Introduction

The Pacific islands, commonly referred to as the State of Hawaii, are regarded as the most geologically isolated pieces of land on our planet. The State is composed of eight main islands that cover 6423.4 miles² (16636.5 km²): Niihau, Kauai, Oahu, Molokai, Lanai, Maui, Kahoolawe, and Hawaii, often referred to as the “Big Island”, and an upcoming island, the seamount named Loihi. All of the islands are volcanic in origin with the Big Island and Loihi still growing in area as a result of them being volcanically active. Due to their remote location and geological youth, their ocean-based biodiversity must be considered as depauperate, which is atypical of a tropical region. In general, moving down the island chain from Niihau to the Big Island reveals a marked decrease in ocean-based biodiversity especially for slow-moving and sessile life forms like nudibranchs, sea hares, algae, corals, sponges, tunicates and the like, and to some extent this is reflected in this review. The review itself covers the primary literature concerning marine natural products isolated from organisms collected around the islands of Hawaii published in the 51-year period 1964 to July 2015. The review is divided into seven main sections based on major taxonomic groupings; algae, sponges, mollusks, miscellaneous invertebrates, cyanobacteria, bacteria, and fungi. The aim of the review is to discuss the compounds and information concerning their original biological activity and other potentially interesting properties. The majority of the 320 structures of isolated compounds are not shown directly in the review but are contained in the Supporting Information section in 22 figures, Figs. 1 S–22 S. The Supporting Information section also contains Table 1 S that has information relating to the taxonomic identification of the source organism of each compound, collection location of the source organism, a trivial or semi-systematic name for each compound, as well as its general structural class. The authors hope that this review will be the spawning ground for other reviews and the basis for a great deal more research into the marine life found in Hawaiian waters.

Abstract

The following review covers the primary literature concerning marine natural products isolated for the first time from organisms collected around the islands of Hawaii published in the 51-year period 1964 to July 2015. The review is divided into seven main sections based on major taxonomic groupings; algae, sponges, mollusks, miscellaneous invertebrates, cyanobacteria, bacteria, and fungi. The aim of the review is to discuss the compounds and information concerning their original biological activity and other potentially interesting properties. The majority of the 320 structures of isolated compounds are not shown directly in the review but are contained in the Supporting Information section in 22 figures, Figs. 1 S–22 S. The Supporting Information section also contains Table 1 S that has information relating to the taxonomic identification of the source organism of each compound, collection location of the source organism, a trivial or semi-systematic name for each compound, as well as its general structural class. The authors hope that this review will be the spawning ground for other reviews and the basis for a great deal more research into the marine life found in Hawaiian waters.

Supporting information available online at http://www.thieme-connect.de/products

Half a Century of Hawaiian Marine Natural Products*

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Key words
- Hawaii
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- fungi

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Where applicable, the review also describes the isolated compounds in terms of their structures and activities as well as other relevant facts the reader may find useful. The review is organized into seven sections. The first four sections cover marine macro-organisms (algae, sponges, mollusks, and miscellaneous invertebrates), while the latter sections cover marine microbes (cyanobacteria, bacteria, and fungi). Fig. 2 shows the number of compounds originally isolated from a Hawaiian source organism according to five-year...
periods after 1970 and the main taxonomic groupings (in the seven sections mentioned above) used in the review. At the end of the review, there is a Concluding Comments section that summarizes the highlights of the marine natural products research undertaken in the 51-year time period covered by the review as well as providing some suggestions and insights into the area in general.

Algae

Brown algae

One of the earliest reported studies into marine natural products elaborated by Hawaiian organisms concerned algae and was conducted by the Moore group in 1968 [1]. In this paper, the authors reported the structure of an unstable dialkenylcyclopropane C\textsubscript{11} hydrocarbon, dictyopterene A (1 [\(\odot\) Fig. 3]), isolated from the brown algae Dictyopteris plagiogramma and Dictyopteris australis [1] from Waikiki, Oahu. In 1970, a trialkenylcyclopropane named dictyopterene B (2) was isolated together with trans,cis,cis-1,3,5,8-undecatetraene (3) from the same algae by Pettus and Moore [2]. Further research into samples of these two algal species, D. plagiogramma and D. australis, by Pettus and Moore [3] yielded dictyopterenes C\textsuperscript{+} (4, 5) and D\textsuperscript{−} (6, 7), the latter compound was shown to be identical with ectocarpene [4], trans,trans,cis-1,3,5,8-undecatetraene (8), trans,cis-undeca-1,3,5-triene (9), and trans,trans-undeca-1,3,5-triene (10). In 1971, Roller et al. worked with a sample of D. plagiogramma, presumably also from Waikiki, Oahu, and found it to contain four new sulphur-containing lipids; S-(3-oxoundecyl)thioacetate (9), bis-(3-oxoundecyl)disulphide (10), 3-hexyl-4,5-dihydroxyheptanone (11), and S-(trans-3-oxoundec-4-enyl)thioacetate (12) [5]. In 1971, Moore investigated two further samples of D. plagiogramma and D. australis, from unspecified locations, but presumably somewhere on Oahu, and isolated two bis-(3-oxoundecyl) polysulphides, bis-(3-oxoundecyl)trisulphide (13) and bis-(3-oxoundecyl)tetrosulphide (14), as low melting point crystalline solids [6]. When left to stand in methanol (\(\text{CH}_3\text{OH}\)) for a prolonged period, the tetrosulphide (14) decomposed to yield the trisulphide (13) and elemental sulphur. From another investigation of D. plagiogramma and D. australis samples, again from an unspecified location in Hawaii, Moore and his colleagues identified a number of hydrocarbons and sulphur-containing compounds, two of which were new natural products (15, 16) [7]. In this report, it is suggested that both (-)-bis-(3-oxoundec-5-enyl)disulphide (15) and (-)-bis-(3-oxoundec-5-enyl)thioacetate (16) are possible precursors of the aforementioned undeca-1,3,5-trienes [3]. Other new natural products reported from algae belonging to the genus Dictyopteris were the two cyclic ketones (+)-(R)-4-butylocyclohepta-2,6-dienone (17 [\(\odot\) Fig. 3]) and (+)-(R)-6-butylocyclohepta-2,4-dienone (18 [\(\odot\) Fig. 3]) [8], both of which were noted for their strong odors. The absolute configurations of both molecules were determined by synthesis and CD spectral comparisons. Surprisingly, the optical rotation of 18 was reported as +1120, while that for 17 was given as +96. It seems likely that there might be a factor of 10 error in the value reported for 18, with +112 being a more realistic value based on what is known about the molecular weights and absolute configurations of the two molecules. The final report concerning the natural products yielded by algae from the genus Dictyopteris found in Hawaii was published in 1974 and was a review summarizing the current knowledge about the odoriferous C\textsubscript{11} hydrocarbon research undertaken by the Moore group since 1968 [9]. In terms of bio- and ecological activity, only the previously reported compound, ectocarpene (dictyopterene D\textsuperscript{−}, 5), is implicated by being the Cope rearrangement product of the sperm-attracting substance 1-((1E,3Z)-hexa-1,3-dien-1-yl)-2-vinylcyclopropane.
Species from the cosmopolitan algal genus Dictyota are relatively common to parts of Hawaii and have been the subject of several investigations. The first of these examined a sample of Dictyota acutiloba collected off Kahala and Ala Moana Reefs, Oahu [10]. Two diterpenes, new and unusual for their time, were isolated and characterized as dictyoxepin (19) and dictyolenne (20). The absolute configuration of dictyoxepin was determined by single-crystal X-ray crystallographic analysis of its p-bromo-phenylethyl derivative. Nineteen years later, the second investigation of this species employed a sample collected from Tunnels Beach, Kauai [11]. This study resulted in the isolation of three bicyclic diterpene metabolites, acutilol A (21 [Fig. 3]), acutilol A acetate (22 [Fig. 3]), and acutilol B (23 [Fig. 3]). All three compounds were shown to be potent herbivore deterrents against both temperate and tropical fishes and sea urchins.

From a sample of Dictyota crenulata collected near Hauula Beach, Oahu, Finer et al. isolated and characterized dictyodial (24), employing both standard spectroscopic methods (NMR, IR, UV, MS), and by X-ray crystallographic analysis of the reduced form of this compound [12]. Dictyodial was found to have good antimicrobial properties but was not responsible for the observed antitumoral activity noted for the original algal extract. A winter collection of D. crenulata yielded β-crenulol (25) [13], which was shown to be identical to sanadaiol isolated from a Japanese sample of the brown alga Pachydictyon coriaceum [14]. Two further diterpenes, 4β-hydroxydictyodial A and 18,0-dihydro-4β-hydroxydictyodial A (26, 27), were isolated and characterized from D. crenulata collected near Kualoa Beach Park, Oahu, reported by Kirkup and Moore in 1983, and brings to an end the direct investigations of Dictyota species in Hawaii [15].

Red algae

As would be expected, specimens belonging to the red algal genus Laurencia, due to the prevalence of this algal genus worldwide, are the most studied of any Hawaiian algal genus. The CH3OH extract of Laurencia nidifica (“non-clumpy” variety) collected from Kahala Reef, Oahu, was found to have antimicrobial properties [16]. Fractionation of this material led to the isolation of a number of known metabolites and two new halogenated chamigrene derivatives, nidificine (28 [Fig. 4]) and nidifidiene (29) [16]. The observed antimicrobial activity of the extract was attributed to the presence of the known compound laurateol (30).

A third new chamigrene derivative was isolated from a “clumpy” variety of L. nidifica, also from Kahala Reef, Oahu, nidifidentol (31) [17]. The third investigation of L. nidifica, this time from Black Point Reef, Oahu, led to the isolation and characterization of two sesquiterpene alcohols, 3-methyl-5-(2,3,6-trimethyl-cyclohexa-2,5-dien-1-yl)pent-1-en-3-ol (32) and 3-methyl-5-(2,3,6-trimethylphenyl)pent-1-en-3-ol (33) [18]. When allowed to stand for several days at 25°C, 32 converts to the more stable 33. From the “non-clumpy” variety of L. nidifica, another chamigrene derivative was isolated, this time one that contained a third ring in the form of an ether (nidifocene, 34) [19]. Treatment of 34 with chromic sulphate cleanly removed the halogens to yield 35. From a green variety of L. nidifica, collected from the southern shores of Oahu, three new C15-halogenated non-terpenoid tricyclic ethers possessing a terminal ene-ene functionality, known as cis-maneonenes A and B (36, 37) and trans-maneonene B (38), were isolated [20]. Continued investigation of the extract yielded a further three new metabolites, iso-maneonenes A and B (39, 40), and cis-maneonene C (41) [21]. In this paper, the authors note that the green variety of L. nidifica from which the latter compounds came, 39-41, may itself consist of several different varieties – chemotypes. Also from the green variety of L. nidifica, from an undefended collection site on Oahu, the unstable selane derivative (+)-selin-4,7(11)-diene (42) was isolated and characterized [22]. The most recent report on L. nidifica (green variety) from Oahu summarized all of the authors’ own work concerning the C15 non-terpenoid halogenated compounds discussed above [23], with the only new experimental data being the addition of X-ray data for iso-maneonene B (40). Only one sample of L. nidifica from another Hawaiian island has been investigated. This sample came from near Port Allen, Kauai, and on workup yielded (+)-2(5)-N-acetamido-3(2)-acetoxoytaedecan-1-ol (43), a diacetate of dihydrophosphosine [24].

The lauroxane (44 [Fig. 4]), at the time of its discovery from Laurencia majuscula, sampled from the north shore of Oahu, was the first example of a C15 compound containing a 2,2′-bistetrahydrofuran moiety [25]. Another sample of L. majuscula was collected on the north shore of Oahu near Kahuku, and found to contain kahukuene A and B (45, 46), unprecedented diterpenes having a prenylated chamigrene structure as part of a decalin ring [26]. Clearly, these compounds are quite stable, as it seems the extract was not processed until many years after the alga was collected. The most recent report on algae from this genus comes from Laurencia cartilaginea, collected from Waianae, Oahu [27]. In this report, Juagnan and his colleagues describe the isolation and structure elucidation of two new halogenated sesquiterpenes, 8-bromo-9-hydroxychamigra-2(3),11(12)-dien-1-one (ma‘iliene) (47) and 2-chloro-1.8-dibromochamigr-11(12)-en-9-ol (allo-isobutusol) (48), together with four known halogenated sesquiterpenes, elatol, [1(15)Z,22,4R,8S,9R]-8,15-dibromochamigr-1(15),2,11(12)-trien-9-ol, [1(15)E,22,4R,8S,9R]-8,15-dibromochamigr-1(15),2,11(12)-trien-9-ol, and iso-obtusadiene.

Asparagopsis taxiformis is an algal species traditionally consumed by Hawaiians known to contain a wealth of halogenated hydrocarbon-based metabolites [28-32]. The essential oil recovered from samples of A. taxiformis collected in Waikiki, Oahu, was ob-
served to have bromoform as a major component, along with 17 other compounds including halogenated carbon tetrabromide, tetrahalopropenes, polyhalo-but-4-en-2-ones, monohalacetones, and 3,3-dihaloacroleins [28]. A second investigation of this alga focused on the volatile halogenated compounds found in its essential oil, collected from Waikiki, Oahu, between 1974 and 1975 [29]. This study resulted in the identification of 24 additional halogenated methanes, ethanes, formaldehydes, acetalddehydes, acetones, 2-propanols, 2-acytoxopropanes, propenes, epoxypropenes, acroleins, and butenones. A sample collected from an unknown location in Hawaii, presumably somewhere on Oahu, was shown to contain five halogenated acetamides, seven halogenated but-3-en-2-ols, and 20 halogenated isopropanols [30]. In the report, there is no clear distinction between the new and known compounds. The last report by the same authors on the same algal species also provides no information on the site of collection, but again we assume it was somewhere on Oahu [31]. In this report, the authors investigated the aqueous extract of the alga and identified nine halogenated acetic acids, like ClCH$_2$COOH and BrCH$_2$COOH, and nine halogenated acrylic acids, like CICH$_2$COOH and BrCH=CHCOOH. Unfortunately, the authors do not indicate which of their isolates are new and which are known.

Chemical investigation of *Anamsia glomerata* from Black Point, Oahu, resulted in the isolation of a mixture of *N*-acylsphingosines (49) that were identified via a series of chemical transformations and separations [24]. These compounds had not previously been found in algae.

The first basic indole alkaloids, fragilamide (50) [Fig. 4]), and martensines A and B (51, 52) to be isolated from a marine eukaryotic plant came from *Martensia fragilis* samples collected at both Black Point and Mokuleia, Oahu [33].

The known toxic alga, *Gracilaria coronopifolia* (34), collected from Waiehu, Maui, yielded the toxic compounds maunaealides A–C (53–55) [Fig. 4]) [35]. Maunaealides A and C (53, 55) are new macrolides, whereas while maunaealide B (54) was previously known as a semisynthetic derivative of debromoaplysiatoxin in (56) [Fig. 4]) [36]. A further investigation of another sample of *G. coronopifolia* from Maui enabled the absolute configuration of maunaealide C (55) to be determined and also led to the isolation of anhydrodebromoaplysiatoxin (57) [37]. In several bioassays, 57 was shown to be inactive, however, low-dose injections into mice caused them to have diarrhea, thus revealing the potentially toxic nature of this and other related compounds. The most recent report on *G. coronopifolia* described the isolation and characterization of malyngamides M and N (58, 59) and malyngamide I acetate (60) from a sample also collected from Waiehu, Maui, one week after a food poisoning event [38]. The absolute configuration of 60 was deduced employing the reverse octant rule. As the type of compounds 58–60 represent are found almost exclusively from cyanobacteria, the authors’ suggest that their collection may well have contained significant quantities of such a contaminant.

More recently, in 2013, molecular techniques were applied to the analysis of microbes associated with native and invasive Hawaiian macro-algae, including samples of *G. coronopifolia* (native), *Gracilaria salicornia* (invasive), and *L. nidifica* (native). The authors found the clone library derived from *G. coronopifolia* contained 28% cyanobacterial sequences, and *G. salicornia* and *L. nidifica* had cyanobacterial sequence frequencies of 71% and 8%, respectively [39]. These findings may provide the basis for the identification of the proposed cyanobacterial origins of *G. coronopifolia* toxins [34, 35, 37, 38].

Investigations of *Chondrococcus hornemanni*, now known as *Porteria hornemanni*, from Hawaii started in the mid-seventies [40, 41]. The first of these describes the isolation, from two different samples, of (3)-cis-octa-1,5-dien-3-ol (61), which is proposed to be a possible precursor of the sperm-attracting compound fusocerratene, known from the brown alga *Fucus serratus* [40]. The samples came from Black Point and Halona Blowhole, both on Oahu. The second report describes a number of linear and bicyclic halogenated monoterpenes, including chondrocroles A and B (62, 63) [41]. These compounds also came from samples collected from Black Point and Halona Blowhole, which demonstrate through their chemical variation that they might belong to different chemotypes. In the third paper related to plants of the genus *Porteria* (=*Chondrococcus*), the authors corrected the structure of 62 to 64 based on an X-ray study of a related compound, chondrocolactone (65) [42], isolated from a sample from Halona Blowhole, Oahu.

The final red alga to be discussed here, *Tricleocarpa fragilis*, was collected off of Nanakuli Beach Park, Oahu [43]. After workup, the extract was fractionated to yield 10 new sulphated terpenoids, including six cycloartenol sulphates (66, 67–71) [Fig. 4]), two 29-nor-cycloartenol sulphates (72, 73), and two 29-nor-lanosterol sulphates (74, 75).

In the brine shrimp bioassay [43] some of the compounds demonstrated moderate to low activity (66, 68). In cell-based cytotoxicity assays, compounds 72–75 demonstrated moderate to low activity, but nothing at a level that would have led to their being further developed.

Green algae

There are only six reports of research being undertaken on green algae from Hawaii, all concerning *Bryopsis* spp., collected around Oahu. The first of these appeared in 1993 and described the depsipeptide kahalalide F (76) isolated from both the sacoglossan mollusk *Elysia rufescens* and one of its dietary components, *Bryopsis* sp. [44]. Kahalalide F (76) [Fig. 5]), a depsipeptide, was shown to have a variety of biological activities, including selective antitumoral, antiviral, and antimicrobial, as well as being somewhat immunosuppressive, and was the only kahalalide to progress to any clinical trials, indeed the only one to have any significant activity in applied assays (see Concluding Comments).

![Fig. 5 Selected isolate from green algae.](image-url)
The next report in 1996 also concerned *E. rufescens* and *Bryopsis* sp. samples [45]. This time a further six new depsipeptides were described of which three kahalalides, A, B, and G (77–79), were found to be in the alga. Of these, none were shown to have any biological activity. In 1999, a Japanese group reported the isolation of kahalalide K (80), a cyclic depsipeptide with a new array of three L- and three D-amino acids. This compound was devoid of bioactivity in the applied assays [46]. Towards the end of the discussion in this paper the authors suggest the origin of the kahalalides is still unclear as their algal samples clearly contained cyanobacterial epiphytes that could be the source of such molecules. Horgen and colleagues described kahalalide O (81) initially from samples of *Elysia ornata* (Mollusk) from Point Black, Oahu, and later from *Bryopsis* sp., collected from the west coast of Oahu [47]. This cyclic depsipeptide was also found to be devoid of activity in the applied cytotoxicity studies. Kahalalides P and Q (82, 83), both cyclic depsipeptides containing a 3-hydroxy-9-methyldecanoic acid residue, were isolated from a sample of *Bryopsis* sp., collected from Kewalo Basin, Oahu [48]. Like most of the other kahalalides discussed here, kahalalides P and Q (82, 83) were found to be inactive in the applied bioassays, including those related to cytotoxicity. The most recent report on *Bryopsis* spp. concerns samples of *Bryopsis penna* collected from Kahala Bay, Oahu [49]. From 20 kg of material, the authors isolated two new cyclic depsipeptides, 5-hydroxykahalalide F (84) and nor-kahalalide A (85). In terms of biological activity, the authors suggest their research results and insights gained from testing their molecules might lead to new research with natural products aimed at the search for ligands selective for the Y1 receptor, a receptor implicated in a variety of psychiatric disorders.

**Microalgae (protista)**

Studies involving microalgae (protists) isolated from the ocean surrounding Hawaii focused on a culture of a free-swimming dinoflagellate, *Symbiodinium* sp. The source of the isolate was initially documented as sand collected from the beach of Coconut Island, Hawaii, in 1996 [50]. In two later reports by Onodera et al. the source was said to be a Hawaiian tide pool [51, 52], and in a further report, from a Hawaiian sand beach [53]. From reading these papers it seems evident that Onodera and collaborators actually worked with a single strain of *Symbiodinium* sp., designated HA3–5, from which they isolated a series of polyhydroxylated diamides named zooxanthellamides A (86 [Fig. 6]), B (87), C-1 (88), C-2 (89), C-3 (90), C-4 (91), and C-5 (92) [51–53]. The C-1 to C-5 (88–92) compounds are macrocyclic lactones. Testing of 88–92 determined they had vasoconstrictive activity, with the lactones being significantly more active than their non-lactonized counterparts [53]. In more recent times, 2010, 2012 and 2014, extracts obtained from Hawaiian algae have been screened for their antioxidant activity and fucoxanthin and polyphenolics have been suggested as likely major contributing constituents responsible for the observed activity in some of the algae [54–56].

**Sponges**

**Order Chondrosiida**

In 1979, sponge samples tentatively identified as *Chondrosia chucalla*, collected from Lanai, and the Blowhole, Oahu, were shown to contain puupehenone (93 [Fig. 7]) [57]. The final structure of this compound was deduced by X-ray analysis of its ozonolysis product (94).

**Order Dictyoceratida**

Ilimaquione (95) was first isolated from *Hippiospongia metachromia* (now *Dactyspongia metachromia*), a bristly yellow orange or brown sponge found in the waters around Lanai, and near...
the Blowhole on the southeast coast and Shark’s Cove on the north shore of Oahu [58]. The structure of 95 (Fig. 7), finally resolved by X-ray analysis, is quite an unusual one being composed of a rearranged drimane sesquiterpene part linked to a penta-substituted benzoquinone. Even though the original organic extract of this sample was shown to have antimicrobial activity, there appears to have been no further investigation of ilimaquinone’s (95) potential as an antibiotic.

Pupehenone (96), a potent antioxidant antimicrobial meroterpenoid, was isolated from a Dactylospongia sp., collected from a depth of 130 m by a remotely operated vehicle (ROV) working in the Au’au channel between Maui and Hawaii [59]. From this same CH3OH extract, a methoxypupehenol dimer was also isolated and characterized (97). In this paper, the authors also report finding pupehenone (93) and propose it as an artifact of isolation.

A Dysidea fragilis sponge, collected from Kaneohe Bay, Oahu, yielded upial (98), an unusual tricyclic non-isoprenoid sesquiterpene aldehyde [60]. The structure of upial was confirmed from the results of a lanthanide shift reagent study performed with upial (99), the reduced form of 98. A second investigation of D. fragilis from Kaneohe Bay, Oahu, as well as two of its known predators, the nudibranchs Hypselodoris godeffroyana and Chromodoris maridadilus, yielded two tricyclic furanosesquiterpenes, nakafuran-8 (100) and nakafuran-9 (101), with fish antifeedant properties [61].

Two sponge samples, Hyrtios spp., [62] one collected from the sandy bottom between Maui and Molokini crater (~30 m) and the other from submerged lava tubes on the north and west shores of Oahu (~10 m), were found to contain three new meroterpenoids (102–104) related to pupehenone (93). Compounds 102 (21-chloropupehenol) and 103 (15-oxopupehenol) were in both sponge samples while 104 (molokinenone – also chlorinated) was only noted in the sample from Maui. In bioassays, 102 was shown to have significant and selective antitumor and antimarial activities. Poipuol (105), isolated from a Hyrtios sp., collected near Brenneke’s Ledge, Kauai, in 2003, is an unusual small polyketide unique to the genus [63]. The structure of 105 suggests that it is more likely of microbial or cyanobacterial origin than being produced by the sponge itself. Cytotoxicity testing of 105 towards several cancer cell lines showed it to be inactive. The most recent investigation of a Hyrtios sp., collected in 2011 from a depth of 85 m in the Au’au channel between Maui and Lanai, led to the isolation of auauamine (106) plus a peroxo dimer (107) [64], probably derived from 93. The sponge was selected for investigation based on its CH3OH extract having antioxidant and antimicrobial properties. Bioassays performed with 106 showed it to have significant antioxidant activity and to be antibacterial. From the south shore of Maui at a depth of about 13 m, a sample of Spongia oceania was collected. The ethanol (EtOH) extract of the dry sample yielded pokepola ester (108 (Fig. 7)), a diester of phosphoric acid of mixed biosynthetic origin, after repeated solvent partitioning, countercurrent chromatography, gel permeation chromatography (LH-20), and finally reversed-phase HPLC (RP-HPLC) [65]. The molecule, like many others from sponges, may be of microbial origin. In bioassays, 108 was shown to have mild HIV inhibitory activity.

Order Haplosclerida

Callospongia diffusa, collected from Kaneohe Bay, Oahu [66], yielded 24-ethyl-D-24,28,25-cholestatrien-3β-ol (109 (Fig. 7)) [67]. This was the first report of a naturally occurring steroidal alene.

Three new pregnanes (110–112) were isolated from a Petrosia sp., formerly Strongyliphora sp., collected at Puako, west Hawaii [68]; all structural deductions were confirmed by X-ray. In cytotoxicity studies, 111 was found to be the most active compound with an MIC of 1 μg/ml towards KB cells and 5 μg/ml towards LoVo cells.

Order Homosclerophorida

Bioassay-guided fractionation (brine shrimp bioassay) of the extract obtained with 80% aqueous CH3OH of a Plakortis sp., a sponge collected between Lehua Rock and Ni‘ihau Island, led to the isolation of four new polyketide derived metabolites, lehuaides A to D (113–116) [69]. Cytotoxicity screening of the isolates showed lehuialide B (114 (Fig. 7)) and lehualide D (116 (Fig. 7)) to have activity towards ovarian and leukemia cancer cell lines.

Order Poecilosclerida

From a sponge only assigned to order the Poecilosclerida, collected near Maalaea Bay, Maui, two mildly cytotoxic steroids oxidized at C-21, kiheisterones A (117 (Fig. 7)) and B (118 (Fig. 7)), were isolated [70]. The first halo-steroids, in this instance chloro-steroids, kiheisterones C-E (119–121) were discovered from an undescribed species of Strongylacidon, collected from Maalaea Bay, Maui [71]. The authors report no biological activity testing of these unusual halo-steroids.

Order Suberitida

From a Halichondria sp., a sample collected by trawling at a depth of 200 m north of Oahu, two of the first marine isocyanides were isolated, a bicyclic sesquiterpene (122 (Fig. 7)) and a acyclic di-terpene (125 (Fig. 7)), together with their corresponding formamides (123, 126) and isothiocyanates (124, 127) [72–74]. Chemical investigation of a nudibranch, Phyllidia varicosa, led the authors to research samples of the off-white sponge Hymeniacidon sp., known to be part of the animal’s diet, collected from the Pupukea Coast, Oahu. From the EtOH extract of the sponge, the authors isolated 9-isocyanopupukeanane (128 (Fig. 7)) and confirmed its structure by X-ray analysis of its phenylthiourea derivative [75].

The sterol composition of the sponge Terpios zetekii (now Suberites aurantiacus) collected from Kaneohe Bay, Oahu, was described by Delseth and collaborators in 1979 [76], and included the structure of a new C26 sterol, 5α-24-norcholestan-3β-ol (129).

There are two reports on sponges from the genus Ciocalypta present in Hawaiian waters. The first of these described a specimen collected from Pupukea, Oahu, and reported the isolation of three nitrogen containing bisabolene sesquiterpenes, 7-isocyanato-7,8-dihydro-α-bisabolene (130), 7-{p-bromobenzyl}ureido)-7,8-dihydro-α-bisabolene (131), and 7-amino-7,8-dihydro-α-bisabolone chloride (132) [77]. The structure of 132 was confirmed by X-ray analysis of its p-bromobenzyl urea derivative. The second report, this time concerning a sponge from Ala Moana Reef on the west shore of Oahu, discussed a tricyclic sesquiterpene, isocyanoneopupukeanane (133) [78]. The structure solution of this rigid cage-like compound took advantage of several diagnostic 2D-NMR C-H long-range correlations (COLOC).
Order Verongida

Other common genera researched from Hawaiian waters are those belonging to the order Verongida. The first isolate from a sponge belonging to this order, with a tentative taxonomic assignment, was 15-cyanopupuhenol (134) [79]. The sample was collected from waters off the south shore of Molokai. Interestingly, the authors make no speculation that this molecule might have been a possible precursor of puupehenone (93). Other specimens of this order collected from Maui and several beaches on Oahu, identified as belonging to either the genus Psammaplysilla or Pseudoceratina, have yielded a variety of different compounds. Moloka’iamine (135 [Fig. 7]), a bromotyramine derivative, and five puupehenone-related compounds (136-140) were isolated from a sample belonging to an undescribed genus closely comparable to Psammaplysilla purpurea.

The samples were collected from a pier in Kaunakakai Harbour, Molokai, several locations along the south shore of Oahu, and waters south of Maui, and their extracts demonstrated activity towards KB cancer cells [80]. The authors report that all isolates exhibit a variety of biological activities, including cytotoxicity, antiviral, antifungal, and immunomodulatory activities. Re-examination of the sample previously discussed collected on the Wai’anae coast, Oahu, yielded moloka’iamine (135), and the new compounds N-methylceratinamine (141), two moloka’iamine derivatives, wai’anaamines A (142) and B (143), together with psammaplysin A (144) [81]. Examination of the ethyl acetate (EtOAc) fraction obtained from the original extract after flash chromatography of the same sponge samples yielded bromotyramine derivatives named mololipids (145) for which there is no complete physical or spectroscopic information [82]. In the paper, the authors provide very general GC-MS data and spectroscopic data of lipid mixtures. Bioassays performed with the lipid mixtures showed them to have some selective activity towards the HIV-1 virus (EC50 of 52.2 µM). The EC50 reported is clearly anomalous, as tests were undertaken with mixtures of lipids of varying molecular weights.

A sample positively identified as P. purpurea collected from a depth of 40 m off south Kihei, Maui, furnished three bromotyrosine derivatives, aplysamines 3–5 (146–148 [Fig. 7]) [83]. All compounds demonstrated moderate to weak nonselective cytotoxicity towards four cancer cell lines (KB, P388, A549, and HT-29), were mildly antibacterial towards various gram-positive bacteria, and were inactive towards the HIV-1 virus.

Mollusks

► Sea hares

The early 1970s saw the first reports on sea hares. Stylocheilus longicauda, collected in Kanehoe Bay, Oahu, yielded two toxins, aplysiatoxin (149) and debromoaplysiatoxin (56), as well as their nontoxic monoacetates (150, 151) [36, 84], together with stylocheilamide (152) [85]. From the same source organism, the new compounds makalika ester (153), makalikone ester (154 [Fig. 8]), malyngamide O (155), and malyngamide P (156) were isolated from animals collected from Black Point, Oahu [86, 87]. The paper concerning two proline esters (153, 154) was also the first report of a naturally occurring lyngbyatoxin A acetate (158) [86].

Malikone ester (154) and lyngbyatoxin A acetate (157 [Fig. 8]) were determined to have moderate (IC50 of 2.5–5 µg/mL) and potent (IC50 of 0.05 µg/mL) activities, respectively, against mouse lymphoma (P-388) cells, human lung carcinoma (A-549) cells, and human colon carcinoma (HTB 38) cells. Malyngamide O (155) showed moderate anticancer activity against mouse lymphoma (P388) cells, human lung carcinoma (A-549) cells, and human colon carcinoma (HT-29) cells.

The lipid extract of a collection of sea hares, Aplysia ocutilera, from the Pupukea Coast, Oahu, where they were observed feeding on an unidentified species of the red alga Laurencia sp., was found to contain two bicyclic di-bromo di-ether C15 enynes, E-ocellenyne (158) and Z-ocellenyne (159) [88]. It is likely that both of the compounds play a role in the defense of the collected animals, but clearly not against humans!

Nudibranchs

From the nudibranch Phyllidia varicosa, collected from the Pupukea Coast, Oahu, 9-isocyanopupukeanane (128) was isolated [75]. The same compound was also isolated from the EtOH extract of a sponge identified as Hymeniacidon sp., which was collected and extracted specifically to provide a sufficient quantity of compound to enable its complete characterization [75]. Four years later, the 2-isomer, 2-isocyanopupukeanane (160), was isolated.
and identified [89]. The final structure solution, including absolute configuration, was achieved through X-ray analysis.

The previously discussed compounds, nakafuran-8 (98) and nakafuran-9 (99), were isolated from two different mollusks, Chromodoris maridaddii and Hypeleodoris godeffroyana, collected in Kaneohe Bay, Oahu. Both organisms had been observed feeding on the marine sponge Dysidea fragilis, suggesting a dietary source [60]. A separate study of the Pupukea Coast, Oahu, inhabitant Chromodoris youngblethi yielded three deacetylscalaradials, only one of which was found in its prey (161), the sponge Spongia oceana [90], and two of which were new products (162, 163).

Assessment of the sesquiterpene contents of eight porostome nudibranchs, two species from Hawaii collected at Ala Moana Reef, Fort Kamehameha, and the Pupukea Coast, belonging to the genus Dendrodoris, Dendrodoris nigra and Dendrodoris tuberculosa, found them to contain two new compounds, olepupuane (164 [Fig. 8]) and its methoxy acetal (165) [91]. Olepupuane was shown to have antifeedant properties toward the Pacific damsel fish (Dascyllus aruanus), with an ED50 of 15–20 µg/mg of food pellet.

The ilkonapryone esters (167–169), all based on the bispyrone alcohol ilkonapryone (166), were isolated from the nudibranch Onchidium verruculatum, collected from Portlock, Oahu [92]. These compounds have purported roles as defense allomones for this mollusk.

An analysis of the carbon tetrachloride (CCl4) partition of the CH3OH extract of eggs of the mollusk Hexabranchus sanguineus collected at Pupukea, Oahu, yielded two antitumor macrolides, both 28-membered lactones with three contiguous oxazole rings, ulapualides A (170 [Fig. 8]) and B (171) [93]. Both compounds inhibited leukemia (L1210) cell proliferation (IC50 of 0.01–0.03 µg/mL) and the growth of Candida albicans [93], and are reported to be present in the adults, but in low concentrations.

Spinholide (172 [Fig. 8]) is a 26-membered macrolide isolated from an unidentified nudibranch found trapped in fishing nets off Oahu [94]. The compound was found to have potent activity against KB cells (IC50 of 35 pg/mL).

With seven publications and twelve compounds, Philinopsis speciosa is one of the most investigated and productive mollusks so far researched in the Hawaiian Islands. Specimens of P. speciosa collected from sandy tide pools at Pupukea, Oahu, led to two reports. The first of these described pulo'upono (173), a C16'-alkadienone-substituted 2-pyridine [95]. The second publication describes two new polypropionates named niuhinone A and B (174, 175) [96]. A larger re-collection of this organism at Shark's Cove, Pupukea, Oahu, in 1994 yielded the depsipeptide kulolide (176 [Fig. 8]), which exhibited significant biological activity against leukemia cells (L1210) and murine leukemia cells (P388) with IC50 values of 0.7 and 2.1 µg/mL, respectively [97]. Lethality of 176 to brine shrimp was not observed at 1.0 ppm. Furthermore, 176 caused a change in rat 3Y1 fibroblast cell morphology at 50 µM. From the same collection, the isolation and characterization of a linear tetrapeptide, pupukeamide (177), was also described [98]. The compound showed no cytotoxicity against murine leukemia (P388) cells. The authors use the presence of pupukeamide (177) to propose an ecological link via bioaccumulation through three trophic levels, Lyngbya spp. to Styloccheitus longicaudus to Philinopsis speciosa. The next report concerning the collection from Shark's Cove in 1994 yielded five new depsipeptides, kulolide-2 (178), kulolide-3 (179), kulokai-nalide-1 (180), kulomo'opunalide-1 (181), kulomo'opunalide-2 (182), and the unprecedented macrolide, tolytoxin-23-acetate (183) [99]. Kulokekahi-lide-1 and -2 (184, 185) represent the most recent depsipeptides isolated from P. speciosa samples [100, 101]. Kulokekahi-lide-2 (185 [Fig. 8]) exhibited potent cytotoxicity towards P388, SK-OV-3, MDA-MB-435, and A-10 cells, with 184 being found to be significantly less active.

One of the more successful natural product stories from Hawaii concerns the genus Elysia. Investigations of this genus and its food source, Bryopsis sp., revealed the group of depsipeptides called the kahalalides. The first report involved both E. rufescens and Bryopsis sp., and yielded the aforementioned kahalalide F (76) [44]. Kahalalides A–E (77, 78, 186, 187, 188) were also reported from a collection of this mollusk [45]. Both collections of the organism occurred at Black Point during 1991. The acrylic octa- and nona-peptides kahalalide H (189) and kahalalide J (190) were also isolated from E. rufescens and, in common with other acyclic peptides, they are reported to lack significant cytotoxicity [102]. The most recent report of kahalalides from Hawaiian E. rufescens specimens details the isolation of four further kahalalides, kahalalides V–Y (191–194) from two collections made in Kahala Bay, Oahu, during the time period 2003–2004 [103]. Surprisingly, none of these new metabolites demonstrates any activity approaching that documented for 76.

Although there are eight reported species of Elysia in Hawaii, only one other species has been studied for its secondary metabolite production/sequestration, E. ornata. This sample was collected from Black Point, Oahu, in 1997, and afforded the biologically inactive kahalalide O (81) [47].

Miscellaneous Invertebrates

Cnidarians

One of the more infamous compounds to be discovered in Hawaii is the marine toxin known as palytoxin (PLTX) (195 [Fig. 9]). Native Hawaiians previously collected a “seaweed” from a tide pool in Muolea, Hana, Maui, and used it to tip their spear points with a preparation that contained palytoxin to make “strikes” more likely to be fatal. It was later discovered that this “seaweed” was actually a species of zoanthid called Palythoa toxi ca. Chemical investigations of P. toxica, collected specifically from Muolea, resulted in Moore and Scheuer’s first report in 1971 on the isolation of PLTX (195) [104]. It took another 10 years before the planar structure of PLTX was reported [105], and an additional year before the structure with its absolute configuration became available [106]. Palytoxin (195) has a molecular weight of approximately 3300 amu and is toxic to mice at 0.15 µg/kg [104], it also possesses potent anticancer activity [107]. Reinvestigations of Palythoa tuberculosa and P. toxica collected from the same location on Maui yielded two 42-hydroxypalytoxin stereoisomers (196, 197) [108]. These compounds exhibited different activities. P. tuberculosa afforded the 42-S-hydroxy-50-S-palytoxin (196) that is cytotoxic to HaCaT keratinocytes (EC50 of 9.3 × 10⁻¹⁰ M). The 42S-hydroxy-50R-palytoxin (197), isolated from P. toxica, had an EC50 of 1.0 × 10⁻¹⁰ M in the same assay. Comparatively, these stereoisomers are at least one order of magnitude less cytotoxic than PLTX (EC50 of 2.7 × 10⁻¹¹ M) [108].

The soft coral Sinularia abrupta collected near the Blowhole on the southeast coast of Oahu, yielded pukalide (Fig. 9 [198]), a highly functionalized furanocembranolide [109], now known to have a significant ecological function in the life cycle of soft corals [110].
Collection of the endemic blue octocoral *Anthelia edmondsonii* (now *Sarcocaula edmondsonii*) collected from the north shore of Oahu, near Waimea Bay, lead to the isolation of the highly oxygenated xeninic diterpenoids waixinicin A and B ([199, 200] [111]).

Punaglandins ([201–204]), a series of eicosanoids containing an unprecedented C-10 chloro-function, were isolated from the octocoral *Telescopium risis* collected at various sites along the coast of Oahu [112]. The octocoral is quite unusual in the respect that it lacks symbiotic algae. The report mentions no biological activity for this interesting class of molecule.

Investigations of a deep-sea coelenterate used in the jewelry making industry, *Gerardia* sp., or gold coral, stemmed from a collection made employing a minisubmarine working at a depth of 350 m. Initially referred to as *Parazoanthus* sp., the animal was later correctly identified as *Gerardia* sp., [113]. Interest in this organism was sparked by complaints of skin and mucous membrane reactions from the handling of freshly harvested coral. Unfortunately, no suitable laboratory bioassay was found to facilitate the hunt for the causative agent, but the brilliant fluorescence of the extract prompted the group to identify the responsible metabolites [113]. An EtOH extract made from the animals was found to be highly fluorescent [114]. Fractionation of this extract yielded 2-amino-3,9-dimethyl-5-dimethylamino-3H-1,3,4,6-tetrazacyclopent[e]azulene monohydrate (205), a zoanthathxin whose structure was solved employing X-ray crystallography [114]. Later in 1978, Schwartz et al. reported the isolation of two new fluorescent nitrogenous pigments. From the acidified aqueous fraction of the EtOH extract of the animal [Fig. 9], 205 and 2-amino-3,9-dimethyl-5-dimethylamino-3H-1,3,4,6-tetrazacyclopent[e]azulene (206 [Fig. 9]) were isolated [113]. In response to the longstanding debate of the biosynthetic origin of organic molecules in marine coelenterates (soft corals) between the animals themselves or the symbiotic zoanxanthellae they harbor, the authors concluded that the pigments recovered from these animals must be synthesized by the animals because of their depth of habitation (~350 m), where photosynthesis is most unlikely to occur.

Another commercially valuable coral, *Corallium* sp., or Hawaiian pink coral, was harvested from depths of 300–350 m from the Molokai Channel off Makapu’u, Oahu. After harvesting, polyps were scraped off of the animals’ endoskeleton and soaked in CH$_3$OH. Fractionation of the resultant extract led to the isolation of five diterpenes structurally related to xenincins, coraxenolide A, B, C, and D ([207–210], and corahobcin [211]) [115]. The structures of all isolates were resolved from the X-ray crystal structure determined for coraxenolide A (207).

Investigations of a collection of six other deep-sea (~360 m) gorgonians from waters off Makapu’u, Oahu, lead to the isolation of papakusterol (212) from all samples and 7-dehydropapakusterol (213) from only one sample. *Acanthagorgia* sp. Identifications of the organisms was pending at the time of publication, with only *Acanthagorgia* sp. being identified in the report [116].

A gorgonian from the family Paramuriceidae collected off Oahu at depths around 350 m yielded the new natural products 3-chloro-7-isopropyl-1,4-dimethyiazulene (214), 3-bromo-7-isopropyl-1,4-dimethyiazulene (215), and ehuazulene (216) [117]. The chloro- and bromo-isolates were previously known from synthesis [118]. A nitrogenous viscous blue oily azulene derivative, N,N-dimethylamino-3-guaiazulenylmethylene (217), was isolated from a different sample of the same species of organism, from the same location, and from the same depth as the one just discussed [119].

Hexane extraction of a deep-sea example of the gorgonian *Placogorgia* sp., collected from a depth of 350 m, yielded a tricyclic yellow crystalline guaianolide pigment that was fully conjugated and contained both keto and lactone functionalities (218) [120]. From the box jellyfish (*Carybdea alata* reclassified as *Alatina alata*), the 43–45 kDa protein toxins CaTX-A and B were isolated, and the CDNA and amino acid sequences for CaTX-A were also reported [121]. Hemolytic activity tests performed with sheep red blood cells showed 50% hemolysis at concentrations of 70 and 80 ng/mL for the two compounds, respectively. A crayfish toxicity assay performed with *Procambarus clarkii*, using CaTX-A, showed it to have an LD$_{50}$ of 5–25 mg/kg.

### Echinoderms

The earliest report concerning a marine natural product from Hawaiian waters concerned spinochrome M ([219] [Fig. 9]), a polyhydroxylated naphthoquinone pigment, isolated from the spines of six species of Hawaiian sea urchins, *Echinometra oblonga*, *Colobocentrotus atratus*, *Tripneustes gratilla*, *Echinithrix diadema*, *E. calamis*, and *Diadema paucispinum* [122]. This study...

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was undertaken to establish whether the chemical diversity of naturally occurring spinochromes actually matched that reported in the literature. Interestingly, the authors’ findings supported their suspicion that the literature contained a larger variety of spinochromes than actually occur in nature!

From the spines of two species of Echinithrix sea urchins, E. diadema and E. calamaris, collected from Kaneohe Bay, Oahu, 16 compounds, predominantly polyhydroxylated naphthoquinones, were isolated, with the following 11 being new natural products: 2-hydroxy-3-acetyl-naphthazarin (220), 2-hydroxy-6-ethyljuglone (221), 2-hydroxy-6-ethylnaphthazarin (222), naphthopurpurin (223), 2,7-dihydroxy-6-acetyljuglone (224 [Fig. 9]), 2,7-dihydroxy-3-ethyljuglone (225), 2,7-dihydroxynaphthazarin (226), 2,5-dihydroxy-3-ethylbenzoquinone (227 [Fig. 9]), 2-hydroxy-6-ethylnaphthazarin (228), 2,3,7-trihydroxy-6-acetyljuglone (229), and 2,3,7-trihydroxy-6-ethyljuglone (230) [123].

In 1968, the structure of the first pigment containing a four carbon unit attached to a naphthoquinone system was described; 2-methyl-8-hydroxy-2 H-pyran[3,2-q]naphthazarin (231 [Fig. 9]) [124].

Annelid
The chloroform (CHCl₃) extract of the annelid Thelepus setosus collected in Kaneohe Bay, Oahu, was separated by preparative TLC and found to contain five new bromophenol-related metabolites (232–236; 235 [Fig. 9]) whose biological activities have yet to be reported [125].

Acorn worms
Investigations of a new species of acorn worm belonging to the genus Ptychodera, collected at a depth of 30 m from a cave at Kinau Point off the island of Maui, led to the isolation of 11 new brominated compounds (237, 238 [Fig. 9], 239–241, 242 [Fig. 9], 243–245, 246 [Fig. 9], 247) [126].

Cyanobacteria

Lyngbya majuscula

Lyngbya majuscula, now Moorea producens [127], is the most studied marine cyanobacterial species, probably due to its notoriety as the causative agent for outbreaks of contact dermatitis, more commonly referred to as “swimmers’ itch,” in Hawaii. The new genus name Moorea is an acknowledgement of the many years of work that Richard E. Moore and his group undertook with this marine cyanobacterium that is phylogenetically distinct from the freshwater Lyngbya, whose name is retained based on precedent. The main toxic component of L. majuscula (now M. producens), lyngbyatoxin A (248 [Fig. 10]), was first isolated in 1971 from a Laie Bay collection on Oahu [128], but its structure was not resolved until eight years later [129]. Other investigations concerning subsequent collections of the Kahala Beach strain of L. majuscula (now M. producens) yielded 18 additional metabolites. Two major constituents of the lipophilic extract, the epimeric lipopeptides majusculamide A and B (249, 250) [130], were the next two compounds to be described, followed by (S)-butyramido-γ-butyrolactone (251) [131], and then (–)-trans-7-(5H)-methoxytetradec-4-enoic acid (252) together with malyngamides A (253) and B, the latter two compounds only being partially characterized [132]. The structure of malyngamide A (253) was eventually published in 1979 [133]. The next examination of the Kahala beach strain yielded malyngolide (254), which was found to have antibiotic activity against Mycobacterium smegmatis, Streptococcus pyogenes, Staphylococcus aureus and Bacillus subtilis [134]. Following this report came the next class of compounds to come from L. majuscula, the pukeleimides, 1H-pyrrol-2(5H)-one derivatives, pukeleimide C (255 [Fig. 10]) being the first one to appear in the literature [135]. The structure of this compound was deduced by X-ray crystallographic examination. The authors also determined that their isolate exists as a racemic mixture having an optical rotation of 0 and no apparent CD activity. From the same sample of L. majuscula that yielded pukeleimide C (255), pukeleimides A, B, and D–G (256–261) were also isolated and their structures proposed on the basis of spectroscopic data interpretation [136]. Lyngbyatoxins B and C (262, 263), also from the Kahala beach strain of L. majuscula, were identified as irritants via a mouse ear irritant test [137]. The final report on L. majuscula compounds described isomalyngamides A and B (264, 265), which were shown to have lethal toxicity towards the crayfish Procambarus clarkii (250 and 500 µg/kg, respectively) [138]. From the dichloromethane (CH₂Cl₂)-soluble part of a 70% EtOH extract made from a sample of L. aestuarii Liebmann ex Gomont collected at Kamalo Jetty on Molokai, 2,5-dimethyldodecanoic acid (266) was reported and found to have pH-dependent herbicidal activity at concentrations above 200 ng/mL (Lemna minor growth inhibition with an ED₅₀ of 0.5 µg/mL) [139]. Three samples of the genus Symplaca, all from Oahu, yielded five new peptides, malyangamides A–E (267–271) [140–142] and symplastatin 3 (272) [143]. In an attempt to investigate Hawaiian samples of Symplaca hynoides, cyanobacterial samples were collected from waters next to Ala Moana Beach Park. Later, it was
discovered that the sample was primarily *Sympla laete-viridis*, which is morphologically similar to *S. hynoides*, and was contaminated with the species of interest. Re-collection, specifically of *S. laete-viridis*, yielded malevamides A–C (267–269) [140]. The second investigation of *S. laete-viridis*, from the same location, led to the isolation of malevamide E (271) [141], which was shown to have a dose-dependent inhibitory effect on the store-operated calcium ion entry in thapsigargin-treated human embryonic kidney (HEK) cells at concentrations ranging from 2–45 µM. This was the first report of this type of depsipeptide as a modulator of calcium ion channels. In the paper, the authors also discuss a potential biosynthetic relationship between malevamide E (271) [Fig. 10]) and dolastatin 14 (273) amongst *S. laete-viridis* and its grazer, *Dolabella auricularia*. Malevamide D (270) was isolated from a sample of *S. hydnoides* collected off the south shore of Oahu [142].

Sympropatin 3 (272), a dolastatin 10 analogue, was isolated from a tumor selective extract of *Sympla* sp., VP452, collected from depths of 3–4 m inside Kaneohe Bay, Oahu [143]. In bioassays aimed at assessing the in vitro cytotoxicity of 272, it was shown to have IC₅₀ ranging from 3.9–10.3 nM. Its mode of action, like that of dolastatin 10, was microtubule disruption.

Two articles by a San Diego-based group report on two new classes of natural products from a sample of *Leptolyngbya crossbyana* collected at a depth of 20 m from Honaunau, Big Island [144, 145]. The first of these reports describes the crossbyanols A–D (274 [Fig. 10], 275–277), toxic penta-cyclic brominated polyphenyl ethers [144]. In a variety of bioassays, antimicrobial, cytotoxicity, voltage-gated sodium channel, and brine shrimp lethality, all compounds, except for crossbyanols C and D, demonstrated activity in at least one assay. The second report on the extract describes the honaucins A–C (278, 279, 280 [Fig. 10]), potent inhibitors of inflammation and bacterial quorum sensing [145].

**Bacteria**

A shallow-water sediment sample collected in 1996 from Waipu Beach Park on the southeast shore of Oahu yielded the first Hawaiian bacterial strain, a *Streptomyces* sp., [strain BD-26T (20)] shown to contain interesting secondary metabolites, four new α-pyrones, wailupemycins A–C (281–283), and 3-epi-5-deoxyenterocin (284 [Fig. 11]). Two of the isolates, wailupemycin A (281) and 284, exhibited selective antibacterial activity towards *E. coli* and *S. aureus*, respectively [146]. *Streptomyces* sp., strain BD-18 T (41), isolated from sediments collected at the mouth of Halawa Stream on the north shore of Oahu, whose CCl₄ and CHCl₃ solubes were shown to be antimicrobial, yielded a group of quinone-containing metabolites called halawanones A–D (285–288), together with the known nanomycin D [147]. The absolute configurations of the new compounds were determined employing both NMR and CD analyses. Strain BD21-2, *Streptomyces* sp., originated from a shallow-water sediment sample from Kailua Beach, Oahu. The EtOAc extract of the whole broth culture yielded the ester bonactin (289 [Fig. 11]), which showed weak to moderate broad spectrum antimicrobial activity towards a variety of microbes at the 100 µg per disc (6 mm dia.) level; *Bacillus megaterium* (zone of inhibition [Zol] = 8 mm), *Micrococcus luteus* (Zol = 8 mm), *Klebsiella pneumoniae* (Zol = 8.5 mm), *S. aureus* (Zol = 7 mm), *Alicyclobacillus faecalis* (Zol = 10 mm), *E. coli* (Zol = 9 mm), and *Saccharomyces cerevisiae* (Zol = 7.5 mm); the first acyclic ester related to the nonactins to do so [148].

*Nocardiosis dasonvillei*, actinomycete strain BH-609, purified from sediments collected along the high-tide line at Kahaka Beach Park, Kauai, was found to produce rare N-glycosyl indoles, kahakamides A and B (290, 291) related to neosidomycin [149]. This class of microbial compound contained only two other members prior to this report. Kahakamide A exhibited weak antimicrobial activity against *B. subtilis*.

From the surface of a nudibranch and the sponge *Mycale armata* recovered from waters off Oahu, pure cultures of *Pseudoalteromonas rubra* were established. The acetone diethyl ether (2:3) extract of the culture was shown to have significant cytotoxicity towards human ovarian adenocarcinoma cells (*SKOV-3*). A work-up of this extract yielded the 2-substituted prodiginine, 2-(*p*-hydroxybenzyl)prodigiosin (292), that was active towards *SKOV-3* cells (IC₅₀ of 1.3 µM) [150]. A second strain of *Pseudoalteromonas* (CMMED 290), also isolated from the surface of a nudibranch, this time collected in Kaneohe Bay, Oahu, produced two highly brominated compounds identified as 2,3,5,7-tetra-bromobenzofuro[3,2-b]pyrrole (293) and 4,4′,6-tribromo-2,2′-biphenol (294). Both compounds exhibited antimicrobial activity against methicillin-resistant *S. aureus* (IC₅₀ of 1.93 µM for 293 [Fig. 11] and 2.19 µM for 294 [Fig. 11]) [151].

From a depth of 1714 m off of Loihi Seamount, 30 km south east of the Big Island, the basalt-weathering bacterium *Halomonas* sp. strain LOB-5 was isolated. Cultivation of the bacterium followed by purification employing solid-phase extraction (XAD-2 resin) and RP-HPLC yielded six new aphilphilic photoreactive siderophores, loihichelins A–F [295 [Fig. 11], 296–300] [152].

**Fungi**

Interestingly, all of the reports concerning fungal isolates derived from Hawaiian waters are from research groups based on the mainland USA. The first of these appeared in 1989 and concerned *Helicascus kanaloanus* ordered from the American Type Culture...
Collection (ATCC 18 591), initially derived from a Hawaiian Mangrove. After cultivation in liquid media and extraction with EtOAc, the fungus was found to have produced two isomeric δ-lactones, helicasolides A and B (301, 302) [153].

The next report concerning a marine fungus did not appear until 2003 and related to the extract made from Myrothecium verrucaria isolated from the sponge Spongia sp., collected from waters off of Maui. This investigation reported three new trichotheccenes (303–305) and their cytotoxic properties. Activity against murine and human tumor cell lines was noted for 3-hydroxyoroidin E (303 [Fig. 12]) and 13′-acetyltrichoverrin B (304 [Fig. 12]), with miophytocen C (305) being found inactive in the same assays [154].

A strain of Exserohilum rostratum, originally associated with a cyanobacterial mat found off the coast of Lanai, yielded rostratins A–D (306–309). All rostratins, for which their absolute configurations are given, showed cytotoxicity against human colon carcinoma (HCT-116) cells with IC50 values of 8.5, 1.9, 0.76, and 16.5 µg/mL for tropolactone A, B, and C (311–313), respectively [157]. The strain of A. insulicola that produced azonazine (315), a unique hexacyclic dipeptide, was isolated from a marine sediment sample from Hawaii, with no further details given on the organism’s origin [158]. Azonazine (315) proved to be inactive in applied assays [158]. A second study of A. insulicola, once again from a sediment collected in Hawaii, exact location not indicated, described the isolation of two new tripeptides, 316 and 317, both of which were devoid of activity in the applied test systems [159].

The final paper included in this review concerns a strain of Malbranchea graminicola isolated from an unidentified invertebrate collected by hand using self-contained underwater breathing apparatus (SCUBA) from Kona, Hawaii [160]. Investigation of the biactive extract produced by the fungal culture led to the isolation of (−)-spiromalbramide (318) and (+)-isomalbrancheamide B (319), both apparently devoid of any bioactivity but of some chemical interest. The inspired part of this research was enrichment of the growth media of the fungus with bromine salts that caused the fungus to also produce the brominated compounds (+)-malbrancheamide C (320 [Fig. 12]) and (+)-isomalbrancheamide C (321) [160], hence revealing something more concerning the biosynthetic power of this microbe.

**Concluding Comments**

Prior to starting this review we had only an inkling of an idea of the amount of research into Hawaiian marine organisms the groups led by Richard E. Moore and Paul J. Scheuer had undertaken. In many ways this is almost a review of their groups’ pioneering research in the area of marine natural products from Hawaiian waters, hence the dedication at the start of the review. This research led to the discovery of many unique molecules being reported for the first time, palytoxin (195) [104] being a prime example. Another highlight would have to be the investigations undertaken with cyanobacteria that spawned a whole new area of research and led to the discovery of many new classes of molecules, including the lyngbyatins, puleuimides, and the malevamides. In reality, much of the research undertaken in Hawaii formed the foundation of what we now know as modern marine natural products research.

Aside from the wonderful achievements highlighted above, our reading of the 160 publications that compose this review, plus many others read during the preparation of this review but not included, have left some other indelible impressions. The first of these is how little we actually still know about the hundreds of chemical entities discussed. Yes, we know a good deal about their chemical structures, their absolute configurations and the like, but for the vast majority, we know little or nothing about their roles in nature and, in a relative sense, our knowledge of their potential value to us as a species is restricted to a hand full of bio-assays that mainly involve anticancer and antimicrobial studies. It is also astounding, given the amount of research funds, probably many millions of dollars, provided to the researchers cited in this review over the past 20–25 years by organizations like the US National Institutes of Health (NIH), that other organizations in Hawaii on islands other than Oahu, particularly in recent times, have not received similar funding or been encouraged to establish centers where the environment has been the subject of little or no scientific research investigation. We had also hoped to...
be citing at least one success story in terms of a compound that made it to the market place, instead we have hundreds of chemical entities that are apparently of no real use! The one exception to this seemingly harsh critique would have to be the antitumoral compound kahalalide F (76) [44], which successfully reached phase II clinical trials for the treatment of patients with severe psoriasis. Unfortunately, the organization behind the development process, the Spanish-based pharmaceutical company PharmaMar, has apparently deprioritized further development of kahalalide F, probably due to a lack of significant efficacy and/ or funds.

Our last two major impressions relate to the general lack of careful documentation of species being investigated and the environments from which they were collected, as well as the continued totally random approach as to how samples are selected for study. In the early years, the 1960s and 1970s, research was being undertaken by groups of chemists who were breaking new ground and probably had limited exposure to biology and to the importance of accurate taxonomic identifications and all this encompasses. Nowadays, most reports have this information in some form, but still we see articles where this is not the case [158, 159], and some that do not even provide identification to the level of order [160]. Molecular taxonomic techniques can now be carried out routinely, and the importance of good taxonomy should be paramount in ensuring that natural products research continues to be relevant and reproducible. Finally, with the advent of the “omics”-age (e.g., genomics, proteomics), it is probably time for researchers to coordinate what they do to ensure approaches become systematized, clearly documented, and that all isolates are assessed in as many and varied bioassay systems as is possible. Also, it would make far more sense to make careful surveys of the biodiversity in specific areas around the Hawaiian Islands and collect samples representative of these so as to enable a meaningful picture of their ecology and bioactivity to be developed. This probably means an organization should become responsible for the creation of a Hawaiian natural products repository. This repository would be responsible for coordination, storage, and documentation of any natural products and natural product-related activities undertaken within the State of Hawaii; Hawaii is an absolutely unique and special place in our world and its natural resources need to be carefully and sustainably managed and used, or not used, for the benefit of everyone now and into the future.

Supporting information

Figs. 1–225 and Table 15 contain the structural formulae of compounds discussed in the review together with the taxonomy and collection location of the compounds' source organism, where known, as well as the main structural class to which the compounds belong, and either their trivial or semi-systemic name.

Conflict of Interest

The authors declare no conflicts of interests.

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