# Synthesis of Lamellarin D Trimethyl Ether and Lamellarin H via 6π-Electrocyclization
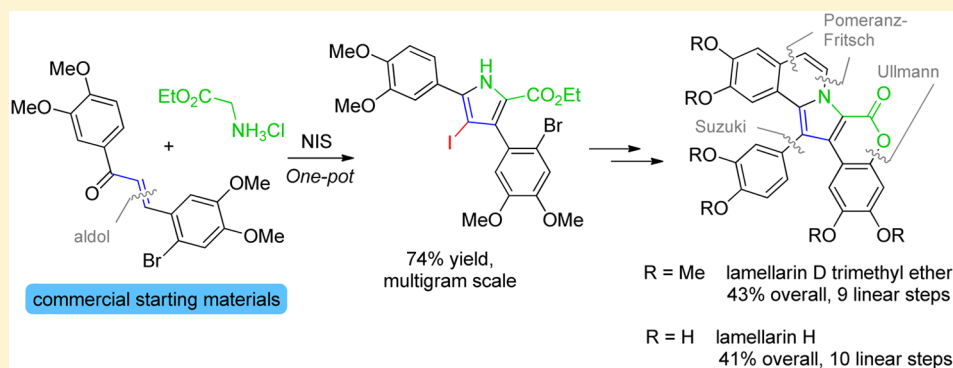
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**S** *Supporting Information*

**ABSTRACT:** An electrocyclic ring closure of a 2-azapentadienyl anion generated in situ from a chalcone and glycine ester is the key step of an efficient synthesis of the pyrrole core of the lamellarin alkaloids. A recently developed scalable one-pot procedure provides multigram quantities of a 3,5-diaryl-4-iodopyrrole-2-carboxylate intermediate which is transformed in four further high-yielding operations including a one-pot Pomeranz–Fritsch alkylation/cyclization and an Ullmann-type lactone ring closure into the pentacyclic lamellarin skeleton.

The lamellarins are a large group of polycyclic marine pyrrole alkaloids highly renowned for their potent cytotoxic activity against a variety of human cancer cell lines.[1−9] On the basis of their molecular skeletons, the lamellarins are commonly subdivided into three groups. A pentacyclic framework of the 6H-chromeno[4′,3′:4,5]pyrrolo-[2,1-a]isoquinolin-6-one type is characteristic for the type 1a (partially saturated) and 1b (fully unsaturated) lamellarins, while the less abundant and structurally simpler type 2 lamellarins contain an unfused 3,4-diarylpyrrole core (Figure 1).[2,3,7,10,11]

Class 1b comprises the representatives with the most potent biological activities such as lamellarin D,[1,6,8,12−15] for which a multidrug resistance reversal activity and a strong proapoptotic effect through the inhibition of human topoisomerase I has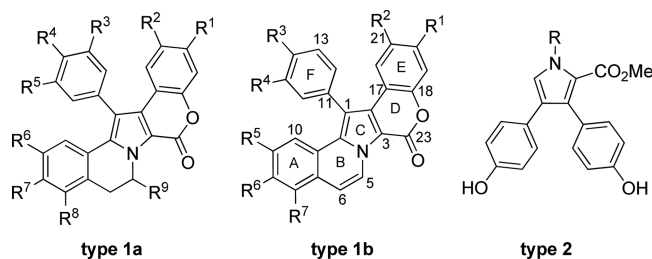 been reported.[4,15,16] The bioactivity correlates with the planarity of the ABCDE-ring system which is ensured by the 5,6-double bond.[2]

Since their discovery in 1985 by Faulkner,[17] more than 50 lamellarins have been isolated, mainly from prosobranch molluscs of the genus *Lamellaria*.[3] Their attractive structure has made them the target of diverse synthetic approaches[18−24] which were reviewed in 2014.[25] Here, we report on the application of a recently developed one-pot synthesis of 3,5-diaryl-4-halopyrrole-2-carboxylates and its extension to a fully modular access to the type 1b lamellarins.

Pyrrole-2-carboxylates represent useful intermediates in the synthesis of more complex heterocyclic systems and are the core structure of all existing lamellarins. In 2014, we reported a facile method for their preparation by means of a cyclo-condensation of enones **A** with glycine esters via the 6π-electrocyclization of intermediate 2-azapentadienyl anions **C** followed by dehydrogenation (Scheme 1).[26]

If chalcones are employed as the electrophilic component, 3,5-diarylpyrrole-2-carboxylates **E** are obtained and the unsubstituted 4-position in the products can be halogenated in situ. Introduction of the third aryl moiety (ring F) to the pyrrole core in a Suzuki coupling allows the completion of the ring system of the type 1b lamellarins in only three additional operations. The annellation of the B-ring can be achieved in a



**Figure 1.** Structure of lamellarins type 1a, 1b, and 2.

**Scheme 1. Three-Step Synthesis of Halopyrrole F**
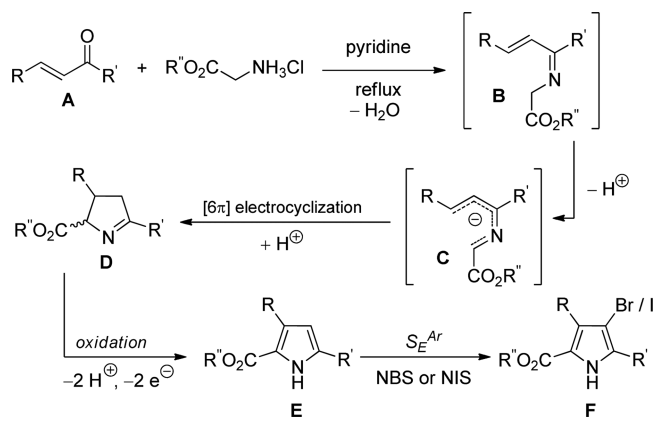


two-step Pomeranz–Fritsch-type cyclization sequence through prior N-alkylation with bromoacetaldehyde dimethyl acetal and subsequent electrophilic closure of the 6,6a-bond under acidic conditions.[27] Finally, the lactone ring D can be closed in a one-pot operation involving the saponification of the ester to the carboxylate salt followed by a Cu-mediated Ullmann-type ring closure onto a preinstalled bromide (position 18, Figure 1). The latter reaction had been successfully employed by Ruchirawat in their synthesis of iso-[28] and azalamellarins[29] as well as by us in a high-yielding lamellarin synthesis based on α-aminonitrile chemistry.[30] It requires stoichiometric amounts of copper(I) due to the poor nucleophilicity of the carboxylate. The retrosynthetic strategy is depicted in Scheme 2.

**Scheme 2. Retrosynthetic Approach**
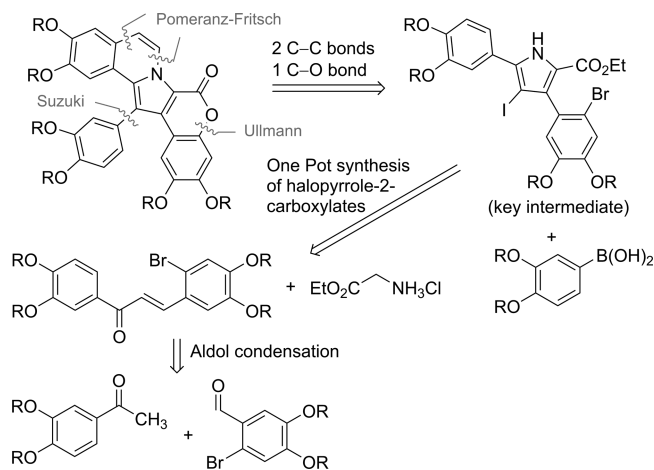


To the best of our knowledge, intermediate **6** carries a substitution pattern hitherto unexploited for lamellarin synthesis.[25] It allows the amalgamation of Banwell's and Handy's iterative cross-coupling concept for the decoration of the pyrrole moiety with Iwao's intramolecular TfOH-mediated cyclization strategy for the unsaturated B-ring and turned out to provide high yields and operational simplicity.[10,24,27,31−34]

The synthesis started with commercial 6-bromoveratraldehyde (**2**), which can alternatively be obtained by bromination of veratraldehyde (**1**) with elemental bromine in 92% yield (Scheme 3).[35]

The subsequent aldol condensation with commercial acetoveratrone (**3**) was accomplished under basic conditions (NaOH) in 78% yield.[36,37] In the key step, enone **4** was reacted

with glycine ethyl ester hydrochloride (**5**) in refluxing pyridine followed by oxidation of the in situ formed $\Delta^1$-pyrroline with stoichiometric amounts of copper(II) acetate and regioselective iodination of the resulting pyrrole with N-iodosuccinimide. Thus, iodopyrrole **6** could be obtained in 39% yield (gram scale) in a one-pot, three-step reaction sequence. However, changing the order and timing of reactant addition permitted a significant improvement. Addition of a pyridine solution of enone **4** to a refluxing solution of glycine ester **5** in pyridine afforded iodopyrrole **6** in 74% yield. A low initial concentration of the glycine ester proved beneficial as concentrated solutions readily form self-condensation products upon heating as judged by HPLC/MS or TLC.
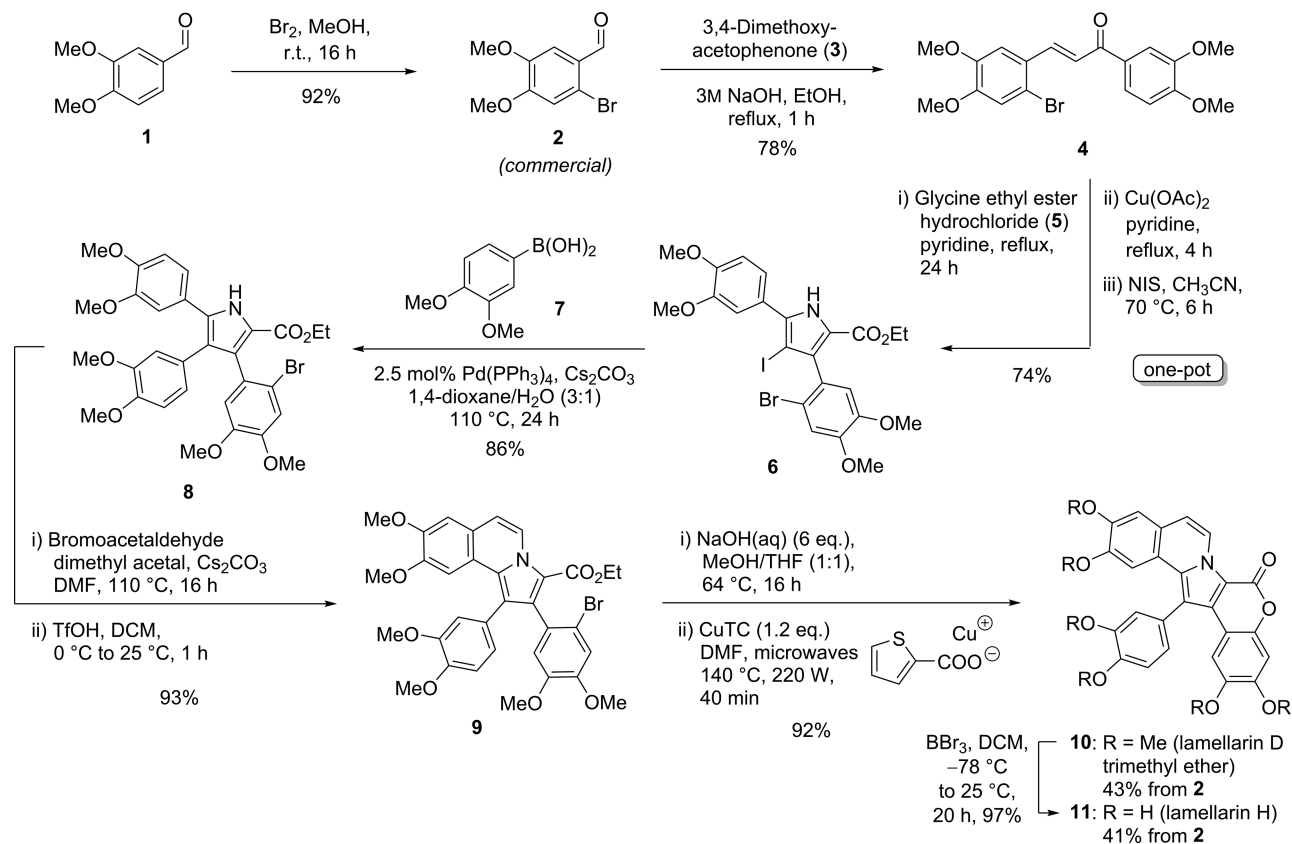
Introduction of the F ring moiety was accomplished by Suzuki−Miyaura cross-coupling with commercial 3,4-dimethoxyphenylboronic acid (**7**). While numerous closely related reactions have been reported,[27,32,34] none of these was designed to tolerate a potentially competing second halide, i.e., the bromine required for the lactone ring closure. Solvent, base, and catalyst screening revealed that intermediate **6** should be reacted with only a slight excess (1.05 equiv) of boronic acid **7** in the presence of $Cs_2CO_3$ and a catalytic amount of $Pd(PPh_3)_4$ under inert atmosphere in a degassed mixture of 1,4-dioxane/$H_2O$ at 100−110 °C for at least 12 h. Under optimized conditions, the cross-coupling furnished intermediate **8** in high yield (86%), which was subsequently N-alkylated with bromoacetaldehyde dimethyl acetal in DMF at 110 °C within 16 h. For analytical characterization, the N-alkylated intermediate was purified by column chromatography, but otherwise, the crude product was directly transformed into isoquinoline **9** in a TfOH-mediated[38] intramolecular cyclization in 93% yield from pyrrole **8**.[27] Treatment of **9** with copper(I) thiophene-2-carboxylate (CuTC) under microwave irradiation without prior hydrolysis of the ester failed as expected, and the dealkoxycarbonylated pyrrole was detected by HPLC/MS instead. For the saponification, it appeared to be important to use a minimum amount of a THF/MeOH (1:1) mixture with aqueous 3 M NaOH (6 equiv) in order to avoid trans-esterification to the methyl ester. Cyclization of the crude sodium carboxylate with CuTC (1.2 equiv) in DMF under microwave irradiation furnished lamellarin D trimethyl ether (**10**) in 92% yield from ester **9**. Its complete O-demethylation with $BBr_3$ furnished lamellarin H (**11**) in 97% yield.

In summary, a very high yielding and fully modular strategy for the synthesis of the type 1b lamellarins with an early diversification of the pyrrole core has been devised. Its key steps are an electrocyclic ring closure of an in situ formed 2-azapentadienyl anion and an Ullmann-like lactone formation. Starting from commercially available 6-bromoveratraldehyde (**2**), the trimethyl ether analogue of the highly bioactive lamellarin D could be prepared in 43% yield over nine linear steps, combined into six discrete transformations. In addition, the alkaloid lamellarin H was obtained in 41% yield over 10 linear steps. This corresponds to an average per step efficiency of 91% in both cases and compares nicely with the most efficient syntheses of the class 1b lamellarins reported so far.[25]

■ **EXPERIMENTAL SECTION**

**General Methods.** All reactions involving air- or moisture-sensitive reagents or intermediates were performed under an inert atmosphere of argon in glassware that was oven-dried. Reaction temperatures refer to the temperature of the particular cooling/heating bath. Microwave-assisted reactions were carried out in a monomode

**Scheme 3. Synthetic Route to Lamellarin D Trimethyl Ether and Lamellarin H**

Br$_2$, MeOH, r.t., 16 h — 92%

3,4-Dimethoxy-acetophenone (**3**) — 3M NaOH, EtOH, reflux, 1 h — 78%

**1** → **2** (commercial) → **4**

i) Glycine ethyl ester hydrochloride (**5**) pyridine, reflux, 24 h
ii) Cu(OAc)$_2$ pyridine, reflux, 4 h
iii) NIS, CH$_3$CN, 70 °C, 6 h — one-pot — 74%

**6**

**7** B(OH)$_2$ — 2.5 mol% Pd(PPh$_3$)$_4$, Cs$_2$CO$_3$ 1,4-dioxane/H$_2$O (3:1) 110 °C, 24 h — 86%

**8**

i) Bromoacetaldehyde dimethyl acetal, Cs$_2$CO$_3$ DMF, 110 °C, 16 h
ii) TfOH, DCM, 0 °C to 25 °C, 1 h — 93%

**9**

i) NaOH(aq) (6 eq.), MeOH/THF (1:1), 64 °C, 16 h
ii) CuTC (1.2 eq.) DMF, microwaves 140 °C, 220 W, 40 min — 92%

BBr$_3$, DCM, −78 °C to 25 °C, 20 h, 97%

**10**: R = Me (lamellarin D trimethyl ether) 43% from **2**
**11**: R = H (lamellarin H) 41% from **2**

microwave apparatus using the built-in external infrared sensor for temperature monitoring. All reagents were reagent grade and were used without further purification unless otherwise noted. Pyridine (99+%, extra dry) and DMF (99+%, extra dry) were purchased from commercial suppliers and were used without further purification. Copper(I) thiophene-2-carboxylate (CuTC) was synthesized according to the procedure of Liebeskind et al.[39] Melting points were determined in open capillary tubes using an electronic apparatus with a resolution of 0.1 °C. NMR spectra were recorded on a 300 or 400 MHz spectrometer equipped with a 5 mm BBFO probehead with z-gradient and ATM capability. Chemical shifts were referenced to the deuterated solvent (for CDCl$_3$, $\delta$ = 7.26 and 77.16 ppm, for DMSO-$d_6$, $\delta$ = 2.50 and 39.52 ppm, for CD$_3$OD, $\delta$ = 3.31 and 49.00 ppm, and for pyridine-$d_5$ $\delta$ = 8.74 and 150.35 ppm for $^1$H and $^{13}$C NMR, respectively) and reported in parts per million (ppm, $\delta$) relative to tetramethylsilane (TMS, $\delta$ = 0.00 ppm).[40] Coupling constants ($J$) are reported in hertz, and the splitting abbreviations used were as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Standard pulse sequences were used for the 2D experiments. Infrared spectra were recorded as FT-IR spectra using a diamond ATR unit and are reported in terms of frequency of absorption ($\nu$, cm$^{-1}$). High-resolution masses were recorded on a QToF-Instrument with a dual electrospray source and a suitable external calibrant. Thin-layer chromatography (TLC) was carried out on 0.25 mm silica gel plates (60F$_{254}$) using UV light as visualizing agent, an ethanolic solution of hydrochloric acid and 4-(dimethylamino)benzaldehyde (Ehrlich's reagent) or an ethanolic solution of diluted aqueous hydrochloric acid and 2,4-dinitrophenylhydrazine (DNPH reagent), and heat as developing agent. Chromatography was performed using flash chromatography of the indicated solvent system on 35−70 $\mu$m silica gel unless otherwise indicated.

*2-Bromo-4,5-dimethoxybenzaldehyde (2).* To a solution of veratraldehyde (15.00 g, 90.26 mmol, 1.00 equiv) in MeOH (675 mL) was added dropwise Br$_2$ (4.86 mL, 94.78 mmol, 1.05 equiv) during 15 min at room temperature with subsequent stirring overnight.

The reaction mixture was quenched with a saturated aqueous solution of Na$_2$S$_2$O$_3$ (300 mL), the contained MeOH was evaporated in vacuo, and the aqueous residue was extracted with CH$_2$Cl$_2$ (3 × 200 mL). The organic layer was washed with brine (500 mL), dried over anhydrous Na$_2$SO$_4$, and concentrated in vacuo. The crude product was recrystallized from 2-propanol to afford the title compound as colorless needles (20.31 g, 92%): $R_f$ = 0.51 (silica gel, cyclohexane/ethyl acetate = 2:1); mp 148.5−149.5 °C (lit.[30] mp 144−145 °C); IR (ATR) $\nu$ (cm$^{-1}$) = 3009, 1667, 1585, 1503, 1398, 1269, 1154, 1015, 866, 737; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 10.18 (s, 1H, C*H*O), 7.41 (s, 1H, H-6), 7.05 (s, 1H, H-3), 3.96 (s, 3H, OC*H*$_3$), 3.92 (s, 3H, OC*H*$_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ (ppm) = 190.9 (*C*=O), 154.6 (C4), 149.0 (C5), 126.7 (C1), 120.6 (C2), 115.6 (C3), 110.6 (C6), 56.7 (OCH$_3$), 56.3 (OCH$_3$); ESI-HRMS calcd for [C$_9$H$_9$($^{79}$Br)O$_3$ + H]$^+$ 244.9813, found 244.9824. The data are in accordance with the literature.[30,35]

*3-(2-Bromo-4,5-dimetohxyphenyl)-1-(3,4-dimethoxyphenyl)-propen-1-one (4).* 6-Bromoveratraldehyde (**2**) (5.00 g, 20.40 mmol, 1.00 equiv) and acetoveratrone (**3**) (6.25 g, 34.68 mmol, 1.70 equiv) were suspended in EtOH (155 mL) and heated to reflux to form a clear solution. The addition of 3 N aqueous NaOH (7.89 mL, 23.67 mmol, 1.16 equiv) effected the formation of a yellow precipitate a few minutes later. The reaction mixture was stirred under reflux for 1 h followed by suction filtration and washing with EtOH (2 × 10 mL). The residue was dissolved in DCM, dried over anhydrous Na$_2$SO$_4$, filtered, and finally concentrated to dryness in vacuo to yield the title compound as an intensely yellow amorphous solid (6.48 g, 78%): $R_f$ = 0.27 (silica gel, cyclohexane/ethyl acetate = 2:1); mp 166.5−167.4 °C (lit.[37] 166−167 °C); IR (ATR) $\nu$ (cm$^{-1}$) = 3012, 2840, 1652, 1593, 1501, 1256, 1159, 1021, 832, 749; $^1$H NMR, COSY, NOESY (400 MHz, CDCl$_3$) $\delta$ (ppm) = 8.03 (d, $J$ = 15.6 Hz, 1H, H-3), 7.65 (dd, $J$ = 8.4, 2.0 Hz, 1H, H-6'), 7.59 (d, $J$ = 2.0 Hz, 1H, H-2'), 7.29 (d, $J$ = 15.6 Hz, 1H, H-2), 7.18 (s, 1H, H-6''), 7.06 (s, 1H, H-3''), 6.92 (d, $J$ = 8.4 Hz, 1H, H-5'), 3.96 (s, 3H, OCH$_3$-4'), 3.95 (s, 3H, OCH$_3$-3'), 3.94 (s, 3H, OCH$_3$-5''), 3.90 (s, 3H, OCH$_3$-4''); $^{13}$C NMR (100.6 MHz,

CDCl$_3$) $\delta$ (ppm) = 189.0 (C1), 153.3 (C4′), 151.5 (C4″), 149.3 (C3′), 148.7 (C5″), 142.6 (C3), 131.3 (C1′), 127.2 (C1″), 123.2 (C6′), 122.9 (C2), 117.9 (C2″), 115.8 (C3″), 111.0 (C2′), 110.0 (C5′), 109.6 (C6″), 56.4 (OCH$_3$), 56.3 (OCH$_3$), 56.20 (OCH$_3$), 56.16 (OCH$_3$); ESI-HRMS calcd for [C$_{19}$H$_{19}$($^{79}$Br)O$_5$ + H]$^+$ 407.0494, found 407.0488. The data are in accordance with the literature.[26,37]

*Ethyl 3-(2-Bromo-4,5-dimethoxyphenyl)-5-(3,4-dimethoxyphenyl)-4-iodo-1H-pyrrole-2-carboxylate (6).* Glycine ethyl ester hydrochloride (5) (1.18 g, 8.47 mmol, 1.15 equiv) was placed in a two-necked round-bottom flask equipped with a reflux condenser, and pyridine (60 mL) was added. The suspension was heated to reflux, and a solution of enone 4 (3.00 g, 7.37 mmol, 1.00 equiv) in pyridine (90 mL) was added dropwise to the clear and colorless refluxing solution. Stirring and reflux were maintained for at least 24 h, and then a solution of copper(II) acetate (2.68 g, 14.73 mmol, 2.00 equiv) in pyridine (115 mL) was added continuously within 15 min to the refluxing brown solution. After 4 h, the temperature of the oil bath was lowered to 70 °C and a solution of N-iodosuccinimide (2.07 g, 9.21 mmol, 1.25 equiv) in acetonitrile (75 mL) was added continuously within 15 min. The reaction mixture was kept at 70 °C for an additional 6 h and then concentrated in vacuo. The residual pyridine was removed by azeotropic distillation with toluene (2 × 100 mL). Further purification was conducted by flash column chromatography (silica gel, cyclohexane/ethyl acetate = 3:1) to afford the title compound as a light yellow to colorless crystalline solid (3.35 g, 74%): $R_f$ = 0.61 (silica gel, cyclohexane/ethyl acetate = 1:1); mp 197.3−199.6 °C; IR (ATR) $\nu$ (cm$^{-1}$) = 3280, 2936, 2838, 1671, 1506, 1432, 1250, 1208, 1178, 1025, 730; $^1$H NMR, COSY, NOESY (400 MHz, CDCl$_3$) $\delta$ (ppm) = 9.56 (br s, 1H, NH), 7.32 (d, $J$ = 2.1 Hz, 1H, H-2″), 7.25 (dd, $^3J$ = 8.4 Hz, $^4J$ = 2.1 Hz, 1H, H-6″), 7.13 (s, 1H, H-3′), 6.96 (d, $J$ = 8.4 Hz, 1H, H-5″), 6.77 (s, 1H, H-6′), 4.18−4.04 (m, 2H, OCH$_2$CH$_3$), 3.96 (s, 3H, OCH$_3$-3″), 3.933 (s, 3H, OCH$_3$-4″), 3.925 (s, 3H, OCH$_3$-4′), 3.87 (s, 3H, OCH$_3$-5′), 1.07 (t, $J$ = 7.1 Hz, 3H, OCH$_2$CH$_3$); $^{13}$C NMR, HSQC, HMBC (100.6 MHz, CDCl$_3$) $\delta$ (ppm) = 160.5 (C=O), 149.6 (C4″), 149.1 (C4′), 149.0 (C3″), 147.9 (C5′), 136.4 (C5), 135.1 (C3), 129.2 (C1′), 124.1 (C1″), 121.0 (C2), 120.8 (C6″), 115.1 (C2′), 115.0 (C3′), 114.6 (C6′), 111.6 (C2″), 111.3 (C5″), 69.7 (C4), 60.7 (OCH$_2$CH$_3$), 56.3 (OCH$_3$), 56.25 (OCH$_3$), 56.23 (OCH$_3$), 56.1 (OCH$_3$), 14.1 (OCH$_2$CH$_3$); ESI-HRMS calcd for [C$_{23}$H$_{23}$($^{79}$Br)INO$_6$ + Na]$^+$ 637.9651, found 637.9657.

*Ethyl 3-(2-Bromo-4,5-dimethoxyphenyl)-4,5-bis(3,4-dimethoxyphenyl)-1H-pyrrole-2-carboxylate (8).* Iodopyrrole 6 (1.00 g, 1.62 mmol, 1.00 equiv), 3,4-dimethoxyphenylboronic acid (7) (0.31 g, 1.70 mmol, 1.05 equiv), Cs$_2$CO$_3$ (1.06 g, 3.25 mmol, 2.00 equiv), and Pd(PPh$_3$)$_4$ (47 mg, 2.5 mol %) were placed in an oven-dried Schlenk tube, and the mixture was dissolved in a degassed 1,4-dioxane/water mixture (3:1, 38 mL). Alternatively, Pd(PPh$_3$)$_4$ may be introduced after addition of the solvent mixture, which is then degassed prior to catalyst addition. After being purged with argon, the tube was sealed and heated to 110 °C during a period of 24 h. The solvent was removed in vacuo by azeotropic distillation with toluene (2 × 25 mL). Purification by flash column chromatography (silica gel, cyclohexane/ethyl acetate = 3:1) yielded the title compound (0.87 g, 86%) as colorless crystals: $R_f$ = 0.44 (silica gel, cyclohexane/ethyl acetate = 1:1); mp 155.2−157.0 °C; IR (ATR) $\nu$ (cm$^{-1}$) = 3307, 2937, 1667, 1507, 1432, 1251, 1026, 914, 861, 730; $^1$H NMR, COSY, NOESY (400 MHz, CDCl$_3$) $\delta$ (ppm) = 9.22 (br s, 1H, NH), 7.02 (s, 1H, H-3′), 6.97 (dd, $^3J$ = 8.4 Hz, $^4J$ = 2.1 Hz, 1H, H-6‴), 6.83 (d, $J$ = 8.4 Hz, 1H, H-5‴), 6.82 (d, $J$ = 2.1 Hz, 1H, H-2‴), 6.66 (d, $J$ = 8.9 Hz, 1H, H-5″), 6.62 (d, $J$ = 1.8 Hz, 1H, H-2″), 6.62 (s, 1H, H-6′), 6.62 (dd, $^3J$ = 8.9 Hz, $^4J$ = 1.8 Hz, 1H, H-6″), 4.25−4.09 (m, 2H, OCH$_2$CH$_3$), 3.88 (s, 3H, OCH$_3$-4‴), 3.86 (s, 3H, OCH$_3$-4′), 3.80 (s, 3H, OCH$_3$-4″), 3.67 (s, 3H, OCH$_3$-5′), 3.63 (s, 3H, OCH$_3$-3‴), 3.58 (s, 3H, OCH$_3$-3″), 1.11 (t, $J$ = 7.1 Hz, 3H, OCH$_2$CH$_3$); $^{13}$C NMR, HSQC, HMBC (100.6 MHz, CDCl$_3$) $\delta$ (ppm) = 161.3 (C=O), 148.9 (2C, C3‴, C4‴), 148.6 (C4′), 148.4 (C3″), 147.7 (C5′), 147.5 (C4′), 132.3 (C5), 130.5 (C3), 128.7 (C1′), 127.1 (C1″), 124.5 (C1‴), 123.6 (C4), 122.8 (C6′), 119.8 (C6‴), 119.4 (C2), 115.7 (C2′), 114.8

(C3′), 114.7 (C6′), 113.8 (C2″), 111.3 (C5‴), 111.1 (C2‴), 110.8 (C5″), 60.4 (OCH$_2$CH$_3$), 56.2 (OCH$_3$-4′), 56.1 (OCH$_3$-4‴), 56.0 (OCH$_3$-5′), 55.83 (OCH$_3$-4″), 55.81 (OCH$_3$-3‴), 55.7 (OCH$_3$-3″), 14.3 (OCH$_2$CH$_3$); ESI-HRMS calcd for [C$_{31}$H$_{32}$($^{79}$Br)NO$_8$ + Na]$^+$ 648.1209, found 648.1215.

*Ethyl 2-(2-Bromo-4,5-dimethoxyphenyl)-1-(3,4-dimethoxyphenyl)-8,9-dimethoxypyrrolo[2,1-a]isoquinoline-3-carboxylate (9).* Pyrrole 8 (1.00 g, 1.60 mmol, 1.00 equiv) and Cs$_2$CO$_3$ (3.12 g, 9.58 mmol, 6.00 equiv) were placed in an oven-dried Schlenk vessel and dissolved in dry DMF (17 mL). Bromoacetaldehyde dimethyl acetal (1.13 mL, 1.62 mmol, 6.00 equiv) was added to the mixture via syringe in one portion, followed by sealing the vessel and heating the reaction mixture to 110 °C for 16 h. Complete conversion was confirmed by HPLC/MS or TLC before the mixture was allowed to reach room temperature followed by dilution with H$_2$O (20 mL) and DCM (35 mL). The organic layer was separated, and the aqueous layer was washed with DCM (2 × 35 mL). The organic layers were combined, subsequently washed with an aqueous LiCl solution (5%, 50 mL, to remove DMF) and H$_2$O (2 × 50 mL), and dried over Na$_2$SO$_4$. Evaporation of the solvent in vacuo afforded the crude title compound as a yellowish viscous oil or an orange foam which can be used for the next step without further purification. Alternatively, the crude product can be purified by flash column chromatography (basic aluminum oxide, Brockmann activity grade I, cyclohexane/ethyl acetate = 3:1). Thus, the N-alkylated pyrrole derivative of 8 was obtained (1.12 g, 98%) as a colorless amorphous solid: $R_f$ = 0.33 (silica gel, cyclohexane/ethyl acetate = 1:1, 2% triethylamine); IR (ATR) $\nu$ (cm$^{-1}$) = 2936, 2836, 1691, 1437, 1415, 1256, 1128, 1092, 1027, 863; $^1$H NMR, COSY, NOESY (400 MHz, CD$_3$OD) $\delta$ (ppm) = 7.13 (s, 1H, H-3′), 6.951 (d, $J$ = 8.3 Hz, 1H, H-5‴), 6.948 (d, $J$ = 1.9 Hz, 1H, H-2‴), 6.89 (dd, $^3J$ = 8.2 Hz, $^4J$ = 1.9 Hz, 1H, H-6‴), 6.70 (s, 1H, H-6′), 6.57 (d, $J$ = 8.3 Hz, 1H, H-5″), 6.49 (d, $J$ = 2.0 Hz, 1H, H-2″), 6.42 (dd, $^3J$ = 8.3 Hz, $^4J$ = 2.0 Hz, 1H, H-6″), 4.56−4.52 (m, 1H, NCH$_2$CH(OCH$_3$)$_2$), 4.52−4.43 (m, 2H, NCH$_2$CH(OCH$_3$)$_2$) 4.04 (m, 2H, OCH$_2$CH$_3$), 3.83 (s, 3H, OCH$_3$-4‴), 3.81 (s, 3H, OCH$_3$-4′), 3.70 (s, 3H, OCH$_3$-3‴), 3.67 (s, 3H, OCH$_3$-4″), 3.62 (s, 3H, OCH$_3$-5′), 3.42 (s, 3H, OCH$_3$-3″), 3.28 (s, 3H, NCH$_2$CH(OCH$_3$)$_2$), 3.26 (s, 3H, NCH$_2$CH(OCH$_3$)$_2$), 0.95 (t, $J$ = 7.1 Hz, 3H, OCH$_2$CH$_3$); $^{13}$C NMR, HSQC, HMBC (100.6 MHz, CD$_3$OD) $\delta$ (ppm) = 161.3 (C=O), 150.6 (C4‴), 150.2 (C3‴), 150.2 (C4′), 149.4 (C3″), 149.3 (C5′), 148.4 (C4″), 139.6 (C5), 132.5 (C3), 131.8 (C1′), 128.6 (C1″), 125.8 (C6‴), 125.3 (C1‴), 125.1 (C4), 123.9 (C6′), 121.1 (C2), 117.1 (C2′), 116.69 (C6′), 116.67 (C5‴), 116.4 (C3′), 115.3 (C2″), 112.6 (C2‴), 112.1 (C5″), 106.3 (NCH$_2$CH(OCH$_3$)$_2$), 60.9 (OCH$_2$CH$_3$), 56.8 (OCH$_3$-4‴), 56.6 (OCH$_3$-3‴), 56.5 (OCH$_3$-3″), 56.4 (OCH$_3$-4′), 56.2 (OCH$_3$-4″), 56.1 (OCH$_3$-5′), 56.0 (NCH$_2$CH(OCH$_3$)$_2$), 55.8 (NCH$_2$CH(OCH$_3$)$_2$), 49.1 (NCH$_2$CH(OCH$_3$)$_2$), 14.1 (OCH$_2$CH$_3$); ESI-HRMS calcd for [C$_{35}$H$_{40}$($^{79}$Br)NO$_{10}$ + Na]$^+$ 736.1734, found 736.1730.

The crude N-alkylated pyrrole (1.03 g, 1.44 mmol) was dissolved in dry DCM (22 mL) and cooled to 0 °C. Anhydrous TfOH (0.19 mL, 0.32 g, 2.16 mmol, 1.50 equiv) was diluted with dry DCM (8 mL), and the solution was added dropwise to the mixture within 10 min. After complete addition, the mixture was allowed to reach room temperature and stirred for 1 h with subsequent addition of NaHCO$_3$ (2 g). In order to permit better miscibility and facilate neutralization, dry ethanol (7 mL) was carefully added. The mixture was filtered, the filter cake was washed thoroughly with DCM, and the combined extracts were concentrated in vacuo. The resulting oil was diluted with DCM (35 mL), filtered from any residual salts and washed with DCM (2 × 20 mL). Final purification by flash column chromatography (silica gel, cyclohexane/ethyl acetate = 3:1) gave the title compound (0.89 g, 95%) as a bright yellow crystalline solid (93% over two steps). In NMR, the compound was found to exist as a mixture of two rotamers (R1:R2 = 3:2): $R_f$ = 0.40 (silica gel, cyclohexane/ethyl acetate = 1:1); mp 106.6−108.6 °C; IR (ATR) $\nu$ (cm$^{-1}$) = 2935, 2836, 1677, 1403, 1379, 1251, 1136, 1069, 1026, 751; $^1$H NMR, COSY, NOESY (400 MHz, CDCl$_3$) $\delta$ (ppm) = 9.35 (d, $J$ = 7.5 Hz, 1H, H-5), 7.23 (R1, s, 0.6H, H-10), 7.16 (R2, s, 0.4H, H-10), 7.02 (s, 1H, H-7), 6.98 (s, 1H, H-3″), 6.97 (d, $J$ = 7.5 Hz, 1H, H-6),

6.93 (dd, $^3J$ = 8.1 Hz, $^4J$ = 1.9 Hz, 1H, H-6′), 6.90 (R1, d, $J$ = 1.9 Hz, 0.6H, H-2′), 6.87 (R2, d, $J$ = 1.9 Hz, 0.4H, H-2′), 6.84 (R1, d, $J$ = 8.1 Hz, 0.6H, H-5′), 6.82 (R2, d, $J$ = 8.1 Hz, 0.4H, H-5′), 6.66 (R2, s, 0.4H, H-6″), 6.60 (R1, s, 0.6H, H-6″), 4.21−4.13 (m, 1H, OC$H_2$CH$_3$), 4.11−4.02 (m, 1H, OC$H_2$CH$_3$), 3.95 (s, 3H, OCH$_3$-8), 3.85 (s, 3H, OCH$_3$-4′), 3.84 (s, 3H, OCH$_3$-4″), 3.74 (R2, s, 1.2H, OCH$_3$-3′), 3.72 (R1, s, 1.8H, OCH$_3$-3′), 3.68 (R2, s, 1.2H, OCH$_3$-5″), 3.67 (R1, s, 1.8H, OCH$_3$-5″), 3.45 (R1, s, 1.8H, OCH$_3$-9), 3.43 (R2, s, 1.2H, OCH$_3$-9), 0.97 (t, $J$ = 7.1 Hz, 3H, OCH$_2$C$H_3$); $^{13}$C NMR, HSQC, HMBC (100.6 MHz, CDCl$_3$) $\delta$ (ppm) = 161.8 (C=O), 149.4 (C8), 149.0 (C9), 148.8 (R1, C3′), 148.6 (R2, C3′), 148.43 (R1, C4″), 148.36 (R2, C4″), 148.14 (R2, C4′), 148.07 (R1, C4′), 147.5 (R1, C5″), 147.4 (R2, C5″), 134.8 (R1, C1″), 134.7 (R2, 1″), 130.3 (R2, C10b), 130.2 (R1, C10b), 129.8 (R1, C2), 129.6 (R2, C2), 128.3 (R1, C1′), 128.0 (R2, C1′), 124.0 (R2, C6′), 123.7 (C5), 123.6 (C6a), 123.5 (R1, C6′), 119.84 (R1, 10a), 119.79 (R2, 10a), 118.22 (R1, C1), 118.20 (R2, C1), 115.39 (R2, C2″), 115.36 (R1, C2″), 114.6 (R1, C2′), 114.54 (2C, R2-C2′, R2, C6″), 114.52 (R1, C6″), 114.4 (R2, C3″), 114.3 (R1, C3″), 112.7 (C3), 112.39 (R2, C6), 112.36 (R1, C6), 111.3 (R2, C5′), 110.6 (R1, C5′), 107.2 (C7), 105.2 (C10), 59.7 (OCH$_2$CH$_3$), 56.2 (C4′), 56.1 (R1, C5″), 56.02 (R2, C5″), 56.98 (2C, C8, C4″), 55.9 (R2, C3′), 55.8 (R1, C3′), 55.43 (R1, OCH$_3$-9), 55.39 (R2, OCH$_3$-9), 13.9 (OCH$_2$CH$_3$); ESI-HRMS calcd for [C$_{33}$H$_{32}$($^{79}$Br)NO$_8$ + Na]$^+$ 672.1209, found 672.1198.

*Lamellarin D Trimethyl Ether (10).* To a solution of *seco*-precursor **9** (142 mg, 0.22 mmol, 1.00 equiv) in THF/MeOH (1:1, 3.17 mL) in a Schlenk tube was added 3 N aqueous NaOH (0.44 mL, 1.31 mmol, 6.00 equiv) in one portion and the mixture was heated to 64 °C overnight. After having confirmed complete conversion to the carboxylate by HPLC−MS, the solvent mixture was evaporated and the residue transferred into a microwave reaction vessel (volume: 10 mL), dissolved in dry DMF (1.90 mL), and mixed with copper(I) thiophene-2-carboxylate (CuTC, 50 mg, 0.26 mmol, 1.20 equiv). The vial was sealed, and the reaction mixture was irradiated via microwave (140 °C, 230 W, 40 min, $p$ < 2 bar). The mixture was concentrated to dryness in vacuo, and the residue was purified by silica gel filtration (DCM/ethyl acetate = 20:1). Final recrystallization from MeOH afforded the title compound as colorless plates (109 mg, 92%): $R_f$ = 0.50 (silica gel, DCM/ethyl acetate, 10:1); mp 278.5−279.8 °C (lit.[41] mp >250 °C); IR (ATR) $\nu$ (cm$^{-1}$) = 2936, 2836, 1697, 1490, 1414, 1265, 1222, 1138, 1009, 727; $^1$H NMR, COSY, NOESY (400 MHz, pyridine-$d_5$) $\delta$ (ppm) = 9.52 (d, $^3J$ = 7.3 Hz, 1H, H-5), 7.56 (d, $J$ = 2.0 Hz, 1H, H-16), 7.46 (dd, $^3J$ = 8.1 Hz, $^4J$ = 2.0 Hz, 1H, H-12), 7.39 (s, 1H, H-10), 7.38 (s, 1H, H-7), 7.35 (d, $J$ = 8.1 Hz, 1H, H-13), 7.26 (d, $J$ = 7.3 Hz, 1H, H-6), 6.90 (s, 1H, H-19), 6.73 (s, 1H, H-22), 4.00 (s, 3H, OCH$_3$-15), 3.95 (s, 3H, OCH$_3$-14), 3.91 (s, 3H, OCH$_3$-8), 3.81 (s, 3H, OCH$_3$-20), 3.47 (OCH$_3$-21), 3.46 (OCH$_3$-9); $^{13}$C NMR, HSQC, HMBC (100.6 MHz, pyridine-$d_5$) $\delta$ (ppm) = 155.9 (C23), 151.6 (C15), 151.5 (C8), 151.0 (C20), 150.6 (C14), 150.4 (C9), 147.8 (C18), 146.8 (C21), 134.9 (C10b), 130.0 (C2), 129.1 (C11), 125.7 (C6a), 125.0 (C12), 123.4 (C5), 120.0 (C10a), 116.2 (C16), 114.1 (C13), 113.4 (C6), 112.0 (C1), 110.8 (C17), 108.9 (C7), 108.7 (C3), 106.6 (C22), 106.3 (C10), 101.9 (C19), 56.9 (OCH$_3$-15), 56.8 (OCH$_3$-8), 56.5 (OCH$_3$-20), 56.3 (OCH$_3$-14), 55.8 (OCH$_3$-9), 55.5 (OCH$_3$-21); $^1$H NMR, COSY, NOESY (400 MHz, CDCl$_3$) $\delta$ (ppm) = 9.20 (d, $^3J$ = 7.3 Hz, 1H, H-5), 7.23 (dd, $^3J$ = 8.1 Hz, $^4J$ = 1.9 Hz, 1H, H-12), 7.17 (d, $J$ = 1.9 Hz, 1H, H-16), 7.164 (s, 1H, H-10), 7.162 (d, $J$ = 8.1 Hz, 1H, H-13), 7.08 (s, 1H, H-7), 7.03 (d, $J$ = 7.3 Hz, 1H, H-6), 6.90 (s, 1H, H-19), 6.73 (s, 1H, H-22), 3.99 (s, 3H, OCH$_3$-15), 3.98 (s, 3H, OCH$_3$-8), 3.89 (s, 3H, OCH$_3$-14), 3.87 (s, 3H, OCH$_3$-20), 3.48 (OCH$_3$-21), 3.47 (OCH$_3$-9); $^{13}$C NMR, HSQC, HMBC (100.6 MHz, CDCl$_3$) $\delta$ (ppm) = 155.6 (C23), 150.3 (C8), 150.0 (C14), 149.7 (C20), 149.3 (C9), 149.2 (C15), 146.8 (C18), 145.7 (C21), 134.5 (C10b), 129.5 (C2), 128.4 (C11), 125.0 (C6a), 124.3 (C12), 123.4 (C5), 119.2 (C10a), 114.6 (C16), 112.5 (C6), 112.1 (C13), 111.1 (C1), 110.0 (C17), 108.0 (C3), 107.5 (C7), 105.4 (C10), 105.2 (C22), 100.7 (C19), 56.4 (OCH$_3$-15), 56.3 (OCH$_3$-14), 56.2 (OCH$_3$-20), 56.1 (OCH$_3$-8), 55.6 (OCH$_3$-9), 55.4 (OCH$_3$-21); ESI-HRMS calcd for [C$_{31}$H$_{27}$NO$_8$ + Na]$^+$ 564.1635, found 564.1632. The data are in accordance with the literature (compound **12**b).[41]

*Lamellarin H (11).* To a stirred solution of **10** (100 mg, 0.19 mmol, 1.00 equiv) in dry DCM (19 mL) under nitrogen, BBr$_3$ (3.32 mL, 3.32 mmol, 1 M in heptane, 18.00 equiv) was added dropwise at −78 °C. This temperature was maintained for another 15 min followed by removal of the cooling bath. The dark-red solution was stirred for an additional 20 h at room temperature and then quenched by addition of MeOH (10 mL). The solvent was removed and the residue suspended in water (20 mL) followed by extraction with ethyl acetate (3 × 20 mL). The combined organic layers were dried over anhydrous Na$_2$SO$_4$, and the solvent was concentrated in vacuo. Upon treatment of the brown residue with a mixture of DCM/MeOH (1:2), lamellarin H (**11**) was obtained (82 mg, 97%) as a brownish amorphous solid: $R_f$ = 0.37 (silica gel, ethyl acetate/methanol = 4:1); mp >300 °C; IR (ATR) $\nu$ (cm$^{-1}$) = 3300, 1701, 1627, 1553, 1474, 1428, 1281, 1188, 1022, 979; $^1$H NMR, COSY, NOESY (400 MHz, DMSO-$d_6$) $\delta$ (ppm) = 9.99 (br s, OH), 9.76 (br s, OH), 9.42 (br s, OH), 9.20 (br s, 2OH), 8.99 (d, $J$ = 7.3 Hz, 1H, H-5), 8.91 (br s, OH), 7.14 (d, $J$ = 7.3 Hz, 1H, H-6), 7.13 (s, 1H, H-7), 6.99 (d, $^3J$ = 8.0 Hz, 1H, H-13), 6.95 (s, 1H, H-10), 6.81 (s, 1H, H-19), 6.79 (d, $^4J$ = 2.0 Hz, 1H, H-16), 6.71 (dd, $^3J$ = 8.0 Hz, $^4J$ = 2.0 Hz, 1H, H-12), 6.57 (s, 1H, H-22); $^{13}$C NMR, HSQC, HMBC 100.6 MHz, DMSO-$d_6$) $\delta$ (ppm) = 154.5 (C23), 147.7 (C8), 146.8 (C20), 146.6 (C9), 146.2 (C15), 145.5 (C14), 145.3 (C18), 142.1 (C21), 133.9 (C10b), 128.9 (C2), 125.4 (C11), 123.8 (C6a), 121.4 (C12), 121.2 (C5), 118.1 (C10a), 117.6 (C16), 117.0 (C13), 112.6 (C6), 111.41 (C7), 111.39 (C1), 109.62 (C10), 109.56 (C22), 108.8 (C17), 106.3 (C3), 103.3 (C19); ESI-HRMS calcd for [C$_{25}$H$_{15}$NO$_8$ + H]$^+$ 458.0876, found 458.0887. The data are in accordance with the literature (compounds **2** in ref 42 and **5** in ref 43).

## ASSOCIATED CONTENT

**Ⓢ Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02194.

$^1$H and $^{13}$C NMR spectra of all synthesized compounds (PDF)

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**Notes**

The authors declare no competing financial interest.

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