Supporting Information

Concise Synthesis of Lamellarin Alkaloids by C–H/N–H Activation: Evaluation of Metal Catalysts in Oxidative Alkyne Annulation

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General Remarks

Catalytic reactions were carried out under a N₂ atmosphere using pre-dried glassware. 1,2-Dichloroethane (DCE) was dried and distilled over CaH₂; Methanol (MeOH) was dried and distilled over magnesium. t-AmOH was dried and distilled over sodium. The following starting materials were synthesized according to previously described procedures: [Ru(O₂CMes)₂(p-cymene)],¹ [CoCp*(CO)]₂,² methyl 2-acetamidoacrylate,³ 3-isopropoxy-4-methoxybenzaldehyde (S4).⁴ Other chemicals were obtained from commercial sources and were used without further purification. Yields refer to isolated compounds, estimated to be > 95% pure as determined by ¹H-NMR and GC-analysis. Chromatography: Merck silica gel 60 (40-63 μm). NMR: Spectra were recorded on VariUnity 300, Mercury 300 or Inova 500 in the solvent indicated; chemical shifts (δ) were given in ppm. All IR spectra were recorded on a Bruker FT-IR Alpha device. MS: EI-MS- and ESI-MS-spectra were recorded with Finnigan MAT 95, 70 eV. High resolution mass spectrometry (HR-MS) with APEX IV 7T FTICR, Bruker Daltonic. M. p.: Stuart melting point apparatus SMP3, Barloworld Scientific, values are uncorrected.
Table S-1: Optimization of Transition Metal-Catalyzed C–H/N–H Activation.\textsuperscript{a} 

\[
\begin{array}{cccccc}
\text{entry} & \text{catalyst} & \text{solvent} & T (^\circ\text{C}) & \text{deviation of general conditions} & \text{3a yield} \% & \text{3a' yield} \% \\
1 & --- & MeOH/DCE (2/1) & 110 & --- & --- & --- \\
2 & \text{[CoCp*(CO)I]}_2 & TFE & 120 & --- & 20 & trace \\
3 & \text{[CoCp*(CO)I]}_2 & MeOH/DCE (2/1) & 110 & --- & --- & --- \\
4 & \text{[Cp*RhCl}_2 & t-AmOH & 60 & Without AgSbF_6 & Cu(OAc)_2\cdot\text{H}_2\text{O} (0.2 equiv) & O_2 (1 atm) & --- & --- \\
5 & \text{[Cp*RhCl}_2 & MeOH/DCE (2/1) & 110 & --- & 94 & trace \\
6 & Pd(OAc)_2 & DMSO & 80 & Without Cu(OAc)_2\cdot\text{H}_2\text{O}; \text{KOAc} (2.0 equiv) & O_2 (1 atm) & 24 & --- \\
7 & Pd(OAc)_2 & MeOH/DCE (2/1) & 110 & --- & 15 & --- \\
8 & \text{[RuCl}_2\text{(p-cymene)}_2 & PEG-400 & 110 & Without AgSbF_6 & Cu(OAc)_2\cdot\text{H}_2\text{O} (3.0 equiv) & 32 & 59 \\
9 & \text{[RuCl}_2\text{(p-cymene)}_2 & PEG-400/\text{H}_2\text{O} (4/1) & 110 & Without AgSbF_6 & Cu(OAc)_2\cdot\text{H}_2\text{O} (3.0 equiv) & 44 & 34 \\
10 & \text{[RuCl}_2\text{(p-cymene)}_2 & PEG-400/TFE (4/1) & 110 & Without AgSbF_6 & Cu(OAc)_2\cdot\text{H}_2\text{O} (3.0 equiv) & 37 & 59 \\
11 & \text{[RuCl}_2\text{(p-cymene)}_2 & t-AmOH & 120 & Without AgSbF_6 & 13 & 80 \\
12 & \text{[RuCl}_2\text{(p-cymene)}_2 & t-AmOH & 120 & --- & 68 & 23 \\
13 & \text{[RuCl}_2\text{(p-cymene)}_2 & t-AmOH/MeOH (1/1) & 120 & --- & 74 & 22 \\
14 & \text{[RuCl}_2\text{(p-cymene)}_2 & t-AmOH/MeOH (2/1) & 120 & --- & 95 & trace \\
15 & \text{[RuCl}_2\text{(p-cymene)}_2 & MeOH/DCE (2/1) & 110 & --- & 97 & --- \\
16 & \text{[RuCl}_2\text{(p-cymene)}_2 & MeOH/DCE (2/1) & 110 & Without AgSbF_6 & 66 & 10 \\
17 & \text{[RuCl}_2\text{(p-cymene)}_2 & MeOH/DCE (2/1) & 110 & Cu(OAc)_2\cdot\text{H}_2\text{O} (0.4 equiv) & O_2 (1 atm) & 51 & 11 \\
\end{array}
\]

\textsuperscript{a}Reaction conditions: \textbf{1a} (0.50 mmol), \textbf{2} (0.55 mmol), [TM] (10 mol %), AgSbF_6 (20 mol %), Cu(OAc)_2\cdot\text{H}_2\text{O} (2.0 equiv), solvent (1.5 mL), 110 °C, 24 h, isolated yield.
Synthesis of 1,2-bis(4-isopropoxy-3-methoxyphenyl)ethyne (1a):

Scheme S-1: Synthesis of 1,2-Bis(4-isopropoxy-3-methoxyphenyl)ethyne (1a)

4-Iodo-2-methoxyphenol (S2)

Following a modified procedure,[5] guaiacol (12.4 g, 100 mmol) was dissolved in MeOH (200 mL), then NaI (22.5 g, 149.5 mmol) and NaOH (6.25 g, 150 mmol) were added. Aqueous NaClO solution (15%, 200 mL, 145 mmol) was added dropwise over 40 min at -4 °C. The mixture was stirred for additional 30 min at this temperature. The mixture was acidified with a HCl solution (4 M) to pH = 7, then Na2S2O3 (10%, 60 mL) was added. MeOH was removed under reduced pressure and the aqueous phase was extracted with EtOAc (3×150 mL). The combined organic phase was washed with saturated aqueous NaHCO3 (2×100 mL) and brine (100 mL), dried over Na2SO4 and concentrated. The residue was filtrated through a short pad of silica gel and further purified by vacuum distillation to give the product S2 (21.0 g, 84%) as an orange oil. 1H NMR (300 MHz, CDCl3) δ = 7.16 (dd, J = 8.3, 1.9 Hz, 1H), 7.09 (d, J = 1.9 Hz, 1H), 6.66 (d, J = 8.3 Hz, 1H), 5.54 (s, 1H), 3.86 (s, 3H). 13C NMR (125 MHz, CDCl3) δ = 147.3 (Cq), 145.6 (Cq), 130.4 (CH), 119.7 (CH), 116.4 (CH), 80.9 (Cq), 56.2 (CH3). IR (neat): 3489, 2941, 2838, 1601, 1491, 1440, 1218, 1020 cm⁻¹. MS (EI) m/z (relative intensity)
250 (100) [M⁺], 234 (50), 206 (30), 179 (5), 126 (10), 108 (10). **HR-MS** (ESI) *m/z* calcd for C₇H₇IO₂ [M⁺] 249.9491, found 249.9495.

The analytical data are in accordance with those previously reported in the literature.[⁵]

![Chemical Structure](image)

**4-Iodo-1-isopropoxy-2-methoxybenzene (S3)**

Following a modified procedure,[⁴] to a suspension of S2 (12.5 g, 50 mmol) and K₂CO₃ (13.8 g, 100 mmol) in DMSO (200 mL) was added i-PrBr (9.2 g, 75 mmol) at ambient temperature and the mixture was heated at 55 °C for 16 h. At ambient temperature, the mixture was diluted with EtOAc (500 mL) and washed with H₂O (4×100 mL) and brine (100 mL). The organic phase was dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography (*n*-hexane/EtOAc, 20/1) to give the product S3 (13.7 g, 94%) as a colorless oil. **¹H NMR** (300 MHz, CDCl₃) δ = 7.17 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.10 (d, *J* = 2.1 Hz, 1H), 6.62 (d, *J* = 8.4 Hz, 1H), 4.46 (hept, *J* = 6.1 Hz, 1H), 3.81 (s, 3H), 1.33 (d, *J* = 6.1 Hz, 6H). **¹³C NMR** (75 MHz, CDCl₃) δ = 151.3 (C₉), 147.4 (C₉), 129.7 (CH), 121.1 (CH), 117.6 (CH), 82.8 (C₉), 71.6 (CH), 56.1 (CH₃), 22.0 (CH₃). **IR** (neat): 2974, 1578, 1489, 1245, 1220, 1134, 1025, 824 cm⁻¹. **MS** (EI) *m/z* (relative intensity) 292 (30) [M⁺], 249 (100), 234 (50), 217 (5), 206 (15), 190 (5). **HR-MS** (EI) *m/z* calcd for C₁₀H₁₃IO₂ [M⁺⁺] 291.9960, found 291.9953.

The analytical data are in accordance with those previously reported in the literature.[⁴]
1,2-Bis(4-isoproxy-3-methoxyphenyl)ethyne (1a)

Following a modified procedure,[6a] aryl iodide S3 (8.70 g, 30 mmol), Pd(PPh3)4 (1.04 g, 6 mol %), CuI (285 mg, 10 mol %) were placed into a 250 mL Schlenk flask under a N2 atmosphere. Benzene (80 mL) and DBU (27 mL, 180 mmol) were added via cannula. Degassed H2O (121 mg, 45 mol %) and ethynyltrimethylsilane (2.10 mL, 15 mmol) were added by syringe sequentially. The mixture was kept in dark by aluminum foil and stirred at 60 ºC for 48 h. At ambient temperature, the mixture was diluted with CH2Cl2 (400 mL) and washed with HCl (3 M, 3×75 mL), sat. aq. NH4Cl/NH3 (1/1, 3×75 mL) and brine (75 mL). The organic phase was dried over Na2SO4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (n-hexane/EtOAc 4/1 to CH2Cl2) to afford the product 1a (3.99 g, 75%) as a white solid. **M. p. = 176–177 °C.**

1H NMR (300 MHz, CDCl3) δ = 7.06 (dd, J = 8.2, 1.9 Hz, 2H), 7.01 (d, J = 1.9 Hz, 2H), 6.82 (d, J = 8.2 Hz, 2H), 4.53 (hept, J = 6.1 Hz, 2H), 3.84 (s, 6H), 1.35 (d, J = 6.1 Hz, 12H). 13C NMR (75 MHz, CDCl3) δ = 149.8 (Cq), 147.6 (Cq), 124.5 (CH), 115.7 (Cq), 115.0 (CH), 114.8 (CH), 88.0 (Cq), 71.3 (CH), 55.9 (CH3), 22.0 (CH3). IR (neat): 2976, 2916, 1509, 1241, 1214, 1135, 1036, 852 cm⁻¹. MS (EI) m/z (relative intensity) 355 (10) [M+H⁺], 354 (30) [M⁺], 312 (15), 270 (100), 255 (20), 227 (20). HR-MS (EI) m/z calcd for C22H26O4 [M⁺] 354.1831, found 354.1828.

The analytical data are in accordance with those previously reported in the literature.[6b]
Synthesis of 7a

Scheme S-2: Synthesis of 2-[4-isopropoxy-5-methoxy-2-(methoxymethoxy)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (7a)

3-Isopropoxy-4-methoxyphenol (S5)

Following a reported procedure,[7] under an argon atmosphere, m-CPBA (70%, 11.8 g, 48 mmol) was added portionwise to a solution of S4 (7.77 g, 40 mmol) in CH2Cl2 (120 mL) at 0 °C. After being stirred at 23 °C for 3 h, to the mixture was added saturated aqueous NaHCO3 (80 mL). The mixture was diluted with H2O (50 mL) and the organic layer was separated. The aqueous layer was extracted with CH2Cl2 (3×80 mL). The combined extract was washed with brine (100 mL), dried over Na2SO4, and evaporated under reduced pressure. The residue was dissolved in MeOH (200 mL) and K2CO3 (13.8 g, 100 mmol) was added portionwise to the solution. After being stirred for 1 h, the mixture was evaporated under reduced pressure. H2O (150 mL) was added to the residue and the aqueous solution was extracted with EtOAc (3×100 mL). The extract was washed with brine (100 mL), dried over Na2SO4, evaporated under reduced pressure. The residue was purified by column
The mixture was washed with brine, dried with sodium sulfate, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (n-hexane/EtOAc 15:1) to yield S5 (6.12 g, 84%) as a colorless solid. 

**1H NMR** (400 MHz, CDCl₃) δ = 6.71 (d, J = 8.6 Hz, 1H), 6.45 (d, J = 2.8, 1H), 6.33 (dd, J = 8.6, 2.8 Hz, 1H), 4.42 (hept, J = 6.1 Hz, 1H), 3.76 (s, 3H), 1.30 (d, J = 6.1 Hz, 6H). **13C NMR** (100 MHz, CDCl₃) δ = 150.2 (Cq), 148.1 (Cq), 144.2 (Cq), 113.5 (CH), 106.5 (CH), 104.1 (CH), 71.3 (CH), 56.8 (CH₃), 21.9 (CH₃). **IR** (neat): 3424, 2977, 1606, 1504, 1460, 1287, 1221, 1126 cm⁻¹. **MS** (EI) m/z (relative intensity) 183 (10) [M+H⁺], 182 (50) [M⁺], 140 (70), 125 (100), 111 (10), 97 (30). **HR-MS** (EI) m/z calcd for C₁₀H₁₄O₃ [M⁺] 182.0943, found 182.0944.

The analytical data are in accordance with those previously reported in the literature.[7]

![Structure of S6](image)

**2-Isopropoxy-1-methoxy-4-(methoxymethoxy)benzene (S6)**

Following a modified procedure,[7] under an argon atmosphere, a solution of S5 (3.64 g, 20 mmol) in THF (20 mL) was added dropwise to a suspension of NaH (60%, 2.40 g, 60 mmol) in THF (30 mL) at 0 °C. After being stirred for 30 min, chloromethyl methyl ether (2.41 g, 30 mmol) was added and the mixture was stirred for 2 h at 0 °C and additional 1 h at ambient temperature. To the mixture was added saturated aqueous NH₄Cl (80 mL) and extracted with EtOAc (3×80 mL). The extract was washed with brine (80 mL), dried over Na₂SO₄, and evaporated under reduced pressure. The residue was purified by column chromatography over silica gel (n-hexane/EtOAc 10/1) to give S6 as a colorless oil (3.62 g, 80%). **1H NMR** (400 MHz, CDCl₃) δ = 6.76 (d, J = 8.8 Hz, 1H), 6.63 (d, J = 2.8 Hz, 1H), 6.57 (dd, J = 8.8, 2.8 Hz, 1H), 5.08 (s, 2H), 4.48 (hept, J = 6.1 Hz, 1H), 3.79 (s, 3H), 3.46 (s, 3H), 1.35 (d, J = 6.1 Hz, 6H). **13C NMR** (100 MHz, CDCl₃) δ = 151.6 (Cq), 148.1 (Cq), 145.6 (Cq), 112.8 (CH), 107.5 (CH), 105.9 (CH), 95.3 (CH₂), 71.4 (CH), 56.6 (CH₃), 55.9 (CH₃), 22.0 (CH₃). **IR** (neat): 2975, 2931, 1595, 1503, 1224, 1150, 1009, 920 cm⁻¹. **MS** (EI) m/z (relative intensity) 227 (10) [M+H⁺], 226 (80) [M⁺], 195 (10), 184 (60), 154 (80), 139 (100). **HR-MS** (EI) m/z calcd for C₁₂H₁₈O₄ [M⁺] 226.1205, found 226.1213.

The analytical data are in accordance with those previously reported in the literature.[7]
1-Bromo-4-isopropoxy-5-methoxy-2-(methoxymethoxy)benzene (S7)

Following a reported procedure,\textsuperscript{[7]} a solution of NBS (2.8 g, 15.7 mmol) in DMF (20 mL) was added dropwise to a solution of S6 (3.39 g, 15 mmol) in DMF (15 mL) at 0 °C. After being stirred for 30 min, the reaction mixture was added H₂O (30 mL) at the same temperature and allowed to warm to ambient temperature. The mixture was diluted with Et₂O (250 mL), washed with H₂O (3×40 mL) and brine (80 mL). The organic phase was dried over Na₂SO₄ and concentrated at ambient temperature. The residue was purified by column chromatography on silica gel (n-hexane/EtOAc 10/1) to yield S7 (4.07 g, 89%) as a pale yellow oil. \textsuperscript{1}H NMR (300 MHz, CDCl₃) δ = 7.00 (s, 1H), 6.79 (s, 1H), 5.12 (s, 2H), 4.46 (hept, J = 6.1 Hz, 1H), 3.79 (s, 3H), 3.51 (s, 3H), 1.33 (d, J = 6.1 Hz, 6H). \textsuperscript{13}C NMR (125 MHz, CDCl₃) δ = 147.8 (C₉), 147.1 (C₉), 146.4 (C₉), 116.6 (CH), 107.0 (CH), 103.2 (C₉), 96.3 (CH₂), 72.1 (CH), 56.7 (CH₃), 56.4 (CH₃), 22.0 (CH₃). IR (neat): 2974, 2903, 2833, 1495, 1374, 1206, 1149, 1010 cm⁻¹. MS (EI) m/z (relative intensity) 304 (10) [M⁺], 262 (10), 232 (30), 217 (20), 189 (10), 43 (100). HR-MS (EI) m/z calcd for C₁₂H₁₇⁷⁹BrO₄ [M⁺] 304.0310, found 304.0310; C₁₂H₁₇⁸₁BrO₄ [M⁺] 306.0290, found 306.0290.

The analytical data are in accordance with those previously reported in the literature.\textsuperscript{[7]}

2-[4-Isopropoxy-5-methoxy-2-(methoxymethoxy)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (7a)

Following a modified procedure,\textsuperscript{[8]} a mixture of S7 (3.05 g, 10 mmol), Et₃N (5.6 mL, 40 mmol), Pd(OAc)₂ (112 mg, 5 mol %), DPEphos (538 mg, 10 mol %), and S8 (3.84 g, 4-tert-butyl-5-methoxy-2-(methoxymethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (7a)
30 mmol) in 1,4-dioxane (20 mL) was heated at 100 °C for 16 h. At ambient temperature, to the mixture was added saturated NH₄Cl (80 mL), and the aqueous solution was extracted with EtOAc (3×60 mL). The organic phase was dried over Na₂SO₄, filtered, and concentrated. The residue was purified by column chromatography (n-hexane/EtOAc/Et₃N 100/10/1) to give 7a (2.92 g, 83%) as a pale yellow oil. ¹H NMR (400 MHz, CDCl₃) δ = 7.14 (s, 1H), 6.61 (s, 1H), 5.04 (s, 2H), 4.51 (hept, J = 6.1 Hz, 1H), 3.79 (s, 3H), 3.48 (s, 3H), 1.31 (d, J = 6.1 Hz, 6H), 1.27 (s, 12H). ¹³C NMR (100 MHz, CDCl₃) δ = 157.2 (Cₗ), 150.5 (Cₗ), 145.3 (Cₗ), 119.0 (CH), 106.1 (CH), 97.1 (CH₂), 83.0 (Cₗ), 70.9 (CH), 56.3 (CH₃), 56.0 (CH₃), 24.6 (CH₃), 21.7 (CH₃). IR (neat): 2976, 2933, 1602, 1507, 1370, 1346, 1202, 1141 cm⁻¹. MS (EI) m/z (relative intensity) 353 (10) [M+H⁺], 352 (100) [M⁺], 310 (10), 278 (30), 236 (30), 194 (80). HR-MS (EI) m/z calcd for C₁₈H₂₉BO₆ [M⁺] 352.2057, found 352.2062.
Synthetic Route to Lamellarins D and H

Scheme S-3. Synthetic Route to Lamellarins D and H
Methyl 4,5-bis(4-isopropoxy-3-methoxyphenyl)-1H-pyrrole-2-carboxylate (3a)

Methyl 2-acetamidoacrylate (2) (787 mg, 5.50 mmol), 1,2-bis(4-isopropoxy-3-methoxyphenylethyne (1a) (1.77 g, 5.00 mmol), [RuCl2(p-cymene)]2 (153 mg, 5.0 mol %), AgSbF6 (343 mg, 20 mol %) and Cu(OAc)2·H2O (2.00 g, 10.0 mmol) was placed into a 100 mL sealed tube under a N2 atmosphere. A solvent mixture of MeOH/DCE (20 mL/10 mL) was added via cannula. The reaction mixture was stirred at 110 °C for 24 h. At ambient temperature, the reaction mixture was dry-loaded onto silica gel and purified by column chromatography (n-hexane/EtOAc 4/1 to 2/1) to afford the desired product 3a (2.11 g, 93%) as colorless solid.

M. p. = 70–71 °C. 1H NMR (400 MHz, CDCl3) δ = 9.16 (s, 1H), 7.01 (d, J = 2.7 Hz, 1H), 6.93–6.77 (m, 5H), 4.56–4.43 (m, 2H), 3.84 (s, 3H), 3.67 (s, 3H), 3.63 (s, 3H), 1.35 (d, J = 6.1 Hz, 6H), 1.34 (d, J = 6.1 Hz, 6H). 13C NMR (100 MHz, CDCl3) δ = 161.6 (Cq), 150.1 (Cq), 150.1 (Cq), 147.2 (Cq), 145.9 (Cq), 133.1 (Cq), 128.6 (Cq), 124.8 (Cq), 123.5 (Cq), 121.4 (Cq), 120.7 (CH), 120.1 (CH), 116.5 (CH), 115.9 (CH), 115.5 (CH), 112.6 (CH), 112.0 (CH), 71.5 (CH), 71.4 (CH), 55.8 (CH3), 55.7 (CH3), 51.5 (CH3), 22.1 (CH3), 22.0 (CH3). IR (neat): 3296, 2975, 2934, 1680, 1517, 1465, 1204, 1106, 765 cm⁻¹. MS (EI) m/z (relative intensity) 454 (100) [M+H⁺], 453 (80) [M⁺], 411 (30), 369 (100), 337 (80). HR-MS (EI) m/z calcd for C26H31NO6 [M⁺] 453.2151, found 453.2151.

Characterization data of 3a’
Methyl 1-acetyl-4,5-bis(4-isopropoxy-3-methoxyphenyl)-1H-pyrrole-2-carboxylate (3a')

Colorless solid. M. p. = 143–144 °C. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta = 7.14\) (s, 1H), 6.88–6.84 (m, 2H), 6.82 (s, 1H), 6.78–6.72 (m, 2H), 6.63 (s, 1H), 4.55 (hept, \(J = 6.1\) Hz, 1H), 4.46 (hept, \(J = 6.1\) Hz, 1H), 3.87 (s, 3H), 3.72 (s, 3H), 3.56 (s, 3H), 2.31 (s, 3H), 1.37 (d, \(J = 6.1\) Hz, 6H), 1.33 (d, \(J = 6.1\) Hz, 6H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta = 174.1\) (C\(_q\)), 161.1 (C\(_q\)), 150.0 (C\(_q\)), 149.8 (C\(_q\)), 147.8 (C\(_q\)), 145.9 (C\(_q\)), 134.1 (C\(_q\)), 127.1 (C\(_q\)), 124.4 (C\(_q\)), 123.4 (CH), 123.2 (C\(_q\)), 122.5 (C\(_q\)), 120.1 (CH), 117.9 (CH), 115.6 (CH), 114.9 (CH), 114.6 (CH), 111.8 (CH), 71.3 (CH), 71.2 (CH), 56.0 (CH\(_3\)), 55.5 (CH\(_3\)), 51.8 (CH\(_3\)), 28.8 (CH\(_3\)), 22.1 (CH\(_3\)), 22.0 (CH\(_3\)). IR (neat): 2983, 2934, 2827, 1749, 1691, 1470, 1227, 850, 769 cm\(^{-1}\). MS (EI) \(m/z\) (relative intensity) 496 (10) [M+H\(^+\)], 495 (40) [M\(^+\)], 453 (60), 411 (40), 369 (100), 337 (60). HR-MS (EI) \(m/z\) calcd for C\(_{29}\)H\(_{33}\)NO\(_7\) [M\(^+\)] 495.2257, found 495.2265.

![Methyl 1-acetyl-4,5-bis(4-isopropoxy-3-methoxyphenyl)-1H-pyrrole-2-carboxylate (3a')](image)

Methyl 3-bromo-4,5-bis(4-isopropoxy-3-methoxyphenyl)-1H-pyrrole-2-carboxylate (S8)

Following a modified procedure,\(^9\) to a solution of 3a (1.40g, 3.09 mmol) in DMF (40 mL) was added a solution of NBS (555 mg, 3.12 mmol) in DMF (5 mL) dropwise within 10 min at 0 °C under a N\(_2\) atmosphere. The reaction mixture was stirred at 0 °C for 1 h. Then, the mixture was diluted with EtOAc (200 mL) and washed with H\(_2\)O (3x60 mL) and brine (60 mL). The organic phase was dried over Na\(_2\)SO\(_4\) and concentrated. The residue was purified by column chromatography over silica gel (n-hexane/EtOAc 5/1) to give S8 (1.61g, 98%) as a colorless solid. M. p. = 71–72 °C. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta = 9.37\) (s, 1H), 6.91–6.75 (m, 5H), 6.69 (d, \(J = 2.0\) Hz, 1H), 4.59–4.45 (m, 2H), 3.90 (s, 3H), 3.73 (s, 3H), 3.54 (s, 3H), 1.37 (d, \(J = 6.1\) Hz, 6H), 1.34 (d, \(J = 6.1\) Hz, 6H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta = 160.9\) (C\(_q\)), 149.8 (C\(_q\)), 149.7 (C\(_q\)), 147.1 (C\(_q\)), 146.4 (C\(_q\)), 133.6 (C\(_q\)), 126.3 (C\(_q\)), 124.2 (C\(_q\)), 123.6 (C\(_q\)), 123.1 (CH), 119.5 (CH), 118.9 (C\(_q\)), 115.2 (CH), 115.0 (CH), 114.6 (CH), 111.5 (CH), 106.0 (C\(_q\)), 71.1 (CH), 55.7 (CH\(_3\)), 55.4 (CH\(_3\)), 51.5 (CH\(_3\)), 21.9 (CH\(_3\)), 21.8 (CH\(_3\)).
**IR (neat):** 3284, 2975, 1671, 1518, 1467, 1383, 1233, 1106, 1032 cm\(^{-1}\). **MS (EI) m/z** (relative intensity) 533 (40)[M⁺], 489 (20), 449 (70), 417 (100), 369 (10), 308 (50). **HR-MS (EI) m/z** calculated for C\(_{26}H_{30}^{79}\)BrNO\(_6\) [M⁺] 531.1257, found 531.1256; C\(_{26}H_{30}^{81}\)BrNO\(_6\) [M⁺] 533.1236, found 533.1240.

![Image](image)

**Methyl 4,5-bis(4-isopropoxy-3-methoxyphenyl)-3-[4-isopropoxy-5-methoxy-2-(methoxy-methoxy)phenyl]-1H-pyrrole-2-carboxylate (S9)**

Following a modified procedure,[9] **S8** (1.06 g, 2.0 mmol), 7a (1.41 g, 4.0 mmol), Pd\(_2\)(dba)\(_3\) (137 mg, 7.5 mol %), dppf (166 mg, 15 mol %) and Na\(_2\)CO\(_3\) (1.40 g, 13.2 mmol) was placed into a 100 mL sealed tube under a N\(_2\) atmosphere. A solvent mixture of DME/H\(_2\)O (30 mL/2.4 mL) was added via cannula. The reaction mixture was kept in the dark and stirred at 110 °C for 24 h. After cooling down to ambient temperature, the mixture was evaporated, the residue was diluted with H\(_2\)O (30 mL) and extracted with CH\(_2\)Cl\(_2\) (4×30 mL). The extracts was washed with brine (2×30 mL), dried over Na\(_2\)SO\(_4\), and evaporated. The residue was purified by column chromatography over silica gel (n-hexane/EtOAc 2/1) to give **S9** (1.18 g, 87%) as a pale yellow solid. **M. p.** = 81–82 °C. **\(^1\)H NMR** (600 MHz, CDCl\(_3\)) δ = 9.23 (s, 1H), 6.92 (dd, J = 8.3, 2.1 Hz, 1H), 6.82 (d, J = 8.3 Hz, 1H), 6.78 (s, 1H), 6.78 (d, J = 2.1 Hz, 1H), 6.65 (d, J = 8.2 Hz, 1H), 6.61 (s, 1H), 6.53 (dd, J = 8.2, 2.0 Hz, 1H), 6.52 (d, J = 2.0 Hz, 1H), 4.75 (d, J = 6.9 Hz, 1H), 4.55–4.43 (m, 3H), 4.39 (hept, J = 6.1 Hz, 1H), 3.68 (s, 3H), 3.62 (s, 3H), 3.54 (s, 3H), 3.44 (s, 3H), 3.21 (s, 3H), 1.34 (d, J = 6.1 Hz, 12H), 1.27 (d, J = 6.1 Hz, 6H). **\(^13\)C NMR** (75 MHz, CDCl\(_3\)) δ = 161.7 (C\(_{q}\)), 149.9 (C\(_{q}\)), 149.8 (C\(_{q}\)), 149.8 (C\(_{q}\)), 147.1 (C\(_{q}\)), 147.0 (C\(_{q}\)), 145.4 (C\(_{q}\)), 145.0 (C\(_{q}\)), 132.4 (C\(_{q}\)), 128.0 (C\(_{q}\)), 127.7 (C\(_{q}\)), 124.7 (C\(_{q}\)), 123.7 (C\(_{q}\)), 122.5
(CH), 119.6 (CH), 118.8 (C₆), 117.1 (C₆), 116.1 (CH), 115.7 (CH), 115.3 (CH), 114.3 (CH), 112.0 (CH), 105.6 (CH), 96.5 (CH₂), 71.4 (CH), 71.3 (CH), 71.3 (CH), 56.4 (CH₃), 55.6 (CH₃), 55.5 (CH₃), 55.4 (CH₃), 51.3 (CH₃), 22.0 (CH₃), 22.0 (CH₃). IR (neat): 3530, 3314, 2976, 1670, 1506, 1440, 1214, 1107, 751 cm⁻¹. MS (EI) m/z (relative intensity) 678 (50) [M+H⁺], 677 (100) [M⁺], 602 (30), 588 (10), 560 (10), 528 (10). HR-MS (ESI) m/z calcd for C₃₈H₄₈NO₁₀ [M+H⁺] 678.3273, found 678.3264.

![Chemical structure of 8a](image-url)

**7-Isopropoxy-1,2-bis(4-isopropoxy-3-methoxyphenyl)-8-methoxychromeno[3,4-b]pyrrolo-4(3H)-one (8a)**

Following a modified procedure,⁹ under a N₂ atmosphere, S9 (1.02 g, 1.50 mmol), TsOH·H₂O (71 mg, 25 mol %) was placed into a 100 mL sealed tube. MeOH (20 mL) was added via cannula. The reaction mixture was stirred at 110 °C for 16 h. At ambient temperature, 40 mL saturated NaHCO₃ solution was carefully added. A large amount of precipitate formed during this process. The solid was collected by filtration and further washed with cold H₂O (2×5.0 mL) and n-hexane (2×5.0 mL). The obtained pale brown solid 8a (776 mg, 86%) was analytic pure and didn’t need further purification. M. p. = 223–224 °C.

¹H NMR (400 MHz, CDCl₃) δ = 10.49 (s, 1H), 7.08 (d, J = 2.1 Hz, 1H), 7.05–6.94 (m, 3H), 6.94 (d, J = 1.7 Hz, 1H), 6.90 (s, 1H), 6.80 (d, J = 8.7 Hz, 1H), 6.77 (s, 1H), 6.61–4.48 (m, 3H), 3.75 (s, 3H), 3.71 (s, 3H), 3.45 (s, 3H), 1.38 (d, J = 6.1 Hz, 12H), 1.35 (d, J = 6.1 Hz, 6H). ¹³C NMR (100 MHz, CDCl₃) δ = 156.1 (C₆), 150.9 (C₆), 150.0 (C₆), 147.5 (C₆), 147.2 (C₆), 146.8 (C₆), 146.7 (C₆), 146.1 (C₆), 139.1 (C₆), 129.0 (C₆), 127.9 (C₆), 123.5 (CH), 123.5 (C₆), 120.0 (CH), 117.2 (C₆), 116.5 (CH), 115.0 (C₆), 114.8 (CH), 114.8 (CH), 111.3 (CH), 110.6 (C₆), 105.0 (CH), 103.8 (CH), 71.6 (CH), 71.5 (CH), 71.2 (CH), 56.1 (CH₂), 55.7 (CH₂), 55.5 (CH₃), 22.0 (CH₃), 21.8 (CH₃). IR (neat): 3275, 2972, 1685, 1521, 1460, 1257, 1146, 870, 642 cm⁻¹. MS (ESI) m/z (relative intensity) 624 (100) [M+Na⁺], 602 (80) [M+H⁺], 563
HR-MS (ESI) m/z calcd for C$_{35}$H$_{40}$NO$_8$ [M+H$^+$] 602.2748, found 602.2747.

The analytical data are in accordance with those previously reported in the literature.$^{[6b]}

3-(2,2-Dimethoxyethyl)-7-isopropoxy-1,2-bis(4-isopropoxy-3-methoxyphenyl)-8-methoxychromeno[3,4-b]pyrrol-4(3H)-one (S10)

Following a modified procedure,$^{[9]}$ under a N$_2$ atmosphere, 8a (867 mg, 1.44 mmol) and Cs$_2$CO$_3$ (3.05 g, 9.36 mmol) were placed in a 100 mL sealed tube. 2-Bromo-1,1-dimethoxyethane (9) (1.60 g, 9.5 mmol) and solvent DMF (30 mL) were added via cannula. The reaction mixture was stirred at 110 °C for 24 h. At ambient temperature, the mixture was diluted with EtOAc (250 mL) and washed with H$_2$O (3×60 mL) and brine (60 mL). The organic phase was dried over Na$_2$SO$_4$ and concentrated. The residue was purified by column chromatography over silica gel (n-hexane/EtOAc 5/1) to give S10 (804 mg, 81%) as a colorless solid. M. p. = 162–163 °C. $^1$H NMR (300 MHz, CDCl$_3$) δ = 6.92 (s, 1H), 6.91 (s, 1H), 6.92–6.78 (m, 4H), 6.79 (d, J = 8.8 Hz, 1H), 6.71 (d, J = 1.1 Hz, 1H), 4.85 (t, J = 5.5 Hz 1H), 4.62–4.41 (m, 5H), 3.65 (s, 3H), 3.63 (s, 3H), 3.45 (s, 3H), 3.31 (s, 3H), 1.38 (d, J = 6.1 Hz, 6H), 1.33 (d, J = 6.1 Hz, 6H), 1.31 (d, J = 6.1 Hz, 6H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ = 155.6 (C$_q$), 150.1 (C$_q$), 149.5 (C$_q$), 147.4 (C$_q$), 147.2 (C$_q$), 146.5 (C$_q$), 146.2 (C$_q$), 146.1 (C$_q$), 144.0 (C$_q$), 127.7 (C$_q$), 127.4 (C$_q$), 123.8 (CH), 123.4 (CH), 122.2 (C$_q$), 118.5 (C$_q$), 115.9 (CH), 115.2 (CH), 115.0 (CH), 114.6 (C$_q$), 114.5 (CH), 110.2 (C$_q$), 105.3 (CH), 104.4 (CH), 103.5 (CH), 71.5 (CH), 71.5 (CH), 71.2 (CH), 55.9 (CH$_3$), 55.8 (CH$_3$), 55.6 (CH$_3$), 55.3 (CH$_3$), 47.9 (CH$_2$), 22.1 (CH$_3$), 21.9 (CH$_3$). IR (neat): 2975, 2931, 1703, 1517, 1463, 1257, 1107, 1031, 752 cm$^{-1}$. MS (ESI) m/z (relative intensity) 712 (100) [M+Na$^+$], 690 (50)
The analytical data are in accordance with those previously reported in the literature.\textsuperscript{[65b]}

\textbf{3,11-Diisopropoxy-14-(4-isopropoxy-3-methoxyphenyl)-2,12-dimethoxy-6H-chromeno[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one (4c)}

Following a modified procedure,\textsuperscript{[9]} under a N\textsubscript{2} atmosphere, a solution of TfOH in CH\textsubscript{2}Cl\textsubscript{2} (1.0 M, 1.1 mL, 1.10 mmol) was added dropwise to a solution of S10 (508 mg, 0.73 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (25 mL) within 10 min at 0 °C. After stirring at 0 °C for 30 min, the mixture was warmed to 23 °C and stirred for additional 1 h. NaHCO\textsubscript{3} (919 mg, 11 mmol) and EtOH (10 mL) were added sequentially. Then, the solvent was removed and the residue was dry-loaded on silica gel and purified by column chromatography on silica gel (n-hexane/EtOAc 4/1) to yield 4c (429 mg, 94%) as a colorless solid. M. p. = 190–191 °C. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta = 9.08 \) (d, \( J = 7.3 \) Hz, 1H), 7.12–7.11 (m, 2H), 7.10–7.09 (m, 2H), 7.02 (s, 1H), 6.91 (d, \( J = 7.3 \) Hz, 1H), 6.85 (s, 1H), 6.70 (s, 1H), 4.67–4.54 (m, 2H), 4.47 (hept, \( J = 6.1 \) Hz, 1H), 3.81 (s, 3H), 3.40 (s, 3H), 3.39 (s, 3H), 1.39–1.36 (m, 12H), 1.34–1.32 (m, 6H). \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \( \delta = 155.2 \) (C\textsubscript{q}), 151.2 (C\textsubscript{q}), 150.0 (C\textsubscript{q}), 148.3 (C\textsubscript{q}), 147.6 (C\textsubscript{q}), 147.0 (C\textsubscript{q}), 146.4 (C\textsubscript{q}), 146.3 (C\textsubscript{q}), 134.1 (C\textsubscript{q}), 129.1 (C\textsubscript{q}), 128.6 (C\textsubscript{q}), 124.5 (C\textsubscript{q}), 123.8 (CH), 122.9 (CH), 118.8 (C\textsubscript{q}), 116.8 (CH), 115.0 (CH), 112.1 (CH), 110.8 (C\textsubscript{q}), 110.3 (CH), 109.8 (C\textsubscript{q}), 107.6 (C\textsubscript{q}), 105.5 (CH), 105.3 (CH), 103.2 (CH), 71.6 (CH), 71.3 (CH), 71.0 (CH), 56.1 (CH\textsubscript{3}), 55.3 (CH\textsubscript{3}), 55.0 (CH\textsubscript{3}), 21.8 (CH\textsubscript{3}), 21.8 (CH\textsubscript{3}), 21.7 (CH\textsubscript{3}), 21.7 (CH\textsubscript{3}), 21.7 (CH\textsubscript{3}). IR (neat): 3011, 2975, 2934, 1701, 1431, 1256, 1203, 1126, 1011 cm\textsuperscript{-1}. MS (ESI) \( m/z \) (relative intensity) 626 (100) [M+H\textsuperscript{+}], 524 (5), 348 (10). HR-MS (ESI) \( m/z \) calcd for C\textsubscript{37}H\textsubscript{46}NO\textsubscript{8} [M+H\textsuperscript{+}] 626.2748, found 626.2744.

The analytical data are in accordance with those previously reported in the literature.\textsuperscript{[65b]}
3,11-Dihydroxy-14-(4-hydroxy-3-methoxyphenyl)-2,12-dimethoxy-6\(H\)-chromeno[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one (4b)

Following a modified procedure,\(^4\) to a solution of 4c (94 mg, 0.15 mmol) in CH\(_2\)Cl\(_2\) (10 mL) was added BCl\(_3\) (1.4 mL, 1.0 M in CH\(_2\)Cl\(_2\), 1.40 mmol) under a N\(_2\) atmosphere at \(-78\) °C. After being stirred for 30 min at this temperature, the reaction mixture was allowed to warm to ambient temperature and stirred for additional 3 h. To the mixture was added saturated aqueous NaHCO\(_3\) (20 mL) and extracted with EtOAc (4×20 mL). The extract was washed with brine (20 mL), dried over Na\(_2\)SO\(_4\), and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/MeOH 1/0 to 10/1) to yield 4b (72 mg, 96%) as a pale green solid. **M. p.** >300 °C. \(^1\)H NMR (400 MHz, DMSO-d\(_6\)) \(\delta = 9.92\) (s, 1H), 9.81 (s, 1H), 9.32 (s, 1H), 8.98 (d, \(J = 7.4\) Hz, 1H), 7.18 (d, \(J = 7.4\) Hz, 1H), 7.17 (s, 1H), 7.15 (d, \(J = 1.9\) Hz, 1H), 7.13 (s, 1H), 7.09 (d, \(J = 8.0\) Hz, 1H), 6.99 (dd, \(J = 8.0, 1.9\) Hz, 1H), 6.86 (s, 1H), 6.71 (s, 1H), 3.77 (s, 3H), 3.38 (s, 3H). \(^13\)C NMR (125 MHz, DMSO-d\(_6\)) \(\delta = 154.0\) (C\(_q\)), 148.4 (C\(_q\)), 148.2 (C\(_q\)), 148.0 (C\(_q\)), 147.6 (C\(_q\)), 146.6 (C\(_q\)), 146.1 (C\(_q\)), 144.3 (C\(_q\)), 133.8 (C\(_q\)), 128.7 (C\(_q\)), 125.3 (C\(_q\)), 124.4 (C\(_q\)), 123.6 (CH), 121.8 (CH), 117.4 (C\(_q\)), 116.2 (CH), 115.0 (CH), 112.1 (CH), 111.3 (CH), 110.6 (C\(_q\)), 108.2 (C\(_q\)), 106.2 (C\(_q\)), 105.7 (CH), 105.3 (CH), 103.5 (CH), 55.9 (CH\(_3\)), 55.0 (CH\(_3\)), 54.4 (CH\(_3\)). IR (neat): 3385, 2933, 2837, 1672, 1595, 1431, 1273, 1154, 1014, 850 cm\(^{-1}\). MS (ESI) \(m/z\) (relative intensity) 522 (100) [M+Na\(^+\)], 500 (40) [M+H\(^+\)], 425 (10), 381 (20). HR-MS (ESI) \(m/z\) calcd for C\(_{28}H\(_{22}\)NO\(_8\) [M+H\(^+\)] 500.1340, found 500.1348; C\(_{28}H\(_{21}\)NO\(_8\)Na [M+Na\(^+\)] 522.1159, found 522.1163.

The analytical data are in accordance with those previously reported in the literature.\(^4,6b\)
14-(3,4-Dihydroxyphenyl)-2,3,11,12-tetrahydroxy-6H-chromeno[4’,3’:4,5]pyrrolo[2,1-a]isoquinolin-6-one (4a)

Following a modified procedure,[4] to a solution of 4c (94 mg, 0.15 mmol) in CH₂Cl₂ (10 mL) was added BBr₃ (2.25 mL, 1.0 M in CH₂Cl₂, 2.25 mmol) under a N₂ atmosphere at –78 °C. After being stirred for 30 min at this temperature, the reaction mixture was allowed to warm to ambient temperature and stirred for additional 16.5 h. After diluting with MeOH (5 mL), the solvent was removed under vacuum. The residue was dissolved in H₂O (20 mL) and extracted with EtOAc (4×20 mL). The extracts was washed with brine (20 mL), dried over Na₂SO₄, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/MeOH 10/1) to yield 4a (64 mg, 93%) as a pale green solid. M. p. >300 °C. ¹H NMR (400 MHz, DMSO-d₆) δ = 9.98 (s, 1H), 9.76 (s, 1H), 9.41 (s, 1H), 9.19 (s, 2H), 8.99 (d, J = 7.4 Hz, 1H), 8.90 (s, 1H), 7.14 (d, J = 7.4 Hz, 1H), 7.13 (s, 1H), 6.99 (d, J = 7.9 Hz, 1H), 6.95 (s, 1H), 6.80 (s, 1H), 6.79 (d, J = 2.1 Hz, 1H), 6.71 (dd, J = 7.9, 2.1 Hz, 1H), 6.57 (s, 1H). ¹³C NMR (125 MHz, DMSO-d₆) δ = 154.2 (C₉), 147.4 (C₉), 146.6 (C₉), 146.3 (C₉), 146.0 (C₉), 145.3 (C₉), 145.1 (C₉), 141.8 (C₉), 133.7 (C₉), 128.6 (C₉), 125.3 (C₉), 123.6 (C₉), 121.3 (CH), 121.0 (CH), 117.9 (C₉), 117.4 (CH), 116.8 (CH), 112.3 (CH), 111.2 (CH), 111.2 (C₉), 109.5 (CH), 109.4 (CH), 108.7 (C₉), 106.2 (C₉), 103.2 (CH). IR (neat): 3363, 1670, 1428, 1274, 1153, 1030, 863, 753 cm⁻¹. MS (El) m/z (relative intensity) 480 (100) [M+Na⁺], 458 (80) [M+H⁺], 441 (30), 425 (10), 413 (5). HR-MS (El) m/z calcd for C₂₅H₁₅NO₈ [M+H⁺] 458.0870, found 458.0883; C₂₅H₁₅NO₈Na [M+Na⁺] 480.0690, found 480.0703.

The analytical data are in accordance with those previously reported in the literature.[4,6b]
Synthesis of Lamellarin Analogue 4d

Scheme S-4. Synthesis of Lamellarin Analogue 4d

1,2-Bis(4-isopropoxy-3-methoxyphenyl)chromeno[3,4-b]pyrrol-4(3H)-one (8b)

Under a N₂ atmosphere, S8 (1.06 g, 2.0 mmol), 7b (414 mg, 3.0 mmol), Pd₂(db₃)₃ (91.6 mg, 5.0 mol %), dppf (111 mg, 10 mol %) and Na₂CO₃ (1.40 g, 13.2 mmol) were placed into a 100 mL sealed tube. A solvent mixture of DME/H₂O (30 mL/2.4 mL) was added via cannula. The reaction mixture was kept in the dark and stirred at 110 °C for 36 h. After cooling down to ambient temperature, the mixture was evaporated, and the residue was diluted with H₂O (30 mL) and extracted with CH₂Cl₂ (4×30 mL). The combined organic phase was washed with brine (2×30 mL), dried over Na₂SO₄, and evaporated. The residue was purified by
column chromatography over silica gel (n-hexane/EtOAc 3/1) to give 8b as a colorless solid (935 mg, 91%).  

**M. p.** = 245–247 °C. **1H NMR** (300 MHz, CDCl₃) δ = 10.93 (s, 1H), 7.43–7.27 (m, 3H), 7.12 (d, J = 2.2 Hz, 1H), 7.10–6.96 (m, 3H), 7.00–6.90 (m, 2H), 6.81 (d, J = 8.5 Hz, 1H), 4.70–4.60 (m, 1H), 4.58–4.46 (m, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 1.44 (d, J = 6.0 Hz, 6H), 1.37 (d, J = 6.1 Hz, 6H). **13C NMR** (75 MHz, CDCl₃) δ = 155.9 (C₉), 151.4 (C₇), 150.8 (C₅), 149.9 (C₆), 147.6 (C₈), 146.9 (C₉), 139.5 (C₉), 128.4 (C₈), 127.6 (C₉), 127.5 (CH), 124.0 (CH), 123.6 (CH), 123.4 (C₇), 123.3 (CH), 120.2 (CH), 118.5 (C₉), 118.1 (C₈), 117.3 (CH), 116.0 (CH), 115.9 (C₆), 114.7 (CH), 114.5 (CH), 111.4 (CH), 71.4 (CH), 71.1 (CH), 56.1 (CH₃), 55.7 (CH₃), 22.1 (CH₃), 22.1 (CH₃). **IR** (neat): 3240, 2976, 1697, 1466, 1416, 1230, 1106, 772 cm⁻¹. **MS** (EI) m/z (relative intensity) 514 (20) [M+H⁺], 513 (40) [M⁺], 471 (10), 429 (100), 369 (10), 337 (10), 325 (10). **HR-MS** (EI) m/z calcd for C₃₁H₃₁NO₆ [M⁺] 513.2151, found 513.2140.

![Chemical Structure](image)

3-(2,2-Dimethoxyethyl)-1,2-bis(4-isopropoxy-3-methoxyphenyl)chromeno[3,4-b]pyrrol-4(3H)-one (S11)

Under a N₂ atmosphere, 8b (514 mg, 1.0 mmol) and Cs₂CO₃ (2.11 g, 6.50 mmol) were placed into a 100 mL sealed tube. 2-Bromo-1,1-dimethoxyethane (9) (1.11 g, 6.60 mmol) and solvent DMF (15 mL) were added via cannula. The reaction mixture was stirred at 110 °C for 36 h. At ambient temperature, the mixture was diluted with EtOAc (200 mL) and washed with H₂O (3x50 mL) and brine (50 mL). The organic phase was dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography over silica gel (n-hexane/EtOAc 6/1) to give S11 as a colorless solid (493 mg, 82%).  

**M. p.** = 169–170 °C. **1H NMR** (600 MHz, CDCl₃) δ = 7.48 (dd, J = 8.0, 1.6 Hz, 1H), 7.36 (dd, J = 8.3, 1.2 Hz, 1H), 7.29–7.26 (m, 1H), 7.02–6.97 (m, 1H), 6.86–6.84 (m, 2H), 6.82 (d, J = 8.1 Hz, 1H), 6.79 (d, J = 8.1 Hz, 1H), 6.77 (dd, J = 8.1, 2.0 Hz, 1H), 6.71 (d, J = 1.9 Hz, 1H), 4.85 (t, J = 5.5 Hz, 1H), 4.59–4.46 (m, 4H), 3.65 (s, 3H), 3.64 (s, 3H), 3.31 (s, 6H), 1.40–1.27 (m, 12H). **13C NMR** (125 MHz, CDCl₃) δ
= 155.2 (C<sub>q</sub>), 151.3 (C<sub>q</sub>), 149.9 (C<sub>q</sub>), 149.5 (C<sub>q</sub>), 147.4 (C<sub>q</sub>), 146.4 (C<sub>q</sub>), 144.2 (C<sub>q</sub>), 127.5 (CH), 127.0 (C<sub>q</sub>), 127.0 (C<sub>q</sub>), 123.8 (CH), 123.6 (CH), 123.5 (CH), 123.3 (CH), 122.2 (C<sub>q</sub>), 119.5 (C<sub>q</sub>), 118.1 (C<sub>q</sub>), 117.0 (CH), 115.4 (C<sub>q</sub>), 115.3 (CH), 114.8 (CH), 114.5 (CH), 104.3 (CH), 71.3 (CH), 71.2 (CH), 55.9 (CH<sub>3</sub>), 55.8 (CH<sub>3</sub>), 55.4 (CH<sub>3</sub>), 48.0 (CH<sub>2</sub>), 22.2 (CH<sub>3</sub>), 22.1 (CH<sub>3</sub>). IR (neat): 2975, 2934, 2833, 1706, 1462, 1439, 1255, 1050 cm<sup>-1</sup>. MS (ESI) m/z (relative intensity) 602 (30) [M+H<sup>+</sup>], 592 (40), 570 (100), 564 (10), 550 (5). HR-MS (ESI) m/z calcld for C<sub>35</sub>H<sub>40</sub>N<sub>2</sub>O<sub>8</sub> [M+H<sup>+</sup>] 602.2748, found 602.2755.

11-Isopropoxy-14-(4-isopropoxy-3-methoxyphenyl)-12-methoxy-6H-chromeno[4′,3′:4,5]pyrrolo[2,1-a]isoquinolin-6-one (4d)

Under a N<sub>2</sub> atmosphere, a solution of TfOH in CH<sub>2</sub>Cl<sub>2</sub> (1.0 M, 1.0 mL, 1.0 mmol) was added dropwise to a solution of S11 (391 mg, 0.65 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (15 mL) within 10 min at 0 °C. After stirring at 0 °C for 30 min, the mixture was warmed to 23 °C and stirred for additional 1 h. NaHCO<sub>3</sub> (819 mg, 9.75 mmol) and EtOH (8.0 mL) were added sequentially. Then, the solvent was removed and the residue was dry-loaded on to silica gel and purified by column chromatography on silica gel (n-hexane/EtOAc 4/1) to yield 4d (318 mg, 91%) as a colorless solid. M. p. = 177–178 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 9.11 (d, J = 7.3 Hz, 1H), 7.35–7.28 (m, 1H), 7.31–7.23 (m, 2H), 7.13–7.03 (m, 4H), 7.02 (s, 1H), 7.02–6.93 (m, 1H), 6.93 (d, J = 7.4 Hz, 1H), 4.69–4.59 (m, 2H), 3.81 (s, 3H), 3.40 (s, 3H), 1.46 (d, J = 6.1 Hz, 3H), 1.41–1.37 (m, 9H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ = 154.9 (C<sub>q</sub>), 151.6 (C<sub>q</sub>), 151.2 (C<sub>q</sub>), 150.1 (C<sub>q</sub>), 148.3 (C<sub>q</sub>), 147.2 (C<sub>q</sub>), 134.3 (C<sub>q</sub>), 128.4 (C<sub>q</sub>), 128.3 (C<sub>q</sub>), 128.1 (CH), 124.5 (C<sub>q</sub>), 124.0 (CH), 123.6 (CH), 123.5 (CH), 122.8 (CH), 118.9 (C<sub>q</sub>), 117.9 (C<sub>q</sub>), 117.1 (CH), 116.4 (CH), 114.7 (CH), 112.6 (CH), 112.0 (C<sub>q</sub>), 110.3 (CH), 108.2 (C<sub>q</sub>), 105.5 (CH), 71.3 (CH), 71.1 (CH), 56.0 (CH<sub>3</sub>), 54.9 (CH<sub>3</sub>), 22.2 (CH<sub>3</sub>), 21.8 (CH<sub>3</sub>), 21.8 (CH<sub>3</sub>), 21.6 (CH<sub>3</sub>). IR (neat): 2976, 2933, 1701, 1473, 1398, 1259, 1218, 1175, 745 cm<sup>-1</sup>. MS (ESI) m/z (relative intensity) 560
(20) [M+Na⁺], 538 (100) [M+H⁺], 478 (20), 443 (10), 381 (20). **HR-MS** (ESI) m/z calcd for C₃₃H₃₂NO₆ [M+H⁺] 538.2224, found 538.2234.

**Synthesis of Lamellarin Analogue 4e**

![Synthesis Scheme S-5](image)

Methyl 2-acetamidoacrylate (2) (472 mg, 3.30 mmol), 1,2-diphenylethyne (1b) (534 mg, 3.00 mmol), [RuCl₂(p-cymene)]₂ (46 mg, 2.5 mol %), AgSbF₆ (103 mg, 10 mol %) and
Cu(OAc)$_2$·H$_2$O (1.20 g, 6.0 mmol) were placed into a 100 mL sealed tube under a N$_2$ atmosphere. A solvent mixture of MeOH/DCE (12 mL/6.0 mL) was added via cannula. The reaction mixture was stirred at 110 °C for 24 h. At ambient temperature, the reaction mixture was dry-loaded onto silica gel and purified by column chromatography (n-hexane/EtOAc 20/1) to afford the desired product 3b (740 mg, 89%) as a colorless solid and 3b’ (57 mg, 6%) as a pale yellow oil.

**Methyl 4,5-diphenyl-1H-pyrrole-2-carboxylate (3b)**

Colorless solid; M. p. = 169–170 °C. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ = 9.55 (s, 1H), 7.44–7.36 (m, 2H), 7.35–7.17 (m, 8H), 7.06 (d, J = 2.7 Hz, 1H), 3.83 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ = 161.8 (C$_q$), 135.3 (C$_q$), 133.5 (C$_q$), 131.8 (C$_q$), 128.6 (CH), 128.4 (CH), 128.4 (CH), 128.0 (CH), 127.9 (CH), 126.3 (CH), 124.1 (C$_q$), 122.0 (C$_q$), 116.8 (CH), 51.6 (CH$_3$). IR (neat): 3258, 1669, 1440, 1226, 1203, 1009, 762, 692, 521 cm$^{-1}$. MS (EI) m/z (relative intensity) 278 (20) [M+H$^+$], 277 (100) [M$^+$], 245 (80), 217 (70), 189 (40), 165 (10). HR-MS (EI) m/z calcd for C$_{18}$H$_{15}$NO$_2$ [M$^+$] 277.1103, found 277.1101.

The analytical data are in accordance with those previously reported in the literature.$^{[10a]}$

**Methyl 1-acetyl-4,5-diphenyl-1H-pyrrole-2-carboxylate (3b’)**

Pale yellow oil; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ = 7.42–7.28 (m, 5H), 7.25–7.11 (m, 6H), 3.88 (s, 3H), 2.32 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ = 173.7 (C$_q$), 161.0 (C$_q$), 134.5 (C$_q$), 133.8 (C$_q$), 130.6 (C$_q$), 130.6 (CH), 128.8 (CH), 128.5 (CH), 128.2 (CH), 127.9 (CH), 126.3 (CH), 124.7 (C$_q$), 122.9 (C$_q$), 118.2 (CH), 51.8 (CH$_3$), 28.8 (CH$_3$). IR (neat): 3392, 1644, 1459, 1440, 1233, 1195, 759, 695 cm$^{-1}$. MS (EI) m/z (relative intensity) 320 (5) [M+H$^+$], 319 (10) [M$^+$], 277 (100), 245 (70), 217 (50), 189 (30). HR-MS (EI) m/z calcd for C$_{20}$H$_{17}$NO$_3$ [M$^+$] 319.1208, found 319.1214.

The analytical data are in accordance with those previously reported in the literature.$^{[10b]}$
Methyl 3-bromo-4,5-diphenyl-1H-pyrrole-2-carboxylate (S12)

Following a modified procedure,\textsuperscript{[9]} to a solution of 3b (693 mg, 2.50 mmol) in DMF (30 mL), the solution of NBS (449 mg, 2.52 mmol) in DMF (5 mL) was added dropwise within 10 min at 0 °C under a N\textsubscript{2} atmosphere. The reaction mixture was stirred at 0 °C for 1 h. Then, the mixture was diluted with EtOAc (200 mL) and washed with H\textsubscript{2}O (3×60 mL) and brine (60 mL). The organic phase was dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated. The residue was purified by column chromatography over silica gel (n-hexane/EtOAc 20/1) to give S12 (881 mg, 99\%) as a colorless solid. M. p. = 190–191 °C. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ = 9.53 (s, 1H), 7.37–7.30 (m, 3H), 7.30–7.20 (m, 7H), 3.89 (s, 3H). \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) δ = 160.9 (C\textsubscript{q}), 133.5 (C\textsubscript{q}), 133.3 (C\textsubscript{q}), 130.8 (C\textsubscript{q}), 130.7 (CH), 128.7 (CH), 128.3 (CH), 128.2 (CH), 127.5 (CH), 127.3 (CH), 125.1 (C\textsubscript{q}), 119.8 (C\textsubscript{q}), 106.0 (C\textsubscript{q}), 51.8 (CH\textsubscript{3}). IR (neat): 3303, 1672, 1461, 1398, 1288, 1206, 774, 693, 537 cm\textsuperscript{-1}. MS (EI) m/z (relative intensity) 355 (80) [M\textsuperscript{+}], 325 (60), 295 (10), 269 (10), 244 (10), 216 (100). HR-MS (EI) m/z calcd for C\textsubscript{18}H\textsubscript{14}\textsuperscript{79}BrNO\textsubscript{2} [M\textsuperscript{+}] 355.0208, found 355.0208; C\textsubscript{18}H\textsubscript{14}\textsuperscript{81}BrNO\textsubscript{2} [M\textsuperscript{+}] 357.0187, found 357.0189.

1,2-Diphenylichromeno[3,4-b]pyrrol-4(3H)-one (8c)

Under a N\textsubscript{2} atmosphere, S12 (712 mg, 2.0 mmol), (2-hydroxyphenyl)boronic acid (7b) (414 mg, 3.0 mmol), Pd\textsubscript{2}(dba)\textsubscript{3} (91.6 mg, 5.0 mol %), dpf (111 mg, 10 mol %) and Na\textsubscript{2}CO\textsubscript{3} (1.40 g, 13.2 mmol) were placed into a 100 mL sealed tube. A solvent mixture of DME/H\textsubscript{2}O (30 mL/2.4 mL) was added via cannula. The reaction mixture was kept in the dark and stirred at 110 °C for 36 h. After cooling to ambient temperature, the mixture was evaporated, and the
residue was diluted with H₂O (30 mL) and extracted with CH₂Cl₂ (4×30 mL). The extract was washed with brine (2×30 mL), dried over Na₂SO₄, and evaporated. The residue was purified by column chromatography over silica gel (n-hexane/EtOAc 3/1) to give 8c as a colorless solid (526 mg, 78%). **M. p. = 273–274 °C.** ¹H NMR (400 MHz, CDCl₃) δ = 10.27 (s, 1H), 7.51–7.38 (m, 6H), 7.37–7.25 (m, 7H), 7.01 (ddd, J = 8.1, 7.1, 1.2 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃) δ = 155.7 (Cₐ), 151.5 (Cₐ), 139.0 (Cₐ), 134.3 (Cₐ), 131.0 (CH), 130.6 (Cₐ), 129.0 (CH), 128.8 (CH), 128.6 (CH), 127.9 (CH), 127.9 (Cₐ), 127.7 (CH), 127.7 (CH), 124.0 (CH), 123.4 (CH), 119.1 (Cₐ), 118.3 (Cₐ), 117.5 (CH), 116.6 (Cₐ). **IR** (neat): 3231, 1692, 1426, 1300, 1131, 977, 749, 703, 535 cm⁻¹. **MS** (EI) m/z (relative intensity) 338 (80) [M+H⁺], 337 (100) [M⁺], 322 (10), 308 (10), 291 (10), 280 (10). **HR-MS** (EI) m/z calcd for C₂₃H₁₅NO₂ [M⁺] 337.1103, found 337.1097.

![Structural formula of S13](image)

3-(2,2-Dimethoxyethyl)-1,2-diphenylchromeno[3,4-b]pyrrol-4(3H)-one (S13)

Under a N₂ atmosphere, 8c (337 mg, 1.0 mmol) and Cs₂CO₃ (2.11 g, 6.5 mmol) were placed into a 100 mL sealed tube. 2-Bromo-1,1-dimethoxyethane (9) (1.11 g, 6.6 mmol) and DMF (15 mL) were added via cannula. The reaction mixture was stirred at 110 °C for 36 h. At ambient temperature, the mixture was diluted with EtOAc (200 mL) and washed with H₂O (3×50 mL) and brine (50 mL). The organic phase was dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography over silica gel (n-hexane/EtOAc 6/1) to give S13 (264 mg, 62%) as a colorless solid. **M. p. = 146–148 °C.** ¹H NMR (300 MHz, CDCl₃) δ = 7.38 (ddd, J = 8.3, 1.4, 0.5 Hz, 1H), 7.36–7.30 (m, 2H), 7.29–7.22 (m, 10H), 6.97 (ddd, J = 7.9, 7.2, 1.3 Hz, 1H), 4.75 (t, J = 5.5 Hz, 1H), 4.51 (d, J = 5.5 Hz, 2H), 2.72 (s, 6H). ¹³C NMR (75 MHz, CDCl₃) δ = 155.4 (Cₐ), 151.4 (Cₐ), 144.2 (Cₐ), 134.2 (Cₐ), 131.3 (CH), 131.0 (CH), 129.8 (Cₐ), 128.6 (CH), 128.3 (CH), 128.2 (CH), 127.6 (CH), 127.3 (CH), 127.1 (Cₐ), 123.7 (CH), 123.5 (CH), 120.0 (Cₐ), 118.1 (Cₐ), 117.1 (CH), 115.8 (Cₐ), 104.3 (CH), 55.3 (CH₃), 47.9 (CH₂). **IR** (neat): 3060, 2927, 2838, 1713, 1607, 1454, 1074, 1048, 706 cm⁻¹.
MS (EI) \( m/z \) (relative intensity) 425 (20) [M\(^+\)], 410 (5), 394 (10), 364 (20), 337 (10), 320 (10), 75 (100). HR-MS (EI) \( m/z \) calcd for C\(_{27}\)H\(_{23}\)NO\(_4\) [M\(^+\)] 425.1627, found 425.1636.

14-Phenyl-6\(H\)-chromeno[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one (4e)

Following a modified procedure,\(^{[11a]}\) S13 (44 mg, 0.10 mmol) was placed into a 25 mL sealed tube under a N\(_2\) atmosphere. A solvent mixture of CF\(_3\)COOH/(CF\(_3\)CO)\(_2\)O (3.0 mL/1.0 mL) was added via cannula. The mixture was stirred at 75 °C for 48 h. At ambient temperature, the excess anhydride and acid were removed by evaporation. NEt\(_3\) (0.50 mL) was added and this mixture was dry-loaded onto silica gel and purified by column chromatography over silica gel (n-hexane/EtOAc 20/1) to give 4e (24 mg, 64%) as a colorless solid. M. p. > 300 °C. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta = 9.36 \) (d, \( J = 7.4 \) Hz, 1H), 7.72–7.69 (m, 1H), 7.67–7.62 (m, 3H), 7.59–7.54 (m, 2H), 7.53–7.42 (m, 3H), 7.41 (d, \( J = 7.4 \) Hz, 1H), 7.11 (ddd, \( J = 7.9, 1.7, 0.5 \) Hz, 1H), 7.00 (ddd, \( J = 8.1, 7.1, 1.4 \) Hz, 1H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta = 155.3 \) (C\(_q\)), 151.7 (C\(_q\)), 135.6 (C\(_q\)), 134.1 (C\(_q\)), 131.0 (CH), 129.9 (CH), 129.7 (C\(_q\)), 128.7 (CH), 128.4 (CH), 128.2 (CH), 127.5 (CH), 127.3 (CH), 125.0 (C\(_q\)), 124.5 (CH), 124.4 (CH), 124.1 (CH), 123.9 (CH), 117.9 (C\(_q\)), 117.4 (CH), 114.3 (C\(_q\)), 113.5 (CH), 109.4 (C\(_q\)). IR (neat): 3059, 3046, 1426, 1701, 1409, 1368, 1178, 1048, 788 cm\(^{-1}\). MS (EI) \( m/z \) (relative intensity) 362 (30) [M+H\(^+\)], 361 (100) [M\(^+\)], 337 (10), 315 (10), 304 (10), 276 (5). HR-MS (EI) \( m/z \) calcd for C\(_{25}\)H\(_{15}\)NO\(_2\) [M\(^+\)] 361.1103, found 361.1092.

The analytical data are in accordance with those previously reported in the literature.\(^{[11]}\)
Reference
$^{1}H$ and $^{13}C$ NMR

![NMR Spectrum S2](image)

S2
(CDCl$_3$, 300 MHz)

![NMR Spectrum S2](image)

S2
(CDCl$_3$, 125 MHz)
S3
(CDCl₃, 300 MHz)

S3
(CDCl₃, 75 MHz)
S5
(CDCl$_3$, 400 MHz)

S5
(CDCl$_3$, 100 MHz)
OMe
O-i-Pr
OMOM
S6
(CDCl₃, 400 MHz)

OMe
O-i-Pr
OMOM
S6
(CDCl₃, 100 MHz)
(CDCl₃, 400 MHz)

(CDCl₃, 100 MHz)
S13
(CDCl₃, 300 MHz)

S13
(CDCl₃, 75 MHz)

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