Total synthesis of lamellarins D, L, and N

Naotaka Fujikawa,[a] Takeshi Ohta,[a] Tomohiro Yamaguchi,[a] Tsutomu Fukuda,[a] Fumito Ishibashi[b] and Masatomo Iwao[c]*

[a]Graduate School of Science and Technology, [b]Division of Marine Life Science and Biochemistry, Faculty of Fisheries, and [c]Department of Applied Chemistry, Faculty of Engineering, Nagasaki University, 1-14 Bunkyo-machi, Nagasaki 852-8521, Japan

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.

*Corresponding author. Tel./fax: +81 95 819 2681; e-mail:iwao@net.nagasaki-u.ac.jp

1. Introduction

Lamellarin-class marine natural products have received considerable attention due to their unique structures and highly useful biological activities.[1] 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.[2a] The combined X-ray crystallographic and spectroscopic studies revealed that these natural products possess the unprecedented 14-phenyl-6*H*-[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.[2] 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 topoisomarase 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.[4j] 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-dihydroxypyrrole 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**[4e]. 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 exachange 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 [$Pd(PPh_3)_4$ (2 mol%), aq. Na_2CO_3, THF, reflux, 4 h][4j] 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) oxide[11] produced **4**. Intramolecular oxidative biaryl coupling of **4** under Kita's conditions[12] using phenyliodine bis(trifluoroacetate) (PIFA)-boron trifluoride etherate afforded the cyclized product **31** in good yield. Pd(II)-mediated decarboxylative ring closure[4j] 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 trichloride[13] 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 lamelarins 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, 1441, 1334, 1262, 1169, 1138, 1113, 1026, 1005, 957, 806 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{12}H_{15}NO_4$: 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 $LiAlH_4$ (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 K_2CO_3, 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, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{12}H_{19}NO_2$ (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 $NaHCO_3$ (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_2SO_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}; ^1H NMR (300 MHz, $CDCl_3$): δ 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 evapolated 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}; ^1H NMR (300 MHz, $CDCl_3$): δ 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, 37.85, 47.75, 51.76, 56.03, 71.60, 110.38, 111.98, 116.90, 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 Na_2SO_4. 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, 1307, 1245, 1131, 987, 973, 812 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 22.06, 37.24, 48.65, 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 $C_{22}H_{23}F_6NO_{12}S_2$: C, 39.35; H, 3.45; N, 2.09. Found: C, 39.32; H, 3.19; N, 2.02.

4.3. Synthesis of arylboronic 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 Na_2SO_4, 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, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 56.08, 111.43, 114.02, 115.60, 124.01, 144.69, 147.03. HREIMS *m/z*. Calcd for $C_7H_7BrO_2$ (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 K_2CO_3 (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 Na_2SO_4. 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, 836 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 21.99, 56.06, 71.80, 113.07, 115.39, 117.27, 123.26, 146.41, 151.16. HREIMS *m/z*. Calcd for $C_{10}H_{13}BrO_2$ (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 NH_4Cl 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 Na_2SO_4, 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, $CDCl_3$): δ 1.44 (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); ^{13}C NMR (100 MHz, $CDCl_3$): 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 Na_2SO_4. 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, $CDCl_3$): δ 3.17 (s, 3H), 3.88 (s, 3H), 6.92-7.03 (m, 2H), 7.23-7.32 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 38.20, 55.91, 112.83, 120.99, 124.39, 128.12, 138.23, 151.25. HREIMS *m/z*. Calcd for $C_8H_{10}O_4S$ (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 Na_2SO_4, 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, $CDCl_3$): δ 3.20 (s, 3H), 3.88 (s, 3H), 6.89 (d, *J*= 8.8 Hz, 1H), 7.39 (dd, *J*= 2.2 and 8.8 Hz, 1H), 7.45 (d, *J*= 2.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 38.48, 56.20, 112.18, 114.07, 127.44, 130.90, 138.43, 150.73. EIMS *m/z* (%): 282 (59), 280 (57), 203 (97), 201 (100), 94 (98). *Anal*. Calcd for $C_8H_9BrO_4S$: C, 34.18; H, 3.23. Found: C, 34.09; H, 2.98.

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_2SO_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 °C; IR (KBr): 3399, 2974, 2942, 2841, 1592, 1492, 1436, 1333, 1290, 1260, 1225, 1126, 1025, 856, 799 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 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 $C_7H_7BrO_2$: 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 °C. 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 °C. 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_2O_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_2SO_3. The product was extracted with diethyl ether and the extract was washed successively with water and brine, dried over Na_2SO_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 °C/ 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, 1254, 1223, 1130, 1020, 958, 839, 794 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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), 7.01 (dd, *J*= 2.2 and 9.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 21.95, 56.06, 71.75, 112.44, 113.15, 118.72, 123.57, 147.99, 149.51. EIMS *m/z* (%): 246 (35), 244 (35), 204 (98), 202 (100), 189 (52), 187 (53). *Anal.* Calcd for $C_{10}H_{13}BrO_2$: 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, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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 $NaHCO_3$. 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 Na_2SO_4, and evaporated under reduced pressure. The residue was dissolved in methanol (240 mL) and K_2CO_3 (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 Na_2SO_4, 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, 1223, 1129, 1032, 995, 918, 856, 803, 772, 719 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{10}H_{14}O_3$: 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 NH_4Cl and the products were extract with diethyl ether. The extract was washed with brine, dried over Na_2SO_4, 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, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 22.03, 55.83, 56.55, 71.32, 95.16, 105.79, 107.42, 112.73, 145.50, 147.91, 151.48. HREIMS *m/z*. Calcd for $C_{12}H_{18}O_4$ (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 Na_2SO_4, 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, 1017, 977, 921, 845, 804 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 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_4Cl and evapolated 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_2SO_4, and evaporated under reduced presssure. 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, $CDCl_3$): δ 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_2CO_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 $Pd(PPh_3)_4$ (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 Na_2SO_4, 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, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{31}H_{36}F_3NO_{11}S$: 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-isopropoxy-1-(4-isopropoxy-3-methoxyphenyl)-3-[2-(3-isopropoxy-4-methoxyphenyl)ethyl]-8-methoxy-4-oxo-[1]benzopyrano[3,4-*b*]pyrrole-2-carboxylate (27). Under an argon atmosphere, a degassed solution of Na_2CO_3 (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 $Pd(PPh_3)_4$ (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 evapolated 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 Na_2SO_4, 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, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{39}H_{45}NO_{10}$: 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 Na_2SO_4, 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 °C; 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, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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(3*H*)-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_2SO_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); ^{13}C 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 $C_{37}H_{43}NO_8$: C, 70.57; H, 6.88; N, 2.22. Found: C, 70.68; H, 6.85; N, 2.23.

4.6.5.

8,9-Dihydro-3,11-diisopropoxy-14-(4-isopropoxy-3-methoxyphenyl)-2,12-dimethoxy-6*H*-[1]benzopyrano[4',3':4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (31). Method 1. Under an argon atmosphere, a solution of PIFA (81.5 mg, 0.190 mmol) and $BF_3{\cdot}OEt_2$ (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 NH_3 and allowed to warm to room temperature. The product was extracted with dichloromethane and the extract was washed with brine, dried over Na_2SO_4, 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, 1213, 1162, 1111, 1038, 1015, 939 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 21.83, 21.89, 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, 114.64, 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 $C_{37}H_{41}NO_8$: 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-6*H*-[1]benzopyrano[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, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 21.82, 21.83, 21.88, 21.89, 21.91, 21.92, 55.10, 55.41, 56.13, 71.17, 71.44, 71.80, 103.42, 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 $C_{37}H_{39}NO_8$: 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 BCl_3 (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 $NaHCO_3$ and extracted with ethyl acetate. The extract was washed with brine, dried over Na_2SO_4, 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.[4b] Mp > 300 °C); IR (KBr): 3378, 2925, 1671, 1595, 1546, 1491, 1459, 1433, 1404, 1369, 1276, 1220, 1155, 1041 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): 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); ^{13}C NMR (100 MHz, DMSO-d_6): 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 $C_{28}H_{21}NO_8$ (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, 1726, 1513, 1438, 1420, 1307, 1263, 1231, 1135, 991, 824 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 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 $C_{31}H_{36}F_3NO_{11}S$: 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]benzopyrano[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}; ^1H NMR (300 MHz, $CDCl_3$): δ 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), 4.47-4.59 (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 $C_{39}H_{45}NO_{10}$: C, 68.11; H, 6.59; N, 2.04. Found: C, 67.85; H,

6.68; N, 2.02.

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]benzopyrano[3,4-*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^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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). *Anal*. Calcd for $C_{38}H_{43}NO_{10}$: 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-methoxyphenyl)ethyl]-8-methoxy-[1]benzopyrano[3,4-*b*]pyrrol-4(3*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^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{37}H_{43}NO_8$: 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-isopropoxy-4-methoxyphenyl)-2,12-dimethoxy-6*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.[4c] Mp 174 °C: the sample containing one molecule of acetone); IR (KBr): 2974, 2933, 1691, 1542, 1509, 1484, 1439, 1417, 1268, 1241, 1211, 1176, 1113, 1042, 940, 850 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.30-1.41 (m, 18H), 3.10 (t, *J*= 6.6 Hz, 2H), 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{37}H_{41}NO_8$: 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-isopropoxy-4-methoxyphenyl)-2,12-dimethoxy-6*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, 1702, 1509, 1487, 1420, 1267, 1223, 1178, 1111, 1037, 971, 939, 857 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{37}H_{39}NO_8$ (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.[4c] Mp 301 °C); IR (KBr): 3423, 2934, 1686, 1586, 1484, 1421, 1275, 1248, 1211, 1164, 1044, 1016 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): 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); ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.36, 41.82, 54.53, 54.90, 55.89, 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 $C_{28}H_{23}NO_8$ (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}; ^{1}H NMR (400 MHz, DMSO-d_6): 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*. Calcd for $C_{28}H_{21}NO_8$ (M^+): 499.1267. Found: 499.1259.

Acknowledgments

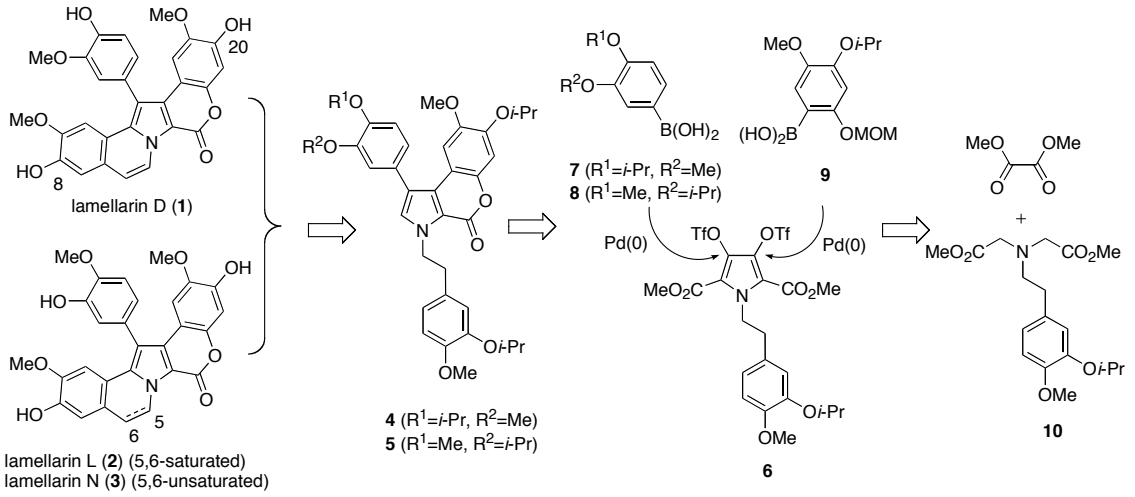
We thank the Ministry of Education, Science, Sports and Culture of Japan for financial support; Grant-in-Aid for Scientific Research (C) (2) (No. 14580612)

References

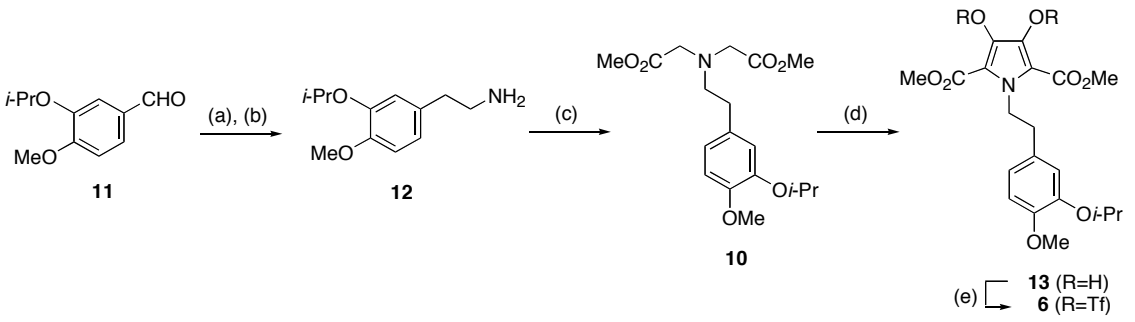
1. For reviews, see: (a) Cironi, P.; Albericio, F.; Álvarez, M. *Progress in Heterocyclic Chemistry* **2004**, *16*, 1-26; (b) Bailly, C. *Curr. Med. Chem. – Anti-Cancer Agents* **2004**, *4*, 363-378.
2. (a) Anderson, R. J.; Faulkner, D. J.; Cun-heng, H.; Van Duyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1985**, *107*, 5492-5495; (b) Lindquist, N.; Fenical, W. *J. Org. Chem.* **1988**, *53*, 4570-4574; (c) Carroll, A. R.; Bowden, B. F.; Coll, J. C. *Aust. J. Chem.* **1993**, *46*, 489-501; (d) Urban, S.; Butler, M. S.; Capton, R. J. *Aust. J. Chem.* **1994**, *47*, 1919-1924; (e) Urban, S.; Hobbs, L.; Hooper, J. N. A.; Capton, R. J. *Aust. J. Chem.* **1995**, *48*, 1491-1494; (f) Urban, S.; Capton, R. J. *Aust. J. Chem.* **1996**, *49*, 711-713; (g) Reddy, M. V. R.; Faulkner, D. J.; Venkateswarlu, Y.; Rao, M. R. *Tetrahedron* **1997**, *53*, 3457-3466; (h) Davis, R. A.; Carroll, A. R.; Pierens, G. K.; Quinn, R. J. *J. Nat. Prod.* **1999**, *62*, 419-424; (i) Reddy, M. V. R.; Rao, M. R.; Rhodes, D.; Hansen, M. S. T.; Rubins, K.; Bushman, F. D.; Venkateswarlu, Y.; Faulkner, D. J. *J. Med. Chem.* **1999**, *42*, 1901-1907; (j) Ham, J.; Kang, H. *Bull. Korean Chem. Soc.* **2002**, *23*, 163-166; (k) Krishnaiah, P.; Reddy, V. L. N.; Venkataramana, G.; Ravinder, K.; Srinivasulu, M.; Raju, T. V.; Ravikumar, K.; Chandrasekar, D.; Ramakrishna, S.; Venkateswarlu, Y. *J. Nat. Prod.* **2004**, *67*, 1168-1171.

3. Quesada, A. R.; Gravalos, M. D. G.; Puentes, J. L. F. *Br. J. Cancer* **1996**, *74*, 677-682.
4. (a) Heim, A.; Terpin, A.; Steglich, W. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 155-156; (b) Ishibashi, F.; Miyazaki, Y.; Iwao, M. *Tetrahedron* **1997**, *53*, 5951-5962; (c) Banwell, M.; Flynn, B.; Hockless, D. *J. Chem. Soc. Chem. Commun.* **1997**, 2259-2260; (d) Banwell, M. G.; Flynn, B. L.; Hockless, D. C. R.; Longmore, R. W.; Rae, A. D. *Aust. J. Chem.* **1998**, *52*, 755-765; (e) Peschko, C.; Winklhofer, C.; Steglich, W. *Chem. Eur. J.* **2000**, *6*, 1147-1152; (f) Ruchirawat, S.; Mutarapat, T. *Tetrahedron Lett.* **2001**, *42*, 1205-1208; (g) Diaz, M.; Guitian, E.; Castedo, L. *Synlett* **2001**, 1164-1166; (h) Ridley, C. P.; Reddy, M. V. R.; Rocha, G.; Bushman, F. D.; Faulkner, D. J. *Bioorg. Med. Chem.* **2002**, *10*, 3285-3290, (i) Ploypradith, P; Jinaglueng, W.; Pavaro, C.; Ruchirawat, S. *Tetrahedron Lett.* **2003**, *44*, 1363-1366; (j) Iwao, M.; Takeuchi, T.; Fujikawa, N.; Fukuda, T.; Ishibashi, F. *Tetrahedron Lett.* **2003**, *44*, 4443-4446; (k) Ploypradith, P.; Mahidol, C.; Sahakitpichan, P.; Wongbundit, S.; Ruchirawat, S. *Angew. Chem. Int. Ed Engl.* **2004**, *43*, 866-868; (l) Handy, S. T.; Zhang, Y.; Bregman, H. *J. Org. Chem.* **2004**, *69*, 2362-2366.
5. Ishibashi, F.; Tanabe, S.; Oda, T.; Iwao, M. *J. Nat. Prod.* **2002**, *65*, 500-504.
6. (a) Facompré, M.; Tardy, C.; Bal-Mahieu, C.; Colson, P.; Perez, C.; Manzanares, I.; Cuevas, C.; Bailly, C. *Canser Res.* **2003**, *63*, 7392-7399; (b) Marco, E.; Laine, W.; Tardy, C.; Lansiaux, A.; Iwao, M.; Ishibashi, F.; Bailly, C.; Gago, F. *J. Med. Chem.* **2005**, *48*, 3796-3807.
7. Merz, A.; Schropp, R.; Dötterl, E. *Synthesis* **1995**, 795-800.
8. (a) Bensel, N.; Pevere, V.; Desmurs, J. R,; Wagner, A.; Mioskowski, C. *Tetrahedron Lett.* **2002**, *43*, 4281-4283; (b) Kraus, G. A.; Cui, W.; Seo, Y. H. *Tetrahedron Lett.* **2002**, *43*, 7077-7078.
9. Ritter, T.; Stanek, K.; Larrosa, I.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 1513-1514.
10. Meyers, A. I.; Snyder, L. *J. Org. Chem.* **1993**, *58*, 36-42.
11. Boger, D. L.; Soenen, D. R.; Boyce, C. W.; Hedrick, M. P.; Jin, Q. *J. Org. Chem.* **2000**, *65*, 2479-2483.
12. (a) Takada, T.; Arisawa, M.; Gyoten, M.; Hamada, R.; Tohma, H.; Kita, Y. *J. Org. Chem.* **1998**, *63*, 7698-7706; (b) Tohma, H.; Morioka, H.; Takizawa, S.; Arisawa, M.; Kita, Y. *Tetrahedron* **2001**, *57*, 345-352; (c) Hamamoto, H.; Anilkumar, G.; Tohma, H.; Kita, Y. *Chem. Eur. J.* **2002**, *8*, 5377-5383.

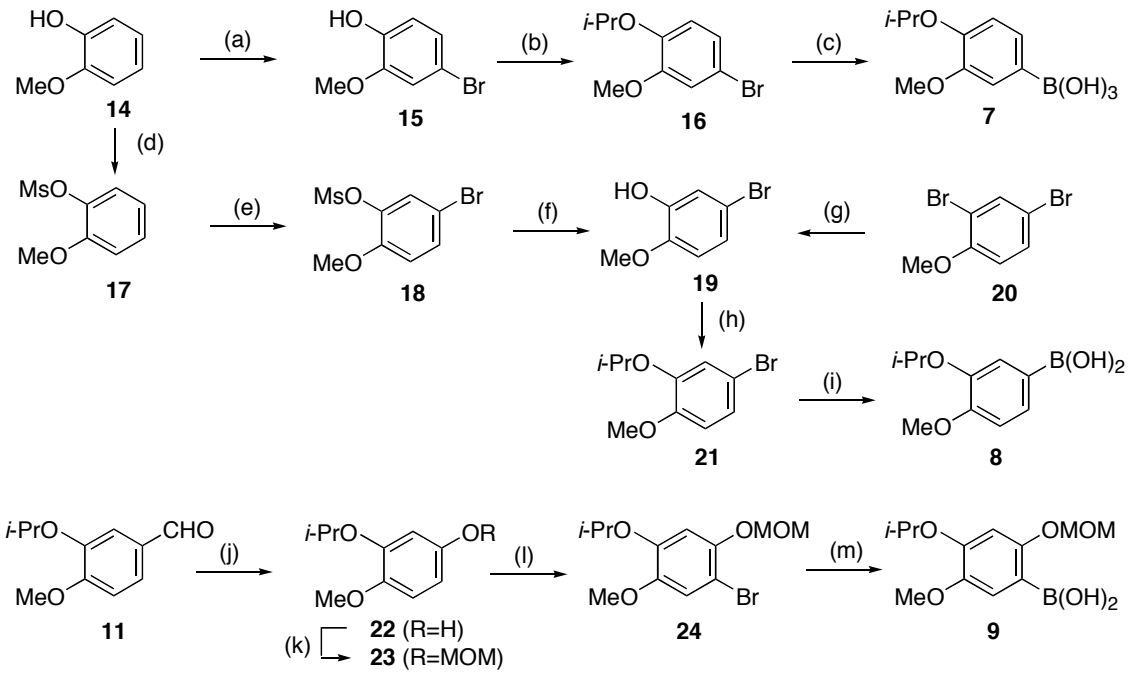
13. (a) Sala, T.; Sargent, M. V. *J. Chem. Soc. Perkin Trans. 1*, **1979**, 2593-2598; (b) Solladié, G.; Pasturel-Jacopé, Y.; Maignan, J. *Tetrahedron* **2003**, *59*, 3315-3321.



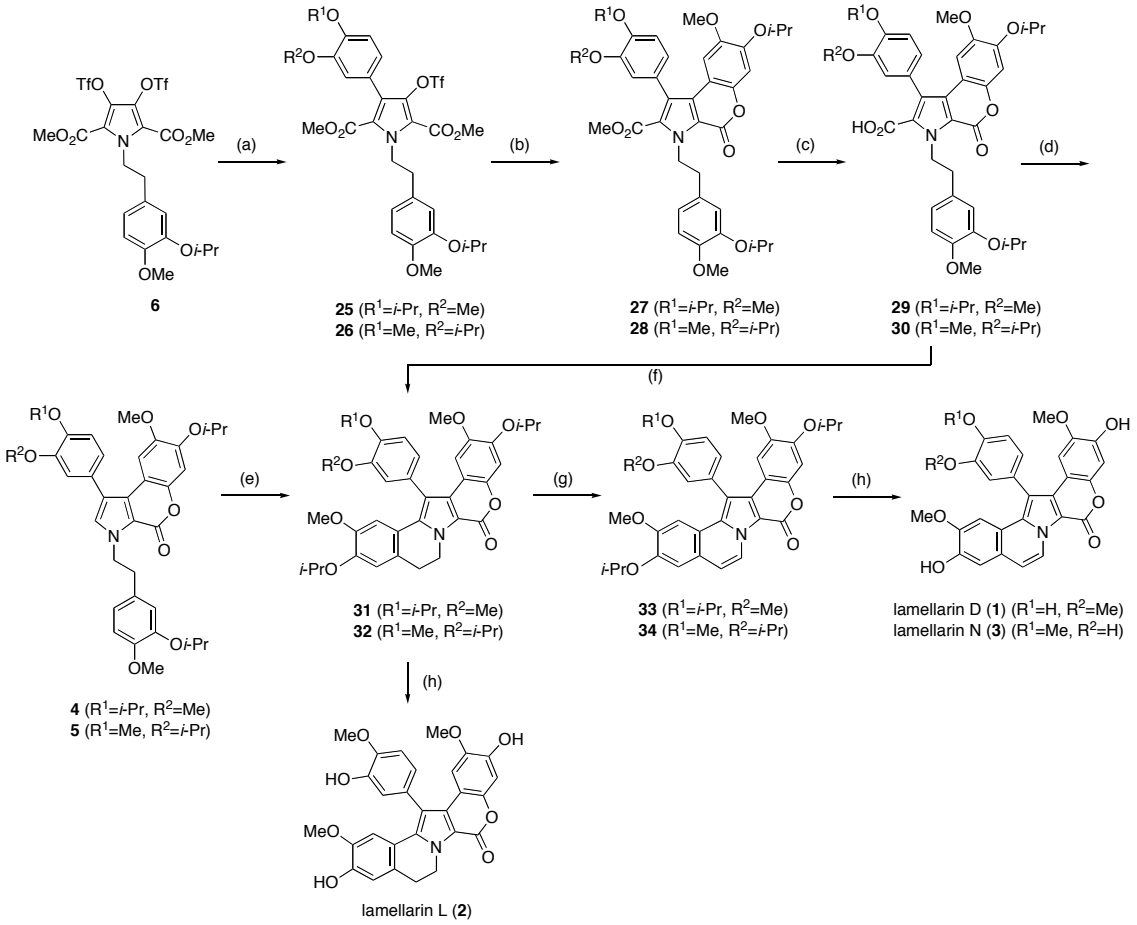
Scheme 1. Retrosynthetic analysis of lamellarins D (**1**), L (**2**), and N (**3**).



Scheme 2. Synthesis of 3,4-dihydroxypyrrole bistriflate **6**. *Reagents and conditions:* (a) CH_3NO_2, $AcO^-NH_4^+$, AcOH, 100 °C, 6 h (74%); (b) $LiAlH_4$, THF, reflux, 7 h (65%); (c) $BrCH_2CO_2Me$, $NaHCO_3$, CH_3CN, reflux, 2 h (83%); (d) $(CO_2Me)_2$, NaH, THF, reflux, 3 h (87%); (e) $(CF_3SO_2)_2O$, 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_2CO_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_3SO_2Cl, Et_3N, CH_2Cl_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_2O, -78 °C, 1 h, (2) $B(OMe)_3$, -78 °C, 1 h, then r.t., 1 h, (3) 30% H_2O_2, AcOH, r.t., 16 h (91%); (h) *i*-PrBr, K_2CO_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) *m*CPBA, CH_2Cl_2, 0 °C, 3 h, (2) K_2CO_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%).

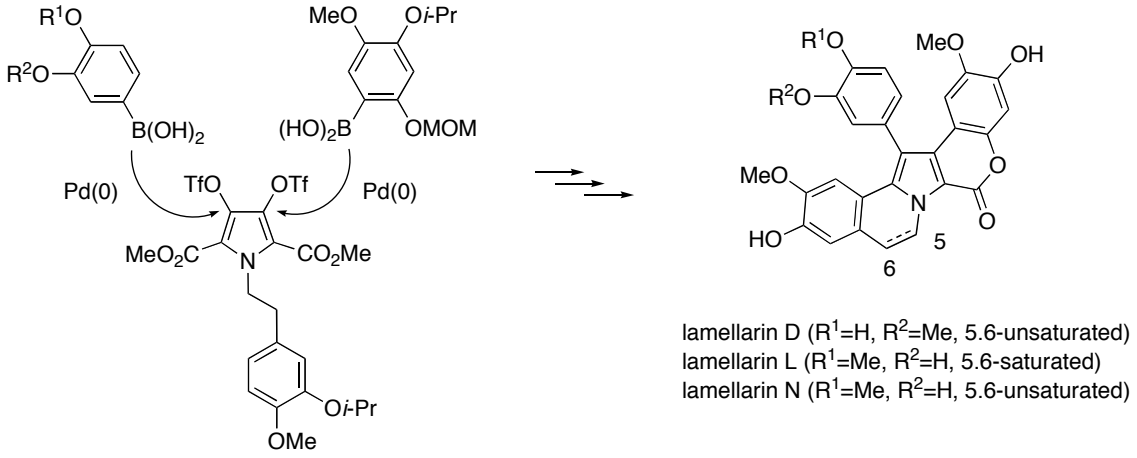


Scheme 4. Synthesis of lamellarins D (**1**), L (**2**), and N (**9**). *Reagents and conditions:* (a) **7** or **8** (1.0 equiv.), $Pd(PPh_3)_4$ (2 mol%), THF, reflux, 4 h (**25**: 76%, **26**: 77%); (b) (1) **9** (2.0 eq), $Pd(PPh_3)_4$ (8 mol%), THF, reflux, 18 h, (2) conc. HCl, MeOH, reflux 1 h (**27**: 98%, **28**: 95%); (c) (1) 40% KOH/EtOH (1:1), reflux, 3 h, (2) cat. *p*-TsOH, CH_2Cl_2, reflux, 1 h (**29**: 90%, **30**: 91%); (d) Cu_2O, quinoline, 220 °C, 7 min (**4**: 94%, **5**: 99%); (e) $PhI(OCOCF_3)_2$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, -40 °C, 1.5 h (**31**: 88%, **32**: 90%); (f) $Pd(OAc)_2$ (1.1 equiv.), CH_3CN, 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) BCl_3, CH_2Cl_2, -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

Naotaka Fujikawa, Takeshi Ohta, Tomohiro Yamaguchi, Tsutomu Fukuda, Fumito Ishibashi and Masatomo Iwao*



lamellarin D (R^1=H, R^2=Me, 5.6-unsaturated)
lamellarin L (R^1=Me, R^2=H, 5.6-saturated)
lamellarin N (R^1=Me, R^2=H, 5.6-unsaturated)