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Total synthesis of lamellarins D, L, and N

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Abstract- Total synthesis of cytotoxic marine alkaloids, lamellarins D, L, and N, has been achieved by using Hinsberg-type pyrrole synthesis and palladium-catalyzed Suzuki-Miyaura coupling of the 3,4-dihydroxypyrrole bistriflate 6 as the key reactions. The total yields of lamellarins D, L, and N from the common intermediate 6 are 54, 58, and 50%, respectively.

Keywords: Total synthesis; Lamellarin; Hinsberg reaction; Suzuki-Miyaura coupling.

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1. Introduction

Lamellarin-class marine natural products have received considerable attention due to their unique structures and highly useful biological activities. In 1985, Faulkner and co-workers reported the first isolation of novel heterocyclic marine natural products named lamellarins A-D from a prosobranch mollusk, Lamellaria sp. a The combined X-ray crystallographic and spectroscopic studies revealed that these natural products possess the unprecedented 14-phenyl-6H-[1]benzopyrano[4′,3′:4,5]pyrrolo[2,1-a]isoquinolin-6-one ring-system. Up to now, over 30 lamellarins (A-Z and α-γ, including acetate and sulfate derivatives) have been isolated from mollusks, tunicates, and sponges. These are different in the number and position of the OH and OMe substituents on the common structural core.
In 1996, Quesada et al. reported that some lamellarins exhibited potent cytotoxicity on P-glycoprotein-mediated multidrug-resistant (MDR) cancer cells as well as their respective parental cell lines.\(^3\) After this important discovery, much attention has been focused on the chemical synthesis of lamellarins.\(^4\) In 1997, we reported the first total synthesis of the lamellarin-class natural products, lamellarins D and H, using \(N\)-ylide-mediated cyclization of a benzylisoquinoline derivative as the key ring-construction procedure.\(^4b\) By using this strategy, we have synthesized ten lamellarin D analogues and carried out a structure-activity relationship (SAR) study.\(^5\) In this study, we revealed that the hydroxyl groups at C-8 and C-20 positions (lamellarin numbering\(^2a\)) are essential for cytotoxic activity. Recently, Bailly and coworkers have reported lamellarin D is a potent inhibitor of DNA topoisomerase I and presented a theoretical model of lamellarin D bound to the covalent topoisomerase I-DNA complex.\(^6\) The model is in perfect agreement with our SAR study.\(^5\) On the other hand, we have lately reported a more general synthetic approach to diverse 3,4-diarylpyrrole marine alkaloids including lamellaris by using Hinsberg-type pyrrole synthesis and palladium-catalyzed coupling as the key reactions.\(^4i\) Herein, we report an efficient total synthesis of lamellarins D, L, and N using this strategy.

2. Results and discussion

The retrosynthetic analysis of lamellarins D (1), L (2), and N (3) is shown in Scheme 1. The lamellarin core can be constructed by intramolecular biaryl coupling of the pyrrole-lactones (4 and 5), which in turn are obtained by the consecutive palladium-catalyzed cross-coupling (Suzuki-Miyaura reaction) of the 3,4-dihydroxy-4-pyrrole bistriflate 6 with the arylboronic acids 7 (or 8) and 9, followed by lactonization, hydrolysis, and decarboxylation. The bistriflate 6 can be prepared by Hinsberg reaction of the iminodiacate 10 with dimethyl oxalate followed by triflation.

Scheme 1

The synthesis of the bistriflate 6 is shown in Scheme 2. Henry reaction of \(O\)-isopropylisovanilin (11) followed by lithium aluminum hydride reduction of the
resulting nitrostyrene intermediate produced 2-arylethylamine \(12^{le}\). The amine was reacted with 2 equiv. of methyl bromoacetate in the presence of sodium hydrogen carbonate in refluxing acetonitrile to give iminodiacetate \(10\) in 83 % yield. Hinsberg reaction of \(10\) with dimethyl oxalate in dry THF using sodium hydride as a base produced the 3,4-dihydroxypyrrole \(13\) in 87% yield. The conventional conditions using sodium methoxide in methanol\(^{4j,7}\) afforded \(13\) in much lower yield (~50%). Triflation of \(13\) with trifluoromethanesulfonic anhydride in pyridine produced the stable bistrifalte \(6\) in excellent yield.

**Scheme 2**

The synthesis of arylboronic acids \(7, 8\) and \(9\) is shown in Scheme 3. Guaiacol (14) was regioselectively brominated by \(N\)-bromosuccinimide (NBS) to give \(15\) in 81% yield. After isopropyl protection of the hydroxyl group, the resulting \(16\) was converted to the boronic acid \(7\) via bromine-lithium exchange with 2 equiv. of tert-butyllithium followed by a reaction with trimethyl borate.

The regioisomeric arylboronic acid \(8\) was prepared as follows. The hydroxyl group of guaiacol (14) was protected by an electron-withdrawing mesyl group at first in order to deactivate the electron-donating effect of the hydroxyl group and alter the most electrophilic site of the aromatic ring from the 4-position to the 5-position.\(^8\) Treatment of the mesylate \(17\) with \(N\)-bromosuccinimide produced indeed the 5-brominated compound \(18\) in excellent yield as a single isomer. Deprotection of the mesyl group using the protocol of Carreira\(^9\) gave 5-bromoguaiacol (19) in excellent yield. This compound can also be prepared more conveniently from commercially available 2,4-dibromoanisole (20) via regioselective bromine-lithium exchange followed by boration and oxidation.\(^10\) The phenol 19 was converted to the boronic acid \(8\) in two steps in a similar manner as described for \(7\). Both \(7\) and \(8\) are stable crystalline solids and can be stored for several months without any deterioration.

Another arylboronic acid \(9\) was prepared in 4 steps from \(O\)-isopropylisovanillin (11). Bayer-Villiger oxidation of \(11\) with \(m\)-chloroperbenzoic acid followed by methanolysis produced phenol \(22\). After protection of the hydroxyl group as methoxymethyl ether,
the resulting 23 was converted to rather unstable bromide 24. Bromine-lithium exchange followed by a reaction with trimethyl borate gave the boronic acid 9. This compound was used for the subsequent cross-coupling reactions immediately after preparation due to its instability.

**Scheme 3**

The synthesis of lamellarins D (1), L (2), and N (3) is shown in **Scheme 4**. At first, the synthesis of lamellarin D (1) was executed. Suzuki-Miyaura coupling of the bistriflate 6 with 1.0 equiv. of an arylboronic acid 7 under the standard conditions [Pd(PPh₃)₄ (2 mol%), aq. Na₂CO₃, THF, reflux, 4 h]⁴ gave the mono-substituted pyrrole 25 in 76% yield. The second cross-coupling of 25 with a freshly prepared boronic acid 9 (2 equiv.) using 8 mol% of the same palladium catalyst, followed by treatment with hydrochloric acid in methanol afforded the lactone-ester 27 in 98% yield. Compound 27 was converted to the acid 29 by alkaline hydrolysis followed by acid-catalyzed relactonization in 90% yield. Decarboxylation of 29 in hot quinoline in the presence of copper(I) oxide¹¹ produced 4. Intramolecular oxidative biaryl coupling of 4 under Kita’s conditions¹² using phenyliodine bis(trifluoroacetate) (PIFA)-boron trifluoride etherate afforded the cyclized product 31 in good yield. Pd(II)-mediated decarboxylative ring closure⁴ of 29 produced 31 directly in 65% yield, accompanied by simply decarboxylated 30 (14%). Treatment of 31 with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in refluxing toluene produced 5,6-dehydrogenated compound 33. Final selective deprotection of the isopropyl group with boron trichloride¹³ proceeded cleanly to give lamellarin D (1).

Total synthesis of lamellarin N (3) was also achieved from 6 in an essentially same sequence except for the use of arylboronic acid 8 at the initial cross-coupling stage. Selective deprotection of the isopropyl groups of an intermediate 5,6-dihydrolamellarin 32 produced lamellarin L (2).

**Scheme 4**
3. Conclusion

We have achieved the total synthesis of lamellarins D (1), L (2), and N (3) in relatively short steps. Although the yield of each step is not fully optimized, the total yields of lamellarins are quite good (1: 54%, 2: 58%, and 3: 50%, respectively, from bistriflate 6). Convergence of the strategy enables the synthesis of a wide range of natural or non-natural lamellarins by simple structural modification of the starting bistriflate and arylboronic acids. Hopefully, this will allow us to produce new antitumor agents based upon the lamallarin motif.

4. Experimental

4.1. General

Melting points were determined with a Yanagimoto micro melting points apparatus and are uncorrected. IR spectra were obtained with a Perkin-Elmer System 2000 instrument. NMR spectra were recorded on a Varian Gemini-300 instrument (300 MHz for \(^{1}\)H) or a JEOL JNM-AL400 instrument (400 MHz for \(^{1}\)H and 100 MHz for \(^{13}\)C) using tetramethylsilane as an internal standard. Mass spectra were recorded on a JEOL JMS-700N spectrometer. Flash chromatography was conducted on Silica Gel 60N, 40-50 µm (Kanto Chemical Co., Inc.). Column chromatography was conducted on Silica Gel 60N, 63-210 µm (Kanto Chemical Co., Inc.) or Chromatorex NH-DM1020 silica gel (Fuji Silysia Chemical Ltd.). tert-Butyllithium was purchased from Kanto Chemical Co., Inc. \(n\)-Butyllithium and lithiumdiisopropylamide (LDA) were purchased from Aldrich Chemical Co., Inc. The alkyllithiums were used after titration with 2,5-dimethoxybenzyl alcohol. Dry diethyl ether and THF were distilled from Na-benzophenone ketyl under argon immediately before use.

4.2. Synthesis of the bistriflate 6

4.2.1. 2-(3-Isopropoxy-4-methoxyphenyl)ethylamine (12). Nitromethane (13.3 mL, 246 mmol) was added as a neat liquid to a solution of 11 (28.0 g, 144 mmol) and
ammonium acetate (33.3 g, 432 mmol) in acetic acid (240 mL) at room temperature and the solution was heated at 100 °C for 6 h. The mixture was cooled to room temperature and then poured into ice-cold water. The precipitates thus formed were collected by filtration, washed with water, and dried under reduced pressure. Recrystallization from diethyl ether gave (E)-β-nitro-3-isopropoxy-4-methoxystyrene as yellow prisms (25.3 g, 74%). Mp 115-115.5 °C (lit.4e Mp 83 °C); IR (KBr): 3110, 2968, 1625, 1594, 1513, 1493, 1334, 1262, 1169, 1138, 1113, 1026, 1005, 957, 806 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.40 (d, J= 6.0 Hz, 6H), 3.92 (s, 3H), 4.57 (m, J= 6.0 Hz, 1H), 6.92 (d, J= 8.3 Hz, 1H), 7.05 (d, J= 1.9 Hz, 1H), 7.17 (dd, J= 1.9 and 8.3 Hz, 1H), 7.51 (d, J= 13.6 Hz, 1H), 7.95 (d, J= 13.6 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): 21.94, 56.00, 71.77, 111.82, 114.85, 122.54, 124.48, 134.90, 139.25, 147.60, 154.03. EIMS m/z (%): 237 (83), 195 (100), 148 (68), 133 (29). Anal. Calcd for C₁₂H₁₅NO₄: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.88; H, 6.42; N, 6.00.

Under an argon atmosphere, (E)-β-nitro-3-isopropoxy-4-methoxystyrene (14.4 g, 60.7 mmol) was added portionwise to a suspension of LiAlH₄ (7.40 g, 195 mmol) in THF (600 mL) at 0 °C and the mixture was refluxed for 7 h. The mixture was cooled to 0 °C and quenched carefully with water (16 mL) and 10% aqueous NaOH (13 mL). After removal of white precipitates by filtration, the filtrate was dried over K₂CO₃, and evaporated under reduced pressure. The residue was purified by distillation (94-98 °C/0.35 mmHg) to give 12 as colorless oil (8.20 g, 65%). IR (neat): 3364, 2976, 1588, 1515, 1505, 1259, 1234, 1138, 1110, 1029, 989, 807 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.36 (d, J= 6.0 Hz, 6H), 2.67 (t, J= 6.7 Hz, 2H), 2.93 (t, J= 6.7 Hz, 2H), 3.83 (s, 3H), 4.52 (m, J= 6.0 Hz, 1H), 6.74 (dd, J= 1.7 and 8.5 Hz, 1H), 6.75 (d, J= 1.7 Hz, 1H), 6.82 (d, J= 8.5 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): 22.13, 39.48, 43.63, 56.00, 71.41, 112.09, 116.85, 121.21, 132.19, 147.05, 148.80. HREIMS m/z. Calcd for C₁₂H₁₉NO₂ (M⁺): 209.1416. Found: 209.1396.

4.2.2. Dimethyl N-[2-(3-isopropoxy-4-methoxyphenyl)ethyl]iminodiacatate (10).

Methyl bromoacetate (5.78 mL, 61.1 mmol) was added as a neat liquid to a suspension of 12 (6.00 g, 28.7 mmol) and NaHCO₃ (10.3 g, 123 mmol) in acetonitrile (60 mL) at room temperature and the mixture was refluxed for 2 h. The mixture was cooled to room temperature and evaporated under reduced pressure. The residue was extracted
with dichloromethane and the extract was washed with brine, dried over Na$_2$SO$_4$, and evaporated under reduced pressure. The residue was purified by distillation (180 °C/0.6 mmHg) to give 10 as colorless oil (8.42 g, 83%). IR (neat): 2952, 2838, 1747, 1732, 1588, 1515, 1505, 1455, 1435, 1372, 1258, 1028, 808 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.36 (d, $J$ = 6.3 Hz, 6H), 2.68-2.75 (m, 2H), 2.90-2.97 (m, 2H), 3.60 (s, 4H), 3.71 (s, 6H), 3.82 (s, 3H), 4.51 (m, $J$ = 6.3 Hz, 1H), 6.70-6.81 (m, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): 22.14, 34.24, 51.49, 54.99, 56.01, 56.48, 71.41, 112.05, 116.80, 121.05, 132.09, 147.01, 148.78, 171.45. HREIMS m/z. Calcd for C$_{18}$H$_{27}$NO$_6$ (M$^+$): 353.1838. Found: 353.1848.

4.2.3. Dimethyl 3,4-dihydroxy-1-[2-(3-isopropoxy-4-methoxyphenyl)ethyl]pyrrole-2,5-dicarboxylate (13). Under an argon atmosphere, a suspension of dimethyl oxalate (6.68 g, 56.6 mmol) and NaH (60% dispersion in mineral oil, 4.53 g, ca. 113 mmol, prewashed with hexane) in THF (50 mL) was heated to reflux. To this suspension was added dropwise a solution of 10 (10.0 g, 28.3 mmol) in THF (100 mL) under reflux. After being refluxed for additional 3 h, the reaction mixture was cooled to room temperature, quenched with acetic acid (6.7 mL) and evaporated under reduced pressure. The residue was poured into ice-cold water and the suspension was adjusted to pH 3 with concentrated HCl. The precipitates thus formed was collected by filtration, washed with water, and dried under reduced pressure to give 13 as colorless powder (10.0 g, 87%). Recrystallization from diethyl ether-hexane gave colorless needles. Mp 116.5-117.5 °C; IR (KBr): 3483, 3420, 2994, 2965, 2938, 1724, 1696, 1515, 1467, 1235, 1191, 1146, 1108, 990 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.36 (d, $J$ = 6.0 Hz, 6H), 2.81 (t, $J$ = 7.4 Hz, 2H), 3.83 (s, 3H), 3.92 (s, 6H), 4.48 (m, $J$ = 6.0 Hz, 1H), 4.68 (t, $J$ = 7.4 Hz, 2H), 6.64 (s, 1H), 6.65 (d, $J$ = 8.8 Hz, 1H), 6.79 (d, $J$ = 8.8 Hz, 1H), 7.51 (br s, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): 22.14, 34.24, 51.49, 54.99, 56.01, 56.48, 71.41, 112.05, 116.80, 121.33, 130.62, 138.57, 147.03, 149.08, 162.32. EIMS m/z (%): 407 (83), 333 (27), 228 (100), 196 (77). Anal. Calcd for C$_{20}$H$_{25}$NO$_8$: C, 58.96; H, 6.18; N, 3.44. Found: C, 58.76; H, 6.18; N, 3.35.

4.2.4. Dimethyl 1-[2-(3-isopropoxy-4-methoxyphenyl)ethyl]-3,4-bis(trifluoromethanesulfonyloxy)py
**rrole-2,5-dicarboxylate (6).** Under an argon atmosphere, trifluoromethanesulfonic anhydride (7.76 mL, 46.1 mmol) was added as a neat liquid to a solution of 13 (8.50 g, 20.9 mmol) in pyridine (35 mL) at 0 °C. After being stirred for 2 h, the reaction mixture was quenched with water at the same temperature and allowed to warm to room temperature. The product was extracted with diethyl ether and the extract was washed successively with 2 M aqueous HCl, water, and brine, and dried over Na₂SO₄. The solvent was removed by evaporation and the residue was purified by column chromatography over Silica Gel 60N (hexane-ethyl acetate=3:1) to give 6 as colorless solid (12.8 g, 91%). Recrystallization from dichloromethane-hexane gave colorless plates. Mp 94-95 °C; IR (KBr): 2967, 1740, 1514, 1434, 1307, 1245, 1131, 987, 973, 812 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.36 (d, J = 6.0 Hz, 6H), 2.97 (t, J= 7.1 Hz, 2H), 3.82 (s, 3H), 3.88 (s, 6H), 4.48 (m, J = 6.0 Hz, 1H), 5.08 (t, J= 7.1 Hz, 2H), 6.60 (dd, J= 1.9 and 8.2 Hz, 1H), 6.66 (d, J= 1.9 Hz, 1H), 6.76 (d, J= 8.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): 22.06, 37.24, 48.20, 52.19, 56.00, 71.39, 112.02, 116.52, 117.13, 118.31 (q, J= 320 Hz), 121.45, 127.67, 128.98, 147.22, 149.27, 157.97. EIMS m/z (%): 671 (78), 629 (95), 363 (27), 272 (33), 150 (90), 137 (100). Anal. Calcd for C₂₂'H₂₅F₆NO₁₂S₂: C, 39.35; H, 3.45; N, 2.09. Found: C, 39.32; H, 3.19; N, 2.02.

**4.3. Synthesis of aryloboric acid 7**

**4.3.1. 4-Bromo-2-methoxyphenol (15).** A solution of NBS (14.3 g, 80.6 mmol) in DMF (50 mL) was added dropwise to a solution of guaiacol (10.0 g, 80.6 mmol) in DMF (50 mL) at 0 °C. After being stirred for 30 min, the reaction mixture was quenched with water at the same temperature and allowed to warm to room temperature. The products were extracted with diethyl ether and the extract was washed with water and brine, dried over Na₂SO₄, and evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N (hexane-ethyl acetate=3:1) to give 15 as colorless oil (14.1 g, 86%). Bp 95-110 °C (1.9 mmHg, bulb-to-bulb); IR (neat): 3521, 2967, 2946, 2842, 1608, 1505, 1445, 1360, 1258, 1224, 1118, 1026, 859, 839, 810, 781 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 3.89 (s, 3H), 5.54 (s, 1H), 6.80 (d, J= 8.0 Hz, 1H), 6.97 (d, J= 2.2 Hz, 1H), 6.99 (dd, J= 2.2 and 8.0 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): 56.08, 111.43, 114.02, 115.60, 124.01, 144.69, 147.03. HREIMS m/z. Calcd for C₇H₇BrO₂ (M⁺): 201.9629. Found: 201.9608.
4.3.2. 4-Bromo-1-isopropoxy-2-methoxybenzene (16). A neat liquid of 2-bromopropane (4.86 mL, 51.8 mmol) was added to a suspension of 15 (7.00 g, 34.5 mmol) and K₂CO₃ (9.54 g, 69.0 mmol) in DMSO (100 mL) at the room temperature and the mixture was heated at 55 °C for 2 h. The reaction mixture was cooled to room temperature and diluted with water. The mixture was extracted with diethyl ether and the extract was washed successively with 10% aqueous NaOH, water, and brine, and dried over Na₂SO₄. The solvent was evaporated under reduced pressure and the residue was purified by bulb-to-bulb distillation (90 °C/ 0.5 mmHg) to give 16 as colorless oil (7.07 g, 84%). IR (neat): 2977, 2934, 1585, 1495, 1464, 1445, 1397, 1383, 1372, 1250, 1224, 1135, 1108, 1031, 1108, 1031, 836 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.35 (d, J = 6.0 Hz, 6H), 3.84 (s, 3H), 4.47 (m, J = 6.0 Hz, 1H), 6.76 (d, J = 9.1 Hz, 1H), 6.99 (d, J = 2.2 Hz, 1H), 6.99 (dd, J = 2.2 and 9.1 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): 21.99, 56.06, 71.80, 113.07, 115.39, 117.27, 123.26, 146.41, 151.16. HREIMS m/z. Calcd for C₁₀H₁₃BrO₂ (M⁺): 244.0099. Found: 244.0083.

4.3.3. 4-Isopropoxy-3-methoxyphenylboronic acid (7). Under an argon atmosphere, a pentane solution of tert-butyllithium (1.38 M, 24.8 mL, 34.2 mmol) was added dropwise to a solution of 16 (4.00 g, 16.3 mmol) in THF (60 mL) at −78 °C. After being stirred for 1 h, trimethyl borate (2.80 mL, 25.1 mmol) was added as a neat liquid and the mixture was stirred for 1 h at −78 °C. The reaction mixture was allowed to warm to room temperature and stirred for an additional 1 h. The mixture was quenched with saturated aqueous NH₄Cl and evaporated under reduced pressure. To the residue was added 3M aqueous HCl to adjust the pH to 3 and then the mixture was extract with dichloromethane. The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure. The residual solid was washed with hexane, filtered, and dried under reduced pressure to give 7 as colorless powder (1.93 g, 56%). This compound was used for the next reaction without further purification. Mp 100-120 °C; IR (KBr): 3219, 2979, 2939, 1599, 1361, 1256, 1220, 1136, 1110, 1029, 955, 818, 770, 741, 714 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.34 (d, J = 6.0 Hz, 6H), 3.99 (s, 3H), 4.69 (m, J = 6.0 Hz, 1H), 7.03 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 1.1 Hz, 1H), 7.82 (dd, J = 1.1 and 8.0 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): 22.01, 55.99, 70.86, 113.85, 118.20, 129.55, 149.38, 151.29.
4.4. Synthesis of arylboronic acid 8

4.4.1. 2-Methoxyphenyl methanesulfonate (17). Under an argon atmosphere, methanesulfonyl chloride (19.5 mL, 252 mmol) was added as a neat liquid to a solution of guaiacol (25.0 g, 201 mmol) and triethylamine (41.8 mL, 300 mmol) in dichloromethane (200 mL) at 0 °C. After being stirred for 30 min, the reaction mixture was diluted with water and the organic layer was separated. The aqueous layer was extracted with dichloromethane. The combined extract was washed successively with water and brine, and dried over Na₂SO₄. The solvent was evaporated under reduced pressure and the residue was purified by distillation (133 °C/0.4 mmHg) to give 17 as colorless oil (39.0 g, 96%). IR (neat): 3022, 2943, 2843, 1605, 1505, 1360, 1282, 1259, 1183, 1155, 1107, 1022, 972, 873, 798, 757 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 3.17 (s, 3H), 3.88 (s, 3H), 6.92-7.03 (m, 2H), 7.23-7.32 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): 38.20, 55.91, 112.83, 120.99, 124.39, 128.12, 138.23, 151.25. HREIMS m/z. Calcd for C₈H₁₀O₄S (M⁺): 202.0300. Found: 202.0280.

4.4.2. 5-Bromo-2-methoxyphenyl methanesulfonate (18). A solution of NBS (2.31 g, 13.0 mmol) in DMF (5.0 mL) was added dropwise to a solution of 17 (2.03 g, 10.0 mmol) in DMF (5.0 mL) at room temperature. After being stirred for 24 h, the reaction mixture was quenched with water. The products were extracted with diethyl ether and the extract was washed with water and brine, dried over Na₂SO₄, and evaporated under reduced pressure. The residue was purified by bulb-to-bulb distillation (150-180 °C/1.1 mmHg) to give 18 as colorless solid (2.71 g, 96%). Recrystallization from diethyl ether-hexane gave colorless prisms. Mp 59-59.5 °C; IR (KBr): 3032, 2944, 1497, 1369, 1330, 1299, 1269, 1166, 1125, 1025, 976, 899, 804 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 3.20 (s, 3H), 3.88 (s, 3H), 6.92-7.03 (m, 2H), 7.23-7.32 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): 38.20, 55.91, 112.83, 120.99, 124.39, 128.12, 138.23, 151.25. HREIMS m/z. Calcd for C₈H₁₀BrO₄S (M⁺): 202.0300. Found: 202.0280.

4.4.3. 5-Bromo-2-methoxyphenol (19). Method 1. Under an argon atmosphere, a heptane-THF-ethylbenzene solution of LDA (2.0 M, 16.1 mL, 32.2 mmol) was added dropwise to a solution of 18 (6.04 g, 21.5 mmol) in THF (21.5 mL) at 0 °C. After being stirred for 5 min, the mixture was quenched with 5% aqueous HCl. The product was extract with diethyl ether and the extract was washed successively with water and brine, dried over Na$_2$SO$_4$, and evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N (hexane-ethyl acetate=3:1) to give 19 as colorless solid (3.98 g, 91%). Recrystallization from diethyl ether-pentane gave colorless prisms. Mp 64-64.5 ºC; IR (KBr): 3399, 2974, 2942, 2841, 1592, 1492, 1436, 1333, 1290, 1260, 1225, 1126, 1025, 856, 799 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 3.87 (s, 3H), 5.64 (s, 1H), 6.71 (d, $J= 8.5$ Hz, 1H), 6.97 (dd, $J = 2.5$ and 8.5 Hz, 1H), 7.07 (d, $J = 2.5$ Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): 56.02, 111.72, 113.13, 117.70, 122.64, 145.69, 146.32. EIMS m/z (%): 204 (98), 202 (100), 189 (63), 187 (64), 161 (29), 159 (29). Anal. Calcd for C$_7$H$_7$BrO$_2$: C, 41.41; H, 3.48. Found: C, 41.58; H, 3.44.

Method 2. Under an argon atmosphere, a hexanes solution of n-butyllithium (1.19 M, 37.0 mL, 44.0 mmol) was added dropwise to a solution of 2,4-dibromoanisole (20) (10.6 g, 39.9 mmol) in diethyl ether (200 mL) at –78 ºC. After being stirred for 1 h, trimethyl borate (7.48 mL, 67.1 mmol) was added as a neat liquid and the mixture was stirred for 1 h at –78 ºC. The reaction mixture was allowed to warm to room temperature and stirred for an additional 1 h. Acetic acid (7.48 mL, 131 mmol) and 30% aqueous H$_2$O$_2$ (13.6 mL, 133 mmol) were added to the mixture. After being stirred for 16 h at room temperature, the mixture was quenched with 10% aqueous Na$_2$SO$_4$. The product was extracted with diethyl ether and the extract was washed successively with water and brine, dried over Na$_2$SO$_4$, and evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N (toluene) to give 19 as colorless solid (7.36 g, 91%).

4.4.4. 4-Bromo-2-isopropoxy-1-methoxybenzene (21). This compound was prepared in a similar manner as described for 16 using 19 (16.2 g, 79.8 mmol) as the starting material. After purification by bulb-to-bulb distillation (88 ºC/ 0.4 mmHg), 21 was obtained as colorless liquid (18.7 g, 96%) which on standing solidified. Mp
46-46.5 °C; IR (KBr): 2976, 2907, 1584, 1500, 1223, 223, 1130, 1020, 958, 839, 794 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.37 (d, J= 6.0 Hz, 6H), 3.82 (s, 3H), 4.50 (m, J= 6.0 Hz, 1H), 6.73 (d, J= 9.1 Hz, 1H), 7.00 (d, J= 2.2 Hz, 1H), 1.01 (dd, J= 2.2 and 9.1 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): 21.95, 56.06, 71.75, 112.44, 113.15, 118.72, 123.60, 147.99, 149.51. EIMS m/z (%): 246 (35), 244 (35), 204 (98), 202 (100), 189 (52), 187 (53). Anal. Calcd for C₁₀H₁₃BrO₂: C, 49.00; H, 5.35. Found: C, 48.92; H, 5.31.

4.4.5. 3-Isopropoxy-4-methoxyphenylboronic acid (8). This compound was prepared in a similar manner as described for 7 using 21 (7.35 g, 30.0 mmol) as the starting material. After washing with hexane, 8 was obtained as colorless powder (5.13 g, 81%). Mp 115-135 °C; IR (KBr): 3220, 2975, 2934, 1596, 1518, 1374, 1268, 1217, 1178, 1136, 1112, 1025, 743, 716 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.45 (d, J= 6.0 Hz, 6H), 3.94 (s, 3H), 4.67 (m, J= 6.0 Hz, 1H), 7.02 (d, J= 8.0 Hz, 1H), 7.72 (d, J= 1.4 Hz, 1H), 7.84 (dd, J= 1.4 and 8.0 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): 22.17, 55.76, 71.63, 111.17, 122.38, 129.94, 146.60, 154.18.

4.5. Synthesis of arylboronic acid 9

4.5.1. 3-Isopropoxy-4-methoxyphenol (22). Under an argon atmosphere, m-chloroperbenzoic acid (a reagent containing 25% water, 16.0 g, 69.5 mmol) was added portionwise to a solution of 11 (12.0 g, 61.8 mmol) in dichloromethane (120 mL) at 0 °C. After being stirred for 3 h, the reaction mixture was quenched with saturated aqueous NaHCO₃. The mixture was diluted with water and the organic layer was separated. The aqueous layer was extracted with dichloromethane. The combined extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure. The residue was dissolved in methanol (240 mL) and K₂CO₃ (21.0 g, 152 mmol) was added portionwise to the solution at room temperature. After being stirred for 1 h, the mixture was evaporated under reduced pressure. Water was added to the residue and the product was extracted with diethyl ether. The extract was washed with brine, dried over Na₂SO₄, evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N (dichloromethane-ethyl acetate=5:1) to give 22 as colorless solid (9.64 g, 86%). Recrystallization from diethyl
ether-pentane gave colorless needles. Mp 121-122 °C; IR (KBr): 3431, 2978, 2934, 1610, 1508, 1459, 1289, 1129, 1032, 995, 918, 856, 803, 772, 719 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.36 (d, J= 6.0 Hz, 6H), 3.80 (s, 3H), 4.49 (m, J= 6.0 Hz, 1H), 4.66 (br s, 1H), 6.34 (dd, J= 2.8 and 8.8 Hz, 1H), 6.48 (d, J= 2.8 Hz, 1H), 6.74 (d, J= 8.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): 21.94, 56.75, 71.31, 104.08, 106.43, 113.41, 144.05, 147.98, 150.08. EIMS m/z (%): 182 (46), 140 (75), 125 (100).

**Anal. Calcd for C₁₀H₁₄O₃:** C, 65.91; H, 7.74. Found: C, 66.19; H, 7.89.

### 4.5.2. 2-Isopropoxy-1-methoxy-4-methoxymethoxybenzene (23).

Under an argon atmosphere, a solution of 22 (2.50 g, 13.7 mmol) in THF (20 mL) was added dropwise to a suspension of NaH (60% dispersion in mineral oil, 2.73 g, 68.3 mmol, prewashed with hexane) in THF (30 mL) at 0 °C. After being stirred for 30 min, chloromethyl methyl ether (1.60 mL, 21.1 mmol) was added as a neat liquid and the mixture was stirred for 2 h at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for an additional 1 h. The mixture was quenched with saturated aqueous NH₄Cl and the products were extract with diethyl ether. The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N (hexane-ethyl acetate=10:1) to give 23 as colorless oil (2.10 g, 68%). Bp 135-140 °C (1.9 mmHg, bulb-to-bulb); IR (neat): 2977, 2902, 2832, 1596, 1505, 1465, 1443, 1259, 1228, 1154, 1077, 1018, 976, 922 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.37 (d, J= 6.0 Hz, 6H), 3.49 (s, 3H), 3.81 (s, 3H), 4.51 (m, J= 6.0 Hz, 1H), 5.11 (s, 2H), 6.59 (dd, J= 2.8 and 8.8 Hz, 1H), 6.65 (d, J= 2.8 Hz, 1H), 6.79 (d, J= 8.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): 22.03, 55.83, 56.55, 71.32, 95.16, 105.79, 107.42, 112.73, 145.50, 147.91, 151.48. HR EIMS m/z. Calcd for C₁₂H₁₄O₄ (M⁺): 226.1205. Found: 226.1189.

### 4.5.3. 1-Bromo-4-isopropoxy-5-methoxy-2-methoxymethoxybenzene (24).

A solution of NBS (2.05 g, 11.5 mmol) in DMF (15 mL) was added dropwise to a solution of 23 (2.50 g, 11.0 mmol) in DMF (10 mL) at 0 °C. After being stirred for 30 min, the reaction mixture was quenched with water at the same temperature and allowed to warm to room temperature. The products were extracted with diethyl ether and the extract was washed with water and brine, dried over Na₂SO₄, and evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N
(hexane-ethyl acetate=3:1) to give 15 as pale yellow oil (3.31 g, 98%). This compound was somewhat unstable and used for the next reaction without further purification. IR (neat): 2977, 2835, 1505, 1374, 1265, 1211, 1152, 1111, 1085, 977, 921, 845, 804 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta 1.36\) (d, \(J = 6.0\) Hz, 6H), 3.54 (s, 3H), 3.81 (s, 3H), 4.49 (m, \(J = 6.0\) Hz, 1H), 5.15 (s, 2H), 6.82 (s, 1H), 7.02 (s, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): 21.95, 56.32, 56.59, 72.00, 96.23, 103.13, 106.92, 116.51, 146.31, 147.06, 147.74. HREIMS m/z. Calcd for C\(_{12}\)H\(_{17}\)BrO\(_4\) (M\(^+\)): 304.0310. Found: 304.0302.

4.5.4. 4-Isopropoxy-5-methoxy-2-methoxymethoxyphenylboronic acid (9). Under an argon atmosphere, a pentane solution of tert-butyllithium (1.17 M, 24.0 mL, 28.1 mmol) was added dropwise to a solution of 24 (4.00 g, 13.1 mmol) in THF (160 mL) at \(-78\) °C. After being stirred for 1 h, trimethyl borate (2.30 mL, 20.6 mmol) was added as a neat liquid and the mixture was stirred for 1 h at \(-78\) °C. The reaction mixture was allowed to warm to room temperature and stirred for an additional 1 h. The mixture was quenched with saturated aqueous NH\(_4\)Cl and evaporated under reduced pressure. The products were adjusted to pH 3 with acetic acid and the mixture was extract with dichloromethane. The extract was washed successively with saturated aqueous NaHCO\(_3\) and brine, dried over Na\(_2\)SO\(_4\), and evaporated under reduced pressure. The residue was washed with hexane and dried under reduced pressure to give 9 as pale brown powder (3.09 g, 87%). This compound was used for the next reaction without further purification. Mp 83-86 °C; IR (KBr): 3499, 3370, 2987, 2939, 1606, 1509, 1400, 1306, 1261, 1211, 1148, 1103, 1020, 971, 816 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta 1.39\) (d, \(J = 6.0\) Hz, 6H), 3.51 (s, 3H), 3.86 (s, 3H), 4.59 (m, \(J = 6.0\) Hz, 1H), 5.23 (s, 2H), 5.82 (s, 2H), 6.79 (s, 1H), 7.30 (s, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): 21.94, 56.30, 56.32, 71.28, 95.39, 102.39, 118.45, 145.15, 150.71, 157.43.

4.6. Synthesis of lamellarin D (1)

4.6.1. Dimethyl 3-(4-isopropoxy-3-methoxyphenyl)-1-[2-(3-isopropoxy-4-methoxyphenyl)ethyl]-4-(trifluoromethanesulfonyloxy)pyrrole-2,5-dicarboxylate (25). Under an argon atmosphere, a degassed solution of Na\(_2\)CO\(_3\) (1.40 g, 13.2 mmol) in water (4.0 mL) was
added to a solution of 6 (1.34 g, 2.00 mmol), 7 (420 mg, 2.00 mmol) and Pd(PPh₃)₄ (48.0 mg, 41.5 µmol) in THF (40 mL) at room temperature and the mixture was refluxed for 4 h. The mixture was cooled to room temperature and evaporated under reduced pressure. The products were extracted with dichloromethane and the extract was washed successively with water and brine, dried over Na₂SO₄, and evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N (toluene-ethyl acetate=10:1) to give 25 as colorless solid (1.05 g, 76%). Recrystallization from dichloromethane-hexane gave colorless prisms. Mp 90-92 °C; IR (KBr): 2977, 2938, 1728, 1705, 1509, 1425, 1304, 1260, 1174, 1135, 1110, 990, 817 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.36 (d, J = 6.6 Hz, 6H), 1.39 (d, J = 6.3 Hz, 6H), 3.01 (t, J = 7.3 Hz, 2H), 3.58 (s, 3H), 3.83 (s, 6H), 3.91 (s, 3H), 4.45-4.62 (m, 2H), 4.95 (t, J = 7.3 Hz, 2H), 6.69-6.82 (m, 4H), 6.89 (d, J = 8.8 Hz, 1H), 7.18 (d, J = 7.7 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): 21.98, 22.13, 37.51, 48.68, 51.65, 51.76, 55.96, 56.03, 71.35, 71.42, 112.07, 114.22, 115.23, 116.70, 117.34, 117.90 (q, J = 321 Hz), 121.44, 122.51, 122.67, 122.72, 122.81, 129.98, 135.76, 146.99, 147.19, 149.13, 149.67, 159.05, 160.76. EIMS m/z (%): 687 (100), 603 (20), 554 (13), 470 (25), 438 (27), 411 (19). Anal. Calcd for C₃₁H₃₆F₃NO₁₁S: C, 54.14; H, 5.28; N, 2.04. Found: C, 53.87; H, 5.25; N, 1.91.

4.6.2. Methyl 3,4-dihydro-7-isoproxy-1-(4-isoproxy-3-methoxyphenyl)-3-[2-(3-isoproxy-4-methoxyphenyl)ethyl]-8-methoxy-4-oxo-[1]benzopyrano[3,4-b]pyrrole-2-carboxylate (27). Under an argon atmosphere, a degassed solution of Na₂CO₃ (2.10 g, 19.8 mmol) in water (6.0 mL) was added to a solution of 25 (2.06 g, 3.00 mmol), 9 (1.62 g, 6.00 mmol) and Pd(PPh₃)₄ (288 mg, 249 µmol) in THF (60 mL) at room temperature and the mixture was refluxed for 18 h. The mixture was cooled to room temperature and evaporated under reduced pressure. The residue was dissolved in methanol (40 mL) and conc. HCl (4.0 mL) was added dropwise to the solution at room temperature. After being refluxed for 1 h, the mixture was cooled to room temperature and evaporated under reduced pressure. The product was extracted with dichloromethane and the extract was washed successively with water and brine, dried over Na₂SO₄, and evaporated under reduced pressure. The residue was purified by column chromatography over Chromatorex NH-DM1020 silica gel (hexane-ethyl acetate=5:1)
to give 27 as colorless solid (2.03 g, 98%). Recrystallization from dichloromethane-hexane gave colorless needles. Mp 149-150 °C; IR (KBr): 2975, 1728, 1702, 1536, 1509, 1438, 1262, 1215, 1158, 1112, 1039, 1012, 940, 859, 768 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.32-1.46 (m, 18H), 3.08 (t, J = 7.6 Hz, 2H), 3.40 (s, 3H), 3.57 (s, 3H), 3.82 (s, 3H), 3.83 (s, 3H), 4.43-4.64 (m, 3H), 5.11 (t, J = 7.6 Hz, 2H), 6.56 (s, 1H), 6.80 (s, 1H), 6.80 (s, 1H), 6.83-6.89 (m, 3H), 6.90 (s, 1H), 6.99 (d, J = 8.0 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): 21.80, 22.13, 22.17, 37.80, 48.63, 51.61, 55.36, 56.03, 71.25, 71.50, 103.32, 104.88, 109.56, 112.00, 114.07, 115.66, 116.57, 117.45, 121.42, 122.45, 124.22, 126.77, 127.21, 129.27, 130.35, 145.72, 146.57, 146.63, 147.16, 147.26, 148.97, 150.12, 155.00, 161.18. EIMS m/z (%) 687 (100), 411 (26), 379 (26). Anal. Calcd for C₃₀H₄₅NO₁₆: C, 68.11; H, 6.59; N, 2.04. Found: C, 68.18; H, 6.68; N, 1.99.

4.6.3.

3,4-Dihydro-7-isopropoxy-1-(4-isopropoxy-3-methoxyphenyl)-3-[2-(3-isopropoxy-4-methoxyphenyl)ethyl]-8-methoxy-4-oxo-[1]benzopyrano[3,4-b]pyrrole-2-carboxylic acid (29). Under an argon atmosphere, a suspension of 27 (250 mg, 0.363 mmol) in a degassed mixture of 40% aqueous KOH (15 mL) and ethanol (15 mL) was refluxed for 3 h. The solution was cooled to room temperature and concentarted under reduced pressure. The pH of the solution was adjusted to 2-3 with conc. HCl and the product was extracted with dichloromethane. The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure. The residue was dissolved in dichloromethane (30 mL) and p-toluenesulfonic acid monohydrate (40 mg, 0.210 mmol) was added. The mixture was refluxed for 1 h and evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N (hexane-ethyl acetate=1:2) to give 29 as pale brown solid (220 mg, 90%). Recrystallization from dichloromethane-hexane gave pale brown powder. Mp 160-161 ºC; IR (KBr): 3232, 2976, 2934, 1720, 1535, 1509, 1438, 1406, 1262, 1138, 1111, 1033, 1012, 943, 921, 853, 769 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.30-1.44 (m, 18H), 3.08 (t, J = 7.7 Hz, 2H), 3.39 (s, 3H), 3.81 (s, 3H), 3.84 (s, 3H), 4.45-4.65 (m, 3H), 5.17 (t, J = 7.7 Hz, 2H), 6.45 (s, 1H), 6.79 (s, 2H), 6.86 (s, 1H), 6.88-6.95 (m, 3H), 7.02 (d, J = 8.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): 21.78, 22.09, 22.22, 37.74, 48.77, 55.35, 56.04, 71.40, 71.42, 71.54, 103.29, 104.83, 109.32, 112.16, 114.15, 115.40,
116.76, 118.40, 121.48, 122.49, 125.71, 126.47, 126.91, 127.70, 130.20, 145.69, 146.64, 147.08, 147.10, 147.38, 149.08, 150.22, 154.94, 163.47. EIMS m/z (%): 673 (100), 629 (43), 397 (41), 379 (30), 353 (20). Anal. Calcd for C_{38}H_{43}NO_{10}: C, 67.74; H, 6.43; N, 2.08. Found: C, 67.79; H, 6.39; N, 2.05.

4.6.4.

7-Isopropoxy-1-(3-isopropoxy-4-methoxyphenyl)-3-[2-(3-isopropoxy-4-methoxyphenyl)ethyl]-8-methoxy-[1]benzopyrano[3,4-b]pyrrol-4(3H)-one (4). Under an argon atmosphere, a mixture of 29 (337 mg, 0.500 mmol) and copper(I) oxide (71.4 mg, 0.499 mmol) in quinoline (15 mL) was heated at 220 °C for 7 min. The mixture was cooled to room temperature and diluted with water. The product was extracted with dichloromethane and the extract was washed succesively with 6 M aqueous HCl and brine, dried over Na_{2}SO_{4}, and evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N (hexane-ethyl acetate=3:1) to give 4 as colorless solid (297 mg, 94%). Recrystallization from dichloromethane-diethyl ether gave colorless powder. Mp 133-134 °C; IR (KBr): 2973, 2931, 1716, 1509, 1466, 1425, 1388, 1261, 1234, 1211, 1166, 1139, 1108, 1030 cm^{-1}; ^1H NMR (300 MHz, CDCl_3): δ 1.25 (d, J= 6.3 Hz, 6H), 1.40 (d, J= 6.0 Hz, 6H), 1.41 (d, J= 6.0 Hz, 6H), 3.09 (t, J= 6.9 Hz, 2H), 3.53 (s, 3H), 3.82 (s, 3H), 3.84 (s, 3H), 4.39 (m, J= 6.0 Hz, 1H), 4.50-4.64 (m, 2H), 4.64 (t, J= 6.9 Hz, 2H), 6.61 (d, J= 1.9 Hz, 1H), 6.69 (dd, J= 1.9 and 8.0 Hz, 1H), 6.73 (s, 1H), 6.80 (d, J= 8.0 Hz, 1H), 6.86-6.98 (m, 4H), 7.10 (s, 1H); ^13C NMR (100 MHz, CDCl_3): 21.83, 22.04, 37.61, 50.98, 55.79, 55.94, 55.95, 71.27, 71.44, 71.67, 103.57, 105.16, 110.49, 112.05, 113.73, 114.75, 116.02, 116.49, 119.07, 121.21, 121.99, 127.09, 127.17, 130.37, 131.67, 145.92, 146.45, 146.55, 147.07, 147.15, 149.02, 150.23, 155.34. EIMS m/z (%): 629 (100), 587 (9), 545 (8), 366 (11), 353 (42). Anal. Calcd for C_{77}H_{63}NO_{10}: C, 70.57; H, 6.88; N, 2.22. Found: C, 70.68; H, 6.85; N, 2.23.

4.6.5.


Under an argon atmosphere, a solution of PIFA (81.5 mg, 0.190 mmol) and BF_3·OEt_2 (48 µL, 0.389 mmol) in dichloromethane (3.8 mL) was added dropwise to a solution of
4 (100 mg, 0.159 mmol) in dichloromethane (16 mL) at –40 °C. After being stirred for 1.5 h, the mixture was quenched with 2 M aqueous NH₃ and allowed to warm to room temperature. The product was extracted with dichloromethane and the extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N (hexane-ethyl acetate=1:1) to give 31 as colorless solid (87.3 mg, 88%). Recrystallization from dichloromethane-diethyl ether gave colorless powder. Mp 229.5-230.5 °C; IR (KBr): 2973, 2932, 1699, 1509, 1483, 1417, 1271, 1240, 1162, 1111, 1038, 1015, 939 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.35-1.43 (m, 18H), 3.10 (t, J = 6.7 Hz, 2H), 3.34 (s, 3H), 3.43 (s, 3H), 3.82 (s, 3H), 4.49-4.65 (m, 3H), 4.71-4.90 (m, 2H), 6.67 (s, 1H), 6.74 (s, 1H), 6.77 (s, 1H), 6.92 (s, 1H), 7.02-7.12 (m, 3H); ¹³C NMR (100 MHz, CDCl₃): 21.83, 21.91, 21.94, 22.06, 28.63, 42.43, 55.09, 55.42, 56.12, 71.33, 71.40, 71.77, 103.46, 104.83, 109.12, 110.31, 113.58, 114.56, 114.74, 116.90, 120.11, 123.31, 126.25, 128.08, 128.49, 135.81, 145.80, 146.39, 146.81, 146.86, 147.17, 148.51, 151.15, 155.45. EIMS m/z (%): 627 (100), 585 (17), 543 (31), 501 (26). Anal. Calcd for C₃₇H₄₁NO₈: C, 70.79; H, 6.58; N, 2.23. Found: C, 70.59; H, 6.61; N, 2.15.

Method 2. Under an argon atmosphere, a mixture of 29 (50.0 mg, 0.0742 mmol) and Pd(OAc)₂ (18.3 mg, 0.0816 mmol) in acetonitrile (22 mL) was refluxed for 12 h. The mixture was cooled to room temperature and evaporated under reduced pressure. The residue was purified by flash chromatography over Silica Gel 60N (hexane-ethyl acetate=2:1) to give 31 (30.2 mg, 65%) and 4 (6.6 mg, 14%).

4.6.6. 3,11-Diisopropoxy-14-(4-isopropoxy-3-methoxyphenyl)-2,12-dimethoxy-6H-[1]benzopyran[4′,3′:4,5]pyrrolo[2,1-a]isoquinolin-6-one (33). A solution of DDQ (54.2 mg, 0.239 mmol) in toluene (10 mL) was added dropwise to a solution of 31 (100 mg, 0.159 mmol) in toluene (10 mL) at room temperature. The mixture was refluxed for 18 h and evaporated under reduced pressure. The residue was purified by column chromatography over Chromatorex NH-DM1020 silica gel (hexane-ethyl acetate=3:1) to give 33 as colorless solid (97.0 mg, 97%). Recrystallization from dichloromethane-diethyl ether gave pale brown needles. Mp 191-192 °C; IR (KBr): 2975, 2933, 1691, 1509, 1487, 1430, 1266, 1223, 1179, 1111, 1035, 944, 855 cm⁻¹; ¹H
NMR (300 MHz, CDCl₃): δ 1.41 (d, J = 6.3 Hz, 6H), 1.44 (d, J = 6.0 Hz, 12H), 3.44 (s, 3H), 3.45 (s, 3H), 3.84 (s, 3H), 4.53-4.76 (m, 3H), 6.76 (s, 1H), 6.98 (s, 1H), 7.03 (d, J = 7.4 Hz, 1H), 7.11 (s, 1H), 7.13 (s, 1H), 7.17-7.20 (m, 3H), 9.24 (d, J = 7.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): 21.82, 21.83, 21.88, 21.91, 21.92, 55.10, 55.41, 56.13, 71.17, 71.44, 71.80, 103.44, 105.44, 105.59, 107.75, 109.88, 110.41, 110.93, 112.19, 114.98, 116.89, 118.92, 123.07, 123.80, 124.59, 128.69, 129.31, 134.27, 146.39, 146.47, 147.04, 147.73, 148.32, 150.04, 151.26, 155.40. EIMS m/z (%): 625 (100), 583 (15), 541 (20), 499 (33). Anal. Calcd for C₇₁H₃₉NO₅: C, 71.02; H, 6.28; N, 2.24. Found: C, 71.24; H, 6.32; N, 2.38.

4.6.7. Lamellarin D (1). Under an argon atmosphere, a heptane solution of BCl₃ (1.0 M, 144 µL, 0.144 mmol) was added dropwise to a solution of 33 (10.0 mg, 0.0160 mmol) in dichloromethane (3.0 mL) at −78 °C. After being stirred for 30 min at this temperature, the reaction mixture was allowed to warm to room temperature and stirred for an additional 3 h. The mixture was quenched with saturated aqueous NaHCO₃ and extracted with ethyl acetate. The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N (hexane-ethyl acetate=1:1) to give 1 as pale brown powder (8.0 mg, quant.). Mp > 300 °C (sealed capillary)(lit.²⁴b Mp > 300 °C; IR (KBr): 3378, 2925, 1671, 1595, 1546, 1491, 1459, 1433, 1404, 1369, 1276, 1220, 1155, 1041 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆): δ 3.38 (s, 3H), 3.39 (s, 3H), 3.77 (s, 3H), 6.71 (s, 1H), 6.87 (s, 1H), 7.01 (dd, J = 2.0 and 8.1 Hz, 1H), 7.10 (d, J = 8.1 Hz, 1H), 7.14 (s, 1H), 7.15 (d, J = 2.0 Hz, 1H), 7.19 (s, 1H), 7.21 (d, J = 7.3 Hz, 1H), 9.00 (d, J = 7.3 Hz, 1H), 9.35 (s, 1H), 9.84 (br s, 1H), 9.95 (br s, 1H); ¹³C NMR (100 MHz, DMSO-d₆): δ 54.36, 54.89, 55.82, 103.49, 105.13, 105.52, 106.15, 108.10, 110.58, 111.26, 112.14, 114.77, 116.17, 117.31, 121.77, 123.55, 124.41, 125.19, 128.71, 133.81, 144.28, 146.03, 146.52, 147.53, 148.00, 148.20, 148.39, 154.05. HREIMS m/z. Calcd for C₂₉H₂₁NO₅ (M⁺): 499.1267. Found: 499.1248.

4.7. Synthesis of lamellarins L (2) and N (3).

4.7.1. Dimethyl 3-(3-isopropoxy-4-methoxyphenyl)-1-[2-(3-isopropoxy-4-methoxyphenyl)ethyl]-4-(t
rifluoromethanesulfonyloxy)pyrrole-2,5-dicarboxylate (26). This compound was prepared from 6 (2.69 g, 4.00 mmol) and 8 (840 mg, 4.00 mmol) in a similar manner as described for 25. After chromatographic purification over Silica Gel 60N (toluene-ethyl acetate=10:1), 26 was obtained as colorless solid (2.11 g, 77%). Recrystallization from diethyl ether-hexane gave colorless prisms. Mp 96.5-98 °C; IR (KBr): 2976, 2952, 1151, 1148, 1420, 1307, 1263, 1231, 1135, 991, 824 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 1.36 (d, \(J = 6.0\) Hz, 6H), 1.37 (d, \(J = 6.0\) Hz, 6H), 3.01 (t, \(J = 7.3\) Hz, 2H), 3.58 (s, 3H), 3.83 (s, 3H), 3.89 (s, 3H), 3.91 (s, 3H), 4.44-4.56 (m, 2H), 4.94 (t, \(J = 7.3\) Hz, 2H), 6.69-6.75 (m, 2H), 6.77-6.82 (m, 3H), 6.87 (d, \(J = 8.8\) Hz, 1H); \(^13\)C NMR (100 MHz, CDCl\(_3\)): 22.02, 22.13, 37.51, 48.70, 51.74, 51.76, 55.82, 56.03, 71.36, 71.65, 111.02, 112.07, 116.72, 117.29, 117.92 (q, \(J = 321\) Hz), 118.49, 121.43, 122.00, 122.76, 122.80, 123.27, 129.99, 135.77, 146.41, 147.19, 149.13, 150.33, 159.08, 160.75. EIMS m/z (%): 687 (100), 645 (23), 603 (23), 554 (21), 470 (41), 438 (29), 411 (37). Anal. Calcd for C\(_{31}\)H\(_{28}\)F\(_3\)NO\(_{10}\): C, 54.14; H, 5.28; N, 2.04. Found: C, 54.18; H, 5.32; N, 1.98.

4.7.2. Methyl 3,4-dihydro-7-isopropoxy-1-(3-isopropoxy-4-methoxyphenyl)-3-[2-(3-isopropoxy-4-methoxyphenyl)ethyl]-8-methoxy-4-oxo-[1]benzopyran[3,4-b]pyrrole-2-carboxylate (28). This compound was prepared from 26 (2.06 g, 3.00 mmol) and 9 (1.62 g, 6.00 mmol) in a similar manner as described for 27. After chromatographic purification over Silica Gel 60N (dichloromethane-dichloromethane-ethyl acetate=5:1), 28 was obtained as colorless solid (1.95 g, 95%). Recrystallization from dichloromethane-diethyl ether gave colorless powder. Mp 163-164 °C; IR (KBr): 2976, 2934, 1711, 1515, 1486, 1439, 1226, 1158, 1109, 1019, 969, 937, 857 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 1.32-1.43 (m, 18H), 3.08 (t, \(J = 7.6\) Hz, 2H), 3.40 (s, 3H), 3.59 (s, 3H), 3.83 (s, 3H), 3.91 (s, 3H), 4.45-4.59 (m, 3H), 5.10 (t, \(J = 7.6\) Hz, 2H), 6.52 (s, 1H), 6.80 (s, 1H), 6.80 (s, 1H), 6.84-6.92 (m, 4H), 6.98 (d, \(J = 8.2\) Hz, 1H); \(^13\)C NMR (100 MHz, CDCl\(_3\)): 21.79, 21.94, 22.06, 22.12, 37.82, 48.67, 51.70, 55.45, 56.05, 71.27, 71.38, 71.44, 103.26, 104.92, 109.57, 111.58, 111.99, 116.61, 117.44, 117.96, 121.44, 122.87, 124.21, 126.67, 126.86, 129.18, 130.38, 145.74, 146.58, 146.86, 147.17, 147.28, 148.98, 149.90, 155.01, 161.19. EIMS m/z (%): 687 (100), 453 (11), 411 (20), 379 (26). Anal. Calcd for C\(_{39}\)H\(_{45}\)NO\(_{16}\): C, 68.11; H, 6.59; N, 2.04. Found: C, 67.85; H,
4.7.3.
3,4-Dihydro-7-isopropoxy-1-(3-isopropoxy-4-methoxyphenyl)-3-[2-(3-isopropoxy-4-methoxyphenyl)ethyl]-8-methoxy-4-oxo-[1]benzopyran[3,4-\textit{b}]pyrrole-2-carboxylic acid (30). This compound was prepared from 28 (250 mg, 0.363 mmol) in a similar manner as described for 29. After chromatographic purification over Silica Gel 60N (ethyl acetate), 30 was obtained as colorless solid (222 mg, 91%). Recrystallization from dichloromethane-hexane gave colorless powder. Mp 204.5-206.5 °C; IR (KBr): 3331, 2977, 2934, 1727, 1702, 1509, 1441, 1405, 1263, 1238, 1181, 1141, 1112, 1017, 773 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \textsuperscript{\delta} 1.31-1.41 (m, 18H), 3.08 (t, J = 7.7 Hz, 2H), 3.40 (s, 3H), 3.82 (s, 3H), 3.91 (s, 3H), 4.46-4.60 (m, 3H), 5.17 (t, J = 7.7 Hz, 2H), 6.45 (s, 1H), 6.79 (s, 2H), 6.87-6.97 (m, 4H), 7.01 (d, J = 8.2 Hz, 1H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): 21.75, 21.93, 21.98, 22.07, 37.75, 48.80, 55.40, 56.01, 56.03, 71.28, 71.36, 71.45, 103.15, 104.78, 109.28, 111.74, 112.06, 116.68, 117.79, 118.40, 121.44, 122.77, 125.77, 126.13, 126.92, 127.59, 130.18, 145.67, 146.60, 147.06, 147.36, 149.03, 150.11, 154.95, 163.68. EIMS m/z (%): 673 (100), 629 (19), 397 (33), 379 (28). \textit{Anal.} Calcd for C\textsubscript{38}H\textsubscript{43}NO\textsubscript{16}: C, 67.74; H, 6.43; N, 2.08. Found: C, 68.06; H, 6.39; N, 2.15.

4.7.4.
7-Isopropoxy-1-(3-isopropoxy-4-methoxyphenyl)-3-[2-(3-isopropoxy-4-methoxyphe
nyl)ethyl]-8-methoxy-[1]benzopyran[3,4-\textit{b}]pyrrol-4(3\textit{H})-one (5). This compound was prepared from 30 (900 mg, 1.34 mmol) in a similar manner as described for 4. After chromatographic purification over Silica Gel 60N (hexane-ethyl acetate=3:1), 5 was obtained as colorless solid (830 mg, 99%). Recrystallization from dichloromethane-hexane gave colorless powder. Mp 113.5-114 °C; IR (KBr): 2978, 2933, 2835, 1710, 1551, 1509, 1460, 1397, 1258, 1175, 1138, 1112, 1025 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \textsuperscript{\delta} 1.27 (d, J = 6.0 Hz, 6H), 1.36 (d, J = 6.0 Hz, 6H), 1.41 (d, J = 6.0 Hz, 6H), 3.09 (t, J = 6.9 Hz, 2H), 3.54 (s, 3H), 3.82 (s, 3H), 3.90 (s, 3H), 4.41 (m, J = 6.0 Hz, 1H), 4.47-4.63 (m, 2H), 4.64 (t, J = 6.9 Hz, 2H), 6.65 (d, J = 1.7 Hz, 1H), 6.68 (dd, J = 1.7 and 8.0 Hz, 1H), 6.74 (s, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.91-6.95 (m, 4H), 7.09 (s, 1H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): 21.82, 22.03, 22.12, 37.63, 50.94, 55.89, 55.96, 56.06, 71.26, 71.38, 71.42, 103.49, 105.23, 110.48, 111.71, 111.99, 114.73,
116.46, 117.24, 119.02, 121.23, 122.36, 126.55, 127.09, 130.33, 131.60, 145.92, 146.44, 146.99, 147.07, 147.14, 149.01, 149.72, 155.34. EIMS m/z (%): 629 (100), 587 (9), 545 (13), 408 (11), 395 (12), 353 (38). Anal. Calcd for C\textsubscript{37}H\textsubscript{43}NO\textsubscript{8}: C, 70.57; H, 6.88; N, 2.22. Found: C, 70.85; H, 6.95; N, 2.16.

4.7.5. 
8,9-Dihydro-3,11-diisopropoxy-14-(3-isoproxy-4-methoxyphenyl)-2,12-dimethoxy-6\textsubscript{H}-[1]benzopyrano[4’,3’:4,5]pyrrolo[2,1-a]isoquinolin-6-one (32). Method 1. This compound was prepared from 5 (470 mg, 0.746 mmol) in a similar manner as described for 31 from 4. After chromatographic purification over Silica Gel 60N (hexane-ethyl acetate=1:1), 32 was obtained as colorless solid (423 mg, 90%). Recrystallization from dichloromethane-diethyl ether gave colorless powder. Mp 206.5-207.5 °C (lit.\textsuperscript{6} Mp 174 °C: the sample containing one molecule of acetone); IR (KBr): 2974, 2933, 1691, 1542, 1509, 1484, 1439, 1268, 1241, 1176, 1113, 1042, 940, 850 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \delta 1.30-1.41 (m, 18 H), 3.10 (t, J = 6.6 Hz, 2H), 3.34 (s, 3H), 3.34 (s, 3H), 3.43 (s, 3H), 3.92 (s, 3H), 4.47-4.61 (m, 3H), 4.70-4.89 (m, 2H), 6.66 (s, 1H), 6.72 (s, 1H), 6.77 (s, 1H), 6.92 (s, 1H), 7.03-7.09 (m, 3H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): 21.82, 21.91, 21.99, 22.05, 28.63, 42.42, 55.07, 55.46, 56.29, 71.28, 71.36, 103.43, 104.86, 109.10, 110.34, 112.59, 113.55, 114.71, 117.86, 120.14, 123.59, 126.23, 127.89, 128.12, 135.83, 145.83, 146.39, 146.87, 147.16, 147.90, 148.55, 149.92, 155.46. EIMS m/z (%): 627 (100), 585 (13), 543 (32), 501 (14). Anal. Calcd for C\textsubscript{37}H\textsubscript{43}NO\textsubscript{8}: C, 70.79; H, 6.58; N, 2.23. Found: C, 71.03; H, 6.53; N, 2.16.

Method 2. This compound was also prepared from 30 (50.0 mg, 0.0742 mmol) in a similar manner as described for 31 from 29. After chromatographic purification over Silica Gel 60N (hexane-ethyl acetate=2:1), 32 (30.5 mg, 65%) and 5 (7.1 mg, 15%) were obtained.

4.7.6. 
3,11-Diisopropoxy-14-(3-isoproxy-4-methoxyphenyl)-2,12-dimethoxy-6\textsubscript{H}-[1]benzopyrano[4’,3’:4,5]pyrrolo[2,1-a]isoquinolin-6-one (34). This compound was prepared from 32 (100 mg, 0.159 mmol) in a similar manner as described for 33. After chromatographic purification over Chromatorex NH-DM1020 silica gel (hexane-ethyl
acetate=3:1), 34 was obtained as pale yellow solid (95.6 mg, 96%). Recrystallization from dichloromethane-diethyl ether gave pale yellow needles. Mp 169-170 °C; IR (KBr): 2976, 2933, 1509, 1487, 1420, 1267, 1223, 1178, 1111, 1037, 971, 939, 857 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.35 (dd, J= 1.4 and 6.0 Hz, 6H), 1.41 (d, J= 6.0 Hz, 6H), 1.44 (d, J= 6.0 Hz, 6H), 3.44 (s, 3H), 3.45 (s, 3H), 3.96 (s, 3H), 4.47-4.63 (m, 2H), 4.70 (m, J= 6.0 Hz, 1H), 6.74 (s, 1H), 6.98 (s, 1H), 7.03 (d, J= 7.3 Hz, 1H), 7.10 (s, 1H), 7.13 (d, J= 1.7 Hz, 1H), 7.15-7.20 (m, 3H), 9.23 (d, J= 7.3 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): 21.80, 21.86, 21.95, 55.08, 55.43, 56.34, 71.09, 71.25, 71.36, 103.32, 105.40, 105.49, 107.66, 109.87, 110.30, 110.90, 112.17, 112.61, 118.07, 118.91, 123.02, 123.97, 124.57, 128.11, 129.31, 134.28, 146.36, 146.46, 147.69, 148.03, 148.28, 150.02, 150.06, 155.38. HREIMS m/z. Calcd for C₁₉H₁₉NO₈ (M⁺): 625.2676. Found: 625.2671.

4.7.7. Lamellarin L (2). This compound was prepared from 32 (20.0 mg, 0.0319 mmol) in a similar manner as describd for 1. After chromatographic purification over Silica Gel 60N (ethyl acetate), 2 was obtained as colorless powder (15.6 mg, 98%). Mp > 300 °C (sealed capillary) (Lit.° Mp 301 °C); IR (KBr): 3423, 2934, 1686, 1586, 1484, 1421, 1275, 1248, 1211, 1164, 1044, 1016 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆): δ 3.01 (t, J= 6.7 Hz, 2H), 3.29 (s, 3H), 3.38 (s, 3H), 3.83 (s, 3H), 4.50-4.59 (m, 1H), 4.60-4.69 (m, 1H), 6.67 (s, 1H), 6.68 (s, 1H), 6.75 (s, 1H), 6.80 (s, 1H), 6.89 (s, 1H), 6.90 (dd, J= 2.0 and 8.3 Hz, 1H), 7.16 (d, J= 8.3 Hz, 1H), 9.30 (s, 1H), 9.44 (s, 1H), 9.67 (s, 1H); ¹³C NMR (100 MHz, DMSO-d₆): δ 27.36, 41.82, 54.53, 54.90, 55.89, 71.09, 103.37, 104.83, 108.46, 109.05, 112.10, 113.22, 113.69, 115.06, 117.61, 117.76, 121.41, 126.94, 127.12, 127.16, 135.51, 144.17, 145.36, 145.69, 146.53, 146.79, 147.21, 147.35, 153.97. HREIMS m/z. Calcd for C₂₅H₃₉NO₈ (M⁺): 501.1424. Found: 501.1420.

4.7.8. Lamellarin N (3). This compound was prepared from 34 (20.0 mg, 0.0320 mmol) in a similar manner as described for 1. After chromatographic purification over Silica Gel 60N (ethyl acetate), 3 was obtained as pale brown powder (14.0 mg, 88%). Mp 280-300 °C (dec.) (sealed capillary); IR (KBr): 3430, 2928, 1671, 1558, 1490, 1425, 1276, 1217, 1082, 1042, 955, 863 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆): δ 3.40 (s, 3H), 3.40 (s, 3H), 3.87 (s, 3H), 6.76 (s, 1H), 6.87 (s, 1H), 7.01 (dd, J= 2.0 and 8.8 Hz, 1H), 7.01 (d, J= 2.0 Hz, 1H), 7.17 (s, 1H), 7.19 (s, 1H), 7.20 (d, J= 7.3 Hz, 1H), 7.23 (d, J=
8.8 Hz, 1H), 8.99 (d, J= 7.3 Hz, 1H), 9.41 (s, 1H), 9.86 (s, 1H), 9.97 (s, 1H); $^{13}$C NMR (100 MHz, DMSO-d$_6$): δ 54.37, 54.89, 55.96, 103.52, 105.07, 105.46, 106.24, 107.99, 110.23, 111.29, 112.14, 113.40, 117.19, 117.99, 121.78, 121.86, 124.41, 127.12, 128.48, 133.59, 144.28, 146.02, 147.42, 147.52, 147.66, 148.00, 148.23, 154.03. HREIMS m/z. Caled for C$_{28}$H$_{21}$NO$_8$ (M$^+$): 499.1267. Found: 499.1259.

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References


Scheme 1. Retrosynthetic analysis of lamellarins D (1), L (2), and N (3).

Scheme 2. Synthesis of 3,4-dihydroxypyrole bistrilate 6. Reagents and conditions: (a) CH$_3$NO$_2$, AcO$^-$NH$_3^+$, AcOH, 100 °C, 6 h (74%); (b) LiAlH$_4$, THF, reflux, 7 h (65%); (c) BrCH$_2$CO$_2$Me, NaHCO$_3$, CH$_3$CN, reflux, 2 h (83%); (d) (CO$_2$Me)$_2$, NaH, THF, reflux, 3 h (87%); (e) (CF$_3$SO$_2$)$_2$O, pyridine, 0 °C, 2 h (91%).
**Scheme 3.** Synthesis of arylboronic acids 7, 8, and 9. *Reagents and conditions:* (a) NBS, DMF, 0 °C, 0.5 h (86%); (b) i-PrBr, K$_2$CO$_3$, DMSO, 55 °C, 2 h (84%); (c) (1) t-BuLi, THF, -78 °C, 1 h, (2) B(OMe)$_3$, -78 °C, 1 h, then r.t., 1 h (56%); (d) CH$_3$SO$_2$Cl, Et$_3$N, CH$_2$Cl$_2$, 0 °C, 0.5 h (96%); (e) NBS, DMF, r.t., 24 h (96%); (f) LDA, THF, 0 °C, 5 min (91%); (g) (1) n-BuLi, Et,O, -78 °C, 1 h, (2) B(OMe)$_3$, -78 °C, 1 h, then r.t., 1 h, (3) 30% H$_2$O$_2$, AcOH, r.t., 16 h (91%); (h) i-PrBr, K$_2$CO$_3$, DMSO, 55 °C, 2 h (96%); (i) (1) t-BuLi, THF, -78 °C, 1 h, (2) B(OMe)$_3$, -78 °C, 1 h, then r.t., 1 h (81%); (j) (1) mCPBA, CH$_2$Cl$_2$, 0 °C, 3 h, (2) K$_2$CO$_3$, MeOH, r.t., 1 h (86%); (k) MOMCl, NaH, THF, 0 °C, 2 h, then r.t., 1 h (68%); (l) NBS, DMF, 0 °C, 0.5 h, (98%); (m) (1) t-BuLi, THF, -78 °C, 1 h, (2) B(OMe)$_3$, -78 °C, 1 h, then r.t., 1 h (87%).
Scheme 4. Synthesis of lamellarins D (1), L (2), and N (9). Reagents and conditions: (a) 7 or 8 (1.0 equiv.), Pd(PPh₃)₄ (2 mol%), THF, reflux, 4 h (25: 76%, 26: 77%); (b) (1) 9 (2.0 eq), Pd(PPh₃)₄ (8 mol%), THF, reflux, 18 h, (2) conc. HCl, MeOH, reflux 1 h (27: 98%, 28: 95%); (c) (1) 40% KOH/EtOH (1:1), reflux, 3 h, (2) cat. p-TsOH, CH₂Cl₂, reflux, 1 h (29: 90%, 30: 91%); (d) Cu₂O, quinoline, 220 °C, 7 min (4: 94%, 5: 99%); (e) PhI(OCCF₃)₂, BF₃·OEt₂, CH₂Cl₂, -40 °C, 1.5 h (31: 88%, 32: 90%); (f) Pd(OAc)₂ (1.1 equiv.), CH₂CN, reflux, 12 h (31: 65%, 4: 14%; 32: 65%, 5: 15%); (g) DDQ (1.5 equiv.), toluene, reflux, 18 h (33: 97%, 34: 96%); (h) BCl₃, CH₂Cl₂, -78 °C, 0.5 h, then r.t., 3 h (1: quant., 2: 98%, 3: 88%).
Graphical abstract

Total synthesis of lamellarins D, L, and N
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lamellarin D (R\textsuperscript{1}=H, R\textsuperscript{2}=Me, 5.6-unsaturated)
lamellarin L (R\textsuperscript{1}=Me, R\textsuperscript{2}=H, 5.6-saturated)
lamellarin N (R\textsuperscript{1}=Me, R\textsuperscript{2}=H, 5.6-unsaturated)