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REVIEW ARTICLE

Isolation, Bioactivities, and Synthesis of Lamellarin Alkaloids: A Review

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ARTICLE HISTORY

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Abstract: Lamellarin alkaloid is a large class of marine alkaloids with diverse bioactivities. These heterocycles have been isolated from diverse marine organisms, mainly ascidians and sponges. They possess a fused 14-phenyl-6H-[1]benzopyrano[40,30:4,5] pyrrolo[2,1-*a*]isoquinoline or non-fused 3,4-diarylpyrrole-2-carboxylate ring systems. Until now, more than 50 lamellarins have been isolated from marine organisms. Various lamellarins exhibit valuable bioactivities, such as cytotoxicity, topoisomerase I inhibition, protein kinases inhibition, multidrug resistance reversal, and anti-HIV-1 activity. Due to their valuable biological activity, the synthesis of lamerallins has received great attention of chemists and a vast number of synthetic methods have been developed. This article gives overview of studies on lamellarins isolation, their bioactivities, and synthetic approaches for their total synthesis.

Dau Xuan Duc

Keywords: Anticancer, marine organism, isoquinoline, fused pyrrole, lactonization, cross-coupling, pyruvic acid.

1. INTRODUCTION

Marine organisms possess a vast chemical, structural, and biological diversity of molecules, often very distinct from those found in terrestrial natural compounds. Common marine species that have been considered sources of bioactive drugs include sponges, ascidians, mollusks, echinoderms, bryozoans, algae, and coelenterates [1]. Many alkaloids with distinct structures have been isolated from marine species, and the number of reported marine alkaloids continues to grow at an increasing rate.

Lamellarins are a large family of marine alkaloids characterized by their unusual structures and important activities. Structurally, lamellarins can be classified into two groups. The larger group has a pentacyclic system of 6- oxobenzo[*b*]pyrano[3,4-*b*]pyrrolo[2,1-*a*] isoquinoline with a substituted phenyl ring at position. The second group of lamellarins, which are less structurally complex, are derivatives of methyl 3,4-bis(*p*-hydroxyphenyl) pyrrole-2-carboxylate, which differ in their *N*-pyrrole substituent. General structure of two of these groups of lamellarins is shown in Fig. (**1**). The lamellarins have been reported to possess a wide range of bioactivities such as cytotoxicity and antitumor activity, reversal of multidrug resistance (MDR), HIV-1 integrase inhibition, antibiotic activity, and antioxidant activity [2-14]. The interesting structure and promising bioactivities of this class of alkaloids have drawn great attention from chemists. Some review articles about isolation, synthesis and bioactivity have been found in the literature [15-19]. However, they are quite outdated or missing details about total synthesis. This article will give an overview of the chemistry of lamellarins. All articles about the isolation and total synthesis of lamellarin alkaloids have been discussed. In addition, a brief summary of bioactivities of lamellarins has also been introduced.

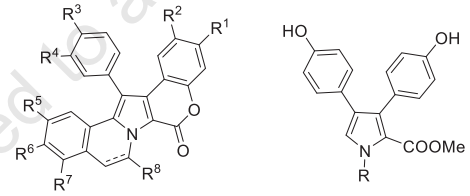

Fig. (1). General structures of two groups of lamellarins

2. ISOLATION OF LAMELLARINS

In 1985, Faulkner *et al*. isolated four new alkaloids from the marine prosobranch mollusc, *Lamellaria* sp collected in Koror, Palau and named them lamellarins A-D (1-4) (Fig. **2**). The structure of lamellarin A was determined by a single-crystal X-ray diffraction analysis, while the structures of other lamellarins were assigned by interpretation of spectral data. Noticeably, dehydration of lamellarin A using *p*-toluenesulfonyl chloride provided lamellarin B [20].

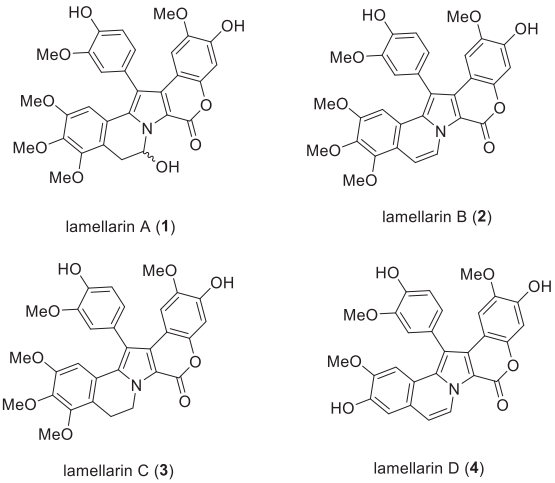

Fig. (2). Structures of lamellarins A-D.

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In 1988, Fenical *et al*. isolated four new lamellarins E-H (**5-8**) from the marine *Didemnum chartaceum* collected in the Indian Ocean on the atoll of Aldabra (Fig. **3**). The structure of lamellarin E was elucidated by the spectroscopic method and confirmed by the X-ray crystallographic method [21].

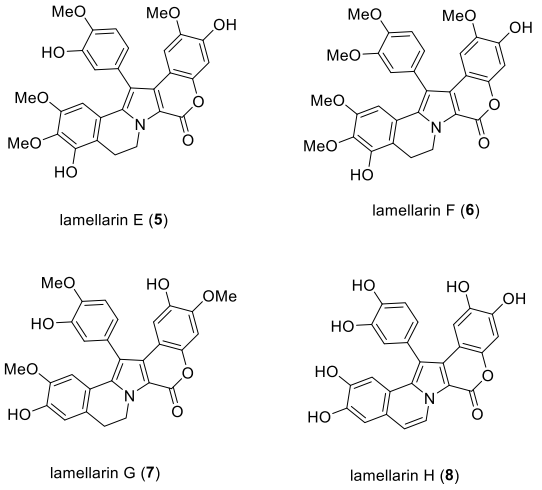


Fig. (3). Structures of lamellarins E-H.

Capon *et al*. described the isolation and structure elucidation of two new alkaloids, lamellarin O (**9**) and lamellarin P (**10**), from a specimen of *Dendrilla cactos* collected during trawling operations in Bass Strait, Australia. In these compounds, the pyrrole ring system is not fused to adjacent aromatic rings (Fig. **3**). The structures of two alkaloids were secured by spectroscopic analysis and partial synthesis [22]. Later, the Capon group also isolated two new alkaloids, lamellarins Q (**11**) and R (**12**), from a specimen of Dendrilla cactos collected off the coast of New South Wales, Australia. The structures of lamellarin alkaloids were elucidated by spectroscopic analysis and by chemical derivatization (Fig. **4**) [23].

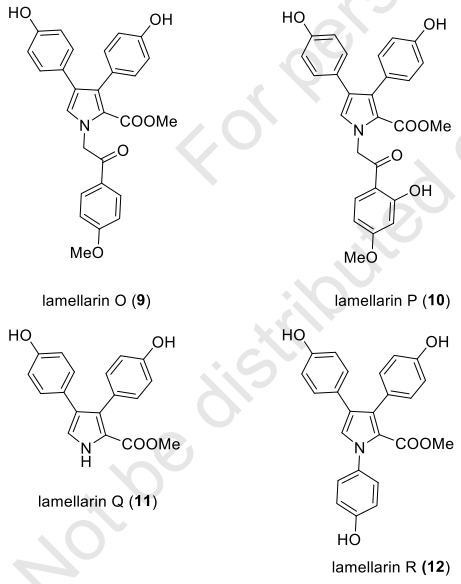


Fig. (4). Structures of lamellarins O-R.

Chemical investigation of the marine ascidian *Didemnum chartaceum* from North Queensland coast, Australia, has resulted in the isolation of six new lamellarins I, J, K, L, M, and lamellarin N triacetate (**13-18**) (Fig. **5**). Four known lamellarin alkaloids A, B, C, and D triacetate were also isolated. Total acetylation of lamellarin L followed by dehydrogenation generated lamellarin N triacetate, and this experiment confirmed the structural relationship between the two compounds. Similarly, the structural relationship between lamellarin K and lamellarin M was elucidated by the experiment, in which the lamellarin M triacetate was obtained from the prepared lamellarin K triacetate by dehydrogenation reaction [24].

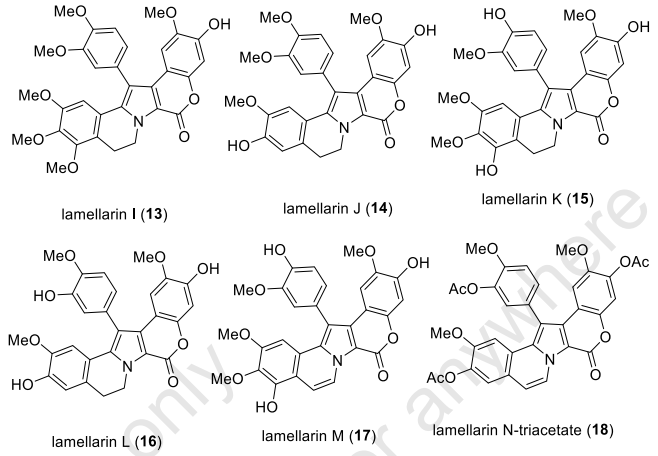


Fig. (5). Structures of lamellarins I-M and lamellarin N triacetate.

Urban and Capon reported the isolation of a new alkaloid lamellarin S (**19)** along with the known compound lamellarin K from an Australian tunicate, Didemnum sp collected in Durras, New South Wales (Fig. **6**). Among natural lamellarin alkaloids, lamellarin S is the only example that demonstrates atropisomerism [25].

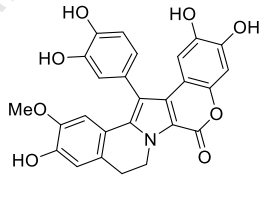


Fig. (6). Structure of lamellarin S.

In 1997, Faulkner *et al*. described the isolation of 9 novel lamellarin alkaloids, including lamellarins T-X, four 20-sulfate derivatives of lamellarins T, U, V, and Y along with lamellarin N (**20-29**) from an unidentified ascidian obtained from the Trivandrum coast of Indian (Fig. **7**). Lamellarin N was previously isolated as the triacetate form. This was the first time lamellarin sulfates were isolated. Structures of all compounds were elucidated by using the spectroscopic method [26].

In 1999, Faulkner *et al.* isolated a new lamellarin alkaloid, lamellarin α 20-sulfate (**30**) along with the known compound lamellarin E 20-sulfate (**31**) from an unidentified ascidian obtained from the Arabian Sea near Trivandrum, India, and the structure of this compound was elucidated based on the spectroscopic method [27]. In the same year, Quinn *et a*l. introduced the isolation of five novel lamellarin-type alkaloids from a Great Barrier Reef ascidian, Didemnum chartaceum, including the 20-sulfated derivatives of lamellarins B, C, and L, the 8-sulfated derivative of lamellarin G, and lamellarin Z (**32**-**36**) along with eight known compounds lamellarins A, B, C, E, G, L, lamellarin D-triacetate (**37**), and N-triacetate (Fig. **8**). The structures of the new lamellarin alkaloids were identified by interpretation of spectroscopic data. Interestingly, lamellarin G 8-sulfate (**36**) is the first example of this class of compounds sulfated at the C-8 position, while lamellarin Z is the first example of a dimethoxylated lamellarin alkaloid [28].

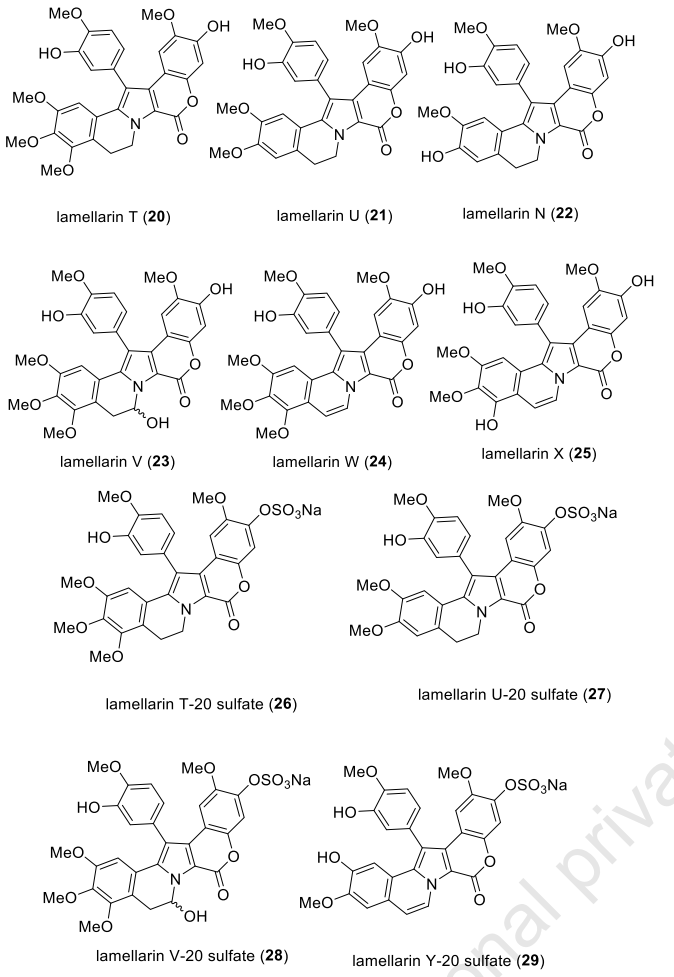


Fig. (7). Lamellarin alkaloids from an unidentified ascidian in India.

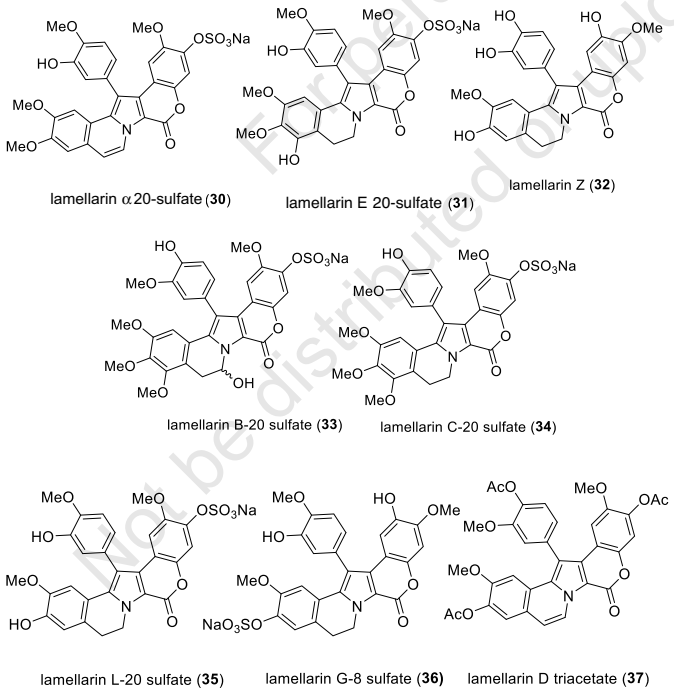


Fig. (8). Lamellarin α 20-sulfate and lamellarin alkaloids from *Didemnum chartaceum*.

In 2002, Ham and Kang described the isolation and structure determination of lamellarin β (**38**) from a purple unidentified Didemnum sp. collected the Indian Ocean (Fig. 9) [29]. In 2004, three new lamellarin alkaloids, lamellarins γ, α, and ε (**39**-**41**), along with eight known lamellarin alkaloids, lamellarins M, K, K-diacetate (**42**), K-triacetate (**43**), U, I, C-diacetate (**44**), and X-triacetate (**45**), were isolated from the red colonial tunicate Didemnum obscurum collected off Tiruchandur, Tamilnadu, India (Fig. **9**). The structures of eleven compounds were established using standard spectroscopic techniques. The structure of lamellarin K-triacetate was further confirmed by X-ray crystallographic analysis [30].

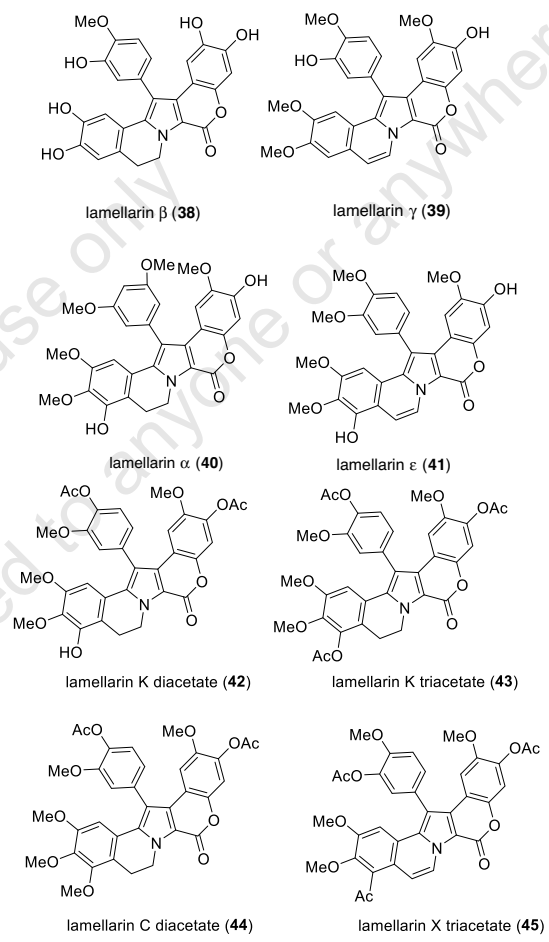


Fig. (9). Lamellarin β and lamellarin alkaloids from *Didemnum obscurum*.

In 2005, Venkateswarlu *et al*. reported the isolation of four new lamellarin alkaloids, lamellarin ξ, lamellarin η, lamellarin Φ, and lamellarin χ, along with seven known lamellarins, lamellarin K, lamellarin I, lamellarin J, lamellarin K triacetate, lamellarin L triacetate, lamellarin F and lamellarin T diacetate (**46**-**51**) obtained from Tiruchandur coast, Tamilnadu, India (Fig. **10**). The structures of all isolated compounds were established by a detailed analysis of NMR spectral data [31].

From Didemnum sp. (CMB-01656) collected off Wasp Island, New South Wales, the Capon group isolated five new lamellarins A1, A2, A3, A4, and A5 (**52**-**56**) and eight known lamellarins, E, K, M, S, T, X, and χ (**32**). Analysis of a second Didemnum sp. (CMB-02127) collected along the Northern Rottnest Shelf, Western Australia, resulted in new lamellarin A6 (**57**) and two known lamellarins G and Z (Fig. **10**). The structures of the novel compounds were assigned to on the basis of detailed spectroscopic analysis,

while known compound structures were confirmed by comparing them to literature data and authentic samples [32]. Later, the Capon group continue to isolate two new lamellarins, lamellarins O1 (**58**) and O2 (**59**), along with the known lamellarin Q from the southern Australian marine sponge, Ianthella sp (Fig. **11**) [33].

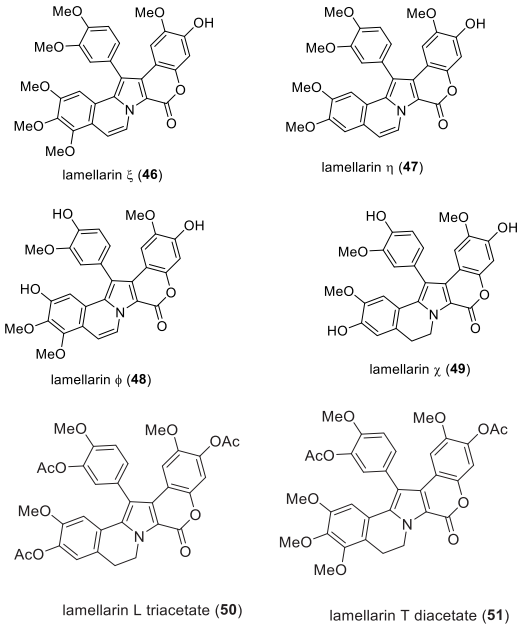


Fig. (10). Lamellarin alkaloids from *Didemnum obscurum* isolated in India.

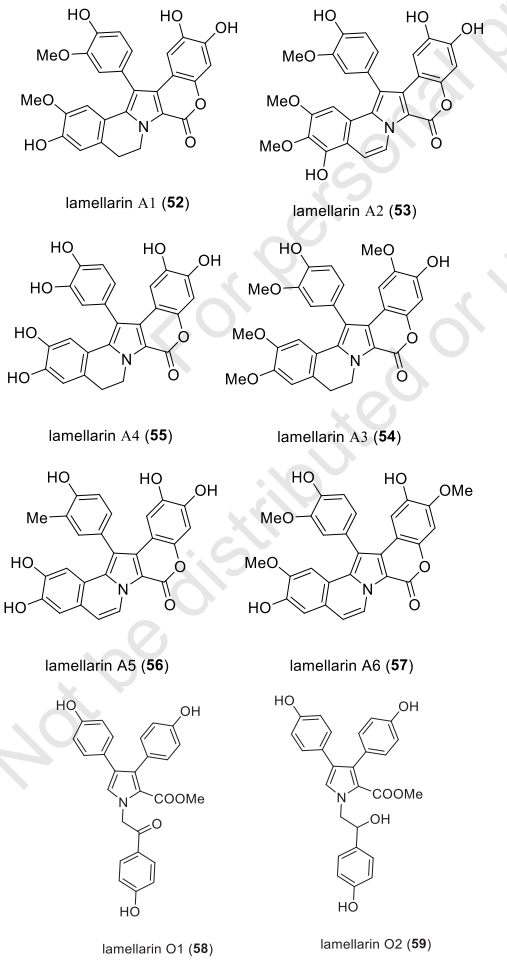


Fig. (11). New lamellarin alkaloids isolated by Capon group.

From the methanolic extract of the Pacific tunicate *Didemnum ternerratum*, collected from the Kingdom of Tonga, Bracegirdle, the Capon group isolated six lamellarin sulfates, namely E, K, A3, B1, B2-20 sulfates and D8-sulfate (**60**-**65**) (Fig. **12**). The structure of all new compounds was elucidated by using the spectroscopic method [34].

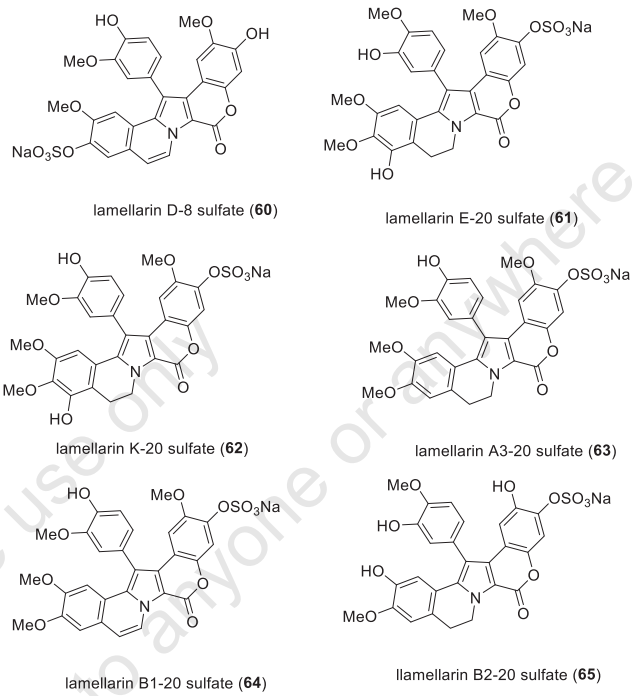


Fig. (12). Lamellarin alkaloids from *Didemnum ternerratum.*

3. BIOACTVITIES OF LAMELLARIN ALKALOIDS

3.1 Cytotoxicity and Antitumor Activity

Quesadal *et al*. investigated the effect of several lamellarin alkaloids on the growth of several tumour cell lines. All lamellarins displayed some level of cytotoxicity on the tumour cells. Among them, lamellarins D-triacetate, K, K-triacetate, M, and N-triacetate exhibited the highest cytotoxic activity on all the cell lines tested, although the model of action of the cytotoxicity is still unknown [1]. Cantrell *et al*. reported the isolation of known compounds lamellarins C and U and the evaluation of their 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). The bioassays showed that they demonstrated potent cytotoxicity with IC50's ranging from 0.4 to 19.4 nM [35]. Faulkner *et al*. accomplished the synthesis of lamellarin α and lamellarin H and evaluated these compounds for cytotoxic toward HeLa cells using MTT as an indicator of cell survival. Both compounds exhibited good potency and selectivity [36]. In an article reported by Han and Kang, lamellarin β showed cytotoxicity against human promyelocytic leukemia HL-60 with an IC50 of 4.8 μg/mL [29]. In a study reported by Facompre *et al*., lamellarin D displayed potent cytotoxic activities against multidrug-resistant tumor cell lines and is highly cytotoxic to prostate cancer cells, bears a 6*H*-[1]benzopyrano[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-one pentacyclic planar chromophore [37]. The cytotoxicity of lamellarin D involves topoisomerase I. In a study reported by Venkateswarlu *et al*. lamellarin ξ, lamellarin χ, lamellarin L triacetate, lamellarin F showed excellent activity against test cancer cell lines [31]. Ruchirawat *et al*. described the examination of 22 natural and 3 unnatural lamellarins against 11 cancer cell lines of 6 different cancer types and 1 normal cell line.

Five natural compounds, lamellarins D, N, M, X, and ε were the most cytotoxic, with IC50 values in the nanomolar to the low-micromolar range. The resistance mechanisms in this cell line have been shown to involve decreased susceptibility to drug-induced DNA damage and reduced levels of topoisomerase II, as well as overexpression of multi-drug-resistance-associated protein [38].

3.2. Anti-HIV-1 Activity

Faulkner group reported that lamellarin α-20 sulfate is a selective inhibitor of HIV-1 integrase both *in vitro* and *in vivo*. This lamellarin alkaloid inhibited the integrase terminal cleavage activity with an IC50 of 16 μM, strand transfer activity with an IC50 of 22 μM, and growth of the HIV-1 virus in cell culture with an IC50 of 8 μM [27]. The group also found that lamellarin H is a more potent inhibitor of HIV-1 integrase (IC50=1.3 μM) but lacked the specificity required to be medicinally useful [36].

3.3. Multidrug Resistance Reversal (MDR) Activity

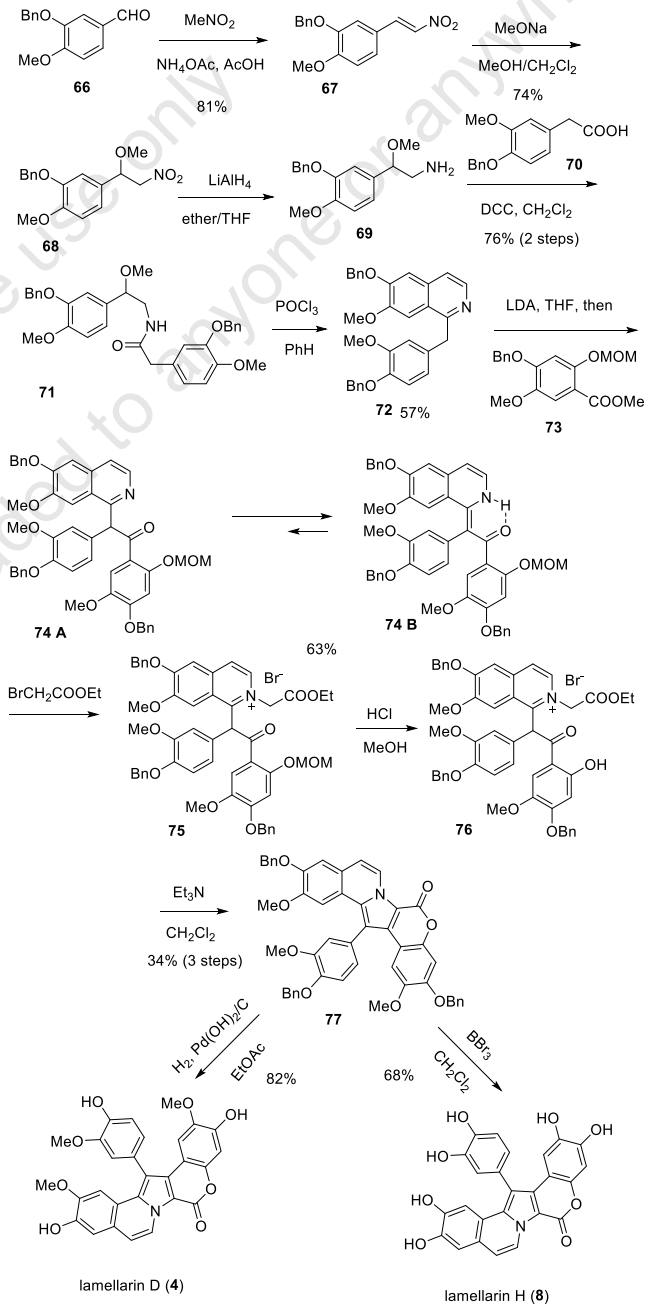
Quesadal *et al*. reported that at nontoxic doses, lamellarin I effectively increased the cytotoxicity of doxorubicin, vinblastine, and daunorubicin in MDR cells, and the effect was observed to be 9- to 16-folds higher than that of verapamil [1]. Capon group evaluated several lamellarins isolated from the Didemnum sp. for P-gp inhibitory activity. The results showed that lamellarins E and K were strong, lamellarin M was moderate, and lamellarin A3, χ, and A6 were weak P-gp inhibitors [32]. This group examined the P-gp, BCRP, and MRP1 inhibitory properties of a series of non-fused lamellarins including lamellarins O, O1, O2, and Q. Among these tested compounds, lamellarin O was found to be a selective and potent inhibitor of BCRP (IC50=4.70.6μM), although its P-gp and MRP1 inhibitory activities were in the moderate range. Further studies revealed that lamellarin O did not reduce the expression of BCRP in NCI-460/MX20 cells, suggesting that it was acting as a small molecule inhibitor of BCRP function [33, 39].

3.4. Other Activities

Meijer *et al*. examined the bioactivity of 22 lamellarins on six cancer- and Alzheimer's disease-relevant protein kinases, including cyclindependent kinase, glycogen synthase kinase-3, protooncogene serine/threonine-protein kinase, dual-specificity tyrosine-phosphorylation-regulated kinase 1A, and casein kinase 1. The bioassay results showed that some lamellarins inhibited the catalytic activity of these kinases, except CK1, at nanomolar concentrations [40]. The authours also evaluated the GSK-3β inhibitory activity of lamellarins D and N. Lamellarin N (IC50=0.036μM with 10μM ATP) was much more active than lamellarin D (IC50=0.32μM with 10μM ATP) [40]. Lamellarins O and O2 exhibited modest β-secretase (BACE) inhibitory activity (IC50>10μM), while lamellarin O1 was more potent (IC50<10μM) [41]. Lamellarins γ, K, U, I, and C-diacetate were isolated and evaluated for their antioxidant activity by Venkateswarlu *et al*. The results showed that all compounds exhibited antioxidant properties only at millimolar range compared with standard antioxidants, which were active in the micromolar range [30].

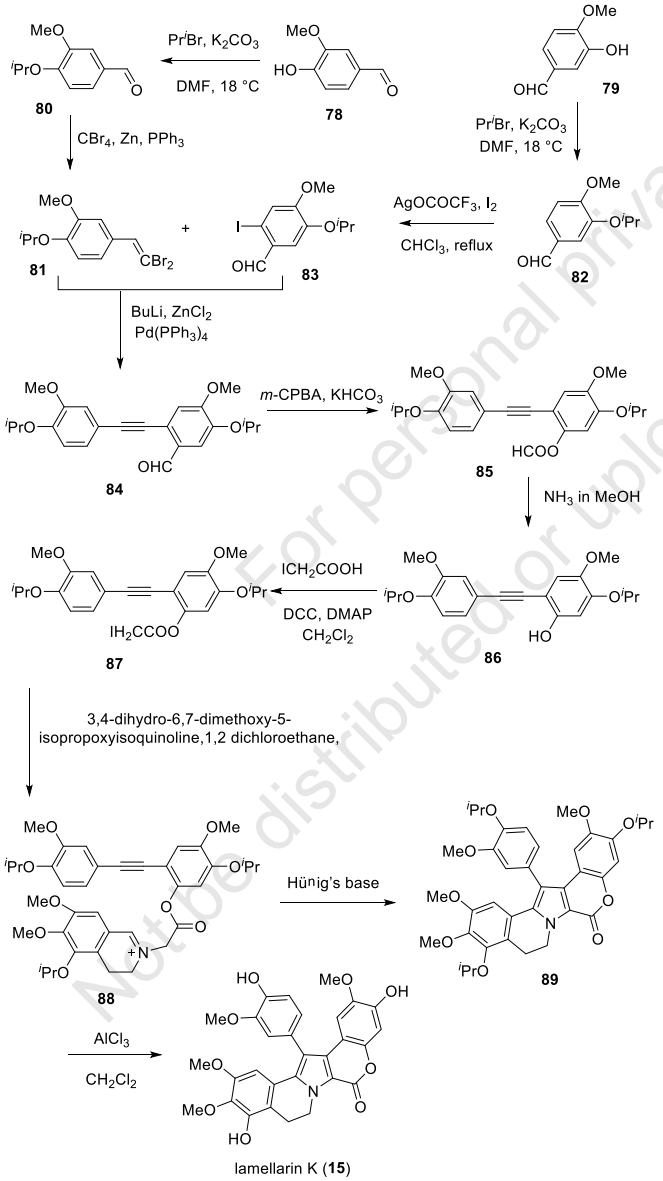
4. TOTAL SYNTHESIS OF LAMELLARIN ALKALOIDS

The first total synthesis of lamellarin-type alkaloids was reported by Ishibashi *et al*. and it involved the synthesis of lamellarins D (**4**) and H (**8**). The synthesis of lamellarins D and H was started from benzaldehyde **66**. Aldol condensation of this aldehyde with $MeNO_2$ formed nitrostyrene **67** in 81% yield. Michael addition of methoxide anion to this compound gave the compound **68**. The primary amine **69** was provided from nitro **68** by a reduction process using $LiAlH_4$. Coupling reaction of this amine with carboxylic acid **70** promoted by DCC produced amide **71**. Treatment of this amine with $POCl_3$ led to the formation of isoquinoline **72**. Metalation of **72** followed by condensation with benzoate **73** furnished a mixture of **74A** and **74B**. Quaterization of this mixture with ethyl bromoacetate provided ammonium salt **75**, which then underwent acid-catalyzed removal of the MOM protecting group yielding compound **76**. The fused pyrrole **77** was furnished from **76** by a lactonization process promoted by triethyl amine. The synthesis of lamellarin H was accomplished by treatment of this compound with PBr_3, while its hydrogenolysis of the benzyl groups over Pearlman catalyst [42] afforded the lamellarin D (Scheme **1**) [43]. This synthesis has laid the foundation for the synthesis of lamellarin alkaloids.



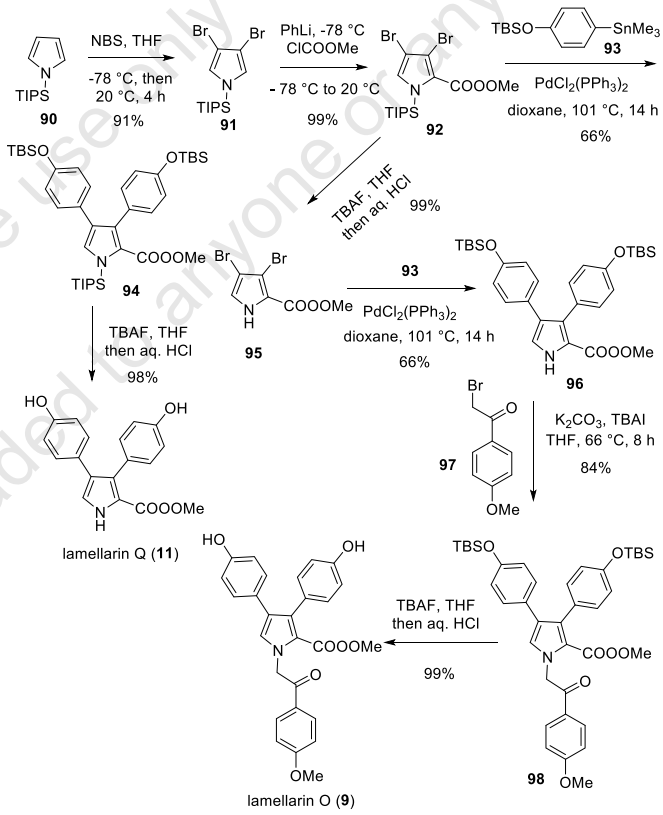
Scheme 1. Total synthesis of lamellarins D and H.

The synthesis of lamellarin K reported by Banwell *et al*. used vanillin **78** and isovanillin **79** as starting materials. Isopropyl protection of **78** followed by a Corey–Fuchs *gem*-dibromomethylenation reaction [44] gave styrene **81**, while a sequence of isopropyl protection and iodination of **79** with $AgOCOCF_3$–I_2 led to the formation of aryl iodide **83**. Styrene **81** was treated with BuLi and then $ZnCl_2$ to generate an alkynylzinc chloride intermediate, which underwent a palladium-mediated cross-coupling with aryl iodide **83**, providing compound **84**. Benzaldehyde **84** was treated with m-CPBA under Baeyer-Villiger conditions [45] to generate formate ester **85**, which was converted to phenol **86** by treatment with NH_3 in MeOH. Esterification of **86** with iodo acetic acid promoted by DCC formed compound **87**, which was reacted with 3,4-dihydro-6,7-dimethoxy-5-isopropoxy-isoquinoline to give salt **88**. Treatment of this salt with Hünig's base at elevated temperature in 1,2-dichloroethane provided the fused pyrrole **89**, which was then transformed into lamellarin K (**15**) by an $AlCl_3$-catalyzed isopropyl deprotection (Scheme **2**) [46]. The most significant feature of the synthesis is the cycloaddition and aromatization for the formation of **89**.



Scheme 2. Total synthesis of lamellarin K.

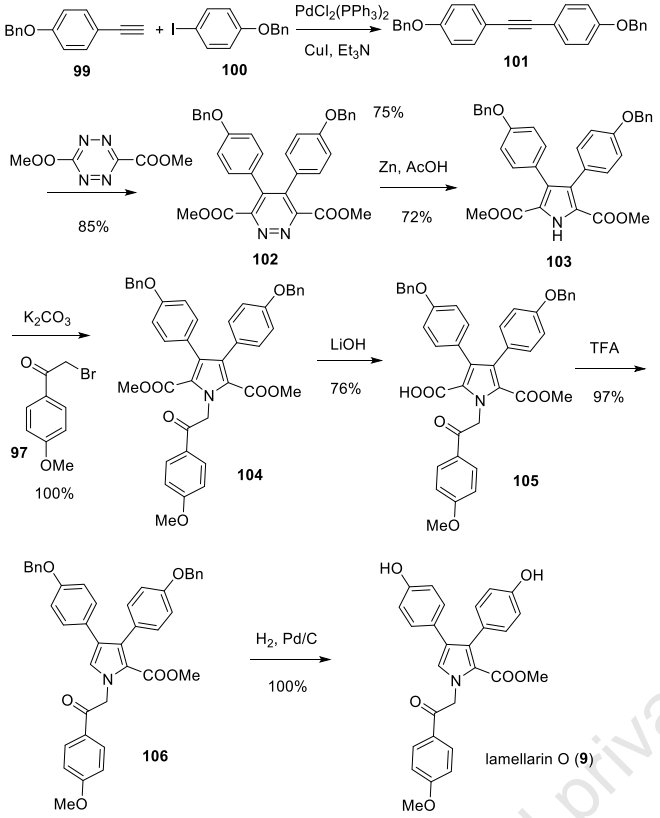
Banwell *et al*. reported the synthesis of lamellarins O and Q starting from pivotal dibromopyrrole **92**, which was prepared from triisopropylsilyl derivative **90** by a sequence of bromination using NBS and insertion of COOMe by treatment with PhLi followed by $ClCO_2Me$ following the reported procedure [46, 47]. Stille cross-coupling of pyrrole **92** with TBS-protected stannane **93** using $Pd(PPh_3)_2Cl_2$ as a catalyst gave compound **94**. Three-fold deprotection of *O*-silylether **94** using TBAF then afforded lamellarin Q (**11**). Desillylation of **92** provided the *NH*-pyrrole **95**, which then was coupled with arylstannane **93** yielded trisubstituted *NH*-pyrrole **96**. Alkylation of this compound with 2-bromo-4' methoxyacetophenone **97** in the presence of base then gave the *N*-substituted pyrrole **98**, which was converted to the natural lamellarins O (**9**) by TBAF-catalyzed deprotection (Scheme **3**) [48]. The syntheses were accomplished in several steps, and products were obtained at high yields.



Scheme 3. Total synthesis of lamellarins O and Q.

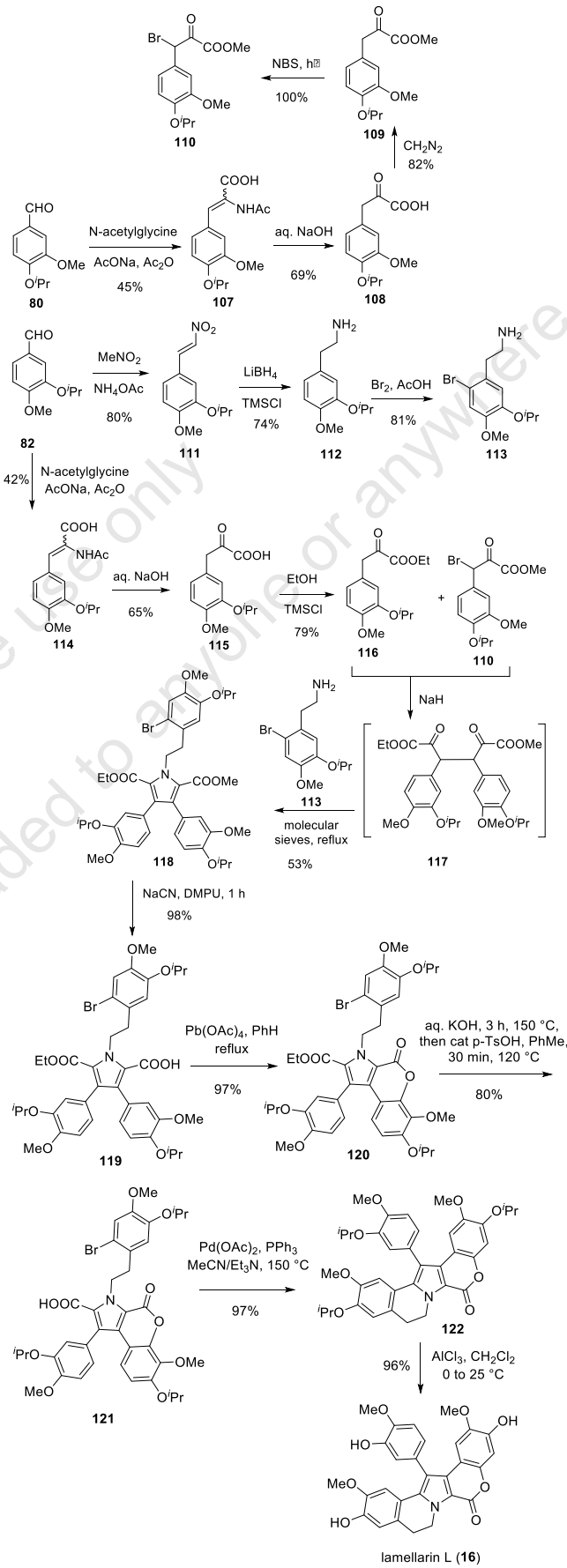
In 1999, Boger *et al*. accomplished the total synthesis of lamellarin O in seven synthetic steps. In the initial step, the Sonogashira coupling reaction between aryl acetylene **99** and aryl iodide **100** formed alkyne **101**. Reaction between this alkyne and 1,2,4,5-tetrazine derivative provided 1,2- diazine **102**, which then underwent a Zinc reductive ring contraction to generate *NH*-pyrrole **103**. Alkylation of this *NH*-pyrrole with 2-bromo-4′-methoxy-acetophenone **97** delivered the pentasubstituted pyrrole **104**. The symmetrical diester **104** was subjected to gratifyingly selective hydrolysis with LiOH to provide monoacid **105**. Decarboxylation of this acid by treatment with trifluoroacetic acid yielded compound **106**. Finally, catalytic hydrogenation of **106** furnished the desired lamellarin O (**9**). All steps of this synthesis were performed with high efficiency (Scheme **4**) [49]. The key steps in this synthesis include the Diels-Alder reaction of the electron-deficient 1,2,4,5-tetrazine

with the electron-rich acetylene following the known method in the literature [50] **101** and Zinc reductive ring contraction of **102**.



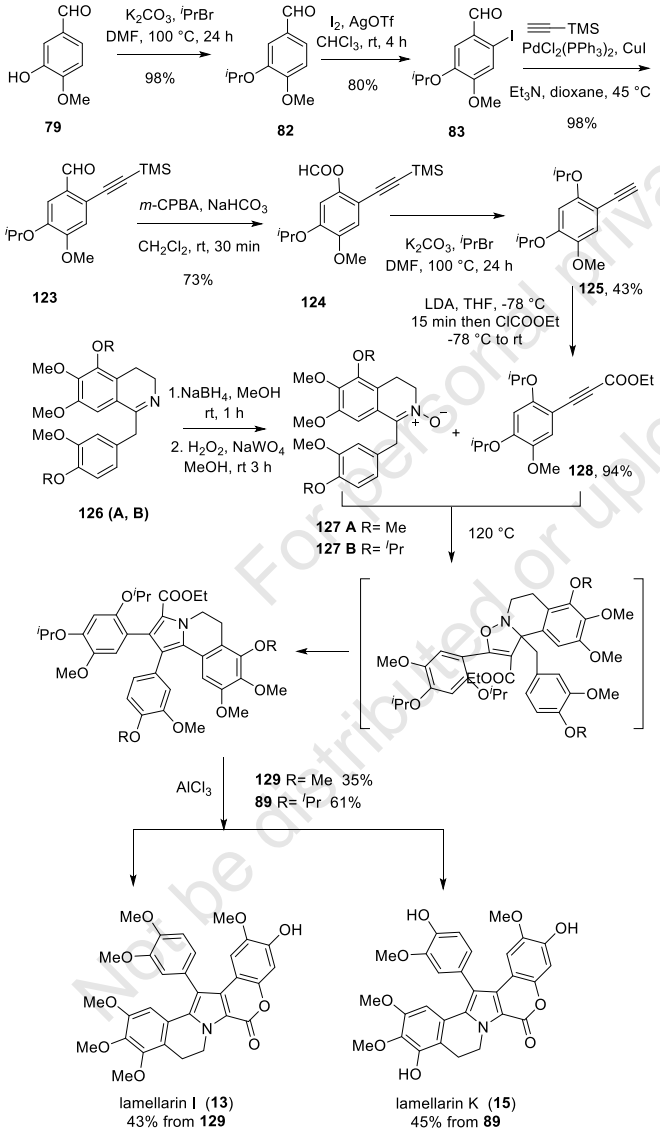
Scheme 4. Total synthesis of lamellarin O.

In 2000, Peschko *et al*. described the synthesis of lamellarin L, which employed arylpyruvates **110** and **116** and 2-arylethylamine **113** as key intermediates. The 2-arylethylamine **113** was obtained from isopropylisovanillin **82** by a sequence of Henry reaction [51] with nitromethane, reduction with $LiBH_4$/ trimethylsilyl chloride, and bromination. The arylpyruvate **110** was achieved from isopropylisovanillin **80** by a sequence of Erlenmeyer azlactone synthesis [52], esterification with diazomethane, and bromination with NBS. Similarly, arylpyruvate **116** was achieved from isopropylisovanillin **82** by a sequence of Erlenmeyer azlactone synthesis, esterification with diazomethane ethanol/TMSCl. Deprotonation of ethyl ester **116** with sodium hydride and coupling of the resulting enolate with bromide **110** generated 1,4-diketone **117**, which was directly converted to pyrrole **118** by reaction with the amine **113** at elevated temperature. Cleavage of the methyl group of **118** was accomplished by treatment with NaCN in 1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1H)-one (DMPU). The pyrrole-carboxylic acid **119** was formed with the ethyl ester group intact. Subsequent reaction of this carboxylic acid with lead (IV) acetate in refluxing benzene afforded lactone **120**. This compound was converted to acid **121** by treatment with 40 % aqueous KOH and then *p*-TsOH in toluene. The Pd(0)-catalyzed Heck cyclization of bromide **121** was performed in $MeCN/Et_3N$ with concomitant decarboxylation resulting in lamellarin L triisopropyl ether **122**. This cyclization with decarboxylation is the most important step of the synthesis. Finally, the removal of the isopropyl protecting groups in **122** by $AlCl_3$ furnished the natural lamellarins L (Scheme **5**) [53].



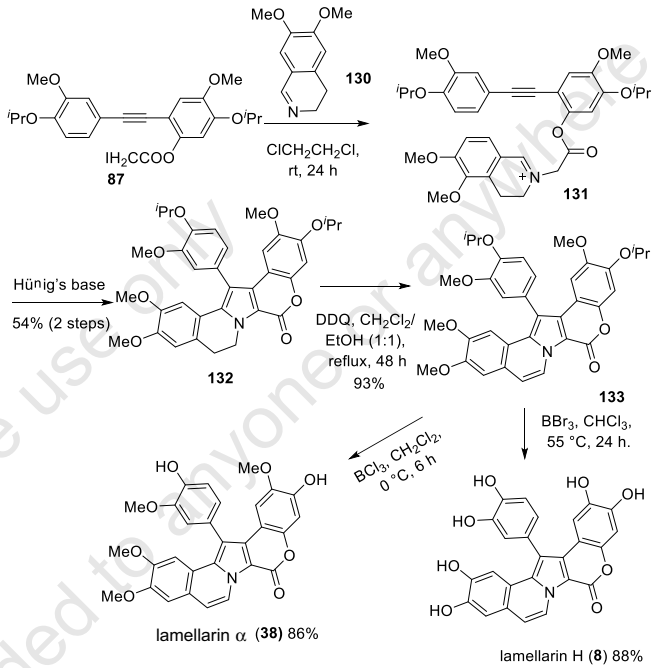
Scheme 5. Total synthesis of lamellarin L.

Diáz *et al*. introduced an efficient strategy for the synthesis of lamellarins I, K starting from isovaniline **79** and dihydroisoquinolines **126**. Isopropyl protection of **79** by treatment with K_2CO_3 and iPrBr, followed by iodination with I_2, AgOTf afforded iodide **83**, which then underwent Sonogashira coupling reaction with trimethylsilylacetylene providing aryl alkyne **123**. Baeyer- Villiger oxidation of aldehyde **123** using *m*-CPBA yielded formate ester **124**, which then was converted to compound **125** by treatment with K_2CO_3 and *i*-PrBr. Deprotonation of the terminal alkyne **125** with LDA and carboxylation with ethyl chloroformate furnished ethyl propiolate **128**. The key cycloaddition step was carried out by heating a mixture of *N*-Oxides **127** (**A** or **B**) and ethyl propiolate **128** under argon for 18 h at elevated temperature to produce the fused pyrroles **129** or **89**. The *N*-Oxides **127** was prepared from dihydroisoquinolines **126** by a sequence of reduction of the imine double bond with sodium borohydride and a non-optimized oxidation with sodium tungstate [54]. Finally, lamellarins I and K were achieved from **129 A** and **89**, respectively, by removal of the isopropyl protecting groups with concomitant acid-catalyzed lactonization (Scheme **6**) [55].



Scheme 6. Total synthesis of lamellarins I and K.

Ridley *et al.* employed the procedure reported by Banwell *et al*. [47] for the synthesis of lamellarins α and H with minor modifications. In this synthesis, the coupling reaction between iodoacetate **86** and 3,4-dihydro-6,7-dimethoxyisoquinoline **130** formed an intermediate salt **131**, which on treatment with Hünig's base underwent a [3+2] cycloaddition to obtain the pyrrole **132**. Heating of **132** with DDQ in DCM provided compound **133**. Removal of the isopropyl groups of **133** by BCl_3 gave lamellarin α (**38**), while treatment with BBr_3 cleaved all ether groups furnishing lamellarin H (Scheme **7**) [36].

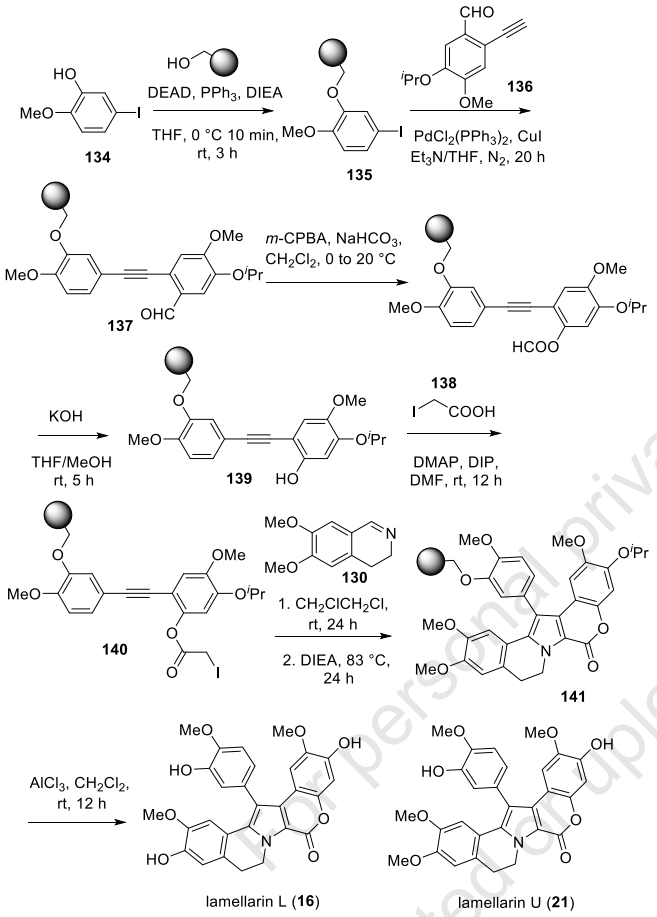


Scheme 7. Total synthesis of lamellarins α and H.

In 2003, Cironi *et al*. demonstrated the solid-phase synthesis of lamellarins U and L. The synthesis was accomplished in 7 steps starting from 5-iodo- 2-methoxyphenol **134**. Treatment of this phenol with hydroxymethyl (Merrifield) resin under Mitsunobu reaction conditions [56] gave compound **135**, which then underwent Sonogashira cross-coupling reaction with aryl acetylene **136** to provide bisarylacetylene-containing resin **137.** Baeyer-Villiger oxidation of aldehyde **137** generated formate **138**, which was converted to the phenol resin **139** by base-catalyzed hydrolysis. Esterification of this phenol with iodoacetic acid under DMAP catalysis in polar solvent afforded the iodoacetate derivative **140**. *N*-alkylation of **140** with 3,4-dihydro-6,7-dimethoxyisoquinoline **130** followed by a [3+2] cycloaddition reaction produced the fused pyrrole **141**. Treatment of **141** with $AlCl_3$ in dry CH_2Cl_2 furnished the mixture of natural lamellarins L and U (Scheme **8**) [57]. The key steps of this process are the solid-phase conversion of an aldehyde group into a formate **138** by a Baeyer-Villiger reaction and the dipolar [3+2] cycloaddition for the the generation of **141** in which a pyrrole and a lactone ring are formed simultaneously.

In 2004, Ploypradith *et al*. accomplished the synthesis of lamellarins K and L, which used the ester nitro styrene **143**, substituted benzyldihydroisoquinolines **145** and **147** as the key building blocks. The nitro styrene **143** was prepared from aldehyde **142** with ethyl nitroacetate *via* the Knoevenagel condensation reaction. The aldehyde **142** was obtained from compound **79** in three steps following the reported procedure [58]. The benzyldihydroisoquinolines **145** and **147** were synthesized from aldehyde **147** and aldehyde **79** or

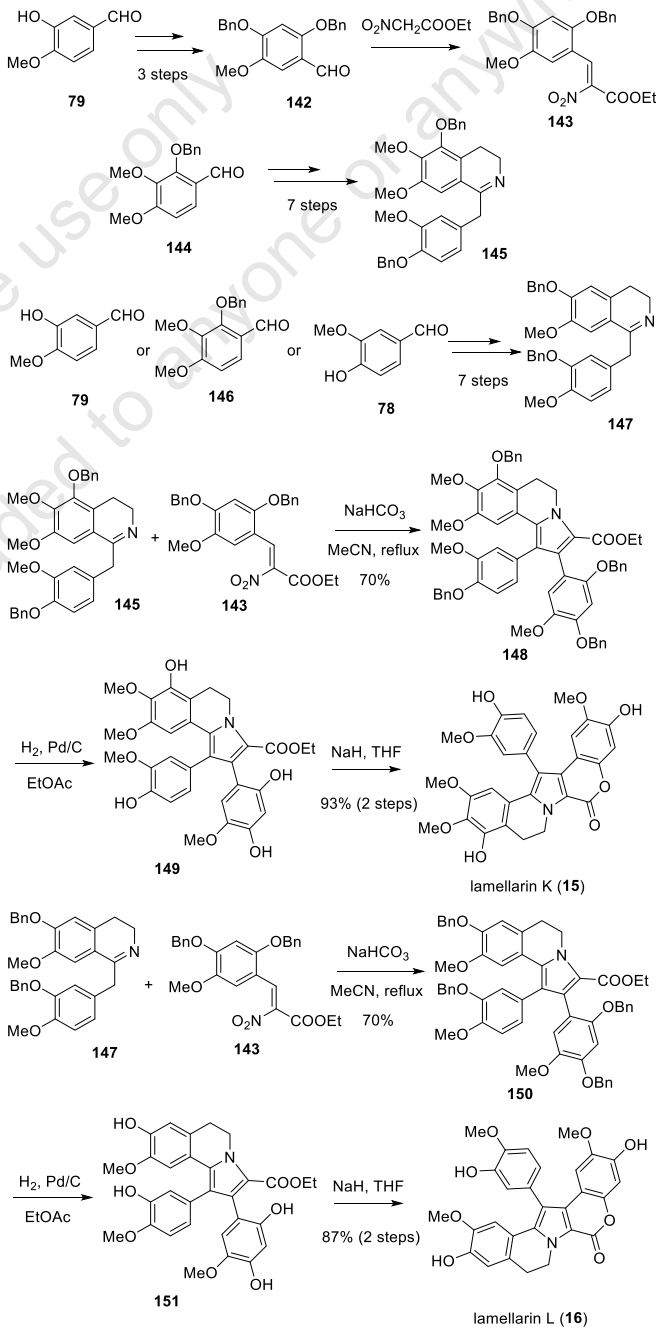
146 or **78** in seven synthetic steps, respectively. The Michael addition/ring-closure reaction of imine **145** with the ester nitrostyrene **143** in refluxing anhydrous acetonitrile in the presence of $NaHCO_3$ to give the desired pyrrole **148**, which was converted to lamellarin K by a sequence of hydrogenolysis debenzylation and a base-mediated lactonization with sodium hydride. A similar procedure was performed for the formation of lamellarin L from benzyldihydroisoquinoline **147** and the nitrostyrene **143** (Scheme **9**) [59]. The significance of the synthesis is the Michael addition/ring-closure reaction for the formation of **148** and **150** which proceeded in 70% yield for both lamellarins.



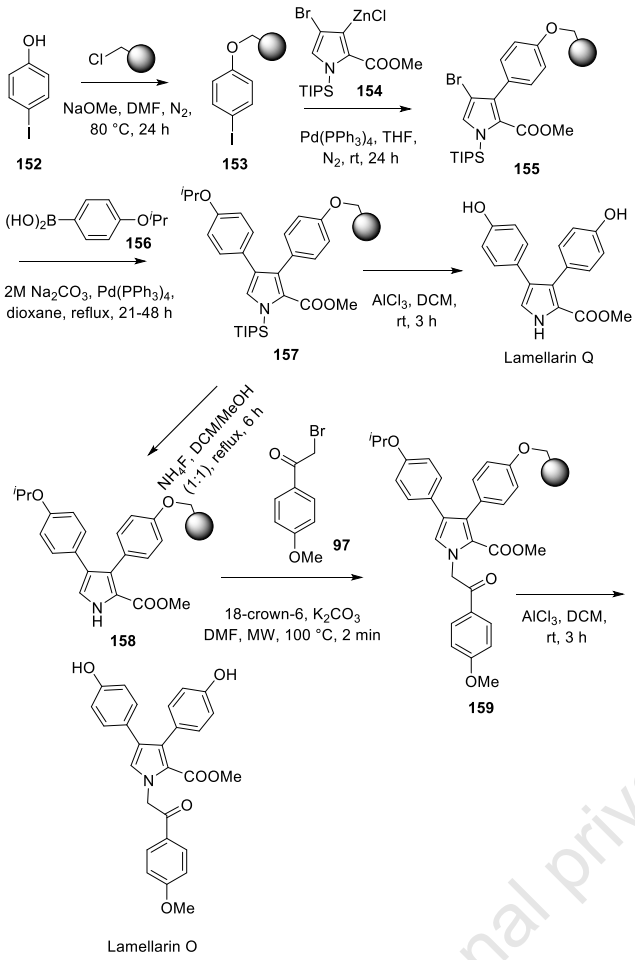
Scheme 8. Total synthesis of lamellarins L and U.

Marfil *et al*. completed an efficient solid-phase synthesis of lamellarins Q and O using Merrifield resin. The resin-bound iodophenol **153** was obtained from Merrifield resin and *p*-iodophenol. Negishi cross-coupling reaction of this iodide with zinc derivative **154** afforded compound **155**, which was converted to compound **157** *via* the Suzuki cross-coupling reaction with 4-isopropoxyphenylboronic acid **156**. Treatment of **157** with $AlCl_3$ in DCM furnished lamellarin Q. For the preparation of lamellarin O, **157** was desillylated to produce *NH*-pyrrole **158**, which was *N*-alkylated by *p*-methoxybromoacetylbenzene **97** giving compound **159**. Removal of the isopropyl group and the resin provided lamellarin O (Scheme **10**) [60].

Pla *et al*. accomplished the synthesis of lamellarin D starting from methyl pyrrole-2-carboxylate **160**. *N*-Alkylation of methyl pyrrole-2-carboxylate with tosylate **161** followed by Heck cyclization gave the fused tricyclic pyrrole **162**. Regioselective bromination of **162** followed by Pd(0)-catalyzed cross-coupling with boronic ester **164** provided compound **165**. Isopropyl protection of phenol **165** afforded compound **166**, which was then brominated at the pyrrole ring using NBS in THF to yield bromide **167**. The Suzuki-Miyaura cross-coupling reaction of bromide **167** with phenylboronic acid **168** to prepare compound **169** was accomplished using $Pd(PPh_3)_4$ as a catalyst, and K_3PO_4 as a base. The aromatization of dihydroisoquinoline **169** to provide **170** was achieved using DDQ in $CHCl_3$ in a sealed tube under microwave irradiation at 120 °C. Treatment of **170** with $AlCl_3$ led to the cleavage of the four isopropoxyether protecting groups giving pyrrole ester **171**. In the last step, lactonization of **171** using NaH as a base furnished lamellarin D (Scheme **11**) [61]. The strategy is based on two consecutive, regioselective bromination-Suzuki cross-coupling steps for introducing the appropriate aryl groups in positions 1 and 2 of scaffold **162**.



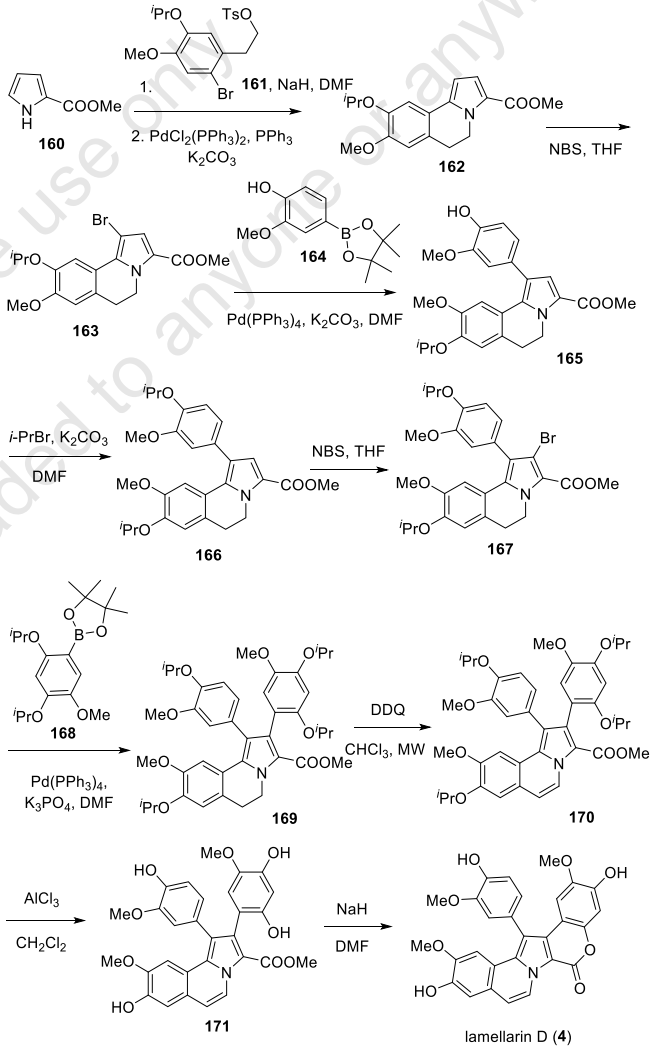
Scheme 9. Total synthesis of lamellarins K and L.



Scheme 10. Total synthesis of lamellarins O and Q.

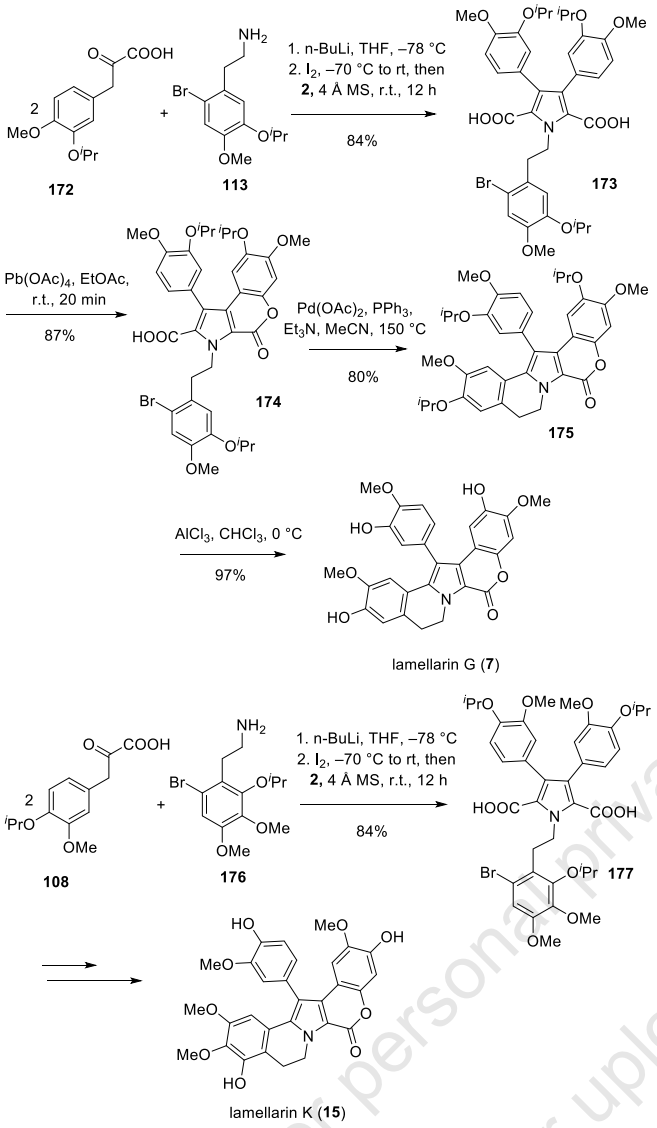
Steglich *et al*. reported the synthesis of lamellarins G and K using pyruvic acids **108**, **172** and amine **113** as key intermediates. The pyruvic acid **108** and amine **113** were synthesized following the procedures described in the literature [53]. Condensation between two substrates provided the pyrrole dicarboxylic acid **173**, which was converted to lactone **174** by treatment with lead(IV) acetate in EtOAc. This compound then was cyclized under Heck conditions to the pentacyclic **175**. Selective deprotection of three isopropyl protecting groups in **175** with $AlCl_3$ yielded lamellarin G. Similar procedure was performed for the synthesis of lamellarin K from pyruvic acid **108** and amine **176** (Scheme **12**) [62]. The formation of 3,4-diarylpyrrole-2,5-dicarboxylic acids **173** and **177** from arylpyruvic acids and 2-arylethylamines was considered as the key step for the synthesis of these alkaloids.

In 2006, the Iwao group described the total synthesis of lamellarins D, L, and N. The synthesis of lamellarins D and N employed amine **112** and phenyl boronic acid **179**, **180**, and **184** as important intermediates. Boronic acid **180** was obtained from 2-methoxyphenol **178** in four steps, while acid **179** was obtained from **178** in five steps. Acid **184** was prepared from aldehyde **82** *via* a sequence of Baeyer-Villiger oxidation, hydrolysis, MOM protection, bromination, lithiation, and insertion of boronic acid. Henry reaction of O-isopropylisovanilin **82** followed by lithium aluminum hydride reduction of the resulting nitrostyrene intermediate produced 2-arylethylamine **112**, which was reacted with 2 methyl bromoacetate in the presence of sodium hydrogen carbonate in refluxing acetonitrile to give iminodiacetate **185**. Hinsberg reaction of **185** with dimethyl oxalate in dry THF catalyzed by sodium hydride provided 3,4- dihydroxypyrrole **186**. Triflation of **186** with trifluoromethanesulfonic anhydride in pyridine produced the stable bistrifalte **187**, which then underwent Suzuki–Miyaura coupling reaction with boronic acid **180** affording compound **188**. The second cross-coupling of **188** with boronic acid **184**, followed by treatment with hydrochloric acid in methanol yielded lactone **189**. Ester **189** was converted to acid **190** by treatment with KOH followed by acid-catalyzed relactonization. Decarboxylation of this acid in hot quinoline catalyzed copper(I) oxide delivered compound **191** [63]. Intramolecular oxidative biaryl coupling of **191** under Kita's conditions using PIFA-BF_3.Et_2O gave the cyclized product **122** [64]. Three-fold removal of isopropyl group of **122** by BCl_3 then furnished lamellarin L. lamellarin D was achieved from **122** by a sequence of DDQ oxidation and BCl_3-catalyzed deisopropylation (Scheme **13**) [65].

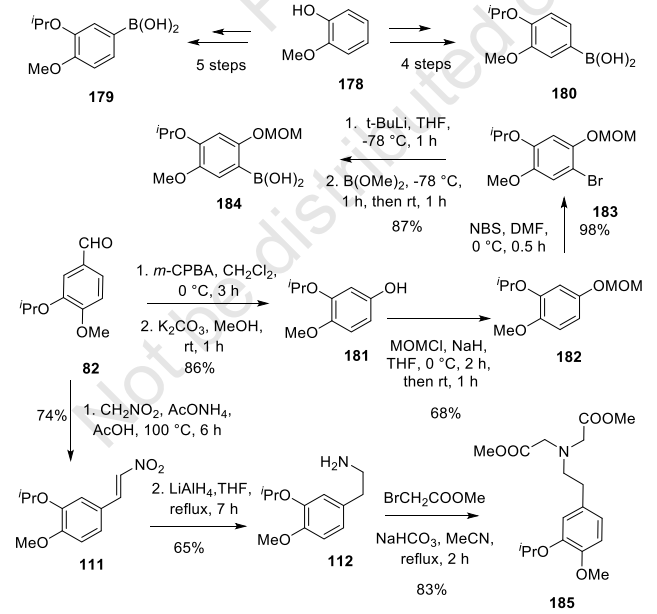


Scheme 11. Total synthesis of lamellarin D.

For the synthesis of lamellarin N, the bistrifalte **187** was reacted with boronic acid **179** *via* the Suzuki–Miyaura coupling reaction, generating compound **193**. Then the same procedure using for the synthesis of lamellarin L from compound **189** was applied to afford the natural lamellarin N from compound **193** (Scheme **13**) [65]. Hinsberg-type pyrrole synthesis of **186** and palladium-catalyzed Suzuki–Miyaura coupling of the 3,4-dihydroxypyrrole bistriflate **187** are the key steps of the synthesis.



Scheme 12. Total synthesis of lamellarins G and K.



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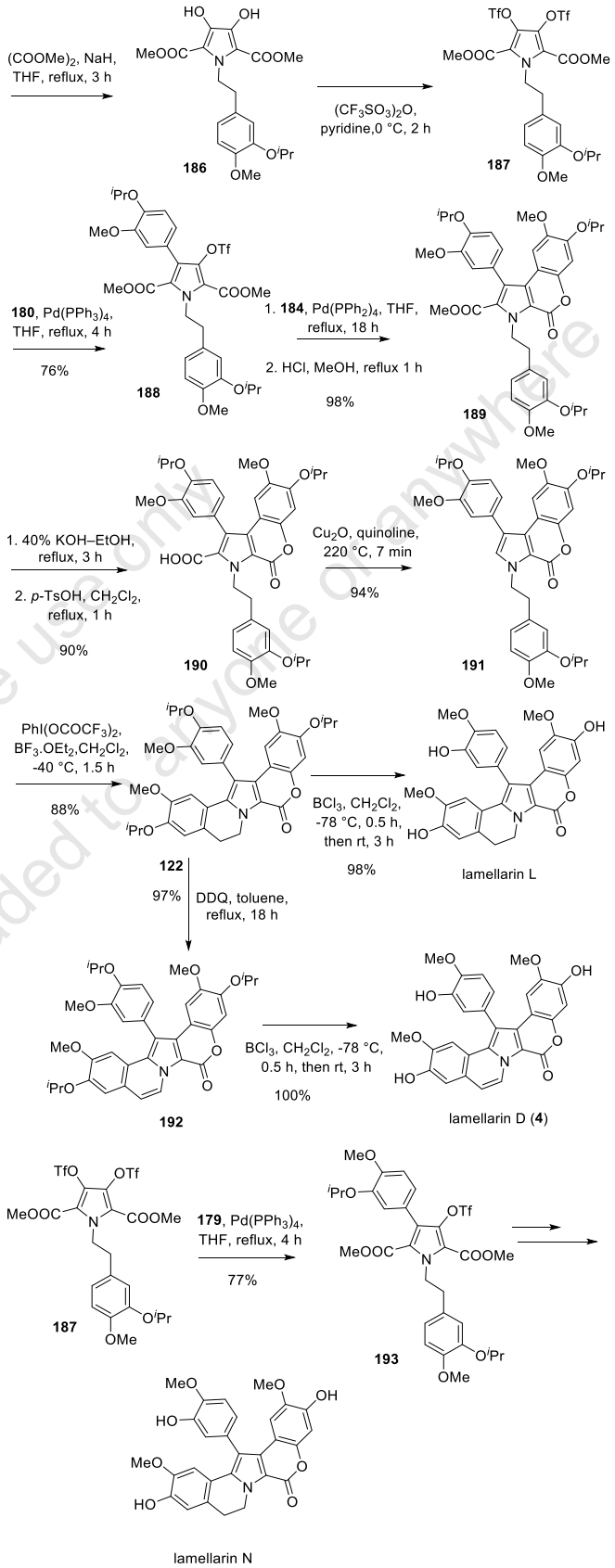
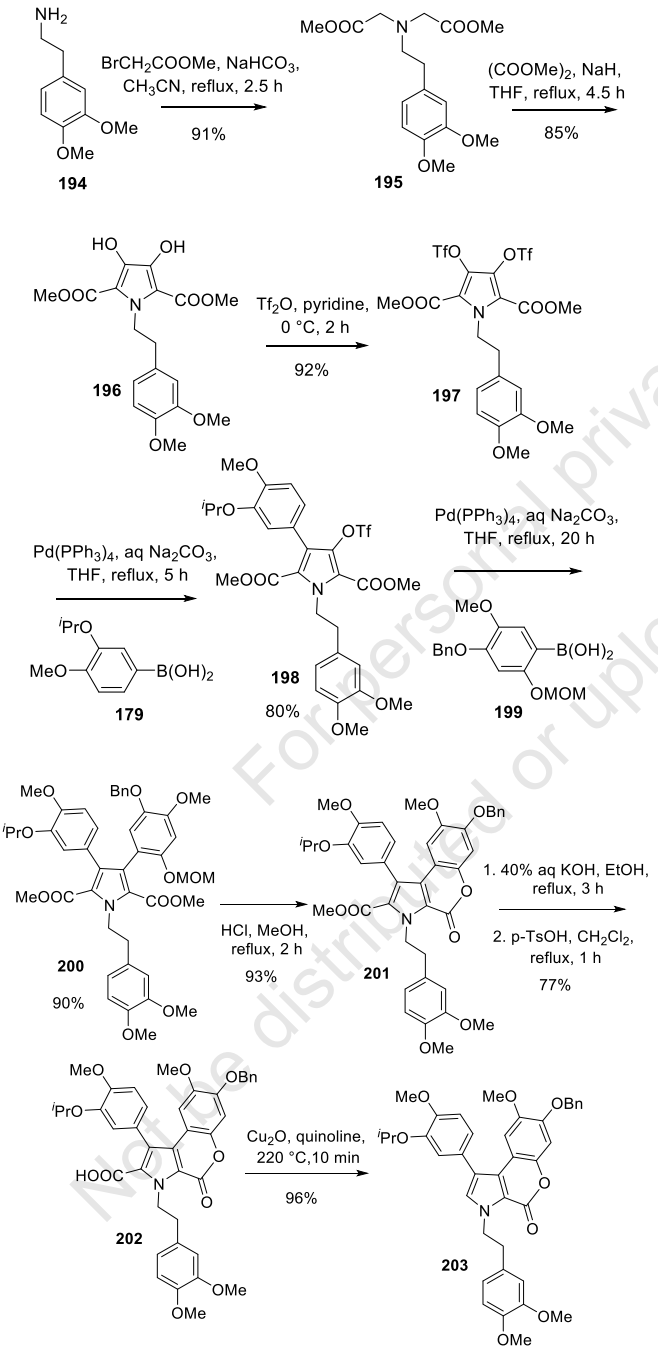


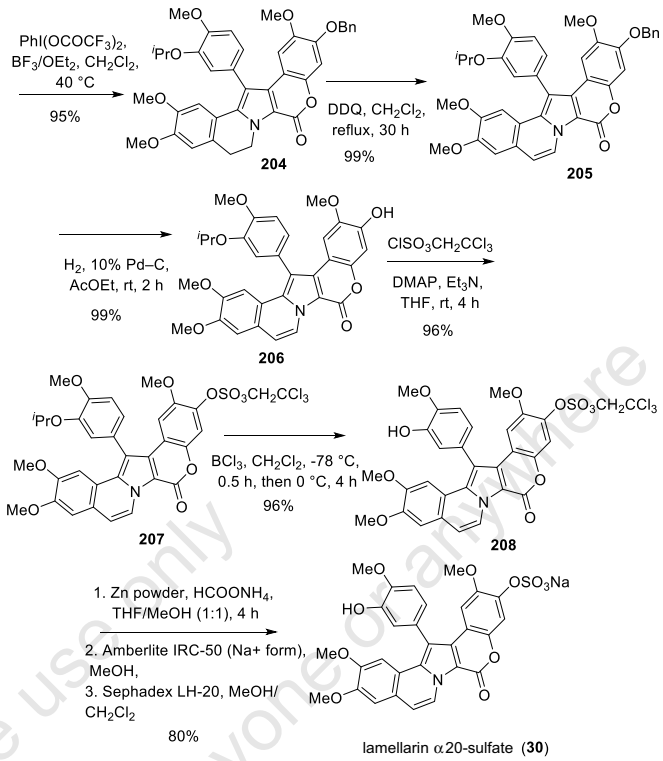
Scheme 13. Total synthesis of lamellarins D, L and N.

The Iwao group also applied above-mentioned procedure for the synthesis of lamellarin α-20 sulfate. Compound **205** was synthesized from amine **194**, boronic acid **179**, and boronic acid **210** fol-

lowing the procedure applied for lamellarin D. Then, debenzylation of **205** by hydrogenolysis over palladium on charcoal produced compound **206**, which was converted to sulfate **207** by reaction with trichloroethyl chlorosulfate in pyridine. Selective removal of the isopropyl protecting group of **207** using boron trichloride provided compound **208** with the trichloroethylsulfate moiety intact. Finally, a sequence of deprotection of the trichloroethyl ester with Zn/$HCOONH_4$-ion exchange over Amberlite IRC-50 (Na^+ form) furnished lamellarin α 20-sulfate (Scheme **14**) [66]. The synthesis of lamellarin α-20-sulfate was accomplished in 14 steps from the commercially available 2-(3,4-dimethoxyphenyl)ethylamine **194** in excellent overall yield (24%).



(Scheme 14) contd….

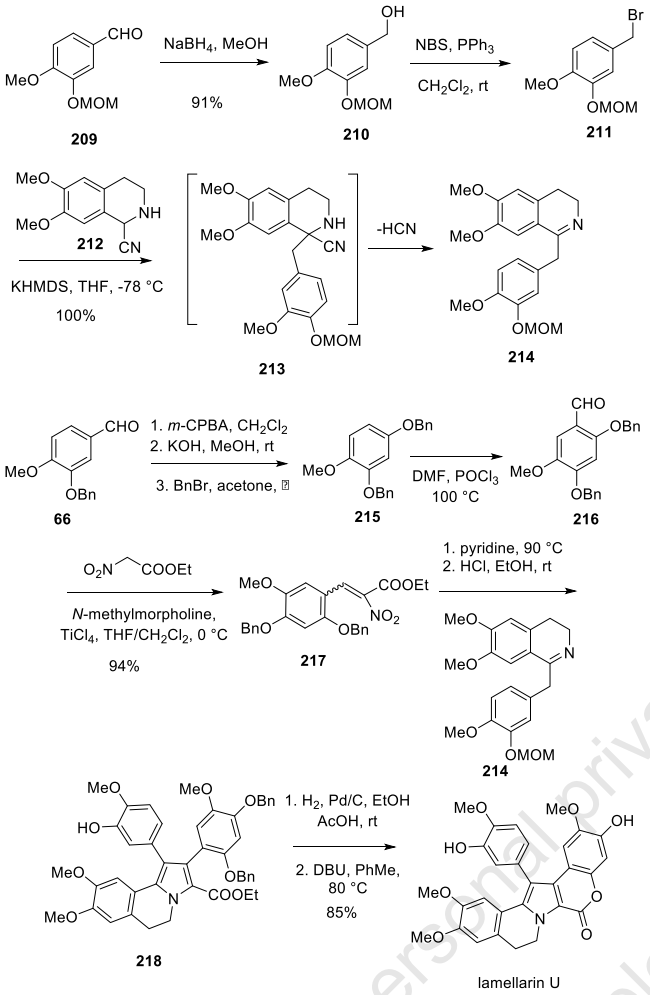


Scheme 14. Total synthesis of lamellarin α-20 sulfate.

In 2008, Liermann and Opatz achieved the synthesis of lamellarin U based on the key building blocks **214** and **217**. The dihydroisoquinoline **214** was prepared from benzaldehyde **209** in three steps. The aldehyde group in **209** was converted to the primary alcohol in **210** by $NaBH_4$ and then methylene bromide in **211** by NBS. Deprotonation of **212** with KHMDS in THF at -78 °C and subsequent reaction with bromide **211** yielded the dihydroisoquinolines **214** *via* the intermediate **213**. Aldehyde **66** was converted to benzyl ether **215** by a sequence of Baeyer-Villiger oxidation/ subsequent hydrolysis of the resulting formate/benzylation. Vilsmeier reaction of **215** with DMF, $POCl_3$ gave aldehyde **216**. Knoevenagel condensation of this aldehyde with ethyl nitroacetate using $TiCl_4$/*N*-methylmorpholine afforded nitrocinnamates **217** as a *E*/*Z*-mixture. The most attractive feature of the synthesis is the formation of fused pyrrole **218** by the Grob reaction [67] of dihydroisoquinoline **214** with nitroalkene **217**. Lamellarin U were obtained from **218** *via* a sequence of debenzylation by hydrogenolysis and lactonization by heating with DBU in toluene (Scheme **15**) [68].

Fukuda *et al*. developed an efficient strategy for the synthesis of lamellarins O, P, Q, and R, starting from pyrrole. *N*-benzensulfynylation of pyrrole followed by direct bromination under Zonta's conditions [69] afforded *N*-benzenesulfonyl-3,4-dibromopyrrole **220**. The cross-coupling reaction between this bromide with boronic acid **221** provided **222**, which underwent lithiation followed by treatment with ClCOOEt to produce ester **223**. Treatment of **223** with TBAF in refluxing THF for 2 h produced compound **224**. Deisopropylation of **224** with BCl_3 furnished lamellarin Q, while alkylation of **224** with bromide **97** followed by treatment with BCl_3 produced lamellarin O. The same route for the preparation of lamellarin P from **224** using phenacyl bromide **226**. The copper(II)-mediated *N*-arylation of **224** with boronic **228** acid produced **229** [70], which was then converted to lamellarin R by treatment with BCl_3 (Scheme **16**) [71]. In this approach, the 3,4-

diarylpyrrole **224** is a versatile precursor for the synthesis of lamellarins O, P, Q, and R.

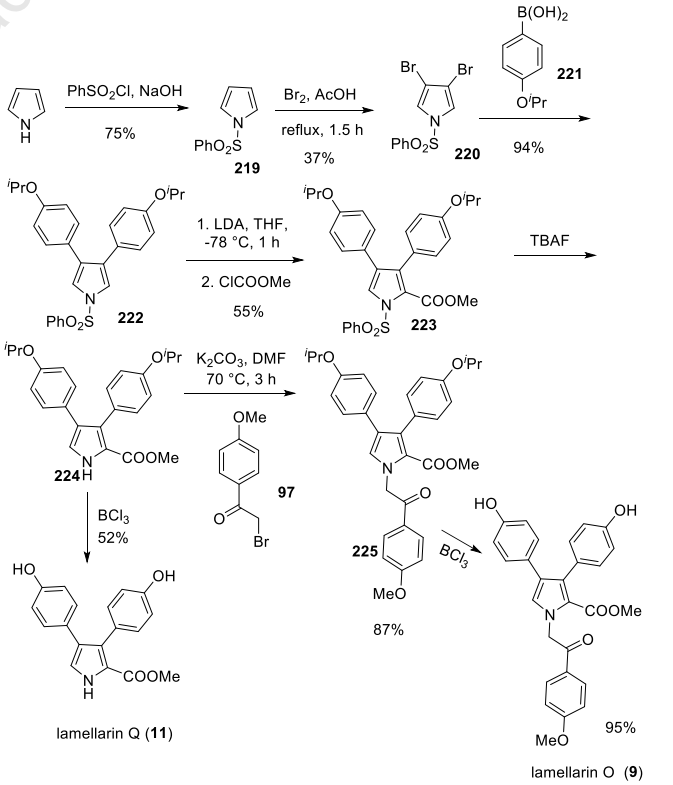


Scheme 15. Total synthesis of lamellarin U.

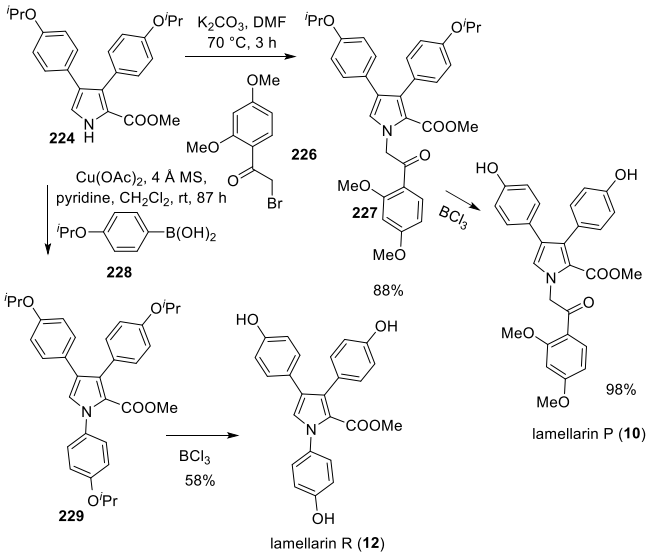
In 2010, Iwao group introduced the synthesis of lamellarin α-20 sulfate based on their previous report with modifications. From previously reported bistriflate **197** [66], compound **230** was provided by the Suzuki-Miyaura coupling reaction with boronic acid **199**. Removal of the MOM group from **230** by treatment with HCl in methanol furnished the lactone **231** with concomitant acid-catalyzed lactonization. The second cross-coupling of triflate **231** with boronic acid **232** formed compound **233**, which was converted to acid **234** by a sequence of alkaline hydrolysis and acid-catalyzed relactonization. Copper(I) oxide-catalyzed decarboxylation of **234** in hot quinoline generated compound **235**, which underwent an intramolecular oxidative biaryl coupling reaction yielding compound **236**. Heating of **236** with DDQ in refluxing dichloromethane delivered compound **237**. Debenzylation of **237** followed by treatment with 2,2,2-trichloroethylsulfonyl chloride produced compound **239**, which was converted to compound **208** by acid-catalyzed MOM-deprotection. Finally, treatment of **208** with Zn/$HCOONH_4$ followed by ion exchange over Amberlite IRC-50 (Na+ form) furnished lamellarin α-20 sulfate after Sephadex purification (Scheme **17**) [72].

In 2011, Li *et al*. accomplished the synthesis of lamellarins D, H, R. The synthesis of lamellarins D and H used aldehyde **241** and amine **112** as key intermediates. Aldehyde **241** was prepared from benzadehyde **78** by a sequence of isopropyl protection, Wittig olefination, and acid-catalyzed hydrolysis. Condensation of **241** with **112** provided compound **242**, which underwent Vilsmeier reaction with $POCl_3$, DMF under microwave irradiation to yield aldehyde **243**. This aldehyde then was oxidized to the corresponding acid **244**. Subsequent reaction of carboxylic acid **244** with $Pb(OAc)_4$ in refluxing EtOAc furnished lactone **191** following the described strategy [73], which was readily converted to compound **122** *via* intramolecular oxidative biaryl coupling reaction. DDQ oxidation of **122** generated **192**, which was converted to lamellarin D by selective deprotection of the isopropyl group on BCl_3. Cleavage of all ether groups in **192** with BBr_3 afforded lamellarin H. Condensation reaction between aldehyde **245** and amine **246** produced pyrrole **247**, which was transformed into aldehyde **248** by the Vilsmeier reaction. This aldehyde then was converted to acid **249** by oxidation and methyl ester **250** by treatment of the corresponding acid with $TMSCHN_2$. Three-fold removal of the isopropyl protecting group in **250** by BBr_3 furnished lamellarin R (Scheme **18**) [74]. The AgOAc-mediated oxidative coupling reaction between amines and phenyl acetaldehydes to construct pyrrole is the most attractive feature of the synthesis.

In 2011, Hasse *et al*. reported the synthesis of lamellarin S from 2,5-dibromopyrrole **251**. Compound **251**, which was prepared from *N*-Boc pyrrole, was reacted with *t*-BuLi followed by treatment with ClCOOMe to afford diester **252**. Iodination of **252** gave **253**, which was converted to **254** by treatment with Zn. The Suzuki–Miyaura cross-coupling of **254** with boronate ester **255** delivered **256**, which was alkylated with alcohol **257** to obtain **258**. Bromination at the pyrrole ring of **258** followed by Suzuki–Miyaura coupling with boronic acid **260** provided **261**. Treatment of **261** with KOH then PTSA resulted in carboxylic acid **262**. Intramolecular decarboxylative Heck reaction of **262** using Pd catalyst yielded compound **263**, which was converted to lamellarin S by treatment with BCl_3 (Scheme **19**) [75].



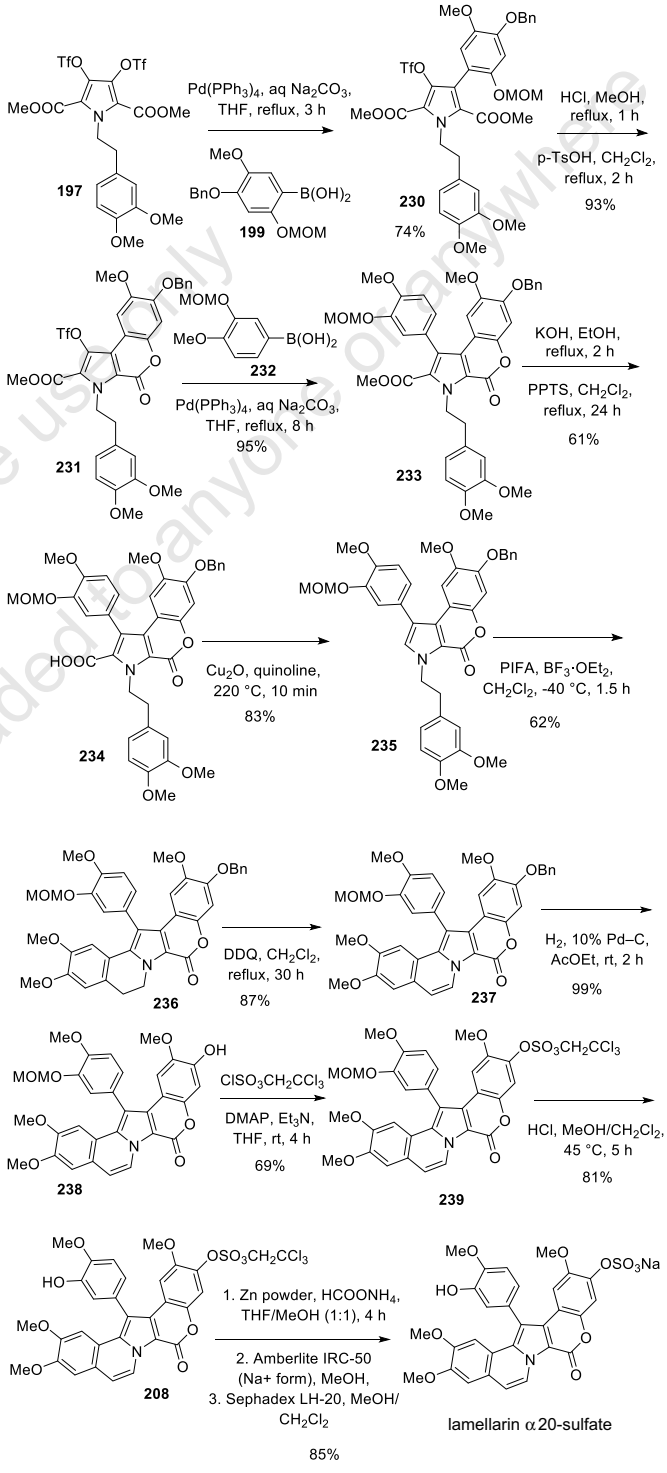
(Scheme 16) contd….



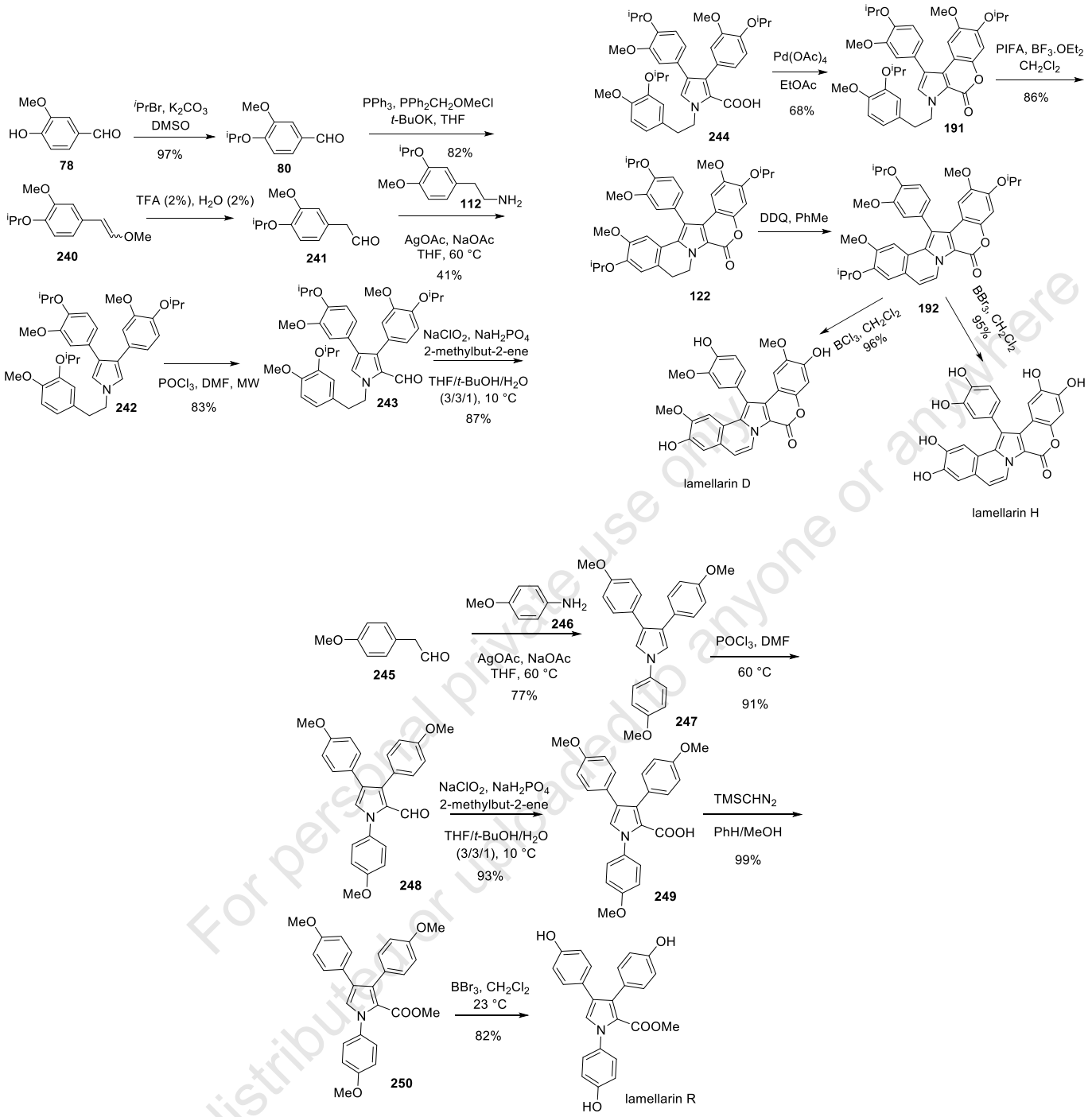
Scheme 16. Total synthesis of lamellarins O, P, Q, and R.

In 2012, Flynn and Banwell demonstrated the synthesis of lamellarins K, T, U, and W. The synthesis of lamellarins K followed the procedure described in the literature [46]. For the synthesis of lamellarin T, aldehyde **82** was converted to β, β-dibromostyrene **271** by the Corey–Fuchs reaction. Treatment of this bromide with BuLi, $ZnCl_2$ followed by cross-coupling with aryl iodide **83** afforded benzaldehyde **273**, which was converted to phenol **274** by treatment with *m*-CPBA in the presence of potassium bicarbonate. The phenol **274** was then esterified with iodoacetic acid in the presence of DMAP and DCC giving ester **275**. Reaction of this ester with 3,4- dihydroisoquinoline **276**, which was prepared following the known procedure [76], to affording salt **277** and then compound **278** after treatment with Hünig's base. Cleavage of isopropyl groups using $AlCl_3$ furnished lamellarin T. Treatment of ester **275** with 3,4- dihydroisoquinoline **130** gave salt **279**, which was transformed into compound **280** by treatment with Hünig's base. The 3,4- dihydroisoquinoline **130** was also prepared following know procedure [77]. Deisopropylation of **280** delivered lamellarin U. Compound **281** was obtained from **278** by DDQ oxidation and removal of the two isopropyl groups in **281** furnished lamellarin W (Scheme **20**) [78]. In this synthesis, the intramolecular [3+2] cycloaddition reaction of 3,4-dihydroisoquinoline salts such as **88**, **277**, and **279** was performed in high yields under mild conditions allowing versatile synthesis of lamellarins.

In 2013, Komatsubara *et al*. reported the synthesis of lamellarins L and N from 2,5-dibromo pyrrole **251** and phenyl boronic acids **179**, **180**, and **184**. Br-Li exchange of **251** with *n*-BuLi followed by reaction with methyl chloroformate afforded the methyl ester **282**. Palladium-catalyzed Suzuki-Miyaura coupling of **282** with arylboronic acid **180** gave compound **283**, which was converted to bromide **284** by treatment with NBS. Second cross-coupling of **284** with boronic acid **179** resulted in trisubstituted pyrrole **285**. Bromination of **285** by NBS provided fully substituted bromopyrrole **286**. Next, the coupling reaction of bromopyrrole **286** with boronic acid **184** yielded **287**, which was transformed into lactone **288** by acid-catalyzed MOM-deprotection and lactonization. Alkylation of *NH*-pyrrole **288** with 2-bromoethyl phenyl sulfide in the presence of Cs_2CO_3 produced sulfide **289**, which underwent oxidation with *m*-CPBA formed sulfoxide **290**. Pummerer cyclization of **290** was performed using base TMSOTf/Hünig's under reported conditions [79] to provide compound **291**. Radical desulfurization of **291** using Bu_3SnH/AIBN in refluxing benzene provided **122** selectively [80], while oxidation of **291** *m*-CPBA in DCM gave **292**. Finally, removal of the isopropyl groups of **122** and **292** by treatment with BCl_3 furnished lamellarin L and lamellarin N, respectively (Scheme **21**) [81]. The key steps of the synthesis involve Br-Li exchange-methoxycarbonylation of 2,5-dibromopyrrole **251** followed by palladium-catalyzed iterative Suzuki-Miyaura coupling of the pyrrole core.

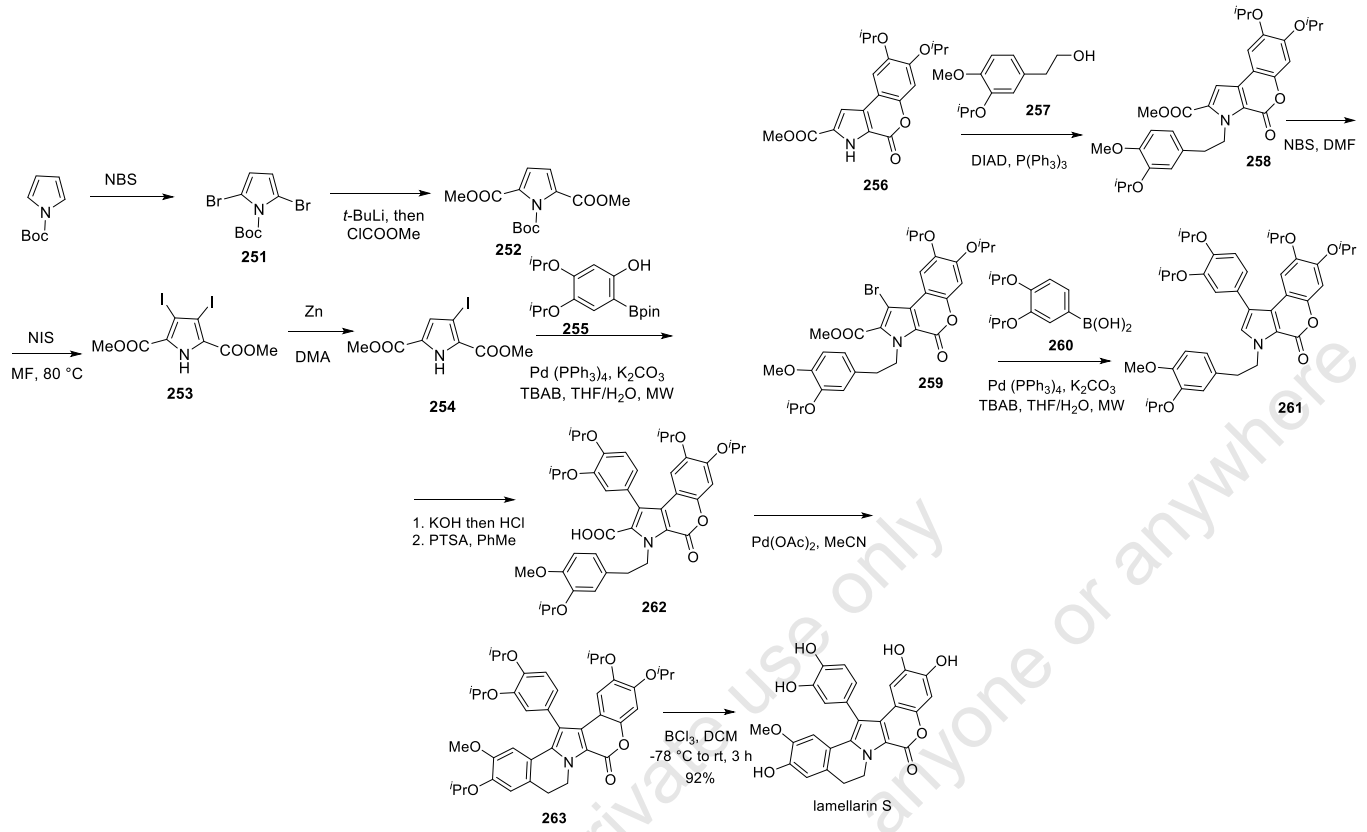


Scheme 17. Total synthesis of lamellarin α-20 sulfate.

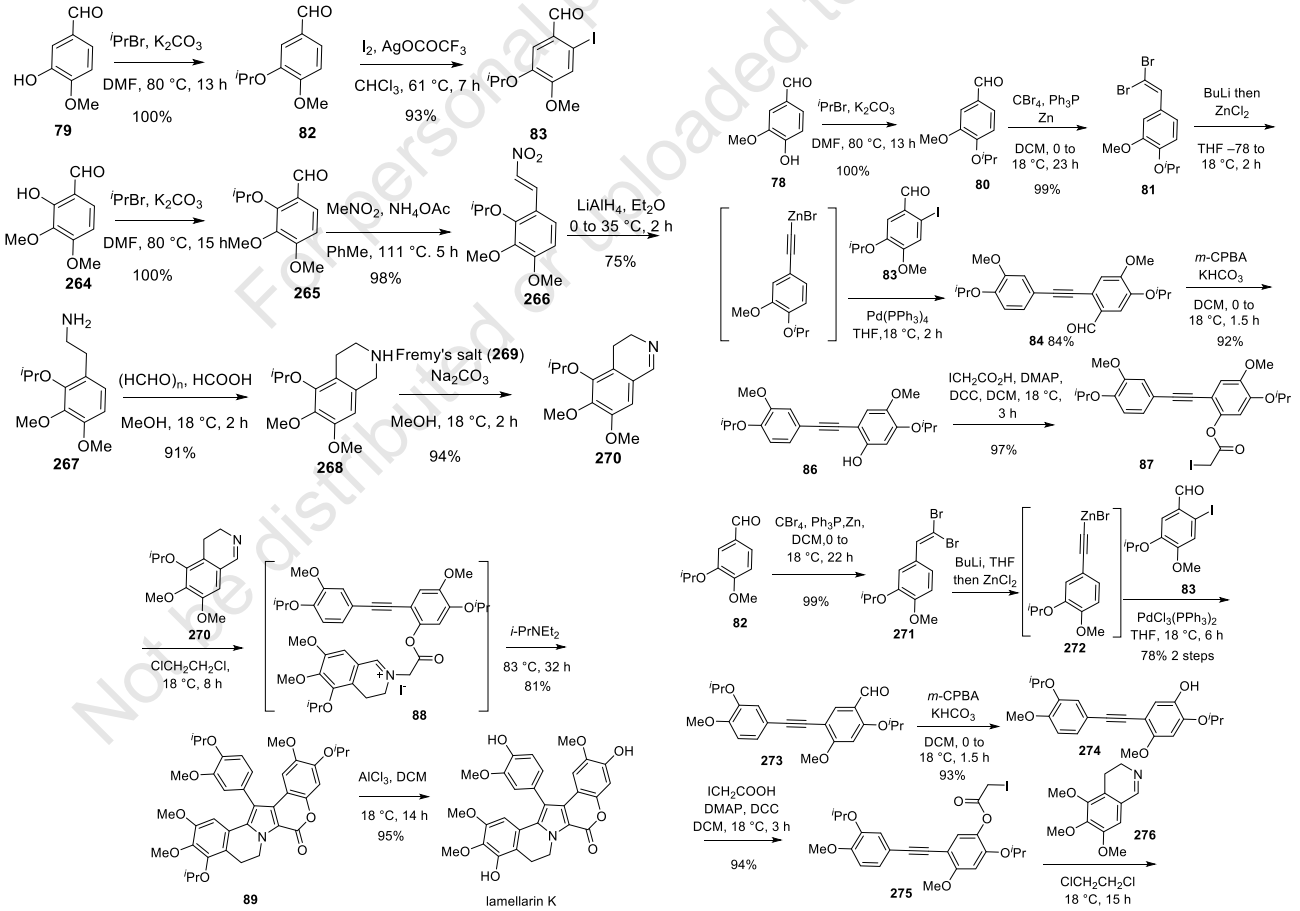


Scheme 18. Total synthesis of lamellarins D, H, and R.

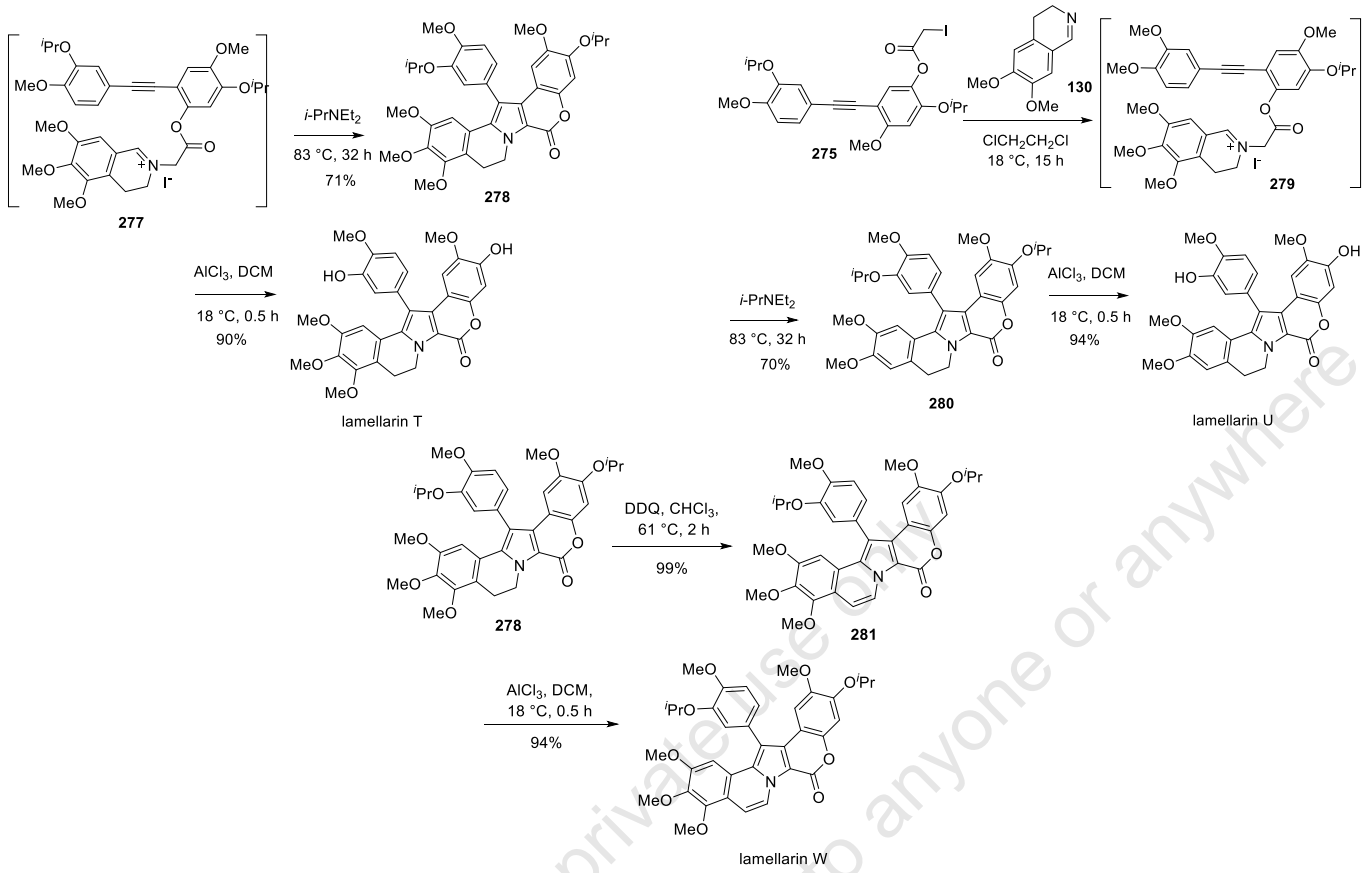
Shen *et al*. performed the lamellarin D synthesis using amine **298**, acid **293**, and phenacyl bromide **297** as key building blocks. Amine **298** was obtained from compound **79** *via* a sequence of Bn-protection of phenol, condensation with nitromethane, and $LiAlH_4$ reduction. Acid **293** was prepared from aldehyde **78** by a sequence of protection, reduction, chlorination of alcohol with thionyl chloride, substitution of chloride by sodium cyanide, and base-catalyzed hydrolysis. Bromide **297** was prepared from **79** *via* a sequential oxidation/ based-catalyzed ester hydrolysis/ Friedele-Crafts acylation/ selective mesylation of phenol/ acylation of phenol/ α-bromination. Condensation reaction between amine **298** and acid **293** afforded amide **299**, which underwent cyclization promoted by $POCl_3$ giving compound **300**. Condensation of isoquinoline **300** with phenacyl bromide **297** under basic condition provided the 1,2-diphenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline **301**. Vilsmeiere-Haack formylation of **301** yielded aldehyde **302**, which was oxidized to acid **303**. Hydrolysis of **303** with NaOH aqueous solution afforded the phenol derivative **304** which was transformed into lactone **305** by intramolecular cyclization reaction. Oxidation of **305** by DDQ formed compound **306**, which was converted to lamellarin D by treatment with TBAF and then $TiCl_4$ to remove all protecting groups (Scheme **22**) [82]. The significance of the synthesis is the formation of the fused pyrrole **301** from the 3,4-dihydro isoquinoline salt **300** and the phenacyl bromide **297**.



Scheme 19. Total synthesis of lamellarin S.



(Scheme 20) contd….

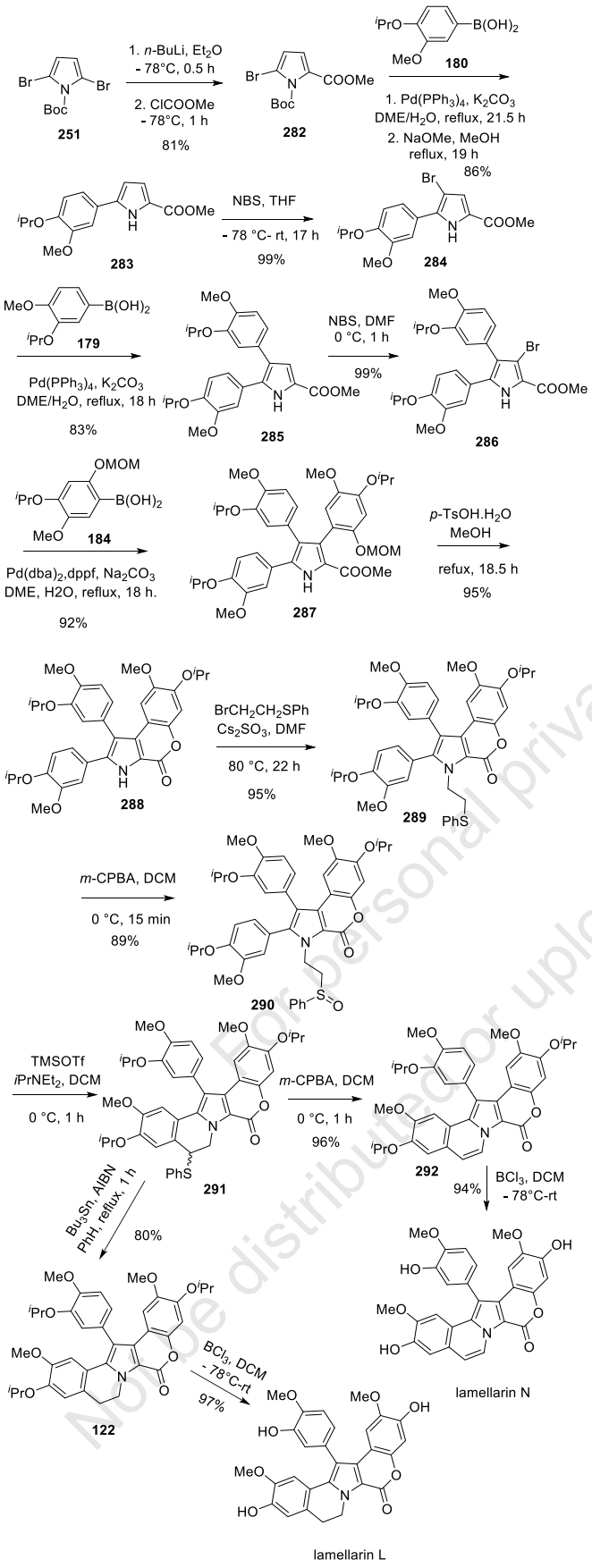


Scheme 20. Total synthesis of lamellarins K, T, U, and W.

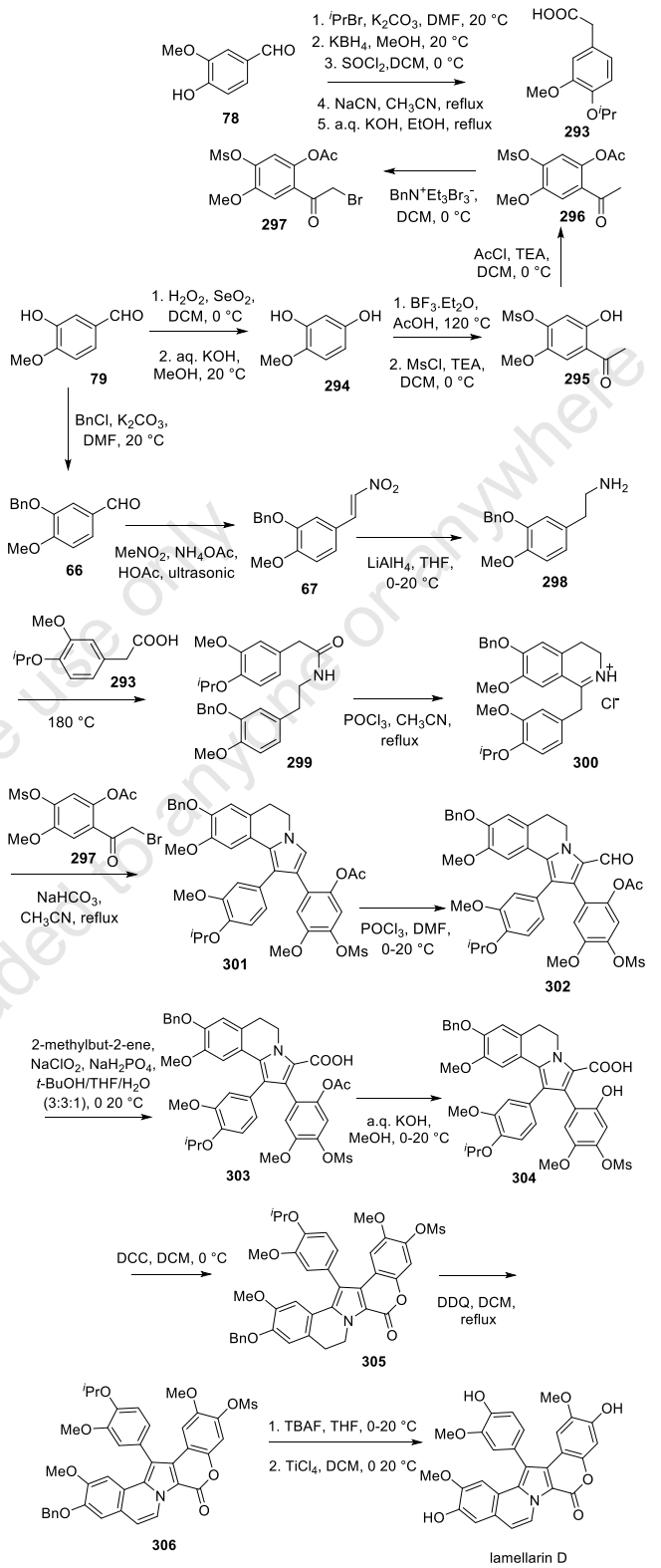
In 2014, Udea *et al.* accomplished the synthesis of lamellarins I and C from benzaldehyde **307**, iodide **311**, and phenol **181**. Aldehyde **307** was transformed into amine **309** by a sequence of nitroaldol reaction and reduction of the nitro group by $LiAlH_4$. Clauson Kaas reaction between amine **309** and 2,5-methoxy-tetrahydrofuran yielded pyrrole **310**, which then underwent β-selective arylation with aryl iodide **311** to give compound **312**. Friedel-Crafts acylation of **312** by trichloroacetyl chloride followed by hydrolysis of the trichloroacetyl group produced the corresponding carboxylic acid, which was converted to ester **313** by condensation with phenol derivative **181**. Compound **313** was treated with stoichiometric $Pd(OAc)_2$, $Cu(OAc)_2$ and K_2CO_3 (reported conditions) [83] furnish product **314**, which underwent isopropyl removal catalyzed by BCl_3 furnishing lamellarin I. β-selective arylation of **310** with aryl iodides **315** produced compound **316**. Then the same procedure performed for the synthesis of lamellarin I from **312** was applied to achieve lamellarin C from compound **316** (Scheme **23**) [84]. The intramolecular β-selective C-H arylation of pyrroles plays an important role in this synthesis.

Dialer *et al*. reported an efficient strategy for the synthesis of lamellarin H. The bromide **320** was obtained by bromination of veratraldehyde **319** with elemental bromine. The Claisen-Schmidt condensation between aldehyde **320** with acetophenone **321** afforded chalcone **322**, which was treated with glycine ethyl ester hydrochloride in refluxing pyridine followed by oxidation of the *in situ* formed Δ1-pyrroline with stoichiometric amounts of copper(II) acetate and regioselective iodination of the resulting pyrrole with NIS to provide iodopyrrole **323**. Suzuki-Miyaura cross-coupling reaction of **323** with 3,4-dimethoxyphenylboronic acid **324** delivered compound **325**. *N*-alkylation of **325** with bromoacetaldehyde dimethyl acetal followed by Iwao's TfOH-mediated intramolecular cyclization produced isoquinoline **326** [65]. Saponification of **326** with aqueous 3M NaOH in THF/MeOH (1:1) followed by treatment with CuTC in DMF under microwave irradiation furnished compound **327**. Finally, removal of all methyl groups by BBr_3 furnished lamellarin H (Scheme **24**) [85]. The electrocyclic ring closure of a 2-azapentadienyl anion generated *in situ* from a chalcone and glycine ester is the key step of this synthesis.

The Iwao group demonstrated the synthesis of lamellarins L and N. Their synthesis started from amino acid ester **328**. Klauson-Kaas reaction of this compound with 2,5-dimethoxy-tetrahydrofuran provided pyrrole **329**, which then underwent an intramolecular palladium-catalyzed Heck reaction to afford compound **330**. A Vilsmeier–Haack reaction of **330** followed by bromination with NBS regioselectively gave 1-bromo-3-formyl derivative **332**. The Suzuki–Miyaura coupling reaction of **332** with phenyl boronic acid **179** delivered compound **333**, which was brominated by NBS in DMF to yield bromide **334**. The second Suzuki–Miyaura coupling reaction of **334** with phenyl boronic acid **184** formed compound **335**, which was converted to **122** by acid-catalyzed deprotection. Tamaru's palladium-catalyzed oxidation [86] reaction of **335** with bromobenzene furnished **122** (Scheme **25**) [87]. Conversion of **122** to lamellarins L and N followed known procedure in the literature [53]. The C3-selective Vilsmeier-Haack formylation ollowed by iterative bromination/cross-coupling of the 5,6-dihydropyrrolo[2,1-*a*]isoquinoline core are the most important features of the synthesis.



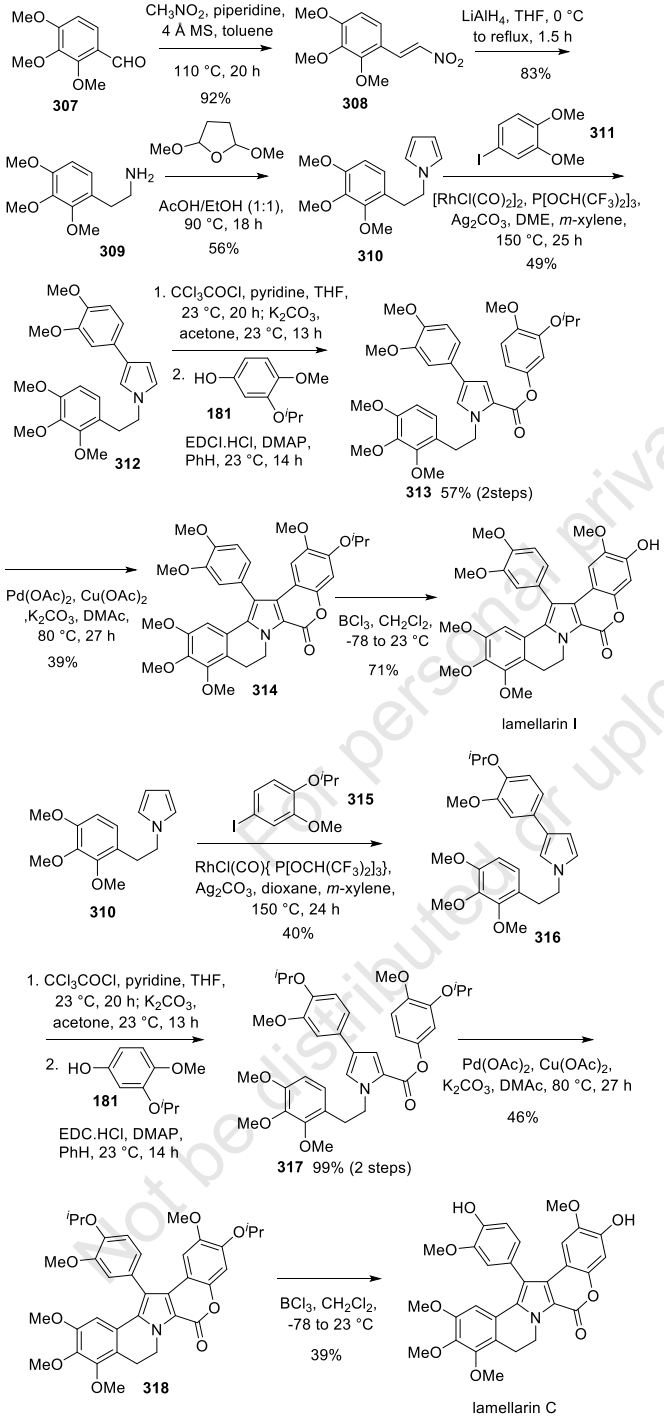
Scheme 21. Total synthesis of lamellarins L and N.



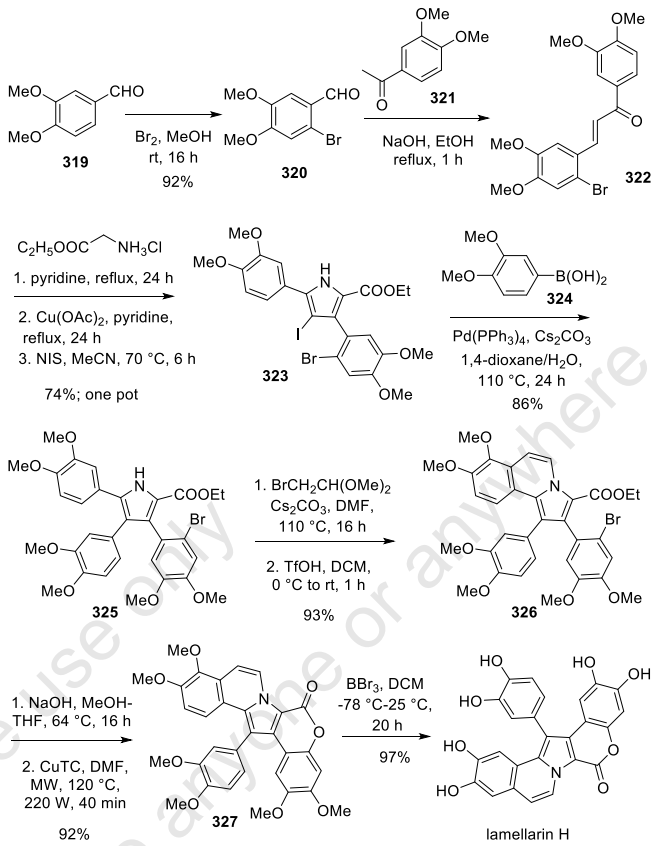
Scheme 22. Total synthesis of lamellarin D.

In 2016, the Iwao group achieved the synthesis of lamellarin U from pyrrole **337** and several boronic acids and boronate esters. Kinetic bromination of **337** with NBS at room temperature in DMF gave 2,5-dibromopyrrole **338**, which then underwent rearrangement to 2,4-dibromopyrrol **339** by treatment with trifluoromethanesulfonic acid followed by the addition of triethylamine. Regioselective bromine-lithium exchange using n-BuLi followed by treatment with

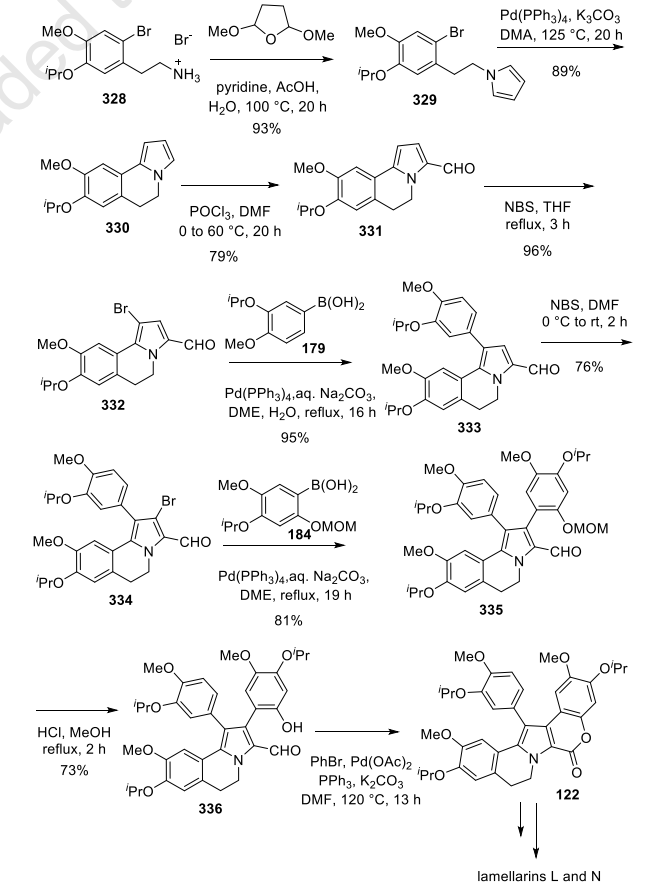
1,2-diiodoethane provided compound **340**. The Suzuki-Miyaura palladium-catalyzed cross-coupling reaction of **340** with aryl-boronate ester **341** selectively yielded compound **342**. The second cross-coupling of **342** with boronic acid **184** gave compound **343**. Treatment of **343** with TBAF in THF at 65 °C resulted in compound **344**. A Vilsmeier–Haack reaction of **344** produced aldehyde **345**, which was transformed into the pentacyclic compound **346** by Tamaru's palladium-catalyzed oxidation. Regioselective bromination at the pyrrole ring of **346** followed by cross-coupling reaction with **179** furnished compound **280**, which underwent isopropyl cleavage with BCl_3 to provide lamellarin U (Scheme **26**) [88].



Scheme 23. Total synthesis of lamellarins C and I.

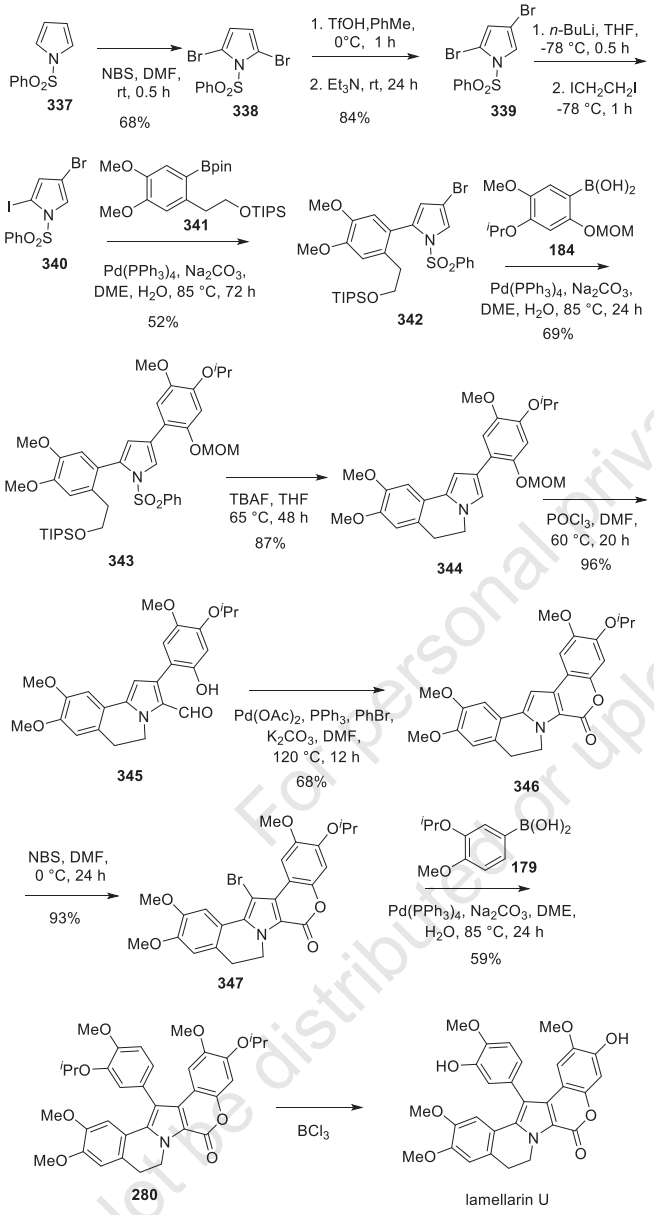


Scheme 24. Total synthesis of lamellarin H.



Scheme 25. Total synthesis of lamellarins L and N.

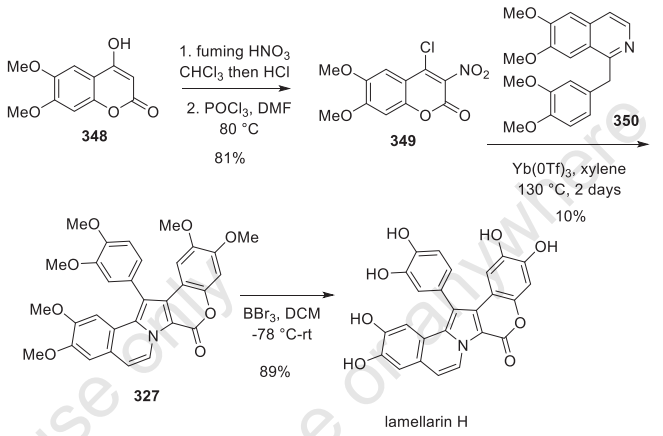
The Yang group developed an efficient method for $Yb(OTf)_3$-catalyzed coupling of 4-chloro-3-nitrocoumarin and 1-methylisoquinoline and applied this method for the synthesis of lamellarin H. The $Yb(OTf)_3$-catalyzed coupling reaction between 4-chloro-3-nitrocoumarin **349** and commercially available isoquinoline **350** furnished compound **327**, which was converted to lamellarin H by treatment with BBr_3. Compound **349** was prepared from coumarin **348** by reaction with fuming HNO_3 in $CHCl_3$ and then HCl followed by treatment with $POCl_3$ in DMF (Scheme **27**) [89]. In this synthesis, the $Yb(OTf)_3$-catalyzed coupling of 4-chloro-3-nitrocoumarin **349** and 1-methylisoquinoline **350** plays the vital role.



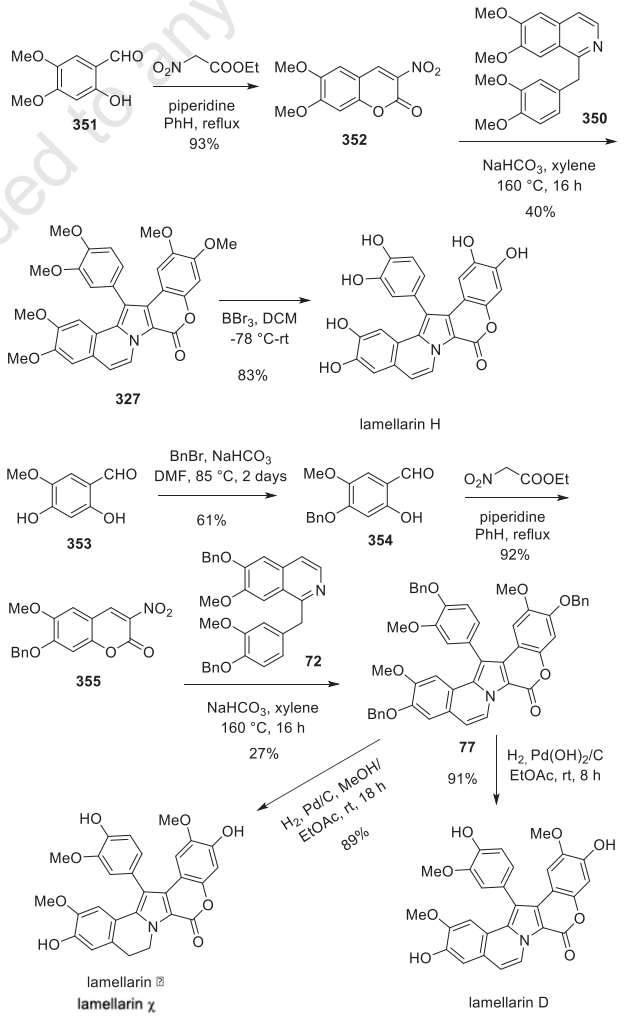
Scheme 26. Total synthesis of lamellarin U.

Later, Yang group expanded this reaction for the synthesis of lamellarins H, D, and χ with modifications. For the synthesis of lamellarin H, condensation between **351** with ethyl nitroacetate afforded nitrocoumarine **352**. The coupling of **352** with isoquinoline **350** in a sealed tube afforded compound **327**, which underwent removal of all methyl groups to provide lamellarin H (Scheme **28**).

For the synthesis of lamellarins D and χ, nitrocoumarine **355** was obtained from compound **353** by a sequence of selective *O*-benzylation, and condensation with ethyl nitroacetate. The coupling of **355** with isoquinoline **72**, which was prepared following a known procedure [43], afforded compound **77**. The subsequent $Pd(OH)_2$-catalyzed debenzylation of **77** in EtOAc under a hydrogen atmosphere furnished the target lamellarin D, while lamellarin χ was furnished under Pd/C catalyst (Scheme **28**) [90].



Scheme 27. Total synthesis of lamellarin H.



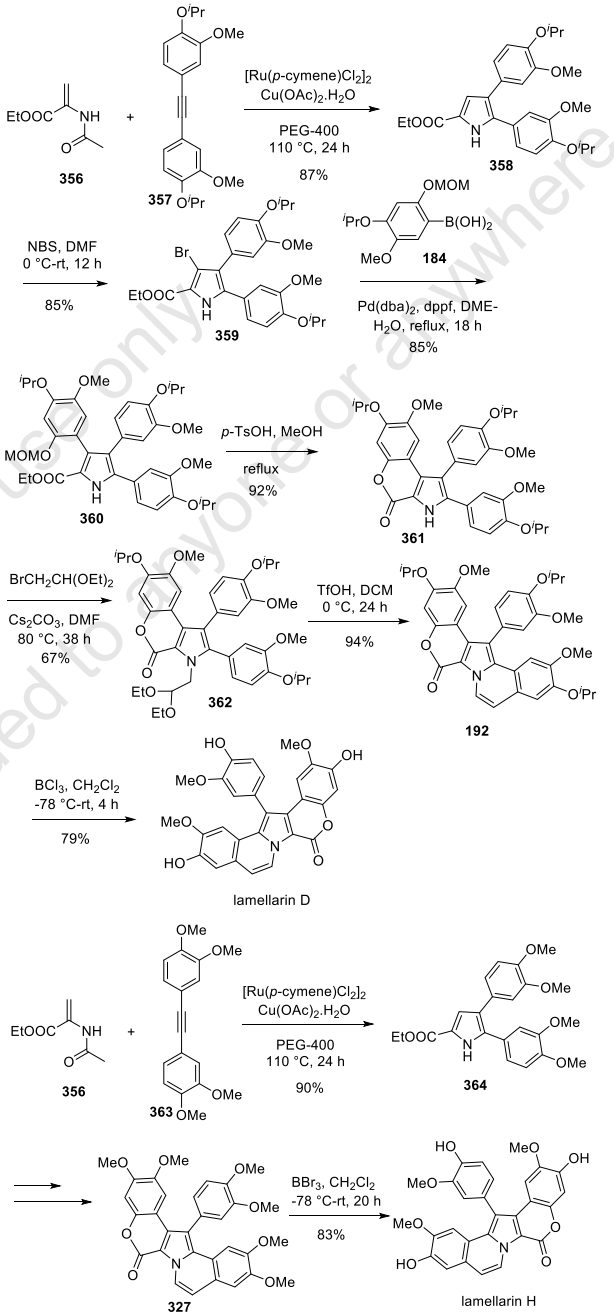
Scheme 28. Total synthesis of lamellarins D, H, and χ.

1n 2017, Lade *et al*. reported the synthesis of lamellarins D and H in 7% overall yield [91]. The synthesis of lamellarin D started from the formation of pyrrole **358** by the annulation reaction between enamide **356** and diarylalkyne **357** in the presence of [Ru(*p*-cymene)Cl_2]$_2$ as a catalyst and Cu(OAc)$_2$.H_2O as an oxidant. Selective bromination at the pyrrole ring of **358** gave bromide **359**, which underwent Suzuki–Miyaura coupling reaction with boronic acid **184** to provide compound **360**. The one-pot MOM deprotection and lactonization of **360** catalyzed by TsOH in MeOH furnished lactone **361**. *N*-alkylation of **361** with bromoacetaldehyde diethyl acetal formed compound **362**, which cyclized to **192** under Iwao's conditions [65]. Finally, removal of the three isopropyl protecting groups in **192** delivered lamellarin D (Scheme **28**) [91]. The synthesis of lamellarin H followed the same route except for the first step. In this step, pyrrole **362** was obtained by the annulation reaction between enamide **356** and diarylalkyne **363** (Scheme **29**) [91]. The key step involves Ru-catalyzed (3+2) annulation between enamide and diarylalkyne to construct the pyrrole ring.

Iwao group continued successfully to synthesize lamellarins α and η from *N*-benzenesulfonylpyrrole **219**. Bromination of **219** in refluxing acetic acid produced 3-bromopyrrole **365**, which was converted to ester **366** by a sequence of lithiation by LDA and treatment with methyl chloroformate. Suzuki–Miyaura coupling reaction of **366** with boronic acid **184** produced compound **367**, which was transformed into lactone **368** by treatment with acid in MeOH, and then TBAF in THF. Bromination of **368** yielded dibromopyrrole **369**, which underwent Suzuki–Miyaura coupling reaction with two molecules of boronic acid **324** to afford compound **370**. Alkylation of **370** with bromoacetaldehyde dimethyl acetal **371** followed by TfOH-mediated cyclization provided **373** which was converted to lamellarin η by treatment with BCl_3 (Scheme **30**) [94]. Selective monobromination of **368** followed by cross-coupling reaction with acid **179** afforded **375**. Bromination at the pyrrole ring of **375** followed by Suzuki–Miyaura coupling reaction with acid **370** produced compound **377**. Lamellarin α was achieved from **377** by a sequence of alkylation with bromoacetaldehyde dimethyl acetal, TfOH-mediated cyclization, and BCl_3-catalyzed deprotection (Scheme **30**) [92]. The key reactions in this synthesis are the assembly of 1,2-diarylated [1]benzopyrano[3,4-*b*]pyrrol-4(3*H*)-ones from [1]benzopyrano[3,4-*b*]pyrrol-4(3*H*)-one core and the appropriate arylboronic acids.

Chiu and Tonks developed an efficient, one-pot, three-component reaction for the synthesis of pyrroles and applied this approach for the synthesis of lamellarin R. Titanium-catalyzed [2+2+1] cycloaddition between 379, 380, and 381 afforded pyrrole 382, which was converted to 383 by treatment with TBAF (Scheme **31**) [93]. Conversion of 383 to lamellarin R followed the reported procedure [74].

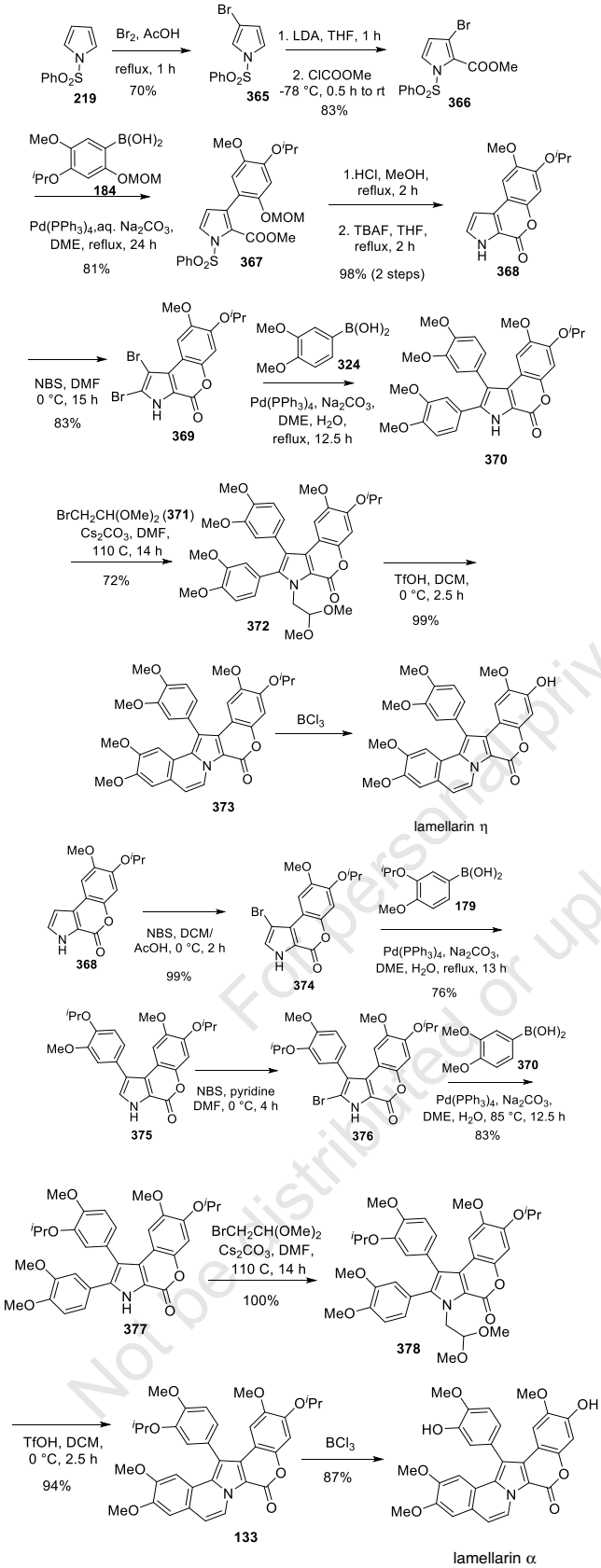
In 2019, Shirley *et al.* accomplished the synthesis of lamellarins D and Q. The synthesis of lamellarin D started from compound **384**. Compound **386** was obtained from **384** *via* a sequence of *O*-alkylation with 2-bromopropane and subsequent nucleophilic aromatic substitution. Coupling reaction between **386** and **387** using *t*-BuONa and Pd(dtbpf)Cl_2 (5 mol%) in THF gave **388**, which was reacted with **390** in the presence of *t*-BuONa generating 1,4-dicarbonyl **391**. **390** was prepared from **389** by a sequence of *O*-protection by isopropyl group and bromination by NBS. Heating **391** and aminoacetaldehyde diethyl acetal at reflux in acetic acid in the presence of water and formic acid produced **392**. Cyclization of **392** to **393** was achieved by transfer hydrogenation using Pd(OH)$_2$/C (Pearlman's catalyst) and 1,4-cyclohexadiene and K_2CO_3-catalyzed lactonisation. C–H arylation of **393** with aryl bromide **394** to yield **192** was successfully operated using KOAc, Pd(PPh$_3$) (5 mol%). Removal of three isopropyl groups using BCl_3 furnished lamellarins D (Scheme **32**) [94]. Key steps in the synthesis involve one-pot double enolate functionalisation of OBO-ketone followed by double annulation to form the target pyrrole/N-vinyl pyrrole core and late-stage direct C–H arylation.



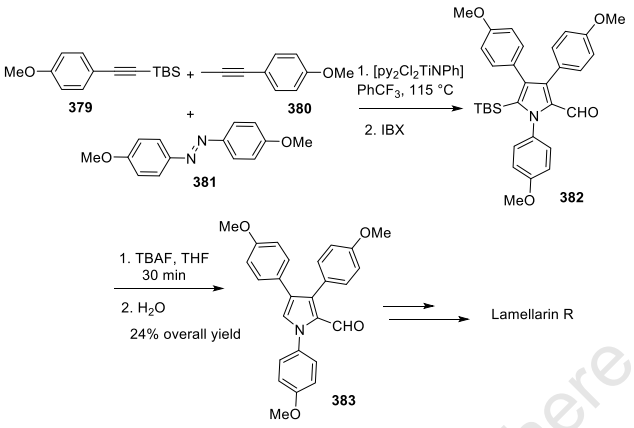
Scheme 29. Total synthesis of lamellarins D and H.

For the synthesis of lamellarin Q, Protection of 4-hydroxybenzyl nitrile **395** with 2-bromopropane formed **396** and benzylic bromination using NBS/dibenzoyl peroxide provided **397**. Coupling reaction between **397**, **398** and methyl-OBO-ketone using Pd(dtbpf)Cl_2, *t*-BuONa in THF afforded compound **399**. Compound **399** was converted to bromopyrrole **400** by acid treatment, and then methyl pyrrole-2- carboxylate **401** by base-catalyzed reaction. Reduction of **401** by H_2 and Pd/C cleanly removed the bromine atom

to produce compound **224**, which then underwent removal of both isopropyl groups using BBr_3 furnished lamellarin Q (Scheme **32**) [94].



Scheme 30. Total synthesis of lamellarins α and η.



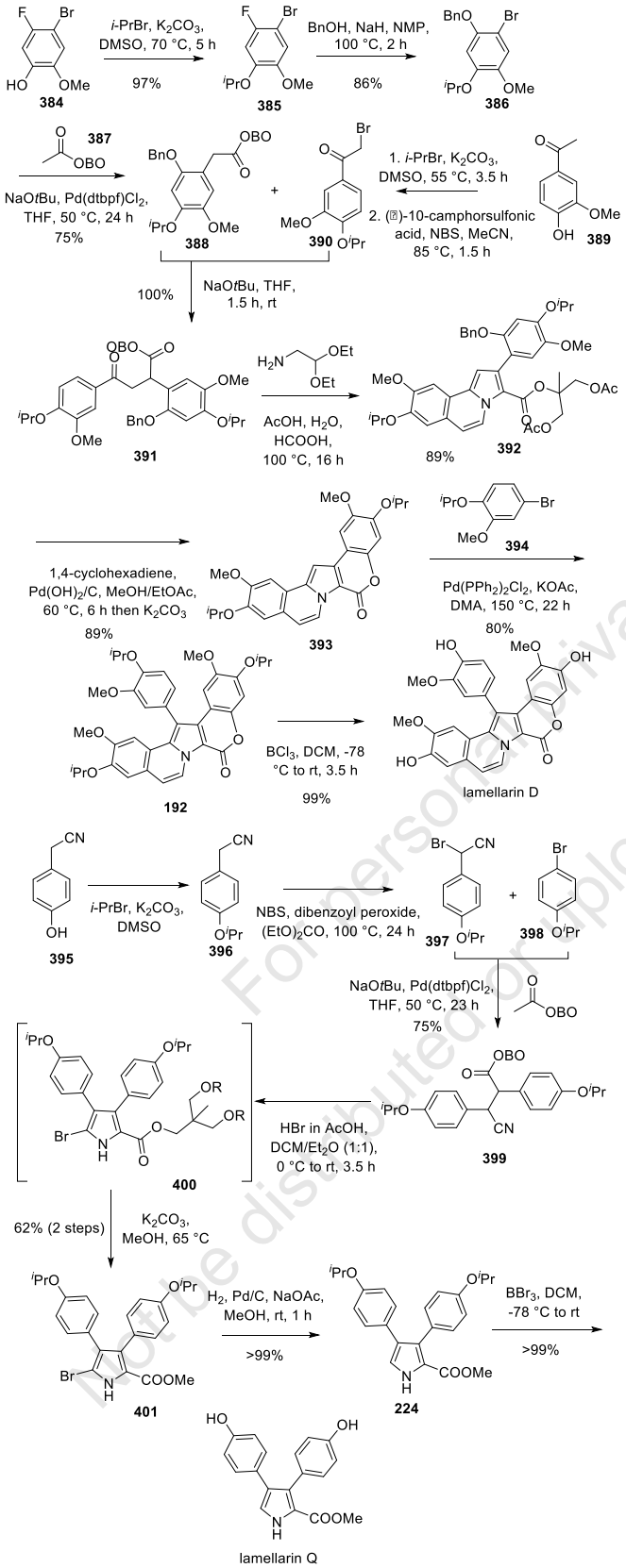
Scheme 31. Total synthesis of lamellarin R.

The synthesis of lamellarins H, η, and U, was successfully achieved by Kumar *et al*. In their lamellarin H synthesis, the annulation reaction of aziridine ester **402** with β-bromo-β-nitrostyrene **403** generated pyrrole **404**. Compound **404** was converted to acid **405** by base-catalyzed hydrolysis and ester **407** by EDCI.HCl-promoted, DMAP-catalyzed esterification with phenol **406**. β-Selective intramolecular C-H arylation of **407** formed **408**, which was oxidized to **327** by DDQ. Removal of six methyl ethers of **327** provided lamellarin H (Scheme **32**) [95]. To prepare lamellarin U, ethyl pyrrole-2-carboxylate **410** was afforded from aziridine ester **402** and β-bromo-β-nitrostyrene **409**. Hydrolysis of **410** by base followed by esterification with phenol **181** using EDCI.HCl and DMAP delivered ester **412**, which was transformed into compound **280** by intramolecular C-H arylation. Cleavage of two isopropyl ethers in **280** then furnished lamellarin U (Scheme **32**) [95]. For lamellarin η, acid **405** was esterified with phenol **181** to generate ester **413**, which underwent intramolecular C-H arylation to provide **414**. DDQ oxidation of **414** followed by $AlCl_3$-catalyzed removal of the isopropyl group the furnished lamellarin η (Scheme **33**) [95]. Significance of the synthesis includes single-step access to the central 1,2,4-trisubstituted pyrrole core in a highly regioselective manner *via* a one-pot [3+2] cycloaddition/ elimination/aromatization sequence-based domino process between aziridine ester with β-bromo-β-nitrostyrene.

In 2020, Hwu *et al*. introduced a short route to synthesize lamellarin R. The key step in their strategy is the three-component annulation reaction between *o*-silylaryl triflate **415**, Schiff base **416**, and alkyne **417** to provide compound **250**. Treatment of **250** to remove all methyl ethers then produced lamellarin R (Scheme **34**) [96]. Lamellarin R was obtained in high yields in two steps.

Satyanarayana *et al*. performed the synthesis of lamellarins R and O based on the reaction between nitro styrenes and methyl isocyanoacetate. To synthesize lamellarin R, β-nitro styrene **418** was brominated at 65 °C to form compound **419**, which underwent Suzuki coupling with *p*-methoxybenzeneboronic **420** acid under basic conditions to afford nitrostilbene **421**. The key Barton-Zard reaction of nitrostilbene **421** with methyl isocyanoacetate occurred in the presence of K_2CO_3 in methanol to provide the key intermediate methyl-3,4- diarylpyrrole-2-carboxylate **422** [97], Arylation of *NH*-pyrrole **422** with *p*-methoxy iodobenzene gave compound **250**, which was converted to lamellarin R by treatment with BBr_3. In the synthesis of lamellarin O, pyrrole **428** was obtained from β-nitro styrene **424** *via* a sequence of bromination, Suzuki coupling with boronic acid **426**, and Barton–Zard reaction with methyl isocyanoacetate. Alkylation of *NH*-pyrrole **428** with phenacyl bromide **97**

yielded compound **106**, which underwent deprotection of two OBn groups with hydrogen catalyzed by $Pd(OH)_2$ furnished lamellarin O (Scheme **35**) [98]. The Barton–Zard reaction for the construction of the pyrrole ring is the key step of the synthesis.



Scheme 32. Total synthesis of lamellarins D and Q.

Morikawa *et al.* achieved the synthesis of lamellarins S and Z from ethyl pyrrole-2-carboxylate. Bromination of this compound with NBS in $CHCl_3$ at 0 °C afforded dibromopyrrole **429**. Protection of the NH with a SEM group delivered α, β-dibromopyrrole **430**, which was treated with LDA at -78 °C resulting in the migration of the α-bromo group and provided β, β'-dibromopyrrole **431** was formed. The Suzuki–Miyaura coupling of **431** with two equivalents of arylboronate ester **432** produced compound **433**. Lactone **434** was obtained from **433** by a sequence of base-catalyzed ester hydrolysis, $Pb(OAc)_4$-mediated lactone formation, and SEM cleavage by TFA. *N*-alkylation of *NH*-pyrrole **434** with alcohol **435** gave compound **436**. PIFA-promoted oxidative C–C bond formation of **436** followed by hydrogenolytic debenzylation furnished lamellarin S (Scheme **36**) [99].

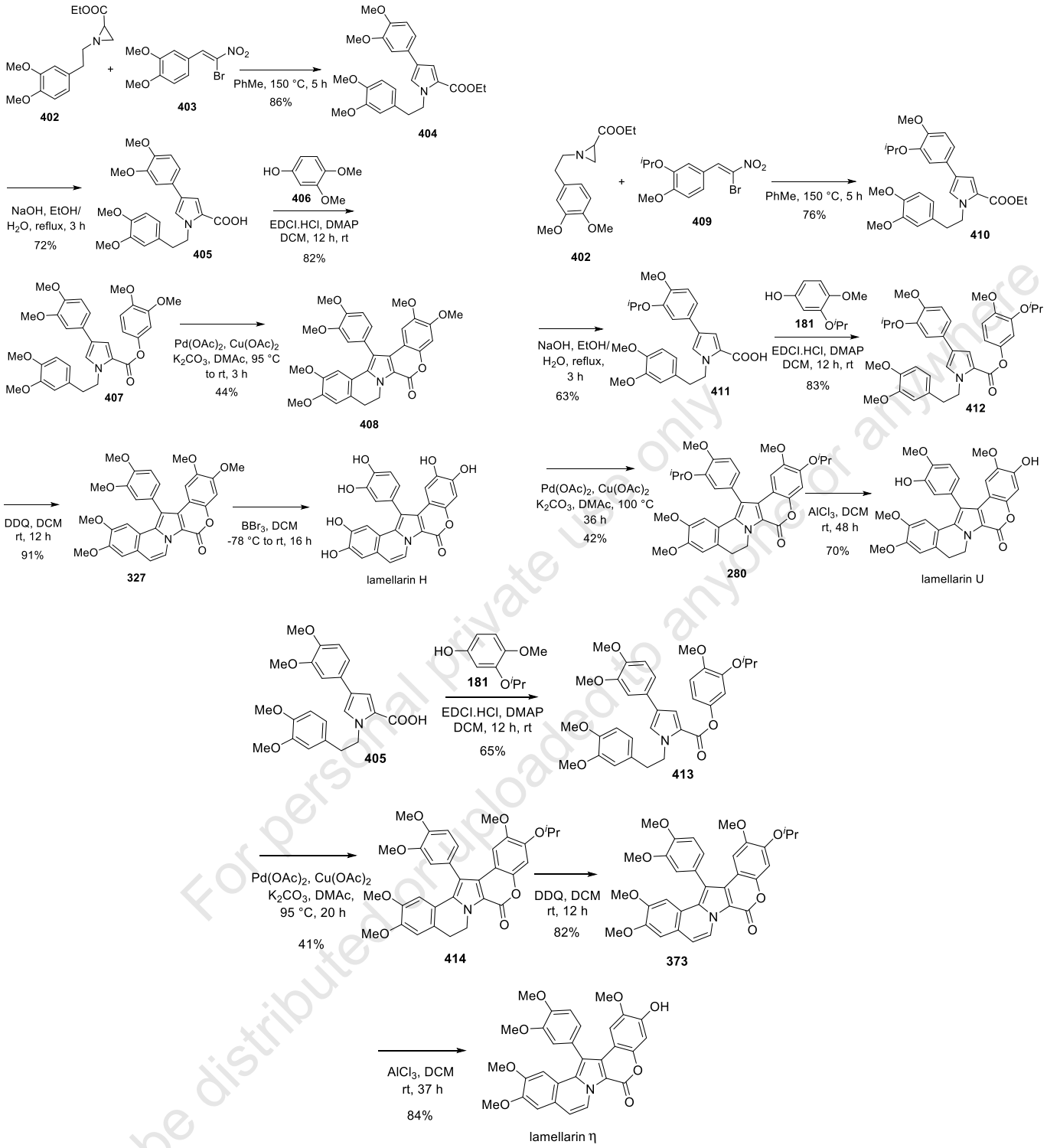
For the synthesis of lamellarin Z, the selective Suzuki–Miyaura coupling of **431** with arylboronate ester **438** generated compound **439**, which was converted to **440** by a second Suzuki–Miyaura coupling with boronate ester **432**. Lactone **441** was obtained from **440** using the same procedure for the formation of **434**. *NH*-pyrrole **441** was alkylated with alcohol **435** to form **442**, which was transformed into lamellarin Z by a sequence of PIFA-promoted oxidative C–C bond formation and hydrogenolysis of the benzyl ethers (Scheme **36**) [99]. Rearrangement of **430** to **432** and $Pb(OAc)_4$-mediated lactone formation of **434** are the most attractive features of the synthesis.

Khan group continued synthesizing lamellarins D, G, L, S, and Z based on their previous study on the synthesis of lamellarins H, η, and U [97]. Condensation between aziridine-2-carboxylate **444** and *β*-bromo-*β*-nitrostyrene **445** gave **446**, which was converted to acid **447** by base-catalyzed hydrolysis. This acid was esterified with phenol **448** using EDCI.HCl and DMAP to provide **449**, which was transformed into **263** by a one-pot Pd-mediated cross-dehydrogenative coupling reaction. Cleavage of all isopropyl groups furnished lamellarin S. Following the same route, replacing phenol **448** by phenol **450** afforded lamellarin U (Scheme **37**) [100].

Meanwhile, condensation between aziridine-2-carboxylate **444** and *β*-bromo-*β*-nitrostyrene **419** generated trisubstituted pyrrole-2-carboxylate **453**. Base-catalyzed hydrolysis of **453** followed by esterification with phenol **450** yielded **455**. Lamellarin G was obtained from **455** by a sequence of a Pd-mediated cross-dehydrogenative coupling reaction and isopropyl cleavage. Similarly, replacing phenol **450** by phenol **181** in this procedure furnished lamellarin L (Scheme **37**) [100].

The synthesis of lamellarin D followed the same route for the synthesis of lamellarin L. However, in this route *β*-bromo-*β*-nitrostyrene **457** was used instead of *β*-bromo-*β*-nitrostyrene **419** (Scheme **37**) [100]. All lamellarins D, G, L, S, and Z were synthesized in five steps with relatively high overall yields.

In 2020, Klintworth *et al*. accomplished the synthesis of lamellarins H and A4. Acylation of **462** with acid **461** del1vered ketone **462**, which was brominated with NBS to produce bromide **464**. Coupling reaction between **464** and thiolactam **466** formed heptamethoxylated enaminone **467**. Thiolactam **466** was generated from amine **465** by treatment with CS_2, Et_3N, and then ClCOOEt. Heating of enaminone **465** in neat ethyl bromoacetate in the presence of $NaHCO_3$ yielded ester **468**, which was converted to acid **469** by hydrolysis. Compound **470** was obtained from **469** by a sequence of chloride acid formation by treatment with oxalyl chloride, selective iodide-mediated demethylation, and lactonization. Removal of six

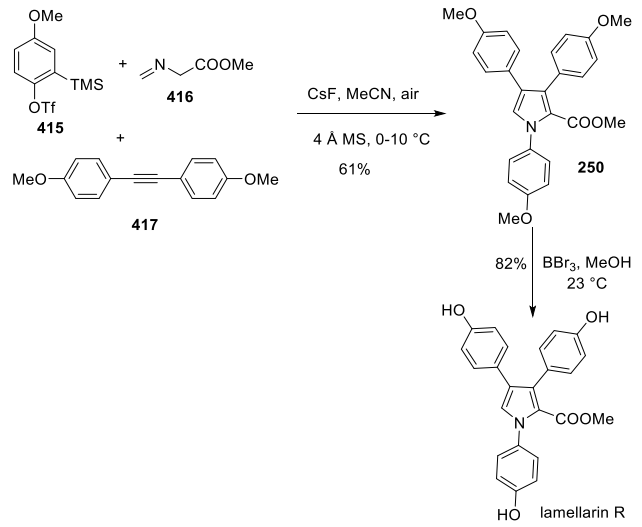


Scheme 33. Total synthesis of lamellarins H, η, and U.

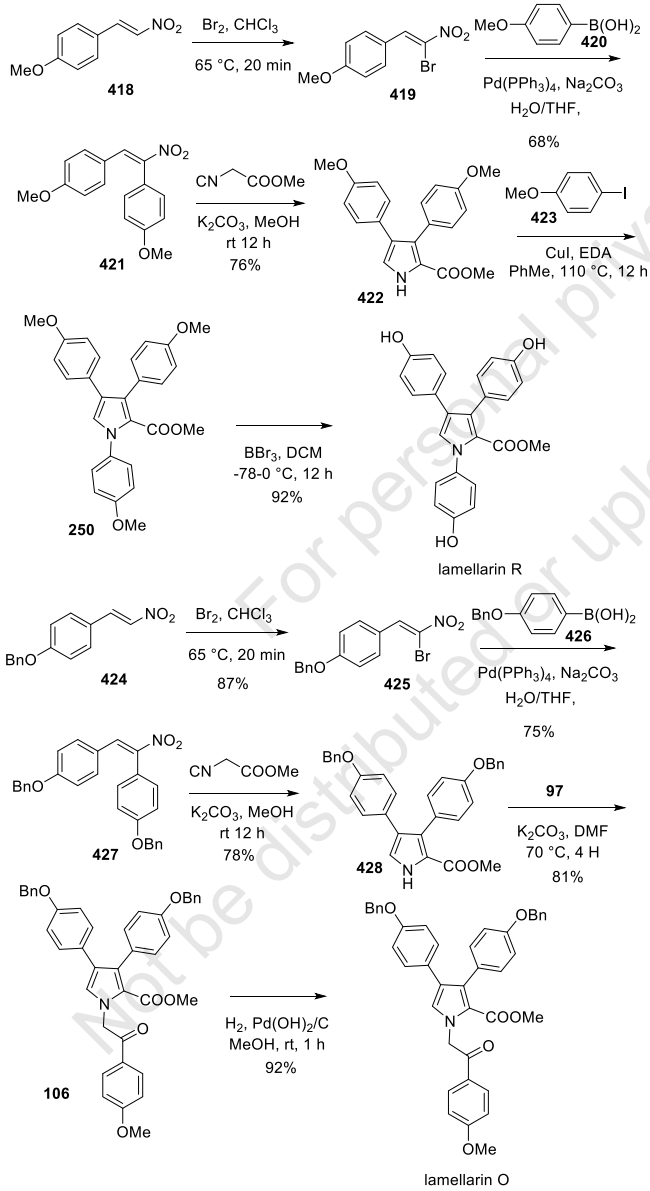
methyl ethers furnished A4. DDQ oxidation of **468** provided **471** and conversion of this compound to lamellarin H was performed using the same procedure for the preparation of lamellarin A4 from **468** (Scheme **38**) [101]. The syntheses of lamellarins H and A4 were accomplished in excellent yields (80% and 84% overall yields, respectively).

CONCLUSION

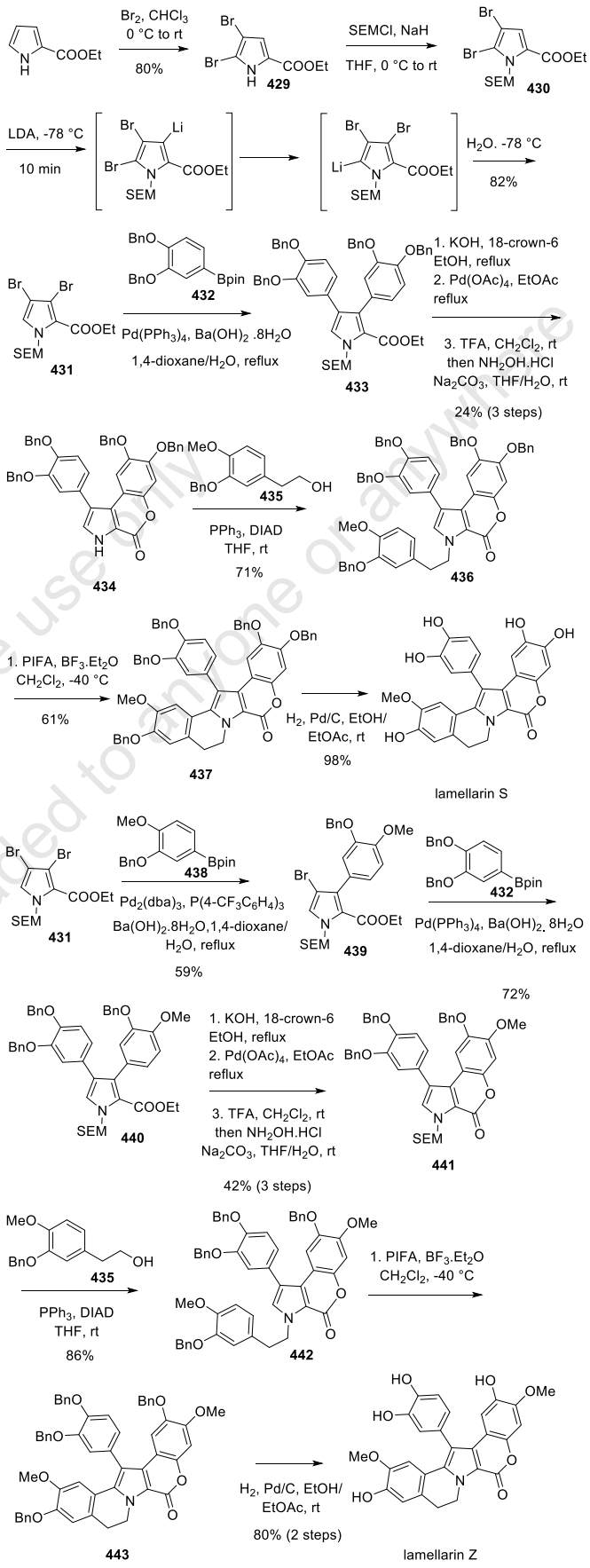
In this review article, we have summarized the scientific reports on the natural lamellarin alkaloids, including isolation, bioactivity, and total synthesis. While few studies on the isolation of this class of alkaloids have appeared in the literature over the years, the total synthesis and therapeutic studies still have drawn extensive attract-



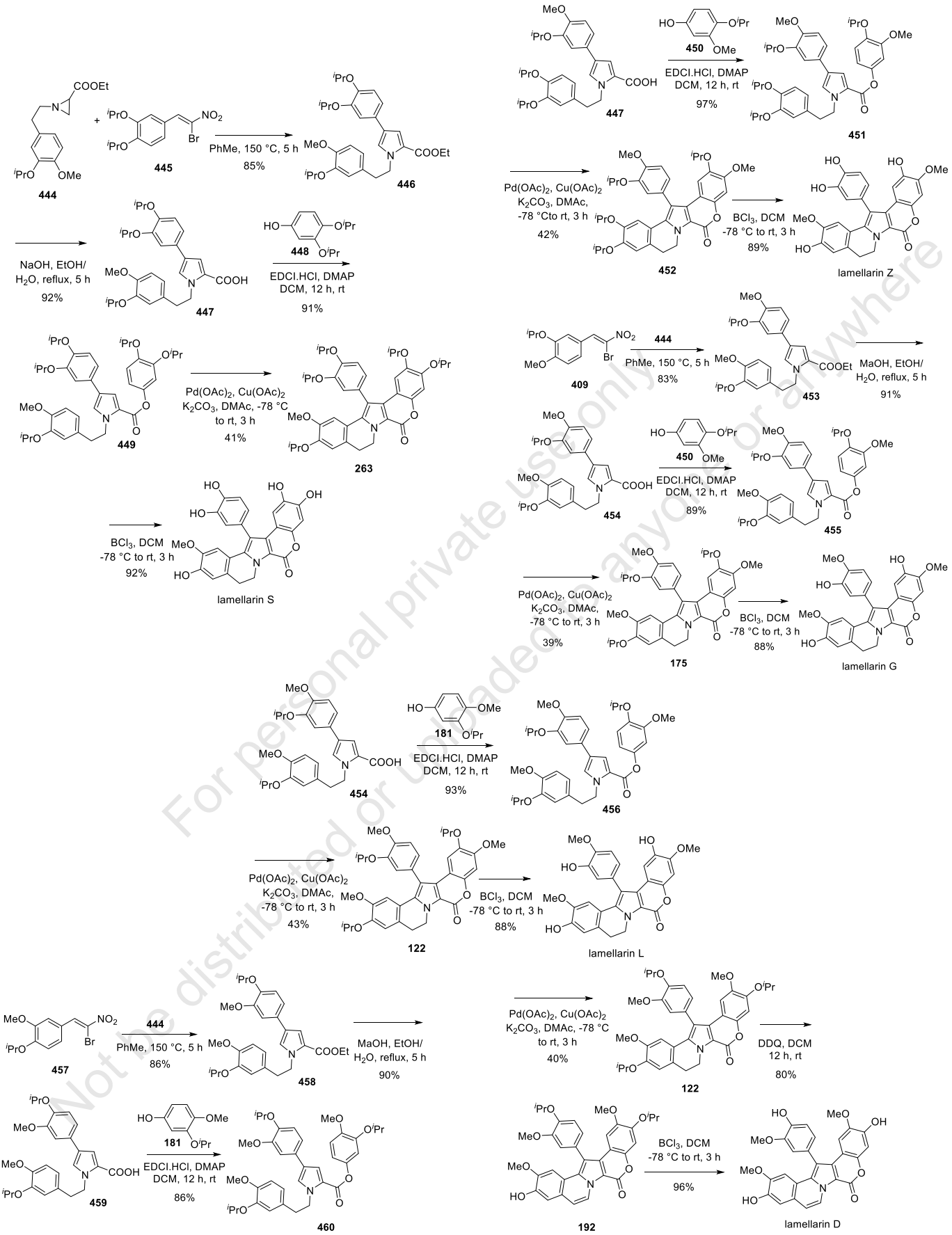
Scheme 34. Short synthesis of lamellarin R.



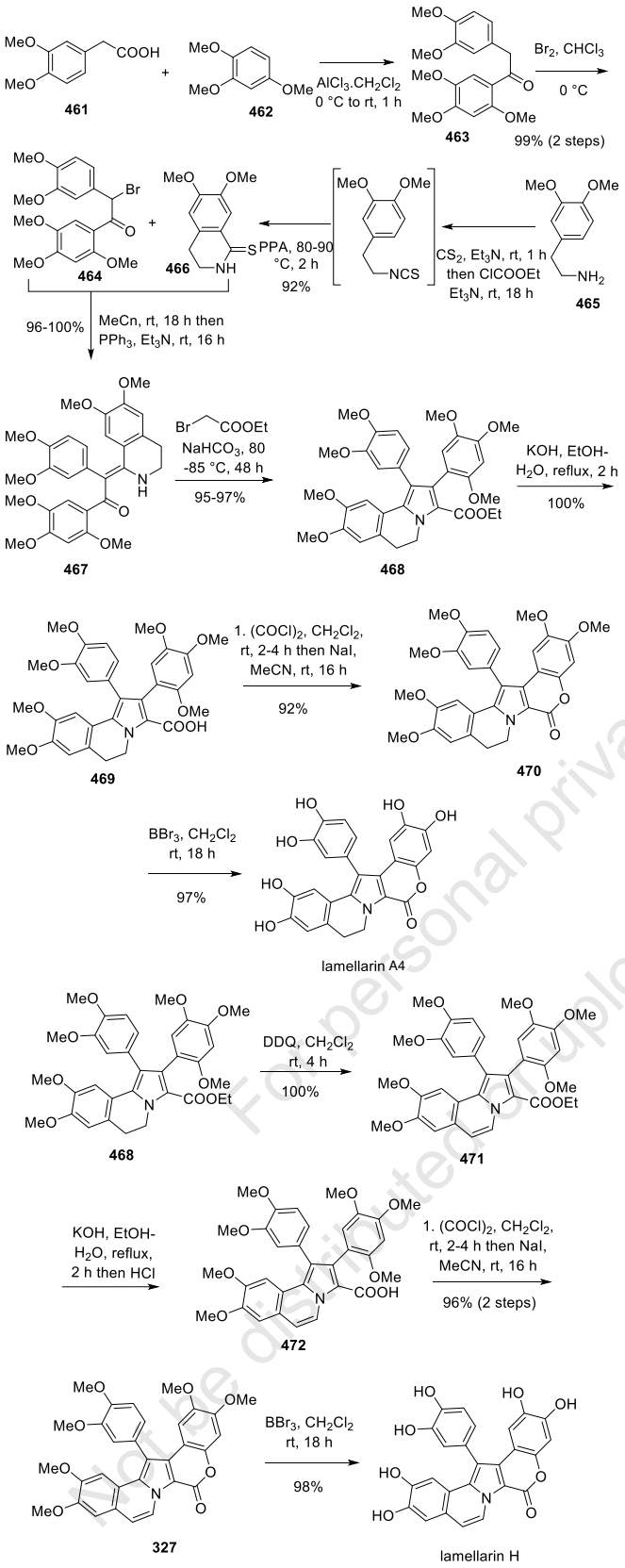
Scheme 35. Total synthesis of lamellarins O and R.



Scheme 36. Total synthesis of lamellarins S and Z.



Scheme 37. Total synthesis of lamellarins S, Z, G, L, and D.



Scheme 38. Total synthesis of lamellarins A4 and H.

tion from chemists. In the future, more efficient and straightforward strategies for the synthesis of lamerallins as well as new bioactivities of these heterocycles might be discovered. Bioactive mechanism of action of these alkaloids at the cellular and molecular level will probably be another direction.

AUTHORS' CONTRIBUTION

Nguyen Van Quoc: Collecting data; Dau Xuan Duc: Writing the article

LIST OF ABBREVIATIONS

Ac	=	Acetyl
AIBN	=	Azobisisobutyronitrile
Ar	=	aryl
Bn	=	Benzyl
Boc	=	*tert*-butyloxycarbonyl
dba	=	dibenzylideneacetone
dppf	=	1,1′-Bis(diphenylphosphino)ferrocene
DBU	=	1,8 Diazabicyclo[2.2.2]octane
DCC	=	N,N′-Dicyclohexylcarbodiimide
DCE	=	1,2-Dichloroethane
DCM	=	Dichloromethane
DDQ	=	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	=	Diethyl azodicarboxylate
DIDA	=	Diisodecyl adipate
DIEA	=	N,N-Diisopropylethylamine
DMA	=	Dimethylacetamide
DMAP	=	4-Dimethylaminopyridine
DME	=	Dimethoxyethane
DMF	=	*N,N*- Dimethylformamide
DMSO	=	Dimethyl sulfoxide
EDA	=	Ethylenediamine
EDCI	=	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
Et	=	Ethyl
KHMDS	=	Potassium hexamethyldisilazide
LDA	=	Lithiumdiisopropyl amide
Me	=	Methyl
m- CPBA	=	*m*- chloroperbenzoic acid
MOM	=	Methoxymethyl
Ms	=	Mesyl
MW	=	microwave
NBS	=	*N*-Bromosuccinimide
NIS	=	*N*-Iodosuccinimide
PEG	=	Polyethyleneglycol
Ph	=	Phenyl
PIFA	=	[Bis(trifluoroacetoxy)iodo]benzene
PPA	=	Phenylpropanolamine
PPTS	=	Pyridinium p-toluenesulfonate
Pr	=	Propyl
Py	=	Pyridine
rt	=	room temperature
SEM	=	2-(Trimethylsilyl)ethoxymethyl
TBAF	=	Tetrabutylamonium fluoride

TBS	=	tert-butyldimethylsilyl
TEA	=	Triethylamine
Tf	=	Triflate
TFA	=	Trifluroacetic acid
THF	=	Tetrahydrofuran
TMS	=	Trimethylsilyl
Ts	=	Tosyl

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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