Lamellarins and Related Pyrrole-Derived Alkaloids from Marine Organisms

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1. Introduction

Marine organisms have proven to be rich sources of unique alkaloids. In earlier surveys we comprehensively reviewed several intriguing groups of marine alkaloids, including the manzamine- and bromotyrosine-derived alkaloids. The number of reported marine alkaloids continues to grow at an increasing rate, and in recent years, the lamellarins and related pyrrole-derived alkaloids (lukianols, polycitrins, polycitones, storniamides, didemnimides, ningalins, and purpurone, Table 1)⁻ have been regarded as a group of marine alkaloids with promising biological activities. As a result, these compounds have been the subject of several previous reviews regarding their chemistry and pharmacology.⁻ In addition, the lamellarins and related pyrrole-derived alkaloids have also provoked a great deal of interest in regard to their synthesis (Table 2).·⁻

Lamellarins are a group of DOPA-(2-amino-3-(3′,4′-dihydroxyphenyl)propionic acid)-derived pyrrole alkaloids that were first isolated from the prosobranch mollusc *Lamellaria* sp. in 1985 by Faulkner and co-workers. Since then, more than 70 different lamellarins and related naturally occurring pyrrole-derived alkaloids have been reported (Table 1). Most of the lamellarins, lukianols, polycitrins, polycitones, storniamides, and ningalins possess a 3,4-diarylated pyrrole 2-carboxylic acid ester or amide moiety as the common structural subunit. They have been isolated from widely varying locations and diverse marine organisms, such as marine prosobranch molluscs,· ascidians (tunicates),"⁻⁻ and sponges."' The diversity of the producing organisms suggests a potential microbial link to their biosynthesis.

The lamellarins and related pyrrole-derived alkaloids have shown a diverse range of bioactivities such as cytotoxicity and antitumor activity,""⁻·⁻ reversal of multidrug resistance (MDR),"""⁻ HIV-1 integrase inhibition,"' antibiotic activity, human aldose reductase (h-ALR2) inhibition, cell division inhibition, immunomodulation,· antioxidant

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activity, and feeding deterrence, making these compounds a particularly important subject for research. In this review we summarize the isolation, structure determination, biological activities, and synthetic studies of lamellarins and related pyrrole-derived alkaloids including lukianols, polycitrins, polycitones, storniamides, didemnimides, ningalins, and purpurone from different marine organisms since the first report of lamellarins in 1985 until April of 2007.

2. Isolation and Structure Determination of Lamellarins and Related Pyrrole-Derived Alkaloids from Marine Organisms

The lamellarin skeleton was first isolated and identified in 1985 from the Palauan marine prosobrach mollusc *Lamellaria* sp.[3] Later in 1988 four additional members, lamellarins E–H **6**–**8** and **37**, were found in the didemnid ascidian *Didemnum chartaceum* collected from the Republic of the Seychelles. In 1992 the related alkaloids lukianols A **56** and B **57** were recovered from an unidentified Pacific tunicate, while in 1993 lamellarins I–M **10**–**12**, **15**, and **38** and the triacetate of lamellarin N **41** were isolated from a Great Barrier Reef colonial ascidian, *Didemnum* sp. In 1994, lamellarins O **52** and P **53** were isolated from a southern Australian marine sponge *Dendrilla cactos*. Lamellarins Q **54** and R **55** were also isolated from a geographically distinct re-collection of *Dendrilla cactos*.

The lamellarins are a growing family of marine alkaloids, and to date, over 70 lamellarins and related pyrrole-derived alkaloids have been isolated and identified (Tables 1, 3, and 4; Figures 1 and 2). The lamellarins and related compounds have a pyrrole ring as a core component of their skeleton. The molecules fall into two structural groups depending on whether the central pyrrole ring is fused (Group I, lamellarins **1**–**51**) or unfused (Group II, lamellarins O–R **52**–**55**). Group I could be further divided into two subsections, viz., compounds possessing an olefin at C-5 and C-6 (Figure 1, Table 4, lamellarins **32**–**51**) and those in which this olefin is saturated (Figure 1, Table 3, **1**–**31**).

2.1. Isolation and Structure Determination of Lamellarins

2.1.1. Lamellarins A–D—In 1985, Faulkner and colleagues reported the isolation and structural elucidation of four aromatic metabolites, which were obtained from the marine prosobranch mollusc *Lamellaria* sp. (family Lamellariidae) collected in the waters of Palau. These compounds comprised a new class of marine natural product and were named lamellarins A–D **1**, **32**, **3**, and **35**. Lamellarin A **1** is an optically inactive pale yellow prism that occurred as an inseparable racemic mixture of two geometrical isomers due to restricted rotation about the C-1 and C-11 bond. Its structure was determined by a single-crystal X-ray crystallographic study, while the structures of lamellarins B–D **32**, **3**, and **35** were assigned by spectroscopic data. Lamellarin C **3** was also isolated from the prosobranch mollusc *Coriocella hibyae*. Lamellarins A **1**, B **32**, and C **3** and the triacetate of lamellarin D **36** were found from both prosobranch molluscs and the marine ascidians.,

2.1.2. Lamellarins E–H—In 1988, Fenical's group reported four new alkaloids of the lamellarin class, lamellarins E–H **6**–**8** and **37**. They were isolated from the Indian Ocean marine colonial didemnid ascidian *Didemnum chartaceum* (Sluiter, 1909, Didemnidae,

Ascidiacea). The structure of lamellarin E **6** was elucidated by spectroscopic and X-ray crystallographic methods, while lamellarins F–H **7**, **8**, and **37** were determined by interpretation of NMR spectral data. Advanced 2D NMR techniques mostly detailed HMBC correlations were utilized in 1996 during the structure assignment of lamellarin H **37**.

2.1.3. Lamellarins I–M and the Triacetate of Lamellarin N—Bowden's group reported six new lamellarin-class alkaloids, lamellarins I **10**, J **11**, K **12**, L **15**, and M **38** and the triacetate of lamellarin N **41** obtained from an Australian colonial ascidian *Didemnum* sp. The structures were deduced by ^{13}C–^{1}H shift-correlated 2D NMR and NOE correlations. Lamellarins A **1**, B **32**, and C **3** and the triacetate of lamellarin D **36** were also isolated from this Pacific ascidian. Moreover, extraction of the same ascidian species collected from Little Broadhurst Reef also yielded lamellarins A **1**, B **32**, C **3**, I **10**, K **12**, and M **38**. These isolation studies suggested that lamellarins A–D **1**, **32**, **3**, and **35**, obtained from *Lamellaria* sp., were likely sequestered from the ascidian diet of this mollusc.

2.1.4. Lamellarins O–R—In 1994, two new unstable, oily lamellarin members, lamellarins O **52** and P **53**, were isolated from the marine sponge *Dendrilla cactos* collected during a trawling operation in Bass Strait, southern Australia, by Capon et al. Both metabolites **52** and **53** readily decomposed with **53** being slightly more stable than **52**. The increased stability was assumed to be a product of hydrogen bonding in **53**. No biological data could be obtained due to their reported instability and the small amounts of these two alkaloids available from natural sources. Later in 1995 two new stable oily alkaloids, lamellarins Q **54** and R **55**, were obtained by the same research group from a geographically distinct recollection of the Australian marine sponge *D. cactos* harvested by SCUBA off the coast of New South Wales. The structures of **52**–**55** were elucidated by spectroscopic analysis and chemical transformation. The structure of lamellarin O **52** was confirmed later by single-crystal X-ray analysis.

2.1.5. Lamellarin S—In 1996, Urban and Capon isolated lamellarin S **18** along with the known lamellarin K **12** from an Australian tunicate *Didemnum* sp. collected by SCUBA near Durras, New South Wales. The structure was determined by spectroscopic analysis. Lamellarin S **18** was the first example that demonstrated atropisomerism. The C-1 phenyl substituent in the lamellarins is generally rotationally restricted and capable of producing atropisomerism. No other lamellarins, however, have been reported to possess optical properties. Lamellarin S **18** initially displayed a positive optical rotation, indicating it is at least enantiomerically enriched. Repeated optical rotation measurements of **18** over several months revealed slow racemization with a half-life calculated to be ca. 90 days. A Serena software molecular modeling experiment indicated that the lowest energy barrier to rotation for **18** was 84 kJ/mol with both atropisomers being of comparable energy.

2.1.6. Lamellarins N and T–X, Lamellarin T 20-Sulfate, Lamellarin U 20-Sulfate, Lamellarin V 20-Sulfate, and Lamellarin Y 20-Sulfate—In 1997, nine new alkaloids of the lamellarin class, lamellarins T **19**, U **22**, V **24**, W **42**, and X **43** and 20-sulfates of lamellarins T **21**, U **23**, V **25**, and Y **27** together with the known lamellarin N **40** were isolated from an unidentified ascidian obtained from the Trivandrum coast of India.

The structures of lamellarins T–X **19**, **22**, **24**, **42**, and **43** and the four 20-sulfate derivatives of lamellarins T **21**, U **23**, V **25**, and Y **27** were identified by interpretation of spectroscopic data. This was the first example of lamellarin sulfates. Lamellarin U **22** was also isolated from the prosobranch mollusc *Coriocella hibyae* in 1999.

2.1.7. Lamellarin Z, Lamellarin B 20-Sulfate, Lamellarin C 20-Sulfate, Lamellarin L 20-Sulfate, and Lamellarin G 8-Sulfate—Five novel lamellarin members, lamellarin Z **28**, the 20-sulfated derivatives of lamellarins B **34**, C **5**, and L **17**, and lamellarin G 8-sulfate **9** along with the known lamellarins A **1**, B **32**, C **3**, E **6**, G **8**, and L **15** plus the triacetate derivatives of lamellarins D **36** and N **41** were isolated from a Great Barrier Reef ascidian *Didemnum chartaceum* Sluiter (Didemnidae). They were identified by interpretation of spectroscopic data. Among them, lamellarin Z **28** is the first example of a dimethoxylated lamellarin, while the 8-sulfated derivative of lamellarin G **9** is the first example of this class of compounds sulfated at the C-8 position.

2.1.8. Lamellarin α 20-Sulfate—In 1999, the lamellarin α 20-sulfate **46** was isolated from an unidentified ascidian collected from the Arabian Sea coast of India. The structure was determined by ^{1}H and ^{13}C NMR data and high-resolution FAB mass measurement. The spectral data indicated that lamellarin α 20-sulfate **46** differs from lamellarin U 20-sulfate **23** by addition of a double bond at C-5 and C-6.

2.1.9. Lamellarin β—A novel lamellarin alkaloid, lamellarin β **29**, along with previously reported lamellarins G **8** and L **15** were obtained from a purple unidentified encrusting marine ascidian *Didemnum* sp. (other than *D. chartaceum*) collected in the Indian Ocean. The structure of lamellarin β **29** was elucidated by spectroscopic methods including 2D NMR experiments. Similar to lamellarin S **18**, energy minimization of **29** was studied using Serena and pcmodel, which adopted an MMX force field. The rotational barrier of the bond between C-1 and C-11 was in excess of 80 kcal/mol. Due to the highly restricted rotation of the catechol ring, the molecule has the potential to adopt a chiral configuration. However, **29** is racemic, as observed in all previously isolated lamellarins (except for lamellarin S **18**) and suggests thermal racemization is a facile process.

2.1.10. Lamellarins γ, α, ε, ζ, η, φ, and χ—In 2004, lamellarins γ **30**, α **45**, and ε **48** along with eight known lamellarin alkaloids, lamellarins I **10**, K **12**, M **38**, U **22**, C-diacetate **4**, K-diacetate **13**, K-triacetate **14**, and X-triacetate **44**, were isolated from the Indian red colonial ascidian *Didemnum obscurum* F. Monniot, 1969 (Didemnidae) collected from the Indian Tiruchandur coast during February 2002. One year later, in 2005, the same research group reported four new lamellarin alkaloids, lamellarins ζ **49**, η **50**, φ **51**, and χ **31** along with seven known lamellarins, lamellarins F **7**, I **10**, J **11**, K **12**, lamellarin K triacetate **14**, lamellarin L triacetate **16**, and lamellarin T diacetate **20** isolated from the same ascidian collected from the same location but in August 2002. Lamellarin α **45** was synthesized in 2002. Structures were established using NMR spectroscopic techniques. The structure of lamellarin K-triacetate **14** was further confirmed by X-ray crystallographic analysis and is optically inactive. The X-ray structure revealed that the crystal was racemic with equal amounts of each atropisomer.

2.2. Isolation and Structure Determination of Pyrrole-Derived Alkaloids Related to Lamellarins

2.2.1. Lukianols A and B—Lukianols A **56** and B **57** were isolated from an unidentified encrusting Pacific tunicate collected by SCUBA in the lagoon of the Palmyra atoll by Scheuer's group in 1992. Their structures were elucidated by spectral methods. Lukianol B **57** is an iodo-substituted lukianol A **56** which may be considered as the ring-closed analogue of lamellarin O **52**. The basic structural feature of the lukianols is an *N*-alkylpyrrolecarboxylic acid, which is quite rare among natural products.

2.2.2. Polycitones A and B, Prepolycitrin A, and Polycitrins A and B—Three alkaloids, polycitone A **58** and polycitrins A **60** and B **61**, were isolated in 1994 from the Indo-Pacific marine ascidian *Polycitor* sp. collected in Sodwana Bay, South Africa. The *Polycitor* sp. is a translucent white colonial tunicate. These three compounds were the first examples of two new classes of marine alkaloids with unprecedented skeletons that maybe biogenetically related to the lamellarins. Six years later, in 2000, two additional related alkaloids, polycitone B **59** and prepolycitrin A **62**, were isolated from the marine ascidian *Polycitor africanus* (order Aplousobranchia, family Polycitoridae). *P. africanus* is also a translucent white or bluish colonial tunicate collected by hand using SCUBA in the lagoon of Toliara, Madagascar, or the lagoon of Mayotte, Comoros Islands. The structures of these compounds were determined using NMR and HREIMS data. Both polycitrins A **60** and B **61** contain a maleimide unit. The structure of polycitone A **58** was confirmed by single-crystal X-ray diffraction analysis. In fact, the crystallographic analysis was performed on the penta-*O*-methyl derivative of **58** with both **58** and the derivative yielding poorly diffracting crystals of highly anisotropic shape. Polycitone B **59** is a highly unsaturated aromatic structure with 21 units of unsaturation. Interestingly, pre-polycitrin A **62** was previously synthesized as an intermediate in a biomimetic synthesis of polycitrin A **60**. Isolation of prepolycitrin A **62** could support the earlier suggestion that it might be the bioprecursor of polycitrin A **60**. The structure relationship between the *N*-substituted polycitone A **58** and polycitone B **59** resembles the relationship between lamellarins O **52** and Q **54**. According to the description of the animal material *Polycitor* sp. and the co-occurrence of the metabolites of **58**, **59**, and **62** from *P. africanus*, the unidentified species collected in July 1992 might be taxonomically identical to the investigated *P. africanus* that was first identified by Monnitor in 1998.

2.2.3. Storniamides A–D—Storniamides A–D **63**–**66**, a new family of peptide alkaloids, were isolated from a Patagonian sponge *Cliona* sp. (family Clionidae) collected during low tide (–0.5 m) at Punta Verde, near San Antonio Oeste province of Rio Negro, Argentina, in 1996. The crude ethanolic extract of the marine sponge showed antibiotic activity against Gram-positive bacteria. Purification of the individual constituents was accomplished by bioassay-guided fractionation and purification to reveal storniamides A–D **63**–**66**. The structures of storniamides A–D **63**–**66** were determined by HRFABMS and a combination of 1D and 2D NMR techniques (COSY, NOESY, homonuclear 2DJ, HETCOR, and COLOC). Storniamide A **63** was a key for the structure elucidation of this family of compounds since the substitution pattern of the aromatic rings in **63** was extremely simple. Characterization showed that each storniamide differs only in the oxygenation pattern within the peripheral aromatic rings.

2.2.4. Didemnimides A–E and Cyclized Didemnimide—In 1997, four predator-deterrent alkaloids possessing a novel indole–maleimide–imidazole carbon skeleton, didemnimides A–D **67**–**70**, were isolated from the Caribbean ascidian *Didemnum conchyliatum* (Sluiter, 1898, family Didemnidae) collected from the blades of the seagrass *Thalassia testudinum* in the mangrove channels of Sweetings Cay, near Grand Bahama Island. The structure of didemnimide A **67** was identified by a single-crystal X-ray diffraction analysis, while didemnimides B–D **68**–**70** were determined by combined spectral methods, especially 1D and 2D NMR methods. The didemnimides **67**–**70** were the first examples of a new alkaloid structural class and add to a relatively small group of naturally occurring maleimides. In 1998, didemnimide E **71** was isolated from the ascidian *Didemnum granulatum* collected in Brazil.

A less polar and deep purple cyclized didemnimide alkaloid **72** was isolated from the same Caribbean mangrove ascidian in 1999. Compound **72** is the cyclization product of didemnimide A **67** formed via a C-2 indole condensation with the imidazole nitrogen and represented the first alkaloid to be isolated with this cyclized indole–maleimide–imidazole structure.

2.2.5. Ningalins A–D—Four aromatic alkaloids, ningalins A–D **73**–**76**, were isolated from an unidentified Western Australian ascidian of the genus *Didemnum* collected in Western Australia near Ningaloo Reef by Fenical's group in 1997. The ningalins are a class of natural alkaloids that have a 3,4-dihydroxy-phenylalanine (DOPA)-derived *o*-catechol moiety. The four polar and highly colored ningalins A–D **73**–**76** are composed of several condensed aromatic systems with the unified theme that all appear derived via condensation of DOPA amino acid units, three of which possess highly unsaturated, new carbon skeletons. Their structures were identified by interpretation of spectral data, especially 2D NMR analysis. In the highly condensed alkaloids, steric crowding forces several catechol rings into twisted configurations, resulting in unexpected shielding and deshielding of several proton shifts in their NMR spectra. NMR analyses and subsequently computer modeling studies illustrate that phenyl rings in ningalins B–D **74**–**76** adopt low-energy conformations at approximately 90° to the planes of the molecules. Although this conformation appears to restrict rotation, creating the possibility of optical activity, the molecules appear to be racemic. Similar to most of the lamellarins, the energy barriers to rotation and helical racemization are low and the racemization is a facile process. Accordingly, ningalins A–D **73**–**76** showed zero rotation at the sodium D line.

2.2.6. Purpurone—Purpurone **77**, whose name reflects the purple color of the natural product, was isolated from the marine sponge *Iotrochota* sp. collected in September 1983 at the Koror Island, Palau. The structures of purpurone **77** and ningalin D **76** are very similar (Figure 2). Purpurone **77** was reported 4 years earlier than that of ningalin D **76**. Purpurone **77** cannot adopt a planar geometry due to the steric interaction between H-12 and H-12′ (Figure 2). This could result in an optically active material; however, no optical rotation was observed for **77**.

3. Biological Activities

At present, more than 70 lamellarins and related pyrrole-derived alkaloids have been isolated and identified. They not only possess unique structural features but also exhibit interesting and significant biological properties, including cytotoxicity and antitumor activity,[""-,-] multidrug resistance (MDR),["""-] HIV-1 integrase inhibition,['"] antibiotic activity, human aldose reductase (h-ALR2) inhibition, cell division inhibition, immunomodulatory activity,[,] antioxidant activity, and feeding deterrence.

3.1. Biological Activities of Lamellarins and Related Pyrrole-Derived Alkaloids

3.1.1. Cytotoxicity and Antitumor Activity—A considerable number of lamellarins and related pyrrole-derived alkaloids have been found to be cytotoxic to a wide range of cancer cell lines. The most potent of these compounds (lamellarins D **35**, K **12**, and M **38**) exhibited cytotoxicity values in the mid-to-high nanomolar range (38–110 nM). Lamellarins C **3** and U **22** demonstrated potent cytotoxicity against 10 human tumor cell lines (A549, HCT-116, LOX IMVI, MALME-3M, MCF-7, MOLT-4, OVCAR-3, PC-3, SF-295, UO-31) with IC_{50}'s ranging from 0.4 to 19.4 nM. Lamellarin D **35** has potent cytotoxic activity against various tumor cells, especially to human prostate cancer cells (DU-145, LNCaP) and leukemia cells (K562). Lamellarin D **35** is a potent inhibitor of DNA topoisomerase I[,] and a potent pro-apoptotic agent with cytotoxic action that is fully maintained in MDR cells compared to the sensitive parental cell line. Lamellarin D **35** maintained a marked cytotoxicity toward cell lines resistant to the reference topoisomerase I poison camptothecin. Bailly's group hypothesized that topoisomerase I is not the only cellular target for camptothecin, and lamellarin D **35** acts on cancer cell mitochondria to induce apoptosis. Such a mechanism would reinforce the pharmacologic interest of the lamellarins and define lamellarin D **35** as a lead in the search for treatments against chemoresistant cancer cells.

Lamellarins I **10**, K **12**, and L **15** exhibited comparable and significant cytotoxicity against P388 and A549 cultured cancer cell lines ($IC_{50} \approx 0.5$ nM against each cell line). The tri-*O*-acetyl derivative of lamellarin K showed remarkable selectivity against the A549 human lung cancer cell line ($IC_{50} \approx 7.6$ nM).[,] In the NCI 60 cell-line panel, lamellarin N **40** showed some selectivity toward the melanoma cell lines SK-MEL-5 ($LC_{50} = 1.87 \times 10^{-7}$ M) and UACC-62 ($LC_{50} = 9.88 \times 10^{-6}$ M). Compounds lamellarin ζ **49**, lamellarin χ **31**, lamellarin L triacetate **16**, and lamellarin F **7** have shown excellent activities against colorectal cancer cells (COLO-205). Cytotoxicity toward HeLa cells of lamellarin H **37**, lamellarin α **45**, and lamellarin α 13, 20-disulfate **47** was measured using the MTT [3-(4,5-dimethythiazol-2-yl)-2,5-diphenyltetrazolium bromide] dye as an indicator of cell survival with LD_{50}s of 5.7, 5.1, and 29 μM, respectively.[,] The MTT assay of lamellarin α-20 sulfate **46** toward HeLa cells displayed the least toxicity with an LD_{50} of 274 μM. Lamellarin H **37** and lamellarin α **45** were tested against a panel of eight human tumor cell lines. Both compounds exhibited good potency and selectivity (**37**, mean $IC_{50} = 4$ μM, min/max IC_{50} ratio = 20; **45**, mean $IC_{50} = 2.9$ μM, min/max IC_{50} ration = 10) although the selectivity patterns differed. Lamellarin β **29** showed cytotoxicity against human promyelocytic leukemia HL-60 cells with an IC_{50} of 11.6 nM. The lamellarin analogues were tested for activity against erythroleukemia, lung carcinoma, malignant melanoma, colon adenocarcinoma, prostate

carcinoma, breast adenocarcinoma, ovary adenocarcinoma, cervix epithelioid carcinoma, and pancreatic epitheloid carcinoma in 2004 by Bailly et al.

Lukianols A **56** and B **57** exhibited moderate activity in the standard bioassay against a cell line derived from human epidermaoid carcinoma (*KB*) with an MIC of 2.4 and 185.9 nM, respectively. A derivative of polycitone A, penta-*O*-methyl polycitone A, was found to inhibit the growth of SV40 transformed fibroblast at concentrations of 7.6 nM. Didemnimides A **67**, D **70**, and E **71** were all proved to be inactive as cell cycle checkpoint inhibitors. Compounds that inhibit the G_2 checkpoint might be valuable in cancer therapy." Ningalin D **76**, permethyl ningalin D, and ningalin D decaacetate were found to exhibit modest cytotoxic activity against a murine leukemia cell line (L1210, IC_{50} = 1–7 μM) and a parental human colon cancer cell line (HCT116, IC_{50} = 1–70 μM).

Lamellarin O **52** and lukianol A **56** proved to be effective cytotoxic agents in a number of leukemia and lymphoma screens. They were also active in human HeLa–S^3 uterine and glioma screens. Lukianol A **56** afforded selective activity against SW-480 colon adenocarcinoma growth, but it in general was less active against the growth of solid tumors. The principal biochemical effect of lamellarin O **52** and lukianol A **56** was inhibition of L1210 lymphocytic leukemia DNA synthesis with less effect on RNA and protein synthesis. They demonstrate a therapeutic profile that is very similar to current clinically used anticancer agents.

3.1.2. Multidrug Resistance Reversal (MDR) Activity—Multidrug resistance (MDR) is a persistent problem limiting the effectiveness of a wide variety of anticancer drugs, antibiotics, and protease inhibitors. Some lamellarins and related pyrrole-derived alkaloids were reported to act as nontoxic inhibitors of acquired MDR in various cancer cell lines, revealing equally effective cytotoxic activity against MDR cell lines and demonstrating that even at noncytotoxic concentrations they reverse MDR by inhibiting P-glycoprotein (P-gp)-mediated drug efflux." It has been claimed that lamellarins I **10** and K **12** not only exhibit potent cytotoxic activity in vitro against MDR tumor cell lines but also reverse MDR at noncytotoxic concentrations," and the results of in vivo tests of lamellarin K **12** are consistent with these claims. Experiments suggested that lamellarin I **10** reversed MDR by directly inhibiting the P-glycoprotein-mediated drug efflux at nontoxic doses and that the potency of lamellarin I **10** as an MDR modulator was 9–16-fold higher than that of approved anticancer agent verapamil, resensitizing the resistant malignant cells to front-line therapeutics.

Permethyl storniamide A, permethyl ningalin B, and much simpler 3,4-diarylpyrrole derivatives also exhibited similar MDR reversal activity at nontoxic concentrations. Lamellarin O **52** and lukianol A **56** were found in Boger's group to exhibit modest cytotoxic activity against both wild-type and MDR tumor cell lines, suggesting they may serve as new leads for development of antitumor agents insensitive to MDR. Permethyl storniamide A and ningalin B **74** were shown to potently reverse MDR phenotype, resensitizing a resistant human colon cancer cell line (HCT116/VM46) to vinblastine and doxorubicin at lower doses than the prototypical agent verapamil. Permethyl storniamide A and ningalin B **74** may constitute the initial members of a new class of MDR reversal agents. Ningalin B

hexamethyl ether was also found to have good MDR activity when used in conjunction with vinblastine or doxorubicin as compared to use of the standard MDR reversal agent verapamil.

In 2003, Soenen and his colleagues made a further study on synthetic derivatives of the ningalins, and permethyl ningalin B dimethylamide was discovered as a potent MDR reversal agent that hypersensitizes P-glycoprotein-resistant tumor cell lines to front-line conventional therapeutic agents. Amide derivatives of permethyl ningalin B were also found as multidrug resistance reversal agents. Ningalin D **76**, permethyl ningalin D, and ningalin D decaacetate were examined against a resistant HCT116 cell line that embodied the MDR phenotype through overexpression of P-gp. This cell line, HCT116/VM46, which is resistant to both vinblastine (IC_{50} = 100 vs 7 nM for parental HCT116) and doxorubicin (IC_{50} = 900 vs 70 nM for parental HCT116), was treated with each of the ningalin derivatives at 1 μM, and the IC_{50} was measured for co-administered vinblastine or doxorubicin. Under these conditions, ningalin D **76** and its decaacetate were inactive, whereas permethyl ningalin D effectively resensitized the resistant HCT116/VM46 cell line to vinblastine (IC_{50} = 8.5 nM, 80% reversion) and doxorubicin (IC_{50} = 100 nM, 70% reversion). Ningalin derivatives have been evaluated for their properties of potent reversal of MDR and use in drug combinations against human colon carcinoma xenograft in nude mice. The profound enhancement of antitumor cytotoxicity of vinblastine and taxol in vitro by ningalin derivatives may have multiple mechanisms including the MDR-reversing effects.

3.1.3. Inhibition of HIV-1 Integrase and MCV Topoisomerase—Human immunodeficiency virus (HIV) encodes three enzymes of reverse transcriptase, protease, and integrase. Anti-HIV drugs targeting the first two enzymes have been successfully employed for the treatment of acquired immune deficiency syndrome (AIDS). HIV-1 integrase is a promising target for anti-retroviral chemotherapy. Faulkner and coworkers reported that lamellarin α-20 sulfate **46** is a selective inhibitor of HIV-1 integrase both in vitro and in vivo. Compound **46** inhibited the integrase terminal cleavage activity with an IC_{50} of 16 μM, strand transfer activity with an IC_{50} of 22 μM, and growth of the HIV-1 virus in cell culture with an IC_{50} of 8 μM. Unlike most other natural product integrase inhibitors, inhibition was not completely regulated by the core domain but also partially by the N- and/or C-terminal domains (IC_{50} for disintegration for the catalytic core 64 μM, for the intact enzyme 7 μM), indicating that some form of unique multisite binding might be responsible for this inhibition. Compound **46** could inhibit viral replication in cultured cells by acting on part of the viral life cycle consistent with inhibition of integration. Firm data arguing for inhibition of integrase in cultured cells awaited the isolation of viral mutants with reduced sensitivity to **46**. Mapping of such mutations to the integrase coding region could argue strongly for inhibition of integrase during viral replication.

Lamellarin H **37**, lamellarin α **45**, and lamellarin α 13,20-disulfate **47** were also studied for their HIV-1 integrase inhibition. The integrase inhibition assay measured the reduction of accumulation of strand transfer products that result from incubation of purified HIV-1 integrase with target DNA and DNA mimicking one end of the unintegrated viral DNA. Lamellarin H **37**, lamellarin α 13,20-disulfate **47**, and lamellarin α-20 sulfate **46** were also screened for inhibition of the type 1B topoisomerase of the *Molluscum contagiosum* virus

(MCV) with IC_{50} (μM) of 0.23, 70, and 170, respectively. This assay, which measured DNA cleavage and religation, was used as a counter-screen to detected nonselective inhibitors. Lamellarin H **37** exhibited very potent inhibition ($IC_{50} = 1.3$ μM) of HIV-1 integrase but unfortunately was even more active in the MCV topo-isomerase counter-screen ($IC_{50} = 0.23$ μM). Lamellarin α 13,20-disulfate **47** was a less effective inhibitor ($IC_{50} = 49$ μM) of HIV-1 integrase than was lamellarin α-20 sulfate **46** ($IC_{50} = 22$ μM). Lamellarin α 13,20-disulfate **47**'s inhibition of HIV-1 integrase was also restrictive due to inhibiting MCV topoisomerase at about the same concentration ($IC_{50} = 70$ μM). Lamellarin H **37** is a more potent inhibitor of HIV-1 integrase but lacked the specificity required to be clinically useful. Polycitone A **58** was found to be a potent inhibitor of retroviral reverse transcriptases (i.e., HIV-1) and cellular DNA polymerases.

3.1.4. Antibiotic Activity and Antibacterial Activity—Storniamides A–D **63**–**66** showed antibiotic activity against Gram-positive bacteria (*Staphylococcus aureus*, *Bacillus subtilis,* and *Micrococcus luteus*) at 50 μg/disk. Lamellarins Q **54** and R **55** have been shown to have no antibiotic activity. Lamellarins A **1**, B **32**, and C **3**, the triacetate of lamellarin D **36**, I **10**, J **11**, K **12**, L **15**, and M **38**, and the triacetate of lamellarin N **41** were also found to have no antibacterial activity.

3.1.5. Inhibition of ATP-Citrate Lyase and Human Aldose Reductase (h-ALR2)—Purpurone **77** is a potent inhibitor of ATP-citrate lyase (ACL). It inhibited ACL in a dose-dependent manner and has an IC_{50} of 7 μM. When tested for cytotoxicity, purpurone **77** was found to be nontoxic to Hep G2 cells, showing no reduction in cellular ATP levels at 143.3 nM. Preliminary biological data indicated that **77** was able to reduce fatty acid but not cholesterol biosynthesis. In 2006, lukianol B **57** was found to be the most active aldose reductase inhibitor (ARI) among all the phenolic derivatives assayed.

3.1.6. Cell Division Inhibition and Immunomodulatory Activity—Lamellarins D **35** and C **3** were shown to inhibit cell division of sea urchin egg at concentrations of 19 μg/mL with 78% and 15% inhibition, respectively, while lamellarins A **1** and B **32** were inactive during the same bioassay. Lamellarins K **12** and L **15** have been observed to possess moderate immunomodulatory effects in the micromolar range (for **12** and **15**, LcV = MLR 147 and 98, respectively). In 2006, there was a patent filed that claimed ningalin compounds for use in modulating immune responses to infection, injury, allergy, and/or transplantation.

3.1.7. Antioxidant Activity—Lamellarins γ **30**, K **12**, U **22**, I **10**, and C-diacetate **4** were evaluated for their antioxidant activity, and the results showed that all of them demonstrated antioxidant properties only at millimolar range compared with standard antioxidants, which were active in the micromolar range. On the basis of the values of IC_{50} and the Trolox equivalent antioxidant capacity (TEAC), the rank order from the most active to the least active compound was **10** > **30** > **12** > **4** > **22**.

3.1.8. Feeding Deterrent—Didemnimides A–D **67**–**70** were reported to be potent feeding deterrents against a natural assemblage of mangrove-specific carnivorous fish. Ecologically relevant field and laboratory experiments have been designed to test the

hypothesis that didemnimides function as predator deterrents. Didemnimides A–D **67**–**70** were found to constitute a significant chemical defense against carnivorous fish in mangrove habitats. Didemnimide D **70**, the most active compound, deterred feeding of carnivorous wrasse *Thalassoma bifasciatum* at natural concentrations in aquarium assays. When tested in the mangrove environment itself, using an established method with control and treated foods, didemnimide D **70** alone significantly reduced consumption relative to controls. The relationship between antipredatory activity and the structure was the subject of additional studies. Fenical et al. found that the activity of the didemnimides was highly dependent on structure. Didemnimide D **70**, the only compound that inhibited feeding in both lab and field assays, bears both a bromine on the indole ring and a methyl group on the imidazole ring.

3.2. Structure–Activity Relationship (SAR) Studies

The first reported study on SAR of lamellarins and related pyrrole-derived alkaloids concerned lamellarin D **35**, one of the most potent lead compounds for the control of cancer. The double bond at C-5 and C-6 in lamellarin D **35** seemed to be an essential element for the antitopoisomerase I activity. A library of open lactone analogues of lamellarin D was generated and tested in a panel of three human tumor cell lines, MDA-MB-231 (breast), A-549 (lung), and HT-29 (colon), to evaluate their cytotoxic potential. From these data it was concluded that more than 75% of the open-chain lamellarin D analogues tested showed cytotoxicity in a low micromolar GI_{50} range. The hydroxyl groups at C-8, C-14, and C-20 in lamellarin D **35** were also important for cytotoxic activity and DNA-topoisomerase I inhibition. Interestingly, derivatization of the these phenolic hydroxyl groups with amino acids, which preserved the hydrogen-bonding capacity at these sites, afforded potent compounds, whereas acylation with various carboxylic acids resulted in a considerable decrease in potency.

Lamellarin D **35**, which displayed potent cytotoxic activities against MDR tumor cell lines and was highly cytotoxic to prostate cancer cells, has a pentacyclic planar chromophore, whereas its synthetic 5,6-dihydro analogue, LAM-501, has a significantly tilted structure. DNA binding measurements by absorbance, fluorescence, and electric linear dichroism spectroscopy showed that lamellarin D **35** was a weak DNA binder that intercalated between base pairs of the double helix. In contrast, the nonplanar LAM-501 did not bind to DNA. LAM-501 was therefore found to be inactive against topoisomerase I and considerably less cytotoxic than the natural product lamellarin D **35**, indicating that the planarity of the hexacyclic chromophore was essential for DNA binding and topoisomerase I inhibition.

Lamellarins B **32**, H **37**, M **38**, N **40**, W **42**, and X **43** also possess a double bond at C-5 and C-6 in the B ring and showed potent inhibition of human topoisomerase I. Ten derivatives of lamellarin D were synthesized with varying substituents on the aromatic rings and evaluated for cytotoxicity against a HeLa cell line to examine their SAR. The study showed that the presence of hydroxyl groups at the C-8 and C-20 positions would be essential for their cytotoxicity, while the hydroxyl group at C-14 and the two methoxy groups at C-13 and C-21 appeared to be less important for the cytotoxic activity. Further studies on the SAR of eight lamellarin derivatives were reported in 2005. The derivatives have been studied as topoisomerase I (Top1) inhibitors. Molecular models of the ternary complexes formed

between the DNA-Top1 ensemble and lamellarin D **35** fully intercalated into the duplex DNA have been built and studied by means of nanosecond molecular dynamics simulations in aqueous solution. The results showed that the C-8 and C-20 hydroxyl groups in the lamellarin series would be the major determinants of both Top1 cleavable complex stabilization and the cytotoxic action. Another report also showed that the absence of a hydroxyl group at C-8 in lamellarins γ **30**, K **12**, U **22**, I **10**, and C-diacetate **4** decreased the potency of antioxidant activity of these compounds, while the presence of different functional groups at C-14 did not produce marked changes in the antioxidant activity.

Faulkner and co-workers studied the SAR of lamellarin α **45** and its 20-sulfate **46** and 13,20-disulfate derivatives **47** for inhibition of HIV-1 integrase. Lamellarin α **45** showed no inhibition of HIV-1 integrase at concentrations up to 1.6 mM, while its sulfate derivatives **46** and **47** had significant IC_{50}s of 22 and 49 μM, respectively. These results showed that the presence of sulfate on the periphery could greatly influence selectivity in HIV-1 integrase inhibition. The results were unexpected because other non-sulfated lamellarins inhibited HIV-1 integrase with IC_{50}s in the low micromolar range. It did however support the idea that the activity of lamellarin α 20-sulfate **46** results from the compound acting as a mimic of the terminal unit of the viral DNA with the sulfate group binding to a site that normally binds the terminal phosphate of the DNA. Lamellarin α 13,20-disulfate **47** was considered as a nonselective HIV-1 integrase inhibitor. Faulkner and co-workers proposed that the nonselective inhibitors with two or more sulfate groups bind to sites that normally bind to two consecutive phosphate units in intact DNA. Cytotoxicity toward HeLa cells of lamellarin H **37**, lamellarin α **45**, lamellarin α 20-sulfate **46**, and lamellarin α 13,20-disulfate **47** was measured, and the results showed that protection of the phenolic hydroxyl group as the sulfate could reduce the cytotoxicity of the parental lamellarins in general.

The didemnimides A **67**, D **70**, and E **71** were inactive as cell cycle checkpoint inhibitors. In order to initiate a quantitative structure–activity relationship (QSAR) study on granulatimide (inhibitor of the G_2 cell cycle checkpoint of mammalian cancer cells) and didemnimides as cell cycle checkpoint inhibitors, Trsic et al. performed molecular orbital calculations for these compounds. The electronic features and structural parameters were compared with inhibition of the G_2 checkpoint. The hydrogen atom attached to the nitrogen atom of the indole moiety has a higher value of electronic charge in the biologically active compounds than in the inactive compounds. The inactive didemnimides A **67**, D **70**, and E **71** were more lipophilic than the active molecules due to the high electron density in the central regions that enhance their hydrophobicity.

4. Synthesis

In light of the fascinating novel structures, intriguing biological properties and the difficulty in obtaining large quantities from the natural sources, the lamellarins and related pyrrole-derived alkaloids have attracted great interest as challenging natural product targets for total synthesis. Several research groups, including Ishibashi, Steglich, Ruchirawat, Banwell, Faulkner, Gupton, Boger, and Handy, have reported synthesis of lamellarins and related pyrrole-derived alkaloids. A number of elegant synthetic strategies have been employed in which highly functionalized precursors are assembled into the pyrrole core by

means of intramolecular ylide cycloaddition,"" azadiene Diels–Alder cycloaddition, oxidative dimerization, or double-barreled Heck cyclization. The postulated biogenetic pathway for the alkaloids thought to be DOPA-derived is shown in Figure 3. A possible biogenetic relationship between the lamellarins and polycitone A **58** and polycitrins A **60** and B **61** was described by Kashman et al. (Figure 4).

Solid-phase combinatorial synthesis is one of the most useful techniques for the preparation of a large number of structurally related molecules. This technique provides fast access to larger collections of products that may possess great diversity and incorporate optimized physical and pharmacological properties into the structures of lamellarins."⁻ Synthetic studies of lamellarins and related pyrrole-derived alkaloids have been summarized in Table 2. Several typical synthetic approaches leading to lamellarins and related compounds are presented in Schemes 1–11.

4.1. Synthesis of Lamellarins

4.1.1. Synthesis of Lamellarins D, H, and N—In 1997, Ishibashi's group accomplished the first total synthesis of lamellarin-class natural alkaloids, lamellarin D **35** and H **37**, using *N*-ylide-mediated cyclization of a benzylisoquinoline derivative as the key ring construction procedure in five steps; yields of **35** and **37** were 18% and 15%, respectively (Scheme 1). In 2005, an efficient and highly convergent total synthetic route to lamellarin D **35** was achieved in eight steps with an overall yield of 18% through sequential and regioselective bromination/Suzuki cross-coupling, microwave-assisted oxidation, phenol group deprotection, and subsequent lactonization (Scheme 2). This synthetic strategy can be exploited for the preparation of other open-chain lamellarins. A library of open lactone analogues of lamellarin D was then prepared from the scaffold of methyl 5,6-dihydropyrrolo [2,1-*a*] isoquinoline-3-carboxylate by introducing various aryl groups through sequential and regioselective bromination followed by Pd (0)-catalyzed Suzuki cross-coupling chemistry in a 24–44% overall yield.

In 2006, lamellarins D **35**, L **15**, and N **40** were efficiently generated in total yields of 54%, 58%, and 50%, respectively, using Hinsberg-type pyrrole synthesis and palladium-catalyzed Suzuki–Miyaura coupling of the common intermediate 3,4-dihydroxypyrrole bistriflate as the key reactions (Scheme 3). Convergence of this synthetic strategy could enable the synthesis of a wide range of natural or non-natural lamellarins by simple structural modification of the starting bistriflate and arylboronic acids in relatively short steps.

The total synthesis of lamellarin H **37** was first reported in 1997. In 2002, lamellarin H **37** was also synthesized by Faulkner and co-workers using a different route (Scheme 4). The two routes were complex and accomplished by more than 10 steps of chemical synthesis. In 2005, a new and simple route was developed to synthesize lamellarin H **37** and its derivatives. The fabricated intermediate, 2,4,5-trimethoxy-α-chloroacetophenone, was the key starting material for this synthesis. The next year the same group reported the synthesis of the second intermediate of lamellarin H **37**, 1-(3,4-dimethoxyphenyl)-8,9-dimethoxy-2-(2,4,5-trimethoxyphenyl)-pyrrolo-[2,1-α]-isoquinoline.

4.1.2. Synthesis of Lamellarin G Trimethyl Ether and Lamellarin G—In 1997, Steglich's group described a biomimetic synthesis of lamellarin G trimethyl ether in 33% overall yield. The key step was the oxidative dimerization of an arylpyruvic acid and condensation of the resulting 1,4-dicarbonyl compound with a suitable 2-arylethylamine. This method could be applied to the synthesis of other lamellarins, especially to those with nonsymmetrically substituted aryl groups. In 2001, a general and efficient synthesis of lamellarin G trimethyl ether was achieved by Ruchirawat et al. in Thailand. The synthesis involved formation of the core pyrrole [2,1-α] isoquinoline followed by formation of the lactone ring. Later on, in 2003, Ruchirawat et al. further developed the synthesis of lamellarins using direct metal–halogen exchange of 2-bromopyrrole carbonate derivatives with *tert*-butyllithium followed by intramolecular lactonization of the resulting 2-pyrrole anion onto the carbonate to generate the corresponding lamellarins in moderate to good yields. The synthesis of lamellarin G trimethyl ether, starting from a symmetric 3,4-dihydroxypyrrole bis-triflate derivative, was reported by Iwao and co-workers in 2003. This short and flexible route was developed using two key reactions: Hinsberg-type condensation and palladium-catalyzed Suzuki cross-coupling starting from a symmetric bis-trifloxy pyrrole. More recently, Handy et al. reported a modular synthesis of the lamellarin G trimethyl ether that was based on application of three iterative sequential and regioselective halogenation/Suzuki cross-coupling events. This route accessed the target structure in 11 steps with 9% overall yield.

In 2006, lamellarin G **8** was synthesized in 57% overall yield by the key step of formation of 3,4-diarylpyrrole-2,5-dicarboxylic acids from arylpyruvic acids and 2-arylethyl-amines.

4.1.3. Synthesis of Lamellarins I, K, L, and U—Banwell's group reported the total synthesis of lamellarin K **12** in 1997. The pivotal step is construction of the central pyrrole ring by an intramolecular 1,3-dipoar cycloaddition between an azomethine ylide and an alkyne. Banwell's synthesis of lamellarin K **12** was particularly interesting because it was convergent, versatile, and high yielding. The highly convergent nature of the reaction sequence would suggest that this approach could be readily adapted to the preparation of lamellarins A–N **1**, **32**, **3**, **35**, **6**–**8**, **37**, **10**–**12**, **15**, **38**, and **40** and S–X **18**, **19**, **22**, **24**, **42**, and **43** as well as many analogues thereof. In 2001, lamellarins I **10** and K **12** were synthesized by a related approach based on a [3 + 2] cycloaddition of a nitrone to an alkyne. The key cycloaddition yielded an isoxazoline which was rear-ranged to afford the central pyrrole ring. In 2004, lamellarins K **12** and L **15** were successfully obtained by Ruchirawat et al. in three steps from benzyldihydroisoquinolines with ester nitrostyrene in 65% and 61% overall yields, respectively. The key step was the Michael addition/ring-closure reaction of benzyldihydroisoquinoline derivatives with ethoxycarbonyl-*β*-nitrostyrenes (Scheme 5). The basic building blocks for the lamellarins are simple and easily prepared substituted-benzaldehyde derivatives. Each lamellarin could be analyzed to consist of three such building blocks: two in the benzyldihydroisoquinoline derivative and the other in the ester nitrostyrene. This convergent synthetic approach could allow easy incorporation of all aryl groups on the lamellarin skeleton without the need for complex protecting group strategies. The benzyl group was chosen as the only necessary hydroxyl protecting group since all the benzyl groups could be removed in the same step by simple palladium-catalyzed

hydrogenolysis. In 2006, bio-mimetic syntheses of lamellarin K **12** were developed by Steglich et al. in four steps and 37% overall yield. In the same year, 28 natural (lamellarins C **3**, E **6**, F **7**, G **8**, I **10**, J **11**, K **12**, L **15**, T **19**, U **22**, Y **26**, and χ **31**) and unnatural lamellarins with either a saturated or an unsaturated D ring were synthesized by Ruchirawat et al. The key step involved the Michael addition/ring closure (Mi-RC) of the benzyldihydroisoquinoline and α-nitrocinnamate derivatives, which provided the 2-carboethoxypyrrole intermediates in moderate to good yields (up to 78% yield).

Biomimetic total synthesis of the nonsymmetrical lamellarin L **15** was developed in 2000 by reaction of the ethyl 3-arylpyruvate with the methyl 2-bromo-3-arylpyruvate in the presence of the 2-arylethylamine, which afforded the pyrrole derivative and was transformed into lamellarin L **15** in five steps. The synthesis proceeded with 38% overall yield and mimicked the probable biosynthesis of the analogues of lamellarin L. Lamellarin L **15** and lamellarin U **22** were generated via a total solid-phase synthesis. The key step of this approach was the solid-phase conversion of an aldehyde group into a formate by a Baeyer–Villiger reaction and an intramolecular [3 + 2] cycloaddition of a 3,4-dihydroisoquinolinium salt over a triple bond. This solid-phase synthetic strategy would enable the construction of related compound libraries for biological evaluation. Lamellarins U **22** and L **15** were generated in 10% and 4% overall yield, respectively, after eight-step solid-supported synthesis (Scheme 6). Lamellarin L **15** was also synthesized by Iwao et al. in 2006 (Scheme 3).

4.1.4. Synthesis of Lamellarins O and Q and Lamellarin O Dimethyl Ether—

In 1997, lamellarins O **52** and Q **54** were synthesized by Banwell et al. using Stille, Suzuki, or Negishi cross-coupling reactions as the key step (Scheme 7). Total synthesis of lamellarin O **52** has also been reported utilizing a common heterocyclic azadiene Diels–Alder reaction by Boger et al. In 2004, Albericio's group described an efficient solid-phase strategy for synthesis of lamellarins O **52** and Q **54** using Merrifield resin and *N*-protected methyl 3,4-dibromopyrrole-2-carboxylate as a scaffold. The process involved incorporation of the appropriately substituted pyrrole ring onto a *p*-alkoxy iodophenyl resin through a Negishi cross-coupling reaction. This step was followed by a Suzuki cross-coupling reaction to introduce the second substituted phenyl ring and *N*-alkylation of the pyrrole. Final cleavage was achieved using Lewis acid to give the desired product. Diversity can be introduced in each step of the synthetic process as well as during the final cleavage using the appropriate Lewis acid conditions, which could generate a compound library of lamellarins O **52** and Q **54**. Lamellarins O **52** and Q **54** were also generated via a solid-phase synthetic approach that was applied to the preparation of lamellarins U **22** and L **15** at the same time.

In 1995, a titanium-induced cyclization of readily accessible amido–enones to substituted pyrrole derivatives was applied to the total synthesis of lamellarin O dimethyl ether (Scheme 8). After that, lamellarin O dimethyl ether was also synthesized by Gupton's group in 1999. The authors demonstrated that the vinylogous amide, the chloropropeniminium salt, and the β-chloroenal react successfully with glycine esters in a regiocontrolled and efficient fashion to produce 2,3,4-trisbututed pyrroles that lead to lamellarin O dimethyl ether.

4.1.5. Synthesis of Lamellarin T Hybrids—The lamellarin T hybrids were synthesized by Banwell et al. in 2006. The key steps included selective lithium-for-halogen exchange, Negishi, and Suzuki–Miyaura cross-coupling reactions.

4.1.6. Synthesis of Lamellarin α, Lamellarin α 13,20-Disulfate, and Lamellarin α 20-Sulfate—In 2002, a synthetic approach to lamellarin α **45** and lamellarin α 13,20-disulfate **47** was reported (Scheme 4). Lamellarin α **45** was generated relying on palladium-mediated and other coupling reactions, and lamellarin α 13,20-disulfate **47** was semi-synthesized by treatment of lamellarin α **45** with the DMF complex of sulfur trioxide in DMF/pyridine. The first total synthesis of lamellarin α 20-sulfate **46** has been just recently developed in 2006 in 14 steps from 2-(3,4-dimethoxyphenyl) ethylamine with an overall yield of 24%. The lamellarin α core in which 13-OH and 20-OH were differentially protected by isopropyl and benzyl groups, respectively, was constructed using Hinsberg-type pyrrole synthesis and Suzuki–Miyaura coupling as the key reactions. The 20-sulfate was prepared by a sequence including debenzylation of 20-OBn, 2,2,2-trichloroethylsulfation of the resulting 20-OH, deprotection of 13-O*i*-Pr, and final reductive cleavage of the 2,2,2-trichloroethyl ester. This synthesis could pave the way to generation of diverse sulfated lamellarins.

4.2. Synthesis of Pyrrole-Derived Alkaloids Related to Lamellarins

4.2.1. Synthesis of Lukianol A—Seven independent total synthetic routes of lukianol A **56** have been reported since 1995.″¯· Structurally, lukianol A **56** possesses a unique methyl 3,4-diarylpyrrole-2-carboxylate skeleton. In 1995, a concise titanium-mediated approach to pyrroles was accomplished, and this method was applied to the first total synthesis of lukianol A **56** (Scheme 8) in eight steps with 12% overall yield starting from commercially available 4,4′-dimethoxychalcone. Lukianol A **56** was also convergently synthesized using Stille, Suzuki, or Negishi cross-coupling reactions as the key step. In 1999, Boger's group reported obtaining lukianol A **56** by utilizing a common heterocyclic azadiene Diels–Alder reaction. In the same year, Gupton et al. reported an efficient relay synthesis of lukianol A **56** and related compounds utilizing vinylogous iminium salt derivatives as key intermediates for the regioselective synthesis of heterocyclic compounds. In 2000, a formal total synthesis of lukianol A **56** was completed by Wong's group. The target alkaloid was prepared through a strategy that utilized the *β* effect of a trimethylsilyl group to a highly regioselective synthesis of 2,3,4-trisubsti-tuted 1*H*-pyrroles as the pivotal step. In 2006, Steglich et al. developed a biomimetic approach to synthesize lukianol A **56** in which the lukianol skeleton is assembled in a single step. The following year, they reported that simple 3,4-diaryl- and 3,4-diindolylpyrrole-2,5-carboxylic acids can be easily obtained from aryl(indolyl)pyruvic acids and ammonia in a reaction that can be applied to a short synthesis of lukianol A **56**.

4.2.2. Synthesis of Polycitrins A and B and Polycitones A and B—Both polycitrins A **60** and B **61** contain a maleimide unit in their structures. Biomimetic total synthesis of polycitrin A **60** was described by Steglich and co-workers in 1995. The synthesis was based on formation of 3,4-bisarylpyrrole-2,5-dicarboxylic acids from 3-arylpyruvic acids by oxidative coupling and consecutive pyrrole ring formation. The pyrrole

dicarboxylic acids were then converted into 3,4-bisaryl maleimides by treatment with hypochlorite. The synthesis was then completed by bromination and introduction of the *N*-alkyl substituent. Polycitrin A **60** was thus obtained in six steps from 3-(4-methoxyphenyl) pyruvic acid with 26% overall yield (Scheme 9). After 11 years the same group reported a considerably shorter synthetic route to polycitrin A **60** starting from 3-(3,4-dibromo-4-methoxyphenyl) pyruvic acid in three steps and in 43% overall yield. Polycitrin A **60** and prepolycitrin A **62** were also reported by Correia's group in 2006. Polycitrin A **60** was obtained from maleic anhydride and 4-methoxybenzenediazonium tetrafluoroborate by palladium-catalyzed Heck diarylation of maleic anhydride in four steps.

In 2000, Italian scientists reported the first total synthesis of polycitrin B **61** based on a palladium-catalyzed cross-coupling reaction (Scheme 10) and starting from 3,5-dibromo-4-methoxy-phenylacetic acid methyl ester. Polycitrin B **61** was obtained in a good yield and crystallized from CH_2Cl_2–pentane as yellow crystals.

Polycitones A **58** and B **59** are polybrominated lamellarin-related alkaloids. Both polycitones A **58** and B **59** were first synthesized in 2002 in Steglich's group. Polycitone B **59** was obtained in four steps from pyrrole dicarboxylic acid, including Friedel–Crafts reaction of the corresponding acid chloride with anisole. Conversion of polycitone B **59** into polycitone A **58** was then achieved in two steps via Mitsunobu alkylation of the pyrrolic NH group. Polycitone A **58** was obtained in eight steps from 3-(4-methoxyphenyl) pyruvic acid with 22% overall yield. The synthesis is very flexible and can be easily adapted to the preparation of analogues with various substituents on the pyrrole ring. In 2006, Gupton's group demonstrated a new and efficient relay strategy to synthesize polycitones A **58** and B **59**. Their approach relied on formation of 2,4-disubstituted pyrroles from vinamidinium salts followed by electrophilic substitution at the 5-position of the pyrrole and halogenation and a microwave-accelerated Suzuki coupling at the 4-position to produce the tetrasubstituted heterocycle efficiently with complete control of regiochemistry. It is important to note that each pyrrole substituent in this strategy was introduced independently and can be easily varied so as to accommodate in-depth SAR studies for polycitones A and B analogues.

4.2.3. Synthesis of Storniamide A Nonamethyl Ether and Permethyl Storniamide A—In 1998, storniamide A nonamethyl ether was concisely obtained by Steglich et al. from 3-(3,4,5-trimethoxyphenyl) pyruvic acid and 2-(4-hydroxyphenyl) ethylamine in three steps. The applied biomimetic methodology is very similar to that of the synthesis of polycitrin A **60**. Storniamide A nonamethyl ether was first obtained as a mixture of the (*E,E*)-, (*E,Z*)-, and (*Z,Z*)-isomers in a ratio of 3:4:1. Isomerization of the mixture with iodine in CHCl$_3$ enriched the (*E,E*)-isomer, giving a ratio of 6:5:1. The three isomers could be separated by chromatography on a silica gel column to yield the desired isomer of (*E,E*)-storniamide A nonamethyl ether with an overall yield of 19%. Experiments to convert (*E,E*)-storniamide A nonamethyl ether into the natural product storniamide A **63** were as yet unsuccessful. Permethyl storniamide A was synthesized utilizing a common heterocyclic azadiene Diels–Alder reaction in 1999. On the basis of palladium-catalyzed Suzuki and Negishi cross-coupling reactions, permethyl storniamide A was synthesized in 2002 by

Fürstner et al. In 2003, a formal syntheses of permethyl storniamide A was reported, which was based on a highly efficient route to 3,4-diarylpyrrole marine alkaloids.

4.2.4. Synthesis of Didemnimides A–C—In 1998, the total syntheses of didemnimides A **67** and B **68** were first reported by Cava and Hughes. They applied the methodology for the synthesis of unsymmetrical bisin-dolylmaleimides via a K^+t-BuO$^-$ catalyzed condensation of indole-3-acetamide with methyl indolyl-3-glyoxylates. The total synthesis of didemnimide A **67** was also developed by Piers et al. In the same year, didemnimide C **69** was synthesized by Steglich's group in four steps in 29% overall yield. The key step in the synthesis is the Stille coupling between the urethane-protected 3-bromo-4-(indol-3-yl)-methylmaleimide and 5-tributylstannyl-1-methylimidazole. Two years later, Piers and co-workers also reported the synthesis of didemnimide C **69** in three steps from 1-methyl-2-phenylthioimidazole in 28% overall yield. It is a shorter synthesis than those previously reported.

4.2.5. Synthesis of Ningalins A–D—The first total syntheses of ningalins A **73** and B **74** were achieved in Boger's lab in 1999 and 2000, respectively. The syntheses were based on a common heterocyclic azadiene Diels–Alder strategy (1,2,4,5-tetrazine → 1,2-diazine → pyrrole) (Scheme 11). The main feature of this strategy is the unusually effective [4 + 2] cycloaddition of the electron-deficient 1,2,4,5-tetrazine with an unsymmetrical and electron-rich alkyne, which was also applied to the synthesis of lamellarin O **52**, lukianol A **56**, and permethyl storniamide A at the same time. Moreover, the methodology may be suitable for construction of other densely functionalized pyrrole cores.

In 2002, Bullington et al. first regioselectively prepared the key intermediate used to generate DOPA-derived *o*-catechol alkaloids, the Fürstner intermediate. Ningalin B **74** was then concisely synthesized in a 51% overall yield. On the basis of the two key reactions, Hinsberg-type pyrrole synthesis and palladium-catalyzed Suzuki cross-coupling of the 3,4-dihydroxypyrrole bis-triflate derivatives, a formal synthesis of ningalin B **74** was reported in 2003. In 2006, a biomimetic synthesis of ningalin B **74** was developed by Steglich et al., starting with the oxidative coupling of two equivalents of 3-(3,4-dimethoxyphenyl) pyruvic acid and in situ reaction of the resulting 1,4-diketone with one equivalent of 2-(3,4-dimethoxyphenyl)ethylamine and obtained in four steps in 52% overall yield. Application of vinylogous iminium salt derivatives to a convenient and efficient synthesis of ningalin B hexamethyl ether was reported by Gupton et al. in 2003. This methodology was an extension from an earlier strategy that was used in the synthesis of lukianol A **56**.

In 2000, Steglich's lab reported the first total synthesis of ningalin C **75** using an intramolecular Friedel–Crafts acylationfrom1-[2-(3,4-dimethoxyphenyl)ethyl]-3,4-bis(3,4-dimeth-oxyphenyl)-1*H*-pyrrole and methyl 2-diazo-2-(3,4-dimethoxyphenyl) acetate in five steps with a total yield of 19%. After that, a new and efficient method for the synthesis of permethyl ningalin C was accomplished with a key step involving formation of a pyrrolinone from an aminoquinone in one pot. Ningalin C **75** was then obtained through demethylation of its permethyl precursor. Ningalin D **76**, the most complicated member of the ningalins, was synthesized in 2005 in Boger's lab in nine steps based on a key 1,2,4,5-tetrazine → 1,2-

diazine → pyrrole Diels–Alder strategy to assemble a fully substituted pyrrole core central to its structure. The overall yield of the total synthesis was 19%.

5. Conclusion

Over the past two decades, more than 70 lamellarins and related pyrrole-derived alkaloids have been isolated from taxonomically quite distinct marine organisms (ascidians, molluscs, and sponges) collected in the Indian or Pacific oceans by SCUBA diving (−5 to −32 m). Among these marine organisms the ascidian *Didemnum* (Didemnidae) is byfarthemostproductivemarinegenusforlamellarins."" ¯ Purification was accomplished with chromatography on silica gel, Sephadex LH-20, or HPLC. The isolated metabolites were elucidated by NMR, HRMS, single-crystal X-ray, and other spectroscopic methods.

Often lamellarins have been reported to be isolated from several marine sources. For example, lamellarins A **1**, B **32**, and C **3** were found in both prosobranch mollusc *Lamellaria* sp. and marine ascidians. The re-isolation of these compounds from other sources indicate that these molluscs likely sequester the compounds from a didemnid ascidian food source. The structures of lamellarins and other pyrrole-derived alkaloids are related, and they likely have a common biogenetic origin. Their common structural feature is a pyrrole ring substituted at positions 3 and 4 by polyhydroxy-or methoxyphenyl groups, a combination was not found outside of this class. The aromatic ring is rotationally highly restricted (600 kcal/mol, MM2 calculation) and exists essentially orthogonal to the plane of the pentacyclic ring. Thus, these molecules should exist as chiral forms due to the atropisomerism. Interestingly, however, all examples (except for lamellarin S **18**) so far isolated were racemic. Faulkner's group even attempted to separate the atropisomers of lamellarin α **45** using chiral reagents such as Mosher's reagent or D-(+)-10-camphorsulfonyl chloride as well as HPLC or chiral TLC but were unsuccessful.

The unique structures and biological activities of the lamellarins and related pyrrole-derived alkaloids have attracted significant attention from synthetic chemists. As the core skeleton of lamellarins and related compounds, pyrroles and pyrrole-containing heterocycles attract numerous approaches for synthetic studies. ¯ These studies have contributed to the development of elegant synthetic routes of lamellarins and related pyrrole-derived alkaloids as well as their key intermediates.

Although numerous lamellarins and related pyrrole-derived alkaloids have been identified and their biological activities studied, very little is known about the mechanism of action at the cellular and molecular level. Further studies could contribute to a better understanding of the mechanism of lamellarins and analogues and will be beneficial for the ongoing development and lead optimization of this class. Development of synthetic methods for lamellarins and related pyrrole-derived alkaloids has provided quantities for study of their mechanism of action and the structure–activity relationship (SAR). At present a few SAR studies have been reported, especially focusing on lamellarin D **35**. Additional lamellarin SAR studies will be useful to fully utilize the lamellarins as leads for the treatment of numerous diseases.

Acknowledgments

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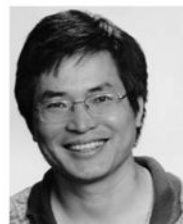
Jin-Feng Hu studied organic chemistry at Lanzhou University, where he obtained his B.Sc. (1990) and Ph.D. (1996) degrees in Natural Organic Chemistry under the supervision of Professor Zhong-Jian Jia. He was a postdoctoral fellow (1996–1998) in the Department of Natural Products Chemistry, Institute of Materia Medica (Chinese Academy of Medical Sciences and Peking Union Medical College), with Professor Xiao-Zhang Feng. He joined the Hans-Knoell-Institute for Natural Products Research as a BMBF & DLR fellow (1998–2000) with Professors Susanne Grabley and Ralf Thiericke. He moved to the United States as a postdoctoral associate at the Department of Pharmacognosy, the University of Mississippi, with Professor Mark T. Hamann (2000–2001) and at the Genomics Institute of the Novartis Research Foundation, The Scripps Research Institute, with Professor Peter G. Schultz (2001–2002). He left his position as a Principal Scientist in Natural Products Chemistry from Sequoia Sciences, Inc. (San Diego, CA), where he worked from 2002 to 2006, and since has been a Professor at East China Normal University. From plants, microorganisms, and marine invertebrates, he has so far isolated and characterized more than 700 natural products, and over 200 of them are novel with broad bioactivities. He is currently engaged in the application of high-throughput natural products chemistry methods

for parallel production and analysis of large natural products libraries for drug discovery and has undertaken the miniaturization of structure elucidation of mass-limited natural products as an initiative at Sequoia Sciences and the Key Laboratory of Brain Functional Genomics in Shanghai. During his research career, he has published over 50 scientific papers, reviews, book chapters, and patents. He is an invited reviewer for *Journal of Natural Products* and currently serves as a member of the Editorial Board of *Chemistry-An Indian Journal*. His group is focusing on natural products as small molecular probes for functional genomics studies that lead to discoveries of new diagnostic markers and neuropharmacological agents for treatment of obesity, age-related memory disorders, and CNS diseases.
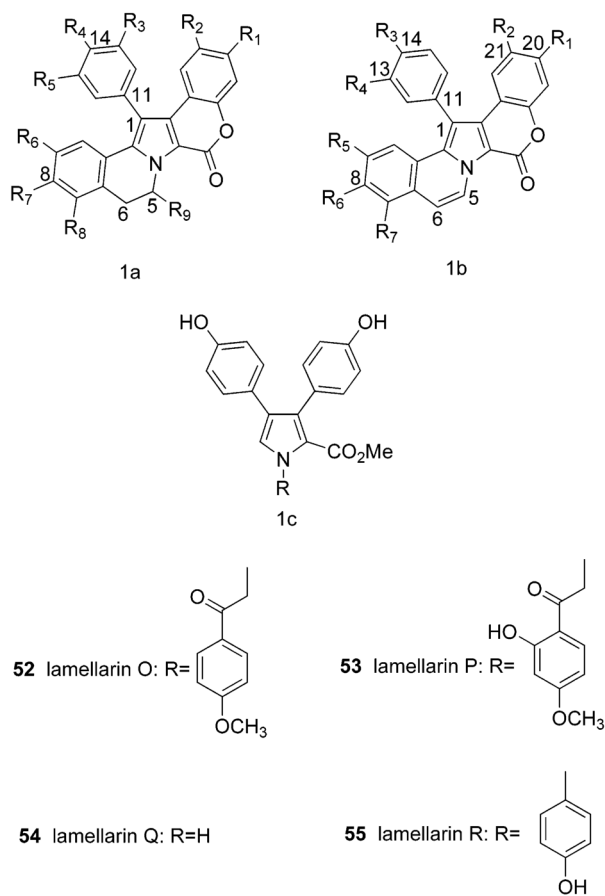
Figure 1.
Structure of lamellarins 1a–c.
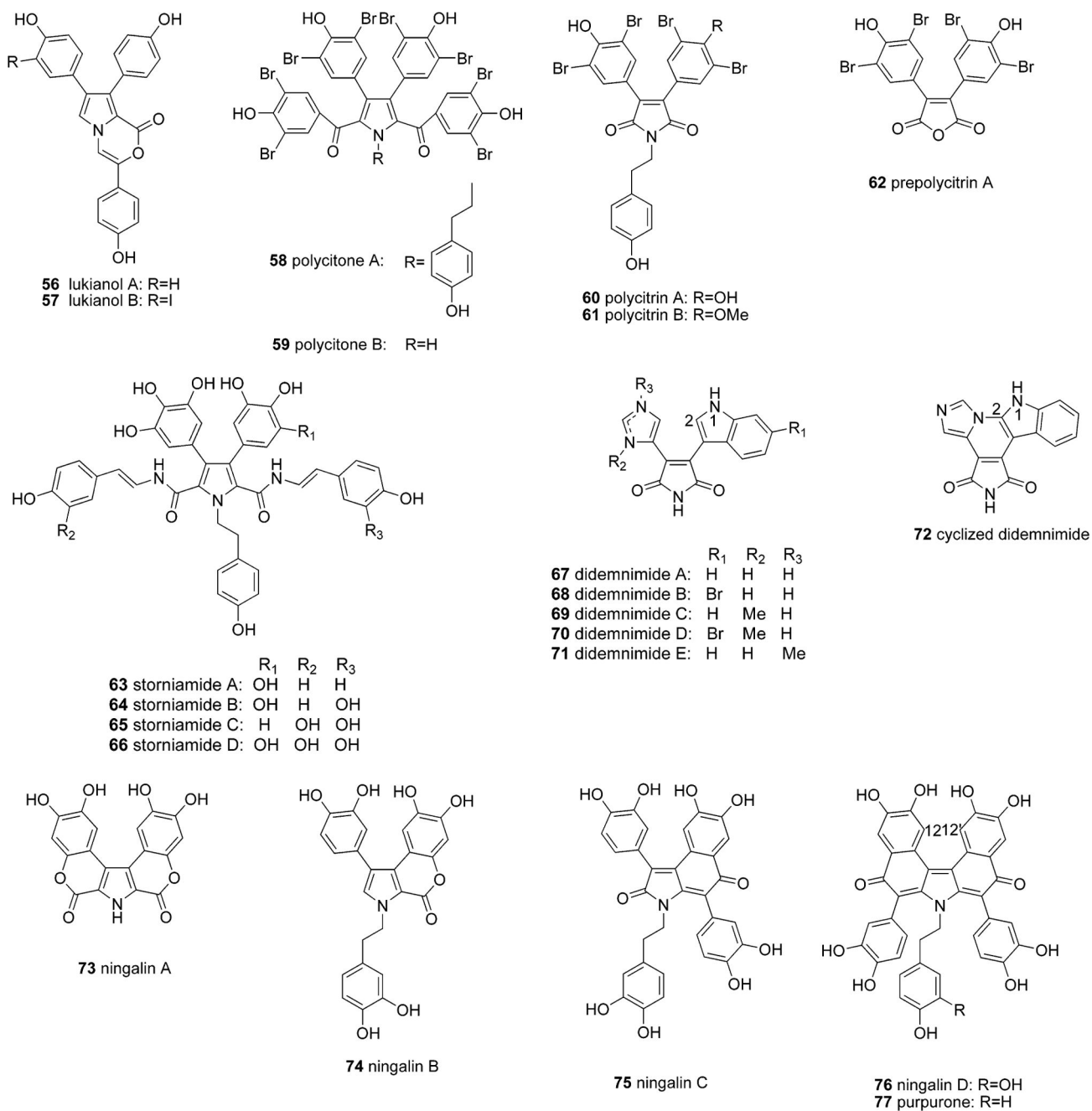
Figure 2.
Structures of lamellarin-related pyrrole-derived alkaloids.
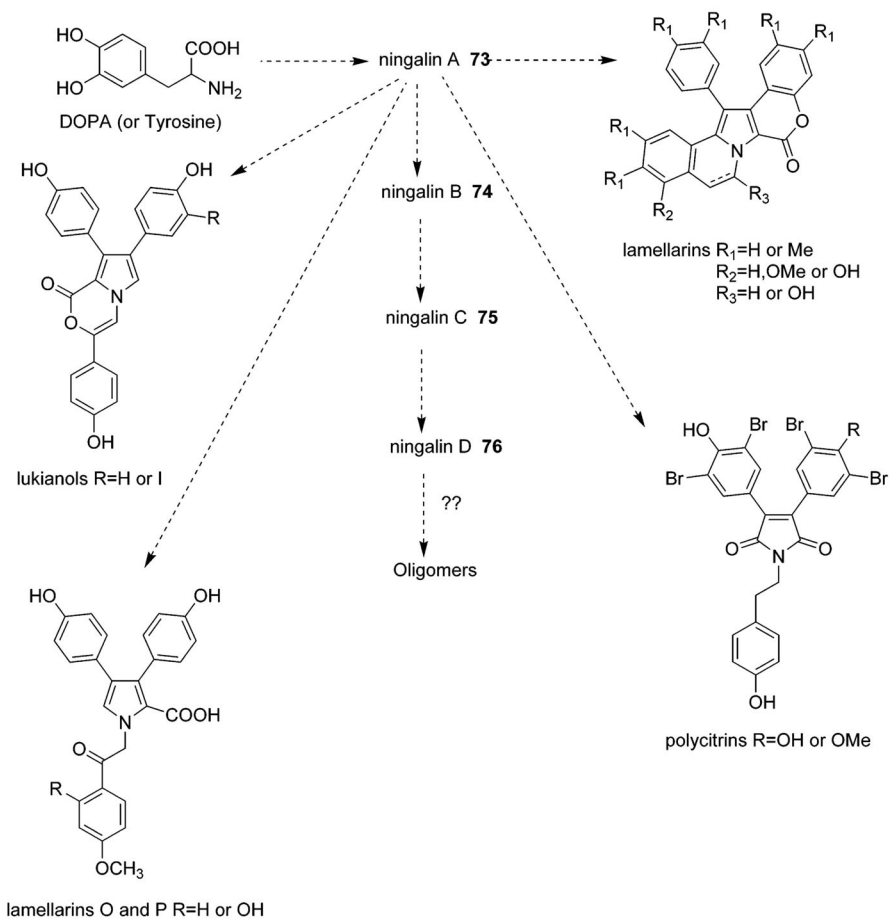
Figure 3.
Possible biogenetic pathways for several apparently DOPA-derived alkaloids from marine ascidians. (Reprinted with permission from ref 23. Copyright 1997 American Chemical Society.)
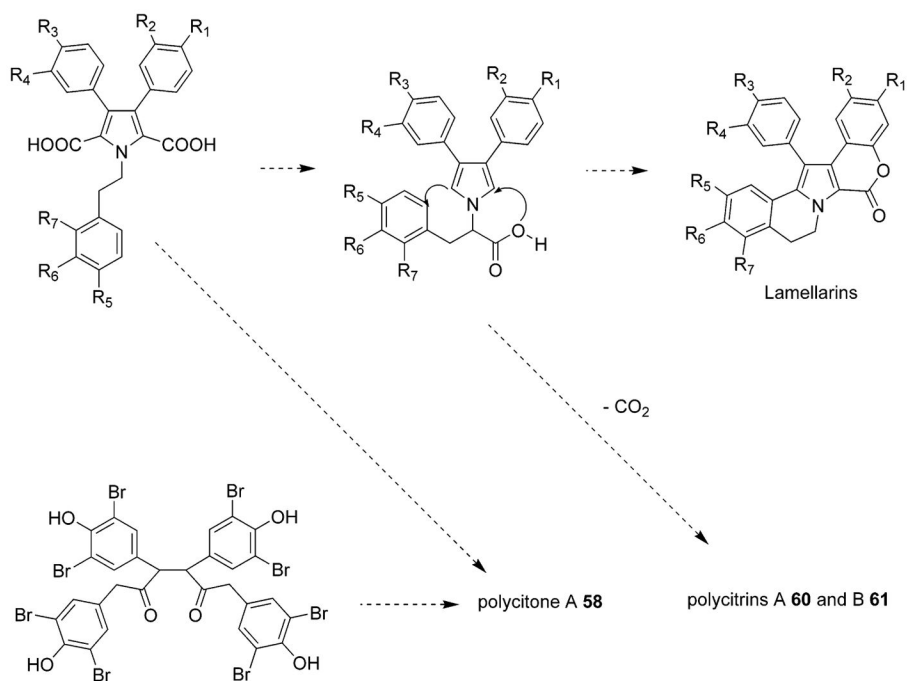
Figure 4.
Possible biogenetic relationship between the lamellarins, polycitone A (**58**) and polycitrins
A (**60**) and B (**61**). (Reprinted with permission from ref 17. Copyright 1994 American
Chemical Society.)
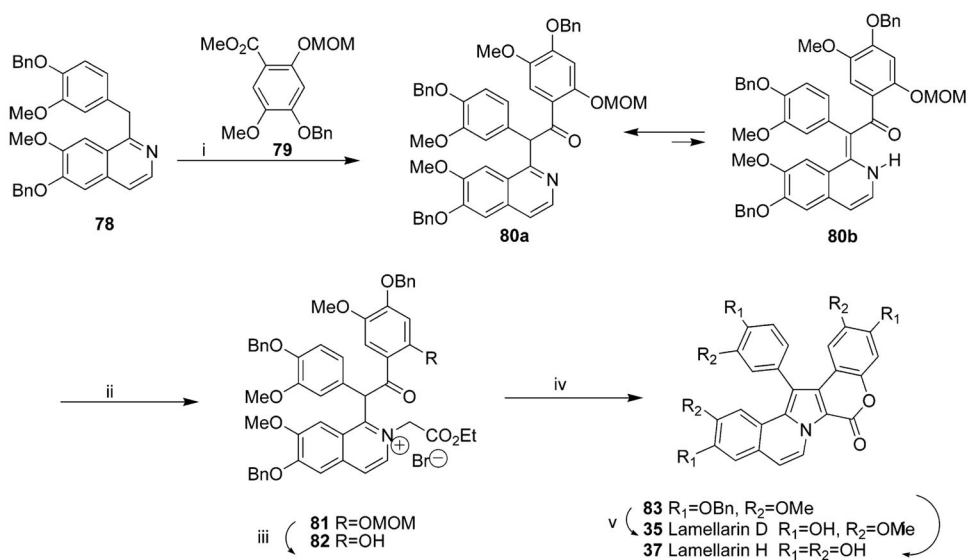
Scheme 1.

Synthesis of Lamellarins D (35) and H (37)^a

^{a} Reagents and conditions: (i) LDA, THF, **79**, 63%; (ii) BrCH$_2$CO$_2$Et; (iii) cat. HCl, MeOH; (iv) Et$_3$N, CH$_2$Cl$_2$, 34% (3 steps); (v) H$_2$, Pd(OH)$_2$/C, EtOAC, 82%; (vi) BBr$_3$, CH$_2$Cl$_2$, 68%. (Reprinted with permission from ref 31. Copyright 1997 Elsevier B.V.)
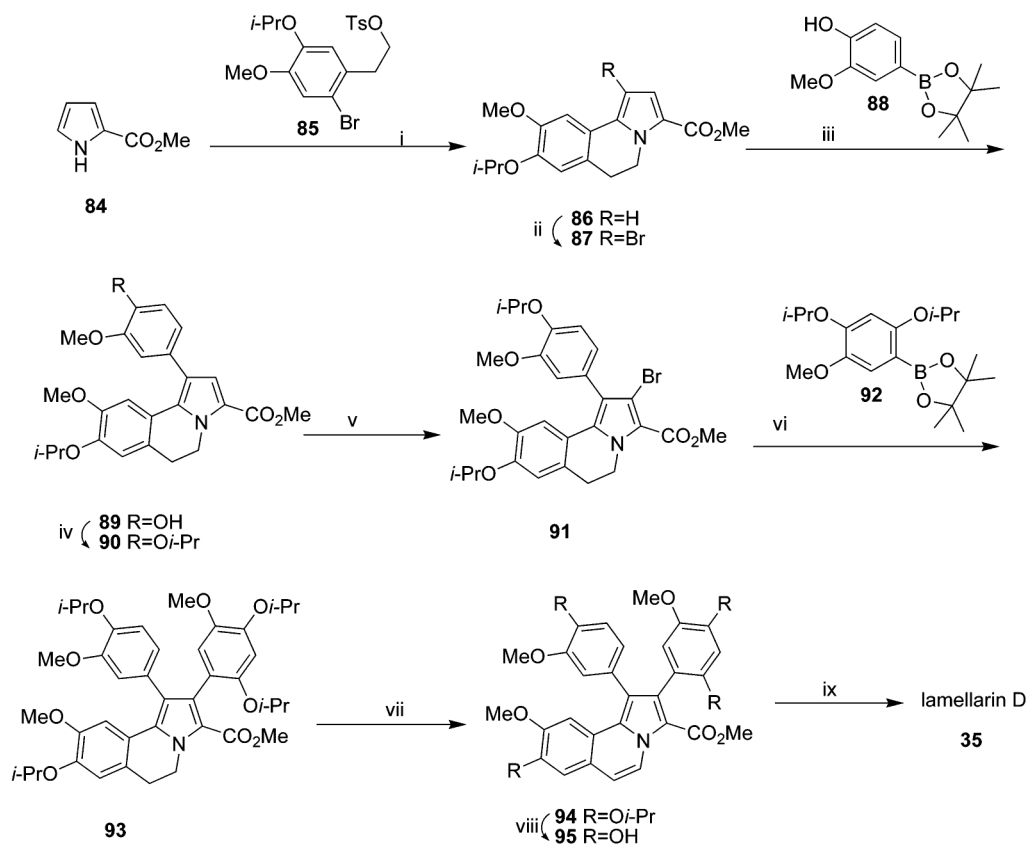
Scheme 2.
Synthesis of Lamellarin D (35)[a]

[a] Reagents and conditions: (i) (1) **85**, NaH, DMF, (2) PdCl$_2$(pph$_3$)$_2$, PPh$_3$, K$_2$CO$_3$; (ii) NBS, THF; (iii) **88**, Pd(PPh$_3$)$_4$, Na$_2$CO$_3$, DMF; (iv) *i*-PrBr, K$_2$CO$_3$, DMF; (v) NBS, THF; (vi) **92**, Pd(PPh$_3$)$_4$, K$_3$PO$_4$, DMF; (vii) DDQ, CHCl$_3$, MW; (viii) AlCl$_3$, CH$_2$Cl$_2$; (ix) NaH, THF. (Reprinted with permission from ref 32. Copyright 2005 American Chemical Society.)
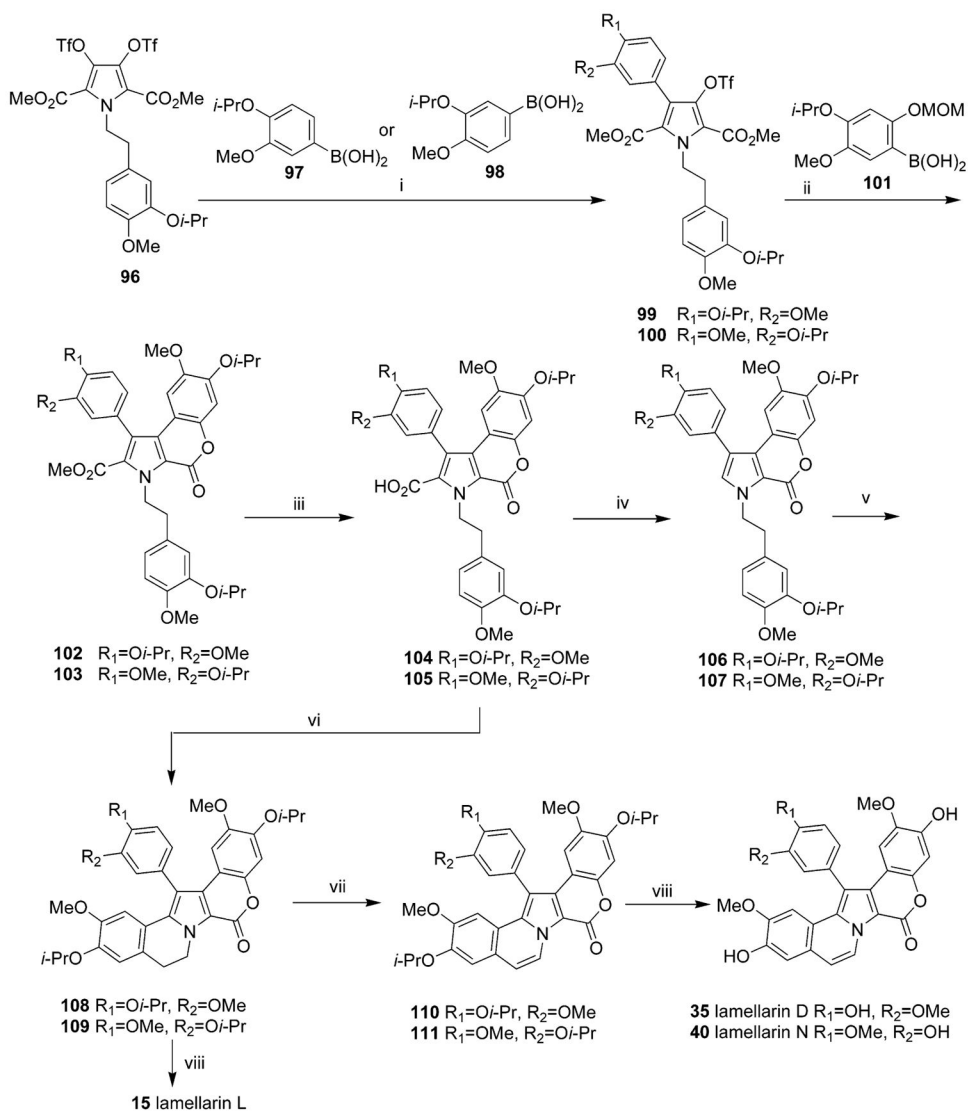
Scheme 3.
Synthesis of Lamellarins D (35), L (15), and N (40)[a]

[a] Reagents and conditions: (i) **97** or **98** (1.0 equiv), Pd(PPh$_3$)$_4$ (2 mol %), THF, reflux, 4 h (**99**, 76%; **100**, 77%); (ii) (1)**101** (2.0 equiv), Pd(PPh$_3$)$_4$ (8 mol %), THF, reflux, 18 h, (2) concd HCl, MeOH, reflux 1 h (**102**, 98%; **103**, 95%); (iii) (1) 40% KOH–EtOH (1/1), reflux, 3 h, (2) cat. *p*-TsOH, CH$_2$Cl$_2$, reflux, 1 h (**104**, 90%; **105**, 91%); (iv) Cu$_2$O, quinoline, 220 °C, 7 min (**106**, 94%; **107**, 99%); (v) PhI(OCOCF$_3$)$_2$, BF$_3$·OEt$_2$, CH$_2$Cl$_2$, –40 °C, 1.5 h (**108**, 88%; **109**, 90%); (vi) Pd(OAc)$_2$ (1.1 equiv), CH$_3$CN, reflux, 12 h (**110**, 65%; **106**, 14%; **109**, 65%; **107**, 15%); (vii) DDQ (1.5 equiv), toluene, reflux, 18 h (**110**, 97%; **111**, 96%); (viii) BCl$_3$, CH$_2$Cl$_2$, –78 °C, 0.5 h, then rt, 3 h (**35**, quant; **15**, 98%; **40**, 88%). (Reprinted with permission from ref 34. Copyright 2006 Elsevier B.V.)
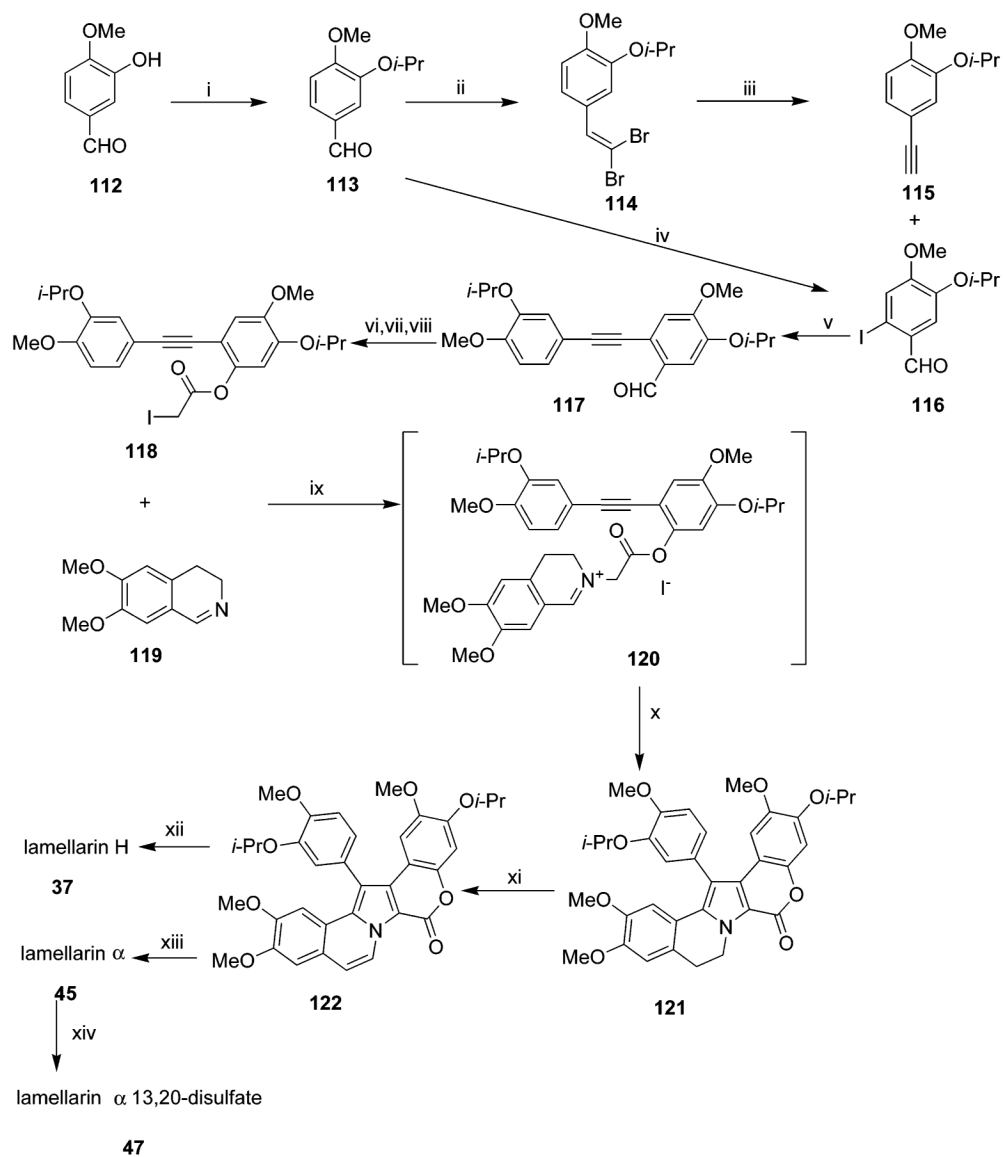
Scheme 4.
Synthesis of Lamellarin H (37), Lamellarin α (45), and Lamellarin α 13,20-Disulfate (47)[a]

[a] Reagents and conditions: (i) *i*-PrBr, K_2CO_3, DMF, rt, 48 h; (ii) CBr_4, Zn, PPh_3, CH_2Cl_2, 0–25 °C, 4 h; (iii) *n*-BuLi, THF, −78 to −25 °C, 2 h; (iv) $AgOCOCF_3$, I_2, CH_2Cl_2, reflux, 12 h; (v) $Pd(PPh_3)_4$, CuI, NEt_3, 45 °C, 5 h; (vi) MCPBA, $KHCO_3$, CH_2Cl_2, rt, 1 h; (vii) NH_3, CH_2Cl_2/MeOH (1:1), rt, 2 h; (viii) ICH_2COOH, DCC, DMAP, CH_2Cl_2, rt, 5 h; (ix) $ClCH_2CH_2Cl$, rt, 24 h; (x) Hunig's base, reflux, 30 h; (xi) DDQ, CH_2Cl_2/EtOH (1:1), reflux, 48 h; (xii) BCl_3, CH_2Cl_2, 0 °C, 6 h; (xiii) $DMF–SO_3$, DMF/pyridine (4:1), 65 °C, 2 h; (xiv) BBr_3, $CHCl_3$, 55 °C, 24 h. (Reprinted with permission from ref 50. Copyright 2002 Elsevier B.V.)
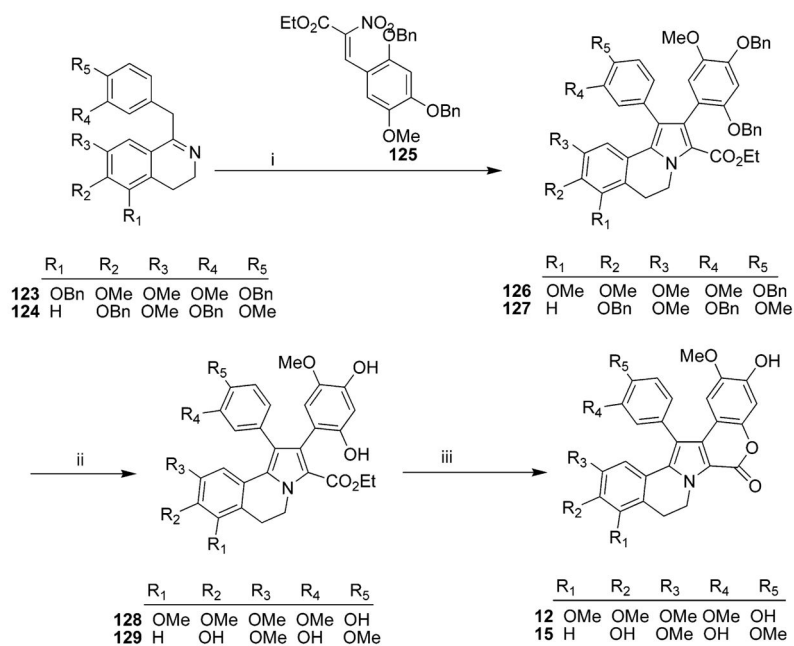
Scheme 5.

Synthesis of Lamellarins K (12) and L (15)[a]

[a] Reagents and conditions: (i) NaHCO$_3$, **125**, CH$_3$CN, reflux, 70% (**126**), 70% (**127**); (ii) H$_2$, Pd/C, EtOAC; (iii) NaH, THF, 93% (**12**, over 2 steps), 87% (**15**, over 2 steps).

(Reprinted with permission from ref 43. Copyright 2004 by John Wiley & Sons, Inc.)
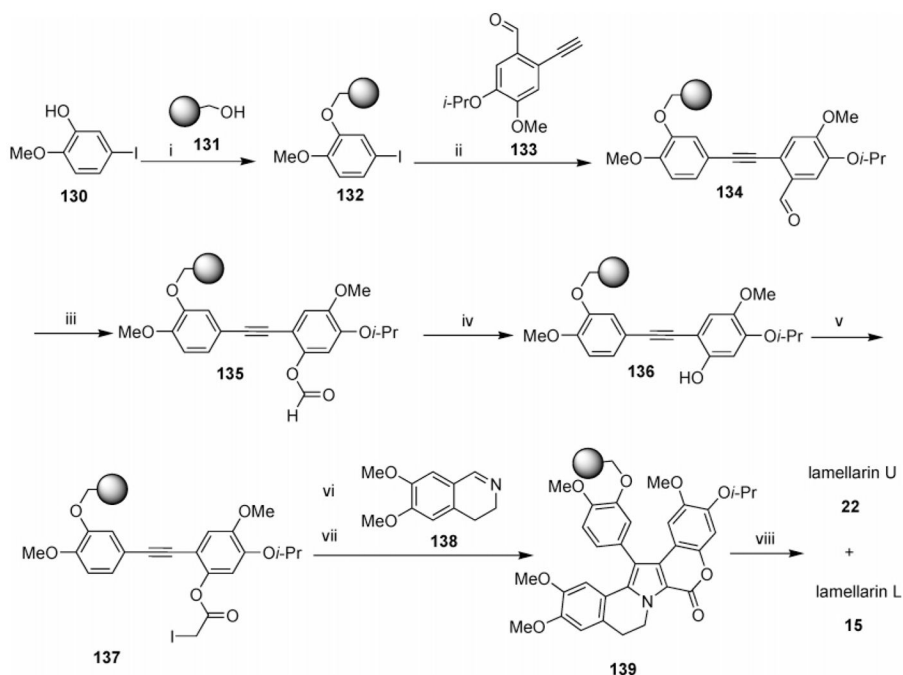
Scheme 6.
Synthesis of Lamellarin U (22) and Lamellarin L (15)[a]

[a] Reagents and conditions: (i) DEAD, PPh₃, DIEA, THF, 0 °C, 10 min, rt, 3 h, loading of Merrifield resin = 0.68 mmol/g; (ii) 2-ethynyl-5-isopropoxy-4-methoxy-benzaldehyde (3 equiv), CuI (0.6 equiv), Pd [(Ph₃)₂Cl₂] (0.3 equiv), THF–Et₃N (3:1), N₂, 20 h; (iii) *m*CPBA (6 equiv), NaHCO₃ (12 equiv), CH₂Cl₂, 0–20 °C, 15 h; (iv) 2 M KOH, THF–MeOH, rt, 5 h; (v) ICH₂CO₂H (10 equiv), DMAP (15%), DIP (10 equiv), DMF, rt, 12 h; (vi) 3,4-dihydro-6,7-dimethoxyisoquinoline (6 equiv), CH₂ClCH₂Cl, rt, 24 h; (vii) DIEA (7 equiv), 83 °C, 24 h; (viii) AlCl₃ (15 equiv), CH₂Cl₂, rt, 12 h. (Reprinted with permission from ref 45. Copyright 2003 American Chemical Society.)
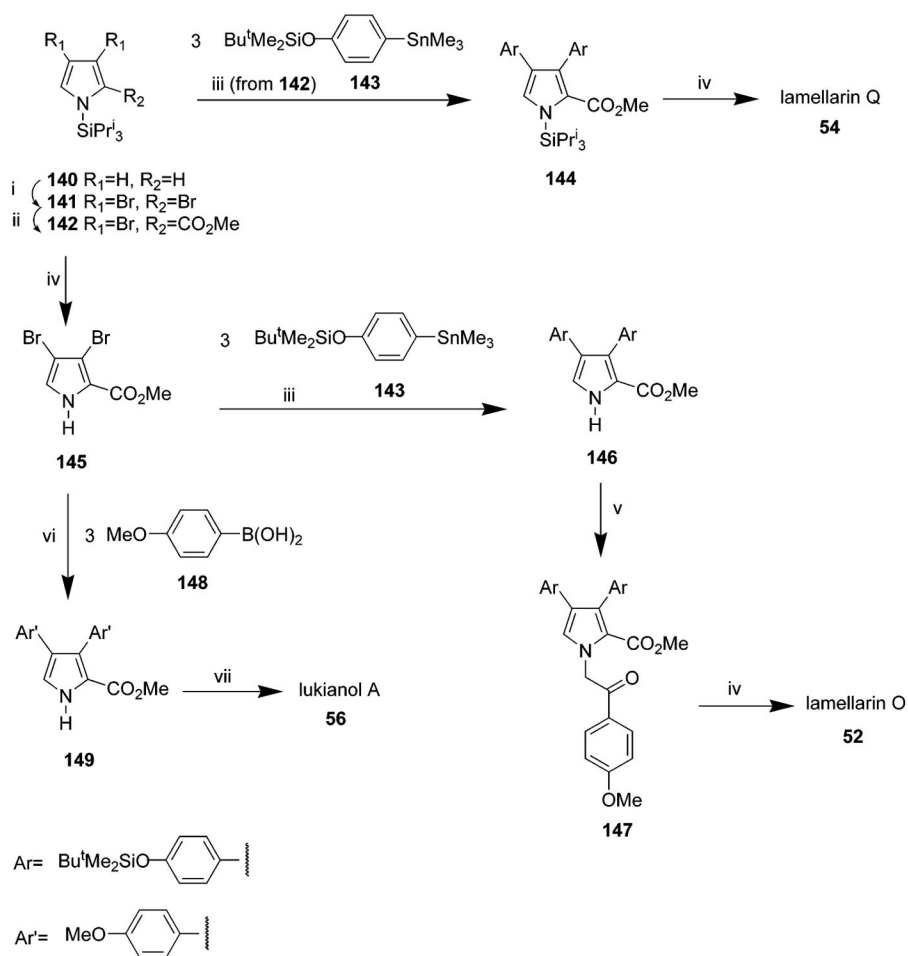
Scheme 7.
Convergent Synthesis of Lamellarins O (52) and Q (54) and Lukianol A (56)[a]

[a] Reagents and conditions: (i) NBS (3 equiv), THF, −78 °C, 1 h then 20 °C for 4 h; (ii) PhLi (1 equiv), −78 °C, 0.16 h then ClCO$_2$Me (1.05 equiv), −78 to 20 °C, 1 h; (iii) Pd(PPh$_3$)$_2$Cl$_2$ (10 mol %), 1,4,-dioxane, 101 °C, 14 h; (iv) Bu$_4$NF (10 mol % excess), THF, 20 °C, 1 h then 0.5 M aq.HCl; (v) *p*-MeOC$_6$H$_4$COCH$_2$Br (3 equiv.), K$_2$CO$_3$ (5 equiv.), Bu$_4$NCl (20 mol %), THF, 66 °C, 7 h; (vi) Pd(PPh$_3$)$_4$ (5 mol %), satd aq. Na$_2$CO$_3$ (6 equiv), DMF, 153 °C, 23 h; (vii) see ref 53. (Reprinted with permission from ref 47. Copyright Royal Society of Chemisty 1997.)
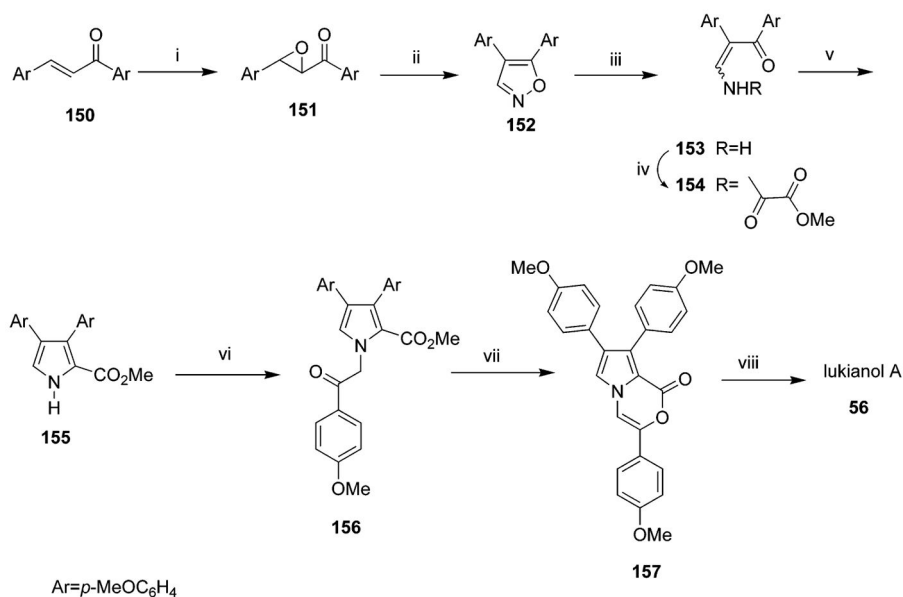
Scheme 8.

Synthesis of Lukianol A (56)[a]

[a] Reagents and conditions: (i) H_2O_2, NaOH, EtOH/H_2O, 0 °C, 98%; (ii) (1) $BF_3 \cdot Et_2O$, Et_2O, reflux; (2) $NH_2OH \cdot HCl$, pyridine, EtOH, reflux, 67% (over 2 steps); (iii) H_2 (1 atm), Pd (5%)/C, THF, 94%, (Z):(E) = 1:1; (iv) $ClOCCO_2Me$, pyridine, THF, 73%, (Z):(E) = 2.5:1; v, Ti–graphite ($TiCl_3$:C_8K = 1:2), DME, reflux, 52%; (vi) p-MeO–$C_6H_4COCH_2Br$, K_2CO_3, acetone, reflux, 91%; (vii) (1) KO–tBu, H_2O, Et_2O, 0 °C; (2) Ac_2O, NaOAC, reflux, 59% (over 2 steps); (viii) BBr_3, CH_2Cl_2, −78 °C, 99%. (Reprinted with permission from ref 53. Copyright 1995 American Chemical Society.)
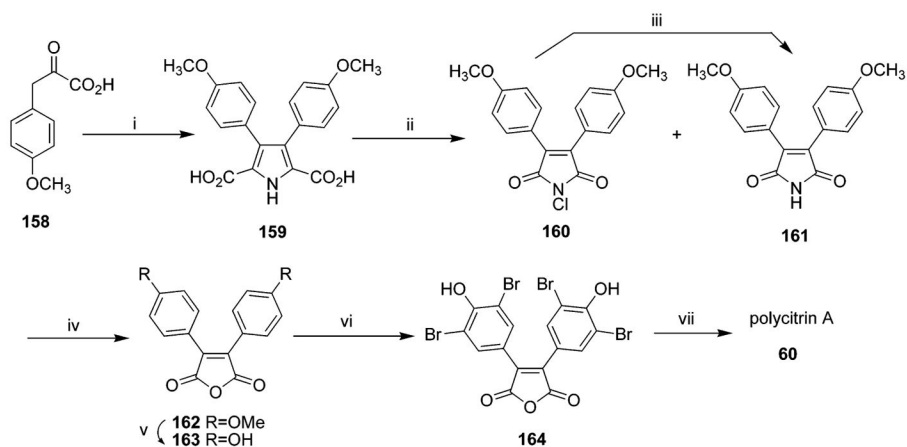
Scheme 9.
Biomimetic Total Synthesis of Polycitrin A (60)[a]

[a] Reagents and conditions: (i) (1) THF, n-BuLi, −78 °C, (2) 0.5 equiv, I_2, −78 to 25 °C, (3) NH_3, $TiCl_4$, 72%; (ii) NaOCl, 95%; (iii) $NaHSO_3$; (iv) (1) KOH, (2) HCl, 75%; (v) BBr_3, 78%; (vi) Br_2, AcOH, 83%; (vii) tyramine, diisopropylethylamine, PhOH (melt), 160 °C, 78%. (Reprinted with permission from ref 57. Copyright 1995 Elsevier B.V.)
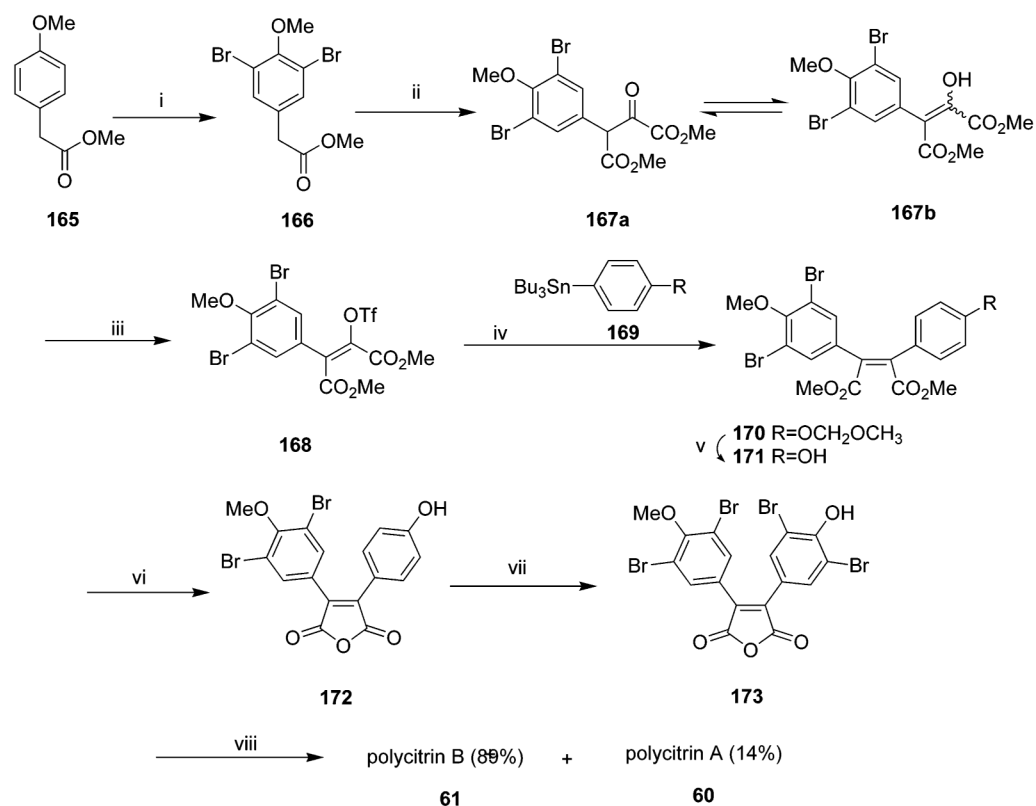
Scheme 10.
Total Synthesis of Polycitrin B (61)[a]

[a] Reagents and conditions: (i) Br$_2$,FeBr$_2$, 80%; (ii) MeONa, MeOH, (CO$_2$Me)$_2$, 99%; (iii) (CF$_3$SO$_2$)$_2$O, *i*Pr$_2$NEt,CH$_2$Cl$_2$, 84%; (iv) **169**, Pd$_2$dba$_3$, Ph$_3$P,DMF, 81%; (v) Me$_3$SiCl, NaI, MeCN, 92%; (vi) NaOH, H$_2$O, MeOH, 77%; (vii) Br$_2$,AcOH, 89%; (viii) tyramine, *i*Pr$_2$NEt, phenol, molecular sieves, 140 °C. (Reprinted with permission from ref 60. Copyright 2000 Elsevier B.V.)
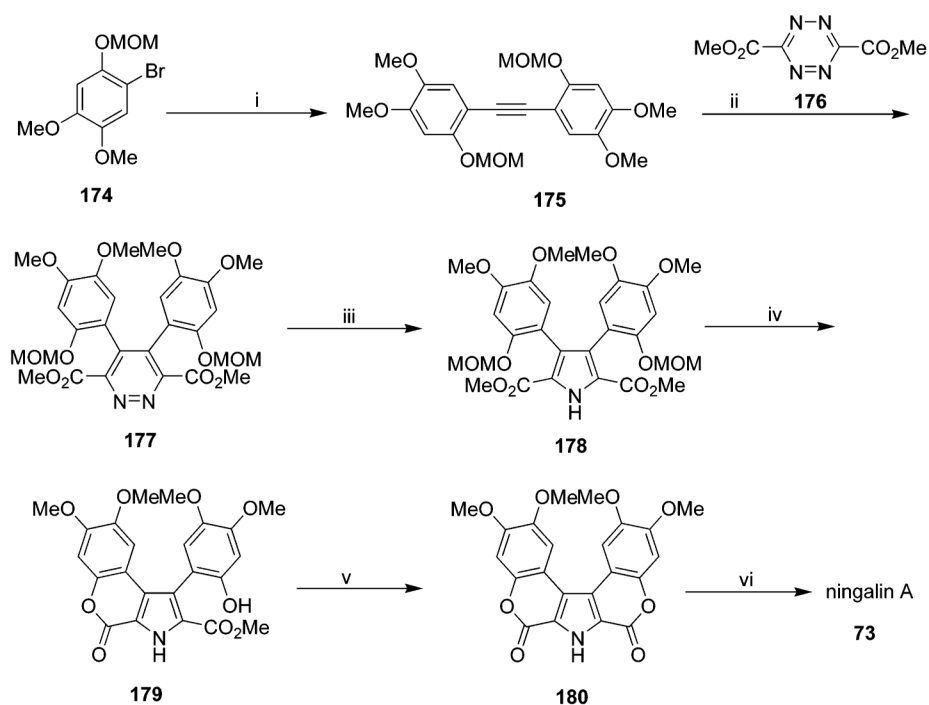
Scheme 11.

Synthesis of Ningalin A (73)[a]

[a] Reagents and conditions: (i) Bu₃SnCCSnBu₃,(Ph₃P)₄Pd, 79%; (ii) **176**, 87%; (iii) Zn, HOAC, 63%; (iv) HCl·EtOAc, 94%; (v) DBU, 100%; (vi) BBr₃, 96%. (Reprinted with permission from ref 68. Copyright 1999 American Chemical Society.)

Table 1

Lamellarins and Related Pyrrole-Derived Alkaloids from Marine Organisms

lamellarin and related alkaloids	marine sources	collection localities	ref
lamellarins A–D (**1**, **32**, **3**, **35**)	prosobranch mollusc *Lamellaria* sp.	peduliaes headland on Ngarol Island at the entrance to Malakal Harbor, Palau	3
lamellarins C, U (**3**, **22**)	prosobranch mollusc *Coriocella hibyae*	around the Feydhoo Islands in the Maldives	4
lamellarins E–H (**6–8**, **37**)	marine ascidian *Didemnum chartaceum*	Indian Ocean on the atoll of Aldabra, Republic of the Seychelles	5
lamellarins I, J–M, triacetate of lamellarin N, lamellarins A–C, the triacetate of lamellarin D (**10–12**, **15**, **38**, **41**, **1**, **32**, **3**, **36**)	marine ascidian *Didemnum* sp.	South West Cay, Lihou Reef, off the North Queensland coast/Little Broadhurst Reef on the Great Barrier Reef	6
lamellarins O, P (**52**, **53**)	southern Australian marine sponge *Dendrilla cactos*	Bass Strait, Australia	7
lamellarins Q, R (**54**, **55**)	Australian marine sponge, *Dendrilla cactos*	coast off Durras, New South Wales, Australia	8
lamellarins S, K (**18**, **12**)	Australian tunicate *Didemnum* sp.	near Durras, New South Wales, Australia	9
lamellarins T–X, N, lamellarin T 20-sulfate, lamellarin U 20-sulfate, lamellarin V 20-sulfate, lamellarin Y 20-sulfate (**19**, **22**, **24**, **42**, **43**, **40**, **21**, **23**, **25**, **27**)	unidentified ascidian	near Trivandrum coast in the Arabian Sea, India	10
lamellarin Z, lamellarin B 20-sulfate, lamellarin C 20-sulfate, lamellarin L 20-sulfate, lamellarin G 8-sulfate, lamellarins A–C, E, G, L, lamellarin D triacetate, lamellarin N triacetate (**28**, **34**, **5**, **17**, **9**, **1**, **32**, **3**, **6**, **8**, **15**, **36**, **41**)	Great Barrier Reef ascidian, *Didemnum chartaceum*	near Friget Cay in the Swains Reef group, Great Barrier Reef	11
lamellarin α 20-sulfate (**46**)	unidentified ascidian	Arabian Sea near Trivandrum, Indian	12
lamellarins *β*, G, L (**29**,**8**,**15**)	purple unidentified encrusting marine ascidian *Didemnum* sp.	Indian Ocean	13
lamellarins *γ*, α, *ε*, lamellarins C-diacetate, I, K, K-diacetate, K-triacetate, M, U, X-triacetate (**30**, **45**, **48**, **4**, **10–14**, **38**, **22**, **44**)	Indian ascidian *Didemnum obscurum*	Tiruchandur coast in the Gulf of Mannar, Tamilnadu, India	14
lamellarins *ζ*, *η*, *φ*, *χ*, lamellarins F, I, J, K, lamellarin K triacetate, lamellarin L triacetate, lamellarin T diacetate (**49–51**, **31**, **7**, **10–12**, **14**, **16**, **20**)	red colonial ascidian *Didemnum obscurum*	Tiruchandur coast, Tamilnadu, India	15
lukianols A, B (**56**, **57**)	unidentified Pacific tunicate	lagoon of the Palmyra atoll	16
polycitone A, polycitrins A, B (**58**, **60**, **61**)	Indo Pacific ascidian *Polycitor* sp.	Sodwana Bay, South Africa	17
polycitone B, prepolycitrin A (**59**, **62**)	Indo Pacific asdidian *Polycitor africanus*	lagoon of Toliara, Madagascar, or in the lagoon of Mayotte, Comoros Islands, northwest of Madagascar	18
storniamides A–D (**63–66**)	Patagonian sponge *Cliona* sp.	Punta Verde, near San Antonio Oeste, Rio Negro, Argentina	19
didemnimides A–D (**67–70**)	Caribbean mangrove ascidian *Didemnum conchyliatum*	blades of the seagrass *Thalassia testudinum* in the mangrove channels of Sweetings Cay, near Grand Bahama Island, Bahamas	20
didemnimides A, D, E (**67**, **70**, **71**)	ascidian *Didemnum granulatum*	rocky shore of Araca beach, Sao Sebastiao (Sao Paulo state, southeastern Brazil)	21
cyclized didemnimide (**72**)	Caribbean ascidian *Didemnum conchyliatum*	blades of the seagrass *T. testudinum* in the mangrove channels of Sweetings Cay, Grand Bahama Island, Bahamas	22

lamellarin and related alkaloids	marine sources	collection localities	ref
ningalins A–D (**73–76**)	western Australian ascidian of the genus *Didemnum*	western Australia near Ningaloo Reef	23
purpurone (**77**)	marine sponge *Iotrochota* sp.	Koror island, Palau	24

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Table 2

Synthesis of Lamellarins and Related Pyrrole-Derived Alkaloids

lamellarin and related alkaloids	research group	synthesis strategy	ref
lamellarins D, H (**35**, **37**)	Iwao, Ishibashi	*N*-ylide-mediated pyrrole formation	31
lamellarin D (**35**)	Albericio, Álvarez	sequential and regioselective bromination/Suzuki cross-coupling procedure	32
lamellarin D analogues	Albericio, Álvarez	sequential and regioselective bromination/palladium-catalyzed Suzuki cross-coupling procedure	33
lamellarins D, L, N (**35**, **15**, **40**)	Iwao, Ishibashi	Hinsberg-type pyrrole synthesis and palladium-catalyzed Suzuki–Miyaura coupling reactions	34
lamellarin H (**37**) and its derivatives	You	intermediate for lamellarin	35
lamellarins I, K (**10**, **12**)	Guitián	intramolecular [3 + 2] cycloadditon pathway	36
lamellarins G, K, lukianol A, ningalin B (**8**, **12**, **56**, **74**)	Steglich	biomimetic synthesis	37
lamellarin G trimethyl ether	Steglich	biomimetic synthesis	38
lamellarin G trimethyl ether	Ruchirawat	*N*-ylide-mediated pyrrole formation	39
lamellarin G trimethyl ether, permethyl storniamide A, ningalin B (**74**)	Iwao, Ishibashi	Hinsberg-type pyrrole synthesis and palladium-catalyzed Suzuki–Miyaura coupling reactions	40
lamellarin G trimethyl ether	Handy	three iterative halogenation/cross-coupling reactions	41
lamellarin K (**12**)	Banwell	intramolecular [3 + 2] cycloadditon pathway	42
lamellarins K, L (**12**,**15**)	Ruchirawat	convergent synthetic approach; Michael addition/ring-closure reaction	43
lamellarin L (**15**)	Steglich	biomimetic total synthesis	44
lamellarins U, L (**22**,**15**)	Albericio, Álvarez	solid-phase total synthesis; Baeyer–Villiger reaction and an intramolucular [3 + 2] cycloaddition	45
lamellarins U, L, O, Q (**22**, **15**, **52**, **54**)	Albericio, Álvarez	solid-phase total synthesis; intramolucular [3 + 2] cycloaddition, two successive and selective cross-coupling reactions	46
lamellarins O, Q, lukianol A (**52**, **54**, **56**)	Banwell	convergent synthesis; Stille, Suzuki, or Negishi cross-coupling reactions	47
lamellarins Q, O (**54**,**52**)	Albericio, Álvarez	solid-phase synthesis; Negishi/Suzuki cross-coupling reactions	48
lamellarin T hybrids	Banwell	Negishi cross-coupling reaction	49
lamellarin α, lamellarin α 13,20-disulfate, lamellarin H (**45**,**47**,**37**)	Faulkner	intramolecular [3 + 2] cycloaddition pathway	50
lamellarin α 20-sulfate (**46**)	Iwao, Ishibashi	Hinsberg-type pyrrole synthesis and Suzuki–Miyaura coupling reaction	51
lamellarins C, E–G, I–L, T, U, Y, χ (**3**, **6–8**, **10–12**, **15**, **19**, **22**, **26**, **31**)	Ruchirawat	Michael addition/ring-closure reaction	52
lukianol A (**56**), lamellarin O dimethyl ether	Fürstner	titanium-mediated formation	53
lukianol A (**56**), lamellarin O dimethyl ether	Gupton	vinylogous iminium chemisty	54
lukianol A (**56**)	Wong	palladium-catalyzed Sonogashira, Heck, and Suzuki cross-coupling reactions	55
lukianol A (**56**)	Steglish	biomimetic synthesis	56
polycitrin A (**60**)	Steglish	biomimetic total synthesis	57
polycitrin A (**60**), prepolycitrin A (**62**)	Correia	palladium-catalyzed Heck diarylation	58
polycitrin A (**60**)	Steglich	biomimetic synthesis	59

lamellarin and related alkaloids	research group	synthesis strategy	ref
polycitrin B (**61**)	Beccalli	palladium-catalyzed cross-coupling reaction	60
polycitones A, B (**58**, **59**)	Steglich	total synthesis; Friedel–Crafts reaction	61
polycitones A, B (**58**, **59**)	Gupton	vinylogous iminium chemisty	62
storniamide A nonamethyl ether	Steglich	biomimetic synthesis	63
permethyl storniamide A	Fürstner	palladium-catalyzed Suzuki and Negishi cross-coupling reactions	64
didemnimide A (**67**)	Berlinck, Piers, Andersen	biomimetic synthesis	21
didemnimides A, B (**67**, **68**)	Cava	K$^+$$t$-BuO$^-$-catalyzed condensation	65
didemnimide C (**69**)	Steglich	Stille coupling reaction	66
didemnimide C (**69**)	Piers	biomimetic synthesis	67
ningalin A (**73**), lamellarin O (**52**), lukianol A (**56**), permethyl storniamide A	Boger	Diels–Alder reaction/ring contraction pathway	68
ningalin B (**74**)	Boger	heterocyclic azadiene Diels–Alder reaction	69
ningalin B (**74**) and its analogs	Boger	heterocyclic azadiene Diels–Alder strategy	70
ningalin B (**74**)	Bullington	regioselective synthesis	71
ningalin B hexamethyl ether	Gupton	vinylogous iminium chemistry	72
ningalin C, purpurone (**75**,**77**)	Steglich	biomimetic total synthesis	73
ningalin C (**75**)	Ruchirawat	one-pot reaction	74
ningalin D (**76**)	Boger	Heterocyclic azadiene Diels–Alder reaction	75

Table 3

Lamellarins (Type 1a)

no.	lamellarin	R₁	R₂	R₃	R₄	R₅	R₆	R₇	R₈	R₉
1	A	OH	OMe	H	OH	OMe	OMe	OMe	OMe	OH
2	A triacetate	OAc	OMe	H	OAc	OMe	OMe	OMe	OMe	OAc
3	C	OH	OMe	H	OH	OMe	OMe	OMe	OMe	H
4	C diacetate	OAc	OMe	H	OAc	OMe	OMe	OMe	OMe	H
5	C 20-sulfate	OSO₃⁻	OMe	H	OH	OMe	OMe	OMe	OMe	H
6	E	OH	OMe	H	OMe	OH	OMe	OMe	OH	H
7	F	OH	OMe	H	OMe	OMe	OMe	OMe	OH	H
8	G	OMe	OH	H	OMe	OH	OMe	OH	H	H
9	G 8-sulfate	OMe	OH	H	OMe	OH	OMe	OSO₃⁻	H	H
10	I	OH	OMe	H	OMe	OMe	OMe	OMe	OMe	H
11	J	OH	OMe	H	OMe	OMe	OMe	OH	H	H
12	K	OH	OMe	H	OH	OMe	OMe	OMe	OH	H
13	K diacetate	OAc	OMe	H	OAc	OMe	OMe	OMe	OH	H
14	K triacetate	OAc	OMe	H	OAc	OMe	OMe	OMe	OAc	H
15	L	OH	OMe	H	OMe	OH	OMe	OH	H	H
16	L triacetate	OAc	OMe	H	OMe	OAc	OMe	OAc	H	H
17	L 20-sulfate	OSO₃⁻	OMe	H	OMe	OH	OMe	OH	H	H
18	S	OH	OH	H	OH	OH	OMe	OH	H	H
19	T	OH	OMe	H	OMe	OH	OMe	OMe	OMe	H
20	T diacetate	OAc	OMe	H	OMe	OAc	OMe	OMe	OMe	H
21	T 20-sulfate	OSO₃Na	OMe	H	OMe	OH	OMe	OMe	OMe	H
22	U	OH	OMe	H	OMe	OH	OMe	OMe	H	H
23	U 20-sulfate	OSO₃Na	OMe	H	OMe	OH	OMe	OMe	H	H
24	V	OH	OMe	H	OMe	OH	OMe	OMe	OMe	OH
25	V 20-sulfate	OSO₃Na	OMe	H	OMe	OH	OMe	OMe	OMe	OH
26	Y	OH	OMe	H	OMe	OH	OH	OMe	H	H
27	Y 20-sulfate	OSO₃Na	OMe	H	OMe	OH	OH	OMe	H	H
28	Z	OMe	OH	H	OH	OH	OMe	OH	H	H

no.	lamellarin	R₁	R₂	R₃	R₄	R₅	R₆	R₇	R₈	R₉
29	β	OH	OH	H	OMe	OH	OH	OH	H	H
30	γ	OH	OMe	OMe	H	OMe	OMe	OMe	OH	H
31	χ	OAc	OMe	H	OAc	OMe	OMe	OAc	H	H

Table 4

Lamellarins (Type 1b)

no.	lamellarin	R_1	R_2	R_3	R_4	R_5	R_6	R_7
32	B	OH	OMe	OH	OMe	OMe	OMe	OMe
33	B diacetate	OAc	OMe	OAc	OMe	OMe	OMe	OMe
34	B 20-sulfate	OSO_3^-	OMe	OH	OMe	OMe	OMe	OMe
35	D	OH	OMe	OH	OMe	OMe	OH	H
36	D triacetate	OAc	OMe	OAc	OMe	OMe	OAc	H
37	H	OH	OH	OH	OH	OH	OH	H
38	M	OH	OMe	OH	OMe	OMe	OMe	OH
39	M triacetate	OAc	OMe	OAc	OMe	OMe	OMe	OAc
40	N	OH	OMe	OMe	OH	OMe	OH	H
41	N triacetate	OAc	OMe	OMe	OAc	OMe	OAc	H
42	W	OH	OMe	OMe	OH	OMe	OMe	OMe
43	X	OH	OMe	OMe	OH	OMe	OMe	OH
44	X triacetate	OAc	OMe	OMe	OAc	OMe	OMe	OAc
45	α	OH	OMe	OMe	OH	OMe	OMe	H
46	α 20-sulfate	OSO_3Na	OMe	OMe	OH	OMe	OMe	H
47	α 13,20-disulfate	OSO_3Na	OMe	OMe	OSO_3Na	OMe	OMe	H
48	ε	OH	OMe	OMe	OMe	OMe	OMe	OH
49	ζ	OH	OMe	OMe	OMe	OMe	OMe	OMe
50	η	OH	OMe	OMe	OMe	OMe	OMe	H
51	φ	OAc	OMe	OAc	OMe	OAc	OMe	OMe