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MARINE NATURAL PRODUCTS: THE PAST TWENTY YEARS AND BEYOND

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Abstract -- Contributions of marine natural products research to organic chemistry, marine biology, and biomedicine are illustrated by examples from the author's laboratory.

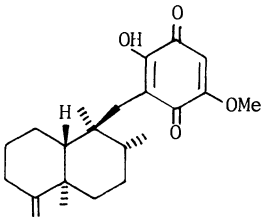
INTRODUCTION

When Professor Julio Martín invited me to present the opening lecture of this Symposium, he suggested a format that might encompass some research from my laboratory as well as my current views of marine natural products research in general. I accepted the invitation without hesitation since, as most of you know, the organic chemistry of marine organisms has been the principal focus of my research for more than twenty years. During that period all of us have witnessed exciting progress in a field of research that was largely unexplored during the preceding one hundred years, when natural products chemistry prospered and was synonymous with terrestrial natural products chemistry, and in many parts of the world it was organic chemistry. In a 1977 review of the chemistry of marine mollusks (1) I observed, "Three major sources have fed this remarkable stream of new chemistry: man's concern for his own species, man's interspecific curiosity, and the nature of man's intellect. In a pragmatic sense, we might think of these sources as medical, scientific, and serendipitous routes to marine natural products." Five years later I still hold these views. In the framework of my own involvement, and hence of this lecture, I will slightly rearrange these three topics. I will begin this talk with serendipitous research, continue with some of our toxin research, and conclude with our attempts to provide chemical clues to unsolved problems in marine ecology.

SERENDIPITOUS STUDIES

When I joined the faculty of the University of Hawaii in 1950, my practical knowledge of marine organisms was entirely culinary. I had never had any formal instruction in any branch of marine biology, and I had never even been to an aquarium. I saw my first sea urchin on a visit to Hanauma Bay--now a protected marine preserve--and I was fascinated by the colors of the shells. Inquiries among my colleagues in marine zoology and a visit to the library convinced me that research in that area might be fruitful, although Japanese and European workers had been studying echinoderm pigments for many years. Before we eventually got off the ground, though, we went through a lengthy induction period: our approach was naive at best, and we were still heavily preoccupied with the chemistry of terrestrial endemic Hawaiian plants. As was the case with much of natural products chemistry of the period, advances in separation methods and in instrumentation, particularly in proton NMR and mass spectrometry, provided the tools for elucidating the structures of these rather simple compounds (2). Our attempts, and those of others, to relate the echinoderm pigments to a biological function in the invertebrate host or to a physiological activity in mammalian systems were never successful. Not surprisingly, the chemistry of echinoderm pigments has received little further attention, even from synthetic chemists, despite the fact that no good methods exist for the synthesis of highly substituted napthoquinones. In contrast to the low level of activity in quinone chemistry, interest in carotenoid pigments has remained high (3), which in a large measure has been due to Professor Liaaen-Jensen's singular devotion and to the well-established biological significance of this class of pigments.

As my knowledge of coral reef biota progressed, I was struck time and again by the exquisite beauty in color--and in shape--of many organisms. It somehow seemed incongruous to me that the entire spectrum of brilliant coloration should result from a few familiar classes of pigments, principally quinones, carotenoids, pyrroles, and indoles. Yet aside from a few compounds of mixed biosynthesis (sesquiterpene + shikimic acid), e.g. ilimaquinone (1) (4)



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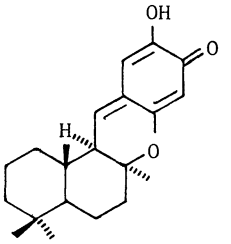

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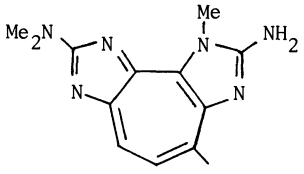
or puupehenone (2) (5), only one new class of pigments, the zoanthoxanthins, have so far been isolated from marine sources. These compounds are tetrazacyclopentazulenes and were first described by Prota and coworkers (6) from Mediterranean coelenterates, then from Japan (7). We encountered a skeletal variant of this class, 2-amino-3,9-dimethyl-5-dimethylamino-3H-1,3,4,6-tetrazacyclopent[e]azulene (3) from a deep-sea (-350 m) coelenterate, Gerardia sp.



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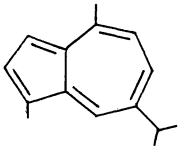
(8). We were fortunate in being able to do this research, since the polished endoskeleton of this zoanthid coral is the gold coral of the jewelry trade. We piggy-backed on a commercial operation, which was leasing a University of Hawaii owned minisubmersible vessel. After the harvesting of gem corals was terminated several years ago, the University of Hawaii sought federal funding in order to operate the submarine entirely for scientific research.

After lengthy delays in funding and logistics my research group was assigned its first two dives aboard the Makali'i in December, 1981. Our initial objective was the exploration of the rich diversity of deep-sea gorgonians in Hawaiian waters. In contrast to the virtual absence of shallow water gorgonians, more than ninety species of deep-sea gorgonians have been described from the Hawaiian islands (9) and no one doubts that many more species remain to be described. Although taxonomic verification has been slow, we have so far collected perhaps twenty species.

To the observer, who gets his first glimpse at the ocean bottom 350 meters below the surface, the most striking sights are some luminescent gorgonians and the brilliantly blue-colored corals.

Our excitement and our hope to find perhaps a new class of blue pigments among the deep-sea fauna prompted us to begin with a study of the pigments of several of these brightly colored gorgonians. We soon discovered that most of these pigments are extremely sensitive when exposed to light and air during normal laboratory operations. Two of the more resistant compounds proved to be the well-known and, by spectral comparison, readily identified guaiazulene (4) and linderazulene (5). Interestingly, these same azulenes have very recently



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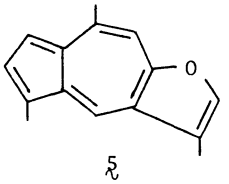

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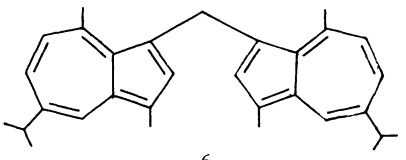
been identified by Fusetani and coworkers (10) from a gorgonian Euplexora erecta (4) collected in Japanese waters, and by Imre et al. (11) from a Sea of Marmara gorgonian, Paramuricea chamaeleon (5), both from shallow waters. Among the less stable pigments of the deep-sea Pseudothesia sp we isolated the aquamarine-colored bis (3,3'-guaiazulenyl) methane (6), which was previously known as a synthetic compound (12,13). For direct comparison we prepared a synthetic sample of 6 from commercial (Aldrich) guaiazulene, formalin, and selenium dioxide by a published procedure (13). These results of our deep-sea collecting have so far been less than spectacular. For a close examination of the sterols of these animals we are collaborating with Professor Djerassi of Stanford. Early indications from



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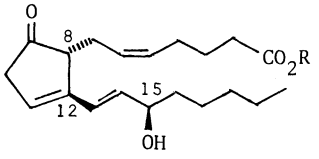
his laboratory (14) show promise of finding unprecedented sterols in the deep-sea gorgonians. I am confident that, in the long run, our systematic exploration of deep-sea biota will enrich our knowledge of marine-derived secondary metabolites.

Without question, a convincing case for serendipitous research, and incidentally for marine natural products research, was made by Weinheimer's isolation of unusually large concentrations of prostaglandins in the Caribbean gorgonian Plexaura homomalla (15). The excitement in the biomedical community over this discovery not only spawned much activity in gorgonian fishery, but also in the question of animal versus symbiotic algal biosynthesis, as many of these animals are associated with symbiotic algae. For a decade after the Weinheimer paper no new marine prostanoids and no new marine sources of prostanoids were found--although the search was more intense than is evident from the published literature! Some ten years after Weinheimer's paper the Roche Institute in Australia reported isolation of a prostanoid from Gracilaria edulis, a red alga (16), and Kashman and coworkers in Israel (17) found a prostaglandin derivative in a soft coral, Lobophyton depressum. Although Weinheimer's PGA_2 (7)



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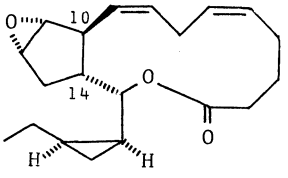
possessed the unnatural configuration at C-15, all reported prostaglandins from marine sources had identical stereochemistry at C-8 and C-12, thereby suggesting identical or closely related biosynthetic pathways. By contrast, hybridalactone (8), which is a C_{20}



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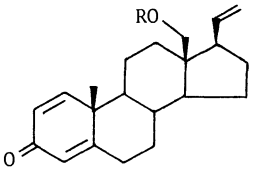
fatty acid derivative reminiscent of prostanoids and which Higgs and Mulheirn (18) isolated from the red alga Laurencia hybrida, appears to have been formed by an alternate biosynthetic route.

In my laboratory we (19) have recently isolated the first naturally occurring halogenated prostanoid from an unexpected source. Several years ago we studied the metabolites of an octocoral belonging to the order Telestacea, Telesto riisei (20). The animal was collected in the Marshall islands and contained two simple pregnane derivatives (9a,b). The coral is



9 a, R = Ac; b, R = H

a member of the fouling community and was introduced to Hawaii rather recently on ships' bottoms. When we collected T. riisei at Ala Moana and at Pupukea, Oahu, the organic extract was devoid of pregnane derivatives. Instead, we isolated a series of prostanoids bearing chlorine at C-10 and a 3° hydroxyl at C-12. Still to be determined is the stereochemistry at C-8 and C-12.

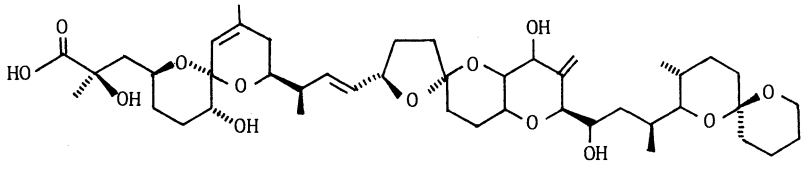
None of the research described in this section is the result of careful planning. Yet the scientific yields have been gratifying. I believe that this approach, although somewhat frowned upon by granting agencies, has its place in marine natural products research and will continue to be productive.

MARINE TOXINS

My involvement with marine toxins work began in 1957, when some of my colleagues in marine zoology invited me to collaborate in a comprehensive multidisciplinary study of ciguatera in the Pacific. Twenty-five years later, ciguatera research is still among my research efforts. Ciguatera is a disabling human illness, recognizable by a combination of gastrointestinal and neurological symptoms, rarely fatal, which may result from eating a variety of tropical reef fishes. Ciguatera incidence is geographically and chronologically unpredictable. For years there was much circumstantial evidence that the ciguatera-causing toxin or toxins were transmitted through the food chain, but it was only in 1977 that Yasumoto, while doing WHO-sponsored field work in French Polynesia, described the evidence that pointed to a benthic dinoflagellate, later named Gambierdiscus toxicus, as the likely biological precursor (21). Unlike the red tides of Gonyaulax spp that cause paralytic shellfish poisoning, no G. toxicus blooms appear, as the alga settles preferencially on various macroalgae. This ecological characteristic accounts for the fact that an outbreak can be recognized only through human intoxications. It may also be the reason that toxin production from cultured G. toxicus in several laboratories has been spotty at best, since the macroalgal substrate may very well provide a chemical clue in addition to a surface for settling.

Structural studies in our laboratories and elsewhere have been hampered by a lack of pure toxin. Concentration of the toxin, which has an LD_{50} of 0.45 μg/kg (ip, mice), in fish is in the parts per billion range. Authentically bioassayed fish, i.e. leftover fish that has caused human illness, is difficult to procure, tends to be small in quantity, and rarely contains the most toxic parts, the viscera. The alternate method, fishing in waters where ciguateric fish have been caught, requires prescreening by oral feeding of a susceptible animal, often a cat or mongoose, prior to extraction. Else it results in at least five-fold dilution. Since Hawaii fortunately is just north of the principal ciguatera belt, we have had virtually no remains from toxic meals for toxin procurement. We either screened moray eels that were speared in toxic fishing grounds by feeding a piece of fish to a mongoose or we extracted only the viscera, which would be toxic even from fish whose flesh would not cause toxicity symptoms in a mongoose.

Through Tachibana's work (22,23), who used high field ^{1}H NMR spectroscopy and, in collaboration with Professor R. D. Macfarlane, ^{252}Cf plasma desorption mass spectrometry, we know that we are dealing with a highly oxygenated lipid molecule of M Wt 1112 daltons. Through Yasumoto's research (24) we have learned that ciguatoxin has chromatographic characteristics which resemble the behavior of the polyether okadaic acid (10). The structure of okadaic



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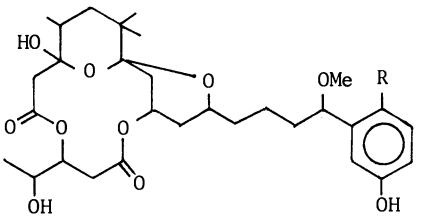
acid became known through our and Schmitz's (25) work on marine sponge constituents. It was subsequently isolated by Yasumoto (24) as a principal constituent of the marine dinoflagellate Prorocentrum lima. Because of the scarcity of ciguatoxin, full structural elucidation will probably be the result of successful single crystal X-ray diffraction studies.

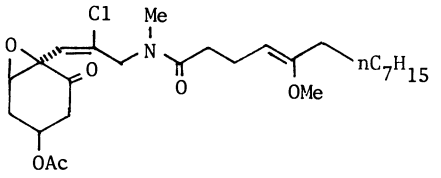
During the early years of our search for the dietary origin of ciguatoxin my collaborator A. H. Banner was struck by an entry, limu-make-o-Hana (deadly seaweed of Hana), while browsing through an Hawaiian-English dictionary (26). This in turn led to a search for, and collection of, this limu which proved to be Palythoa toxica. Superficial toxicity studies revealed that the fast action of this toxin, later to be isolated and named palytoxin, could have no bearing on ciguatoxin (27). In a remarkable parallel, the late Professor Hashimoto,

while engaged in ciguatera research, screened toxic fish in the Ryukyus and isolated a toxin from the gut of a filefish, Alutera scripta (28), which proved to be palytoxin derived from P. tuberculosa that the fish had eaten (29). Professor Hirata's successful palytoxin research (30) is a direct sequel of the Hashimoto discovery, as Moore's work (31) is of the ciguatera research in Hawaii.

Our work on sea hare toxins (32-34), while not a direct spin-off of our ciguatera research, arose from our long-time collaboration with University of Hawaii marine zoologists. It led to the successful isolation from Stylocheilus longicauda and subsequent structural elucidation of aplysiatoxin (11a) and debromoaplysiatoxin (11b) and of the nontoxic stylocheilamide (12) (35). Subsequently, Mynderse et al. (36) isolated 11b but not 11a from the blue-green



11 a, R = Br; b, R = H



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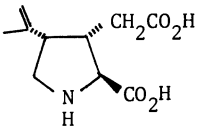
alga Lyngbya majuscula. Although debromoaplysiatoxin has been crystallized, the molecule has so far resisted successful X-ray diffraction studies, which would clear up the remaining stereochemical ambiguities (37). Interest in the aplysiatoxins continues because of their activity as tumor promoters (38). It is perhaps not surprising that substances that exhibit toxicity toward mammalian systems attract the attention of the biomedical community. Such substances may serve as synthetic model compounds or as pharmacological probes (39). Even relatively innocuous compounds, as e.g. the red algal-derived anthelmintic α-kainic acid (13), which was first isolated in 1953 (40), has very recently become recognized as a



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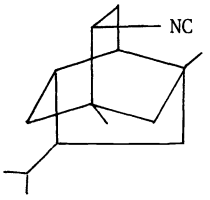
neurobiological probe (41) as a rigid analog of glutamic acid. Occasionally it is even claimed that powerful toxins, as e.g. palytoxin with an LD_{50} of 0.15 μg/kg, is used as a local anesthetic in maxillofacial surgery (42), where it is said to permit operations lasting many hours!

CHEMICAL MARINE ECOLOGY

The final topic of this lecture may be looked upon as the third step in our evolution as marine-oriented organic chemists. You will recall that our adventure began when we were fascinated with the brilliant colors of a tropical coral reef. Isolation of pure compounds--though by no means trivial thirty years ago--involved nothing more than the discovery of an effective chromatographic adsorbent. Anyone who was not color-blind could monitor the isolation. From there we progressed to our study of marine toxins--our first venture into biology, since we had to learn how to inject a mouse, which can be a bit tricky or even unpleasant for a chemist, but certainly not intricate. As for the endpoint-survival or death of the assay animal is as unambiguous as the color change in an acid-base titration. Eventually, our interest in marine ecology problems was stimulated through our continued association with marine biologists. We learned of challenging problems, among them the

nature of sex pheromones of crustaceans, chemically mediated symbiotic associations, or defensive strategies based on chemistry. We wanted to tackle all of them--only to discover that in virtually all cases there were no simple bioassays--at least not until the active principle was partially characterized. Ideally, these research projects should be undertaken with active participation of biologists who will either carry out or supervise bioassays which are behavioral in nature or which require highly specific biological techniques. Frequently, these ideal circumstances are not attainable, and chemists have to try and learn enough biology to be able to monitor an isolation.

Perhaps the least complex ecological problems deal with various chemically mediated defensive strategies of invertebrates that lack physical protection. I have recently reviewed (43) our initial entry into this research area, which constituted the first successful demonstration that a nudibranch, Phyllidia varicosa, accumulates from a specific sponge on which it feeds a substance, 9-isocyanopupukeanane (14), which is lethal to its own predators, fish and



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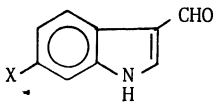
crustaceans. Other research groups have followed our lead and have carried out similar studies, although at times the biological role of nudibranch metabolites has been implied, rather than demonstrated (44). Despite these uncertainties, ample evidence has shown that nudibranchs are capable of selectively adapting a wide range of organic compounds as their defensive arsenal. The intriguing biological questions of the evolution and the underlying forces of this amazing selectivity and adaptability remain to be solved.

Nudibranchs, while often feeding on sponges, are also known to prey on specific bryozoans and coelenterates. We have not yet studied a nudibranch-bryozoan association. We have, however, investigated the cryptically colored bright orange nudibranch Phestilla melanobrachia, which feeds on the equally brilliantly colored ahermatypic coral Tubastrea coccinea (45). The organic metabolites of T. coccinea are many and varied, and the mollusk appears to be selective in its retention of certain compounds. However, caution must be exercised as the total organic extract of the much smaller nudibranch may contain trace constituents beyond the limits of detection. Interestingly, though, P. melanobrachia extract contains as a major constituent an as yet incompletely characterized aromatic compound which is absent in the coral T. coccinea. To our knowledge, T. coccinea is the only food of P. melanobrachia. The entire story is still incomplete, but we have learned enough for an initial report.

Most of the constituents of these two animals are alkaloids derived from 6-bromoindole. It is not at all surprising that an increasing number of alkaloids are reported from marine sources. The apparent dearth of these compound for a number of years is largely a reflection on the predominant methodology of terrestrial natural products research, where alkaloids often were the only sought after constituents.

Both animals were collected from several sites, but most frequently from Pupukea on the north shore of Oahu. Isolation was initiated by ethanol extraction and solvent partition of the alcoholic residue. No metabolites were detected in the nonpolar solvent (hexanes, CCl_4) extracts. All isolated substances were found in the chloroform or aqueous methanol fractions. Crude ^1H NMR spectra of these fractions displayed an abundance of aromatic signals. Chromatography on Sephadex LH-20 or on neutral alumina, followed by reversed phase HPLC, led to the successful isolation of all metabolites.

The two simplest compounds, 3-indolecarboxaldehyde (15a) and its 6-bromo analog (15b) were

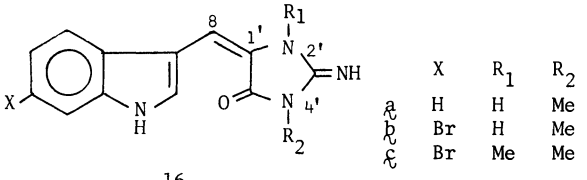


15 a, X = H; b, X = Br

pure after alumina chromatography of the aqueous methanol residue from the coral only. They were readily identified by comparison of their spectral data with published literature values (46,47).

Five additional indole derivatives (16a-e and 17a,b) two of them (16a,b) common to both animals, the other three exclusively from the coral, were isolated in this work. Two of the compounds proved to be identical with the known sponge metabolites 4'-de-N-methylaplysinopsin (16a) and 6-bromo-4'-de-N-methylaplysinopsin. Both compounds were reported by Djura and Faulkner (48) from a Caribbean sponge, Dercitus sp., and are closely related to the tumor-inhibiting parent compound aplysinopsin, which was isolated by Kazlauskas et al. (49) from a sponge, Thorecta sp., and by Hollenbeak and Schmitz from the sponge Verongia spengelii (50). The identity of the two compounds was proven by spectral comparison.

Compound 16c, not found in the nudibranch, is a new compound. Its ^{1}H NMR spectrum has a signal at δ 3.46 assigned to the 2'-methyl of aplysinopsin (δ 3.26) and an aromatic pattern as well as the appropriate mass spectral fragmentation of a 6-bromoindole (46,47). Consequently, it is 6-bromoaplysinopsin.



	X	R_1	R_2
a	H	H	Me
b	Br	H	Me
c	Br	Me	Me

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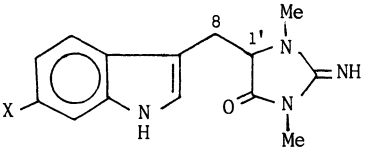

17 a, X = H; b, X = Br

Also new, and not detected in P. melanobrachia, were 1',8-dihydroaplysinopsin (17a) and 6-bromo-1',8-dihydroaplysinopsin (51), which we isolated from the chloroform fraction of the solvent partition. The ^{1}H NMR spectra of these compounds while having much in common with the compounds reported above lacked the olefinic signals of 16a-e in the 6.65-6.80 ppm range. Instead, a two-proton multiplet at δ 3.20 and a doublet of doublets at δ 3.94 were seen to be at vicinal carbons by double resonance experiments. Their chemical shifts necessitated assignment of these signals to C-8 and C-1'.

A final metabolite, which is common to both animals, is a purine base, which will be described elsewhere.

CONCLUSION

Hopefully, this selective account of some of our work, has indicated some of the directions, in which, in my opinion, marine natural products will develop. As I look at some of the research that is carried out by our colleagues who study the chemistry of terrestrial insects, I admire the extent to which it has been possible to provide chemical answers to biological phenomena. I cannot help but be convinced that increasingly we will be able to handle sophisticated bioassays and difficult separations of highly polar and complex mixtures, which will enable us to build a molecular basis for many aspects of marine ecology.

What about our contributions to biomedicine--"drugs from the sea"? We must remember in this connection that Bergmann's discoveries of the fifties entered the Pharmacopeias as Ara-A and Ara-C more than twenty years later--not an unreasonable time for the development of a useful drug. I am much encouraged by the vigorous efforts in drug discovery and development which are underway in Japan and elsewhere. I mentioned some developments in the use of marine natural products as biological probes.

And finally--as long as organic chemists enjoy snorkeling, diving, and going down to the sea in ships, marine natural products will continue to provide chemical solutions, some carefully planned and thoughtfully executed, and some arrived at by chance discovery.

Acknowledgments -- I thank all of my coworkers, past and present, who are not coauthors or are mentioned in the references for their all-important role in making this talk possible. John Beard, Steve Coval, and Patrick Yu assisted with our first deep-sea collections in December, 1981. I am grateful to the National Science Foundation, the University of Hawaii Sea Grant College Program, and to the Hawaii Undersea Research Laboratory for generous funding of some of the research reported in this paper. We also thank Scott Johnson for P. melanobrachia, Gary Schulte and Rob Armstrong for T. coccinea collections.

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