara, *Tetrahedron* **54**, 8975-8984 (1998).
18. C.J. Smith, R.L. Hettich, J. Jompa, A. Tahir, M.V. Buchanan, and C.M. Ireland, *J. Org. Chem.* **63**, 4147-4150 (1998).

19. K. Inaba, H. Sato, M. Tsuda, and J. Kobayashi, *J. Nat. Prod.* **61**, 693-695 (1998).
20. R.A. Davis, A.R. Carroll, and R.J. Quinn, *J. Nat. Prod.* **61**, 959 (1998).
21. H. Sato, M. Tsuda, K. Watanabe, and J. Kobayashi, *Tetrahedron* **54**, 8687-8690 (1998).
22. R.J. Capon, F. Rooney, L.M. Murray, E. Collins, A.T.R. Sim, J.A.P. Rostas, M.S. Butler, and A.R. Carroll, *J. Nat. Prod.* **61**, 660-662 (1998).
23. R.B. Kinnel, H.-P. Gehrken, R. Swali, G. Skoropowski, and P.J. Scheuer, *J. Org. Chem.* **63**, 3281-3286 (1998).
24. J.A. Palermo, M.F.R. Brasco, E. Cabezas, V. Balzaretto, and A.M. Seldes, *J. Nat. Prod.* **61**, 488-490 (1998).
25. W.F. Tinto, A.J. Lough, S. McLean, W.F. Reynolds, M. Yu, and W.R. Chan, *Tetrahedron* **54**, 4451-4458 (1998).
26. H. Uemoto, Y. Yahiro, H. Shigemori, M. Tsuda, T. Takao, Y. Shimonishi, and J. Kobayashi, *Tetrahedron* **54**, 6719-6724 (1998).
27. H. Jayasuriya, G.M. Salituro, S.K. Smith, J.V. Heck, S.J. Gould, S.B. Singh, C.F. Homnick, M.K. Holloway, S.M. Pitzenberger, and M.A. Patane, *Tetrahedron Lett.* **39**, 2247-2248 (1998).
28. V.R. Hegde, P. Dai, M. Patel, and V.P. Gullo, *Tetrahedron Lett.* **39**, 5683-5684 (1998).
29. L. Vertesy, H.-W. Fehlhaber, H.-W. Fehlhaber, H. Kogler, and M. Limbert, *J. Antibiot.* **49**, 115-118 (1996).
30. N. Sitachitta, J. Rossi, M.A. Roberts, W.H. Gerwick, M.D. Fletcher, and C.L. Willis, *J. Am. Chem. Soc.* **120**, 7131-7132 (1998).
31. P.J.M. Teunissen, H.J. Swarts, and J.A. Field, *Appl. Microbiol. Biotechnol.* **47** 695-700 (1997).
32. V.B. Oza, G.M. Salamonczyk, Z. Guo, and C.J. Sih, *J. Am. Chem. Soc.* **119**, 11315-11316 (1997).
33. K.A. Reid, J.T.G. Hamilton, R.D. Bowden, D. O'Hagen, L. Dasaradhi, M.R. Amin, and D.B. Harper, *Microbiology* **141**, 1385-1393 (1995).
34. F.J.M. Verhagen, F.B.J. Van Assema, B.K.H.L. Boekema, H.J. Swarts, J.B.P.A. Wijnberg, and J.A. Field, *FEMS Microbiol. Lett.* **158**, 167-178 (1998).

35. D.B. Harper in "Metal Ions in Biological Systems," Eds. H. Sigel and A. Sigel, Vol. 29, "Biological Properties of Metal Alkyl Derivatives," Marcel Dekker, New York, 1993, Chapter 11.
36. P. Barnett, "The Fungal Vanadium Chloroperoxidase: From Primary Structure to Function," Ph.D. Thesis, E.C. Slater Institute, The Netherlands, 1997.
37. P.E. Hammer, D.S. Hill, S.T. Lam, K.-H. van Pée, and J.M. Ligon, *Appl. Environ. Microbiol.* **63**, 2147-2154 (1997).
38. S. Kirner, P.E. Hammer, D.S. Hill, A. Altmann, I. Fischer, L.J. Weislo, M. Lanahan, K.-H. van Pée, and J. Ligon, *J. Bacteriol.* **180**, 1939-1943 (1998).
39. S. Franzen, M.P. Roach, Y.-P. Chen, R.B. Dyer, W.H. Woodruff, and J.H. Dawson, *J. Am. Chem. Soc.* **120**, 4658-4661 (1998).
40. V. Renganathan, K. Miki, and M.H. Gold, *Biochemistry* **26**, 5127-5132 (1987).
41. D. Sheng and M.H. Gold, *Arch. Biochem. Biophys.* **345**, 126-134 (1997).
42. E.J. Hoekstra, F.J.M. Verhagen, J.A. Field, E.W.B. de Leer, and U.A.T. Brinkman, *Phytochemistry* in press.
43. R. Watling and D.B. Harper, *Mycological Res.* **102**, 769-787 (1998).
44. W.C. Keene and D.J. Jacob, *Atmospheric Environ.* **30**, No. 6, i-iii (1996).
45. C.E. Castro, *Rev. Environ. Contam. Toxicol.* **155**, 1-67 (1998).
46. F.C. Lightstone, Y.-J. Zheng, and T.C. Bruice, *J. Am. Chem. Soc.* **120**, 5611-5621 (1998).
47. Y.P. Chen, S.A. Woodin, D.E. Lincoln, and C.R. Lovell, *J. Biol. Chem.* **271**, 4609-4612 (1996).
48. K. Monde, H. Satoh, M. Nakamura, M. Tamura, and M. Takasugi, *J. Nat. Prod.* **61**, 913-921 (1998).
49. S. Borah, M.S. Melvin, N. Lindquist, and R.A. Manderville, *J. Am. Chem. Soc.* **120**, 4557-4562 (1998).
50. K. Hinterding, P. Hagenbuch, J. Rétey, and H. Waldmann, *Angew. Chem. Int. Ed.* **37**, 1236-1239 (1998).
51. D.H. Williams, A.J. Maguire, W. Tsuzuki, and M.S. Westwell, *Science* **280**, 711-714 (1998).

52. J. Rao, J. Lahiri, L. Isaacs, R.M. Weis, and G.M. Whitesides, *Science* **280**, 708-711 (1998).
53. G. Bifulco, A. Galeone, K.C. Nicolaou, W.J. Chazin, and L. Gomez-Paloma, *J. Am. Chem. Soc.* **120**, 7183-7191 (1998).
54. D.B. Harper, W.C. McRoberts, and J.T. Kennedy, *Appl. Environ. Microbiol.* **62**, 3366-3370 (1996).
55. G.M. König, A.D. Wright, O. Sticher, C.K. Angerhofer, and J.M. Pezzuto, *Planta Med.* **60**, 532-537 (1994).
56. E. Strauss, *Science* **279**, 32-33 (1998).