Marine Natural Products as Prototype Insecticidal Agents

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In an attempt to characterize additional structural classes that could serve as prototypes for insecticides, 26 structurally diverse marine compounds were examined for insecticidal activity in a diet overlay assay against newly hatched larvae of the southern corn rootworm, *Diabrotica undecimpunctata howardi*, and the tobacco budworm, *Heliothis virescens*. Several new classes of compounds have been identified as having potential as lead compounds for the development of new marine-derived insecticides.

Keywords: *Insecticidal activity; marine natural products; briaranes; halichondramide; swinholides*

INTRODUCTION

Insects, weeds, and phytopathogenic microorganisms cause great damage to agriculture. Where pests and disease are not systematically controlled, an estimated one-third of a typical crop is lost (Melnikov, 1971). Much of the increase in agricultural productivity over the past half century has been due to the control of these pests with synthetic chemical pesticides (SCPs) (Duke, 1993). Crop protection chemicals continue to be the major tool for protecting food and fiber crops from damaging pests. In 1990, the world market value of pesticides totaled nearly $23 billion, 28% of which was for insecticides (Duke, 1993).

There are, however, several reasons to search for alternative compounds to the SCPs for controlling pests. One problem has been a significant level of resistance developing to current insecticides. From 1984 to 1990, the number of documented cases (504) of resistance by species of insects and mites increased by 13% (Georghiou, 1990). There has also been a continued and growing social legislative pressure to replace or reduce the use of SCPs in pest control because of their toxicological and environmental risks. There is, therefore, a vital interest in discovering new insecticides with fewer environmental and toxicological risks to which there is no resistance.

In the search to discover new prototype insecticides, three basic approaches are taken: using natural products as models, following a design based on biochemical principles, or employing quantitative structure−activity relationship (QSAR) analysis (Duke, 1993). The goal in all of these pursuits is to find novel chemical compounds exhibiting activities which can serve as leads to developing useful insecticides.

Since time immemorial, people have used plants with insecticidal properties to alleviate insect parasitism and protect their food supplies. Although exploitation of these traditional methods for new insecticide development is still far from complete, there is an area that was less accessible to early man which has a great potential for new insecticides. The plants, animals, and microorganisms of the marine environment, with their wide range of chemical diversity, are still an unexplored resource for new agrochemical agents (Crombie, 1990).

Marine Natural Products as Insecticides: An Overview. To date, research focused on isolating insecticidal prototype leads from marine origin has resulted in the report of about 40 active compounds. In an attempt to summarize these compounds and their activity margins, they have been categorized into six classes of chemical structures.

(1) Polyhalogenated Monoterpenes. 1α-(2-(*E*)-Chlorovinyl)-2α,4*β*,5α-trichloro-1*β*,5*β*-dimethylcyclohexane (**1**), 1α-(2-(*E*)-chlorovinyl)-2α,4α,5*β*-trichloro-1*β*,5α-dimethylcyclohexane (**2**), 1*β*-(2-(*E*)-chlorovinyl)-2*β*,4α,5α-trichloro-1α,5*β*-dimethylcyclohexane (**3**), and violacene (**4**) are cyclic polyhalogenated monoterpenes isolated from the Chilean red alga *Plocamium cartilagineum*. These compounds show insecticidal activity against the Aster leafhopper, *Macrosteles pacifrons* (San-Martin et al., 1991). Telfairine (**5**) is another related monoterpene reported from the red alga *Plocamium telfairiae*, with strong insecticidal activity against the mosquito larvae, *Culex pipiens pallens* (Watanabe et al., 1989a).

(2) Polyhalogenated C-15 Metabolites. Laurepinnacin (**6**) and isolaurepinnacin (**7**) are acetylenic cyclic ethers from the red alga *Laurencia pinnata* Yamada that demonstrate insecticidal activity (Fukuzawa and Masamune, 1981). (*Z*)-Laureatin (**8**), (*Z*)-isolaureatin (**9**), and deoxyprepacifenol (**10**) are other related compounds from the red alga *Laurencia nipponica* Yamada. They show strong insecticidal activity against the mosquito larvae, *C. pipiens pallens* (Watanabe et al., 1989b).

(3) Diterpenes. Many marine-derived diterpenes show significant insecticidal activity. They are categorized into three major subclasses.

(A) Briaranes. The briaranes are a group of highly oxidized diterpene *γ*-lactones of a highly substituted bicyclo[8.4.0] system obtained from gorgonians, soft corals, and sea pens (Grode et al., 1983). Four briaranes have been reported to be active as insecticidal agents. Brianthein Y (**11**), a briarane diterpene isolated from the Bermudian soft coral *Briareum polyanthes*, demonstrates toxicity to the grasshopper *Melanoplus bivittatus* (Grode et al., 1983). Ptilosarcenone (**12**), ptilosarcone (**13**), and ptilosarcen-12-propionate (**14**) are other insecticidal briaranes isolated from the sea pen *Ptilosa-*

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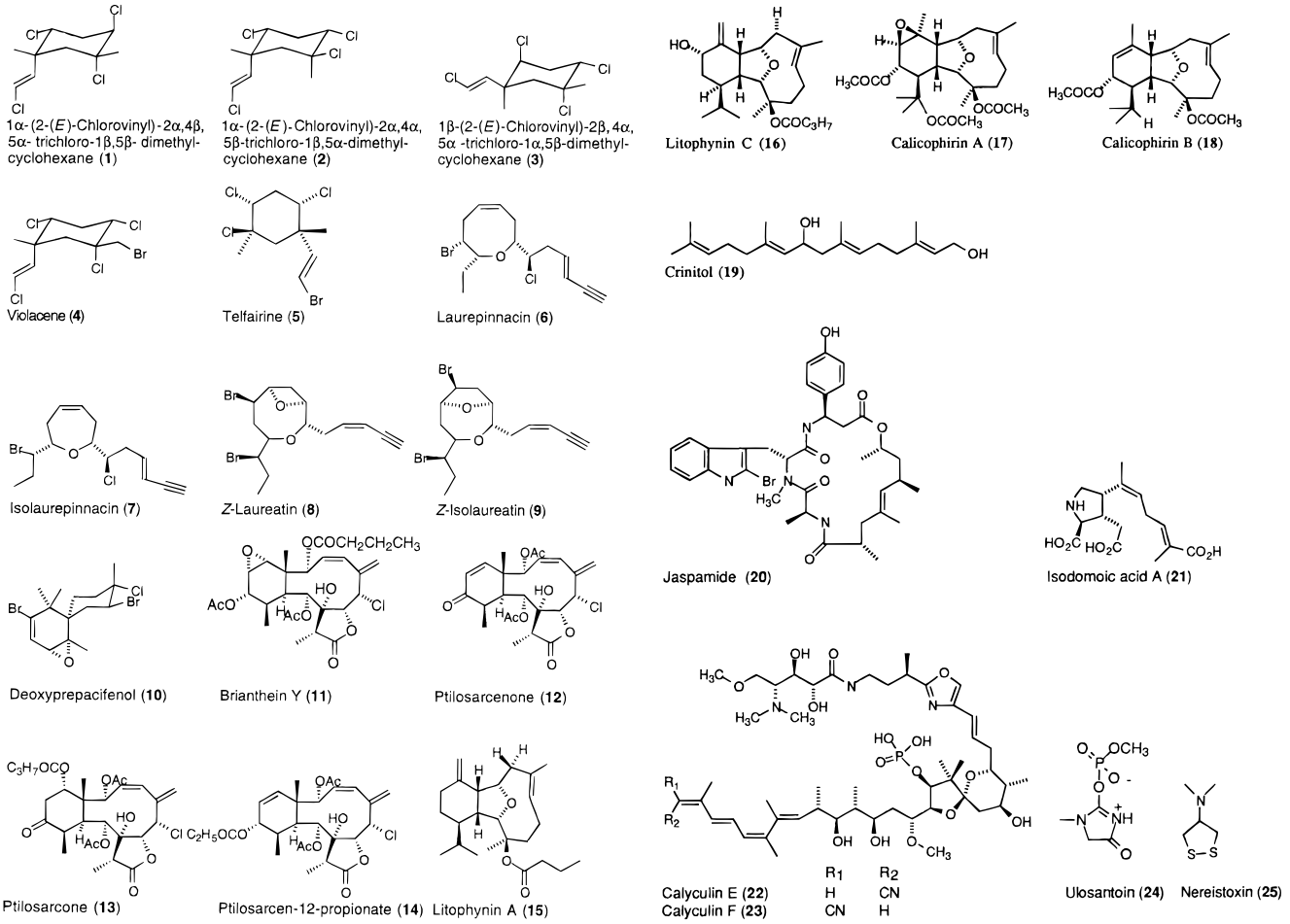
Chart 1



rcus gurney (Hendrickson and Cardellina, 1986). Ptilosarcenone (**12**) shows toxicity to the larvae of the tobacco hornworm *Manducasexta* at 250 ppm, inducing 40% mortality in the first 3 days and 90% mortality after the next 3 days. Surviving insects grew only to 20−35% of the weight of the controls during the test. Ptilosarcone (**13**) and ptilosarcen-12-propionate (**14**) did not show toxicity at 125 ppm, but the insect larvae were only 20−25% of the size of the controls (Hendrickson and Cardellina, 1986).

(B) Asbestinin-Related. Litophynins A (**15**) and C (**16**) are additional examples of highly oxidized asbestinin-related diterpene esters isolated from the soft coral *Liptophyton* sp. They showed insect growth inhibitory activity (Ochi et al., 1987, 1988). Calicophirins A (**17**) and B (**18**) are related insect growth inhibitor diterpenes isolated from the gorgonian coral *Calicogorgia* sp. (Ochi et al., 1991).

(C) Acyclic. Crinitol (**19**) is an acyclic diterpene isolated from the brown alga *Sargassumm tortile*, also showing insect growth inhibitory activity (Matsumoto and Ichikawa, 1985).

(4) Peptides and Amino Acids. Jaspamide (**20**) is a modified peptide isolated from a *Jaspis* sponge. Jaspamide shows insecticidal activity against *Heliothis virescens* with a LC_{50} of 4 ppm, as compared to 1 ppm for azadirachtin (Zabriskie et al., 1986). Isodomoic acids A (**21**), B, and C are novel amino acids from the red alga *Chondria armata*. They show significant insecticidal activity when they are injected subcutaneously into the abdomen of the American cockroach (*Periplaneta americana*) (Maeda et al., 1986).

(5) Phosphorylated Derivatives. Calyculin E (**22**) and F (**23**) are novel insecticidal metabolites isolated from the marine sponge *Discodermia* sp. They show 100% mortality against the German cockroach (*Blattella germanica*) by abdominal injection of 10 μg/male as well as against mosquito larvae (*C. pipiens pallens*) in a 10 ppm solution (Okada et al., 1991). Ulosantoin (**24**) is a phosphorylated hydantoin found in the lipophilic extract of the sponge *Ulosa ruetzleri*. Ulosantoin causes 100% mortality of tobacco hornworm larvae at 250 ppm within 24 h, and its LD_{50} value is 6 ppm. Ulosantoin is also topically lethal to the Mexican bean beetle and the southern armyworm at 0.2 and 2.0 μg, respectively. Ulosantoin is equivalent in potency to paraoxon in inhibiting acetylcholinesterase and, hence, is considered the most potent insecticide from marine origin (VanWagenen et al., 1993).

(6) Sulfur-Containing Derivatives. Nereistoxin (**25**) is a 1,2-dithiolane neurotoxic derivative isolated from a marine annelid, *Lumbriconercis heteropoda* Marenz (Okaichi and Hashimoto, 1962). Nereistoxin served as a model for the commercial insecticide Padan (VanWagenen et al., 1993).

MATERIALS AND METHODS

Marine-Derived Compounds. The 26 compounds tested represent our small marine-derived compounds library. The structure elucidation of each compound was based on the detailed analysis of 1-D and 2-D NMR and mass spectra, authenticated by comparison of their data with literature values.

Assay Insects. Two economically significant insects were used in the assay: the southern corn rootworm, *Diabrotica*

Table 1. Insecticidal Activity of the Tested Marine-Derived Compounds in Diet Overlay Feeding Assays[a]

compound	class	ref	CR		TB	
			RSt	% Mrt	RSt	% Mrt
jaspamide (**20**)	modified peptide	Zabriskie et al., 1986	3	72.5	3	87.5
juncin E (**26**)	briarane diterpene	Hamann et al., 1996	3	86.3	3	93.8
gemmacolide A (**27**)	briarane diterpene	He and Faulkner, 1991	3	79.4	2	25.0
gemmacolide D (**28**)	briarane diterpene	He and Faulkner, 1991	0	0.0	0	0.0
halichondramide (**29**)	macrolide	Kernan and Faulkner, 1987	3	86.3	3	75.0
swinholide A (**30**)	dimeric macrolide	Kitagawa et al., 1990	3	93.1	3	100.0
swinholide B (**31**)	dimeric macrolide	Kobayashi et al., 1990	3	93.1	2.5	56.3
kahalalide F	cyclic polypeptide	Hamann and Scheuer, 1993	1	38.2	2.5	12.5
10-isothiocyanto-4-amorphene	sesquiterpene	Burreson et al., 1975	1	3.9	2	6.3
sarasinoside C_1	norlanostane oligoglycoside	Kitagawa et al., 1987	0	3.9	0	0.0
heteronemin	sesterterpene	Kazlauskas et al., 1976	2	0.0	2.5	18.8
latrunculin B	macrolide	Groweiss et al., 1983	2	0.0	3	31.3
puupehenone	shikimate sesquiterpene	Hamann et al., 1993	0	0.0	1	6.3
15-oxopuupehenol	shikimate sesquiterpene	Nasu et al., 1995	0	0.0	0	0.0
puupehedione	shikimate sesquiterpene	Hamann et al., 1993	0	0.0	0	0.0
sigmosceptrellin	norsesterterpene peroxide	Albericci et al., 1979	0	0.0	0	6.3
muqubilin	norsesterterpene peroxide	Kashman and Rotem, 1979	0	0.0	0	0.0
guaiane-4,10-diol	sesquiterpene	Faulkner, 1984	0	0.0	0	6.3
5-*epi*-sinuleptolide	cembranoid diterpene	Bowden et al., 1978	0	0.0	0	6.3
sinuleptolide	cembranoid diterpene	Shoji et al., 1993	0	0.0	0	0.0
singardin	norcembranoid dimer	El Sayed and Hamann, 1996	0	0.0	0	0.0
sarcophine	cembranoid diterpene	Groweiss et al., 1974	0	0.0	0	0.0
kahalalide A	cyclic polypeptide	Hamann, 1992	0	0.0	0	0.0
moloka'iamine	dibrominated tyrosine	Hamann et al., 1993	0	0.0	0	0.0
ircinin-1	furanosesterterpene	Cimino et al., 1972	0	0.0	0	0.0
peridinin	carotene	McLean et al., 1992	0	0.0	0	0.0

[a] Against corn rootworm (*Diabrotica undecimpunctata howardi*) (CR) and tobacco budworm (*Heliothis virescens*) (TB) larvae, at 100 ppm. RSt = relative stunting compared to untreated controls: 0 = no stunting; 1 = 25−50% stunting; 2 = 50−75% stunting; 3 = 75−95% stunting. % Mrt = % mortality (wells with no survivors).

undecimpunctata howardi (Barber), order Coleoptera, family Chrysomelidae, and the tobacco budworm, *Heliothis virescens* (Fabr.), order Lepiduptera, family Sphingidae (Davidson and Peairs, 1966).

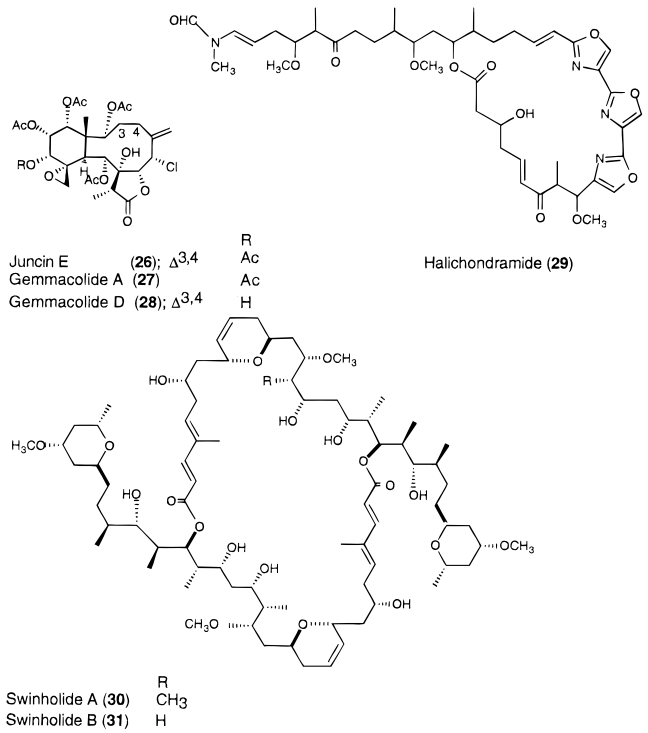
Assay Procedure. Purified samples (1 mg each) were dissolved in 50 μL of DMSO or acetone and diluted to 1 mg/mL with either 1% DMSO or 50% acetone. Only one dilution per sample was used (100 ppm). Ethanol was not used due to its insect toxicity. Microtiter plates with 96 wells were prepared with a synthetic insect diet (0.2 mL/well), and 20 μL of the 1 mg/mL sample solution was pipetted onto the top of each of 16 wells for each insect. Negative controls of 6% DMSO and 51% acetone were similarly added to diet wells. Plates were allowed to surface dry under a hood. After drying, 4−6 insect eggs (12−24 h from hatching) were pipetted into each well in 25 μL of 0.2% agar. The plates were again allowed to surface dry and then were covered with a layer of Mylar film and sealed with a tacking iron. An insect pin was used to create an aeration hole in the Mylar over each well. Plates were incubated at 26 °C for 6 days, at which time the plates were evaluated; wells with survivors were counted, and a qualitative assessment of survivor size was made.

Titration. The six most active compounds were diluted to 100, 10, and 1 ppm in the appropriate diluent (either 6% DMSO or 51% acetone) and overlaid on diet as described above. Final concentrations of compounds **26**−**28**, **30**, and **31** in diet were 10, 1, and 0.1 ppm. Halichondramide (**29**) was limited in quantity and, therefore, was tested in final concentrations of 3, 0.3, and 0.03 ppm. Sixteen individual diet wells per dilution (48 diet wells) were used for each compound. Assays were incubated and evaluated as described in the initial testing. To avoid any misleading results due to *H. virescens* cannibalism, the mortality results are qualified as "wells with no survivors".

RESULTS AND DISCUSSION

Twenty-six structurally diverse marine-derived compounds were tested (Table 1). Juncin E (**26**) (Hamann et al., 1996), gemmacolide A (**27**) (He and Faulkner, 1991), halichondramide (**29**) (Kernan and Faulkner, 1987), and swinholides A and B (**30, 31**) (Kitagawa et al., 1990; Kobayashi et al., 1990), as well as the previously tested depsipeptide jaspamide (**20**) (Zabriskie et al., 1986), showed more than 70% mortality to both test insects.

Chart 2



The antifungal macrolide halichondramide (**29**) (Kernan and Faulkner, 1987), isolated from the Kwajalein sponge of the genus *Halichondria*, showed significant insecticidal activity at 3 ppm, especially against tobacco budworm (Tables 1 and 2). We isolated swinholides A (**30**) and B (**31**) from the Red Sea sponge *Theonella swinhoei* (Kitagawa et al., 1990; Kobayashi et al., 1990).

Table 2. Quantitative Insecticidal Activity of the Preliminary Active Compounds in Diet Overlay Feeding Assays[a]

	corn rootworm			tobacco budworm		
		% LSt[c]			% LSt[c]	
compound	est LC_{50}[b]	10 ppm	1 ppm	est LC_{50}[b]	10 ppm	1 ppm
jaspamide (**20**)	10−100	15	0	10−100	85	15
juncin E (**26**)	10−100	0	0	10−100	15	0
gemmacolide A (**27**)	10−100	30	15	>100	15	0
halichondramide (**29**)	10−100	30[d]	0[e]	10−100	85[d]	0[e]
swinholide A (**30**)	10−100	85	30	10−100	85	0
swinholide B (**31**)	10−100	30	15	~100	0	0

[a] Against corn rootworm (*Diabrotica undecimpunctata howardi*) and tobacco budworm (*Heliothis virescens*) larvae. [b] est LC_{50} = estimated LC_{50} range. [c] LSt = larval stunting. [d] At 3 ppm. [e] At 0.3 ppm.

This is the first report of swinholide B (**31**) in the Red Sea collection of the sponge *T. swinhoei*. Swinholides A and B are dimeric macrolides that show potent *in vitro* cytotoxic activity against murine leukemia L1210 and KB human epidermoid carcinoma cell lines (IC_{50} (μg/mL) 0.004 and 0.011, respectively) (Kobayashi et al., 1994). We have reported the *in vitro* antimalarial activity of halichondramide and swinholide A elsewhere (El Sayed et al., 1996). Compounds **29**−**31** display in the initial testing 75−100% mortality of both corn rootworm and tobacco budworm (Table 1). On titration, they display an LC_{50} range of 10−100 ppm and induce 30, 85, and 30% corn rootworm larval stunting, respectively. Both halichondramide and swinholide A cause 85% tobacco budworm larval stunting (Table 2). The insecticidal activity of these compounds (**29**−**31**) is reported here for the first time, and further QSAR studies are planned. This report illustrates the necessity to examine various marine macrolides as potential prototype insecticides.

Gemmacolide A (**27**) showed high activity (79.4%) against corn rootworm with severely stunted survivors, indicating insect growth inhibition (Tables 1 and 2). The significance of this first report of insecticidal activity of the two known briarane diterpenes, juncin E (**26**) and gemmacolide A (**27**), is their low cytotoxic activity, unlike the swinholides and halichondramide. The high yield of both compounds (**26**, **27**) and the selectivity of **27** to the corn rootworm render them suitable candidates for further investigations.

Compared with the previously reported insecticidal briaranes **11**−**14**, both juncin E and gemmacolide A differ in having an 11,20-epoxy function instead of β-methyl groups. Unlike all other tested briaranes, gemmacolide A has a saturated 3,4 position, and it is worth noting that gemmacolide D (**28**), possessing a 12-hydroxyl instead of an acetate group, as in juncin E, lacks any insecticidal activity, indicating that the 12-hydroxyl group has a negative effect on activity. Testing of this entire group of diterpenes in various insect assays should provide an indication of the structure−activity relationship and the required functional group(s) for the observed activity (Cardellina, 1986).

CONCLUSION

The identification of new natural product structural classes active against insects will overcome the pest-resistance problem and provide environmentally safer insecticides. The marine environment, with its chemical diversity, clearly holds an enormous potential to provide leads for the development of insecticidal agents. Since more than 70% of the planet is covered by oceans, the marine flora offers an important resource of new chemotypes to combat harmful insects. Many marine-derived structural classes have not yet been examined for their insecticidal activity. Further QSAR studies of these marine natural products could lead to new and more selective insecticidal agents.

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LITERATURE CITED

Albericci, M.; Collart-Lampereur, M.; Braekman, J. C.; Daloze, D.; Tursch, B.; Declercq, J. P.; Germain, G.; Van Meerssche, M. Chemical studies of marine invertebrates XLI: Sigmosceptrellin-A methyl ester; a norsesterterpeneoid peroxide from the sponge *Sigmosceptrella laevis*. *Tetrahedron Lett.* **1979**, *20*, 2687−2690.

Bowden, B. F.; Coll, J. C.; Mitchell, S. J.; Mulder, J.; Stokie, G. J. Studies of Australian soft corals. IX. A novel norditerpene from the soft coral *Sinularia leptoclados*. *Aust. J. Chem.* **1978**, *31*, 2049−2056.

Burreson, B. J.; Christophersen, C.; Scheuer, P. J. Co-occurrence of two terpenoid isocyanide-formamide pairs in a marine sponge (*Halichondrida* sp.) *Tetrahedron* **1975**, *31*, 2015−2018.

Cardellina, J. H., II. Marine natural products as leads to new pharmaceutical and agrochemical agents. *Pure Appl. Chem.* **1986**, *58*, 365−374.

Cimino, G.; De Stefano, S.; Minale, L.; Fattorusso, E. Ircinin-1 and -2, linear sesterterpenes from the sponge *Ircinia oros*. *Tetrahedron* **1972**, *28*, 333−341.

Crombie, L. Natural models for the design of insect control compounds: the mammeins. In *Recent Advances in the Chemistry of Insect Control II*; The Royal Society of Chemistry Special Publication 79; Crombie, L., Ed.; The Royal Society of Chemistry: Cambridge, England, 1990; pp 23−51.

Davidson, R. H.; Peairs, L. M., *Insect Pests of Farm, Garden and Orchard*, 6th ed.; John Wiley and Sons: New York, 1966; pp 182−185 and 284−287.

Duke, S. O.; Menn, J. J.; Plimmer, J. R. Challenges of pest control with enhanced toxicological and environmental safety, an overview. In *Pest Control with Enhanced Environmental Safety*; ACS Symposium Series 524; Duke, S. O., Menn, J. J., Plimmer, J. R., Eds.; American Chemical Society: Washington, DC, 1993; pp 1−13.

El Sayed, K. A.; Hamann, M. T. A new norcembranoid dimer from the Red Sea soft coral *Sinularia gardineri*. *J. Nat. Prod.* **1996**, *59*, 687−689.

El Sayed, K. A.; Dunbar, D. C.; Goins, D. K.; Cordova, C. R.; Perry, T. L.; Wesson, K. J.; Sanders, S. C.; Janus, S. A.; Hamann, M. T. The marine environment: A resource for prototype antimalarial agents. *J. Nat. Toxins* **1996**, *5*, 261−285.

Faulkner, D. J. Marine natural products. *Nat. Prod. Rep.* **1984**, *1*, 551−598.

Fukuzawa, A.; Masamune, T. Laurepinnacin and isolaurepinnacin; new acetylenic cyclic ethers from the marine red alga *Laurencia pinnata* Yamada. *Tetrahedron. Lett.* **1981**, *22*, 4081−4084.

Georghiou, G. P. Managing resistance to agrochemicals from fundamental research to practical strategies. In *Overview of Insecticide Resistance*; ACS Symposium Series 421; Green,

M. B., LeBaron, H. M., Moberg, W. K., Eds.; American Chemical Society: Washington, DC, 1990; pp 18−41.
Grode, S. H.; James, T. R., Jr.; Cardellina, J. H., II. Molecular structures of Briantheins, new insecticidal diterpenes from *Briareum polyanthes*. *J. Org. Chem*. **1983**, *48*, 5203−5207.
Groweiss, A.; Shmeuli, U.; Zadock, E.; Kashman, Y.; Neeman, I. Sarcophine, a new epoxy cembranoid from marine origin. *Tetrahedron* **1974**, *30*, 2817−2824.
Groweiss, A.; Shmeuli, U.; Kashman, Y. Marine toxins of *Latrunculia magnifica*. *J. Org. Chem*. **1983**, *48*, 3512−3516.
Hamann, M. T. Biologically active constituents of some marine invertebrates. Ph.D. Dissertation, University of Hawaii, Honolulu, HI, 1992; *Chem. Abstr*. **1992**, *120* (19), 240579k.
Hamann, M. T.; Scheuer, P. J. Kahalalide F: A bioactive depsipeptide from the sacoglossan mollusk *Elysia rufescens* and the green alga *Bryopsis* sp. *J. Am. Chem. Soc*. **1993**, *115*, 5825−5826.
Hamann, M. T.; Scheuer, P. J.; Kelly-Borges, M. Biogenetically diverse, bioactive constituents of a sponge, order Verongida: bromotyramines and sesquiterpene-shikimate derived metabolites. *J. Org. Chem*. **1993**, *58*, 6565−6569.
Hamann, M. T.; Harisson, K. N.; Carroll, A. R.; Scheuer, P. J. Briarane diterpenes from Micronesian gorgonians. *Heterocycles* **1996**, *42*, 325−331.
He, H. Y.; Faulkner, D. J. New chlorinated diterpenes from the gorgonian *Junceella gemmacea*. *Tetrahedron* **1991**, *47*, 3271−3280.
Hendrickson, R. L.; Cardellina, J. H., II. Structure and stereochemistry of insecticidal diterpenes from the sea pen *Ptilosarcus gurneyi*. *Tetrahedron* **1986**, *42*, 6565−6570.
Kashman, Y.; Rotem, M. Muqubilin, a C24-isoprenoid from a marine sponge. [(brown; *Prianos* (Gray) sp. Hymeniacidonidae)]. *Tetrahed*ron *Lett*. **1979**, *20*, 1707−1708.
Kazlauskas, R.; Murphy, P. T.; Quinn, R. J.; Wells, R. J. Heteronemin, a scalarin type sesterterpene from the sponge *Heteronema erecta*. *Tetrahedron Lett*. **1976**, *17*, 2631−2634.
Kernan, M. R.; Faulkner, D. J. Halichondramide, an antifungal macrolide from the sponge *Halichondria* sp. *Tetrahedron Lett*. **1987**, *28*, 2809−2812.
Kitagawa, I.; Kobayashi, M.; Okamoto, Y.; Yoshikawa, M.; Hamamoto, Y. Sarasinosides A1, B1, and C1; norlanostane-triterpenoid oligoglycosides from sponge *Asteropus sarasinosum*. *Chem. Pharm. Bull*. **1987**, *35*, 5036−5039.
Kitagawa, I.; Kobayashi, M.; Katori, T.; Yamashita, M. Absolute stereostructure of swinholide A, a potent cytotoxic macrolide from the Okinawan marine sponge *Theonella swinhoei*. *J. Am. Chem. Soc*. **1990**, *112*, 3710−3712.
Kobayashi, M.; Tanaka, J.; Katori, T.; Kitagawa, I. Three new cytotoxic dimeric macrolides, swinholides B, and C, and isoswinholide A, congeners of swinholide A, from the marine sponge *Theonella swinhoei*. *Chem. Pharm. Bull*. **1990**, *38*, 2960−2966.
Kobayashi, M.; Kawazoe, K.; Okamoto, T.; Sasaki, T.; Kitagawa, I. Marine natural products. 31. Structure−activity correlation of a potent cytotoxic dimeric macrolide swhinolide A, from Okinawan marine sponge *Theonella swinhoei*. *Chem. Pharm. Bull*. **1994**, *42*, 19−26.
Maeda, M.; Kodama, T.; Tanaka, T.; Yoshizumi, H.; Takemoto, T.; Nomoto, K.; Fujita, T. Structures of isodomoic acids A, B, and C, novel insecticidal amino acids from the red alga *Chondria armata*. *Chem. Pharm. Bull*. **1986**, *34*, 4892−4895.
Matsumoto, K.; Ichikawa, T. Absolute configuration of crinitol. An acyclic diterpene insect growth inhibitor from the brown alga *Sargassum tortile*. *Chem. Lett*. **1985**, 249−252.
McLean, S.; Reynolds, W. F.; John, L. M. D.; Tinto, W. F. Total assignment of the ^{1}H- and ^{13}C- spectra of peridinin. *Magn. Reson. Chem*. **1992**, *30*, 362−363.
Melnikov, N. N. In *Chemistry of Pesticides*; Gunther, F. A., Gunther, J. D., Eds.; Springer-Verlag: New York, 1971; p 1.
Nasu, S. S.; Yeung, B. K. S.; Hamann, M. T.; Scheuer, P. J.; Kelly-Borges, M.; Goins, D. K. Puupehenone-related metabolites from Hawaiian sponge, *Hyrtios* sp. *J. Org. Chem*. **1995**, *60*, 7290−7292.
Ochi, M.; Futatsugi, K.; Kotsuki, H.; Ishii, M.; Shibata, K. Litophynin A and B, two new insect growth inhibitory diterpenoids from the soft coral *Litophyton* sp. *Chem. Lett*. **1987**, 2207−2210.
Ochi, M.; Futatsugi, K.; Kume, Y.; Kotsuki, H.; Asao, K.; Shibata, K. Litophynin C, a new insect growth inhibitory diterpenoid from a soft coral *Litophyton* sp. *Chem. Lett*. **1988**, 1661−1662.
Ochi, M.; Yamada, K.; Shirase, K.; Kotsuki, H. Calicophirins A and B, two new insect growth inhibitory diterpenoids from a gorgonian coral *Calicogorgia* sp. *Heterocycles* **1991**, *32*, 19−21.
Okada, A.; Watanabe, K.; Umeda, K.; Miyakado, M. Calyculin E and F, novel insecticidal metabolites, from the marine sponge, *Discodermia* sp. *Agric. Biol. Chem*. **1991**, *55*, 2765−2771.
Okaichi, T.; Hashimoto, Y. The structure of nereistoxin. *Agric. Biol. Chem*. **1962**, *26*, 224−227.
San-Martin, A.; Negrete, R.; Rovirosa, J. Insecticide and acaricide activities of polyhalogenated monoterpenes from Chilean *Plocamium cartilagineum*. *Phytochemistry* **1991**, *30*, 2165−2169.
Shoji, N.; Umeyama, A.; Arihara, S. A novel norditerpenoid from the Okinawan soft coral *Sinularia* sp. *J. Nat. Prod*. **1993**, *56*, 1651−1653.
VanWagenen, B. C.; Larsen, R.; Cardellina, J. H., II; Randazzo, D.; Lidert, Z. C.; Swithenbank, C. Ulosantoin, a potent insecticide from the sponge *Ulosa ruetzleri*. *J. Org. Chem*. **1993**, *58*, 335−337.
Watanabe, K.; Miyakado, M.; Ohno, N.; Okada, A.; Yanagi, K.; Moriguchi, K. A polyhalogenated insecticidal monoterpene from the red alga, *Plocamium telfairiae*. *Phytochemistry* **1989a**, *28*, 77−78.
Watanabe, K.; Umeda, K.; Miyakado, M. Isolation and identification of three insecticdal principles from the red alga *Laurencia nipponica* Yamada. *Agric. Biol. Chem*. **1989b**, *53*, 2513−2515.
Zabriskie, M. T.; Klocke, J. A.; Ireland, C. M.; Marcus, A. H.; Molinski, T. F.; Faulkner, D. J.; Xu, C.; Clardy, J. C. Jaspamide; a modified peptide from a *Jaspis* sponge; with insecticidal and antifungal activity. *J. Am. Chem. Soc*. **1986**, *108*, 3123−3124.

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