A SYNTHESIS OF LAMELLARINS VIA REGIOSELECTIVE ASSEMBLY OF 1,2,3-DIFFERENTIALLY SUBSTITUTED 5,6-DIHYDROPYRROLO[2,1-\textit{a}]ISOQUINOLINE CORE

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Abstract – A modular synthesis of the marine natural products lamellarins has been developed. The key reactions utilized are C3-selective Vilsmeier-Haack formylation followed by iterative bromination/cross-coupling of the 5,6-dihydropyrrolo[2,1-\textit{a}]isoquinoline core. The 1,2-diaryl-5,6-dihydropyrrolo[2,1-\textit{a}]isoquinoline-3-carbaldehyde thus synthesized was readily converted to the lamellarin skeleton by mean of palladium-catalyzed oxidative lactonization.

INTRODUCTION

Lamellarins constitute an important class of natural products of marine origin.\(^1\) Since the first isolation of lamellarins A–D from \textit{Lamellaria} sp. by Faulkner in 1985,\(^2\) more than 50 lamellarins (A–Z, \(\alpha\)–\(\chi\), A1–A6, and O1–O2, including their acetate and sulfate derivatives) have been isolated from marine organisms such as tunicates, sponges, and prosobranchs.\(^2\) With a very few exceptions, lamellarins possess a unique 14-phenyl-6\(H\)-[1]benzopyrano[4′,3′:4,5]pyrrolo[2,1-\textit{a}]isoquinolin-6-one ring system (Figure 1). Furthermore, these lamellarins exhibit various interesting biological activities including potent antiproliferative activity against several cancer cell lines,\(^2\) anti-HIV activity,\(^2\) multi-drug resistance (MDR) reversal activity,\(^2\) anti-HIV activity,\(^2\) topoiso merase I inhibitory activity,\(^5\) inhibition of mitochondrial function,\(^6\) and protein kinases inhibitory activity.\(^7\) Because of their unique structure and significant biological activities, lamellarins have attracted considerable attention from organic and medicinal chemists. Consequently, various synthetic methods for the preparation of lamellarins have been exploited so far.\(^8\) The synthetic methods can be classified broadly into two categories: one utilizes formation of the pyrrole core as the key step and the other employs regioselective functionalization of the pre-existing pyrrole core. Compared to the former approaches, the latter syntheses are more effective because a wide range of natural and artificial lamellarins can be obtained easily by simple modification of
the aromatic building blocks substituted on the central pyrrole core (C-ring). Actually, the synthesis of lamellarins by using such modular approaches have been developed by several groups. Recently, we also developed a modular synthesis of lamellarins L and N via regioselective assembly of 3,4,5-differentially arylated pyrrole-2-carboxylates followed by construction of the D-ring of lamellarins by annulation between the pyrrole nitrogen and the lateral aromatic ring (E-ring).\textsuperscript{9} Tiring our attention to the lamellarin scaffold again, we designed an alternative modular synthesis of lamellarins via a regioselective assembly of 1,2,3-trisubstituted 5,6-dihydropyrrolo[2,1-a]isoquinoline core (Figure 1). The present approach is similar to that of Álvarez in so far as the 5,6-dihydropyrrolo[2,1-a]isoquinoline is utilized as a platform of the lamellarin scaffold. However, the sequence of the ring construction and the functionalization of the key 5,6-dihydropyrrolo[2,1-a]isoquinoline core is different from those employed by Álvarez.\textsuperscript{8i}

RESULTS AND DISCUSSION

We selected lamellarins L (1) and N (2) as the targets of this synthetic approach. Our retrosynthetic analysis of 1 and 2 via 5,6-dihydropyrrolo[2,1-a]isoquinoline (5) is shown in Scheme 1. The conversion of lamellarin L triisopropyl ether (3) to the target lamellarins L (1) and N (2) have been established by
The compound (3) can be obtained by oxidation of 1,2-diaryl-5,6-dihydropyrrolo[2,1-a]-isoquinoline-3-carbaldehyde (4) followed by acid-mediated methoxymethyl (MOM) deprotection–lactonization of the resulting phenolic acid. The intermediate (4) may be assembled from 5,6-dihydropyrrolo[2,1-a]isoquinoline (5) via following sequences: 1) C3-selective formylation of 5 under Vilsmeier-Haack reaction conditions, 2) C1-selective bromination followed by cross-coupling with arylboronic acid (6), 3) C2-selective bromination followed by cross-coupling with arylboronic acid (7). The key tricyclic compound (5) will be prepared in two steps from the phenethylamine (9) via the Paal-Knorr pyrrole synthesis and subsequent palladium-catalyzed intramolecular direct arylation of the pyrrole (8). Based on the retrosynthetic analysis, we performed the synthesis of 5,6-dihydropyrrolo[2,1-a]-isoquinoline (5) at first. The starting material (9) was readily obtained by simple bromination of the known phenylethylamine (10) in good yield (Scheme 2). The compound (9) was isolated as its hydrobromide salt.

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Scheme 2

We next examined the Paal-Knorr reaction of 9·HBr. The results are summarized in Table 1. Since D’Silva and Walker reported that treatment of the benzylamine hydrochlorides with 2,5-dimethoxytetrahydrofuran (DMT) in a mixture of pyridine, acetic acid, and water gave the corresponding pyrroles in moderate to good yields, we carried out the reactions under the similar conditions.

Table 1. Paal-Knorr reaction of the phenethylamine (9·HBr) with 2,5-dimethoxytetrahydrofuran (DMT)

<table>
<thead>
<tr>
<th>entry</th>
<th>DMT (equiv)</th>
<th>8 (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>11 (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>12 (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
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<tr>
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<td>4</td>
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<td>0</td>
<td>6</td>
<td>24</td>
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<sup>a</sup> Isolated yield. <sup>b</sup>The yields of 11 and 12 were estimated by 1H NMR analysis of the inseparable mixture. See ref. 15.
conditions. The phenethylamine (9·HBr) was treated with 1.0 equiv of DMT in a mixture of pyridine, acetic acid, and water at 100 °C for 20 h, the desired pyrrole (8) was obtained in 93% yield (entry 1). When the amount of DMT was increased to 2.0 equiv, the indole (11) and the carbazole (12) were obtained in 34% and 6% yields, respectively (entry 2). These compounds may be formed by further condensation of 8 with DMT. The increasing amount of DMT under the similar conditions did not improve the yields of 11 or 12 due to formation of unidentified polymeric materials (entries 3 and 4).

Next, the palladium-catalyzed intramolecular direct arylation of the phenethylpyrrole (8) thus synthesized was tested (Scheme 3). Of our delight, the desired 5,6-dihydropyrrolo[2,1-a]isoquinoline (5) was obtained in good yield under the conditions previously established in our laboratories for a transformation of 3-[2-(2-bromophenyl)ethyl][1]benzopyrano[3,4-b]pyrrol-4(3H)-one to the pentacyclic lamellarin scaffold [10 mol% of Pd(PPh₃)₄, K₂CO₃, N,N-dimethylacetamide (DMA), 125 °C].

With sufficient amount of the key 5,6-dihydropyrrolo[2,1-a]isoquinoline (5) in hand, we next focused on its conversion to lamellars L (1) and N (2) (Scheme 4). Vilsmeier-Haack reaction of 5 using phosphoryl chloride in dimethylformamide (DMF) gave C3-selectively formylated 13 in 79% yield. Subsequent reaction of 13 with N-bromosuccinimide (NBS) in DMF gave compound 14 in 96% yield. The regioselectivity of this reaction was controlled by the electron-withdrawing formyl group. Similar regioselectivity has been reported for the bromination of 5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate by Álvarez. Suzuki–Miyaura cross-coupling of 14 with arylboronic acid (6) proceeded smoothly to give the arylated compound (15) in good yield. Bromination of 15 with NBS followed by the cross-coupling with arylboronic acid (7) yielded 1,2-differentially arylated 5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbaldehyde (4) in good yield. For the conversion of 4 to 3, Pinnick oxidation (NaClO₂, 2-methyl-2-butene) of the aldehyde was tested at first. However, the reaction was sluggish and the starting material was recovered. The reason for the failure may be accounted for by the influence of the steric hindrance and the electron-donating nature of the pyrrole moiety adjacent to the formyl group. To avoid this problem, the reaction sequence was changed to perform MOM-deprotection at first, followed by oxidation. Thus, the aldehyde (4) was treated with concd HCl in MeOH to give 17. The successful conversion of this type of phenolic aldehyde to the lactone has been reported by Ruchirawat in their lamellarin synthesis. In fact, application of their
conditions [PhBr (1.2 equiv), Pd(OAc)2 (10 mol%), PPh3 (30 mol%), K2CO3 (1.1 equiv), DMF, 120 °C] to 17 provided the desired lamellarin (3) in moderate yield. Since the conversion of 3 to lamellarins L (1) and N (2) has been established in our laboratories, the formal syntheses of these lamellarins were thus achieved.

In conclusion, we have developed a new modular synthesis of lamellarins via regioselective assembly of 1,2,3-differentially substituted 5,6-dihydropyrrolo[2,1-\(\alpha\)]isoquinoline (5) followed by oxidative lactonization. This route may be applicable to the synthesis of a wide range of lamellarin derivatives by simple structural modification of 5,6-dihydropyrrolo[2,1-\(\alpha\)]isoquinoline core and arylboronic acids.

**EXPERIMENTAL**

Melting points were determined with a Yanagimoto micro melting points apparatus and are uncorrected. IR spectra were obtained with a Thermo Nicolet Nexus 670 NT FT-IR instrument and are reported in terms of frequency of absorption (cm\(^{-1}\)). NMR spectra were recorded on a JEOL JNM-AL400 instrument (400 MHz for \(^1\)H and 100 MHz for \(^{13}\)C) or a Varian NMR System 500PS SN instrument (500 MHz for \(^1\)H and 125 MHz for \(^{13}\)C). Chemical shifts for \(^1\)H NMR are expressed in parts per million (ppm) relative to tetramethylsilane (δ 0.0 ppm). Data for \(^1\)H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, dd = double of doublets, t = triplet, sep = septet, m = multiplet, br s = broad signal), coupling constant (Hz), and integration. Chemical shifts for \(^{13}\)C NMR are expressed in ppm relative to the following internal standards: CDCl\(_3\) (tetramethylsilane, δ
0.0 ppm), DMSO-d_6 (DMSO-d_6, δ 39.52 ppm). Data for 13C NMR spectra are reported in terms of chemical shift. High resolution mass spectra were recorded on a JEOL JMS-T100TD (direct analysis in real time mass spectrometry, DARTMS). Elemental analysis was performed for C, H, and N using a Perkin Elmer 2400II instrument. Column chromatography was conducted on silica gel 60N, 63–210 μm (Kanto Chemical Co., Inc.). Flash chromatography was conducted on silica gel 60N, 40–50 μm (Kanto Chemical Co., Inc.) or Chromatorex NH-DM2035 silica gel (Fuji Silysia Chemical Ltd.).

2-(2-Bromo-5-isopropoxy-4-methoxyphenyl)ethylamine hydrobromide (9·HBr). A solution of bromine (8.40 g, 52.6 mmol) in AcOH (30 mL) was added dropwise to a solution of 10^8k (7.33 g, 35.0 mmol) in AcOH (160 mL) at rt. After stirring for 0.5 h at rt, the reaction mixture was concentrated under reduced pressure. The residue was diluted with EtOAc and the resulting white precipitate was corrected by filtration, washed with EtOAc, and dried under reduced pressure to give 9·HBr as a colorless powder (10.1 g, 78%). Mp 179.5–181.5 °C (sealed capillary). [lit.Mp 224 °C]. IR (KBr): 2970, 1594, 1511, 1266, 1171, 1109, 1031 cm⁻¹. 1H NMR (400 MHz, DMSO-d_6): δ 1.25 (d, J = 6.0 Hz, 6H), 2.90–3.06 (m, 4H), 3.76 (s, 3H), 4.56 (sep, J = 6.0 Hz, 1H), 7.02 (s, 1H), 7.15 (s, 1H), 7.95 (br s, 3H). 13C NMR (100 MHz, DMSO-d_6): δ 21.8, 32.7, 38.6, 55.9, 70.7, 113.7, 116.1, 117.6, 128.1, 146.3, 149.7. HRMS m/z. Calcd for C_{12}H_{19}BrNO_2 [(M–Br)+]: 288.0599. Found: 288.0602. These spectroscopic data are in good agreement with those previously reported.8d

Typical procedure for Paal-Knorr reaction of the phenethylamine (9·HBr) with DMT. Under an argon atmosphere, a mixture of 9·HBr (150 mg, 0.406 mmol), an appropriate amount of DMT, pyridine (723 μL, 8.94 mmol), AcOH (511 μL, 8.94 mmol), and water (286 μL, 15.8 mmol) was heated in a sealed tube at 100 °C for 20 h. After cooling to rt, the mixture was diluted with EtOAc and the product was washed with 1 M aqueous HCl and brine, dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography over Chromatorex NH-DM2035 silica gel (hexane–EtOAc = 30:1) to give 8 or a mixture of 11 and 12. Since all attempts to separation of 11 and 12 by flash chromatography were failed, the yields of 11 and 12 were estimated by integration of 1H NMR absorption of H4 of 11 and H4 and H5 of 12. All the results were shown in Table 1.

1-[2-(2-Bromo-5-isopropoxy-4-methoxyphenyl)ethyl]-1H-pyrrole (8). Colorless granules. Mp 57.5–58.5 °C (Et_2O–hexane). IR (KBr): 1507, 1253, 1211, 1034, 848, 729, 705 cm⁻¹. 1H NMR (400 MHz, CDCl_3): δ 1.28 (d, J = 6.1 Hz, 6H), 3.06 (t, J = 7.1 Hz, 2H), 3.82 (s, 3H), 4.07 (t, J = 7.1 Hz, 2H), 4.33 (sep, J = 6.1 Hz, 1H), 6.09 (t, J = 2.1 Hz, 2H), 6.42 (s, 1H), 6.57 (t, J = 2.1 Hz, 2H), 7.02 (s, 1H). 13C NMR (100 MHz, CDCl_3): δ 22.0, 38.3, 49.4, 56.2, 71.8, 108.1, 114.3, 116.0, 118.0, 118.0, 120.5, 129.4, 146.6, 149.9. Anal. Calcd for C_{16}H_{20}BrNO_2: C, 56.82; H, 5.96; N, 4.14. Found: C, 57.03; H, 5.78; N, 4.09.

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1-[2-(2-Bromo-5-isopropoxy-4-methoxyphenyl)ethyl]-1H-indole (11).  
\[ \delta 1.15 (d, J = 6.1 Hz, 6H), 3.13 (t, J = 7.0 Hz, 2H), 3.81 (s, 3H), 4.09 (sep, J = 6.1 Hz, 1H), 4.35 (t, J = 7.0 Hz, 2H), 6.27 (s, 1H), 6.41 (d, J = 3.1 Hz, 1H), 6.92 (d, J = 3.1 Hz, 1H), 7.02 (s, 1H), 7.05–7.37 (m, 3H), 7.59 (d, J = 7.9 Hz, 1H). \]  
HRMS (m/z) Calcd for C_{20}H_{23}BrNO_{2} [(M+H)+]: 388.0912.  Found: 388.0919.  

9-[2-(2-Bromo-5-isopropoxy-4-methoxyphenyl)ethyl]-9H-carbazole (12).  
\[ \delta 1.05 (d, J = 6.1 Hz, 6H), 3.17 (t, J = 7.1 Hz, 2H), 3.79 (s, 3H), 3.98 (sep, J = 6.1 Hz, 1H), 4.54 (t, J = 7.1 Hz, 2H), 6.28 (s, 1H), 7.02 (s, 1H), 7.16–7.44 (m, 6H), 8.06 (d, J = 7.8 Hz, 2H). \]  
HRMS (m/z) Calcd for C_{20}H_{23}BrNO_{2} [(M+H)+]: 438.1069.  Found: 438.1097.  

5,6-Dihydro-8-isopropoxy-9-methoxypyrrolo[2,1-a]isoquinoline (5).  
Under an argon atmosphere, a mixture of 8 (2.71 g, 8.01 mmol), K_{2}CO_{3} (2.43 g, 17.6 mmol) and Pd(PPh_{3})_{4} (925 mg, 0.800 mmol) in DMA (110 mL) was heated at 125 °C for 20 h. After cooling to rt, the mixture was diluted with water and extracted with CH_{2}Cl_{2}. The extract was washed with water and brine, dried over Na_{2}SO_{4}, and evaporated. The residue was purified by column chromatography over silica gel 60N (hexane–EtOAc = 10:1) to give 5 as a pale blue solid (1.84 g, 89%). Recrystallization from Et_{2}O–hexane gave colorless granules. Mp 70.5–71.5 °C. IR (KBr): 1505, 1451, 1265, 1210, 1112, 864, 714 cm \(^{-1}\).  
\[ \delta 1.37 (d, J = 6.1 Hz, 6H), 2.96 (t, J = 6.6 Hz, 2H), 3.88 (s, 3H), 4.04 (t, J = 6.6 Hz, 2H), 4.49 (sep, J = 6.1 Hz, 1H), 6.19 (t, J = 3.0 Hz, 1H), 6.39 (d, J = 3.5 Hz, 1H), 6.64 (s, 1H), 6.72 (s, 1H), 7.02 (s, 1H). \]  
\[ \delta 22.2, 29.0, 44.3, 56.1, 71.8, 102.3, 106.6, 108.3, 116.4, 120.4, 122.8, 123.2, 130.0, 145.4, 149.8. \]  
Anal. Calcd for C_{16}H_{19}NO_{2}: C, 74.68; H, 7.44; N, 5.44.  
Found: C, 74.66; H, 7.74; N, 5.33.  

5,6-Dihydro-8-isopropoxy-9-methoxypyrrolo[2,1-a]isoquinoline-3-carbaldehyde (13). Phosphorus oxychloride (40.0 µL, 0.429 mmol) was added dropwise to DMF (3.2 mL) at 0 °C. After stirring for 1 h at 0 °C, 5 (100 mg, 0.389 mmol) was added and then the mixture was allowed to warm to rt. The reaction mixture was heated at 60 °C and stirring was continued for 20 h. After cooling to rt, the mixture was quenched with saturated aqueous NaHCO_{3} and the product was extracted with CH_{2}Cl_{2}. The extract was washed with water and brine, dried over Na_{2}SO_{4}, and evaporated. The residue was purified by column chromatography over silica gel 60N (hexane–EtOAc = 3:1) to give 13 as a colorless solid (88.0 mg, 79%). Recrystallization from Et_{2}O–hexane gave colorless needles. Mp 69–70 °C. IR (KBr): 1641, 1494, 1402, 1236, 1156, 1040, 803 cm \(^{-1}\).  
\[ \delta 1.40 (d, J = 6.1 Hz, 6H), 3.00 (t, J = 6.9 Hz, 2H), 3.90 (s, 3H), 4.58 (sep, J = 6.1 Hz, 1H), 4.64 (t, J = 6.9 Hz, 2H), 6.50 (d, J = 4.2 Hz, 1H), 6.77 (s, 1H), 6.97 (d, J = 4.2 Hz, 1H), 7.07 (s, 1H), 9.50 (s, 1H). \]  
\[ \delta 22.1, 28.2, 42.4, 56.3, 71.6, 104.9, 108.3, 115.1, 120.3, 125.3, 125.7, 131.1, 139.0, 148.0, 149.6, 179.0. \]  
HRMS (m/z) Calcd for C_{17}H_{21}NO_{3} [(M+H)+]: 286.1443.  Found: 286.1454.
1-Bromo-5,6-dihydro-8-isopropoxy-9-methoxypyrrolo[2,1-a]isoquinoline-3-carbaldehyde (14). Under an argon atmosphere, NBS (62.9 mg, 0.353 mmol) was added portionwise to a solution of 13 (100 mg, 0.350 mmol) in THF (5 mL) at rt, and the mixture was refluxed for 3 h. After cooling to rt, the mixture was evaporated under reduced pressure. The residue was purified by column chromatography over silica gel 60N (hexane–EtOAc = 3:1) to give 14 as a colorless solid (123 mg, 96%). Recrystallization from Et2O–hexane gave colorless plates. Mp 90.5–91 °C. IR (KBr): 1660, 1481, 1399, 1208, 1126, 808 cm–1. 1H NMR (400 MHz, CDCl3): δ 1.41 (d, J = 6.1 Hz, 6H), 2.97 (t, J = 6.7 Hz, 2H), 3.92 (s, 3H), 4.60 (sep, J = 6.1 Hz, 1H), 4.63 (t, J = 6.7 Hz, 2H), 6.78 (s, 1H), 6.99 (s, 1H), 8.01 (s, 1H), 9.46 (s, 1H). 13C NMR (100 MHz, CDCl3): δ 22.1, 28.8, 42.7, 56.2, 71.5, 93.8, 109.3, 114.7, 119.3, 126.8, 127.1, 129.7, 134.0, 147.8, 149.0, 178.7. HRMS (m/z) Calcd for C17H19BrNO3 [(M+H)+]: 364.0548. Found: 364.0530.

5,6-Dihydro-8-isopropoxy-1-(3-isopropoxy-4-methoxyphenyl)-9-methoxypyrrolo[2,1-a]isoquinoline-3-carbaldehyde (15). Under an argon atmosphere, a mixture of 14 (600 mg, 1.65 mmol), 6 (520 mg, 2.48 mmol), Pd(PPh3)4 (191 mg, 0.165 mmol), Na2CO3 (1.15 g, 10.9 mmol), DME (40 mL), and degassed water (5 mL) was refluxed for 16 h. After cooling to rt, the mixture was evaporated and the products were extracted with CH2Cl2. The extract was washed with water and brine, dried over Na2SO4, and evaporated. The residue was purified by flash chromatography over silica gel 60N (toluene–EtOAc = 10:1) to give 15 as a colorless solid (704 mg, 95%). Recrystallization from CH2Cl2–hexane gave colorless powder. Mp 143–143.5 °C. IR (KBr): 1650, 1545, 1434, 1240, 1123, 1023, 805 cm–1. 1H NMR (400 MHz, CDCl3): δ 1.34 (d, J = 6.1 Hz, 6H), 1.38 (d, J = 6.1 Hz, 6H), 3.02 (t, J = 6.7 Hz, 2H), 3.40 (s, 3H), 3.88 (s, 3H), 4.49 (sep, J = 6.1 Hz, 1H), 4.56 (sep, J = 6.1 Hz, 1H), 4.65 (t, J = 6.7 Hz, 2H), 6.75 (s, 1H), 6.88 (s, 1H), 6.91 (s, 1H), 6.92 (d, J = 7.9 Hz, 1H), 6.98 (s, 1H), 6.99 (dd, J = 1.9 and 7.9 Hz, 1H), 9.52 (s, 1H). 13C NMR (100 MHz, CDCl3): δ 22.1, 22.1, 28.7, 42.6, 55.4, 56.1, 71.4, 71.4, 109.6, 112.1, 114.7, 116.9, 120.2, 122.1, 123.2, 125.7, 126.7, 128.6, 129.6, 134.5, 147.3, 147.3, 148.7, 149.6, 179.1. HRMS (m/z) Calcd for C27H32NO5 [(M+H)+]: 450.2280. Found: 450.2282.

2-Bromo-5,6-dihydro-8-isopropoxy-1-(3-isopropoxy-4-methoxyphenyl)-9-methoxypyrrolo[2,1-a]isoquinoline-3-carbaldehyde (16). Under an argon atmosphere, a solution of NBS (29.7 mg, 0.167 mmol) in DMF (1.0 mL) was added dropwise to a solution of 15 (50.0 mg, 0.111 mmol) in DMF (2.0 mL) at 0 °C. After stirring for 0.5 h at 0 °C, the mixture was allowed to warm to rt. After stirring for 2 h at rt, the mixture was quenched with 10% aqueous Na2SO3 and diluted with EtOAc. The product was washed with water and brine, dried over Na2SO4, and evaporated. The residue was purified by flash chromatography over silica gel 60N (hexane–EtOAc = 3:1) to give 16 as a pale yellow solid (44.5 mg, 76%). Recrystallization from CH2Cl2–hexane gave a pale yellow powder. Mp 128–129 °C. IR (KBr): 1643, 1465, 1370, 1240, 1135, 817, 728 cm–1. 1H NMR (500 MHz, CDCl3): δ 1.36 (d, J = 6.1 Hz,
6H), 1.36 (d, J = 6.1 Hz, 6H), 3.00 (t, J = 6.8 Hz, 2H), 3.32 (s, 3H), 3.89 (s, 3H), 4.52 (sep, J = 6.1 Hz, 1H), 4.54 (sep, J = 6.1 Hz, 1H), 4.66 (br s, 1H), 6.72 (s, 1H), 6.91 (dd, J = 1.9 and 8.7 Hz, 1H), 6.91 (d, J = 1.9 Hz, 1H), 6.96 (d, J = 8.7 Hz, 1H), 9.75 (s, 1H). 13C NMR (125 MHz, CDCl3): δ 22.0, 22.1, 28.3, 42.4, 55.2, 56.1, 71.3, 71.4, 109.6, 112.0, 114.5, 114.6, 118.1, 119.2, 122.6, 123.5, 125.0, 126.0, 126.5, 134.5, 147.4, 147.6, 148.7, 150.1, 179.4. HRMS (m/z) Calcd for C27H31BrNO5 [(M+H)+]: 528.1386. Found: 528.1399.

5,6-Dihydro-8-isopropoxy-1-(3-isopropoxy-4-methoxyphenyl)-2-[4-isopropoxy-5-methoxy-2-(methoxy)methoxyphenyl]-9-methoxypyrrolo[2,1-a]isoquinoline-3-carbaldehyde (4). According to the procedure described for the preparation of 15, 16 (341 mg, 0.645 mmol), 7 (262 mg, 0.970 mmol), and Pd(PPh3)4 (74.9 mg, 64.8 µmol) were reacted. After chromatographic purification over silica gel 60N (hexane–EtOAc = 3:2), 4 was obtained as a pale yellow solid (358 mg, 82%). Recrystallization from CH2Cl2–hexane gave a yellow powder. Mp 103–105 °C. IR (KBr): 1649, 1429, 1261, 1213, 1112, 1027 cm–1. 1H NMR (500 MHz, CDCl3): δ 1.15 (d, J = 6.1 Hz, 3H), 1.18 (d, J = 6.1 Hz, 3H), 1.35 (d, J = 6.1 Hz, 3H), 1.37 (d, J = 6.1 Hz, 3H), 1.38 (d, J = 6.1 Hz, 6H), 3.04 (t, J = 6.6 Hz, 2H), 3.29 (s, 3H), 3.34 (s, 3H), 3.61 (s, 3H), 3.68 (s, 3H), 3.81 (s, 3H), 4.25 (sep, J = 6.1 Hz, 1H), 4.49 (sep, J = 6.1 Hz, 1H), 4.55 (sep, J = 6.1 Hz, 1H), 4.65 (br s, 1H), 4.73 (d, J = 6.6 Hz, 1H), 4.80 (br s, 1H), 4.86 (d, J = 6.6 Hz, 1H), 6.56 (s, 1H), 6.71 (d, J = 1.8 Hz, 1H), 6.76 (s, 1H), 6.79 (d, J = 8.2 Hz, 1H), 6.79 (s, 2H), 6.82 (dd, J = 1.8 and 8.2 Hz, 1H), 9.41 (s, 1H). 13C NMR (125 MHz, CDCl3): δ 21.8, 21.9, 22.0, 22.1, 22.1, 28.7, 42.3, 55.3, 55.8, 55.9, 56.1, 56.4, 71.1, 71.4, 71.4, 96.3, 105.2, 109.8, 111.7, 114.6, 116.4, 118.1, 120.3, 122.1, 123.4, 126.4, 126.7, 127.6, 133.6, 135.0, 145.0, 147.0, 147.1, 147.7, 148.5, 149.2, 149.7, 180.8. HRMS (m/z) Calcd for C39H48NO9 [(M+H)+]: 674.3329. Found: 674.3347.

5,6-Dihydro-2-(2-hydroxy-4-isopropoxy-5-methoxyphenyl)-8-isopropoxy-1-(3-isopropoxy-4-methoxyphenyl)-9-methoxypyrrolo[2,1-a]isoquinoline-3-carbaldehyde (17). To a solution of 4 (50.0 mg, 74.2 µmol) in MeOH (2.0 mL) was added concd HCl (0.2 mL) and the mixture was refluxed for 2 h. After cooling to rt, the mixture was evaporated. The products were extracted with CH2Cl2 and the extract was washed with water and brine, dried over Na2SO4, and evaporated. The residue was purified by column chromatography over silica gel 60N (hexane–EtOAc = 2:1) to give 17 as brown semisolid (34.2 mg, 73%). This compound was rather unstable and was used for the next reaction without further purification. IR (KBr): 3433, 1647, 1429, 1261, 1207, 1109 cm–1. 1H NMR (400 MHz, CDCl3): δ 1.15 (d, J = 6.1 Hz, 3H), 1.19 (d, J = 6.1 Hz, 3H), 1.35 (d, J = 6.1 Hz, 3H), 1.37 (d, J = 6.1 Hz, 3H), 1.38 (d, J = 6.1 Hz, 6H), 3.01–3.10 (m, 2H), 3.35 (s, 3H), 3.68 (s, 3H), 3.82 (s, 3H), 4.26 (sep, J = 6.1 Hz, 1H), 4.47 (sep, J = 6.1 Hz, 1H), 4.57 (sep, J = 6.1 Hz, 1H), 4.58 (br s, 1H), 4.89 (br s, 2H), 6.46 (s, 1H), 6.62 (s, 1H), 6.71 (d, J = 1.8 Hz, 1H), 6.77 (s, 1H), 6.79 (s, 1H), 6.81 (d, J = 8.2 Hz, 1H), 6.85 (dd, J = 1.8 and 8.2 Hz, 1H), 9.41 (s, 1H). 13C NMR (100 MHz, CDCl3): δ 21.7, 21.9, 22.0, 22.1, 22.1, 28.7, 42.4, 55.3,
56.0, 56.7, 71.1, 71.2, 71.4, 103.2, 109.5, 109.8, 111.9, 114.6, 116.1, 117.9, 119.7, 122.3, 123.1, 126.3, 126.8, 126.9, 132.9, 134.4, 143.8, 147.3, 147.6, 148.0, 148.6, 148.7, 149.7, 180.1. HRMS (m/z) Calcd for C_{37}H_{44}NO_8 [(M+H)^+]: 630.3067. Found: 630.3054.

8,9-Dihydro-3,11-diisopropoxy-14-(3-isopropoxy-4-methoxyphenyl)-2,12-dimethoxy-6H-[1]benzopyrano[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one (lamellarin L triisopropyl ether) (3). Under an argon atmosphere, a mixture of 17 (30.3 mg, 2.72 µmol), bromobenzene (6.0 µL, 56 µmol), Pd(OAc)$_2$ (1.1 mg, 4.9 µmol), triphenylphosphine (3.9 mg, 15 µmol), K$_2$CO$_3$ (7.3 mg, 53 µmol), and DMF (2.0 mL) was heated in a sealed tube at 120 °C for 13 h. After cooling to rt, the mixture was diluted with water and extracted with CH$_2$Cl$_2$. The extract was washed with water and brine, dried over Na$_2$SO$_4$, and evaporated. The residue was purified by column chromatography over silica gel 60N (hexane–EtOAc = 2:1) to give 3 as a colorless solid (15.7 mg, 52%). Recrystallization from CH$_2$Cl$_2$–Et$_2$O gave a colorless powder. Mp 207–208 °C. [lit. 8k Mp 206.5–207.5 °C]. IR (KBr): 1712, 1511, 1418, 1270, 1212, 1164, 1111, 1039, 939 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 1.33 (d, $J = 6.1$ Hz, 3H), 1.34 (d, $J = 6.1$ Hz, 3H), 1.37 (d, $J = 6.1$ Hz, 3H), 1.37 (d, $J = 6.1$ Hz, 3H), 1.39 (d, $J = 6.1$ Hz, 6H), 3.10 (t, $J = 6.8$ Hz, 2H), 3.34 (s, 3H), 3.43 (s, 3H), 3.92 (s, 3H), 4.48–4.58 (m, 3H), 4.73–4.86 (m, 2H), 6.66 (s, 1H), 6.73 (s, 1H), 6.77 (s, 1H), 6.92 (s, 1H), 7.05 (d, $J = 1.6$ Hz, 1H), 7.07 (d, $J = 8.1$ Hz, 1H), 7.09 (dd, $J = 1.6$ and 8.1 Hz, 1H), 13C NMR (125 MHz, CDCl$_3$): $\delta$ 21.8, 21.9, 22.0, 22.1, 28.7, 42.5, 55.1, 55.5, 56.3, 71.3, 71.4, 71.4, 103.5, 104.9, 109.2, 110.4, 112.7, 113.7, 114.8, 114.8, 117.9, 120.3, 123.7, 126.4, 128.0, 128.3, 136.0, 146.0, 146.5, 147.0, 147.3, 148.1, 148.7, 150.1, 155.7. HRMS (m/z) Calcd for C_{37}H_{42}NO_8 [(M+H)^+]: 628.2910. Found: 628.2938. These physical and spectroscopic data are in good agreement with those previously reported. 8k

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REFERENCES AND NOTES


15. In case $x$ mol of the amine hydrobromide (9·HBr) was reacted to give $y$ g of a mixture of the indole (11) and the carbazole (12) and the molar fractions of 11 and 12 in the mixture were determined to be $N_{11}$ and $N_{12}$, the yields of 11 and 12 were estimated by using the following equations:

The yield of 11 ($Y_{11}$) = \[
\frac{yN_{11}}{x \left( MW_{11}N_{11} + MW_{12}N_{12} \right)} \times 100 \quad (\%) \]

The yield of 12 ($Y_{12}$) = \[
\frac{yN_{12}}{x \left( MW_{11}N_{11} + MW_{12}N_{12} \right)} \times 100 \quad (\%)
\]

where $MW_{11}$ and $MW_{12}$ are molecular weights of 11 and 12.