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Convergent Total Synthesis of Lamellarins and Their Congeners

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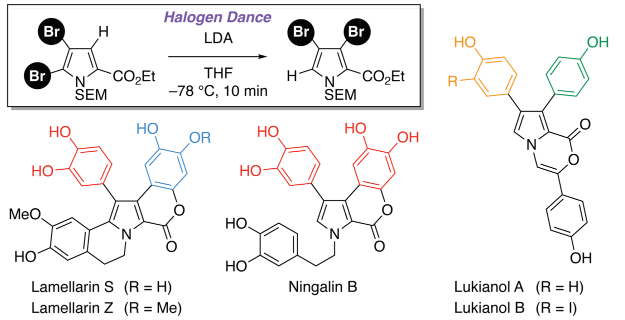


ABSTRACT: A convergent total synthesis of lamellarins S and Z is described. The synthesis features a halogen dance of an easily accessible α,β-dibromopyrrole promoted by an ester moiety. The resultant β,β'-dibromopyrrole undergoes a ligand-controlled Suzuki–Miyaura coupling to provide a range of diarylated pyrrole derivatives. The established synthetic method was also applicable to the synthesis of ningalin B, and lukianols A and B.

INTRODUCTION

The number of pyrrole alkaloids have continued to grow over recent years.[1] Among them, more than 50 lamellarins have been reported[2] since lamellarins A–D were isolated in 1985 by Faulkner and Clardy from the marine prosobranch mollusks.[3] Ningalins, lukianols, didemnimides, dictyodendrins, polycitrins, and storniamides are also part of this class, as related pyrrole alkaloids, which possess various aryl groups at the two β positions of the pyrrole ring (Figure 1).[2,4] In addition to their structural diversity, their wide range of biological activities attract considerable interest as synthetic targets.[5] The common key feature of the synthesis of these pyrrole alkaloids is construction of the polysubstituted pyrrole core. Most of the reported synthetic methods use a symmetrical pyrrole diester or diarylacetylene as the synthetic intermediates, and most of the syntheses focus on symmetrical natural products.[2,6] To the best of our knowledge, there are only a limited number of synthetic methods that can be applied to a series of these unsymmetrical lamellarins.[7] Herein, we describe an approach toward a divergent synthesis of symmetrical/unsymmetrical lamellarins and their congeners, featuring a halogen dance[8,9] of a dibromopyrrole derivative.

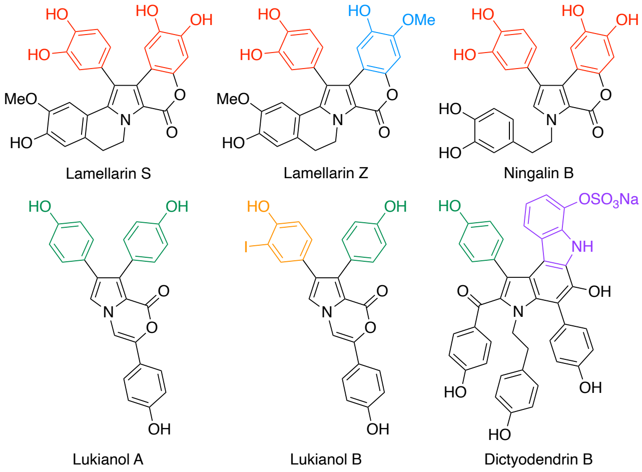
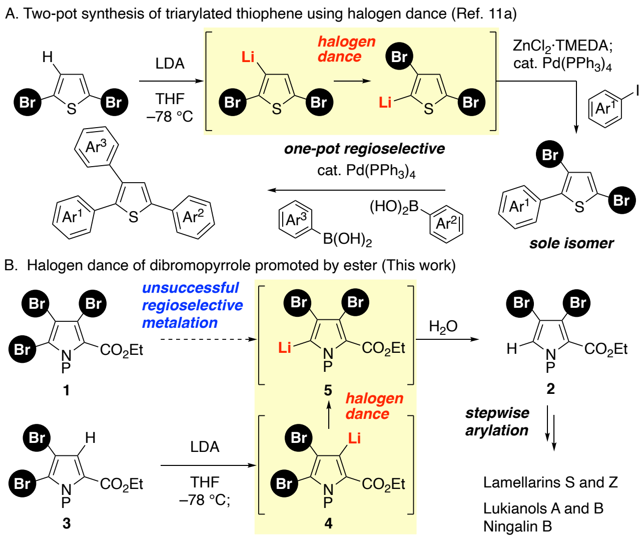


Figure 1. Lamellarins and the related pyrrole alkaloids.

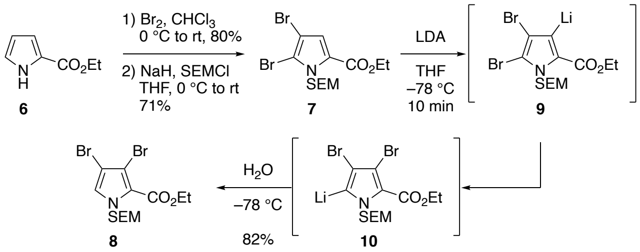
The major challenge toward accomplishing a convergent total synthesis of lamellarins and their congeners is the construction of a multiply arylated pyrrole. We describe an inventive method for introducing the desired functional groups onto the pyrrole in a straightforward and divergent synthesis, superior to the classical Parr–Knorr synthesis and Hantzsch syntheses for this purpose.[10] Recently we have been investigating the synthetic potential of a halogen dance for the regiocontrolled and step-economical synthesis of tri- and tetra-substituted thiophenes and furans (Scheme 1A).[11] Differential reactivity of the bromo groups enabled a one-pot double Suzuki-Miyaura coupling, and afforded a triarylated thiophene in a regioselective manner. In contrast, attempted regioselective cross-coupling reaction of 2,3,5-tribromothiophene was difficult, and the same compound was afforded in low yield.[12] In addition to the superior regioselectivity, this reaction allows migration of the bromo group which can be used as a handle for further transformation. This enables a highly efficient atom-economical process, and importantly, also avoids late-stage bromination, which often causes side reactions in the presence of highly reactive electron-rich aromatic rings such as pyrrole. A halogen dance with a bromopyrrole derivative has not yet been reported, possibly due to the lower acidity of the pyrrole compared with thiophene and furan. We started the synthetic studies toward the pyrrole alkaloids based on our recent observation that an ester group significantly promoted the halogen dance (Scheme 1B).[13] In preliminary experiments, we investigated the regioselective metalation of tribromopyrrole **1** to obtain dibromopyrrole **2** as a common intermediate for the synthesis of these pyrrole alkaloids through regioselective arylation; however, the use of several organolithiums or Grignard reagents provided **2** as a major product, but with several inseparable byproducts. We anticipated that the readily available dibromopyrrole **3** could be converted into the desired **2** by protonation of organolithium **5**, derived from the first-generated organolithium **4** through a halogen dance.



Scheme 1. Strategy for the convergent synthesis of lamellarins and their congeners.

RESULTS AND DISCUSSION

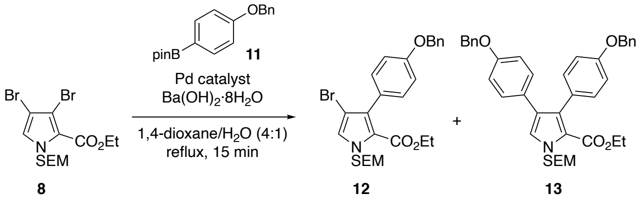
The synthesis began with the regioselective dibromination of the commercially available pyrrole carboxylic acid ethyl ester (**6**) (Scheme 2). Protection of the pyrrole nitrogen with a 2-(trimethylsilyl)ethoxymethyl (SEM) group provided α,β-dibromopyrrole **7** for the key halogen dance step. Treatment with LDA at −78 ° C resulted in the smooth migration of the α-bromo group within 10 min, and aqueous workup provided β,β'-dibromopyrrole **8** in 82% yield on a multi-gram scale. Based on our preliminary experiments, two bromo groups and an ester moiety are essential for this halogen dance of a bromopyrrole derivative.[14] Both the reaction temperature and the reaction time proved critical for a high-yielding process, due to the instability of either β-lithio-α,β-dibromopyrrole **9** or α-lithio-β,β'-dibromopyrrole **10**.[15]



Scheme 2. Halogen dance of α,β-dibromopyrrole **7**.

With β,β'-dibromopyrrole **8** in hand, we then explored suitable palladium catalysts for the regioselective Suzuki-Miyaura coupling with two equivalents of arylboronate ester **11** (Table 1). First, the reaction with $Pd(PPh_3)_4$ furnished monoarylated pyrrole **12**[16] and diarylated pyrrole **13** in 13% and 52% yields, respectively (entry 1). This monoarylation proceeded in a completely regiospecific manner, despite the expected difficulty in controlling the reactivities of two bromo groups at the β positions.[17] A combination of $Pd_2(dba)_3$ (5 mol%) and PPh_3 (20 mol%) led to the formation of a 1:1 mixture of **12** and **13** with 36% recovery of the starting dibromopyrrole **8** (entry 2). Prolonged reaction time resulted in significant reduction of the yields of the products, due to hydrolysis of the ester moiety. The use of $Pd(PCy_3)_2$ and $Pd(t\text{-}Bu_3P)_2$ provi-

Table 1. Effects of phosphine ligands[a]

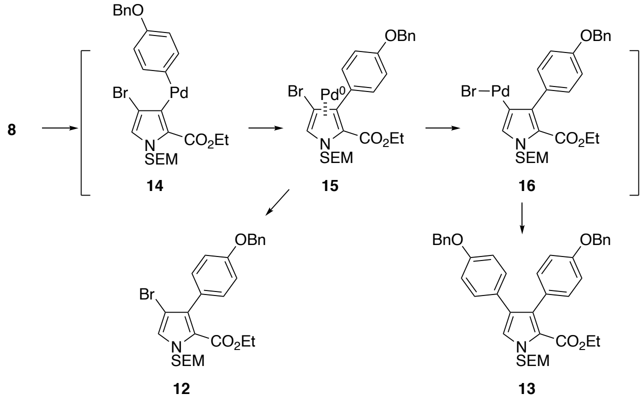


entry	catalyst	**8**[b] (%)	**12**[b] (%)	**13**[b] (%)
1	$Pd(PPh_3)_4$	3	13	52
2	$Pd_2(dba)_3$, PPh_3	36	22	19
3	$Pd(PCy_3)_2$	10	3	63
4	$Pd(t\text{-}Bu_3P)_2$	2	3	75
5[d]	$Pd(t\text{-}Bu_3P)_2$	21	–[c]	36
6[d]	$Pd(t\text{-}Bu_3P)_2$ + Ph_2S (1.0 equiv)	26	<1	36
7[d]	$Pd(t\text{-}Bu_3P)_2$ + THT (1.0 equiv)	41	7	8
8	$Pd_2(dba)_3$, $P(4\text{-}CF_3C_6H_4)_3$	14	36	24
9	$Pd_2(dba)_3$, $P[3,5\text{-}(CF_3)_2C_6H_3]_3$	85	–[c]	–[c]

[a] Reaction conditions: dibromopyrrole **8** (1.0 equiv, 0.30 mmol), **11** (2.0 equiv, 0.60 mmol), Pd source (0.030 mmol for palladium, 10 mol%), phosphine ligand (0.060 mmol, 20 mol%) $Ba(OH)_2·8H_2O$ (6.0 equiv, 1.8 mmol), 1,4-dioxane/H_2O (4:1), reflux, 15 min. [b] The yield

was determined from the ^{1}H NMR spectrum of the crude product using 1,1,2,2-tetrachloroethane as an internal standard. [c] Not detected in the crude ^{1}H NMR spectrum. [d] Arylboronate ester **11** (1.0 equiv, 0.30 mmol).

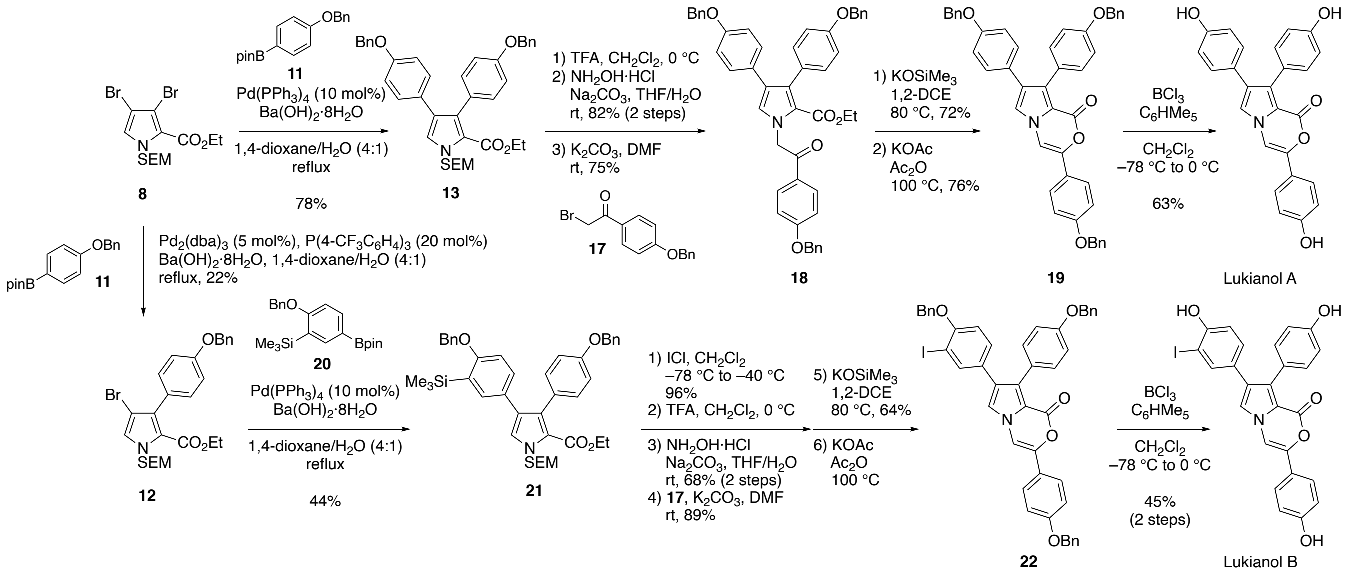
ded diarylated pyrrole **13** in 63% and 75% yields, respectively (entries 3 and 4). Encouraged by this superior catalytic activity, we performed the same reaction with one equivalent of arylboronate ester **11** in order to obtain monoarylated pyrrole **12**; however, Pd(t-Bu$_3$P)$_2$ favored the exclusive formation of **13** with 21% recovery of the starting dibromopyrrole **8** (entry 5). These results can be rationalized by "intramolecular catalyst transfer",[18] which has been observed in a Ni-/Pd-catalyzed living chain-growth polymerization (Scheme 3). The complex **14** formed after transmetalation is converted to palladium (0)-π complex **15**. Dissociation of the π complex **15** gives the monoarylated pyrrole **12**. In contrast, the palladium (0) in **15** is transferred to the distal C‑Br bond through oxidative addition to form palladium (II) species **16**. Subsequent Suzuki‑Miyaura coupling furnishes the diarylated pyrrole **13**. We next examined the effects of an additive to suppress the catalyst transfer. Apart from the recent report by Yokozawa's group,[18e] stoichiometric amount of Ph$_2$S did not suppress the formation of the diarylated pyrrole,[19] whereas tetrahydrothiophene (THT) reduced the catalytic activity (entries 6 and 7). Additional PhSMe and 1,5-cyclooctadiene[20] did not provide satisfactory results. Among a series of phosphine ligands tested, P(4-CF$_3$-C$_6$H$_4$)$_3$ led to the formation of monoarylated pyrrole **12** in 36% yield (entry 8); however, more electron-deficient P[3,5-(CF$_3$)$_2$C$_6$H$_3$]$_3$ provided neither **12** nor **13** with 85% recovery of the starting dibromopyrrole **8** (entry 9).



Scheme 3. Potential catalyst transfer mechanism of the exclusive formation of the diarylated pyrrole.

In this Suzuki–Miyaura cross coupling the use of Ba(OH)$_2$ proved effective for the smooth arylation; however, the strongly basic conditions led to a significant reduction of the yield of the products after prolonged reaction time, probably due to hydrolysis of the ethyl ester. This limitation prohibited our further optimization to improve the yield of monoarylated pyrrole **12**. In addition, laborious purification process was required to obtain the monoarylated pyrrole **12** in a pure form on a preparative scale. The monoarylated pyrrole **12** was separated from the diarylated pyrrole **13** by column chromatography. Subsequent preparative SEC-HPLC was necessary for separating the monoarylated pyrrole **12** from a minute amount of an unidentified byproduct. During the process, substantial amount of the monoarylated pyrrole was not recovered, which resulted in the low isolated yield (22% in Scheme 4) compared to the NMR yield (36% in Table 1).

This catalyst screening enabled a stepwise and regiocontrolled introduction of two aryl groups, which led to the synthesis of lukianols A[6c,21] and B[21a,21g] (Scheme 4). Similar to the report by Banwell,[7a] dibromopyrrole **8** underwent a one-pot double Suzuki‑Miyaura coupling with catalytic Pd(PPh$_3$)$_4$, providing the desired product **13** in 78% yield. Deprotection of the SEM group was performed in a stepwise manner,[22] namely, TFA-promoted removal of the (trimethylsilyl)ethyl group and subsequent treatment of the resulting hemiaminal with aqueous sodium carbonate in the presence of hydroxylamine as a formaldehyde scavenger. The unprotected pyrrole underwent *N*-alkylation with **17** to provide the desired product **18**, which was then transformed to the fused pyrrole **19** through hydrolysis of the ester by KOSiMe$_3$[23] followed by cyclization.[21b] Removal of the benzyl groups with a combination of BCl$_3$ and C$_6$HMe$_5$[24] provided lukianol A. The established stepwise arylation was effective for the synthesis of lukianol B bearing different aromatic rings. The trimethylsilyl group of the obtained diarylated pyrrole **21** was converted to an iodo group by ICl at ‑78 ° C, without affecting the reactive pyrrole ring. Deprotection of the SEM group, lactone formation, and removal of the benzyl groups completed the synthesis of lukianol B. This catalyst-controlled arylation strategy allows introduction of two different aryl groups in a completely regioselective manner. This proved effective for the synthesis of these pyrrole alkaloids, as a late-stage iodination of lukianol A was not regioselective due to the multiple phenol moieties and reactive pyrrole α-position.[21g]



Scheme 4. Regiocontrolled synthesis of lukianol A and B.

The β,β'-dibromopyrrole **8** was also the common intermediate for the synthesis of ningalin B[6f,6h,25], and lamellarins S[26] and Z[27] (Scheme 5). A one-pot double Suzuki-Miyaura coupling with arylboronate ester **23** took place to give the corresponding pyrrole **24** in 59% yield. Hydrolysis of the ester and $Pb(OAc)_4$-mediated lactone formation proceeded smoothly. Removal of the SEM group was carried out to provide the compound **25** in 24% yield over three steps from compound **24**. *N*-Alkylation was performed with phenylethyl alcohol **26** under Mitsunobu conditions, and subsequent hydrogenolysis of the six benzyl ethers was carried out to provide ningalin B in 97% yield. The lactone-fused pyrrole **25** was also a synthetic intermediate for the total synthesis of lamellarin S. Thus, *N*-alkylation was carried out with phenylethyl alcohol **27** under the standard Mitsunobu conditions to provide compound **28** in 71% yield. Subsequent treatment with PIFA[28] achieved the oxidative C-C bond formation to construct the lamellarin skeleton. Hydrogenolysis of the benzyl ethers gave lamellarin S in 98% yield. In addition to these natural products, lamellarin Z, which has different aryl groups at the two β positions, was synthesized using the established stepwise arylation from the synthesis of lukianol B. The optimal monoarylation conditions were effective for arylboronate ester **29**, and the corresponding monoarylated pyrrole **30** was isolated in 30% yield, with the excellent regioselectivity. The second arylation was performed with arylboronate ester **23** in the presence of catalytic $Pd(PPh_3)_4$ to provide the desired compound **31** in moderate yield. Similar to the synthetic route of lamellarin S, the ethyl ester was then converted to the lactone. Removal of the SEM group and subsequent *N*-alkylation took place smoothly with phenylethyl alcohol **27** to provide the desired compound **32**. The PIFA-promoted oxidative formation of the lamellarin skeleton and subsequent palladium-catalyzed hydrogenolysis of the benzyl ethers provided lamellarin Z in 80% yield over two steps from compound **32**.

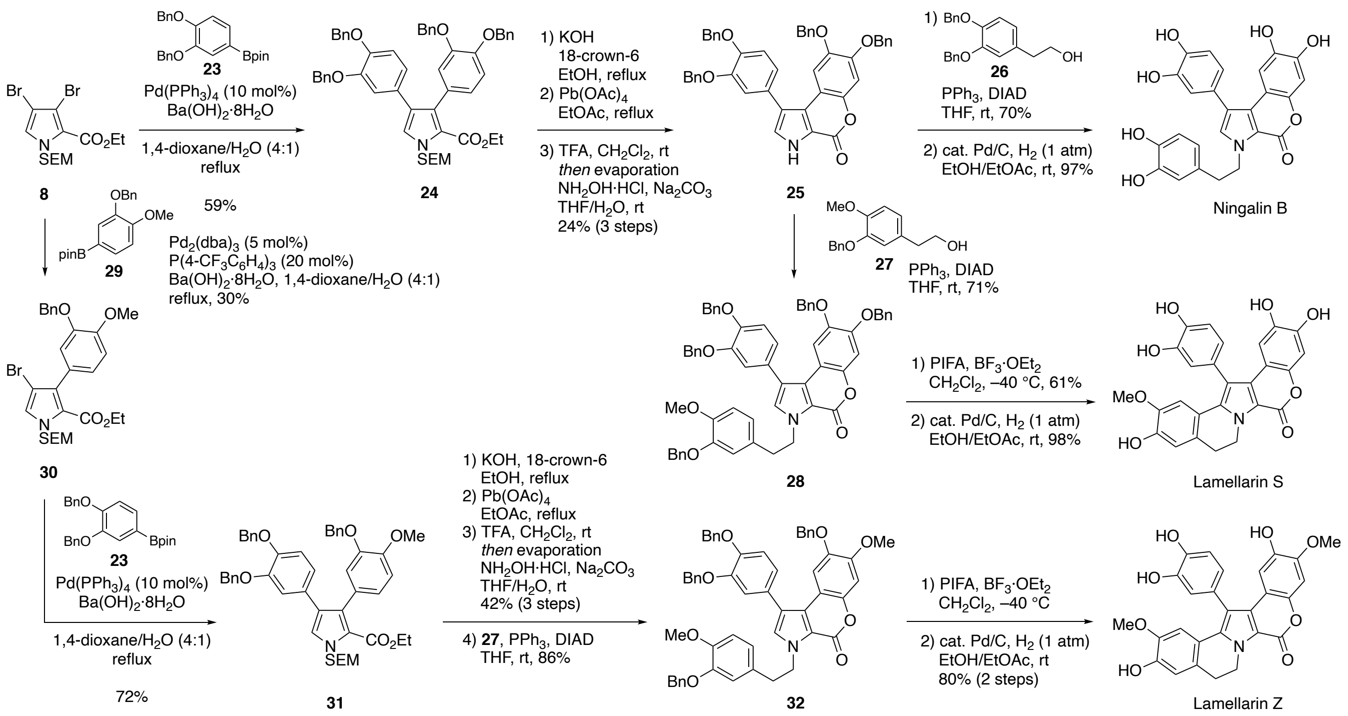
CONCLUSIONS

In summary, we have achieved the convergent total synthesis of ningalin B, lukianols A and B, and lamellarins S and Z, by developing an unprecedented ester-promoted halogen dance of the α,β-dibromopyrrole derivative. The two bromo groups at the β positions were converted to the corresponding aryl groups by a regioselective Suzuki-Miyaura coupling. Significant ligand effects were observed for the ratio of monoarylated and diarylated products, which paved the way for the straightforward syntheses of the related pyrrole alkaloids.

EXPERIMENTAL SECTION

GENERAL

Analytical thin layer chromatography (TLC) was performed on Merck 60 F_{254} aluminum sheets precoated with a 0.25 mm thickness of silica gel. Melting points (m.p.) were measured on a Yanaco MP-J3 and are uncorrected. Infrared (IR) spectra were recorded on a Bruker Alpha with an ATR attachment (Ge) and are reported in wave numbers (cm^{-1}). ^{1}H NMR (400 MHz) and ^{13}C{^{1}H} NMR (100 MHz) spectra were measured on a JEOL ECZ400 spectrometer. Chemical shifts for ^{1}H NMR are reported in parts per million (ppm) downfield from tetramethylsilane with the solvent resonance as the internal standard ($CHCl_3$: δ 7.26 ppm, THF-d_7: δ 1.72 ppm, DMSO-d_5: δ 2.50 ppm, CHD_2OD: δ 3.31 ppm, acetone-d_5: δ 2.05 ppm, tetramethylsilane: δ 0 ppm) and coupling constants are in Hertz



Scheme 5. Convergent synthesis of lamellarins and their congeners.

(Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet, and br = broad. Chemical shifts for $^{13}C\{^{1}H\}$ NMR are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 77.16 ppm, THF-d_8: δ 67.21 ppm, DMSO-d_6: δ 39.52 ppm, CD_3OD: δ 49.00 ppm, acetone-d_6: δ 29.84 ppm). High-resolution mass spectra (HRMS) were performed on a JEOL JMS-T100LP AccuTOF LC-Plus (ESI) with a JEOL MS-5414DART attachment.

MATERIALS

Unless otherwise stated, all reactions were conducted in flame-dried glassware under an inert atmosphere of nitrogen. All work-up and purification procedures were carried out with reagent solvents in air. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Flash column chromatography was performed on Wakogel® 60N (45-75 μm, Wako Pure Chemical Industries, Ltd.). Recycling preparative SEC-HPLC was performed with LC-9201 (Japan Analytical Industry Co., Ltd.) equipped with preparative SEC columns (JAI-GEL-1H and JAI-GEL-2H). Anhydrous THF (>99.5%, water content: < 10 ppm) was purchased from Kanto Chemical Co., Inc. and further dried by passing through a solvent purification system (Glass Contour) prior to use. LDA (2.0 M in THF/heptane /ethylbenzene) was purchased from Sigma-Aldrich Co. (Product number: 361798).

SYNTHESIS OF DIPROMOPYRROLE 8

Ethyl 4,5-dibromo-1*H*-pyrrole-2-carboxylate (S1).

A 1-L round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was charged with ethyl 1*H*-pyrrole-2-carboxylate (**6**) (11.20 g, 80.5 mmol, 1.0 equiv) and $CHCl_3$ (400 mL). After the solution was cooled to 0 ° C, Br_2 (25.56 g, 160 mmol, 2.0 equiv) in $CHCl_3$ (8 mL) was added dropwise to the flask over 5 min. The reaction mixture was allowed to warm to room temperature with stirring over 5 h, at which time the mixture was treated with saturated aqueous sodium thiosulfate (200 mL). After partitioned, the aqueous layer was extracted with $CHCl_3$ (200 mL). The organic extracts were washed with water (200 mL) and brine (200 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was recrystallized from hexane to provide the title compound **S1** as a colorless solid (19.00 g, 64.0 mmol, 80%), whose ^{1}H NMR spectra was identical to that reported in the literature.[29] R_f = 0.21 (hexane/diethyl ether = 6:1); M.p. 111-112 ° C; IR (ATR, cm^{-1}): 3230, 2925, 1694, 1412, 1385, 1319, 1235, 1205, 1022, 973, 830, 759, 637, 622; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.45 (br s, 1H), 6.88 (d, 1H, J = 3.2 Hz), 4.33 (q, 2H, J = 7.2 Hz), 1.36 (t, 3H, J = 7.2 Hz); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 160.5, 124.0, 118.0, 107.6, 100.5, 61.5, 14.5; HRMS (DART/TOF) m/z: $[M + H]^+$ Calcd for $C_7H_8{}^{79}Br^{81}BrNO_2$ 297.8901; Found 297.8905.

Ethyl 4,5-dibromo-1-[[2-(trimethylsilyl)ethoxy]methyl]-1*H*-pyrrole-2-carboxylate (7).

A flame-dried 500-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with **S1** (3.715 g, 15.0 mmol, 1.0 equiv) and anhydrous THF (50 mL). After the solution was cooled to 0 ° C, SEMCl (3.367 g, 20.2 mmol, 1.3 equiv) and NaH (771.9 mg, 19.3 mmol, 1.3 equiv) were added to the Schlenk tube at 0 ° C. The reaction mixture was allowed to warm to room temperature with stirring over 80 min, at which time the mixture was treated with water (50 mL). The resulting mixture was extracted twice with diethyl ether (70 mL). The combined organic extracts were washed with water (100 mL) and brine (100 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/CH_2Cl_2 = 1:1) to provide the corresponding product **7** as a brown oil (4.517 g, 10.6 mmol, 71%). R_f = 0.78 (hexane/diethyl ether = 6:1); IR (ATR, cm^{-1}): 1712, 1415, 1315, 1220, 1094, 859, 836, 757, 635; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06 (s, 1H), 5.83 (s, 2H), 4.29 (q, 2H, *J* = 7.2 Hz), 3.57 (t, 2H, *J* = 8.2 Hz), 1.34 (t, 3H, *J* = 7.2 Hz), 0.90 (t, 2H, *J* = 8.2 Hz), -0.03 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 159.5, 124.5, 120.5, 113.4, 100.5, 75.3, 66.1, 60.6, 17.8, 14.4, -1.4; HRMS (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{13}H_{21}{}^{79}Br^{81}BrNO_3SiNa$ 449.9535; Found 449.9520.

Ethyl 3,4-dibromo-1-[(2-(trimethylsilyl)ethoxy)methyl]-1*H*-pyrrole-2-carboxylate (8).

A flame-dried 500-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with **7** (3.66 g, 8.56 mmol, 1.0 equiv) and anhydrous THF (86 mL). After the solution was cooled to -78 °C, LDA (2.0 M in THF/heptane/ethylbenzene, 4.7 mL, 9.4 mmol, 1.1 equiv) was added to the Schlenk tube and stirred at -78 °C for 10 min. The reaction mixture was treated with water (2 mL) at -78 °C and allowed to warm to room temperature with stirring over 1 h, at which time the resulting mixture was treated with saturated aqueous ammonium chloride (90 mL) and extracted twice with diethyl ether (100 mL). The combined organic extracts were washed with water and brine, dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/CH_2Cl_2 = 1:1) to provide the title product **8** as a yellow oil (2.99 g, 7.01 mmol, 82%). R_f = 0.32 (hexane/CH_2Cl_2 = 1:1); IR (ATR, cm^{-1}): 3118, 1692, 1394, 1375, 1312, 1281, 1248, 1168, 1096, 1081, 834; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06 (s, 1H), 5.63 (s, 2H), 4.36 (q, 2H, *J* = 7.6 Hz), 3.51 (t, 2H, *J* = 8.0 Hz), 1.40 (t, 2H, *J* = 7.6 Hz), 0.90 (t, 3H, *J* = 8.0 Hz), -0.02 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 159.7, 126.6, 121.0, 108.6, 101.6, 78.6, 66.8, 61.1, 17.9, 14.3, -1.3; HRMS (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{13}H_{21}{}^{79}Br^{81}BrNO_3SiNa$ 449.9535; Found 449.9534.

CATALYST SCREENING IN SUZUKI-MIYAURA COUPLING

A 50-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was charged with **8** (0.30 mmol, 1.0 equiv), **11** (0.60 mmol, 2.0 equiv), $Ba(OH)_2 \cdot 8H_2O$ (1.8 mmol, 6.0 equiv), palladium catalyst (30 µmol for palladium, 10 mol%), phosphorus ligand (60 µmol, 20 mol%), water (0.6 mL), and 1,4-dioxane (2.4 mL). The flask was placed in a preheated oil bath and heated at 100 °C for 15 min, at which time the reaction mixture was treated with water (3 mL). The resulting mixture was extracted with diethyl ether (5 mL) three times. The combined organic extracts were washed with water and brine, dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product. The yields of the monoarylated pyrrole **12** and diarylated pyrrole **13** were determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard by comparing relative values of integration for the peaks observed at 5.71 ppm (2 protons for **13**), 5.66 ppm (2 proton for **12**), and 5.63 ppm (2 proton for **8**) with that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm.

TOTAL SYNTHESIS OF LUKIANOL A

Ethyl 3,4-bis(4-(benzyloxy)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrole-2-carboxylate (13).

A 100-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was charged with **8** (438.5 mg, 1.03 mmol, 1.0 equiv), **11** (1.270 g, 4.09 mmol, 4.0 equiv), $Ba(OH)_2 \cdot 8H_2O$ (1.946 g, 6.17 mmol, 6.0 equiv), $Pd(PPh_3)_4$ (115.7 mg, 0.100 mmol, 10 mol%), water (2 mL), and 1,4-dioxane (8 mL). The flask was placed in a preheated oil bath and heated at 100 °C for 15 min, at which time the solution was treated with saturated aqueous ammonium chloride (30 mL). The resulting mixture was extracted twice with ethyl acetate (30 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 8:1 to 3:1, gradient) to provide the corresponding product **13** as a brown oil (511.0 mg, 0.806 mmol, 78%). R_f = 0.27 (hexane/diethyl ether = 3:1); IR (ATR, cm^{-1}): 2953, 1694, 1240, 1176, 1104, 1082, 834, 697; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46-7.31 (m, 10H), 7.12 (d, 2H, *J* = 8.8 Hz), 7.10 (s, 1H), 7.00 (d, 2H, *J* = 8.8 Hz), 6.90 (d, 2H, *J* = 8.8 Hz), 6.81 (d, 2H, *J* = 8.8 Hz), 5.71 (s, 2H), 5.08 (s, 2H), 5.00 (s, 2H), 4.06 (q, 2H, *J* = 7.2 Hz), 3.62 (t, 2H, *J* = 8.0 Hz), 0.99-0.93 (m, 5H), 0.00 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 161.7, 157.6, 157.2, 137.2, 137.1, 131.8, 131.6, 129.3, 128.5, 128.3, 127.9, 127.5, 127.2, 125.4, 124.6, 120.2, 114.5, 114.0, 77.7, 69.9, 66.2, 59.8, 17.9, 13.8, -1.3; HRMS (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{39}H_{43}NO_5SiNa$ 656.2808; Found 656.2831.

Ethyl 3,4-bis(4-(benzyloxy)phenyl)-1*H*-pyrrole-2-carboxylate (S2).

A 100-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was charged with **13** (115.8 mg, 0.183 mmol, 1.0 equiv) and CH_2Cl_2 (4 mL). The solution was cooled to 0 °C. TFA (100 µL, 1.31 mmol, 7.3 equiv) was added to the flask and the resulting mixture was stirred at 0 °C for 4 h, at which time the reaction mixture was treated with water (8 mL) and extracted with CH_2Cl_2 (10 mL) three times. The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (30 mL), water (30 mL), and brine (30 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude hemiaminal (118.8 mg), which was used for the next step without further purification.

A 20-mL test tube equipped with a Teflon-coated magnetic stirring bar was charged with the crude hemiaminal, sodium carbonate (152.4 mg, 1.44 mmol, 7.9 equiv), $NH_2OH \cdot HCl$ (13.7 mg, 0.21 mmol, 1.1 equiv), water (0.3 mL), and THF (1.2 mL). The resulting mixture was stirred at room temperature for 4.5 h, at which time the reaction mixture was treated with 1 M aqueous hydrochloric acid (2 mL) and extracted with ethyl acetate (4 mL) three times. The combined organic extracts were washed with water (20 mL) and brine (20 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/methyl acetate = 5:1) to provide the title product **S2** as a colorless solid (75.0 mg, 0.15 mmol, 82%). R_f = 0.50 (hexane/CH_2Cl_2 = 1:2); M.p. 82-85 °C; IR (ATR, cm^{-1}): 3301, 1681, 1535, 1455, 1379, 1289, 1239, 1176, 1025, 833, 737, 698; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.12 (br s, 1H), 7.47-7.30 (m, 10H), 7.20 (d, 2H, *J* = 8.8 Hz), 7.05-7.03 (m, 3H), 6.92 (d, 2H, *J* = 8.8 Hz), 6.83 (d, 2H, *J* = 8.8 Hz), 5.07 (s, 2H), 5.01 (s, 2H), 4.19 (q, 2H, *J*

= 7.2 Hz), 1.17 (t, 3H, *J* = 7.2 Hz); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 161.3, 157.9, 157.4, 137.3, 137.2, 132.1, 129.6, 129.0, 128.7, 128.07, 128.05, 127.74, 127.65, 127.5, 126.9, 126.5, 120.0, 119.9, 114.7, 114.1, 70.1, 60.3, 14.3; HRMS (ESI/TOF) *m*/*z*: [M + Na]$^+$ Calcd for $C_{33}H_{29}NO_4Na$ 526.1994; Found 526.2018.

Ethyl 3,4-bis(4-(benzyloxy)phenyl)-1-(2-(4-(benzyloxy)phenyl)-2-oxoethyl)-1*H*-pyrrole-2-carboxylate (18).

A 50-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was charged with **S2** (109.0 mg, 0.216 mmol, 1.0 equiv), **17** (93.0 mg, 0.305 mmol, 1.4 equiv), K_2CO_3 (59.9 mg, 0.433 mmol, 2.0 equiv), and DMF (720 μL). After stirring at room temperature for 3 h, the reaction was quenched with water (4 mL). The resulting mixture was washed twice with diethyl ether (4 mL). The aqueous layer was extracted twice with ethyl acetate (4 mL). The combined organic extracts were washed with brine (8 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to provide the title product **18** as a colorless solid (118.0 mg, 0.162 mmol, 75%), which was used for the next step without further purification. R_f = 0.53 (hexane/methyl acetate = 3:2); M.p. 152-153 °C; IR (ATR, cm^{-1}): 2932, 1688, 1600, 1373, 1233, 1171, 1102, 1015, 834, 739, 697; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.02 (d, 2H, *J* = 8.8 Hz), 7.46-7.30 (m, 15H), 7.17 (d, 2H, *J* = 8.8 Hz), 7.06 (d, 2H, *J* = 8.8 Hz), 7.03 (d, 2H, *J* = 8.8 Hz), 6.92 (s, 1H), 6.90 (d, 2H, *J* = 8.8 Hz), 6.80 (d, 2H, *J* = 8.8 Hz), 5.74 (s, 2H), 5.16 (s, 2H), 5.08 (s, 2H), 5.00 (s, 2H), 3.93 (q, 2H, *J* = 7.3 Hz), 0.85 (t, 3H, *J* = 7.3 Hz); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 191.9, 163.3, 162.0, 157.6, 157.2, 137.34, 137.25, 136.2, 132.1, 131.1, 130.5, 129.5, 128.9, 128.7, 128.4, 128.2, 128.04, 128.00, 127.7, 127.6, 127.5, 127.0, 124.6, 120.3, 115.1, 114.6, 114.0, 70.3, 70.1, 59.8, 55.6, 13.8; HRMS (ESI/TOF) *m*/*z*: [M + Na]$^+$ Calcd for $C_{48}H_{41}NO_6Na$ 750.2832; Found 750.2850.

3,4-Bis(4-(benzyloxy)phenyl)-1-(2-(4-(benzyloxy)phenyl)-2-oxoethyl)-1*H*-pyrrole-2-carboxylic acid (S3).

A 10-mL screw-top test tube equipped with a Teflon-coated magnetic stirring bar was charged with **18** (61.0 mg, 83.8 μmol, 1.0 equiv), potassium trimethylsilanolate (66.3 mg, 0.465 mmol, 5.6 equiv), and 1,2-dichloroethane (840 μL). The test tube was placed in a preheated aluminum block and heated at 80 °C for 15 min. The reaction was quenched with 1 M aqueous hydrochloric acid (5 mL). The resulting mixture was extracted with CHCl$_3$ (4 mL) three times. The combined organic extracts were washed with brine (10 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was washed with the mixture of diethyl ether (4 mL) and hexane (2 mL) to provide the title compound **S3** as a colorless solid (42.2 mg, 60.3 μmol, 72%). R_f = 0.37 (hexane/methyl acetate = 3:2); M.p. 177-180 °C; IR (ATR, cm^{-1}): 2922, 1650, 1600, 1454, 1240, 1171, 1026, 835, 735, 697, 639; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.01 (d, 2H, *J* = 8.8 Hz), 7.46-7.30 (m, 16H), 7.06 (d, 2H, *J* = 8.8 Hz), 7.00-6.96 (m, 6H), 6.80 (d, 2H, *J* = 8.8 Hz), 5.76 (s, 2H), 5.15 (s, 2H), 5.07 (s, 2H), 5.00 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz, THF-*d*$_8$): δ 191.8, 163.6, 163.1, 158.4, 157.9, 138.6, 138.5, 137.7, 132.8, 130.9, 130.7, 129.8, 129.6, 129.0, 128.9, 128.7, 128.5, 128.11, 128.07, 128.0, 127.7, 124.7, 121.0, 115.2, 114.8, 114.0, 70.5, 70.2, 56.0; HRMS (ESI/TOF) *m*/*z*: [M + Na]$^+$ Calcd for $C_{46}H_{37}NO_6Na$ 722.2519; Found 722.2545.

3,7,8-Tris(4-(benzyloxy)phenyl)-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-one (19).

A 50-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was charged with **S3** (65.4 mg, 93.5 μmol, 1.0 equiv), potassium acetate (162.5 mg, 1.66 mmol, 18 equiv), and acetic anhydride (9.4 mL). The flask was placed in a preheated oil bath and heated at 100 °C for 30 min. After cooling to room temperature, the acetic anhydride was removed azeotropically with toluene (60 mL) under reduced pressure. The oily residue was dissolved in ethyl acetate (10 mL) and the resulting mixture was washed with saturated aqueous ammonium chloride (5 mL). After partitioned, the aqueous layer was extracted twice with ethyl acetate (5 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/methyl acetate = 3:1) to provide the corresponding product **19** as a yellow amorphous (48.6 mg, 71.3 μmol, 76%). R_f = 0.59 (hexane/methyl acetate = 3:2); IR (ATR, cm^{-1}): 1732, 1608, 1514, 1429, 1415, 1242, 1176, 1026, 834, 751, 697; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.66 (d, 2H, *J* = 9.2 Hz), 7.46-7.29 (m, 18H), 7.22 (s, 1H), 7.09 (d, 2H, *J* = 8.8 Hz), 7.04 (d, 2H, *J* = 8.8 Hz), 6.96 (d, 2H, *J* = 8.8 Hz), 6.88 (d, 2H, *J* = 8.8 Hz), 5.12 (s, 2H), 5.08 (s, 2H), 5.04 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 159.8, 158.4, 158.0, 154.5, 142.1, 137.2, 137.0, 136.7, 132.2, 130.0, 129.8, 128.8, 128.73, 128.71, 128.3, 128.2, 128.1, 127.8, 127.6, 126.2, 126.0, 125.1, 123.5, 119.1, 115.3, 114.9, 114.3, 113.1, 102.9, 70.2, 70.1; HRMS (DART/TOF) *m*/*z*: [M + H]$^+$ Calcd for $C_{46}H_{36}NO_5$ 682.2594; Found 682.2608.

Lukianol A.

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with **19** (23.7 mg, 34.8 μmol, 1.0 equiv), pentamethylbenzene (31.0 mg, 209 μmol, 6.0 equiv), and CH$_2$Cl$_2$ (3.5 mL). The solution was cooled to -78 °C. BCl$_3$ (1 M in CH$_2$Cl$_2$, 209 μL, 0.21 mmol, 6.0 equiv) was added dropwise to the Schlenk tube. After stirring at -78 °C for 30 min, the reaction mixture was allowed to warm to 0 °C and stirred for 20 min, at which time the mixture was treated with methanol (4 mL) and concentrated under reduced pressure. The residue was dissolved in methanol (3 mL), washed twice with hexane (2 mL), and concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/acetone = 1:1). The obtained product was washed with a mixture of acetone (2.3 mL) and hexane (0.75 mL) to provide lukianol A as a colorless solid (9.0 mg, 22 μmol, 63%), whose ^{1}H and ^{13}C NMR spectra (DMSO-*d*$_6$) were identical to those reported in the literature.[21a] R_f = 0.28 (hexane/acetone = 1:1); M.p. 210-214 °C; IR (ATR, cm^{-1}): 3321, 1703, 1612, 1544, 1537, 1519, 1504, 1421, 1259, 1236, 1203, 1174, 1042, 1023, 836, 759, 635, 608; ^{1}H NMR (400 MHz, CD$_3$OD): δ 7.84 (s, 1H), 7.61 (d, 2H, *J* = 8.4 Hz), 7.49 (s, 1H), 7.13 (d, 2H, *J* = 8.4 Hz), 7.01 (d, 2H, *J* = 8.4 Hz), 6.87 (d, 2H, *J* = 8.4 Hz), 6.74 (d, 2H, *J* = 8.4 Hz), 6.67 (d, 2H, *J* = 8.4 Hz); ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 9.88 (s, 1H), 9.45 (s, 1H), 9.41 (s, 1H), 8.08 (s, 1H), 7.59 (s, 1H), 7.56 (d, 2H, *J* = 8.4 Hz), 7.05 (d, 2H, *J* = 8.4 Hz), 6.95 (d, 2H, *J* = 8.4 Hz), 6.87 (d, 2H, *J* = 8.4 Hz), 6.70 (d, 2H, *J* = 8.4 Hz), 6.66 (d, 2H, *J* = 8.4 Hz); ^{13}C{^{1}H} NMR (100 MHz, DMSO-*d*$_6$): δ 158.4, 156.6, 156.3, 153.6, 140.8, 131.8, 129.5, 128.8, 127.4, 125.5, 123.9, 123.2, 121.3, 120.0, 115.8, 115.3, 114.6, 111.9, 103.1; HRMS (DART/TOF) *m/z*: $[M + H]^+$ Calcd for $C_{25}H_{18}NO_5$ 412.1185; Found 412.1170.

1-Bromo-4-(phenylmethoxy)-benzene (S4).

A 500-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was charged with 4-bromophenol (6.961 g, 40.2 mmol, 1.0 equiv), potassium carbonate (11.15 g, 81.0 mmol, 2.0 equiv), benzyl bromide (5.0 mL, 42.2 mmol, 1.05 equiv), and acetonitrile (40 mL). The flask was placed in a preheated oil bath and heated at reflux for 1 h. After cooling to room temperature, the resulting mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to provide the corresponding product **S4** as a colorless solid (9.79 g, 37.2 mmol, 93%), whose ^{1}H and ^{13}C NMR spectra were identical to those reported in the literature.[30]

4,4,5,5-Tetramethyl-2-[4-(phenylmethoxy)phenyl]-1,3,2-dioxaborolane (11).

A flame-dried 50-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with **S4** (1.00 g, 3.80 mmol, 1.0 equiv) and anhydrous THF (19 mL). After the solution was cooled to −78 ° C, *n*-BuLi (1.59 M in *n*-hexane, 2.62 mL, 4.18 mmol, 1.1 equiv) was added to the Schlenk tube. The reaction mixture was stirred at −78 ° C for 10 min. To the white suspension was added *i*-PrOBpin (850.0 mg, 4.57 mmol, 1.2 equiv) at −78 ° C. After stirring at −78 ° C for 10 min, the resulting mixture was allowed to warm to room temperature with stirring over 30 min, at which time the reaction mixture was treated with water (20 mL). The mixture was extracted twice with diethyl ether (20 mL). The combined organic extracts were washed with brine (40 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/CH_2Cl_2 = 10:1 to hexane/methyl acetate = 3:1, gradient) to provide the corresponding product **11** as a colorless solid (922.5 mg, 2.97 mmol, 78%), whose ^{1}H and ^{13}C NMR spectra were identical to those reported in the literature.[31]

2-Bromo-1-[4-(phenylmethoxy)phenyl]-ethanone (17).

A 100-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was charged with 1-[4-(benzyloxy)phenyl]-ethanone (452.6 mg, 2.00 mmol, 1.0 equiv), $CuBr_2$ (893.8 mg, 4.00 mmol, 2.0 equiv), $CHCl_3$ (4 mL), and ethyl acetate (4 mL). The flask was placed in a preheated oil bath and heated at 80 ° C for 3 h. After cooling to room temperature, the resulting mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/CH_2Cl_2 = 3:1 to hexane/diethyl ether = 10:1, gradient) to provide the corresponding product **17** as a colorless solid (350.6 mg, 1.15 mmol, 57%), whose ^{1}H and ^{13}C NMR spectra were identical to those reported in the literature.[32]

TOTAL SYNTHESIS OF LUKIANOL B

Ethyl 3-(4-(benzyloxy)phenyl)-4-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrole-2-carboxylate (12).

A 100-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was charged with **8** (427.0 mg, 1.00 mmol, 1.0 equiv), **11** (465.8 mg, 1.50 mmol, 1.5 equiv), $Ba(OH)_2 \cdot 8H_2O$ (1.893 g, 6.00 mmol, 6.0 equiv), $Pd_2(dba)_3$ (45.9 mg, 50.1 μmol, 5 mol%), tris[4-(trifluoromethyl)phenyl]phosphine (92.0 mg, 0.197 mmol, 20 mol%), water (2 mL), and 1,4-dioxane (8 mL). The flask was placed in a preheated oil bath and heated at 100 ° C for 15 min, at which time the reaction was quenched with water (10 mL) and saturated aqueous ammonium chloride (10 mL). The resulting mixture was extracted with ethyl acetate (15 mL) three times. The combined organic extracts were washed with water (40 mL) and brine (40 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 10:1 to 5:1, gradient) followed by preparative SEC-HPLC to provide the title compound **12** as a colorless oil (118 mg, 0.222 mmol, 22%). R_f = 0.31 (hexane/diethyl ether = 3:1); IR (ATR, cm^{-1}): 1699, 1288, 1246, 1179, 1100, 1084, 1018, 858, 833, 736, 697; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, 2H, *J* = 7.6 Hz), 7.40 (dd, 2H, *J* = 8.0, 7.6 Hz), 7.33 (t, 1H, *J* = 8.0 Hz), 7.22 (d, 2H, *J* = 8.2 Hz), 7.08 (s, 1H), 7.00 (d, 2H, *J* = 8.2 Hz), 5.66 (s, 2H), 5.11 (s, 2H), 4.06 (q, 2H, *J* = 7.2 Hz), 3.58 (t, 2H, *J* = 8.2 Hz), 0.99–0.91 (m, 5H), 0.00 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 160.8, 158.2, 137.1, 132.9, 131.6, 128.6, 128.0, 127.6, 126.7, 119.8, 113.9, 99.4, 77.8, 70.0, 66.5, 60.2, 17.9, 13.8, −1.3; HRMS (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{26}H_{32}{}^{81}BrNO_4SiNa$ 554.1161; Found 554.1165.

Ethyl 4-(4-(benzyloxy)-3-(trimethylsilyl)phenyl)-3-(4-(benzyloxy)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrole-2-carboxylate (21).

A 50-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was charged with **12** (288.1 mg, 0.543 mmol, 1.0 equiv), **20** (621.5 mg, 1.63 mmol, 3.0 equiv), $Ba(OH)_2 \cdot 8H_2O$ (1.026 g, 3.25 mmol, 6.0 equiv), $Pd(PPh_3)_4$ (62.2 mg, 53.8 μmol, 10 mol%), water (1.1 mL), and 1,4-dioxane (4.3 mL). The flask was placed in a preheated oil bath and heated at 100 ° C for 15 min, at which time the reaction was quenched with saturated aqueous ammonium chloride (10 mL). The resulting mixture was extracted twice with ethyl acetate (10 mL). The combined organic extracts were washed with brine (20 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 10:1) followed by preparative SEC-HPLC to provide the title compound **21** as a colorless oil (167.8 mg, 0.238 mmol, 44%). R_f = 0.43 (hexane/diethyl ether = 3:1); IR (ATR, cm^{-1}): 1693, 1236, 1175, 1104, 1080, 836, 736, 696; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46–7.31 (m, 10H), 7.14–7.05 (m, 5H), 6.91 (d, 2H, *J* = 8.0 Hz), 6.73 (d, 1H, *J* = 8.0 Hz), 5.72 (s, 2H), 5.07 (s, 2H), 5.01 (s, 2H), 4.06 (q, 2H, *J* = 7.2 Hz), 3.62 (t, 2H, *J* = 8.2 Hz), 0.99–0.93 (m, 5H), 0.09 (s, 9H), 0.00 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 161.8, 161.7, 157.7, 137.3, 137.2, 135.2, 131.8, 131.7, 130.1, 128.5, 128.4, 127.9, 127.7, 127.4, 126.6, 125.2, 124.8, 120.2, 114.0, 110.2, 77.6, 70.0, 69.8, 66.2, 59.8, 17.9, 13.8, −0.9, −1.3; HRMS (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{42}H_{51}NO_5Si_2Na$ 728.3203; Found 728.3184.

Ethyl 4-(4-(benzyloxy)-3-iodophenyl)-3-(4-(benzyloxy)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrole-2-carboxylate (S5).

A 20-mL test tube equipped with a Teflon-coated magnetic stirring bar was charged with **21** (46.7 mg, 66.1 μmol, 1.0 equiv) and CH_2Cl_2 (1.7 mL). After the solution was cooled to -78 ° C, ICl (0.1 M in CH_2Cl_2, 730 μL, 73 μmol, 1.1 equiv) was added dropwise to the test tube. After stirring at -78 ° C for 20 min, the mixture was allowed to warm to -40 ° C for 20 min, at which time the mixture was treated with saturated aqueous sodium thiosulfate (3 mL). After partitioned, the aqueous layer was extracted with CH_2Cl_2 (2 mL) three time. The combined organic extracts were washed with brine (6 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to provide the title compound **S5** as a brown oil (48.4 mg, 63.7 μmol, 96%). R_f = 0.47 (hexane/diethyl ether = 2:1); M.p. 187-188 ° C; IR (ATR, cm^{-1}): 1695, 1281, 1240, 1176, 1104, 1082, 1043, 1020, 858, 834, 805, 735, 697; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, 1H, *J* = 2.2 Hz), 7.48-7.31 (m, 10H), 7.12-7.09 (m, 3H), 6.92 (d, 2H, *J* = 8.7 Hz), 6.87 (dd, 1H, *J* = 8.6, 2.2 Hz), 6.63 (d, 1H, *J* = 8.6 Hz), 5.71 (s, 2H), 5.09 (s, 2H), 5.08 (s, 2H), 4.06 (q, 2H, *J* = 7.2 Hz), 3.61 (t, 2H, *J* = 8.2 Hz), 0.99-0.94 (m, 5H), 0.01 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 161.7, 157.8, 155.6, 139.0, 137.2, 136.7, 131.8, 131.7, 129.4, 129.3, 128.7, 128.6, 128.0, 127.9, 127.6, 127.1, 125.4, 123.2, 120.4, 114.2, 112.3, 86.5, 77.8, 70.9, 70.1, 66.4, 60.0, 17.9, 13.9, -1.3; HRMS (DART/TOF) *m*/*z*: [M + H]$^+$ Calcd for $C_{39}H_{43}INO_5Si$ 760.1955; Found 760.1927.

Ethyl 4-(4-(benzyloxy)-3-iodophenyl)-3-(4-(benzyloxy)phenyl)-1*H*-pyrrole-2-carboxylate (S6).

A 50-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was charged with **S5** (220 mg, 0.290 mmol, 1.0 equiv) and CH_2Cl_2 (18 mL). After the solution was cooled to 0 ° C, TFA (222 μL, 2.90 mmol, 10 equiv) was added dropwise to the flask. After stirring at 0 ° C for 4 h, to the flask was added TFA (111 μL, 1.45 mmol, 5.0 equiv). The reaction mixture was stirred at 0 ° C for 4 h, at which time the reaction was quenched with water. After partitioned, the aqueous layer was extracted twice with CH_2Cl_2 (6 mL). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (20 mL) and brine (20 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude hemiaminal (186 mg) as a yellow amorphous, which was used for the next step without further purification.

A 50-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was charged with the crude hemiaminal, Na_2CO_3 (246 mg, 2.32 mmol, 8.0 equiv), $NH_2OH \cdot HCl$ (20.4 mg, 0.316 mmol, 1.1 equiv), THF (1.9 mL), and water (0.44 mL). After stirring at room temperature for 15 h, the reaction was quenched with water (5 mL) and 1 M aqueous hydrochloric acid (2 mL). The resulting mixture was extracted with ethyl acetate (5 mL) three times. The combined organic extracts were washed with brine (20 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/CH_2Cl_2 = 1:2 to hexane/methyl acetate = 3:1, gradient). The obtained product was washed with hexane to provide the title compound **S6** as a yellow amorphous (123 mg, 0.196 mmol, 68%). R_f = 0.43 (hexane/CH_2Cl_2 = 1:2); IR (ATR, cm^{-1}): 1669, 1530, 1454, 1378, 1282, 1240, 1175, 1040, 1024, 834, 736, 697; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.20 (br s, 1H), 7.66 (d, 1H, *J* = 2.3 Hz), 7.49-7.31 (m, 10H), 7.18 (d, 2H, *J* = 8.7 Hz), 7.03 (d, 1H, *J* = 3.2 Hz), 6.94-6.89 (m, 3H), 6.65 (d, 1H, *J* = 8.7 Hz), 5.09 (s, 2H × 2), 4.20 (q, 2H, *J* = 7.2 Hz), 1.17 (t, 3H, *J* = 7.2 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 161.4, 157.9, 155.6, 138.9, 137.1, 136.6, 132.0, 129.6, 129.4, 128.8, 128.6, 128.5, 127.93, 127.86, 127.6, 127.0, 126.7, 124.7, 120.3, 119.9, 114.1, 112.3, 86.5, 70.8, 70.0, 60.3, 14.2; HRMS (DART/TOF) *m*/*z*: [M + H]$^+$ Calcd for $C_{33}H_{29}INO_4$ 630.1141; Found 630.1136.

Ethyl 4-(4-(benzyloxy)-3-iodophenyl)-3-(4-(benzyloxy)phenyl)-1-(2-(4-(benzyloxy)phenyl)-2-oxoethyl)-1*H*-pyrrole-2-carboxylate (S7).

A 10-mL screw-top test tube equipped with a Teflon-coated magnetic stirring bar was charged with **S6** (116 mg, 0.185 mmol, 1.0 equiv), **17** (84.5 mg, 0.277 mmol, 1.5 equiv), K_2CO_3 (50.9 mg, 0.368 mmol, 2.0 equiv), and DMF (620 μL). After stirring at room temperature for 4 h, the reaction was quenched with water (4 mL). The resulting mixture was extracted twice with diethyl ether (4 mL). The combined organic extracts were washed with water (5 mL) and brine (5 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/CH_2Cl_2 = 1:1 to hexane/methyl acetate = 3:1, gradient) to provide the title compound **S7** as a yellow amorphous (141 mg, 0.165 mmol, 89%). R_f = 0.43 (hexane/diethyl ether = 2:1); IR (ATR, cm^{-1}): 1688, 1681, 1600, 1280, 1233, 1171, 1100, 833, 736, 697, 632; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, 2H, *J* = 8.8 Hz), 7.66 (d, 1H, *J* = 2.3 Hz), 7.48-7.31 (m, 15H), 7.16 (d, 2H, *J* = 8.8 Hz), 7.07 (d, 2H, *J* = 8.8 Hz), 6.93-6.89 (m, 4H), 6.63 (d, 1H, *J* = 8.8 Hz), 5.74 (s, 2H), 5.16 (s, 2H), 5.10 (s, 2H), 5.07 (s, 2H), 3.94 (q, 2H, *J* = 7.2 Hz), 0.85 (t, 3H, *J* = 7.2 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 191.7, 163.1, 161.7, 157.6, 155.4, 138.9, 137.2, 136.6, 136.0, 131.9, 130.9, 130.3, 130.0, 129.5, 129.2, 128.7, 128.52, 128.50, 128.3, 128.2, 128.0, 127.84, 127.80, 127.5, 127.0, 122.8, 120.3, 114.9, 114.0, 112.2, 86.4, 70.7, 70.1, 69.9, 59.7, 55.5, 13.7; HRMS (ESI/TOF) *m*/*z*: [M + Na]$^+$ Calcd for $C_{48}H_{40}INO_6Na$ 876.1798; Found 876.1786.

4-(4-(Benzyloxy)-3-iodophenyl)-3-(4-(benzyloxy)phenyl)-1-(2-(4-(benzyloxy)phenyl)-2-oxoethyl)-1*H*-pyrrole-2-carboxylic acid (S8).

A 10-mL screw-top test tube equipped with a Teflon-coated magnetic stirring bar was charged with **S7** (38.3 mg, 44.9 μmol, 1.0 equiv), potassium trimethylsilanolate (38.7 mg, 0.271 mmol, 6.0 equiv), and 1,2-dichloroethane (0.45 mL). The test tube was placed in a preheated aluminum block and heated at 80 ° C for 15 min, at which time the reaction mixture was treated with 1 M aqueous hydrochloric acid (3 mL). After partitioned, the aqueous layer was extracted with $CHCl_3$ (3 mL) three times. The combined organic extracts were washed with brine (3 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was washed with the mixture of diethyl ether (2 mL) and hexane (1 mL) to provide the title compound **S8** as a colorless solid (23.8 mg, 28.8 μmol, 64%). R_f = 0.18 (hexane/methyl acetate = 2:1); M.p. 187-188 ° C; IR (ATR, cm^{-1}): 1686, 1650, 1600, 1451, 1287, 1239, 1172, 1011, 736, 696; ^{1}H NMR (400 MHz, THF-*d*$_8$): δ 8.02 (d, 2H, *J* =

8.8 Hz), 7.64 (d, 1H, *J* = 2.0 Hz), 7.48-7.24 (m, 15H), 7.14 (d, 2H, *J* = 8.8 Hz), 7.11-7.09 (m, 3H), 6.91-6.87 (m, 3H), 6.74 (d, 1H, *J* = 8.8 Hz), 5.84 (s, 2H), 5.18 (s, 2H), 5.064 (s, 2H), 5.059 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, THF-*d*$_8$): δ 191.6, 163.6, 162.9, 158.6, 156.2, 139.4, 138.6, 138.0, 137.7, 132.7, 130.94, 130.87, 130.7, 129.8, 129.5, 129.3, 129.0, 128.9, 128.5, 128.1, 128.0, 127.9, 127.6, 123.1, 121.2, 115.2, 114.2, 112.6, 86.4, 71.1, 70.6, 70.2, 56.0; HRMS (ESI/TOF) *m*/*z*: $[M - H]^-$ Calcd $C_{46}H_{35}INO_6$ 824.1509; Found 824.1533.

Lukianol B.

A 50-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was charged with **S8** (44.4 mg, 53.8 μmol, 1.0 equiv), potassium acetate (95.7 mg, 0.975 mmol, 18 equiv), and acetic anhydride (5.4 mL). The flask was placed in a preheated oil bath and heated at 100 ° C for 30 min. After cooling to room temperature, the acetic anhydride was removed azeotropically with toluene (50 mL) under reduced pressure. The residue was dissolved in ethyl acetate (6 mL) and the resulting mixture was washed with saturated aqueous ammonium chloride (6 mL). After partitioned, the aqueous layer was extracted twice with ethyl acetate (6 mL). The combined organic extracts were washed with brine (10 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/methyl acetate = 3:1) to provide the corresponding product **22** (27.3 mg) as a yellow amorphous, which was used for the next reaction without further purification. R*f* = 0.29 (hexane/methyl acetate = 3:1).

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with **22** (27.3 mg, 33.8 μmol, 1.0 equiv), pentamethylbenzene (29.3 mg, 198 μmol, 6.0 equiv), and CH_2Cl_2 (3.4 mL). The solution was cooled to -78 ° C. BCl_3 (1 M in CH_2Cl_2, 200 μL, 0.20 mmol, 6.0 equiv) was added dropwise to the Schlenk tube. After stirring at -78 ° C for 30 min, the reaction mixture was allowed to warm to 0 ° C and stirred for 20 min, at which time the mixture was treated with methanol (4 mL) and concentrated under reduced pressure. The residue was dissolved in methanol (3 mL) and the resulting mixture was washed with hexane (3 mL) three times. The methanol layer was concentrated under reduced pressure to give a crude product, which was washed with acetone (2 mL) to provide lukianol B as a colorless solid (13.1 mg, 24.4 μmol, 45% over 2 steps), whose ^1H and ^{13}C NMR spectra (acetone-*d*$_6$) were identical to those reported in the literature.[21a] R*f* = 0.26 (CH_2Cl_2/methanol = 20:1); M.p. >275 ° C; IR (ATR, cm^{-1}): 2924, 1697, 1680, 1658, 1612, 1536, 1518, 1503, 1433, 1422, 1415, 1408, 1274, 1239, 1208, 1181, 836; ^1H NMR (400 MHz, acetone-*d*$_6$): δ 9.15 (s, 1H), 8.81 (s, 1H), 8.44 (s, 1H), 7.93 (s, 1H), 7.65 (d, 2H, *J* = 8.8 Hz), 7.63 (d, 1H, *J* = 2.0 Hz), 7.61 (s, 1H), 7.18 (d, 2H, *J* = 8.8 Hz), 7.00 (dd, 1H, *J* = 8.8, 2.0 Hz), 6.96 (d, 2H, *J* = 8.8 Hz), 6.84-6.81 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, acetone-*d*$_6$): δ 159.5, 157.9, 156.5, 154.4, 142.9, 140.1, 133.0, 130.9, 130.5, 128.5, 127.3, 126.8, 124.9, 123.4, 120.8, 116.8, 115.7, 115.6, 113.8, 103.8, 84.4; HRMS (DART/TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{25}H_{17}INO_5$ 538.0151; Found 538.0177.

2,4-Diiodophenol (S9).

A 500-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was charged with 2-iodo-phenol (3.820 g, 17.4 mmol, 1.0 equiv), NaOH (1.114 g, 28.9 mmol 1.7 equiv), and methanol (43 mL). After the solution was cooled to 0 ° C, I_2 (6.166 g, 24.3 mmol, 1.4 equiv) in methanol (43 mL) was added dropwise to the flask at 0 ° C. After stirring for 85 min at 0 ° C, I_2 (668.0 mg, 2.63 mmol, 0.15 equiv) in methanol (5 mL) was added dropwise to the flask at 0 ° C and the resulting mixture was stirred for 40 min, at which time the reaction mixture was treated with saturated aqueous sodium thiosulfate (100 mL) and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 mL) and the resulting mixture was washed with saturated aqueous ammonium chloride (50 mL). After partitioned, the aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined organic extracts were washed with brine (100 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/CH_2Cl_2 = 2:1) to provide the corresponding product **S9** as a colorless solid (3.966 g, 11.5 mmol, 66%), whose ^1H and ^{13}C NMR spectra were identical to those reported in the literature.[33]

2,4-Diiodo-1-(phenylmethoxy)-benzene (S10).

A 200-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was charged with **S9** (3.732 g, 10.8 mmol, 1.0 equiv), potassium carbonate (2.986 g, 21.6 mmol, 2.0 equiv), benzyl bromide (1.849 g, 10.8 mmol, 1.0 equiv), and acetonitrile (22 mL). The flask was placed in a preheated oil bath and heated at 80 ° C for 30 min. After cooling to room temperature, the resulting mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane) to provide the corresponding product **S10** as a colorless solid (4.389 g, 10.1 mmol, 93%), whose ^1H and ^{13}C NMR spectra were identical to those reported in the literature.[34]

(2-(Benzyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)trimethylsilane (20).

A flame-dried 100-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with **S10** (1.005 g, 2.30 mmol, 1.0 equiv), TMSCl (1.5 mL, 12 mmol, 5 equiv), and anhydrous THF (11.5 mL). After the solution was cooled to -78 ° C, *n*-BuLi (1.55 M in *n*-hexane, 1.48 mL, 2.3 mmol, 1.0 equiv) was added to the Schlenk tube. The reaction mixture was stirred at -78 ° C for 30 min, the resulting mixture was allowed to warm to room temperature with stirring over 1 h, at which time the reaction mixture was treated with water (20 mL) and saturated aqueous ammonium chloride (5 mL). The resulting mixture was extracted twice with diethyl ether (15 mL). The combined organic extracts were washed with brine (30 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane) to provide a mixture of the corresponding product **S11** and the disilylated byproduct (673.3 mg).

A flame-dried 50-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with **S11** (673.3 mg, 1.51 mmol, 1.0 equiv) and anhydrous THF (7.6 mL). After the solution was cooled to -78 ° C, *n*-BuLi (1.55 M in *n*-hexane, 1.1 mL, 1.7 mmol, 1.1 equiv) was added to the Schlenk tube. The reaction mixture was stirred at -78 °C for 5 min, to the solution was added *i*-PrOBpin (337.4 mg, 1.81 mmol, 1.2 equiv) at -78 °C. After stirring at -78 °C for 10 min, the resulting mixture was allowed to warm to room temperature with stirring over 1 h, at which time the reaction mixture was treated with water (10 mL). The resulting mixture was extracted twice with diethyl ether (10 mL). The combined organic extracts were washed with brine (20 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane to hexane/CH_2Cl_2 = 2:1, gradient) to provide the corresponding product **20** as a colorless solid (388.7 mg, 1.02 mmol, 44% over 2 steps). R_f = 0.26 (hexane/CH_2Cl_2 = 2:1); M.p. 99-100 °C; IR (ATR, cm^{-1}): 1588, 1371, 1352, 1279, 1231, 1145, 1102, 854, 838, 695, 669; ^1H NMR (400 MHz, $CDCl_3$): δ 7.83 (s, 1H), 7.78 (d, 1H, *J* = 8.2 Hz), 7.41-7.30 (m, 5H), 6.85 (d, 1H, *J* = 8.2 Hz), 5.09 (s, 2H), 1.31 (s, 12H), 0.24 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 166.0, 142.1, 138.3, 137.0, 128.6, 127.9, 127.6, 127.4, 120.7, 109.9, 83.6, 69.8, 25.0, -0.7; HRMS (ESI/TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{22}H_{32}BO_3SiNa$ 405.2148; Found 405.2145.

TOTAL SYNTHESIS OF NINGALIN B

Ethyl 3,4-bis[3,4-bis(benzyloxy)phenyl]-1-[(2-(trimethylsilyl)ethoxy)methyl]-1*H*-pyrrole-2-carboxylate (24).

A 50-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was charged with **8** (424.6 mg, 0.994 mmol, 1.0 equiv), $Ba(OH)_2 \cdot 8H_2O$ (1.88 g, 5.97 mmol, 6.0 equiv), **23** (1.66 g, 3.99 mmol, 4.0 equiv), $Pd(PPh_3)_4$ (113.9 mg, 98.6 μmol, 10 mol%), water (2 mL), and 1,4-dioxane (8 mL). The flask was placed in a preheated oil bath and heated at 100 °C for 15 min, at which time the solution was treated with water (5 mL). The reaction mixture was extracted twice with diethyl ether (10 mL). The combined organic extracts were washed with water and brine, dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 5:1 to hexane/diethyl ether = 3:1, gradient) and followed by preparative SEC-HPLC to provide the title product **24** as a pale yellow oil (499 mg, 0.590 mmol, 59%). R_f = 0.21 (hexane/diethyl ether = 3:1); IR (ATR, cm^{-1}): 2949, 1695, 1530, 1498, 1455, 1426, 1373, 1355, 1247, 1212, 1136, 1081, 1023, 836; ^1H NMR (400 MHz, $CDCl_3$): δ 7.44-7.21 (m, 20H), 7.07 (s, 1H), 6.89 (d, 1H, *J* = 8.2 Hz), 6.84 (d, 1H, *J* = 1.6 Hz), 6.76 (d, 1H, *J* = 8.2 Hz), 6.73 (dd, 1H, *J* = 8.0 Hz, 2.3 Hz), 6.65 (dd, 1H, *J* = 8.2, 2.3 Hz), 6.61 (d, 1H, *J* = 2.3 Hz), 5.69 (s, 2H), 5.15 (s, 2H), 5.10 (s, 2H), 5.02 (s, 2H), 4.75 (s, 2H), 3.98 (q, 2H, *J* = 7.2 Hz), 3.60 (t, 2H, *J* = 8.1 Hz), 0.95 (t, 2H, *J* = 8.1 Hz), 0.89 (t, 3H, *J* = 7.2 Hz), -0.01 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 161.7, 148.6, 148.3, 147.8, 147.2, 137.6, 137.5, 137.4, 131.5, 129.5, 128.6, 128.5, 127.9, 127.8, 127.7, 127.4, 127.3, 127.2, 125.2, 124.5, 123.9, 120.6, 120.3, 117.7, 115.0, 114.8, 114.4, 77.7, 71.4, 71.3, 70.9, 66.4, 59.9, 17.9, 13.9, -1.3; HRMS (ESI/TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{53}H_{55}NO_7SiNa$ 868.3646; Found 868.3667.

7,8-Bis(benzyloxy)-1-[3,4-bis(benzyloxy)phenyl]chromeno[3,4-*b*]pyrrol-4(3*H*)-one (25).

A 10-mL screw-top test tube equipped with a Teflon-coated magnetic stirring bar was charged with compound **24** (245.1 mg, 0.290 mmol, 1.0 equiv), 18-crown-6 (153.3 mg, 0.580 mmol, 2.0 equiv), KOH (162.7 mg, 10.0 mmol, 10.0 equiv), and EtOH (1.5 mL). The test tube was placed in a preheated aluminum block and heated at reflux for 14.5 h, at which time the resulting mixture was added 18-crown-6 (76.2 mg, 0.288 mmol, 1.0 equiv) and KOH (80.3 mg, 1.43 mmol, 4.9 equiv). After stirring at reflux for 20.5 h, the reaction mixture was treated with 1 M aqueous hydrochloric acid, at which time yellow solid was precipitated and filtered to give a crude **S12** as a yellow solid (281.0 mg), which was used for the next step without further purification.

A 50-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was charged with the crude **S12** (281.0 mg) and anhydrous ethyl acetate (29 mL). To the solution was added $Pb(OAc)_4$ (258.4 mg, 0.58 mmol), and the flask was placed in a preheated oil bath and heated at reflux for 30 min. $Pb(OAc)_4$ (130.2 mg, 0.29 mmol) was added to the solution, and the reaction mixture was heated at reflux for 20 min. Pinacol (113.2 mg, 0.956 mmol) was added to the flask, and the reaction mixture was treated with water (30 mL). The resulting mixture was extracted with ethyl acetate (30 mL) three times. The combined organic extracts were washed with water and brine, dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/CH_2Cl_2 = 1:1 to CH_2Cl_2, gradient) to provide the corresponding product **S13** as a yellow solid (89.6 mg, 0.110 mmol).

A 50-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was charged with compound **S13** (89.6 mg, 0.110 mmol, 1.0 equiv) and CH_2Cl_2 (2.8 mL). TFA (0.60 mL, 18 mmol, xs) was added to the flask. The resulting mixture was stirred at room temperature for 10 min. After the reaction mixture was concentrated under reduced pressure, the flask was charged with anhydrous THF (0.8 mL), water (0.2 mL), $NH_2OH \cdot HCl$ (6.9 mg, 99 μmol, 0.90 equiv), and Na_2CO_3 (35.1 mg, 0.331 mmol, 3.0 equiv). After stirring at room temperature for 25 min, the reaction mixture was treated with water (1 mL). The resulting mixture was extracted with ethyl acetate (2 mL) three times. The combined organic extracts were washed with water and brine, dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was washed with diethyl ether (10 mL) to provide the title compound **25** as a pale yellow solid (48.3 mg, 70.4 μmol, 24% over 3 steps). R_f = 0.30 (CH_2Cl_2/methanol = 100:1); M.p. 178-179 °C; IR (ATR, cm^{-1}): 3242, 3063, 3033, 1696, 1549, 1516, 1499, 1272, 1207, 1023, 735, 695; ^1H NMR (400 MHz, $CDCl_3$): δ 9.60 (br s, 1H), 7.51-7.29 (m, 15H), 7.22-7.19 (m, 3H), 7.17 (s, 1H), 7.14 (d, 1H, *J* = 3.2 Hz), 7.12-7.08 (m, 2H), 7.07 (d, 1H, *J* = 1.8 Hz), 7.03 (d, 1H, *J* = 8.2 Hz), 6.965 (dd, 1H, *J* = 7.8, 1.8 Hz), 6.959 (s, 1H), 5.26 (s, 2H), 5.21 (s, 2H), 5.18 (s, 2H), 4.84 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 156.7, 149.1, 148.8, 148.7, 146.1, 145.2, 137.3, 137.1, 136.6, 136.5, 128.73, 128.70, 128.66, 128.5, 128.3, 128.2, 128.1, 128.0, 127.8, 127.6, 127.5, 127.4, 126.6, 123.0, 121.3, 116.7, 116.4, 115.0, 111.1, 108.1, 103.6, 71.5, 71.1, 70.9; HRMS (ESI/TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{45}H_{35}NO_6Na$ 708.2362; Found 708.2367.

7,8-Bis(benzyloxy)-3-[3,4-bis(benzyloxy)phenethyl]-1-[3,4-bis(benzyloxy)phenyl]chromeno[3,4-*b*]pyrrol-4(3*H*)-one (S14).

A 10-mL screw-top test tube equipped with a Teflon-coated magnetic stirring bar was charged with compound **25** (42.9 mg, 62.4 μmol, 1.0 equiv), 2-[3,4-bis(benzyloxy)-phenyl]ethanol (**26**) (31.3 mg, 93.6 μmol, 1.5 equiv), and PPh_3 (48.9 mg, 0.187 mmol, 3.0 equiv). After the flask was evacuated and backfilled with N_2, anhydrous THF (0.3 mL) and DIAD (1.9 M, 99 μL, 0.19 mmol, 3.0 equiv) were added to the flask. The solution was stirred at room temperature for 15 min, at which time the reaction mixture was treated with water (1 mL). The resulting mixture was extracted with diethyl ether (1 mL) three times. The combined organic extracts were washed with water and brine, dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/CH_2Cl_2 = 4:1 to CH_2Cl_2, gradient). The amorphous was washed with hexane (2 mL) to provide the titled product **S14** as a white amorphous (43.9 mg, 43.7 μmol, 70%). R_f = 0.21 (hexane/CH_2Cl_2 = 4:1); IR (ATR, cm^{-1}): 1714, 1510, 1499, 1454, 1376, 1262, 1229, 1159, 1024, 745, 695; ^1H NMR (400 MHz, $CDCl_3$): δ 7.48-7.28 (m, 21H), 7.24-7.17 (m, 6H), 7.11 (s, 1H), 7.10-7.08 (m, 2H), 6.96 (d, 2H, *J* = 7.8 Hz), 6.93 (d, 1H, *J* = 1.8 Hz), 6.83-6.80 (m, 2H), 6.61 (dd, 1H, *J* = 8.2, 2.3 Hz), 6.56 (d, 1H, *J* = 1.8 Hz), 6.51 (s, 1H), 5.21 (s, 2H×2), 5.10 (s, 2H), 5.08 (s, 2H), 4.97 (s, 2H), 4.79 (s, 2H), 4.53 (t, 2H, *J* = 6.6 Hz), 3.00 (t, 2H, *J* = 6.6 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 155.5, 149.1, 149.0, 148.7, 148.6, 147.8, 146.3, 144.9, 137.4, 137.3, 137.2, 137.0, 136.7, 136.6, 132.2, 131.5, 128.8, 128.7, 128.58, 128.55, 128.51, 128.4, 128.1, 128.0, 127.9, 127.8, 127.59, 127.56, 127.4, 127.35, 127.32, 127.1, 122.9, 121.8, 119.0, 116.5, 115.7, 115.5, 115.0, 114.9, 111.0, 108.1, 103.5, 71.6, 71.5, 71.3, 71.2, 71.1, 70.9, 51.0, 37.6; HRMS (ESI/TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{67}H_{55}NO_8Na$ 1024.3825; Found 1024.3788.

Ningalin B.

A 25-mL pear-shaped flask equipped with a Teflon-coated magnetic stirring bar was charged with compound **S14** (31.9 mg, 31.8 μmol, 1.0 equiv), Pd/C (31.9 mg, 100 wt%), EtOH (0.5 mL), and ethyl acetate (0.5 mL). After the flask was evacuated and backfilled with H_2 three times, the resulting mixture was stirred at room temperature for 30 min. The resulting mixture was filtered through a pad of Celite, and the filter cake was washed with hot methanol (10 mL). The filtrate was concentrated under reduced pressure to provide ningalin B as a pale gray solid (14.3 mg, 30.8 μmol, 97%), whose ^1H and ^{13}C NMR spectra (DMSO-d_6/CD_3OD (4:1)) were not in good agreement with those reported in the literature.[25a] The ^1H NMR spectrum (CD_3OD) was identical to that reported in Fenical's supporting information (page 10). ^1H and ^{13}C NMR spectra (DMSO-d_6/CD_3OD (4:1)) were in good agreement with those reported.[6h,25b] R_f = 0.52 (CH_2Cl_2/methanol = 3:1); M.p. >250 °C; IR (ATR, cm^{-1}): 3269, 2927, 1682, 1416, 1366, 1255, 1230, 1168, 816; ^1H NMR (400 MHz, CD_3OD) δ 7.14 (s, 1H), 6.89 (s, 1H), 6.84 (d, 1H, *J* = 7.8 Hz), 6.82 (d, 1H, *J* = 1.8 Hz), 6.79 (s, 1H), 6.71-6.65 (m, 2H), 6.54 (d, 1H, *J* = 1.8 Hz), 6.46 (dd, 1H, *J* =8.2, 1.8 Hz), 4.56 (t, 2H, *J* = 7.0 Hz), 2.96 (t, 2H, *J* = 7.0 Hz); ^1H NMR (400 MHz, DMSO-d_6/CD_3OD (4:1)) δ 7.19 (s, 1H), 7.06 (s, 1H), 6.81 (d, 1H, *J* = 8.4 Hz), 6.77 (d, 1H, *J* = 2.0 Hz), 6.75 (s, 1H), 6.63 (dd, 1H, *J* = 7.6, 2.4 Hz), 6.62 (d, 1H, *J* = 7.8 Hz), 6.59 (d, 1H, *J* = 2.0 Hz), 6.43 (dd, 1H, *J* = 8.0, 2.0 Hz), 4.49 (t, 2H, *J* = 7.4 Hz), 2.87 (t, 2H, *J* = 7.4 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6/CD_3OD (4:1)): δ 155.2, 146.3, 145.5, 145.4, 145.3, 145.0, 144.1, 142.4, 133.0, 129.5, 126.8, 125.7, 121.1, 120.0, 119.5, 117.3, 116.5, 116.1, 115.8, 114.3, 110.0, 108.9, 103.7, 50.3, 37.5; HRMS (ESI/TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{25}H_{19}NO_8Na$ 484.1008; Found 484.1031.

2-[3,4-Di(benzyloxy)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (23).

A flame-dried 100-mL two-necked test tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with 3,4-dibenzyloxy-1-iodobenzene[35] (1.04 g, 2.53 mmol, 1.0 equiv) and anhydrous THF (13 mL). After the solution was cooled to -78 °C, the resulting mixture was treated with *n*-BuLi (1.59 M in *n*-hexane, 1.65 mL, 2.63 mmol, 1.0 equiv) and stirred at -78 °C for 5 min. To the solution was added *i*-PrOBpin (522.2 mg, 2.81 mmol, 1.1 equiv) at -78 °C. After stirring at -78 °C for 10 min, the resulting mixture was allowed to warm to room temperature with stirring over 40 min, at which time the reaction mixture was treated with saturated aqueous ammonium chloride (10 mL). After partitioned, the aqueous layer was extracted with diethyl ether (10 mL) three times. The combined organic extracts were washed with water and brine, dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 10:1) to provide the title product **23** as a colorless solid (795.6 mg, 1.91 mmol, 76%), whose ^1H and ^{13}C NMR spectra were identical to those reported in the literature.[36]

2-[3,4-Di(benzyloxy)phenyl]ethanol (26).

A 50-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was charged with 2-(3,4-dihydroxyphenyl)ethyl alcohol (347.4 mg, 2.25 mmol, 1.0 equiv), K_2CO_3 (937.3 mg, 6.75 mmol, 3.0 equiv), benzyl bromide (643 μL, 5.41 mmol, 2.4 equiv), and acetonitrile (2.25 mL). The flask was placed in a preheated oil bath and heated at reflux for 15 h. After cooling to room temperature, the resulting mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 3:1) to provide the title product **26** as a colorless solid (631 mg, 1.88 mmol, 84%), whose ^1H NMR spectrum was identical to that reported in the literature.[37]

TOTAL SYNTHESIS OF LAMELLARIN S

7,8-Bis(benzyloxy)-3-[3-(benzyloxy)-4-methoxyphenethyl]-1-[3,4-bis(benzyloxy)phenyl]chromeno[3,4-*b*]pyrrol-4(3*H*)-one (28).

A 10-mL screw-top test tube equipped with a Teflon-coated magnetic stirring bar was charged with compound **25** (55.0 mg, 80.0 μmol, 1.0 equiv), 3-benzyloxy-4-methoxybenzeneethanol (**27**) (31.9 mg, 0.123 mmol, 1.5 equiv), PPh_3 (61.8 mg, 0.236 mmol, 3.0 equiv). After the flask was evacuated and backfilled with N_2, anhydrous THF (0.4 mL), and DIAD (1.9 M, 126 μL, 0.240 mmol, 3.0 equiv) were added to the flask. The solution was stirred at room temperature for 20 min, at which time the reaction mixture was treated with water (1 mL). The resulting mixture was extracted with diethyl ether (1 mL) three times. The combined organic extracts were washed with water and brine, dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/CH_2Cl_2 = 1:3 to hexane/CH_2Cl_2 = 1:4, gradient) to provide the title product **28** as a yellow amorphous (52.4 mg, 56.6 µmol, 71%). R$_f$ = 0.34 (hexane/CH_2Cl_2 = 1:4); IR (ATR, cm^{-1}): 1709, 1588, 1513, 1419, 1260, 1137, 1025, 736, 696; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49-7.28 (m, 15H), 7.25-7.16 (m, 7H), 7.13 (s, 1H), 7.11-7.07 (m, 2H), 6.98 (d, 1H, *J* = 8.2 Hz), 6.95 (s, 1H), 6.91 (d, 1H, *J* = 1.8 Hz), 6.83 (dd, 1H, *J* = 8.2, 2.1 Hz), 6.78 (d, 1H, *J* = 8.2 Hz), 6.65 (dd, 1H, *J* = 8.0, 2.1 Hz), 6.48 (d, 1H, *J* = 2.3 Hz), 6.47 (s, 1H), 5.222 (s, 1H), 5.219 (s, 2H), 5.11 (s, 2H), 4.94 (s, 2H), 4.80 (s, 2H), 4.52 (t, 2H, *J* = 6.9 Hz), 3.81 (s, 3H), 3.00 (t, 2H, *J* = 6.9 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 155.4, 149.1, 148.7, 148.5, 148.1, 146.3, 144.9, 137.3, 137.1, 137.0, 136.64, 136.58, 132.2, 130.5, 128.73, 128.66, 128.6, 128.5, 128.4, 128.1, 128.01, 127.99, 127.83, 127.76, 127.60, 127.56, 127.3, 127.1, 122.9, 121.6, 119.0, 116.5, 115.0, 114.8, 112.0, 111.0, 108.1, 103.5, 71.5, 71.3, 71.1, 70.87, 70.86, 56.1, 51.1, 37.5 (five aromatic carbon signals are missing due to overlapping); HRMS (ESI/TOF) *m*/*z*: [M + Na]$^+$ Calcd for $C_{61}H_{51}NO_8Na$ 948.3512; Found 948.3548.

2,3,11-Tris(benzyloxy)-14-(3,4-bis(benzyloxy)phenyl)-12-methoxy-8,9-dihydro-6*H*-chromeno[4',3':4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (S15).

A 50-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was charged with compound **28** (33.1 mg, 35.7 µmol, 1.0 equiv) and anhydrous CH_2Cl_2 (1 mL). After the resulting solution was cooled to -40 ° C, a solution of PIFA (18.1 mg, 42.1 µmol, 1.2 equiv) and $BF_3 \cdot OEt_2$ (11 µL, 87 µmol, 2.4 equiv) in anhydrous CH_2Cl_2 (2.6 mL) was added dropwise to the flask. The reaction mixture was stirred at -40 ° C for 1 h, at which time the reaction was quenched with 2 M aqueous NH_3 (3 mL). The reaction mixture was extracted twice with CH_2Cl_2 (3 mL). The combined organic extracts were washed with water and brine, dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 1:1 to CH_2Cl_2, gradient). The solid was washed twice with diethyl ether (2 mL) to provide the titled product **S15** as a colorless solid (20.1 mg, 21.8 µmol, 61%). R$_f$ = 0.14 (hexane/diethyl ether = 1:1); M.p. 167-168 ° C; IR (ATR, cm^{-1}): 1704, 1543, 1512, 1484, 1454, 1420, 1270, 1210, 1165, 1037, 1026, 735, 696; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48-7.28 (m, 19H), 7.24-7.21 (m, 4H), 7.17-7.15 (m, 2H), 7.10 (d, 1H, *J* = 8.2 Hz), 7.05 (d, 1H, *J* = 1.8 Hz), 6.98 (dd, 1H, *J* = 8.2, 1.8 Hz), 6.92 (s, 1H), 6.73 (s, 1H), 6.72 (s, 1H), 6.53 (s, 1H), 5.29 (d, 1H, *J* = 12.4 Hz), 5.24 (d, 1H, *J* = 12.4 Hz), 5.19 (s, 2H), 5.148 (s, 2H), 5.145 (d, 1H, *J* = 12.4 Hz), 5.10 (d, 1H, *J* = 12.4 Hz), 4.85-4.78 (m, 1H), 4.73 (d, 1H, *J* = 12.8 Hz), 4.68 (d, 1H, *J* = 12.4 Hz), 4.64-4.57 (m, 1H), 3.18 (s 3H), 3.06-2.92 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 155.6, 149.6, 148.7, 148.5, 148.2, 148.1, 146.2, 144.9, 137.2, 136.83, 136.77, 136.7, 136.0, 128.8, 128.7, 128.60, 128.56, 128.5, 128.14, 128.08, 128.0, 127.8, 127.4, 127.32, 127.27, 127.20, 127.18, 126.4, 124.0, 120.5, 117.3, 115.4, 114.9, 113.8, 113.3, 110.9, 109.1, 107.8, 103.3, 71.3, 71.02, 70.97, 70.5, 55.2, 42.5, 28.7 (four aromatic carbon signals and a benzylic position carbon are missing due to overlapping); HRMS (ESI/TOF) *m*/*z*: [M + Na]$^+$ Calcd for $C_{61}H_{49}NO_8Na$ 946.3356; Found 946.3365.

Lamellarin S.

A 10 mL pear-shaped flask equipped with a Teflon-coated magnetic stirring bar was charged with compound **S17** (17.1 mg, 18.5 µmol, 1.0 equiv), Pd/C (17.1 mg, 100 wt%), EtOH (0.3 mL), and EtOAc (0.3 mL). After the flask was evacuated and backfilled with H_2 three times, the resulting mixture was stirred at room temperature for 14 h. The resulting mixture was filtered through a pad of Celite, and the filter cake was washed with hot methanol (8 mL). The filtrate was concentrated under reduced pressure to provide lamellarin S as a pale gray solid (8.6 mg, 18 µmol, 98%), whose ^{1}H and ^{13}C NMR spectra (CD_3OD) were identical to those reported in the literature.[26a,26b] R$_f$ = 0.69 (chloroform/ethanol = 3:1); M.p. >250 ° C; IR (ATR, cm^{-1}): 3251, 2929, 2854, 1680, 1597, 1420, 1279, 1252, 1201, 1159, 1040; ^{1}H NMR (400 MHz, CD_3OD) δ 6.99 (d, 1H, *J* = 8.0 Hz), 6.88 (d, 1H, *J* = 1.4 Hz), 6.83 (s, 1H), 6.77 (dd, 1H, *J* = 8.0, 1.4 Hz), 6.76 (s, 1H), 6.71 (s, 1H), 6.62 (s, 1H), 4.73-4.53 (m, 2H), 3.38 (s, 3H), 3.01 (t, 2H, *J* = 6.2 Hz); ^{13}C{^{1}H} NMR (100 MHz, CD_3OD): δ 157.6, 148.1, 147.4, 147.3, 146.7, 146.6, 143.4, 138.6, 129.9, 128.7, 128.1, 123.7, 120.2, 119.1, 117.5, 116.4, 115.8, 113.8, 111.3, 110.4, 109.8, 104.2, 55.6, 43.5, 29.3; HRMS (ESI/TOF) *m*/*z*: [M + Na]$^+$ Calcd for $C_{26}H_{19}NO_8Na$ 496.1008; Found 496.1028.

4-Methoxy-3-(phenylmethoxy)-benzeneethanol (27).

A 500-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring was charged with (methoxymethyl)triphenylphosphonium chloride (14.18 g, 41.4 mmol, 1.5 equiv) and THF (140 mL). After the solution was cooled to 0 ° C, potassium *tert*-butoxide (6.184 g, 55.1 mmol, 2.0 equiv) was added potionwise over 3 min to the flask and the resulting mixture was stirred at 0 ° C for 30 min. To the solution was added 4-methoxy-3-(phenylmethoxy)-benzaldehyde (6.701 g, 27.7 mmol, 1.0 equiv) at 0 ° C. The resulting mixture was allowed to warm to room temperature with stirring over 2 h, at which time the reaction mixture was treated with saturated aqueous ammonium chloride (70 mL). The resulting mixture was extracted twice with diethyl ether (50 mL). The combined organic extracts were washed with water (70 mL) and brine (70 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was dissolved in diethyl ether (40 mL) and CH_2Cl_2 (40 mL). To the resulting solution was added hexane (300 mL), the resulting precipitate (triphenylphosphine oxide) was removed by filtration. The filtrate was concentrated under reduced pressure to give a colorless solid (13.96 g). This procedure was repeated once again to provide a crude enol ether **S16** as a colorless solid (8.94 g), which was used for the next step without further purification.

A 1-L round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was charged with the enol ether **S16**, THF (50 mL), and 6 M aqueous hydrochloric acid (50 mL). The resulting mixture was stirred at room temperature for 45 min, at which time the mixture was extracted with diethyl ether (100 mL) three times. The combined organic extracts were washed with water (100 mL) three times and brine (20 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude aldehyde **S17**, which was used for the next step without further purification.

A 500-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was charged with the crude aldehyde **S17** and methanol (50 mL). After cooling to 0 ° C, $NaBH_4$ (3.021 g, 79.9 mmol) was added potionwise to the flask at 0 ° C. The resulting mixture was allowed to warm to room temperature with stirring over 2 h. Additional $NaBH_4$ (1.496 g, 39.5 mmol) was added potionwise to the reaction mixture at 0 ° C. The resulting mixture was stirred for 17 h, at which time the reaction mixture was treated with water (80 mL) and concentrated under reduced pressure. The resulting mixture was extracted with ethyl acetate (80 mL) three times. The combined organic extracts were washed with brine (80 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/methyl acetate = 4:1 to 2:1, gradient) followed by SEC-HPLC to provide the title compound **27** as a colorless solid (2.346 g, 9.08 mmol, 33% over 3 steps), whose ^{1}H NMR spectrum was identical to that reported in the literature.[38]

TOTAL SYNTHESIS OF LAMELLARIN Z

Ethyl 3-[3-(benzyloxy)-4-methoxyphenyl]-4-bromo-1-[(2-(trimethylsilyl)ethoxy)methyl]-1*H*-pyrrole-2-carboxylate (30).

A 100-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was charged with **8** (512.5 mg, 1.20 mmol, 1.0 equiv), $Ba(OH)_2 \cdot 8H_2O$ (2.27 g, 7.18 mmol, 6.0 equiv), **29** (557.0 mg, 1.64 mmol, 1.4 equiv), $Pd_2(dba)_3 \cdot CHCl_3$ (55.2 mg, 60.3 μmol, 5 mol%), tris[4-(trifluoromethyl)phenyl]-phosphine (111.7 mg, 0.24 mmol, 20 mol%), water (2.4 mL), and 1,4-dioxane (9.6 mL). The flask was placed in a preheated oil bath and heated at 100 ° C for 15 min, at which time the solution was treated with water (10 mL). The reaction mixture was extracted with diethyl ether (10 mL) three times. The combined organic extracts were washed with water and brine, dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 10:1 to hexane/diethyl ether = 5:1, gradient) and followed by preparative SEC-HPLC to provide the title product **30** as a pale yellow oil (202.0 mg, 0.36 mmol, 30%). R_f = 0.23 (hexane/diethyl ether = 5:1); IR (ATR, cm^{-1}): 1700, 1541, 1508, 1428, 1377, 1253, 1223, 1106, 1181, 1024, 856, 745, 702; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, 2H, *J* = 7.3 Hz), 7.39-7.27 (m, 3H), 7.04 (s, 1H), 6.91 (d, 1H, *J* = 8.2 Hz), 6.88 (d, 1H, *J* = 1.8 Hz), 6.86 (dd, 1H, *J* = 8.2, 1.8 Hz), 5.64 (s, 2H), 5.15 (s, 2H), 4.00 (q, 2H, *J* = 7.1 Hz), 3.92 (s, 3H), 3.57 (t, 2H, *J* = 8.2 Hz), 0.96 (t, 3H, *J* = 7.1 Hz), 0.93 (q, 2H, *J* = 8.2 Hz), 0.00 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 160.7, 149.1, 147.3, 137.3, 132.8, 128.5, 127.8, 127.4, 126.7, 126.5, 123.5, 119.9, 116.6, 110.9, 99.4, 77.8, 71.1, 66.5, 60.1, 56.0, 17.8, 13.8, -1.4; HRMS (ESI/TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{27}H_{34}NO_5SiNa$ 584.1267; Found 584.1291.

Ethyl [3-(benzyloxy)-4-methoxyphenyl]-4-[3,4-bis(benzyloxy)phenyl]-1-[(2-(trimethylsilyl)ethoxy)methyl]-1*H*-pyrrole-2-carboxylate (31).

A 50-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was charged with **30** (110.0 mg, 0.196 mmol, 1.0 equiv), $Ba(OH)_2 \cdot 8H_2O$ (370.1 mg, 1.17 mmol, 6.0 equiv), **23** (163.7 mg, 0.393 mmol, 2.0 equiv), $Pd(PPh_3)_4$ (22.6 mg, 19.6 μmol, 10 mol%), water (0.4 mL), and 1,4-dioxane (1.6 mL). The flask was placed in a preheated oil bath and heated at 100 ° C for 15 min, at which time the solution was treated with water (2 mL). The reaction mixture was extracted with diethyl ether (3 mL) three times. The combined organic extracts were washed with water and brine, dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 5:1 to hexane/diethyl ether = 3:1) followed by preparative SEC-HPLC to provide the title product **31** as a pale yellow oil (109.5 mg, 0.142 mmol, 72%). R_f = 0.20 (hexane/diethyl ether = 3:1); IR (ATR, cm^{-1}): 2954, 1695, 1530, 1506, 1455, 1355, 1249, 1217, 1102, 1024, 859, 737, 697; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.23 (m, 15H), 7.06 (s, 1H), 6.84 (d, 1H, *J* = 8.2 Hz), 6.81 (d, 1H, *J* = 1.8 Hz), 6.78-7.75 (m, 2H), 6.64 (dd, 1H, *J* = 8.2, 2.3 Hz), 6.61 (d, 1H, *J* = 1.8 Hz), 5.69 (s, 2H), 5.10 (s, 2H), 5.01 (s, 2H), 4.77 (s, 2H), 4.01 (q, 2H, *J* = 7.2 Hz), 3.88 (s, 3H), 3.61 (t, 2H, *J* = 8.2 Hz), 0.96 (t, 3H, *J* = 7.2 Hz), 0.95 (t, 2H, *J* = 8.2 Hz), 0.00 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 161.6, 148.6, 148.5, 147.4, 147.2, 137.5, 137.3, 137.1, 131.5, 128.5, 128.44, 128.39, 127.9, 127.8, 127.72, 127.65, 127.30, 127.25, 127.1, 125.1, 124.5, 123.6, 120.6, 120.3, 116.8, 114.91, 114.88, 111.1, 77.7, 71.3, 70.92, 70.86, 66.3, 59.8, 56.0, 17.9, 13.9, -1.4; HRMS (ESI/TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{47}H_{51}NO_7SiNa$ 792.3333; Found 792.3345.

8-(Benzyloxy)-1-(3,4-bis(benzyloxy)phenyl)-7-methoxychromeno[3,4-*b*]pyrrol-4(3*H*)-one (S20).

A 10-mL screw-top test tube equipped with a Teflon-coated magnetic stirring bar was charged with compound **31** (108.5 mg, 0.141 mmol, 1.0 equiv), 18-crown-6 (74.3 mg, 0.281 mmol, 2.0 equiv), KOH (79.0 mg, 1.41 mmol, 10 equiv), and EtOH (705 μL). The test tube was placed in a preheated aluminum block and heated at reflux for 19 h, at which time the solution was treated with 1 M aqueous hydrochloric acid. The desired carboxylic acid **S18** was collected by filtration as a yellow solid (108.4 mg), which was used for the next step without further purification.

A 50-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was charged with the crude **S18** (108.4 mg) in anhydrous ethyl acetate (14 mL). To the solution was added $Pb(OAc)_4$ (93.8 mg, 0.212 mmol). The flask was placed in a preheated oil bath and heated at reflux for 20 min. After $Pb(OAc)_4$ (31.5 mg, 0.0710 mmol) was added to the solution, and the reaction mixture was heated at reflux for 15 min. Pinacol (43.2 mg, 0.366 mmol) was added to the flask, and resulting mixture was treated with water (14 mL). The reaction mixture was extracted with diethyl ether (10 mL) three times. The combined organic extracts were washed with water and brine, dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 3:1) to provide the corresponding product **S19** as a yellow solid (54.1 mg, 73.1 μmol).

A 10-mL screw-top test tube equipped with a Teflon-coated magnetic stirring bar was charged with compound **S19** (54.1 mg, 73.1 μmol, 1.0 equiv) and CH_2Cl_2 (1.8 mL). TFA (400 μL, 5.22 mmol) was added to the flask. The resulting mixture was stirred at room temperature for 15 min. After the reaction mixture was concentrated under reduced pressure, the flask was charged with anhydrous THF (585 μL), water (146 μL),

$NH_2OH\cdot HCl$ (4.7 mg, 68 μmol, 0.92 equiv), and Na_2CO_3 (23.8 mg, 0.225 mmol, 3.1 equiv). The reaction mixture was stirred at room temperature for 3 h, at which time $NH_2OH\cdot HCl$ (4.9 mg, 71 μmol, 1.0 equiv) and Na_2CO_3 (22.3 mg, 0.210 mmol, 3.0 equiv) were added to the flask. After stirring at room temperature for 4 h, the reaction mixture was treated with water (0.6 mL). The resulting mixture was extracted with ethyl acetate (1 mL) three times. The combined organic extracts were washed with water and brine, dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was washed with diethyl ether (5 mL) to provide the title compound **S20** as a pale yellow solid (36.1 mg, 59.2 μmol, 42% over 3 steps). R_f = 0.31 (hexane/CH_2Cl_2 = 100:1); IR (ATR, cm^{-1}): 3237, 1696, 1549, 1494, 1402, 1272, 1192, 1026, 736, 696; ^1H NMR (400 MHz, $CDCl_3$): δ 9.56 (br s, 1H), 7.51-7.45 (m, 4H), 7.38-7.28 (m, 6H), 7.23-7.17 (m, 3H), 7.15 (d, 1H, *J* = 2.3 Hz), 7.14 (s, 1H), 7.09-7.05 (m, 3H), 7.02 (d, 1H, *J* = 8.2 Hz), 6.97 (dd, 1H, *J* = 8.2, 1.8 Hz), 6.95 (s, 1H), 5.25 (s, 2H), 5.18 (s, 2H), 4.82 (s, 2H), 3.92 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 156.5, 149.8, 149.2, 148.7, 146.3, 144.6, 137.3, 137.1, 136.4, 128.71, 128.68, 128.5, 128.1, 128.0, 127.9, 127.6, 127.5, 127.40, 127.35, 126.7, 123.0, 121.4, 116.7, 116.5, 115.0, 110.5, 107.4, 101.2, 71.50, 71.46, 70.7, 56.3 (one aromatic carbon signal is missing due to overlapping); HRMS (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{39}H_{31}NO_6Na$ 632.2049; Found 632.2035.

8-(Benzyloxy)-3-[3-(benzyloxy)-4-methoxyphenethyl]-1-[3,4-bis(benzyloxy)phenyl]-7-methoxychromeno[3,4-*b*]pyrrol-4(3*H*)-one (32).

A 10-mL screw-top test tube equipped with a Teflon-coated magnetic stirring bar was charged with compound **S20** (38.3 mg, 62.8 μmol, 1.0 equiv), 3-benzyloxy-4-methoxybenzeneethanol (**27**) (24.3 mg, 94.2 μmol, 1.5 equiv), and PPh_3 (49.3 mg, 0.188 mmol, 3.0 equiv). After the flask was evacuated and backfilled with N_2, anhydrous THF (320 μL) and DIAD (1.9 M, 100 μL, 0.19 mmol, 3.0 equiv) were added to the flask. The solution was stirred at room temperature for 15 min, the resulting mixture was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/CH_2Cl_2 = 1:3 to CH_2Cl_2, gradient). The amorphous was washed twice with methanol (1 mL) to provide the title compound **32** as a white amorphous (46.0 mg, 54.1 μmol, 86%). R_f = 0.21 (hexane/CH_2Cl_2 = 1:3); IR (ATR, cm^{-1}): 1707, 1513, 1455, 1419, 1260, 1235, 1137, 1025, 739, 697; ^1H NMR (400 MHz, $CDCl_3$): δ 7.47-7.43 (m, 4H), 7.37-7.28 (m 6H), 7.25-7.16 (m, 7H), 7.10 (s, 1H), 7.08-7.04 (m, 2H), 6.97 (d, 1H, *J* = 8.2 Hz), 6.94 (s, 1H), 6.91 (d, 1H, *J* = 2.3 Hz), 6.83 (dd, 1H, *J* = 8.2, 1.8 Hz), 6.79 (d, 1H, *J* = 8.2 Hz), 6.67 (dd, 1H, *J* = 8.2, 1.8 Hz), 6.51 (d, 1H, *J* = 1.8 Hz), 6.49 (s, 1H), 5.22 (s, 2H), 5.10 (s, 2H), 4.95 (s, 2H), 4.78 (s, 2H), 4.54 (t, 2H, *J* = 6.8 Hz), 3.92 (s, 3H), 3.81 (s, 3H), 3.02 (t, 2H, *J* = 6.8 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 155.5, 149.7, 149.1, 148.54, 148.51, 148.1, 146.5, 144.3, 137.3, 137.1, 137.0, 136.4, 132.2, 130.5, 128.7, 128.6, 128.54, 128.46, 128.02, 127.99, 127.9, 127.8, 127.6, 127.35, 127.31, 127.1, 122.9, 121.6, 118.9, 116.5, 115.0, 114.8, 112.0, 110.4, 107.3, 101.0, 71.5, 71.3, 70.9, 70.6, 56.3, 56.1, 51.1, 37.6 (four aromatic carbon signals are missing due to overlapping); HRMS (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{55}H_{47}NO_8Na$ 872.3229; Found 872.3199.

Lamellarin Z.

A 25-mL two-necked pear-shaped flask equipped with a Teflon-coated magnetic stirring bar was charged with compound **32** (45.0 mg, 52.9 μmol, 1.0 equiv) and anhydrous CH_2Cl_2 (4.4 mL). After the resulting solution was cooled to −40 °C, a solution of PIFA (26.5 mg, 61.6 μmol, 1.2 equiv) and $BF_3\cdot OEt_2$ (17 μL, 0.14 mmol, 2.6 equiv) in anhydrous CH_2Cl_2 (0.9 mL) was added dropwise to the flask. The reaction mixture was stirred at −40 °C for 1.5 h, at which time the resulting mixture was treated with 2 M aqueous NH_3 (5 mL). The mixture was extracted with CH_2Cl_2 (5 mL) three times. The combined organic extracts were washed with water and brine, dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was washed with diethyl ether (6 mL) to provide the corresponding product **S21** as a colorless solid (36.9 mg).

A 25-mL two-necked pear-shaped flask equipped with a Teflon-coated magnetic stirring bar was charged with compound **S21** (36.1 mg, 42.6 μmol, 1.0 equiv), Pd/C (35.8 mg, 100 wt%), EtOH (0.7 mL), and ethyl acetate (0.7 mL). After the flask was evacuated and backfilled with H_2 three times, the resulting mixture was stirred at room temperature for 17 h, at which time the resulting mixture was filtered through a pad of Celite with hot methanol (15 mL) followed by DMSO (3 mL). The filtrate was concentrated under reduced pressure to provide lamellarin Z as a gray solid (20.7 mg, 42.5 μmol, 80% over 2 steps), whose ^1H and ^{13}C NMR spectra (DMSO-d_6) were identical to those reported in the literature.[27] R_f = 0.43 (CH_2Cl_2/methanol = 10:1); M.p. >250 °C; IR (ATR, cm^{-1}): 3410, 1684, 1587, 1488, 1425, 1276, 1245, 1206, 1158, 1041, 1024, 870, 761; ^1H NMR (400 MHz, DMSO-d_6) δ 9.41 (s, 1H), 9.19 (s, 1H), 9.14 (s, 1H), 8.98 (s, 1H), 7.00 (s, 1H), 6.94 (d, 1H, *J* = 7.8 Hz), 6.76 (s, 1H), 6.73 (s, 1H), 6.71-6.67 (m, 2H), 6.54 (s, 1H), 4.72-4.63 (m, 1H), 4.55-4.46 (m, 1H), 3.81 (s, 3H), 3.28 (s, 3H), 3.04-2.93 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ 154.5, 147.9, 147.0, 146.2, 146.0, 145.4, 144.7, 142.8, 136.1, 127.2, 127.0, 125.5, 121.6, 118.2, 117.8, 116.7, 115.3, 114.8, 112.5, 110.3, 109.3, 108.4, 100.7, 55.9, 54.7, 42.0, 27.6; HRMS (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{27}H_{21}NO_8Na$ 510.1165; Found 510.1165.

2-Benzyloxy-4-bromo-1-methoxybenzene (S22).

A 100-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was charged with 5-bromo-2-methoxy-phenol (3.05 g, 15.0 mmol, 1.0 equiv), K_2CO_3 (4.15 g, 30.0 mmol, 2.0 equiv), benzyl bromide (2.57 g, 15.0 mmol, 1.0 equiv), and acetonitrile (15 mL). The flask was placed in a preheated oil bath and heated at reflux for 4 h. After cooling to room temperature, the resulting mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to give the title product **S22** as a colorless solid (4.35 g, 14.8 mmol, 99%), whose ^1H and ^{13}C NMR spectra were identical to those reported in the literature.[39]

2-[3-(Benzyloxy)-4-methoxyphenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (29).

A flame-dried 100-mL two-necked round-bottomed flask equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with 2-benzyloxy-4-bromo-1-methoxybenzene (**S22**) (880.2 mg, 3.00 mmol, 1.0 equiv) and anhydrous THF (15 mL). After the solution was cooled to −78 °C, the reaction mixture was treated with *n*-BuLi (1.59 M in *n*-hexane, 1.9 mL, 3.0 mmol, 1.0 equiv) and stirred at −78 °C for 5 min. To the solution was added *i*-PrOBpin (658.3

mg, 3.54 mmol, 1.2 equiv) at -78 °C. After stirring at -78 °C for 10 min, the reaction mixture was allowed to warm to room temperature with stirring over 1 h, at which time the reaction mixture was treated with saturated aqueous ammonium chloride (15 mL). The reaction mixture was extracted with diethyl ether (15 mL) three times. The combined organic extracts were washed with water and brine, dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/CH_2Cl_2 = 1:1 to hexane/diethyl ether = 10:1, gradient) to provide the title product **29** as a colorless solid (795.6 mg, 2.34 mmol, 78%). R_f = 0.21 (hexane/CH_2Cl_2 = 1:1); M.p. 112-113 °C; IR (ATR, cm^{-1}): 2978, 1600, 1416, 1372, 1352, 1295, 1257, 1219, 1137, 1026, 966, 855, 737, 698, 685; ^1H NMR (400 MHz, $CDCl_3$): δ 7.51-7.28 (m, 7H), 6.91 (d, 1H, J = 8.2 Hz), 5.15 (s, 2H), 3.89 (s, 3H), 1.33 (s, 12H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 152.4, 147.8, 137.2, 129.1, 128.5, 127.8, 127.6, 120.8, 119.3, 111.1, 83.6, 70.9, 55.8, 24.9; HRMS (DART/TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{26}BO_4$ 341.1924; Found 341.1909.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.xxxxxxx. Tabular comparisons of NMR data with the natural products and copies of ^1H and ^{13}C NMR spectra for all new compounds (PDF).

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Notes

The authors declare no competing financial interest.

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(14) Instead of the ester group, an oxazoline was also an effective substituent on the pyrrole for the halogen dance, to provide the corresponding β,β'-dibromopyrrole. However, introduction of the aryl groups did not proceed smoothly.

(15) The desired compound **8** was not obtained at -40 ° C or 0 ° C. Prolonged reaction time (1 h) resulted in significant reduction in the yield of compound **8** (<10% yield).

(16) The regioselectivity was determined by further transformation of the ethyl ester to its lactone. The chemical shift of the methylene protons of the ethyl ester was shifted to 4.0 ppm from 4.3 ppm (the methylene protons of the ethyl ester of compound **8**), indicating that the installed aryl group shielded the methylene protons.

(17) Handy reported Suzuki-Miyaura cross coupling of a quite similar β,β'-dibromopyrrole; however, they obtained almost equimolar amounts of the monoarylated pyrrole and the diarylated pyrrole, even with substoichiometric amount (0.6 equiv to the β,β'-dibromopyrrole) of an arylboronic acid, see: (a) Handy, S. T.; Zhang, Y. Regioselective couplings of dibromopyrrole esters. *Synthesis* **2006**, 3883-3887. α-Selective Suzuki-Miyaura coupling of α,β-dibromopyrroles, see: (b) Handy, S. T.; Sabatini, J. J. Regioselective dicouplings: application to differentially substituted pyrroles. *Org. Lett.* **2006**, *8*, 1537-1539. (c) Zhang, Y.; Handy, S. T. A solvent-induced reversal of regioselectivity in the Suzuki coupling of pyrrole esters. *Open Org. Chem. J.* **2008**, *2*, 58-64. For recent reviews, see: (d) Rossi, R.; Bellina, F.; Lessi, M. Selective palladium-catalyzed Suzuki-Miyaura reactions of polyhalogenated heteroarenes. *Adv. Synth. Catal.* **2012**, *354*, 1181-1255. (e) Fairlamb, I. J. S. Regioselective (site-selective) functionalisation of unsaturated halogenated nitrogen, oxygen and sulfur heterocycles by Pd-catalysed cross-couplings and direct arylation processes. *Chem. Soc. Rev.* **2007**, *36*, 1036-1045. (f) Banwell, M. G.; Goodwin, T. E.; Ng, S.; Smith, J. A.; Wong, D. J. Palladium-catalysed cross-coupling and related reactions involving pyrroles. *Eur. J. Org. Chem.* **2006**, 3043-3060.

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