Review

Synthetic Approaches to the Lamellarins—A Comprehensive Review

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Abstract: The present review discusses the known synthetic routes to the lamellarin alkaloids published until 2014. It begins with syntheses of the structurally simpler type-II lamellarins and then focuses on the larger class of the 5,6-saturated and -unsaturated type-I lamellarins. The syntheses are grouped by the strategy employed for the assembly of the central pyrrole ring.

Keywords: lamellarins; pyrroles; alkaloids; marine natural products; total synthesis

1. Introduction

The Lamellarins were first isolated by Faulkner and co-workers in 1985 from the prosobranch mollusc Lamellaria sp. [1–11] and represent a group of more than 50 polycyclic marine alkaloids which contain a central pyrrole moiety. The pyrrole ring may be part of a fused pentacyclic skeleton of the 6H-chromeno[4’,3’:4,5]pyrrolo[2,1-a]isoquinolin-6-one type possessing a partially saturated (type Ia) or fully unsaturated (type Ib) isoquinoline moiety [12–15]. Furthermore, structurally simpler representatives of the lamellarins containing a 3,4-diaryl substituted pyrrole core (type II) are known (Figure 1) [4,5]. Their substitution in terms of a varying oxygenation and O-substitution pattern provides the basis for their structural diversity as well as for notable differences in their biological activity.
Many lamellarins were found to exhibit significant biological effects on mammalian cells or even viruses, such as antiproliferative and multidrug resistance reversal activity, cytotoxicity, or the inhibition of HIV-1 integrase [17–23]. Structure activity relationships were investigated with a particular emphasis on lamellarin D, the most cytotoxic representative of the lamellarins [24–28]. These studies resulted in a pharmacophore model explaining the structural features required for inhibiting the action of eukaryotic topoisomerase I, an enzyme required for transcription and replication of DNA [29–36]. In order to provide samples of the natural lamellarins or their synthetic derivatives for biomedical research [37–41], various synthetic strategies have been developed. While synthetic, biological and biomedical as well as biophysical aspects of the lamellarins have already been the subject of various reviews [42–64], we herein present an overview of all synthetic approaches published until today (2014). The syntheses are grouped by the class of the lamellarin synthesized (type II vs. type Ia/Ib) as well as by the strategy used for the construction and/or decoration of the central pyrrole ring.

2. Syntheses of type-II Lamellarins

2.1. Fürstner 1995 [65]

A decade after the discovery of the lamellarins [1] Fürstner and co-workers reported in 1995 the first total synthesis of a type-II lamellarin [65] characterized by a non-fused pyrrole moiety. In his approach to lukinaol A (6), lamellarin O dimethyl ether (5) was used as an intermediate. The route started with a Scheffer-Weitz-epoxidation of enone 1 followed by Lewis acid-mediated rearrangement and condensation with hydroxylamine to afford isoxazole 2. Upon reductive cleavage of the N-O bond, condensation with methyl oxalyl chloride and McMurry-type cyclization with Ti-graphite, the 3,4,5-trisubstituted pyrrole was formed which readily yielded lamellarin O dimethyl ether (5) upon N-alkylation with 2-bromo-4’-methoxyacetophenone (4) in 21% over six steps (Scheme 1).

This and any further mentioned yields as well as the numbers of synthetic steps given in this review will, if not stated otherwise, refer to the respective data of the longest linear sequence as provided by the authors themselves. In case of convergent syntheses with a shorter but lower-yielding branch, the overall yield stated refers to the yield-limiting sequence.
2.2. Banwell 1997 [66]

Cross-couplings such as Stille, Suzuki or Negishi reactions served as the key steps in the synthesis of lamellarin O, lamellarin Q and lukianol A by Banwell and co-workers. The TIPS-protected pyrrole 7 was tribrominated with three equivalents of N-bromosuccinimide to form the tribromo derivative which was subjected to halogen-lithium exchange with phenyllithium followed by quenching with methyl chloroformate to afford dibromopyrrole 2-carboxylate 8. Lamellarin Q (10) was then synthesized by twofold Stille cross-coupling with aryl stannane 9 and subsequent desilylation with Bu4NF in 58% over four steps starting from 7. To prevent O-alkylation, the synthesis of lamellarin O was initiated with an N-desilylation followed by twofold Stille cross-coupling with aryl stannane 9. The coupling product 11 was subjected to N-alkylation with 2-bromo-4'-methoxyacetophenone (4) followed by desilylation with Bu4NF to provide lamellarin O (12) in 45% over six steps. The authors reported that no significant quantities of mono-arylated pyrroles were formed even in the case of shorter reaction times or equimolar amounts of the coupling partner. Hence, differentially diarylated pyrroles were not readily accessible by this approach (Scheme 2).

Banwell and co-workers demonstrated a method to overcome this limitation by regioselective halogen-lithium exchange and subsequent transmetallation into an organozinc derivative, thus allowing the differentiation between positions 3 and 4 in the pyrrole unit.

2.3. Boger 1999 [67]

An azadiene Diels-Alder strategy, namely a 1,2,4,5-tetrazine-1,2-diazine-pyrrole transformation sequence, was used by Boger and co-workers for the construction of the lamellarin framework. The pyrrole moiety was thus assembled by a [4+2] cycloaddition/cycloreversion reaction followed by a reductive ring transformation, a method infrequently used for the construction of five membered heteroaromatic systems. Starting from benzyl protected aryl acetylene 13 and aryl iodide 14, the acetylenic precursor 15 was prepared by Sonogashira-coupling. The undesired homocoupling of the alkyne component was suppressed by its slow addition to a solution of the iodide 14.
Cycloaddition/cycloreversion of tolan 15 to 1,2,4,5-tetrazine 16 gave 1,2-diazine 17 which was subjected to zinc-mediated reductive ring contraction followed by N-alkylation with 2-bromo-4′-methoxyacetophenone (4). Selective hydrolysis of the symmetrical diester 18 with lithium hydroxide provided the monoacid 19 which was decarboxylated in the presence of an excess of trifluoroacetic acid. Subsequent hydrogenolysis afforded lamellarin O (12) in 34% overall yield over seven steps (Scheme 3).

Scheme 2. Synthesis of lamellarins O and Q by Banwell et al. [66].

Scheme 3. Synthesis of lamellarin O by Boger et al. [67].
2.4. Álvarez 2004 [68]

A solid phase synthesis of lamellarin Q and O was reported by Álvarez and co-workers. They employed a variation of Banwell’s route of 1997 (vide supra) [66] which was adapted to the requirements of solid phase organic chemistry. Different strategies of linking the central pyrrole unit to the resin were investigated while linking through the nitrogen was ruled out due to the lacking flexibility in introducing diversity at this position.

The resin-bound pyrrole 23 was obtained by Negishi cross-coupling of the highly functionalized organozinc reagent 22, the preparation and utility of which had been demonstrated earlier by Banwell, with the resin-bound iodophenol 21. A quantitative coupling yield was ensured by using a tenfold excess of the haloarene. Two possible routes, either with the zinc attached to the immobilized reactant or to the soluble coupling partner, were taken into account. While the zinc derivative of resin-bound pyrrole failed to meet the expectations, Suzuki-Miyaura cross-coupling reaction of 23 with boronic acid 24 provided the corresponding diarylpyrrole 25. Treatment with AlCl₃ induced a simultaneous N- and O-deprotection as well as the cleavage from the resin, yielding lamellarin Q (10) in 13% yield. On the other hand, N-desilylation with NH₄F followed by N-alkylation of 26 with 2-bromo-4′-methoxyacetophenone (4) and subsequent O-deprotection/cleavage with AlCl₃ provided lamellars O (12) and Q (10) as a mixture which proved to be impossible to separate by HPLC (Scheme 4).

Scheme 4. Synthesis of lamellarins O and Q by Álvarez et al. [68].

2.5. Iwao 2008 [69]

The Suzuki-Miyaura cross-coupling approach used by Banwell in 1997 (vide supra) [66] was refined by Iwao and co-workers in the synthesis of lamellarins O, P, Q, and R. Therefore, N-benzenesulfonyl-3,4-dibromopyrrole (28) was subjected to twofold Suzuki-Miyaura cross-coupling providing the diarylpyrrole 29. The dibromopyrrole intermediate 28 is readily available from pyrrole (27) by sulfonylation and bromination with Br₂ in acetic acid in 28% over two steps. The kinetically
disfavored β-bromination becomes practicable under thermodynamic conditions in acidic medium. In contrast to the Banwell route, the ester moiety was introduced on a later stage by lithiating diarylpyrrole 29 with LDA and subsequent quenching with methyl chloroformate. Upon N-deprotection with Bu4NF, pyrrole 30 was obtained which was further deprotected with BCl3 (Iwao had demonstrated already in his synthesis of 2005 that BCl3 is a selective reagent for the cleavage of benzyl or isopropyl ethers in lamellarin precursors without affecting methyl ethers, which on the other hand are easily removed by BBr3—vide infra) to afford lamellarin Q (10) in 7% over seven steps (25% from dibromopyrrole 28). N-Alkylation of 30 with the corresponding bromide 31 followed by cleavage of the isopropyl ethers with BCl3 afforded lamellarin O (12) and P (32) in 11% and 12% over eight steps, respectively (40% and 43% from 28). Lamellarin R (33) was synthesized by a Chan-Lam-Evans-type N-arylation of 30 followed by O-deprotection with BCl3 in 8% over eight steps (29% from 28, Scheme 5).

Scheme 5. Synthesis of lamellarins O, P, Q and R by Iwao et al. [69].

2.6. Jia 2011 [70]

Keeping the structural properties of the lamellarins in mind and considering the differences between type I and type II lamellarins, it appears reasonable to assume that the type II structures precede those of type I in the biosynthesis. In this context, Jia and co-workers reported a biomimetic approach comprising three oxidative ring closures, reactions that are commonly seen in biosynthetic pathways towards densely functionalized secondary metabolites.

Starting from p-methoxyphenylacetaldehyde (34) and p-anisidine (35), AgOAc-mediated oxidative coupling afforded pyrrole 36 in the key step of Jia’s elegant synthesis. Vilsmeier-Haack formylation followed by Pinnick/Lindgren oxidation (under the optimized conditions discussed in 5.4) provided carboxylic acid 37 which was methylated with TMSCHN2 to afford lamellarin R (33) after a threefold O-demethylation with BBr3 in 53% over five steps (Scheme 6).
2.7. Vazquez 2012 [71]

The Paal-Knorr pyrrole synthesis has been chosen by Vazquez and co-workers as an alternative key step for their synthesis of lamellarins O (12) and Q (10). Here, a 2,3-diarylsuccinonitrile was used as a 1,4-dicarbonyl analogue. The approach is based on the Knoevenagel condensation between aldehyde 38 and arylacetonitrile 39 followed by conjugate addition of cyanide to the resulting cyanostilbene. Upon reduction with DIBAL-H the dialdehyde was formed in situ and cyclized to the diarylpyrrole 40 under slightly acidic pH by addition of sodium dihydrogen phosphate. Introduction of the ester moiety by trichloroacetyl chloride failed. However, addition of Steglich’s 4-dimethylaminopyridine circumvented this problem. The methyl ester 41 resulted from methanolysis of the trichloroacetylated compound. Direct hydrogenolysis of the benzyl ethers afforded lamellarin Q (10) in 28% over six steps, whereas preliminary N-alkylation with 2-bromo-4′-methoxyacetophenone (4) followed by hydrogenolysis provided lamellarin O (12) in 25% over seven steps. The use of benzyl ethers remediated the need for strong Lewis-acids for O-protection (Scheme 7).

**Scheme 6.** Synthesis of lamellarin R by Jia *et al.* [70].

**Scheme 7.** Synthesis of lamellarins O and Q by Vazquez *et al.* [71].
3. Syntheses of Type I-Lamellarins—Approaches via Halogenation and Cross-Coupling Reactions

3.1. Iwao 2003 (lamellarin G trimethyl ether) [72]-2006 (lamellarin D, L and N) [73]-2006 (lamellarin α 20-sulfate) [74]-2010 (lamellarin α 20-sulfate, α 13-sulfate and α 13,20-disulfate) [75]

The strategy of using cross-coupling reactions to form the diarylpyrrole moiety for type II lamellarins was further investigated by Iwao and co-workers to allow the synthesis of the more complex type I-lamellarins. Commonly, lamellarin G trimethyl ether serves as a benchmark compound for comparing the efficiency of syntheses of the lamellarins as it obviates any protecting group chemistry and lacks the structural differentiation of the E- and F-ring precursor.

For lamellarin G trimethyl ether (48), the synthesis started with commercially available homoveratrylamine (42). N-dialkylation with methyl bromoacetate followed by Hinsberg pyrrole cyclization with dimethyl oxalate provided the pentasubstituted pyrrole 43 (Scheme 8). Suzuki-Miyaura cross-coupling of the bistriflate derived from 43 to an arylboronic acid 44 (2.2 to 3.0 equiv.) afforded the diarylated pyrrole, whereas a stoichiometric amount of the arylboronic acid 44 primarily produced the monoarylated pyrrole 45. Therefore, the sequential introduction of different arylboronic acids was feasible, a necessity for the formation of type I-lamellarins with respect to the regioselective construction of the D-ring lactone, i.e., the discrimination of the rings E and F. Thus, one of the arylboronic acids (46) incorporated a MOM-protected phenolic function in ortho position to achieve lactonization upon acidic deprotection. To a small extent, lactone 47 was already formed as a by-product of the cross-coupling reaction. Saponification of the second methyl ester followed by Cu$_2$O-catalyzed decarboxylation afforded the per-O-methylated ningalin B. Formation of the dihydroisoquinoline moiety (AB unit) was effected with a hypervalent iodine reagent under Kita’s biaryl coupling conditions (PIFA/BF$_3$·Et$_2$O) [76]. Lamellarin G trimethyl ether (48) was obtained in 12% yield over nine steps.

The synthesis could be shortened by applying a Pd(II)-mediated decarboxylative cyclization on monoacid 47, a method inspired by the Pd(0)-mediated decarboxylative cyclization of the analogous bromoacid 159 described by Steglich and co-workers in a previous article [77]. In this case, lamellarin G trimethyl ether (48) was obtained in 10% yield over eight steps. The ring closure via the Pd(II) salt proceeded regioselectively, presumably due to steric hindrance. As a side reaction, the unproductive decarboxylation of the pyrrole was observed (12%).

In contrast, predefining the hydroxy-methoxy-substitution pattern of the A-subunit, as found in lamellarins D (57), L (55) and N (58), was achieved by their introduction as a 3,4-dialkoxy-substituted aryl aldehyde. Starting from isopropyl-protected isovanillin, a sequence comprising nitroaldol condensation with CH$_3$NO$_2$, LiAlH$_4$-reduction, N-dialkylation with methyl bromoacetate and Hinsberg pyrrole cyclization with dimethyl oxalate provided the common pentasubstituted pyrrole 49 (Scheme 9). Double O-triflylation with Tf$_2$O furnished the pivotal bistriflate 50 in 32% over five steps.
Along these lines, the target compounds were obtained in total yields of 18% (lamellarin D, 12 steps), 19% (lamellarin L, 11 steps) and 16% (lamellarin N, 12 steps), respectively. Similar results as for the synthesis of lamellarin G trimethyl ether (48) were encountered in the alternative construction of the AB-subunit by Pd(II)-mediated decarboxylative cyclization with slightly lower yields (14%, 14%, and 12%, respectively) and the concomitant formation of the decarboxylated by-products (14% for lamellarin D-precursor, 15% for lamellarin N-precursor, Scheme 9).

In 2006, Iwao and co-workers extended their protocol by employing differentially protected aryl subunits E and F (isopropyl ether on F, benzyl ether on E) to obtain the selectively mono-protected pyrrole 60 in 32% over eleven steps, starting from homoveratrylamine (42). Thereby, diverse sulfated lamellarins should be available for structure-activity relationship studies. Treatment with trichloroethyl chlorosulfate followed by isopropyl ether cleavage with BCl₃ provided the trichloroethyl sulfate. Finally, reductive deprotection with Zn/ammonium formate and subsequent ion exchange (Amberlite IRC-50, Na⁺-form) gave lamellarin α 20-sulfate (61) in 24% over 14 steps (Scheme 10). Analogously, lamellarin α 13-sulfate (67) and lamellarin α 13,20-disulfate (68) were successfully synthesized from common differentially protected intermediate 66 by Iwao’s group in 5%, 6% and 9% yield over 15, 15, and 14 steps, respectively (starting from 42). In contrast to their previous work, MOM-protection instead of the isopropyl ethers was used in combination with a different order of the Suzuki cross-couplings and closure of the lactone ring prior to the second arylation (Scheme 11).
Scheme 9. Synthesis of lamellars D, N and L by Iwao et al. [73].

Scheme 10. Synthesis of lamellarin α 20-sulfate by Iwao et al. [74].
Scheme 11. Synthesis of lamellarins α 13-sulfate, α 20-sulfate and α 13,20-disulfate by Iwao et al. [75].

3.2. Handy 2004 [78]

The first total synthesis of type I-lamellarins starting from pyrrole itself was reported by Handy and co-workers in 2004. A triply iterative halogenation/cross-coupling reaction sequence was applied in a regioselective fashion to obtain lamellarin G trimethyl ether as the benchmark compound for a modular synthesis of natural lamellarins.

Initially, bromopyrrole ester 69 (prepared in three steps from pyrrole, no yield stated) was N-protected with a Boc-group prior to Suzuki-Miyaura coupling with 3,4-dimethoxyphenylboronic acid to avoid extensive dehalogenation. A modest excess (2–3 equiv.) of the boronic acid was required to achieve full conversion. Regioselective bromination with NBS at the more reactive 5-position of pyrrole 70 followed by a second Suzuki coupling with arylboronic acid 71 provided pyrrole 72, while no protection of the free hydroxyl group was necessary. The dihydroisoquinoline moiety was established by O-tosylation of the primary alcohol and subsequent intramolecular N-alkylation. A final bromination followed by a third Suzuki coupling with arylboronic acid 74 and simultaneous lactonization afforded lamellarin G trimethyl ether (48) in 10% over eight steps starting from pyrrole.
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It is noteworthy that the final cross-coupling required extensive optimization due to low initial yields, and an improvement from 8% to 46% in that particular step could be achieved although a large excess of boronic acid was necessary (8 equiv.) and the main product (51%) still was the dehalogenated compound 73 (Scheme 12).

**Scheme 12.** Synthesis of lamellarin G trimethyl ether by Handy et al. [78].

3.3. Álvarez 2005 [79]

Lamellarin D was synthesized by Álvarez and co-workers starting from pyrrole ester 75 (available in two steps from pyrrole itself), thus presenting a generally applicable synthesis for other lamellarins, as lamellarin D already requires a regiodifferentiation strategy due to its unsymmetrical hydroxy/methoxy substitution pattern.

The AB subunit of the lamellarins was established by N-alkylation of pyrrole ester 75 with tosylate 76 which itself was prepared in a six step reaction sequence including Baeyer-Villiger oxidation, O-isopropylation, bromination, Wittig homologation, reduction and O-tosylation in 27% overall yield. Palladium-catalyzed Heck-type cyclization followed by a regioselective bromination provided tricyclic building block 77 which was subjected to Suzuki-Miyaura cross-coupling, subsequent O-isopropylation of the phenolic group and a second bromination-Suzuki cross-coupling sequence, as already described by Handy and co-workers [78]. The introduction of the aryl unit requires a large excess of boronic acid 80, presumably due to its steric hindrance. Introduction of the 5,6-double bond was accomplished by DDQ oxidation. Finally, cleavage of the isopropyl ethers with AlCl3 followed by acidic lactonization afforded lamellarin D (57) in 3% over 16 steps (Scheme 13).
3.4. Banwell 2011 [80]

An entirely modular approach to the type I-lamellarins was reported by Banwell and co-workers. It consists of the successive attachment of prefunctionalized aryl units to the pyrrole moiety via Suzuki-Miyaura cross-couplings and a decarboxylative Heck reaction to close the B-ring.

The construction of the regioselectively functionalized pyrrole 84 started from Boc-protected pyrrole 82 with a double bromination at C2 and C5, double halogen-lithium exchange and quenching with methyl chloroformate to afford diester 83. Treatment of 83 with N-iodosuccinimide (2 equiv.) followed by zinc promoted desymmetrization provided iodopyrrole 84 which was subjected to Suzuki coupling with ortho-hydroxy boronate ester 85, simultaneously forming the lactone subunit as already encountered in Iwao’s approach [72]. Thereafter, bromination with N-bromosuccinimide followed by N-alkylation under Mitsunobu conditions and Suzuki coupling with the corresponding boronate ester afforded pyrrole 88. Saponification and treatment with p-toluenesulfonic acid gave the fused pyrrole carboxylate which underwent palladium-mediated cyclization under decarboxylation.

Accordingly, lamellarin G trimethyl ether (48) was obtained in 3% over 10 steps and general applicability was shown with the first total synthesis of lamellarin S (90) in 7% over 11 steps from 3,4-diisopropoxybenzaldehyde. In the latter case, the isopropyl ethers were cleaved following the commonly used BCl3 protocol (Scheme 14).
3.5. Iwao 2014 [81]

Iwao and co-workers recently developed a slightly different route from dibromopyrrole 91, the intermediate also used in Banwell’s previously described strategy (vide supra) [80]. Instead of converting both bromine substituents into methoxycarbonyl units, the authors chose to convert only one, and attached the A-ring at an early stage, a connection done at a much later stage by Banwell and co-workers who attached the A-ring by closing the B-ring in the ultimate step (except deprotections). Suzuki-Miyaura cross-coupling with boronic acid 92 affords arylated pyrrole 93. Bromination of 93 proceeded regioselectively as in the synthesis of Álvarez [79]. Suzuki coupling, final bromination at the remaining position of the pyrrole ring, followed by another Suzuki coupling (each with a different arylboronic acid) yielded the lactone precursor 97. Acidic removal of the MOM group resulted in closure of the lactone ring. Two possible pathways for annulation of the B-ring via initial N-alkylation were attempted, with 2-bromoethyl phenyl sulfide (Pummerer route) or bromoacetaldehyde dimethyl acetal as two-carbon homologation agents. N-alkylation of the lactone with 2-bromoethyl phenyl sulfide followed by oxidation and TMSOTf mediated Pummerer cyclization (Craig-modification) provided phenylthio-lamellarin 99, whereas the application of standard reaction conditions (excess of triflic anhydride) mainly led to the reduced precursor. Radical desulfurization of 99 with Bu3SnH/AIBN provided access to saturated lamellarins (type Ia), whereas oxidation with m-CPBA followed by elimination of the intermediate sulfoxide generated unsaturated lamellarins (type Ia). Hence, an
additional oxidative step as hitherto realized by treatment with DDQ was not required. Alternatively, N-alkylation of the lactone with bromoacetaldehyde dimethyl acetal followed by acid catalyzed cyclization (TfOH) of acetal 100 afforded unsaturated lamellarins in a more convenient and shorter fashion. In summary, lamellarin L (55) and N (58) were obtained in 29% and 34% over 13 steps, respectively. Alternatively, lamellarin N was obtained in 42% yield over 11 steps using the acetal based annulation route (Scheme 15).

4. Syntheses of Type I-lamellarins—Approaches via N-Ylide-Mediated Pyrrole Ring Formation

4.1. Iwao 1997 [82]

Iwao and co-workers reported the earliest synthesis of the most cytotoxic and potent representative of the lamellarins, lamellarin D [24] as well as the fully demethylated lamellarin H by assembly of the pyrrole unit at a later stage. The required papaverine derivative 101 was obtained from O-benzylisovanillin after a sequence of nitroaldol condensation, conjugated addition of methanol, LiAlH₄-reduction, amide condensation and Bischler-Napieralski cyclization in 26% over five steps.
The MOM-protected benzoate 102 was obtained in 49% over four steps from methyl 2,4-dihydroxybenzoate by O-benzylation, bromination, Br/OMe exchange and protection with MOM-Cl.

After benzylic deprotonation with LDA, 101 was reacted with benzoate 102 and furnished ketone 103 which was subsequently N-alkylated with ethyl bromoacetate followed by closure of the pyrrole ring. Acidic removal of the MOM-group and base promoted lactonization provided the protected type Ib-lamellarin 104. The final deprotection was achieved by hydrogenolysis to provide lamellarin D (57) in 5% over 10 steps. Alternatively, complete O-deprotection was affected by BBr₃ providing lamellarin H (105) in 4% over 10 steps from benzyl-protected isovanillín (Scheme 16).

**Scheme 16.** Synthesis of lamellarins D and H by Iwao et al. [82].

4.2. Guitián 2001 [83]

In the approach of Guitián, the pyrrole core was constructed in a [3+2]-cycloaddition of nitrone 110, obtained by a reduction/oxidation sequence from dihydropapaverine derivative 109, to arylpropiolic acid ester 108. The alkyne component 107 was synthesized starting from O-isopropylisovanillin (106) by iodination and Sonogashira coupling with TMS-acetylene. The latter compound was subjected to Baeyer-Villiger oxidation followed by hydrolysis of the resulting formate and protection as an isopropyl ether. Finally, the lithiation of the alkyne deprotected in the oxidation step and carboxylation with ethyl chloroformate provided arylpropiolate 108.

Dihydropapaverine derivative 109 was transformed into nitrone 110 by reduction with sodium borohydride followed by oxidation with disodium tungstate. [3+2]-Cycloaddition to alkyne 108 afforded the protected lamellarins. Cleavage of the isopropyl ethers with AlCl₃ provided lamellarins I (111) and K (112) in 4% and 6% over nine steps, respectively (Scheme 17).
Scheme 17. Synthesis of lamellarins I and K by Guitián et al. [83].

4.3. Ruchirawat 2001 [84]

The cyclocondensation of commercially available dihydropapaverine hydrochloride 113 with phenacyl bromide 114 was utilized by Ruchirawat and co-workers in their key step to construct almost the entire lamellarin framework with the exception of the D-ring in a single operation. Vilsmeier formylation of the free position in the pyrrole ring followed by basic deprotection and manganese (IV) oxidation of the cyclic hemiacetal 117b or, alternatively, palladium-catalyzed oxidation with bromobenzene afforded lamellarin G trimethyl ether (48) in 7% or 27% over five steps starting from 2'-hydroxy-4',5'-dimethoxyacetophenone (Scheme 18).
4.4. Ruchirawat 2004 (lamellarin K&L) [85]-2006 (28 different lamellarins) [86]-Opatz 2008 (lamellarin G trimethyl ether & lamellarin U) [87]

The Ruchirawat-group envisioned that the pentasubstituted pyrrole moiety could also arise from a cyclocondensation of a 1-benzyl-3,4-dihydroisoquinoline (122), serving as an enamine precursor, with an α-nitrocinnamate (123) in a Grob pyrrole synthesis. Both components could easily be prepared from simple starting materials, allowing a highly modular and straightforward access to the lamellarins.

At first, Ruchirawat and co-workers reported the synthesis of lamellarin L and K employing the aforementioned strategy. Later on, the authors reported the hitherto most comprehensive synthetic work including the synthesis of 28 natural and non-natural lamellarins (125). The required dihydroisoquinolines 122 were prepared in an eight step synthesis as the longest sequence starting from vanillin, isovanillin and 2,3,4-trimethoxybenzaldehyde by O-benzylation followed by nitroaldol condensation, LiAlH₄- or NaBH₄-reduction to the 2-arylethylamines 120. Treatment of these intermediates with sodium nitrite produced arylacetic acids 121, the other coupling partners for preparing the intermediates 122. This was achieved by conversion into acid chlorides and subsequent amide formation with amines 120 followed by Bischler-Napieralski cyclization. The α-nitrocinnamates 123 were in turn prepared starting from protected aromatic aldehydes in a five step sequence including Baeyer-Villiger oxidation, basic hydrolysis, repeated benzylation, Vilsmeier formylation and final Knoevenagel condensation with ethyl nitroacetate. The Grob cyclization smoothly provided the highly functionalized pyrroles 124 which were transformed into the lamellarins with a saturated B subunit by hydrogenolysis and basic lactonization. An additional three step protocol comprising O-acetylation, DDQ oxidation to establish the 5,6-double bond and subsequent deacetylation was developed for the transformation of type Ia- into type Ib-lamellarins. Unfortunately, this strategy leads to inferior yields and requires more difficult workup procedures compared to the strategy of Iwao and co-workers [73]. Nonetheless, Ruchirawat’s approach permitted the straightforward synthesis of more than two dozen lamellarins, unifying an inexpensive and a labor saving method, as only two of the steps require a chromatographic purification of the reaction products (Scheme 19).

In 2008, Opatz and co-workers reported a modified version of Ruchirawat’s synthesis which emphasized the advantages of using tetrahydroisoquinoline-1-carbonitrile 126 as a key building block for the otherwise analogous route. Acid-sensitive groups could be included in the dihydroisoquinoline moiety as the harsh conditions of the Bischler-Napieralski reaction were avoided at that stage. The pivotal α-aminonitrile 126 was prepared from homoveratrylamine in three steps and 64% yield (later improved to 84%, vide infra). Its C-benzylation after deprotonation with KHMDS directly furnished the dihydroisoquinolines 131 which were then reacted with α-nitrocinnamates 123 to produce lamellarin U (132) and lamellarin G trimethyl ether (48) in 14% and 18% overall yield over nine and eight steps, respectively (Scheme 20).
Scheme 19. Synthesis of natural and non-natural occurring lamellarins by Ruchirawat et al. [86].

Scheme 20. Synthesis of lamellarin G trimethyl ether and lamellarin U by Opatz et al. [87].

5. Synthesis of type-I Lamellarins—Miscellaneous Approaches

5.1. Banwell 1997 [88] / Faulkner 2002 [89] / Alvarez 2003 [90]

Banwell and co-workers were first to report a convergent total synthesis of type I lamellarins via an intramolecular [3+2] cycloaddition of an azomethine ylide derived from the tolane-linked dihydroisoquinolinium salt 140. The pivotal tolane 137 was synthesized from dibromostyrene 134 and iodide 136, both accessed from vanillin (two steps—quantitative yield) and isovanillin (two
steps—93%), respectively. Styrene 134 formed the lithium acetylide upon treatment with °BuLi which was transmetallated into the alkynylzinc chloride to provide tolane 137 after Negishi cross-coupling with iodide 136. Baeyer-Villiger oxidation, basic hydrolysis and DCC-mediated condensation with iodoacetic acid provided the ester 138 which readily formed the dihydroisoquinolinium salt 140. Upon deprotonation, the 1,3-dipole underwent cyclization to triisopropyllamellarin K (141). Final cleavage with AlCl₃ gave lamellarin K (112) in 58% over eight steps (Scheme 21). Along the same lines, the Banwell group reported the synthesis of lamellarin T (41%, six steps), U (132, 45%, six steps), and W (42%, seven steps), all starting from 3-isoproxy-4-methoxybenzaldehyde, in 2012 [91].

Scheme 21. Synthesis of lamellarin K by Banwell et al. [88].

Faulkner and co-workers modified Banwell’s method by introducing the 5,6-double bond at a later stage, i.e., after the pyrrole forming [3+2] cycloaddition [88] Lamellarin α (149) and lamellarin H (105) were each synthesized in 17% overall yield, starting from the isopropyl ether of isovanillin (142). Treatment of lamellarin α with DMF·SO₃ in a mixture of DMF/pyridine (4:1) provided lamellarin α 13,20-disulfate (68) in 83% yield. However, attempts to introduce a single sulfate group were unsuccessful (Scheme 22).
Álvarez and co-workers developed a solid-phase supported version of Banwell’s route [88] and were able to synthesize lamellarin U (132) in 10% overall yield. Iodophenol 151 was linked to hydroxymethyl polystyrene resin by a Mitsunobu reaction and was subjected to Sonogashira cross-coupling with acetylene 152. Lamellarin L was also obtained by an unexpected demethylation in the cleavage step and was isolated in 4% yield (Scheme 23).

5.2. Steglich 1997 (lamellarin G trimethyl ether) [92]-2000 (lamellarin L) [77]-2006 (lamellarin G & K) [93]-2009 Guptón (Steglich Synthon) [94]

Steglich and co-workers reported the very first synthesis of lamellarin G trimethyl ether (48) in a short, elegant and biomimetic fashion. Thus, a symmetrical pyrrole-2,5-dicarboxylic acid 158 containing rings A, E, and F was prepared by oxidative dimerization of 3-arylpyruvic acid 155
followed by Paal-Knorr cyclization with 2-arylethylamine 157. Treatment of dicarboxylate 158 with lead (IV) acetate led to oxidative formation of the lactone ring. The B-ring was closed by an intramolecular palladium-mediated Heck decarboxylation to afford lamellarin G trimethyl ether (48) in 33% over four steps. Until today, no shorter access to the core of the type I-lamellarins has been published (Scheme 24).

**Scheme 24.** Synthesis of lamellarin G trimethyl ether by Steglich et al. [92].

For the synthesis of lamellarin L (55), the carboxylate groups on the pyrrole ring were differentiated as a methyl and ethyl ester. Selective cleavage of the methyl ester applying a suspension of sodium cyanide in 1,3-dimethyl-3,4,5,6-tetrahydropyrimidine-2(1H)-one (DMPU), leaving the ethyl ester intact, allowed the discrimination of the attachment points for rings E and F. The required starting materials were all synthesized from the appropriate 3,4-disubstituted aromatic aldehydes which provided 2-arylethylamine 162, ethyl arylpyruvate 160 and α-brominated methyl arylpyruvate 161 in 48%, 22% and 25% over three steps, respectively. Cyclization to key intermediate 163 was initiated by deprotonation of the ethyl ester with sodium hydride followed by C-alkylation with bromide 161 and condensation of in situ formed 1,4-diketone with arylethylamine 162. After the above-mentioned differentiation of the ester units, monoacid 163 was subjected to lead (IV)-induced lactonization which exclusively formed the desired regioisomer. Saponification of the ethyl ester was effected with potassium hydroxide and the palladium-mediated decarboxylative cyclization afforded the isopropyl ether of 55. Deprotection by AlCl$_3$ gave lamellarin L (55) in 18% over nine steps (starting from O-isopropylisovanillin, Scheme 25).
The same reaction sequence was applied to the synthesis of lamellarin G (167) and K (112) which were obtained in 27% over seven steps and 18% over nine steps, respectively. The lower yield of lamellarin K may be due to the increased sterical hindrance imposed by the additional ortho-substituent (Scheme 26).

Later on, Gupton and co-workers reported two new methods for the synthesis of the intermediate 158 used by the Steglich group, one being sequential and the other one being convergent. Hence, the common intermediate 158 was prepared by the sequential route in 27% over five steps (starting from already prefunctionalized 2,3,5-trisubstituted pyrrole 168) or by the convergent route in 16% over eight steps (starting from desoxyveratroin 171, Scheme 27). Gupton also developed approaches to functionalized pyrroles suitable as precursors to type-I and type-II lamellarins and most recently published a second formal total synthesis of lamellarin G trimethyl ether [95,96].
Scheme 27. Synthesis of common intermediate 158 by Gupton et al. [94].

Scheme 28. Synthesis of lamellarin G trimethyl ether by Yadav et al. [97].

5.3. Yadav 2009 [97]

An efficient, elegant, and very short access to lamellarin G trimethyl ether (48) was published by Yadav and co-workers. Starting with a Friedel-Crafts acylation of veratrole (175) with maleic anhydride to trans-acid 176, esterification with 3,4-dimethoxyphenol (177) and intramolecular haloarylation furnished α-bromolactone 179. A substitution reaction with 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (180) and aerobic oxidation/deprotonation provided the azomethine ylide which underwent a cyclocondensation to the target lamellarin 48 which was obtained in 44% over four steps. The synthesis represents the first example of an early construction of subunit E and lactone-subunit D before the construction of the pyrrole moiety (Scheme 28).
5.4. Jia 2011 [70]

The same biomimetic approach comprising three oxidative ring closures as used in their synthesis of lamellarin R (vide supra) was employed by Jia and co-workers for a concise route to lamellarin D and H.

Starting from O-isopropylvanillin (183) and O-isopropylisovanillin (181), O-protected 2-arylethylamine 182 and 3,4-dialkoxy-substituted phenylacetaldehyde 184 were prepared. AgOAc-mediated oxidative coupling afforded pyrrole 185 in the key step. Vilsmeier-Haack formylation under standard conditions led to either decomposition or resulted in no conversion at all. However, microwave irradiation solved that problem and after various attempts, Pinnick/Lindgren oxidation was found to provide carboxylic acid, albeit in a low yield. Further optimization revealed that the ratio of the solvents dramatically affected the conversion and the outcome of the oxidation, indicating that THF/BuOH/H2O (3:3:1) as the solvent system afforded carboxylic acid 186 in high yield. Oxidative lactonization according to Steglich and annulation according to Iwao followed by DDQ-mediated dehydrogenation of the B-ring provided lamellarin D (55) after BCl3-mediated deprotection in 13% over nine steps. Cleavage of all ether groups by the stronger Lewis acid BBr3 gave lamellarin H (105) in 13% over ten steps as well (Scheme 29).

Scheme 29. Synthesis of lamellarins D and H by Jia et al. [70].

5.5. Opatz 2013 [16]

The so far highest yielding and fully modular total synthesis of the type I-lamellarins was recently reported by Opatz and co-workers. In a first key step, an extended von Miller-Plöchtl-type reaction of a quantitatively deprotonated α-aminonitrile 190 to α,β-unsaturated aldehydes 188 provided pyrrolo[2,1-a]isoquinolines 191 in high yield (both 93%). The Michael acceptors 188 as well as the bicyclic α-aminonitrile 190 were readily prepared from vanillin and homoveratrylamine (42). Vilsmeier formylation followed by Pinnick/Lindgren oxidation provided pyrrole carboxylic acids which were used without purification as crude DMF solutions due to their instability which was
observed by Jia and Ruchirawat as well [70,85]. In contrast to Jia’s protocol, 1,4-dioxane/H$_2$O (7:1) was used as the solvent in the oxidation step. Ullmann-like lactone formation mediated by copper thiophene-2-carboxylate (CuTC) served as the second key step and completed the lamellarin core. Lamellarin G trimethyl ether (48) was obtained in 67% over seven steps, dihydrolamellarin η (194) and lamellarin η (193) were obtained in 62% (eight steps) and 57% (nine steps), respectively, after optional dehydrogenation (DDQ) and BCl$_3$-promoted deprotection (Scheme 30).

Scheme 30. Synthesis of lamellarin G trimethyl ether, dihydrolamellarin η and lamellarin η by Opatz et al. [16].

5.6. Yamaguchi 2014 [98]

A concise synthesis of lamellarin C (201) and I (111) was recently presented by Yamaguchi and co-workers. The first general β-selective C-H-arylation of pyrroles was combined with an intramolecular double oxidative biaryl coupling to generate the B- and the D-ring in a single operation. Starting from 2,3,4-trimethoxybenzaldehyde (195), a sequence comprising nitroaldol condensation, LiAlH$_4$ reduction and Paal-Knorr pyrrole synthesis was employed to obtain the N-substituted pyrrole 196. Rhodium-catalyzed arylation with iodoarenes 197 occurred exclusively at C3 and was followed by treatment with trichloroacetyl chloride. Hydrolysis and esterification of the produced carboxylic acid provided phenolic ester 200. Oxidation with palladium (II)-acetate (2 equiv.) and copper (II)-acetate (6 equiv.) furnished the pentacyclic ABCDE-framework after preparative thin layer chromatography (22 and 46% yield over 3 steps, respectively). The singly coupled side product could be isolated by gel permeability chromatography from the complex residual mixture. Global deprotection with BCl$_3$ afforded lamellarins I (111) and C (201) in 3% over eight steps (Scheme 31).
6. Conclusions

Since their discovery in 1985, the lamellarin alkaloids have attracted the attention of scientists from the areas of biochemistry, synthetic organic chemistry, pharmaceutical and medicinal chemistry as well as biology, pharmacology, and medicine. Since 1995, more than 30 syntheses of the original lamellarins have been published. If related pyrrole-derived alkaloids such as lukianol A, the polycitrins A and B, the polycitones A and B, storniamide A, the didemnimide A–C and the ningalin A–D are also taken into account, this number is easily doubled. The synthetic approaches to the lamellarins are not limited to the naturally occurring representatives but also permit the preparation of analogues. Moreover, they allow substantial amounts of the lamellarins to be made which are required for investigations of their biological properties. Some of the syntheses rely on hidden symmetry in their target and are not suitable for the preparation of the majority of the other lamellarins.

On the other hand, modular strategies were reported which build up the lamellarin scaffold from commercial or readily available simple starting materials. A major class of syntheses employs a cyclocondensation or a cycloaddition reaction to establish the pyrrole core from precursors already carrying the alkoxylated benzene units later to become rings A, E, and F. In a second large class of syntheses, a simple pyrrole derivative is sequentially decorated with the required aryl moieties, mostly using halogenation/cross-coupling methodology.

The most prominent advantage of the cross-coupling based strategies is the possibility to generate a multitude of substitution patterns from libraries of differentially protected or O-methylated 3,4-dihydroxyphenylboronic acids in a combinatorial fashion. On the other hand, cyclocondensation or cycloaddition based strategies allow the construction of the entire lamellarin framework from prefunctionalized precursors under avoidance of yield-diminishing long linear reaction sequences. Thus, it is not surprising that the most efficient routes belong to the latter category. A comparison of the reported syntheses of the type-I lamellarins can be found in Table 1.
| Lead Author | Year | Lamellarin | Overall Yield | Linear Steps | Starting from |
|-------------|------|------------|---------------|--------------|---------------|
| Steglich    | 1997 | G trimethyl ether | 33% | 4 | 3-(3,4-Dimethoxyphenyl)pyruvic acid |
| Banwell     | 1997 | K          | 58% | 7 | 4-Isopropoxy-3-methoxybenzaldehyde |
| Iwao        | 1997 | H          | 4%  | 10 | 3-Benzylloxy-4-methoxybenzaldehye |
| D           | 5%  | 10         | 3-Benzylloxy-4-methoxybenzaldehye |
| Steglich    | 2000 | L          | 18% | 9 | 3-Isopropoxy-4-methoxybenzaldehyde |
| Guiñán     | 2001 | I          | 4%  | 9 | 3-Isopropoxy-4-methoxybenzaldehyde |
|             |      | K          | 6%  | 9 | 3-Isopropoxy-4-methoxybenzaldehyde |
| Ruchirawat  | 2001 | G trimethyl ether | 27% | 5 | 2’-Hydroxy-4’,5’-dimethoxyacetophenone |
| Faulkner    | 2002 | H          | 17% | 9 | 3-Isopropoxy-4-methoxybenzaldehyde |
|             |      | α          | 17% | 9 | 3-Isopropoxy-4-methoxybenzaldehyde |
|             |      | α 13,20-disulfate | 14% | 10 | 3-Isopropoxy-4-methoxybenzaldehyde |
| Iwao        | 2003 | G trimethyl ether | 12% | 9 | Homoveratrylamine |
| Handy       | 2004 | G trimethyl ether | 10% | 8 | Ethyl 4-bromopyrrole-2-carboxylate |
| Álvarez     | 2005 | D          | 3%  | 16 | 3-Isopropoxy-4-methoxybenzaldehyde |
| Iwao        | 2006 | N          | 16% | 12 | 3-Isopropoxy-4-methoxybenzaldehyde |
| D           | 18% | 12         | 3-Isopropoxy-4-methoxybenzaldehyde |
| L           | 19% | 11         | 3-Isopropoxy-4-methoxybenzaldehyde |
|             |      | α 20-sulfate | 24% | 14 | Homoveratrylamine |
| Steglich    | 2006 | K          | 18% | 9 | 4-Bromo-2,3-dimethoxybenzaldehyde |
|             |      | G          | 27% | 7 | 3-Isopropoxy-4-methoxybenzaldehyde |
|             |      | I, C, T, F, K, E, dihydro-η, G trimethyl ether, J, U, L, G, χ, Y ξ, B, W, ε, M, X, η, J-DB, α, N, G-DB, D, Y-DB | 5%–34% | 8–9 | Veratraldehyde |
|             |      |            | (saturated) | (unsaturated) | 2,3,4-Trimethoxybenzaldehyde |
|             |      |            | (saturated) | (unsaturated) | 2,4-Dibenzyllox-5-methoxybenzaldehyde |
|             |      |            |           |            | 2,5-Dibenzyllox-4-methoxybenzaldehyde |
|             |      |            |           |            | 2-Benzylloxy-4,5-dimethoxybenzaldehyde |
Table 1. Cont.

| Authors | Year | Building Block | Percentage | Steps | Product Name |
|---------|------|----------------|------------|-------|--------------|
| Opatz   | 2008 | U G trimethyl ether | 14% | 9 | 3-Benzyl-oxy-4-methoxybenzaldehyde |
| Yadav   | 2009 | G trimethyl ether | 18% | 8 | Veratraldehyde |
| Iwao    | 2010 | α 20-sulfate G trimethyl ether | 6% | 15 | 3-Isopropoxy-4-methoxybenzaldehyde |
| Iwao    | 2010 | α 13-sulfate | 4% | 15 | 3-Isopropoxy-4-methoxybenzaldehyde |
| Iwao    | 2010 | α 13,20-disulfate | 9% | 14 | 3-Isopropoxy-4-methoxybenzaldehyde |
| Banwell | 2011 | G trimethyl ether S | 7% | 11 | N-Boc-pyrrole |
| Banwell | 2011 | D 3,4-Diisopropoxybenzaldehyde | 13% | 9 | 4-Isopropoxy-3-methoxybenzaldehyde |
| Banwell | 2011 | H 4-Isopropoxy-3-methoxybenzaldehyde | 13% | 9 | |
| Banwell | 2012 | T 3-Isopropoxy-4-methoxybenzaldehyde | 41% | 6 | |
| Banwell | 2012 | W 3-Isopropoxy-4-methoxybenzaldehyde | 42% | 7 | |
| Banwell | 2012 | U 3-Isopropoxy-4-methoxybenzaldehyde | 45% | 6 | |
| Opatz   | 2013 | η 4-Benzyloxy-3-methoxyphenylacetonitrile | 57% | 9 | |
| Opatz   | 2013 | dihydro-η 4-Benzyloxy-3-methoxyphenylacetonitrile | 62% | 8 | |
| Opatz   | 2013 | G trimethyl ether 3,4-Dimethoxyphenylacetonitrile | 69% | 7 | |
| Iwao    | 2014 | L N-Boc-2,5-dibromopyrrole | 30% | 13 | |
| Iwao    | 2014 | N N-Boc-2,5-dibromopyrrole | 42% | 11 | |
| Yamaguchi | 2014 | C 2,3,4-Trimethoxybenzaldehyde | 3% | 8 | |
| Yamaguchi | 2014 | I 2,3,4-Trimethoxybenzaldehyde | 3% | 8 | |

The steps in the longest linear sequence were counted from the O-protected building blocks as the majority of the authors used this definition.
In the history of lamellarin synthesis, around 20 more or less different strategies have been devised until today. They exhibit a significant span of overall yields as well as the numbers of steps in the longest linear sequence but clearly, a decision on the suitability of an approach for solving a given synthetic problem also has to take into account the availability and price of the starting materials as well as the catalysts and reagents involved, let alone ecological issues which may become key factors in large-scale synthesis.

Due to the considerable attractivity of the lamellarin alkaloids, both from a biomedical and from a synthetic perspective, new approaches will continue to be developed. They will contribute to a better understanding of the chemistry as well as the biological activity of this compound class and may allow the rational design and preparation of more potent and/or more selective derivatives for prospective medicinal and pharmacological research.

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Author Contributions

This review was conceived, designed, written and polished by Dennis Imbri, Johannes Tauber and Till Opatz. All authors discussed the content of the review.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Andersen, R.J.; Faulkner, D.J.; He, C.H.; Van Duyne, G.D.; Claridy, J. metabolites of the marine prosobranch mollusk Lamellaria sp. J. Am. Chem. Soc. 1985, 107, 5492–5495.
2. Lindquist, N.; Fenical, W.; van Duyne, G.D.; Claridy, J. New alkaloids of the lamellarin class from the marine ascidian Didemnum chartaceum. J. Org. Chem. 1988, 53, 4570–4574.
3. Carroll, A.R.; Bowden, B.F.; Coll, J.C. Studies of Australian ascidians. I. Six new lamellarin-class alkaloids from a colonial ascidian, Didemnum sp. Aust. J. Chem. 1993, 46, 489–501.
4. Urban, S.; Butler, M.S.; Capon, R.J. Lamellarins O and P: New aromatic metabolites from the Australian marine sponge Dendrilla cactos. Aust. J. Chem. 1994, 47, 1919–1924.
5. Urban, S.; Hobbs, L.; Hooper, J.N.A.; Capon, R.J. Lamellarins Q and R: New aromatic metabolites from an Australian marine sponge, Dendrilla cactos. Aust. J. Chem. 1995, 48, 1491–1494.
6. Urban, S.; Capon, R.J. Lamellarin-s: A new aromatic metabolite from an Australian tunicate, Didemnum sp. Aust. J. Chem. 1996, 49, 711–713.
7. Reddy, M.V.R.; Faulkner, D.J.; Venkateswarlu, Y.; Rao, M.R. New lamellarin alkaloids from an unidentified ascidian from the Arabian Sea. Tetrahedron 1997, 53, 3457–3466.
8. Davis, R.A.; Carroll, A.R.; Pierens, G.K.; Quinn, R.J. New lamellarin alkaloids from the Australian ascidian, Didemnum chartaceum. J. Nat. Prod. 1999, 62, 419–424.

9. Ham, J.; Kang, H. A novel cytotoxic alkaloid of lamellarin class from a marine ascidian Didemnum sp. Bull. Korean Chem. Soc. 2002, 23, 163–166.

10. Krishnaiah, P.; Reddy, V.L.N.; Venkataramana, G.; Ravinder, K.; Srinivasulu, M.; Raju, T.V.; Ravikumar, K.; Chandrasekar, D.; Ramakrishna, S.; Venkateswarlu, Y. New lamellarin alkaloids from the Indian ascidian Didemnum obscurum and their antioxidant properties. J. Nat. Prod. 2004, 67, 1168–1171.

11. Reddy, S.M.; Srinivasulu, M.; Satyanarayana, N.; Kondapi, A.K.; Venkateswarlu, Y. New potent cytotoxic lamellarin alkaloids from Indian ascidian Didemnum obscurum. Tetrahedron 2005, 61, 9242–9247.

12. Koeck, M.; Reif, B.; Fenical, W.; Griesinger, C. Differentiation of HMBC two-and three-bond correlations: A method to simplify the structure determination of natural products. Tetrahedron Lett. 1996, 37, 363–366.

13. Reif, B.; Kock, M.; Kerssebaum, R.; Kang, H.; Fenical, W.; Griesinger, C. Adequate, a new set of experiments to determine the constitution of small molecules at natural abundance. J. Magn. Reson. Ser. A 1996, 118, 282–285.

14. Reif, B.; Koeck, M.; Kerssebaum, R.; Schleucher, J.; Griesinger, C. Determination of $^1J$, $^2J$, and $^3J$ carbon-carbon coupling constants at natural abundance. J. Magn. Reson. Ser. B 1996, 112, 295–301.

15. Fukuda, T.; Itoyama, R.; Minagawa, T.; Iwao, M. Rotational energy barrier around the C1-C11 single bond in lamellarins: A study by variable-temperature NMR. Heterocycles 2014, 88, 1121–1133.

16. Imbri, D.; Tauber, J.; Opatz, T. A high-yielding modular access to the lamellarins: Synthesis of lamellarin G trimethyl ether, lamellarin η and dihydrolamellarin η. Chem. Eur. J. 2013, 19, 15080–15083.

17. Quesada, A.R.; Gravalos, M.D.G.; Puentes, J.L.F. Polyaromatic alkaloids from marine invertebrates as cytotoxic compounds and inhibitors of multidrug resistance caused by P-glycoprotein. Br. J. Cancer 1996, 74, 677–682.

18. Burnham, B.S.; Gupton, J.T.; Krumpe, K.; Webb, T.; Shuford, J.; Bowers, B.; Warren, A.E.; Barnes, C.; Hall, I.H. Cytotoxicity of substituted alkyl-3,4-bis(4-methoxyphenyl) pyrrole-2-carboxylates in L1210 lymphoid leukemia cells. Arch. Pharm. 1998, 331, 337–341.

19. Reddy, M.V.R.; Rao, M.R.; Rhodes, D.; Hansen, M.S.T.; Rubins, K.; Bushman, F.D.; Venkateswarlu, Y.; Faulkner, D.J. Lamellarin α 20-sulfate, an inhibitor of HIV-1 integrase active against HIV-1 virus in cell culture. J. Med. Chem. 1999, 42, 1901–1907.

20. Liu, R.; Liu, Y.; Zhou, Y.-D.; Nagle, D.G. Molecular-targeted antitumor agents: Neolamellarins from the marine sponge Dendrilla nigra inhibit hypoxia-inducible factor-1 activation and secreted vascular endothelial growth factor production in breast tumor cells. J. Nat. Prod. 2007, 70, 1741–1745.

21. Baunbaek, D.; Trinkler, N.; Ferandin, Y.; Lozach, O.; Ploypradith, P.; Rucirawat, S.; Ishibashi, F.; Iwao, M.; Meijer, L. Anticancer alkaloid lamellarins inhibit protein kinases. Mar. Drugs 2008, 6, 514–527.
22. Gallego, M.A.; Ballot, C.; Kluza, J.; Hajji, N.; Martorati, A.; Castera, L.; Cuevas, C.; Formstecher, P.; Joseph, B.; Kroemer, G.; et al. Overcoming chemoresistance of non-small cell lung carcinoma through restoration of an AIF-dependent apoptotic pathway. Oncogene 2008, 27, 1981–1992.

23. Huang, X.-C.; Xiao, X.; Salim, A.A.; Capon, R.J.; Zhang, Y.-K.; Talete, T.T.; Chen, Z.-S. Lamellarin O, a pyrrole alkaloid from an Australian marine sponge, Ianthella sp., reverses BCRP-mediated drug resistance in cancer cells. Mar. Drugs 2014, 12, 3818–3837.

24. Vanhuyse, M.; Kluza, J.; Tardy, C.; Otero, G.; Cuevas, C.; Bailly, C.; Lansiaux, A. Lamellarin D: A novel pro-apoptotic agent from marine origin insensitive to P-glycoprotein-mediated drug efflux. Cancer Lett. 2005, 221, 165–175.

25. Kluza, J.; Gallego, M.-A.; Loyens, A.; Beauvillain, J.-C.; Fernandez Sousa-Faro, J.-M.; Cuevas, C.; Marchetti, P.; Bailly, C. Cancer cell mitochondria are direct proapoptotic targets for the marine antitumor drug lamellarin D. Cancer Res. 2006, 66, 3177–3187.

26. Ballot, C.; Kluza, J.; Martorati, A.; Nyman, U.; Formstecher, P.; Joseph, B.; Bailly, C.; Marchetti, P. Essential role of mitochondria in apoptosis of cancer cells induced by the marine alkaloid lamellarin D. Mol. Cancer Ther. 2009, 8, 3307–3317.

27. Ballot, C.; Kluza, J.; Lancel, S.; Martorati, A.; Hassoun, S.M.; Mortier, L.; Vienne, J.-C.; Briand, G.; Formstecher, P.; Bailly, C.; et al. Inhibition of mitochondrial respiration mediates apoptosis induced by the anti-tumoral alkaloid lamellarin D. Apoptosis 2010, 15, 769–781.

28. Khiati, S.; Seol, Y.; Agama, K.; Dalla Rosa, I.; Agrawal, S.; Fesen, K.; Zhang, H.; Neuman, K.C.; Pommie, Y. Poisoning of mitochondrial topoisomerase I by lamellarin D. Mol. Pharmacol. 2014, 86, 193–199.

29. Facompre, M.; Tardy, C.; Bal-Mahieu, C.; Colson, P.; Perez, C.; Manzanares, I.; Cuevas, C.; Bailly, C. Lamellarin D: A novel potent inhibitor of topoisomerase I. Cancer Res. 2003, 63, 7392–7399.

30. Tardy, C.; Facompre, M.; Laine, W.; Baldeyrou, B.; Garcia-Gravalos, D.; Francesch, A.; Mateo, C.; Pastor, A.; Jimenez, J.A.; Manzanares, I.; et al. Topoisomerase I-mediated DNA cleavage as a guide to the development of antitumor agents derived from the marine alkaloid lamellarin D: Triester derivatives incorporating amino acid residues. Bioorg. Med. Chem. 2004, 12, 1697–1712.

31. Marco, E.; Laine, W.; Tardy, C.; Lansiaux, A.; Iwao, M.; Ishibashi, F.; Bailly, C.; Gago, F. Molecular determinants of topoisomerase I poisoning by lamellarins: Comparison with camptothecin and structure-activity relationships. J. Med. Chem. 2005, 48, 3796–3807.

32. Chittchang, M.; Batsomboon, P.; Ruchirawat, S.; Ploypradith, P. Cytotoxicities and structure-activity relationships of natural and unnatural lamellarins toward cancer cell lines. ChemMedChem 2009, 4, 457–465.

33. Pla, D.; Sischka, A.; Albericio, F.; Alvarez, M.; Fernandez-Busquets, X.; Anselmetti, D. Optical-tweezers study of topoisomerase inhibition. Small 2009, 5, 1269–1272.

34. Bayet-Robert, M.; Lim, S.; Barthomeuf, C.; Morvan, D. Biochemical disorders induced by cytotoxic marine natural products in breast cancer cells as revealed by proton NMR spectroscopy-based metabolomics. Biochem. Pharmacol. 2010, 80, 1170–1179.

35. Khadka, D.B.; Cho, W.-J. Topoisomerase inhibitors as anticancer agents: A patent update. Expert Opin. Ther. Pat. 2013, 23, 1033–1056.
36. Ballot, C.; Martoriat, A.; Jendoubi, M.; Buche, S.; Formstecher, P.; Mortier, L.; Kluza, J.; Marchetti, P. Another facet to the anticancer response to lamellarin D: Induction of cellular senescence through inhibition of topoisomerase I and intracellular ROS production. *Mar. Drugs* **2014**, *12*, 779–798.

37. Pungkham, H.; Swatdipakdi, N.; Theerasilp, M.; Karnkla, S.; Chittchang, M.; Ploypradith, P.; Nasongkla, N. PEG-b-PCL and PEG-b-PLA polymeric micelles as nanocarrieres for lamellarin N delivery. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* **2011**, *2011*, 3245–3248.

38. Chittchang, M.; Paul Gleeson, M.; Ploypradith, P.; Ruchirawat, S. Assessing the drug-likeness of lamellarins, a marine-derived natural product class with diverse oncological activities. *Eur. J. Med. Chem.* **2010**, *45*, 2165–2172.

39. Thipnate, P.; Chittchang, M.; Thasana, N.; Saparpakorn, P.; Ploypradith, P.; Hannongbua, S. Exploring the molecular basis for selective cytotoxicity of lamellarins against human hormone-dependent T47D and hormone-independent MDA-MB-231 breast cancer cells. *Monatsh. Chem.* **2011**, *142*, 97–109.

40. Plisson, F.; Conte, M.; Khalil, Z.; Huang, X.-C.; Piggott, A.M.; Capon, R.J. Kinase inhibitor scaffolds against neurodegenerative diseases from a southern Australian ascidian, *Didemnum* sp. *ChemMedChem* **2012**, *7*, 983–990.

41. Davis, R.A.; Vullo, D.; Maresca, A.; Supuran, C.T.; Poulsen, S.-A. Natural product coumarins that inhibit human carbonic anhydrases. *Bioorg. Med. Chem.* **2013**, *21*, 1539–1543.

42. Bailly, C. Lamellarins, from A to Z: A family of anticancer marine pyrrole alkaloids. *Curr. Med. Chem. Anti-Cancer Agents* **2004**, *4*, 363–378.

43. Cironi, P.; Albericio, F.; Alvarez, M. Lamellarins: Isolation, activity and synthesis. *Prog. Heterocycl. Chem.* **2004**, *16*, 1–26.

44. Handy, S.T.; Zhang, Y. Approaches to the synthesis of the lamellarins and related natural products. A review. *Org. Prep. Proced. Int.* **2005**, *37*, 411–445.

45. Yang, G.; Wang, A.-L.; Chen, H.-L.; You, Y.-C. Recent research progresses on lamellarins and analogous alkaloids of bioactive marine mollusce. *Chin. J. Org. Chem.* **2005**, *25*, 641–653. (In Chinese)

46. He, Y.-R.; Li, D.-P.; Yang, G.; Wang, A.-L.; You, Y.-C.; Hu, D.-H.; Yu, X.-S. Recent research progress on biological activity of lamellarins and analogous alkaloids. *Chin. J. Nat. Med.* **2007**, *5*, 150–156. (In Chinese)

47. Fan, H.; Peng, J.; Hamann, M.T.; Hu, J.-F. Lamellarins and related pyrrole-derived alkaloids from marine organisms. *Chem. Rev.* **2008**, *108*, 264–287.

48. Pla, D.; Albericio, F.; Alvarez, M. Recent advances in lamellarin alkaloids: Isolation, synthesis and activity. *Anti-Cancer Agents Med. Chem.* **2008**, *8*, 746–760.

49. You, Y.-C.; Hu, D.-H.; Li, D.-P.; Wang, A.-L.; Yu, X.-S. Recent research progress in lamellarin D and its derivatives. *Chin. J. Org. Chem.* **2008**, *28*, 797–803. (In Chinese)

50. Shen, L.; Hu, Y. Recent advances in the synthesis of lamellarins as anticancer alkaloids. *Chin. J. Org. Chem.* **2009**, *29*, 867–875. (In Chinese)

51. Fan, A.-L.; Lin, W.-H.; Jia, Y.-X. Recent progress in the research on lamellarins and related pyrrole-derived alkaloids from marine organisms. *J. Chin. Pharm. Sci.* **2011**, *20*, 425–441. (In Chinese)
52. Fukuda, T.; Ishibashi, F.; Iwao, M. Synthesis and biological activity of lamellarin alkaloids. *Heterocycles* **2011**, *83*, 491–529.

53. Liao, S.; Li, D.; Liu, R.; Wang, A. Research progress in lamellarin H. *Chem. Res. Appl.* **2011**, *23*, 961–966. (In Chinese)

54. Pla, D.; Albericio, F.; Alvarez, M. Progress on lamellarins. *Med. Chem. Commun.* **2011**, *2*, 689–697.

55. Wang, A.; Zhao, Z.; Zheng, X.; Cao, H. Recent research progress in anticancer alkaloid lamellarin N and lamellarin L. *Chin. J. Org. Chem.* **2013**, *33*, 483–491. (In Chinese)

56. Urban, S.; Hickford, S.J.H.; Blunt, J.W.; Munro, M.H.G. Bioactive marine alkaloids. *Curr. Org. Chem.* **2000**, *4*, 76–807.

57. Fernandez, D.; Ahaidar, A.; Danelon, G.; Cironi, P.; Marfil, M.; Perez, O.; Cuevas, C.; Albericio, F.; Joule, J.A.; Alvarez, M. Synthesis of polyheterocyclic nitrogen-containing marine natural products. *Monatsh. Chem.* **2004**, *135*, 615–627.

58. Dias, N.; Vezin, H.; Lansiaux, H.; Lansiaux, A.; Bailly, C. Topoisomerase inhibitors of marine origin and their potential use as anticancer agents. *Top. Curr. Chem.* **2005**, *253*, 9–108.

59. Wang, W.; Namikoshi, M. Bioactive nitrogenous metabolites from ascidians. *Heterocycles* **2007**, *74*, 53–88.

60. Barthomeuf, C.; Bourguet-Kondracki, M.-L.; Kornprobst, J.-M. Marine metabolites overcoming or circumventing multidrug resistance mediated by ATP-dependent transporters: A new hope for patient with tumors resistant to conventional chemotherapy. *Anti-Cancer Agents Med. Chem.* **2008**, *8*, 886–903.

61. Gong, W.; Li, L.; Yi, Y.; Zhang, D. Research progress in the studies on the synthesis of marine alkaloids. *Chin. Pharm. J.* **2008**, *26*, 327–333. (In Chinese)

62. Elyashberg, M.; Williams, A.J.; Blinov, K. Structural revisions of natural products by computer-assisted structure elucidation (CASE) systems. *Nat. Prod. Rep.* **2010**, *27*, 1296–1328.

63. Menna, M.; Fattorusso, E.; Imperatore, C. Alkaloids from marine ascidians. *Molecules* **2011**, *16*, 869–8732.

64. Menna, M. Important classes of bioactive alkaloids from marine ascidians: Structures, isolation and bioactivity. *Curr. Top. Med. Chem.* **2014**, *14*, 207–223.

65. Fuerstner, A.; Weintritt, H.; Hupperts, A. A new, titanium-mediated approach to pyrroles: First synthesis of lukianol A and lamellarin O dimethyl ether. *J. Org. Chem.* **1995**, *60*, 6637–6641.

66. Banwell, M.G.; Flynn, B.L.; Hamel, E.; Hockless, D.C.R. Convergent syntheses of the pyrrolic marine natural products lamellarin O, lamellarin Q, lukianol A and some more highly oxygenated congeners. *Chem. Commun.* **1997**, *2*, 207–208.

67. Boger, D.L.; Boyce, C.W.; Labroli, M.A.; Sehon, C.A.; Jin, Q. Total syntheses of ningalin A, lamellarin O, lukianol A, and permethyl storniamide A utilizing heterocyclic azadiene diels-alder reactions. *J. Am. Chem. Soc.* **1999**, *121*, 54–62.

68. Marfil, M.; Albericio, F.; Alvarez, M. Solid-phase synthesis of lamellarins Q and O. *Tetrahedron* **2004**, *60*, 8659–8668.

69. Fukuda, T.; Sudo, E.-I.; Shimokawa, K.; Iwao, M. Palladium-catalyzed cross-coupling of N-benzenesulfonyl-3,4-dibromopyrrole and its application to the total syntheses of lamellarins O, P, Q and R. *Tetrahedron* **2008**, *64*, 328–338.
Li, Q.; Jiang, J.; Fan, A.; Cui, Y.; Jia, Y. Total synthesis of lamellarins D, H, and R and ningalin B. *Org. Lett.* **2011**, *13*, 312–315.

Ramirez-Rodriguez, A.; Mendez, J.M.; Jimenez, C.C.; Leon, F.; Vazquez, A. A Paal-Knorr approach to 3,4-diaryl-substituted pyrroles: Facile synthesis of lamellarins O and Q. *Synthesis* **2012**, *44*, 3321–3326.

Iwao, M.; Takeuchi, T.; Fujikawa, N.; Fukuda, T.; Ishibashi, F. Short and flexible route to 3,4-diarylpyrrole marine alkaloids: Syntheses of permethyl storniamide A, ningalin B, and lamellarin G trimethyl ether. *Tetrahedron Lett.* **2003**, *44*, 4443–4446.

Iwao, M.; Takeuchi, T.; Fujikawa, N.; Fukuda, T.; Ishibashi, F.; Iwao, M. Total synthesis of lamellarins D, L, and N. *Tetrahedron* **2006**, *62*, 594–604.

Yamaguchi, T.; Fukuda, T.; Ishibashi, F.; Iwao, M. The first total synthesis of lamellarin α 20-sulfate, a selective inhibitor of HIV-1 integrase. *Tetrahedron Lett.* **2006**, *47*, 3755–3757.

Fukuda, T.; Ohta, T.; Saeki, S.; Iwao, M. Divergent synthesis of lamellarin α 13-sulfate, 20-sulfate, and 13,20-disulfate. *Heterocycles* **2010**, *80*, 841–846.

Takada, T.; Arisawa, M.; Gyoten, M.; Hamada, R.; Tohma, H.; Kita, Y. Oxidative biaryl coupling reaction of phenol ether derivatives using a hypervalent iodine(III) reagent. *J. Org. Chem.* **1998**, *63*, 7698–7706.

Fujikawa, N.; Ohta, T.; Yamaguchi, T.; Fukuda, T.; Ishibashi, F.; Iwao, M. Divergent synthesis of lamellarin α 13-sulfate, 20-sulfate, and 13,20-disulfate. *Heterocycles* **2010**, *80*, 841–846.

Handy, S.T.; Zhang, Y.; Bregman, H. A modular synthesis of the lamellarins: Total synthesis of lamellarin G trimethyl ether. *J. Org. Chem.* **2004**, *69*, 2362–2366.

Pla, D.; Marchal, A.; Olsen, C.A.; Albericio, F.; Alvarez, M. Modular total synthesis of lamellarin D. *J. Org. Chem.* **2005**, *70*, 8231–8234.

Hasse, K.; Willis, A.C.; Banwell, M.G. Modular total syntheses of lamellarin G trimethyl ether and lamellarin S. *Eur. J. Org. Chem.* **2011**, 88–99.

Komatsubara, M.; Umeki, T.; Fukuda, T.; Iwao, M. Modular synthesis of lamellarins via regioselective assembly of 3,4,5-differentially arylated pyrrole-2-carboxylates. *J. Org. Chem.* **2014**, *79*, 529–537.

Ishibashi, F.; Miyazaki, Y.; Iwao, M. Total syntheses of lamellarin D and H. The first synthesis of lamellarin-class marine alkaloids. *Tetrahedron* **1997**, *53*, 5951–5962.

Diaz, M.; Guitian, E.; Castedo, L. Syntheses of lamellarins I and K by [3+2] cycloaddition of a nitrone to an alkyne. *Synlett* **2001**, 1164–1166.

Ruchirawat, S.; Mutarapat, T. An efficient synthesis of lamellarin alkaloids: Synthesis of lamellarin G trimethyl ether. *Tetrahedron Lett.* **2001**, *42*, 1205–1208.

Ploypradith, P.; Mahidol, C.; Sahakitpinchan, P.; Wongbundit, S.; Ruchirawat, S. A highly efficient synthesis of lamellarins K and L by the Michael addition/ring-closure reaction of benzyldihydroisoquinoline derivatives with ethoxycarbonyl-β-nitrostyrenes. *Angew. Chem. Int. Ed.* **2004**, *43*, 866–868.
86. Ploypradith, P.; Petchmanee, T.; Sahakitpichan, P.; Litvinas, N.D.; Ruchirawat, S. Total synthesis of natural and unnatural lamellarins with saturated and unsaturated D-rings. *J. Org. Chem.* **2006**, *71*, 9440–9448.

87. Liermann, J.C.; Opatz, T. Synthesis of lamellarin U and lamellarin G trimethyl ether by alkylation of a deprotonated α-aminonitrile. *J. Org. Chem.* **2008**, *73*, 4526–4531.

88. Banwell, M.G.; Flynn, B.L.; Hockless, D.C.R. Convergent total synthesis of lamellarin K. *Chem. Commun.* **1997**, *23*, 2259–2260.

89. Ridley, C.P.; Reddy, M.V.R.; Rocha, G.; Bushman, F.D.; Faulkner, D.J. Total synthesis and evaluation of lamellarin α 20-sulfate analogues. *Bioorg. Med. Chem.* **2002**, *10*, 3285–3290.

90. Cironi, P.; Manzanares, I.; Albericio, F.; Alvarez, M. Solid-phase total synthesis of the pentacyclic system lamellarins U and L. *Org. Lett.* **2003**, *5*, 2959–2962.

91. Flynn, B.L.; Banwell, M.G. Convergent total syntheses of the pentacyclic lamellarins K, T, U and W via the addition of azomethine ylides to tethered tolans. *Heterocycles* **2012**, *84*, 1141–1170.

92. Heim, A.; Terpin, A.; Steglich, W. Alkaloids from marine organisms. 2. Biomimetic synthesis of lamellarin G trimethyl ether. *Angew. Chem. Int. Ed.* **1997**, *36*, 155–156.

93. Peschko, C.; Winklhofer, C.; Terpin, A.; Steglich, W. Biomimetic syntheses of lamellarin and lukianol-type alkaloids. *Synthesis* **2006**, *18*, 3048–3057.

94. Gupton, J.T.; Giglio, B.C.; Eaton, J.E.; Rieck, E.A.; Smith, K.L.; Keough, M.J.; Barelli, P.J.; Firich, L.T.; Hempel, J.E.; Smith, T.M.; et al. The application of vinylogous iminium salt derivatives to efficient formal syntheses of the marine alkaloids lamellarin G trimethyl ether and ningalin B. *Tetrahedron* **2009**, *65*, 4283–4292.

95. Gupton, J.T.; Krumpe, K.E.; Burnham, B.S.; Webb, T.M.; Shuford, J.S.; Sikorski, J.A. The application of vinylogous iminium salt derivatives to a regiocontrolled and efficient relay synthesis of lukianol A and related marine natural products. *Tetrahedron* **1999**, *55*, 14515–14522.

96. Gupton, J.T.; Telang, N.; Patteson, J.; Lescalleet, K.; Youdall, S.; Sobieski, J.; Harrison, A.; Curry, W. The application of formyl group activation of bromopyrrole esters to formal syntheses of lycogarubin C, permethyl storniamide A and lamellarin G trimethyl ether. *Tetrahedron* **2014**, *70*, 9759–9767.

97. Yadav, J.S.; Gayathri, K.U.; Reddy, B.V.S.; Prasad, A.R. Modular total synthesis of lamellarin G trimethyl ether. *Synlett* **2009**, *1*, 43–46.

98. Ueda, K.; Amaiike, K.; Macieczyk, R.M.; Itami, K.; Yamaguchi, J. β-selective C-H arylation of pyrroles leading to concise syntheses of lamellarins C and I. *J. Am. Chem. Soc.* **2014**, *136*, 13226–13232.

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