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<td>著者</td>
<td>光田、俊文; 諏訪野、栄一; 島川、小湖; 岩尾、正文</td>
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Palladium-catalyzed cross-coupling of \(N\)-benzenesulfonyl-3,4-dibromopyrrole and its application to the total syntheses of lamellarins O, P, Q, and R

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\textbf{Abstract}—Palladium-catalyzed Suzuki-Miyaura coupling of \(N\)-benzenesulfonyl-3,4-dibromopyrrole with a variety of arylboronic acids gave the corresponding 3,4-diarylpyrroles in high yields. The 3,4-differentially arylated pyrroles could also be prepared by stepwise cross-coupling approach. The total syntheses of lamellarins O, P, Q, and R have been achieved by using the cross-coupling and the directed lithiation as key reactions.

1. Introduction

Recently, much attention has been focused on a family of heterocyclic marine natural products having 3,4-diarylpyrrole as the common structural unit.\textsuperscript{1} It is comprised of lamellarins, ningalins, polycitones, purprone, halitulin, dictyodendrins and so on. The biological activities of this class of compounds are pronounced. For example, polycitone A (\textbf{1}) strongly inhibits both retroviral reverse transcriptases and cellular DNA polymerases.\textsuperscript{2} Halitulin (\textbf{2}) exhibits strong cytotoxicity against several human tumor cell lines with IC\textsubscript{50} value in the 0.012-0.025 µg/mL range.\textsuperscript{3} Lamellarins D (\textbf{3}) and N (\textbf{4}) exhibit potent cytotoxicity against P-glycoprotein-mediated multi-drug resistant (MDR) cancer cell lines as well as their parental cell.\textsuperscript{4} The lamellarin derivatives have been extensively studied as the potential leads of new anticancer agent.\textsuperscript{5} Lamellarin \(\alpha\) 20-sulfate (\textbf{5}), on the other hand, is an inhibitor of HIV-1 integrase and is active against live HIV-1 virus in vitro at non-toxic concentrations.\textsuperscript{6} Dictyodendrin A (\textbf{6}) inhibits telomerase completely at a concentration of 50
Although a variety of synthetic routes to this class of compounds have been developed, the strategy via palladium-catalyzed arylation of the central pyrrole core may be most versatile and straightforward.\textsuperscript{8} Banwell reported the first cross-coupling approach to the simple lamellarins O and Q using 3,4-dibromopyrrole-2-carboxylate 7a as a substrate.\textsuperscript{9} The selective introduction of different aryl groups at C3 and C4 was effected by regioselective Br-Li exchange of 7b followed by transmetallation and Negishi cross-coupling reaction. Wong reported regioselective ipso-iodination of 3,4-disilylpyrrole 8 and consequently achieved the selective functionalization of the pyrrole core via a range of cross-coupling reactions.\textsuperscript{10} Fürstner synthesized 3,4-dibromopyrrole-2,5-dicarboxylate 9 from N-(\textit{tert}-butoxycarbonyl)pyrrole in three-steps and utilized this compound as a substrate for the Suzuki-Miyaura coupling.\textsuperscript{11} He also tested the utility of

\[ \text{Figure 1. 3,4-Diarylpyrrole marine alkaloids} \]
3,4-dibromo-N-(triisopropylsilyl)pyrrole (10) for the synthesis of halitulin core.\textsuperscript{11} Banwell and Steglich, on the other hand, utilized the umpoled pyrrole 11 in their total synthesis of halitulin (2).\textsuperscript{12} We prepared 3,4-dihydroxypyrrole bistriflates 12 from 2-arylethylamines in three-steps \textit{via} Hinsberg reaction and demonstrated that 12 are the excellent substrates for Suzuki-Miyaura coupling.\textsuperscript{13} Total syntheses of lamellarins D (3), L, N (4), and α 20-sulfate (5) have been achieved starting from 12.\textsuperscript{14} Handy developed the iterative halogenation/cross-coupling strategy for the synthesis of lamellarin G trimethyl ether starting from simple 4-bromo-pyrrole-2-carboxylate 13.\textsuperscript{15} Finally, Smith devised a protocol for regioselective arylation of pyrrole-2-carboxylate core utilizing chlorine as a protecting group. The 3,4-diarylpyrrole-2-carboxylates can be produce from 14 after selective cross-coupling at 3,4-positions followed by hydrogenolysis of the chlorine at 5-position.\textsuperscript{16} In this paper, we present a new cross-coupling approach to the 3,4-diarylpyrrole marine alkaloids using N-benzenesulfonyl-3,4-dibromopyrrole (15).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{pyrrole_substrates.png}
\caption{Pyrrole substrates used for cross-coupling reactions}
\end{figure}

2. Results and Discussion

2.1. Synthesis and palladium-catalyzed cross-coupling of
**N-benzenesulfonfyl-3,4-dibromopyrrole (15)**

It is well-known that the electrophilic substitutions of N-protected pyrroles proceed at the α position selectively. Recently, however, Zonta reported the synthesis of 3,4-dibromo-N-(p-toluenesulfonyl)pyrrole via the direct bromination of N-(p-toluenesulfonyl)pyrrole under thermodynamically controlled conditions (2 equivalent Br₂, acetic acid, reflux). Based upon the procedure of Zonta, we prepared N-benzenesulfonfyl-3,4-dibromopyrrole (15) in two steps from pyrrole (16) (Scheme 1).

Although the yield of the direct bromination of N-benzenesulfonfylpyrrole (17) is modest (37%), easy availability of 17 from inexpensive starting materials may compensate this drawback. An attempted synthesis of 15 via acid-catalyzed isomerization (TFA/CH₂Cl₂/rt, CF₃SO₂H/toluene/rt, AcOH/reflux) of easily available of N-benzenesulfonfyl-2,5-dibromopyrrole failed.

![Scheme 1. Synthesis of N-benzenesulfonfyl-3,4-dibromopyrrole (15)](image)

Next, we examined palladium-catalyzed Suzuki-Miyaura coupling of 15 with arylboronic acids 18. A mixture of 15 (1.0 mmol), arylboronic acid 18 (2.0 or 3.0 mmol), Pd(PPh₃)₄ (0.1 mmol), aqueous Na₂CO₃ (6.6 mmol in 2 mL of H₂O) in THF or DME (10 mL) was heated under reflux for 24 h (Table 1). At the THF-refluxing temperature (65 °C), the cross-coupling reactions of 18a were insufficiently fast, and as a result, a mixture of starting material 15, monoarylpyrrole 19a, and diarylpyrrole 20a were obtained (entries 1 and 2). As shown in entry 3, however, the coupling reaction of 18a (3 equivalent) became fast at the DME-refluxing temperature (85 °C) to give diarylpyrrole 20a as the sole product in excellent yield. Under the similar conditions, a variety of arylboronic acids 18b-h, having electron-donating or electron-withdrawing or sterically demanding substituent at the aryl ring, were reacted smoothly to produce the corresponding diarylpyrroles 20b-h in excellent yields (>90%) (entries 4-10). Of our delight, cleavage of the alkaline-sensitive N-benzenesulfonfyl
protecting group of the pyrrole was negligible under the reaction conditions.

Table 1. Palladium-catalyzed cross-coupling of N-benzenesulfonyl-3,4-dibromopyrrole (15)

<table>
<thead>
<tr>
<th>Entry</th>
<th>18 (equiv)</th>
<th>Ar</th>
<th>Solvent</th>
<th>15 (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>19 (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>20 (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>18a (2.0)</td>
<td>4-methoxyphenyl</td>
<td>THF</td>
<td>23</td>
<td>56</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>18a (3.0)</td>
<td>4-methoxyphenyl</td>
<td>THF</td>
<td>5</td>
<td>56</td>
<td>32</td>
</tr>
<tr>
<td>3</td>
<td>18a (3.0)</td>
<td>4-methoxyphenyl</td>
<td>DME</td>
<td>0</td>
<td>0</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>18b (3.0)</td>
<td>4-isopropoxyphenyl</td>
<td>DME</td>
<td>0</td>
<td>0</td>
<td>94</td>
</tr>
<tr>
<td>5</td>
<td>18c (3.0)</td>
<td>4-fluorophenyl</td>
<td>DME</td>
<td>0</td>
<td>0</td>
<td>96</td>
</tr>
<tr>
<td>6</td>
<td>18d (3.0)</td>
<td>4-chlorophenyl</td>
<td>DME</td>
<td>0</td>
<td>0</td>
<td>95</td>
</tr>
<tr>
<td>7</td>
<td>18e (3.0)</td>
<td>2-methoxyphenyl</td>
<td>DME</td>
<td>0</td>
<td>0</td>
<td>93</td>
</tr>
<tr>
<td>8</td>
<td>18f (3.0)</td>
<td>2,6-dimethoxyphenyl</td>
<td>DME</td>
<td>0</td>
<td>0</td>
<td>93</td>
</tr>
<tr>
<td>9</td>
<td>18g (3.0)</td>
<td>3,4,5-trimethoxyphenyl</td>
<td>DME</td>
<td>0</td>
<td>0</td>
<td>91</td>
</tr>
<tr>
<td>10</td>
<td>18h (3.0)</td>
<td>3,4,5-trimethoxyphenyl</td>
<td>DME</td>
<td>0</td>
<td>0</td>
<td>91</td>
</tr>
</tbody>
</table>

<sup>a</sup>Isolated yields.

Selective monoarylation of 15 is also useful for the synthesis of 3,4-unsymmetrically arylated pyrroles. It was assumed from the results indicated in entries 1 and 2 of Table that the preferential monoarylation could be achieved by using reduced amount of arylboronic acid at lower temperatures. In fact, the cross-coupling of 15 with 1.5 equivalent 18a in refluxing THF for 24 h afforded 41% of monoarylpyrrole 19a, 5% of diarylpyrrole 20a, and 41% of starting material 15. Somewhat improved selectivity was realized by using less reactive pinacol borate 21 (Scheme 2). For example, when 15 was reacted with 1.5 equivalent 21 in the presence of 10 mol% of tetrakis(triphenylphosphine)palladium (0) in THF at 70 °C for 48 h, monoarylpyrrole 19a was isolated in 44% yield accompanied by a trace amount (<3%) of diarylated pyrrole 20a and 47% of unreacted 15. The yield of 19a based upon the consumed starting material was 83%. Cross-coupling of 19a with 1.5 equivalent 3,4-dimethoxyphenylboronic acid (18g) afforded 3,4-unsymmetrically substituted pyrrole 22 in quantitative yield.
Scheme 2. Synthesis of 3,4-unsymmetrically arylated pyrrole 22.

The N-triisopropylsilyl protected 3,4-dibromopyrrole 10 has been widely used as a versatile intermediate for the synthesis of a variety of 3,4-disubstituted pyrroles.11,18 Fürstner has reported successful Negishi coupling of 10 in his synthesis of halitulin core.11 Thus, we tested Suzuki-Miyaura coupling of 10 with 3.0 equivalent boronic acid 18a under the conditions utilized for dicoupling of 15 (Scheme 3). Under these conditions, however, expected dicoupling product 23a and deprotected 23b were isolated in only 5% and 6% yields, respectively, from a complex mixture of the products. This result indicated N-benzenesulfonyl-3,4-dibromopyrrole (15) is far superior to 3,4-dibromo-N-triisopropylsilylpyrrole (10) as a substrate at least in Suzuki-Miyaura coupling. It is reasonable to assume that the electron-withdrawing N-benzenesulfonyl group facilitates the initial oxidative addition of C-Br bonds to Pd(0) and, as a consequence, promotes overall cross-coupling reaction cleanly.


2.2. Total syntheses of lamellarins O, P, Q, and R

Simple and non-fused 3,4-diarylpyrrole marine alkaloids, lamellarins O, P, Q, and R, were
isolated from the southern Australian sponge *Dendrilla cactos* by Capton and co-workers. Boger reported lamellarin O (24) exhibits micromolar cytotoxic activity against wild-type and multidrug-resistant tumor cell-lines, suggesting it may serve as a new lead for the development of antitumor agents insensitive to MDR. The syntheses of lamellarins O and Q were achieved by several groups using independent synthetic strategies. The syntheses of lamellarins P and R have not been reported so far. Due to our continuous interests on lamellarin alkaloids, we planned to perform the total syntheses of all of these four natural products. The retrosynthetic analysis shown in Scheme 4 indicates the alkaloids could be obtained by simple transformations of the common intermediate 28, which in turn could be synthesized by directed α-lithiation of the cross-coupling product 20b.

Scheme 4. Retrosynthetic analysis of lamellarins O, P, Q, and R
Synthesis of the common intermediate 28 is shown in Scheme 5. Directed lithiation of 20b with 2 equivalent LDA in THF at -78 °C for 1 h followed by a reaction with methyl chloroformate provided methyl ester 29 in 55% yield accompanied by unreacted 20b (37%). Although we tested a variety of lithiation conditions (longer reaction time, larger amount of LDA, other bases such as LTMP and BuLi), the yield of 29 was not improved. Treatment of 29 with 1.5 equivalent tetrabutylammonium fluoride (TBAF) in refluxing THF for 2 h produced 28 in 94% yield.  

![Scheme 5. Synthesis of the common intermediate 28](image)

Total syntheses of lamellarins O, P, Q, and R from 28 are shown in Scheme 6. Alkylation of 28 with phenacyl bromide 30 in the presence of K$_2$CO$_3$ in DMF produced 32 in 87% yield. Selective deprotection of isopropyl group of 32 with 6 equivalent BCl$_3$ provided lamellarin O (24) in 94% yield. In a similar manner, lamellarin P (25) was synthesized using a different phenacyl bromide 31 at the initial step in comparable overall yield. It is noteworthy that one of the methoxy group in the phenacyl moiety of 33 was selectively deprotected under the BCl$_3$ conditions. This is apparently due to assistance of the $ortho$-carbonyl function. Lamellarin Q (26) was synthesized in a single step by deprotection of 28. The copper (II)-mediated N-arylation of 28 with boronic acid 18b produced 34 in excellent yield. Deprotection of 34 provided lamellarin R (27). Modest yields of the deprotection steps of 28 and 34 were due to partial demethylation of the ester moiety by BCl$_3$. 
alcohol. Dry diethyl ether and THF were distilled from Na Chemical Co., Inc. The alkylolithiums were used after titration with 2,5-dimethoxybenzyl alcohol. Dry diethyl ether and THF were distilled from Na Chemical Co., Inc. or Chromatorex NH-DM1020 silica gel (Fuji Silysia Chemical Ltd.). n-Butyllithium was purchased from Aldrich Chemical Co., Inc. tert-Butyllithium was purchased from Kanto Chemical Co., Inc. The alkylolithiums were used after titration with 2,5-dimethoxybenzyl alcohol. Dry diethyl ether and THF were distilled from Na-benzophenone ketyl under argon.

**Scheme 6.** Synthesis of lamellarins O, P, Q, and R

3. Conclusion

We have disclosed N-benzenesulfonyl-3,4-dibromopyrrole (15) is an excellent substrate for palladium-catalyzed Suzuki-Miyaura coupling to produce 3,4-symmetrically or unsymmetrically diarylated pyrroles. N-Benzenesulfonyl group in the coupling products can serve as a directing group for α-lithiation of the pyrrole ring. Combination of these reactions allowed us to synthesize marine alkaloids, lamellarins O, P, Q, and R.

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 1H), or a JEOL JNM-AL400 instrument (400 MHz for 1H and 100 MHz for 13C) using tetramethylsilane as an internal standard. High resolution mass spectra were recorded on a JEOL JMS-700N spectrometer. HPLC analyses were performed on a Shimadzu LC-6A apparatus. 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.).
4.2. Synthesis of \(N\)-benzenesulfonyl-3,4-dibromopyrrole (15)

4.2.1. \(N\)-Benzenesulfonylpyrrole (17). A solution of benzenesulfonic chloride (47.2 mL, 370 mmol) was added as a neat liquid to a suspension of pyrrole (20.0 g, 298 mmol) and powdered NaOH (47.8 g, 1.20 mol) in dichloroethane (200 mL) at 0 °C. After being stirred for 30 min, the reaction mixture was allowed to warm to room temperature and stirred overnight. The mixture was quenched with water and the products were extracted with dichloromethane. The extract was washed successively with water, dried over \(\text{Na}_2\text{SO}_4\), and evaporated under reduced pressure to give 17 as colorless solid (46.4 g, 75%). This crude product was found to be essentially pure and used for the next reaction without further purification. Recrystallization from methanol gave colorless cube. Mp 87-88 °C; IR (KBr): 1454, 1367, 1186, 1170, 1059 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 6.30 (t, \(J = 2.3\) Hz, 2H), 7.17 (t, \(J = 2.3\) Hz, 2H), 7.47-7.52 (m, 2H), 7.56-7.62 (m, 1H), 7.83-7.88 (m, 2H); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 113.70, 120.80, 126.75, 129.37, 133.82, 139.07. Anal. Calcd for \(\text{C}_{10}\text{H}_9\text{NO}_2\text{S}\): C, 57.95; H, 4.38; N, 6.76. Found: C, 57.92; H, 4.28; N, 6.60.

4.2.2. \(N\)-benzenesulfonyl-3,4-dibromopyrrole (15). A solution of bromine (25.4 g, 159 mmol) in acetic acid (100 mL) was added dropwise to a solution of 17 (13.2 g, 63.7 mmol) in acetic acid (100 mL) at room temperature. After being stirred for 1 h, the reaction mixture was refluxed for 1.5 h. The mixture was cooled to room temperature, and evaporated under reduced pressure. The residue was added saturated aqueous NaHCO\(_3\) and the mixture was extracted with dichloromethane. The extract was washed with saturated aqueous NaHCO\(_3\), dried over \(\text{Na}_2\text{SO}_4\), and evaporated under reduced pressure. The residue was purified by flash chromatography over silica gel 60N (hexane-toluene=2:1) to give 3,4-dibromopyrrole 15 as colorless solid (8.50 g, 37%). Recrystallization from methanol gave colorless needles. Mp 116.5-117 °C; IR (KBr): 1380, 1242, 1184, 1173, 1091, 1057, 957 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.20 (s, 2H), 7.56 (t, \(J = 7.6\) Hz, 2H), 7.70 (t, \(J = 7.6\) Hz, 1H), 7.89 (d, \(J = 7.6\) Hz, 2H); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 105.52, 120.05, 127.17, 129.76, 134.65, 137.92. Anal. Calcd for \(\text{C}_{10}\text{H}_7\text{Br}_2\text{NO}_2\text{S}\): C, 32.90; H, 1.93; N, 3.84. Found: C, 32.99; H, 1.75; N, 3.76.
4.3. Synthesis of arylboronic acids 18a-h and pinacol ester 21

Except for 18f, arylboronic acids were prepared from the corresponding aryl bromide or iodide (for 18h) via halogen-lithium exchange reaction. Boronic acid 18f was prepared by directed lithiation of 1,3-dimethoxybenzene. All boronic acids and a pinacol ester used in this research are known compounds.

4.3.1. 4-Methoxyphenylboronic acid (18a). Under an argon atmosphere, a pentane solution of tert-butyllithium (1.28 M, 51.5 mL, 66.0 mmol) was added dropwise to a solution of 4-bromoanisole (5.61 g, 30.0 mmol) in THF (150 mL) at –78 °C. After being stirred for 1 h, trimethyl borate (5.02 mL, 45.0 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 3 M 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 18a as colorless powder (2.70 g, 59%). This compound was used for the next reaction without further purification. ¹H NMR (300 MHz, CDCl₃): δ 3.89 (s, 3H), 7.01 (d, J = 8.6 Hz, 2H), 8.17 (d, J = 8.6 Hz, 2H).

4.3.2. 4-Isopropoxyphenylboronic acid (18b). This compound was prepared from 4-isopropoxybromobenzene in 71% yield in a similar manner as described for 18a. ¹H NMR (300 MHz, CDCl₃): δ 1.39 (d, J = 6.0 Hz, 6H), 4.60-4.75 (m, 1H), 6.99 (d, J = 8.6 Hz, 2H), 8.15 (d, J = 8.6 Hz, 2H).

4.3.3. 4-Fluorophenylboronic acid (18c). This compound was prepared from 4-bromofluorobenzene in 59% yield in a similar manner as described for 18a. ¹H NMR (300 MHz, CDCl₃): δ 7.19 (t, J = 8.5 Hz, 2H), 8.22 (dd, J = 6.3 and 8.5 Hz, 2H).

4.3.4. 4-Chlorophenylboronic acid (18d). This compound was prepared from 4-bromochlorobenzene in 74% yield in a similar manner as described for 18a. ¹H NMR (300 MHz, CDCl₃): δ 7.67 (d, J = 8.6 Hz, 2H), 8.04 (d, J = 8.6 Hz, 2H).
MHz, CDCl$_3$): $\delta$ 7.49 (d, $J$= 8.1 Hz, 2H), 8.13 (dd, $J$= 8.1 Hz, 2H).

4.3.5. **2-Methoxyphenylboronic acid (18e).** This compound was prepared from 2-bromoanisole in 87% yield in a similar manner as described for 18a. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 3.92 (s, 3H), 6.13 (s, 2H), 6.92 (d, $J$= 8.3 Hz, 1H), 7.04 (t, $J$= 7.3 Hz, 1H), 7.45 (dd, $J$= 7.3 and 8.3 Hz, 1H), 7.85 (d, $J$= 7.3 Hz, 1H).

4.3.6. **2,6-Dimethoxyphenyl boronic acid (18f).** Under an argon atmosphere, a hexane solution of $n$-butyllithium (1.54 M, 3.24 mL, 5.00 mmol) was added dropwise to a solution of 1,3-dimethoxybenzene (655 µL, 5.00 mmol) and TMEDA (750 µL, 5.00 mmol) in diethyl ether (25 mL) at 0 °C. After being stirred for 1 h, the reaction mixture was allowed to warm to room temperature and stirred for an additional 25 h. After being cooled to 0 °C, trimethyl borate (836 µL, 7.50 mmol) was added as a neat liquid and the mixture was stirred for 30 min 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$_4$Cl and evaporated under reduced pressure. To the residue was added 3 M 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$_2$SO$_4$, and evaporated under reduced pressure. The residual solid was washed with hexane, filtered, and dried under reduced pressure to give 18f as pale brown powder (553 mg, 61%). This compound was used for the next reaction without further purification. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 3.92 (s, 6H), 6.64 (d, $J$= 8.4 Hz, 2H), 7.23 (s, 2H), 7.40 (t, $J$= 8.4 Hz, 1H).

4.3.7. **3,4-Dimethoxyphenylboronic acid (18g).** This compound was prepared from 1-bromo-3,4-dimethoxybenzene in 39% yield in a similar manner as described for 18a. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 3.97 (s, 3H), 4.02 (s, 3H), 7.02 (d, $J$= 7.9 Hz, 1H), 7.68 (d, $J$= 1.2 Hz, 1H), 7.86 (dd, $J$= 1.2 and 7.9 Hz, 1H).

4.3.8. **3,4,5-Trimethoxyphenylboronic acid (18h).** This compound was prepared from 1-iodo-3,4,5-trimethoxybenzene in 69% yield in a similar manner as described for 18a. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 3.96 (s, 3H), 3.99 (s, 6H), 7.44 (s, 2H).

4.3.9. **4-Methoxyphenylboronic acid pinacol ester (21).** Boronic acid 18a (200 mg, 1.32
mmol) was added to a suspension of pinacol (157 mg, 1.33 mmol), MgSO$_4$ (317 mg, 2.63 mmol) in dichloromethane (6.6 mL) and the mixture was stirred for 20 h at room temperature. After removal of MgSO$_4$ by filtration, the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N (hexane-ethyl acetate=3:1) to give 21 as colorless solid (283 mg, 92%). $^1$H NMR (300 MHz, CDCl$_3$): δ 1.33 (s, 12H), 3.82 (s, 3H), 6.89 (d, $J$= 8.7 Hz, 2H), 7.75 (d, $J$= 8.7 Hz, 2H).

4.4. Synthesis of 3,4-symmetrically arylated N-benzenesulfonylpyrroles 20a-h

4.4.1. N-Benzencesulfonyl-3,4-bis(4-methoxyphenyl)pyrrole (20a). Under an argon atmosphere, a degassed solution of Na$_2$CO$_3$ (1.92 g, 18.1 mmol) in water (6.0 mL) was added to a solution of 15 (1.00 g, 2.74 mmol), 18a (1.25 g, 8.22 mmol) and Pd(PPh$_3$)$_4$ (317 mg, 0.274 mmol) in 1,2-dimethoxyethane (25 mL) at room temperature and the mixture was refluxed for 24 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$_2$SO$_4$, and evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N (hexane-toluene=1:3~toluene) to give 20a as pale yellow solid (1.07 g, 93%). Recrystallization from dichloromethane-hexane gave pale yellow needles. Mp 140-142 °C; IR (KBr): 1541, 1505, 1375, 1243, 1172, 1094, 1058 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 3.78 (s, 6H), 6.79 (d, $J$= 8.8 Hz, 4H), 7.10 (d, $J$= 8.8 Hz, 4H), 7.19 (s, 2H), 7.52 (t, $J$= 7.6 Hz, 2H), 7.61 (t, $J$= 7.6 Hz, 1H), 7.94 (d, $J$= 7.6 Hz, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): 55.21, 113.76, 118.30, 125.93, 126.97, 128.50, 129.46, 129.66, 133.90, 139.00, 158.74. Anal. Calcd for C$_{24}$H$_{21}$NO$_4$S: C, 68.72; H, 5.05; N, 3.34. Found: C, 68.77; H, 5.02; N, 3.29.

4.4.2. N-Benzencesulfonyl-3,4-bis(4-isopropoxyphenyl)pyrrole (20b). This compound was prepared from 15 (730 mg, 2.00 mmol) and 18b (1.08 g, 6.00 mmol) in a similar manner as described for 20a. After chromatographic purification over Silica Gel 60N (hexane-toluene=1:1~1:2), 20b was obtained as pale yellow solid (891 mg, 94%). Recrystallization from dichloromethane-hexane gave colorless needles. Mp 123-124 °C; IR (KBr): 1612, 1537, 1502, 1376, 1244, 1183, 1093, 1050, 948 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 1.32 (d, $J$= 6.0 Hz, 12H), 4.45-4.56 (m, 2H), 6.77 (d, $J$= 8.7 Hz, 2H); 7.09 (d, $J$=
8.7 Hz, 4H), 7.18 (s, 2H), 7.52 (t, J = 7.6 Hz, 2H), 7.61 (t, J = 7.6 Hz, 1H), 7.93 (d, J = 7.6 Hz, 2H); 13C NMR (100 MHz, CDCl3): 22.0, 69.80, 115.58, 118.27, 125.70, 126.95, 128.58, 129.44, 129.65, 133.86, 139.03, 157.05. Anal. Calcd for C28H29NO4S: C, 70.71; H, 6.15; N, 2.95. Found: C, 70.65; H, 6.33; N, 2.96.

4.4.3. N-Benzanesulfonyl-3,4-bis(4-fluorophenyl)pyrrole (20c). This compound was prepared from 15 (183 mg, 0.500 mmol) and 18c (210 mg, 1.50 mmol) in a similar manner as described for 20a. After chromatographic purification over Silica Gel 60N (hexane-dichloromethane=2:1), 20c was obtained as colorless solid (189 mg, 96%). Recrystallization from diethyl ether-hexane gave colorless needles. Mp 112-113 °C; IR (KBr): 1536, 1504, 1448, 1380, 1223, 1186, 1172, 1091, cm⁻¹; 1H NMR (400 MHz, CDCl3): δ 6.94 (t, J = 8.8 Hz, 4H), 7.11 (dd, J = 5.4 and 8.8 Hz, 4H), 7.23 (s, 2H), 7.55 (t, J = 7.6 Hz, 2H), 7.64 (t, J = 7.6 Hz, 1H), 7.96 (d, J = 7.6 Hz, 2H); 13C NMR (100 MHz, CDCl3): 22.0, 69.80, 115.58, 118.27, 125.70, 126.95, 128.58, 129.44, 129.65, 133.86, 139.03, 157.05. Anal. Calcd for C28H29NO4S: C, 70.71; H, 6.15; N, 2.95. Found: C, 70.65; H, 6.33; N, 2.96.

4.4.4. N-Benzanesulfonyl-3,4-bis(4-chlorophenyl)pyrrole (20d). This compound was prepared from 15 (334 mg, 0.916 mmol) and 18d (432 mg, 2.76 mmol) in a similar manner as described for 20a. After chromatographic purification over Silica Gel 60N (hexane-toluene=1:2→toluene), 20d was obtained as colorless solid (375 mg, 95%). Recrystallization from dichloromethane-pentane gave colorless needles. Mp 60-163 °C; IR (KBr): 1525, 1488, 1378, 1185, 1172, 1094 cm⁻¹; 1H NMR (400 MHz, CDCl3): δ 7.05-7.10 (m, 4H), 7.21-7.25 (m, 4H), 7.25 (s, 2H), 7.53-7.59 (m, 2H), 7.62-7.68 (m, 1H), 7.94-7.98 (m, 2H); 13C NMR (100 MHz, CDCl3): 119.04, 127.10, 127.07, 127.70, 129.24 (d, J = 3.4 Hz), 129.58, 130.15 (d, J = 8.0 Hz), 134.14, 138.80, 162.12 (d, J = 247 Hz). Anal. Calcd for C22H15F2NO2S: C, 66.82; H, 3.82; N, 3.54. Found: C, 67.08; H, 3.80; N, 3.47.

4.4.5. N-Benzanesulfonyl-3,4-bis(2-methoxyphenyl)pyrrole (20e). This compound was prepared from 15 (183 mg, 0.500 mmol) and 18e (228 mg, 1.50 mmol) in a similar manner as described for 20a. After purification by flash chromatography over Silica Gel 60N (hexane-toluene=1:2→toluene), 20e was obtained as colorless solid (196 mg, 93%). Mp 47-51 °C; IR (KBr): 1585, 1529, 1478, 1370, 1245, 1175, 1079, 1025 cm⁻¹; 1H NMR (400
MHz, CDCl$_3$: $\delta$ 3.42 (s, 6H), 6.78-6.83 (m, 4H), 7.04 (dd, $J= 1.7$ and $7.4$ Hz, 2H), 7.17 (dt, $J= 1.7$ and $7.8$ Hz, 2H), 7.36 (s, 2H), 7.51 (t, $J= 7.6$ Hz, 2H), 7.60 (t, $J= 7.6$ Hz, 1H), 7.95 (d, $J= 7.6$ Hz, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): 55.05, 111.00, 119.60, 120.29, 123.78, 125.75, 127.05, 128.13, 129.37, 130.33, 133.76, 139.21, 156.44. HREIMS $m/z$. Calcd for C$_{24}$H$_{21}$NO$_4$S (M$^+$): 419.1191. Found: 441.1194.

4.4.6. N-Benzylsulfonyl-3,4-bis(2,6-dimethoxyphenyl)pyrrole (20f). This compound was prepared from 15 (183 mg, 0.500 mmol) and 18f (273 mg, 1.50 mmol) in a similar manner as described for 20a. After successive purification by flash chromatography over Silica Gel 60N (hexane-ethyl acetate=2:1) and column chromatography over Chromatorex NH-DM1020 silica gel (hexane-ethyl acetate=1:1), 20f was obtained as colorless solid (223 mg, 93%). Recrystallization from dichloromethane-diethyl ether gave colorless plates. Mp 232-233 °C; IR (KBr): 1589, 1471, 1366, 1251, 1179, 1112, 1072 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 3.40 (s, 12H), 6.44 (d, $J= 8.3$ Hz, 4H), 7.07 (t, $J= 8.3$ Hz, 2H), 7.31 (s, 2H), 7.46-7.52 (m, 2H), 7.54-7.60 (m, 1H), 7.90-7.95 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): 55.39, 104.00, 113.32, 120.87, 121.72, 126.87, 127.80, 129.11, 133.37, 139.80, 157.62. Anal. Calcd for C$_{26}$H$_{25}$NO$_6$S: C, 65.12; H, 5.25; N, 2.92. Found: C, 65.22; H, 5.13; N, 2.94.

4.9.7. N-Benzylsulfonyl-3,4-bis(3,4-dimethoxyphenyl)pyrrole (20g). This compound was prepared from 15 (365 mg, 1.00 mmol) and 18g (545 mg, 3.00 mmol) in a similar manner as described for 20a. After chromatographic purification over Silica Gel 60N (hexane-toluene=1:2~toluene~toluene-ethyl acetate=10:1), 20g was obtained as colorless solid (436 mg, 91%). Recrystallization from dichloromethane-hexane gave colorless needles. Mp 187-188 °C; IR (KBr): 1589, 1372, 1253, 1177, 1140, 1096, 1059, 1026 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 3.67 (s, 6H), 3.86 (s, 6H), 6.70 (s, 2H), 6.78 (s, 2H), 7.23 (s, 2H), 7.52-7.58 (m, 2H), 7.62-7.67 (m, 1H), 7.95-7.99 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): 55.72, 55.88, 111.01, 111.99, 118.25, 120.89, 126.12, 127.06, 128.52, 129.52, 133.99, 138.92, 148.17, 148.53. Anal. Calcd for C$_{26}$H$_{23}$NO$_6$S: C, 65.12; H, 5.25; N, 2.92. Found: C, 65.03; H, 5.16; N, 2.88.

4.4.8. N-Benzylsulfonyl-3,4-bis(3,4,5-trimethoxyphenyl)pyrrole (20h). This compound was prepared from 15 (183 mg, 0.500 mmol) and 18h (318 mg, 1.50 mmol) in a similar manner as described for 20a. After successive purification by flash chromatography over
Silica Gel 60N (hexane-ethyl acetate=2:1) and column chromatography over Chromatorex NH-DM1020 silica gel (hexane-ethyl acetate=1:1), 20h was obtained as colorless solid (246 mg, 91%). Recrystallization from dichloromethane-hexane gave colorless plates. Mp 159.5-162 °C; IR (KBr): 1586, 1500, 1450, 1412, 1359, 1240, 1175, 1127, 1063 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 3.69\) (s, 12H), 3.82 (s, 6H), 6.42 (s, 4H), 7.28 (s, 2H), 7.57 (t, \(J=7.6\) Hz, 2H), 7.66 (t, \(J=7.6\) Hz, 1H), 7.99 (d, \(J=7.6\) Hz, 2H); \(^13\)C NMR (100 MHz, CDCl\(_3\)): 56.06, 60.92, 106.01, 118.44, 127.13, 128.61, 128.80, 129.60, 134.13, 137.36, 138.84, 153.02.

**4.5. Synthesis of 3,4-unsymmetrically arylated N-benzenesulfonylpyrrole 22**

4.5.1. **N-Benzenesulfonyl-3-bromo-4-(4-methoxyphenyl)pyrrole (19a).** Under an argon atmosphere, a mixture of 15 (73.0 mg, 0.200 mmol), 21 (70.2 mg, 0.300 mmol), Pd(PPh\(_3\))\(_4\) (23.1 mg, 20.0 µmol), Na\(_2\)CO\(_3\) (140 mg, 1.32 mmol), water (0.40 mL) and THF (2.0 mL) was heated in a sealed tube at 70 °C for 48 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\(_2\)SO\(_4\), and evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N (hexane-toluene=1:1~1:2~toluene) to give 19a as pale yellow semisolid (34.5 mg, 44%) and unreacted 15 (34.1 mg, 47%). IR (KBr): 1511, 1376, 1315, 1250, 1178, 1134, 1057 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 3.82\) (s, 3H), 6.89-6.94 (m, 2H), 7.17 (d, \(J=2.7\) Hz, 1H), 7.27 (d, \(J=2.7\) Hz, 1H), 7.39-7.44 (m, 2H), 7.51-7.57 (m, 2H), 7.62-7.67 (m, 1H), 7.89-7.93 (m, 2H); \(^13\)C NMR (100 MHz, CDCl\(_3\)): 55.30, 102.83, 113.90, 117.44, 120.68, 124.37, 127.06, 128.91, 129.43, 129.62, 134.30, 138.41, 159.29. HREIMS m/z. Calcd for C\(_{17}\)H\(_{14}\)BrNO\(_2\)S (M\(^+\)): 390.9878. Found: 390.9868.

4.5.2. **N-Benzenesulfonyl-4-(3,4-dimethoxyphenyl)-3-(4-methoxyphenyl)pyrrole (22).** Under an argon atmosphere, a degassed solution of Na\(_2\)CO\(_3\) (469 mg, 4.42 mmol) in water (2.0 mL) was added to a solution of 19a (264 mg, 0.672 mmol), 18g (182 mg, 1.00 mmol) and Pd(PPh\(_3\))\(_4\) (77.4 mg, 67.0 µmol) in 1,2-dimethoxyethane (10 mL) at room temperature and the mixture was refluxed for 24 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 successively by column chromatography over Silica Gel 60N (hexane-toluene=1:1~toluene) and over Chromatorex NH-DM1020 silica gel (toluene) to give 22 as colorless solid (302 mg, quant.). Recrystallization from dichloromethane-pentane gave colorless needles. Mp 73-75 °C; IR (KBr): 1509, 1374, 1249, 1177, 1096, 1059 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 3.64 (s, 3H), 3.78 (s, 3H), 3.86 (s, 3H), 6.65 (s, 1H), 6.77 (s, 1H), 6.78 (s, 1H), 6.78-6.82 (m, 2H), 7.09-7.14 (m, 2H), 7.20 (d, J= 2.5 Hz, 1H), 7.23 (d, J= 2.5 Hz, 1H), 7.51-7.57 (m, 2H), 7.60-7.65 (m, 1H), 7.93-7.98 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): 56.25, 55.63, 55.82, 111.04, 111.93, 113.71, 118.19, 118.30, 120.65, 125.87, 126.15, 127.01, 128.47, 128.54, 129.49, 129.82, 133.95, 138.93, 148.11, 148.50, 158.76. Anal. Calcd for C₂₅H₂₃NO₅S: C, 66.80; H, 5.16; N, 3.12. Found: C, 66.52; H, 5.10; N, 2.99.

4.6. Cross-coupling of 3,4-dibromo-N-triisopropylsilylpyrrole (10) with 18a

Under an argon atmosphere, a degassed solution of Na₂CO₃ (700 mg, 6.60 mmol) in water (2.0 mL) was added to a solution of 10 (381 mg, 1.00 mmol), 18a (456 mg, 3.00 mmol) and Pd(PPh₃)₄ (116 mg, 0.100 mmol) in 1,2-dimethoxyethane (10 mL) at room temperature and the mixture was refluxed for 24 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 flash chromatography over Silica Gel 60N (hexane-dichloromethane=10:1~5:1~3:1~2:1~ethyl acetate) to give 23a (22.1 mg, 5%) and 23b (15.4 mg, 6%).

4.6.1. 3,4-Bis(4-methoxyphenyl)-N-triisopropylsilylpyrrole (23a). White solid. ¹H NMR (400 MHz, CDCl₃): δ 1.15 (d, J= 7.4 Hz, 18H), 1.42-1.55 (m, 3H), 3.80 (s, 6H), 6.78 (s, 2H), 6.79-6.84 (m, 4H), 7.18-7.23 (m, 4H); ¹³C NMR (100 MHz, CDCl₃): 11.66, 17.91, 55.22, 113.55, 123.01, 124.92, 128.92, 129.43, 157.66. HREIMS m/z. Calcd for C₂₇H₂₇NO₂Si (M⁺): 435.2594. Found: 435.2593.

4.6.2. 3,4-Bis(4-methoxyphenyl)pyrrole (23b). Yellow solid. ¹H NMR (400 MHz, CDCl₃):
δ 3.80 (s, 6H), 6.79-6.84 (m, 4H), 6.85 (s, 2H), 7.17-7.22 (m, 4H), 8.24 (br s, 1H); 13C NMR (100 MHz, CDCl3): 55.20, 113.63, 116.74, 123.10, 128.37, 129.60, 157.81. HREIMS m/z. Calcd for C18H17NO2 (M⁺): 279.1259. Found: 279.1249.

4.7. Total synthesis of lamellarins O, P, Q, and R

4.7.1. Methyl N-benzenesulfonyl-3,4-bis(4-isopropoxyphenyl)pyrrole-2-carboxylate (29). Under an argon atmosphere, a hexanes solution of n-butyllithium (1.42 M, 297 µL, 0.422 mmol) was added dropwise to a solution of diisopropylamine (73.7 µL, 0.526 mmol) in THF (5.0 mL) at -78 °C. The mixture was allowed to warm to 0 °C and immediately re-cooled to -78 °C. A solution of 20b (100 mg, 0.210 mmol) in THF (3.0 mL) was added dropwise to the mixture at -78 °C. After being stirred for 1 h, methyl chloroformate (48.7 µL, 0.630 mmol) was added as a neat liquid and the mixture was stirred for 30 min at -78 °C. The reaction mixture was allowed to warm to room temperature, quenched with saturated aqueous NH4Cl, 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=100:1) to give 29 as yellow solid (61.9 mg, 55%). Recrystallization from diethyl ether-hexane gave yellow needles. Mp 166-167 °C; IR (KBr): 1711, 1611, 1532, 1505, 1364, 1245, 1173, 1132, 1049, 954 cm⁻¹; ¹H NMR (400 MHz, CDCl3): δ 1.30 (d, J = 6.3 Hz, 6H), 1.32 (d, J = 6.3 Hz, 6H), 3.61 (s, 3H), 4.44-4.58 (m, 2H), 6.73 (d, J = 8.7 Hz, 2H), 6.77 (d, J = 8.7 Hz, 2H), 6.98 (d, J = 8.7 Hz, 2H), 7.04 (d, J = 8.7 Hz, 2H), 7.55 (s, 1H), 7.57 (t, J = 7.6 Hz, 2H), 7.65 (t, J = 7.6 Hz, 1H), 8.04 (d, J = 7.6 Hz, 2H); ¹³C NMR (100 MHz, CDCl3): 22.04, 22.06, 52.00, 69.78, 69.79, 115.15, 115.56, 122.47, 122.83, 124.45, 124.71, 127.46, 127.76, 129.02, 129.60, 131.23, 132.98, 133.87, 139.21, 157.12, 157.39, 161.47. HREIMS m/z. Calcd for C30H31NO6S (M⁺): 533.1872. Found: 533.1870.

4.7.2. Methyl 3,4-bis(4-isopropoxyphenyl)pyrrole-2-carboxylate (28). Under an argon atmosphere, a THF solution of tetrabutylammonium fluoride (1.0 M, 157 µL, 0.157 mmol) was added dropwise to a solution of 29 (56.0 mg, 0.105 mmol) in THF (5.0 mL) at room temperature and the mixture was refluxed for 2 h. The mixture was cooled to room temperature, quenched with water, 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=20:1) to give 28 as yellow solid (38.7 mg, 94%). Recrystallization from ethyl acetate-hexane gave yellow needles. Mp 141-141.5 °C; IR (KBr): 3420, 1697, 1486, 1372, 1241, 1118 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.30 (d, J= 6.0 Hz, 6H), 1.34 (d, J= 6.0 Hz, 6H), 3.72 (s, 3H), 4.44-4.58 (m, 2H), 6.71 (d, J= 8.8 Hz, 2H), 6.81 (d, J= 8.8 Hz, 2H), 6.97-7.01 (m, 3H), 7.16 (d, J= 8.8 Hz, 2H), 9.23 (br s, 1H); ¹³C NMR (100 MHz, CDCl₃): 22.06, 22.12, 51.16, 69.66, 69.69, 114.85, 115.37, 119.11, 119.93, 126.05, 126.35, 126.72, 128.96, 129.26, 131.71, 156.10, 156.63, 161.42. Anal. Calcd for C₂₄H₂₇NO₄: C, 73.26; H, 6.92; N, 3.56. Found: C, 73.14; H, 7.00; N, 3.47.

4.7.3. Methyl 1-[2-(4-methoxyphenyl)-2-oxoethyl]-3,4-bis(4-isopropoxyphenyl)pyrrole-2-carboxylate (32). Under an argon atmosphere, a mixture of 28 (100 mg, 0.254 mmol), 2-bromo-4′-methoxycacetophenone (30) (146 mg, 0.635 mmol), K₂CO₃ (105 mg, 0.762 mmol), and DMF (6.0 mL) was stirred for 3 h at 70 °C. The reaction mixture was cooled to room temperature and quenched with water. The product was diluted with ethyl acetate, washed successively with water and brine, dried over Na₂SO₄, and evaporated under reduced pressure. The residue was purified by flash chromatography over Silica Gel 60N (hexane-ethyl acetate=3:1) to give 32 as colorless solid (119 mg, 87%). Recrystallization from diethyl ether-hexane gave pale yellow plates. Mp 135-136 °C; IR (KBr): 1698, 1602, 1533, 1443, 1367, 1235, 1170, 1103, 957 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.29 (d, J= 6.0 Hz, 6H), 1.34 (d, J= 6.0 Hz, 6H), 3.46 (s, 3H), 3.88 (s, 3H), 4.41-4.60 (m, 2H), 5.71 (s, 2H), 6.69 (d, J= 8.8 Hz, 2H), 6.80 (d, J= 8.8 Hz, 2H), 6.91 (s, 1H), 6.98 (d, J= 8.8 Hz, 4H), 7.13 (d, J= 8.8 Hz, 2H), 8.01 (d, J= 8.8 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): 22.10, 22.12, 51.16, 69.66, 69.71, 69.84, 114.10, 114.98, 115.41, 119.75, 124.71, 126.72, 128.96, 129.26, 131.71, 156.10, 156.63, 161.42. Anal. Calcd for C₃₃H₃₅NO₆ (M⁺): 541.2464. Found: 541.2465.

4.7.4. Methyl 1-[2-(2,4-dimethoxyphenyl)-2-oxoethyl]-3,4-bis(4-isopropoxyphenyl)pyrrole-2-carboxylate (33). This compound was prepared from 28 (50.0 mg, 0.127 mmol) and
2-bromo-2',4'-dimethoxyacetophenone (31)\(^{26}\) (82.3 mg, 0.318 mmol) in a similar manner as described for 32. After chromatographic purification over Silica Gel 60N (hexane-ethyl acetate=2:1), 33 was obtained as colorless solid (64.0 mg, 88%). Recrystallization from diethyl ether-hexane gave pale yellow needles. Mp 138-139 °C; IR (KBr): 1685, 1599, 1529, 1443, 1368, 1243, 1129, 1100 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.29 (d, \(J = 6.0 \text{ Hz}, 6 \text{H}\)), 1.34 (d, \(J = 6.0 \text{ Hz}, 6 \text{H}\)), 3.46 (s, 3H), 3.87 (s, 3H), 3.97 (s, 3H), 4.41-4.60 (m, 2H), 5.64 (s, 2H), 6.50 (d, \(J = 2.3 \text{ Hz}, 1 \text{H}\)), 6.59 (dd, \(J = 2.3 \text{ and } 8.8 \text{ Hz}, 1 \text{H}\)), 6.68 (d, \(J = 8.8 \text{ Hz}, 2 \text{H}\)), 6.80 (d, \(J = 8.8 \text{ Hz}, 2 \text{H}\)), 6.90 (s, 1H), 6.98 (d, \(J = 8.8 \text{ Hz}, 2 \text{H}\)), 7.15 (d, \(J = 8.8 \text{ Hz}, 2 \text{H}\)), 7.26 (s, 1H), 8.00 (d, \(J = 8.8 \text{ Hz}, 1 \text{H}\)); \(^1\)C NMR (100 MHz, CDCl\(_3\)): 22.11, 22.14, 50.62, 55.60, 55.62, 60.24, 69.70, 69.83, 98.22, 105.85, 114.95, 115.37, 118.52, 119.92, 124.32, 127.03, 127.09, 128.10, 129.36, 130.85, 131.91, 133.36, 156.05, 156.48, 161.35, 165.23, 192.64. HREIMS \(m/z\). Calcd for C\(_{34}\)H\(_{37}\)NO\(_7\) (M\(^+\)): 571.2570. Found: 571.2567.

4.7.5. Lamellarin O (24). Under an argon atmosphere, a heptane solution of BCl\(_3\) (1.0 M, 583 µL, 0.583 mmol) was added dropwise to a solution of 32 (52.7 mg, 0.0973 mmol) in dichloromethane (5.0 mL) at −78 °C. After being stirred for 30 min at this temperature, the reaction mixture was allowed to warm to 0 °C and stirred for an additional 3 h. The mixture was quenched with water and extracted with ethyl acetate. The extract was washed with brine, dried over Na\(_2\)SO\(_4\), and evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N (ethyl acetate) to give 24 as pale brown solid (41.8 mg, 94%). Recrystallization from ethyl acetate-hexane gave pale brown powder. Mp 225-235 °C (dec.) (sealed capillary); IR (KBr): 3357, 1686, 1598, 1536, 1443, 1369, 1244, 1170, 1102, 835 cm\(^{-1}\); \(^1\)H NMR (400 MHz, acetone-d\(_6\)): \(\delta\) 3.39 (s, 3H), 3.90 (s, 3H), 5.88 (s, 2H), 6.66 (d, \(J = 8.7 \text{ Hz}, 2 \text{H}\)), 6.77 (d, \(J = 8.7 \text{ Hz}, 2 \text{H}\)), 6.94 (d, \(J = 8.7 \text{ Hz}, 2 \text{H}\)), 7.03 (d, \(J = 8.7 \text{ Hz}, 2 \text{H}\)), 7.08 (d, \(J = 9.0 \text{ Hz}, 2 \text{H}\)), 7.17 (s, 1H), 8.06 (d, \(J = 9.0 \text{ Hz}, 2 \text{H}\)), 8.17 (s, 1H), 8.24 (s, 1H); \(^1\)C NMR (100 MHz, acetone-d\(_6\)): \(\delta\) 50.63, 55.98, 56.35, 114.75, 115.06, 115.68, 120.59, 124.99, 127.06, 127.95, 128.13, 129.07, 129.99, 130.88, 131.33, 132.54, 156.32, 156.76, 162.62, 164.67, 192.41. HREIMS \(m/z\). Calcd for C\(_{27}\)H\(_{23}\)NO\(_6\) (M\(^+\)): 457.1525. Found: 457.1527.

4.7.6. Lamellarin P (25). This compound was prepared from 33 (64.0 mg, 0.112 mmol) and BCl\(_3\) (1.0 M, 1.01 mL, 1.01 mmol) in a similar manner as described for 24. After chromatographic purification over Silica Gel 60N (ethyl acetate), 25 was obtained as pale
brown solid (51.7 mg, 98%). Recrystallization from ethyl acetate-hexane gave pale brown needles. Mp 230-245 °C (dec.) (sealed capillary); IR (KBr): 3312, 1681, 1639, 1442, 1365, 1238, 1173, 1130, 1084, 837 cm⁻¹; ¹H NMR (400 MHz, acetone-d₆): δ 3.41 (s, 3H), 3.89 (s, 3H), 5.92 (s, 2H), 6.50 (d, J= 2.5 Hz, 1H), 6.59 (dd, J= 2.5 and 9.0 Hz, 1H), 6.66 (d, J= 8.7 Hz, 2H), 6.78 (d, J= 8.7 Hz, 2H), 6.95 (d, J= 8.7 Hz, 2H), 7.03 (d, J= 8.7 Hz, 2H), 7.14 (d, J= 3.2 Hz, 1H), 8.23 (br s, 2H), 10.90 (br s, 1H); ¹³C NMR (100 MHz, acetone-d₆): 50.99, 115.18, 115.77, 120.02, 121.37, 126.90, 126.97, 127.45, 129.73, 130.22, 132.80, 156.50, 157.01, 161.89. HREIMS m/z. Calcd for C₁₈H₁₅NO₄ (M⁺): 309.1001. Found: 309.0983.

4.7.7 Lamellarin Q (26). Under an argon atmosphere, a heptane solution of BCl₃ (1.0 M, 723 µL, 0.723 mmol) was added dropwise to a solution of 28 (31.6 mg, 0.0803 mmol) in dichloromethane (5.0 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 4 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~ethyl acetate) to give 26 as yellow powder (12.9 mg, 52%). Mp 145-210 °C (dec.) (sealed capillary); IR (KBr): 3310, 1687, 1509, 1486, 1441, 1370, 1251, 1177, 1085, 835 cm⁻¹; ¹H NMR (400 MHz, acetone-d₆): δ 3.44 (s, 3H), 3.89 (s, 3H), 5.92 (s, 2H), 6.67 (d, J= 8.8 Hz, 2H), 6.76 (d, J= 8.8 Hz, 2H), 6.99 (d, J= 8.8 Hz, 2H), 7.06 (d, J= 8.8 Hz, 2H), 7.14 (d, J= 3.2 Hz, 1H), 8.23 (br s, 2H), 10.90 (br s, 1H); ¹³C NMR (100 MHz, acetone-d₆): 50.71, 55.69, 56.15, 101.70, 108.40, 112.66, 115.01, 115.62, 120.60, 125.17, 126.93, 127.78, 128.28, 130.01, 131.48, 131.98, 132.52, 156.29, 156.73, 162.65, 165.49, 167.21, 198.56. HREIMS m/z. Calcd for C₂₇H₂₃NO₇ (M⁺): 473.1475. Found: 473.1464.

4.7.8. Methyl 1,3,4-tris(4-isopropoxyphenyl)pyrrole-2-carboxylate (34). Under an argon atmosphere, a suspension of 4-isopropoxyphenylboronic acid (137 mg, 0.762 mmol) and powdered molecular sieves 4A (350 mg) in dichloromethane (5.0 mL) was stirred for 3 h. After successive addition of 28 (100 mg, 0.254 mmol), pyridine (82.2 µL, 1.02 mmol) and Cu(OAc)₂ (92.3 mg, 0.508 mmol) to the suspension, the mixture was stirred for 87 h. The mixture was passed through a pad of Celite and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N (dichloromethane) to give 34 as pale yellow semisolid (127 mg, 95%). IR (KBr): 1708, 1509,
1373, 1243, 1120, 951, 835 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.30 (d, J= 6.0 Hz, 6H), 1.35 (d, J= 6.0 Hz, 6H), 1.37 (d, J= 6.0 Hz, 6H), 3.46 (s, 3H), 4.42-4.63 (m, 3H), 6.71 (d, J= 8.8 Hz, 2H), 6.83 (d, J= 8.8 Hz, 2H), 6.92 (d, J= 8.8 Hz, 2H), 6.99 (s, 1H), 7.04 (d, J= 8.8 Hz, 2H), 7.18 (d, J= 8.8 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): 22.08, 22.10, 22.15, 50.83, 69.74, 69.83, 70.22, 115.06, 115.52, 115.57, 121.25, 124.96, 126.49, 126.65, 126.98, 127.16, 129.33, 131.03, 131.83, 133.78, 156.31, 156.75, 157.29, 161.73. HREIMS m/z. Calcd for C₃₃H₃₇NO₅ (M⁺): 527.2672. Found: 527.2678.

4.7.9. Lamellarin R (27). Under an argon atmosphere, a heptane solution of BCl₃ (1.0 M, 358 µL, 0.358 mmol) was added dropwise to a solution of 34 (21.0 mg, 0.0398 mmol) in dichloromethane (5.0 mL) at −78 °C. After being stirred for 30 min at this temperature, the reaction mixture was allowed to warm to 0 °C and stirred for an additional 2 h. The mixture was quenched with water 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~ethyl acetate) to give 27 as brown powder (9.2 mg, 58%). Mp 140-240 °C (dec.) (sealed capillary); IR (KBr): 3347, 1670, 1611, 1519, 1441, 1373, 1238, 1130, 834 cm⁻¹; ¹H NMR (400 MHz, acetone-d₆): δ 3.40 (s, 3H), 6.68 (d, J= 8.7 Hz, 2H), 6.78 (d, J= 8.7 Hz, 2H), 6.92 (d, J= 8.7 Hz, 2H), 7.00 (d, J= 8.7 Hz, 2H), 7.08 (d, J= 8.7 Hz, 2H), 7.12 (s, 1H), 7.24 (d, J= 8.7 Hz, 2H), 8.20 (br s, 1H), 8.28 (br s, 1H), 8.61 (br s, 1H); ¹³C NMR (100 MHz, acetone-d₆): δ 50.90, 115.28, 115.83, 116.09, 122.42, 125.82, 126.64, 126.85, 127.17, 127.55, 130.24, 131.24, 132.71, 134.07, 156.70, 157.13, 157.61, 162.15. HREIMS m/z. Calcd for C₂₄H₁₉NO₅ (M⁺): 401.1263. Found: 401.1254.

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References


Graphical abstract

Palladium-catalyzed cross-coupling of \( N \)-benzenesulfonyl-3,4-dibromopyrrole and its application to the total syntheses of lamellarins O, P, Q, and R

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