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Total Synthesis of Lamellarins U and A3 by Interrupting Halogen Dance

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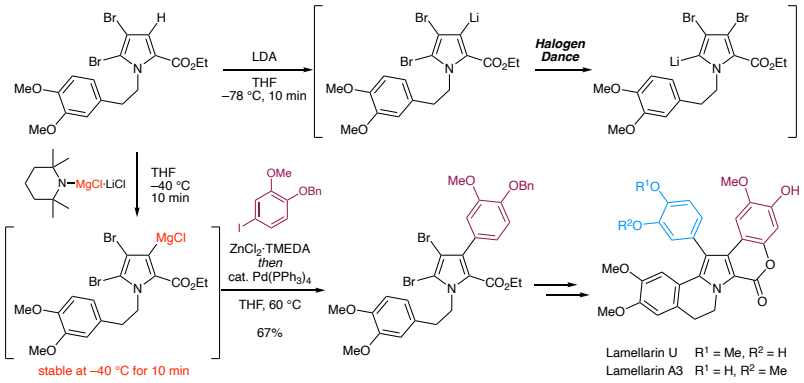

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Abstract A total synthesis of lamellarins U and A3 is described. The synthesis features interruption of a halogen dance reaction of a metalated α,β-dibromopyrrole. The pyrrolylmagnesium reagent, generated by deprotonative metalation using (TMP)MgCl·LiCl (TMP: 2,2,6,6-tetramethylpiperidide) as base, was transmetalated to the corresponding organozinc species without causing the halogen dance reaction, which underwent a Negishi coupling to incorporate an aryl group onto the pyrrole ring. The arylated α,β-dibromopyrrole was then converted into lamellarins U and A3 through an α-selective halogen–magnesium exchange followed by carboxylation and subsequent palladium-mediated cyclization. The late-stage introduction of another aryl group was performed using a Kosugi–Migita–Stille coupling to provide lamellarins U and A3.

Key words lamellarins, halogen dance, pyrroles, alkaloids, total synthesis, lithiation, metalation, deprotonation

Since lamellarins A–D were isolated and reported by Faulkner and Clardy in 1985,[1] more than seventy lamellarins and their congeners have been reported[2] (Figure 1). Lamellarins are categorized into types Ia/Ib and II, with the majority belonging to type Ia/Ib. Their structural complexity regarding substituents on the aromatic rings has led to lamellarins possessing various biological activities.[3] Tremendous synthetic efforts toward the total synthesis of lamellarins have been made by the Fürstner,[4] Steglich,[5] Banwell,[6] Iwao/Ishibashi,[7] Boger,[8] Gupton,[9] Ruchirawat,[10] Álvarez,[11] Handy,[12] Opatz,[13] Jia,[14] Itami/Yamaguchi,[15] Yang,[16] Wu/Wu,[17] Chandrasekhar,[18] Khan,[19] and Michael[20] groups. These synthetic strategies can be classified into two categories, namely, pyrrole construction from acyclic precursors[4,5,6b,6d,7a,7b,7c,8,9a,10,11a,13,14,16,17,18,19,20] and stepwise functionalization of the pivotal pyrrole skeleton.[6a,6c,7d,7e,9b,9c,11b,11c,12,15] Recently, our research groups achieved the total synthesis of lamellarins and their congeners using the latter method.[21] Herein, we report the total synthesis of structurally similar lamellarins U[6d,7e,10c,11a,13a,19a,22] and A3[6d,23,24] through development of a stereoselective functionalization of a multiply halogenated pyrrole.

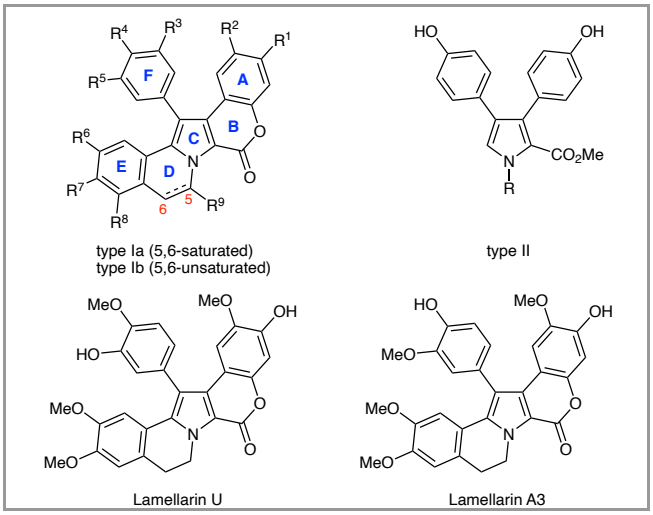
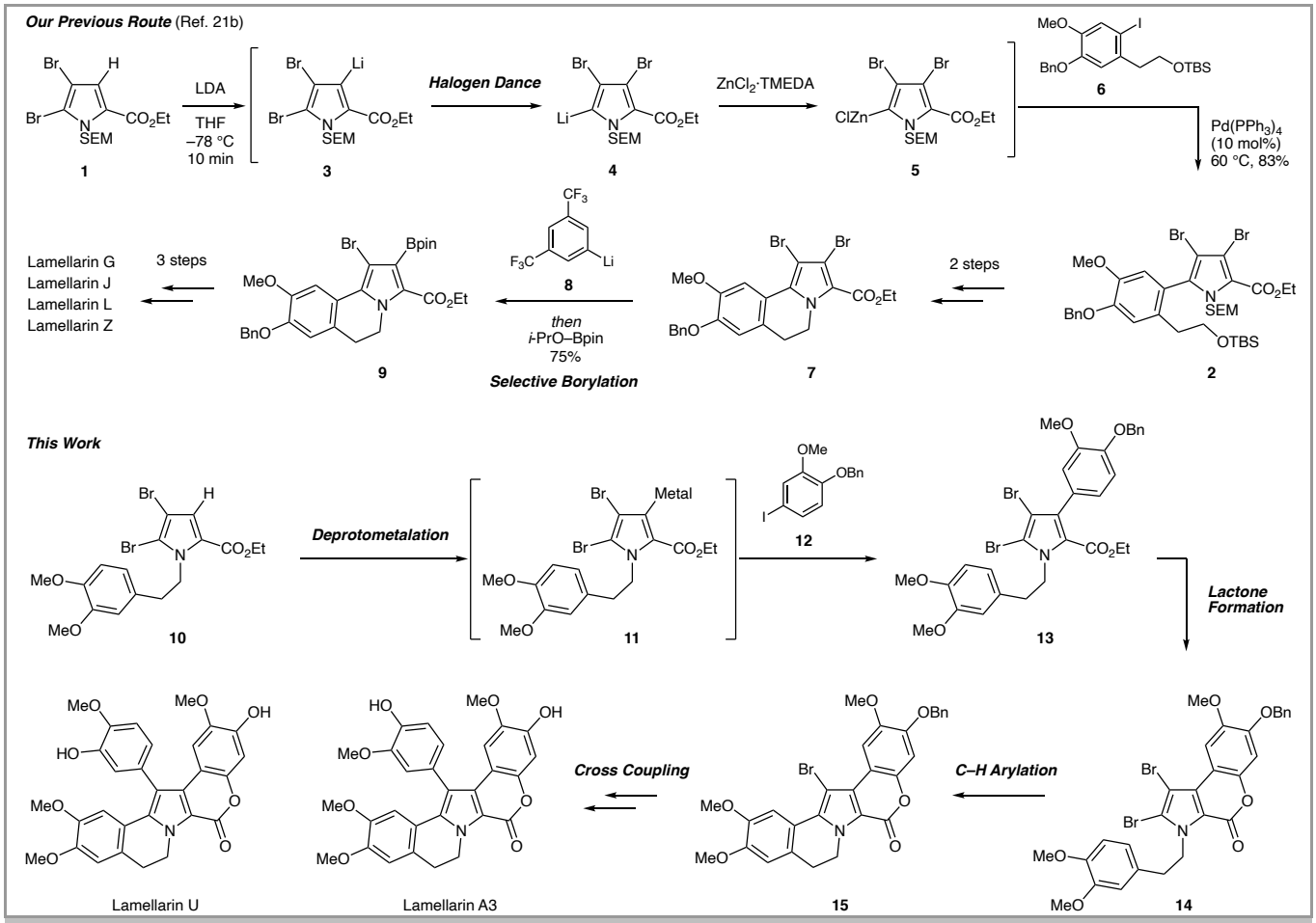


Figure 1 Classification of lamellarins and structures of lamellarins U and A3.

We recently achieved a total synthesis of lamellarins through the halogen dance[25–27] of α,β-dibromopyrrole **1**, which featured a successive halogen dance–Negishi coupling[28] performed in a single flask to provide arylated β,β'-dibromopyrrole **2** (Scheme 1).[21b] Lithiated dibromopyrrole **3**, generated by deprotolithiation of **1**, underwent halogen dance to afford thermodynamically more stable α-pyrrolyllithium **4**. After transmetalation with $ZnCl_2$·TMEDA, organozinc species **5** was converted into **2** by Negishi coupling with aryl iodide **6**. After a two-step ring closure, treatment of β,β'-dibromopyrrole **7** with elaborated phenyllithium **8** allowed regioselective bromine–lithium exchange followed by borylation. Substituted pyrrole **9** can be converted into the type Ia lamellarins. Accordingly, we devised a new approach using the distinct reactivity of the α- and β-bromo groups in compound **10**. If metalated dibromopyrrole **11** does not undergo halogen dance and can be subjected to a cross coupling with aryl iodide **12** with the bromo groups intact, pyrrole **13** would be transformed into lamellarins U and A3 via compounds **14** and **15**.

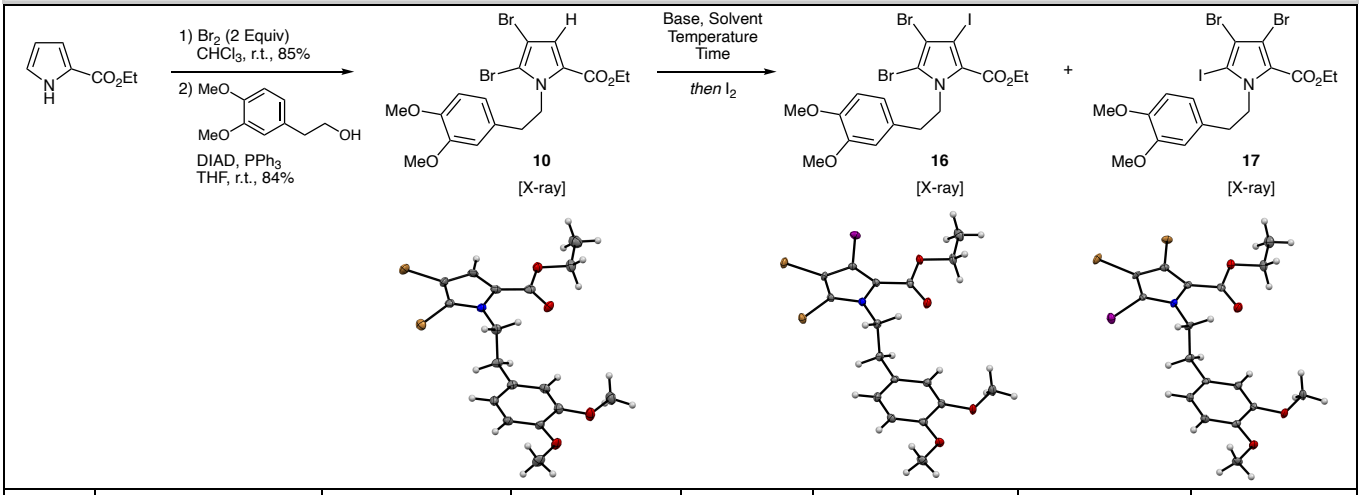


Scheme 1 Our previous synthetic route and the alternative synthetic strategy to interrupt the halogen dance reaction.

First, we investigated suitable metals in compound **11** to suppress the halogen dance reaction using dibromopyrrole **10** as the substrate (Table 1). Preparation of **10** commenced with a regioselective dibromination of pyrrole carboxylic acid ethyl ester using two equivalents of bromine.[21] The resultant unprotected pyrrole was then subjected to Mitsunobu conditions[29] using diisopropyl azodicarboxylate (DIAD) to provide corresponding alkylated pyrrole **10** in 84% yield. According to our previous reports,[21] dibromopyrrole **10** was treated with LDA in THF at –78 °C for 10 min, followed by addition of iodine. A trace amount (2%) of desired product **16** was observed in the ^{1}H NMR spectrum of the crude product, while only undesired constitutional isomer **17** was isolated in 79% yield (entry 1). These results indicated that the halogen dance of the lithiated dibromopyrrole proceeded smoothly, even at –78 °C within 10 min. On the basis of control experiments, which showed that compound **10** did not react with iodine at room temperature for 1 h, affording 99% recovery, and that compound **16** was not observed in the ^{1}H NMR spectrum of the crude product, a tiny amount of **16** must be generated from the corresponding lithiated pyrrole **11** and not from starting material **10**. The structures of compounds **10**, **16**, and **17** were unambiguously confirmed by X-ray crystallography.[30] To circumvent the fast halogen dance reaction, less polar solvents were investigated next. The reaction was performed in THF/hexane (1:1) at 0 °C, because the starting dibromopyrrole **10** did not completely dissolve at –78 °C. The yield of **16** was not improved, but **10** was consumed (entry 2). Using Et_2O slightly increased the yield of desired product **16**, albeit in 15% yield (entry 3). These results indicated that the pyrrolyllithium species was a transient intermediate that was not suitable to react with an electrophile prior to the halogen dance reaction. We next employed commercially available (TMP)MgCl·LiCl[31] (Knochel–Hauser base; TMP: 2,2,6,6-tetramethylpiperidide) as base to stabilize the corresponding metalated intermediate. When the reaction was performed at –78 °C, desired product **16** was obtained in 17% NMR yield (entry 4). Notably, undesired isomer **17** was not observed in the ^{1}H NMR spectrum of the crude product, while 79% recovery of the starting material was confirmed. We next optimized the reaction temperature. Although the reaction did not reach completion at –40 °C after 10 min, desired product **16** was exclusively obtained and isolated in 74% yield (entry 5). We further investigated the kinetic stability of magnesiated pyrrole **11** at elevated reaction temperatures to examine the possible practical synthetic utility of this chemical species. Magnesiated pyrrole **11** was found to be stable at 0 °C and room temperature; however, **17** was observed in each ^{1}H NMR spectrum of the crude product (entries 6 and 7). When the reaction was performed at 40 °C, a substantial amount of **17** was generated (entries 8 and 9). Commercially available $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$[32] resulted in clean conversion, even at 60 °C, but did not achieve completion of the deprotometalation

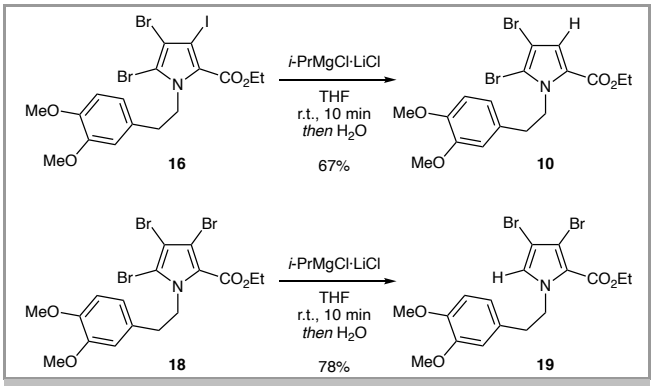
(entries 10–12). The undesired halogen dance was hampered by the low reactivity of the generated pyrrolylzinc species **11**.[33]

Table 1 Screening of reaction conditions to suppress halogen dance through deprotometalation.



Entry	Base	Solvent	Temperature	Time	Recovery of **10** (%)[a]	Yield of **16** (%)[a]	Yield of **17** (%)[a]
1	LDA	THF	–78 °C	10 min	–[b]	2	98 (79[c])
2	LDA	THF/hexane (1:1)	0 °C	10 min	2	4	33
3	LDA	Et_2O	0 °C	10 min	7	15	20
4	(TMP)MgCl·LiCl	THF	–78 °C	10 min	79	17	–[b]
5	(TMP)MgCl·LiCl	THF	–40 °C	10 min	2	94 (74[c])	–[b]
6	(TMP)MgCl·LiCl	THF	0 °C	10 min	5	74	2
7	(TMP)MgCl·LiCl	THF	r.t.	10 min	7	80	8
8	(TMP)MgCl·LiCl	THF	40 °C	10 min	5	75	6
9	(TMP)MgCl·LiCl	THF	40 °C	3 h	1	48	14
10	$(TMP)_2Zn·2MgCl_2·2LiCl$	THF	40 °C	10 min	75	20	–[b]
11	$(TMP)_2Zn·2MgCl_2·2LiCl$	THF	60 °C	10 min	59	41	–[b]
12	$(TMP)_2Zn·2MgCl_2·2LiCl$	THF	60 °C	3 h	31	67	–[b]

[a] Yield was determined by ^1H NMR spectrum of the crude product with 1,1,2,2-tetrachloroethane as an internal standard.
[b] Not detected in the ^1H NMR spectrum of the crude product.
[c] Isolated yield.

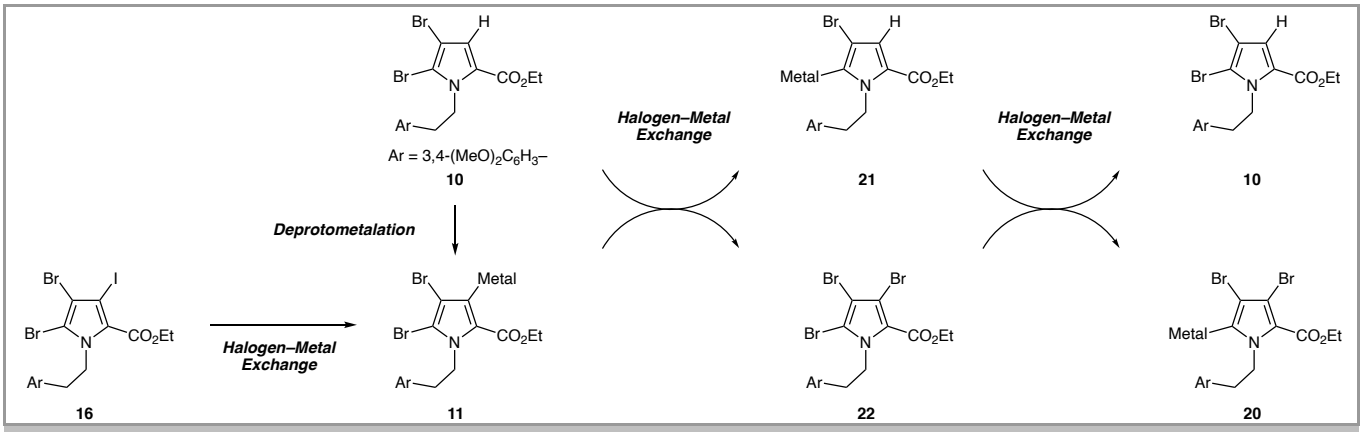


Scheme 2 Another approach to generate β-metalated pyrrole.

We also examined another approach to generate magnesiated pyrrole intermediate **11** by halogen–metal exchange of trihalopyrroles **16** or **18** and found that iodinated dibromopyrrole **16** served as an alternative substrate for this purpose (Scheme 2). The iodine-selective halogen–magnesium exchange proceeded at room temperature for 10 min using *i*-PrMgCl·LiCl,[34] and the reaction mixture was treated with water to provide α,β-dibromopyrrole **10** in 67% yield as the major product, along with a trace amount (2%) of **19**. In contrast, tribromopyrrole **18** was converted into β,β'-dibromopyrrole **19**[35] exclusively in 78% yield, with a minute amount (4%) of **10** recovered. Owing to the kinetic stability of magnesiated pyrrole **11** (Table 1, entry 7), the halogen–magnesium exchange of tribromopyrrole **18** seemed to proceed exclusively at the α-position. These results corresponded with the report of Christophersen, in which 2-bromo-3-iodothiophene underwent iodine-selective halogen–metal exchange with EtMgCl at room temperature to form 2-bromo-3-thienylmagnesium chloride, while 2,3-dibromothiophene was converted to 3-bromo-2-thienylmagnesium chloride under the same reaction conditions.[36]

The rationale for the results shown in Table 1 and Scheme 2 is described in Scheme 3. Deprotolithiation of dibromopyrrole **10** led to the formation of organolithium **11**, which was immediately converted into α-pyrrolyllithium **20** after halogen dance. This outcome was attributed to the relative reaction rates of deprotolithiation and halogen–lithium exchange. Generally, deprotometalation is much slower than halogen–metal exchange.[37] When metalated pyrrole **11** is formed by deprotometalation of **10**, it undergoes halogen–metal exchange with another molecule of **10** to provide α-metalated pyrrole **21** and tribromopyrrole **22**, which further react to give α-metalated pyrrole **20** with regeneration of dibromopyrrole **10**. On the basis of the experimental results, we are convinced that α-metalated pyrrole **20** is thermodynamically more favored than α-metalated pyrrole **21**, due to the inductive effect of the two bromo groups.[38] The halogen–metal exchange of metalated pyrrole **11** and tribromopyrrole **22** is also a plausible pathway

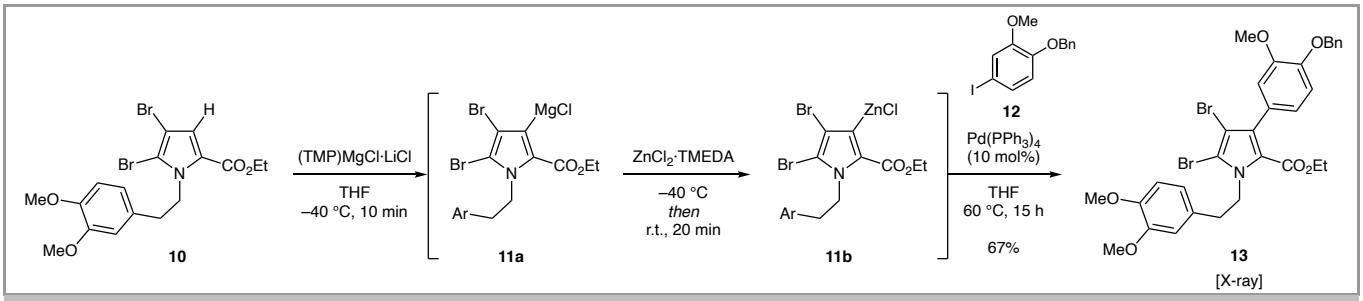
for the halogen dance reaction. When (TMP)MgCl·LiCl was used instead of LDA, the reaction rate of the second step (from β-metalated pyrrole **11** and dibromopyrrole **10** to tribromopyrrole **22** and α-metalated pyrrole **21**) was slower than that of the first step to form β-metalated pyrrole **11**, which suppressed the halogen dance. The results obtained for iodinated dibromopyrrole **16** can be explained in the same manner, based on iodine–magnesium exchange (**16** to **11**) being faster than deprotomagnesiation (**10** to **11**).



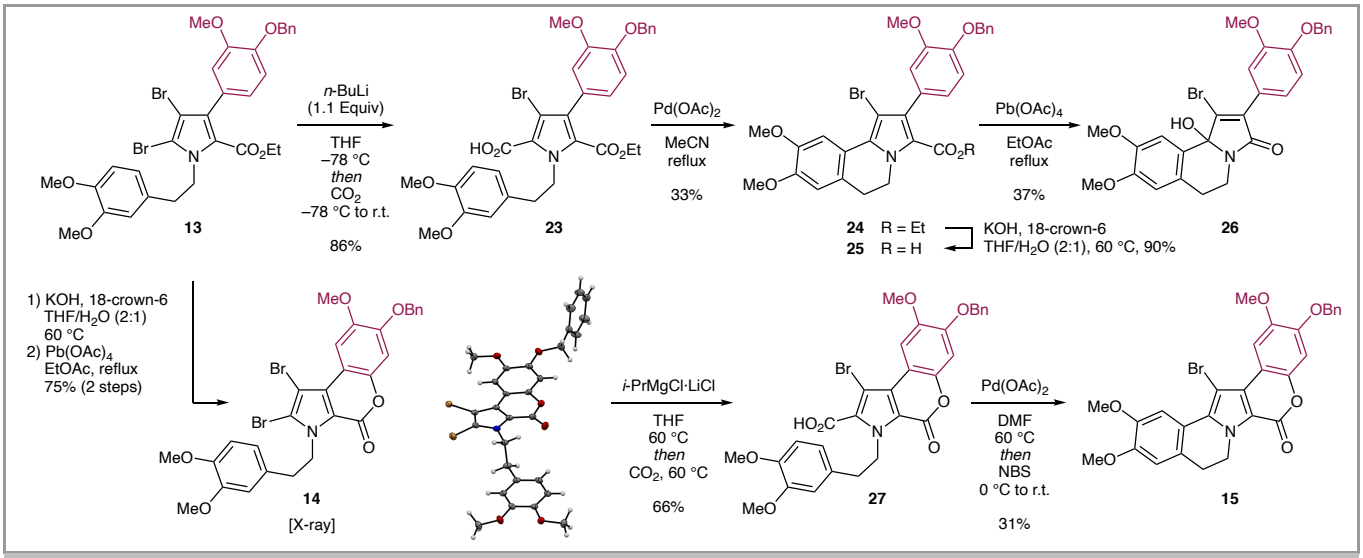
Scheme 3 Rationale for the outcome of deprotometalation of the dibromopyrrole and the alternative approach to suppress the halogen dance.

Having established optimal conditions to generate β-magnesiated pyrrole **11a**, this compound was subjected to Negishi coupling to incorporate the A ring (Scheme 4). After deprotomagnesiation was completed at −40 °C using (TMP)MgCl·LiCl, magnesiated pyrrole **11a** was treated with $ZnCl_2$·TMEDA for conversion into corresponding pyrrolylzinc **11b**. To this reaction mixture were added aryl iodide **12** and $Pd(PPh_3)_4$ (10 mol%) at room temperature, and the resulting mixture was heated at 60 °C for 15 h to provide desired product **13** in 67% yield. The pyrrolylzinc species was found to be kinetically stable, even at 60 °C, and no halogen dance occurred, according to the ^{1}H NMR spectrum of the crude product. These results corresponded with those in Table 1, entry 12. The structure of arylated dibromopyrrole **13** was confirmed by X-ray crystallography.[39] Another approach to introduce the aryl group followed by dibromination was unsuccessful, utilizing the ester-directed deprotolithiation followed by *in situ* transmetalation[40] using a combination of LDA and $ZnCl_2$·TMEDA. These results indicated that the two bromo groups were effective for the deprotometalation of pyrrole.

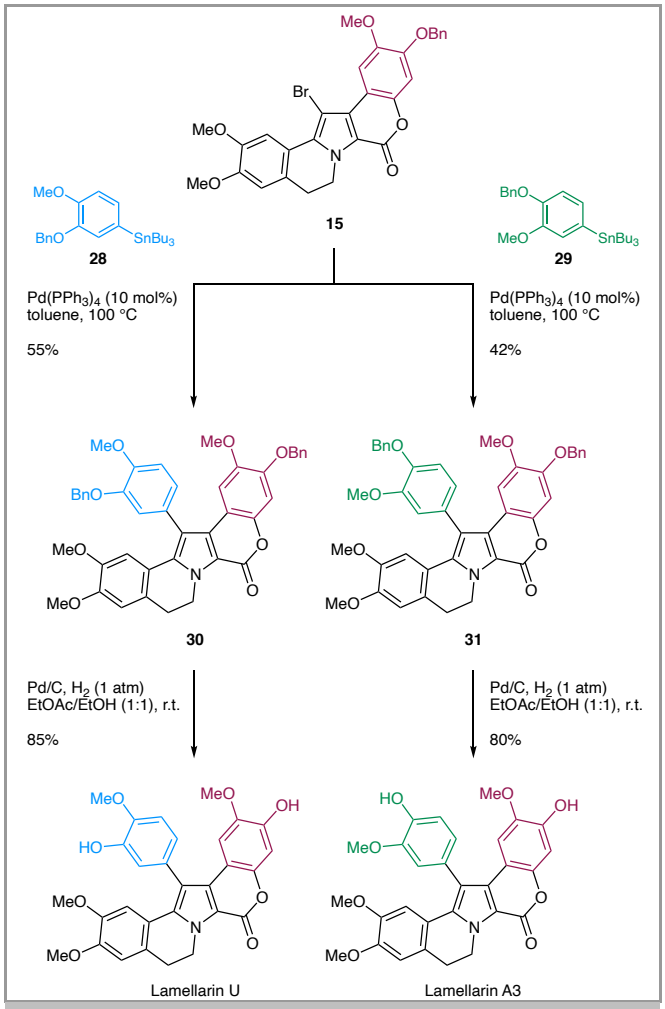
With arylated α,β-dibromopyrrole **13** in hand, we next focused on constructing the lamellarin skeleton (Scheme 5). First, halogen–lithium exchange of α,β-dibromopyrrole **13** was examined. Regioselective lithiation was performed with *n*-BuLi at −78 °C and subsequent treatment with CO_2 gas furnished pyrrole carboxylic acid **23** in 86% yield. According to the reports of Iwao,[7b,41] the tethered aromatic ring was incorporated to the pyrrole skeleton through decarboxylative cyclization with a stoichiometric amount of $Pd(OAc)_2$. The ethyl ester of compound **24** was hydrolyzed to provide the corresponding carboxylic acid **25** under basic conditions. Although several examples of lactone moiety construction by $Pb(OAc)_4$ have been reported,[5] desired product **15** was observed in 8% NMR yield, despite complete consumption of pyrrole carboxylic acid **25**. Instead, unsaturated γ-lactam **26** was obtained as a major product in 37% yield. The structure was identified according to the reports of Opatz[13a] and Wu/Wu.[17] The common structural feature of these examples was the 5-arylpyrrole-2-carboxylic acid, and the pyrrole nucleus was oxidized to the hydroxylated γ-lactam. Because prevention of this oxidation was difficult, an alternative synthetic route was investigated to form the lamellarin skeleton. Basic hydrolysis of the ethyl ester and subsequent oxidative lactonization proceeded smoothly to provide desired product **14** in 75% yield over two steps. The structure of **14** was confirmed by X-ray crystallography.[42] Next, we attempted to introduce the carboxylic group at the α-position. However, in contrast to dibromopyrrole **13**, lactone-tethered dibromopyrrole **14** was almost insoluble in THF at −78 °C, resulting in recovery of the substrate. After further optimization, **14** was found to be soluble in THF at 60 °C and treatment with *i*-PrMgCl·LiCl proved effective for the transformation with the lactone moiety kept intact. Pyrrole carboxylic acid **27** was subjected to the palladium-mediated cyclization conditions to form the lamellarin skeleton, providing key synthetic intermediate **15** in 31% yield, after addition of NBS. In preliminary experiments, a significant amount of the debrominated pyrrole was observed, which was difficult to separate from the desired bromopyrrole **15**. Treatment with NBS proved effective to convert the debrominated pyrrole into bromopyrrole **15**.



Scheme 4 Interrupted halogen dance of magnesiated pyrrole and subsequent Negishi coupling.



Scheme 5 Effect of the lactone moiety on construction of the tricyclic skeleton.



Scheme 6 Total synthesis of lamellarins U and A3.

The obtained bromopyrrole **15** was a useful common synthetic intermediate for producing lamellarins U and A3 (Scheme 6). The Kosugi–Migita–Stille coupling[43] with arylstannane **28** or **29** to install the F ring proceeded under the standard reaction conditions, providing corresponding products **30** and **31** in moderate yields, associated with reduction of the bromo group. Attempted Suzuki–Miyaura cross-coupling reactions also resulted in lower yields of the products owing to the undesired debromination.[44] The two benzyl groups in compound **30** were removed by palladium-catalyzed hydrogenolysis to afford lamellarin U in 85% yield. The same reaction conditions were applied to compound **31** to synthesize lamellarin A3 in 80% yield. The ^{1}H and ^{13}C{^{1}H} NMR data of the synthetic lamellarins were identical to those reported.[6d,22a,23]

In conclusion, an improved synthetic route for type Ia lamellarins has been developed by prohibiting halogen dance using pyrrolylmagnesium chloride as the useful reaction intermediate. This synthetic route allows late-stage derivatization of the F ring of lamellarins, and is a potentially powerful and efficient tool for synthesizing various congeners.

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Analytical thin-layer chromatography was performed on Merck 60 F_{254} aluminum sheets precoated with a 0.25 mm thickness of silica gel. Melting points (mp) 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, DMSO-d_5: δ 2.50 ppm, tetramethylsilane: δ 0 ppm), and coupling constants are given in hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, 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, DMSO-d_6: δ 39.52 ppm, THF-d_8: 67.21 ppm). High-resolution mass spectroscopy (HRMS) was performed on a JEOL JMS-T100LP AccuTOF LC-Plus [electrospray ionization (ESI)] with a JEOL MS-5414DART attachment. Unless otherwise stated, all reactions were conducted in a flame-dried glassware under an inert atmosphere of nitrogen or argon. All workup and purification procedures were carried out with reagent-grade 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 (63–212 μm, FUJIFILM Wako Pure Chemical Co., 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), *i*-PrMgCl·LiCl (1.3 M in THF), TMPMgCl·LiCl (1.0 M in THF/toluene), and $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (12 wt% in THF/toluene) were purchased from Sigma-Aldrich Co. and used as received. *n*-BuLi (1.6 M in *n*-hexane) was purchased from Kanto Chemical Co. and used as received.

Procedures

Ethyl 4,5-dibromo-1-(3,4-dimethoxyphenethyl)-1*H*-pyrrole-2-carboxylate (10)

A 50-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar, a rubber septum, and a three-way stopcock was charged with ethyl 4,5-dibromo-1*H*-pyrrole-2-carboxylate (1.256 g, 5.09 mmol, 1.0 equiv), 3,4-dimethoxyphenylethanol (1.123 g, 6.16 mmol, 1.2 equiv), and PPh_3 (1.609 g, 6.14 mmol, 1.2 equiv). After the flask was evacuated and backfilled with N_2, anhydrous THF (10 mL) and diisopropyl azodicarboxylate (DIAD) (1.9 M in toluene, 3.3 mL, 6.3 mmol, 1.2 equiv) were added to the flask. The solution was stirred at room temperature for 30 min, at which time the reaction mixture was treated with water (10 mL). The resulting mixture was extracted twice with Et_2O (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/Et_2O = 20:1 to 6:1, gradient) to provide the title compound **10** as a colorless solid (1.965 g, 4.28 mmol, 84%).

Mp 56–58 °C; R_f = 0.12 (hexane/Et_2O = 3:1).

IR (ATR): 1707, 1516, 1417, 1405, 1328, 1262, 1233, 1178, 1158, 1094, 1031 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.03 (s, 1H), 6.80 (d, 1H, *J* = 8.1 Hz), 6.75 (dd, 1H, *J* = 8.1, 1.9 Hz), 6.63 (d, 1H, *J* = 1.9 Hz), 4.63 (t, 2H, *J* = 7.7 Hz), 4.27 (q, 2H, *J* = 7.0 Hz), 3.86 (s, 3H), 3.85 (s, 3H), 2.91 (t, 2H, *J* = 7.7 Hz), 1.34 (t, 3H, *J* = 7.0 Hz).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 159.5, 148.9, 147.9, 130.2, 123.6, 121.1, 119.6, 112.8, 112.2, 111.3, 99.1, 60.5, 56.0, 55.9, 49.9, 36.7, 14.4.

HRMS (ESI/TOF): *m/z* $[M + Na]^+$ calcd for $C_{17}H_{19}{}^{79}Br_2NO_4Na$: 481.9579; found: 481.9562.

Ethyl 4,5-dibromo-3-iodo-1*H*-pyrrole-2-carboxylate (S1)

A 300-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was charged with ethyl 4,5-dibromo-1*H*-pyrrole-2-

carboxylate (3.635 g, 12.2 mmol, 1.0 equiv) and $CHCl_3$ (122 mL). After NIS (3.312 g, 14.7 mmol, 1.2 equiv) was added to the flask, the mixture was stirred at room temperature for 7 h, at which time the mixture was treated with saturated aqueous sodium thiosulfate (50 mL). The resulting mixture was extracted with $CHCl_3$ (80 mL) three times. The combined organic extracts were washed with 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 $CHCl_3$ to provide the title compound **S1** as a colorless solid (4.340 g, 10.3 mmol, 84%).

Mp 129–130 °C; R_f = 0.47 (hexane/Et_2O = 6:1).

IR (ATR): 3210, 1679, 1436, 1415, 1402, 1383, 1244, 733 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 9.47 (br s, 1H), 4.38 (q, 2H, *J* = 7.0 Hz), 1.41 (t, 3H, *J* = 7.0 Hz).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 158.8, 125.6, 110.5, 106.3, 75.7, 61.8, 14.4.

HRMS (DART/TOF): *m/z* $[M + H]^+$ calcd for $C_7H_7{}^{81}Br_2INO_2$: 425.7847; found: 425.7835.

Ethyl 4,5-dibromo-1-(3,4-dimethoxyphenethyl)-3-iodo-1*H*-pyrrole-2-carboxylate (16)

A 50-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar, a rubber septum, and a three-way stopcock was charged with dibromoiodopyrrole **S1** (3.855 g, 9.12 mmol, 1.0 equiv), 3,4-dimethoxyphenylethanol (2.000 g, 11.0 mmol, 1.2 equiv), and PPh_3 (2.872 g, 10.9 mmol, 1.2 equiv). After the flask was evacuated and backfilled with N_2, anhydrous THF (18 mL) and diisopropyl azodicarboxylate (DIAD) (1.9 M in toluene, 5.8 mL, 11 mmol, 1.2 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 (20 mL). The resulting mixture was extracted twice with Et_2O (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 = 1:1 to 1:4, gradient) followed by recrystallization from EtOH to provide the title compound **16** as a colorless solid (4.623 g, 7.88 mmol, 86%).

Mp 96–98 °C; R_f = 0.33 (hexane/Et_2O = 1:1).

IR (ATR): 2953, 2832, 1699, 1516, 1420, 1397, 1382, 1261, 1237, 1157, 1100, 1030 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 6.80 (d, 1H, *J* = 8.2 Hz), 6.73 (dd, 1H, *J* = 8.2, 2.0 Hz), 6.58 (d, 1H, *J* = 2.0 Hz), 4.66 (t, 2H, *J* = 7.7 Hz), 4.33 (q, 2H, *J* = 7.3 Hz), 3.86 (s, 3H), 3.85 (s, 3H), 2.91 (t, 2H, *J* = 7.7 Hz), 1.42 (t, 3H, *J* = 7.3 Hz).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 158.8, 148.9, 148.0, 129.8, 125.7, 121.0, 112.08, 112.05, 111.3, 109.6, 77.0, 61.2, 56.0, 55.9, 51.6, 36.7, 14.3.

HRMS (ESI/TOF): *m/z* $[M + Na]^+$ calcd for $C_{17}H_{18}{}^{79}Br^{81}BrINO_4Na$: 609.8525; found: 609.8555.

Ethyl 3,4-dibromo-1-(3,4-dimethoxyphenethyl)-5-iodo-1*H*-pyrrole-2-carboxylate (17)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with dibromopyrrole **10** (138.2 mg, 300 μmol, 1.0 equiv) and anhydrous THF (3.0 mL). After the solution was cooled to –78 °C, LDA (2.0 M in THF/heptane/ethylbenzene, 0.35 mL, 0.69 mmol, 2.3 equiv) was added dropwise to the Schlenk tube. After stirring at –78 °C for 10 min, to the solution was added I_2 (152.4 mg, 600 μmol, 2.0 equiv). After the resulting mixture was stirred for 1 h, at which time the reaction mixture was treated with saturated aqueous sodium thiosulfate (3 mL). After being partitioned, the aqueous layer was extracted twice with Et_2O (5 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/Et_2O = 1:1) to provide the title product **17** as a colorless solid (160.0 mg, 273 μmol, 91%).

Mp 105–107 °C; R_f = 0.56 (hexane/Et_2O = 1:1).

IR (ATR): 1738, 1515, 1454, 1377, 1354, 1322, 1261, 1233, 1217, 1157, 1094, 1030, 763, 657, 647 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 6.80 (d, 1H, *J* = 8.2 Hz), 6.75 (dd, 1H, *J* = 8.2, 1.8 Hz), 6.61 (d, 1H, *J* = 1.8 Hz), 4.65 (t, 2H, *J* = 7.7 Hz), 4.32 (q, 2H, *J* = 7.3 Hz), 3.86 (s, 3H), 3.85 (s, 3H), 2.90 (t, 2H, *J* = 7.7 Hz), 1.39 (t, 3H, *J* = 7.3 Hz).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 158.9, 149.0, 148.0, 129.8, 124.8, 121.1, 112.2, 111.4, 111.3, 107.0, 86.3, 61.1, 56.0, 55.9, 54.2, 36.8, 14.2.

HRMS (ESI/TOF): *m/z* $[M + Na]^+$ calcd for $C_{17}H_{18}{}^{81}Br_2INO_4Na$: 611.8504; found: 611.8515.

Screening of metal amides and reaction conditions (Table 1)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with dibromopyrrole **10** (0.30 mmol, 1.0 equiv) and anhydrous THF (3.0 mL). After the solution was cooled to –78 °C, a metal amide was added dropwise to the Schlenk tube. After the reaction mixture was stirred at –78 °C for 10 min, to the solution was added I_2 (0.60 mmol, 2.0 equiv). After the resulting mixture was stirred for 1 h, at which time the reaction mixture was treated with saturated aqueous sodium thiosulfate (3 mL). After being partitioned, the aqueous layer was extracted twice with Et_2O (3 mL). The combined organic extracts were washed with brine (5 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product. The yields of the desired iodinated pyrrole **16** and undesired iodinated pyrrole **17** were determined by ^1H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard by comparing relative values of integration for the peaks observed at 6.63 ppm (1 proton for **10**), 6.61 ppm (1 proton for **17**), and 6.58 ppm (1 proton for **16**) with that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm.

Ethyl 3,4,5-tribromo-1*H*-pyrrole-2-carboxylate (*S*2)

A 100-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was charged with ethyl 1*H*-pyrrole-2-carboxylate (1.942 g, 14.0 mmol, 1.0 equiv) and DMF (14 mL). After the solution was cooled to 0 °C, NBS (8.687 g, 48.8 mmol, 3.5 equiv) was added to the flask. The reaction mixture was allowed to warm to room temperature with stirring for 4 h, at which time the mixture was treated with saturated aqueous sodium thiosulfate (20 mL). After being partitioned, the aqueous layer was extracted twice with ethyl acetate (30 mL). The organic extracts were washed with water (120 mL) and brine (90 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was recrystallized from $CHCl_3$ to provide the title compound **S2** as a colorless solid (3.732 g, 9.93 mmol, 71%).

Mp 178–180 °C; R_f = 0.16 (hexane/Et_2O = 3:1).

IR (ATR): 3225, 1670, 1654, 1442, 1411, 1384, 1354, 1250, 1205, 1013, 715, 609 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 9.50 (br s, 1H), 4.42–4.34 (m, 2H), 1.39 (t, 3H, *J* = 7.0 Hz).

^1H NMR (400 MHz, DMSO-d_6): δ 4.26 (q, 2H, *J* = 7.1 Hz), 1.29 (t, 3H, *J* = 7.1 Hz).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 159.0, 122.3, 106.5, 106.3, 105.6, 61.7, 14.5.

$^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ 158.0, 121.8, 107.5, 104.9, 103.7, 60.7, 14.3.

HRMS (DART/TOF): *m/z* $[M + H]^+$ calcd for $C_7H_7{}^{79}Br_2{}^{81}BrNO_2$: 375.8007; found: 375.8016.

Ethyl 3,4,5-tribromo-1-(3,4-dimethoxyphenethyl)-1*H*-pyrrole-2-carboxylate (18)

A 50-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar, a rubber septum, and a three-way stopcock was charged with tribromopyrrole **S2** (1.128 g, 3.00 mmol, 1.0 equiv), 3,4-dimethoxyphenylethanol (656.0 mg, 3.60 mmol, 1.2 equiv), and PPh_3 (948.8 mg, 3.62 mmol, 1.2 equiv). After the flask was evacuated and backfilled with N_2, anhydrous THF (6 mL) and diisopropyl azodicarboxylate (DIAD) (1.9 M in toluene, 1.9 mL, 3.6 mmol, 1.2 equiv) were added to the flask. The solution was stirred at room temperature for 1 h, at which time the reaction mixture was treated with water (6 mL). The resulting mixture was extracted twice with ethyl acetate (10 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/CH_2Cl_2 = 1:3) followed by recrystallization from EtOH to provide the title compound **18** as a colorless solid (1.214 g, 2.25 mmol, 75%).

Mp 113–115 °C; R_f = 0.19 (hexane/CH_2Cl_2 = 1:3).

IR (ATR): 2939, 1701, 1516, 1455, 1424, 1398, 1383, 1323, 1262, 1237, 1173, 1157, 1141, 1100, 1030, 801, 767, 645, 620 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 6.80 (d, 1H, *J* = 8.3 Hz), 6.73 (dd, 1H, *J* = 8.3, 1.9 Hz), 6.60 (d, 1H, *J* = 1.9 Hz), 4.65 (t, 2H, *J* = 7.6 Hz), 4.32 (q, 2H, *J* = 7.3 Hz), 3.86 (s, 3H), 3.85 (s, 3H), 2.91 (t, 2H, *J* = 7.6 Hz), 1.40 (t, 3H, *J* = 7.3 Hz).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 159.1, 149.0, 148.0, 129.8, 122.4, 121.1, 112.3, 112.1, 111.4, 107.2, 104.5, 61.1, 56.0, 55.9, 51.2, 36.7, 14.3.

HRMS (ESI/TOF): *m/z* $[M + Na]^+$ calcd for $C_{17}H_{18}{}^{79}Br_2{}^{81}BrNO_4Na$: 561.8663; found: 561.8645.

Ethyl 3,4-dibromo-1-(3,4-dimethoxyphenethyl)-1*H*-pyrrole-2-carboxylate (19)

A flame-dried 50-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with dibromopyrrole **10** (405.2 mg, 879 μmol, 1.0 equiv) and anhydrous THF (8.8 mL). After the solution was cooled to –78 °C, LDA (2.0 M in THF/heptane/ethylbenzene, 0.79 mL, 1.6 mmol, 1.8 equiv) was added dropwise to the Schlenk tube. After stirring at –78 °C for 20 min, LDA (2.0 M in THF/heptane/ethylbenzene, 0.22 mL, 0.44 mmol, 0.50 equiv) was added dropwise to the Schlenk tube at –78 °C. The resulting mixture was stirred for 15 min, at which time the reaction mixture was treated with water (10 mL). After being partitioned, the aqueous layer was extracted twice with Et_2O (10 mL). 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/Et_2O = 1:1) to provide the title product **19** as a yellow solid (398.0 mg, 863 μmol, 98%).

Mp 56–58 °C; R_f = 0.34 (hexane/Et_2O = 1:1).

IR (ATR): 1699, 1516, 1472, 1396, 1380, 1328, 1262, 1237, 1177, 1158, 1141, 1090, 1028, 803, 625 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 6.78 (d, 1H, *J* = 7.9 Hz), 6.64 (dd, 1H, *J* = 7.9, 2.1 Hz), 6.62 (s, 1H), 6.46 (d, 1H, *J* = 2.1 Hz), 4.47 (t, 2H, *J* = 7.0 Hz), 4.35 (q, 2H, *J* = 7.2 Hz), 3.86 (s, 3H), 3.82 (s, 3H), 2.93 (t, 2H, *J* = 7.0 Hz), 1.41 (t, 3H, *J* = 7.2 Hz).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 159.7, 149.0, 147.9, 130.2, 127.6, 120.9, 120.4, 112.0, 111.4, 107.5, 100.3, 60.9, 56.0, 55.9, 52.9, 37.8, 14.3.

HRMS (ESI/TOF): *m/z* $[M + Na]^+$ calcd for $C_{17}H_{19}{}^{79}Br^{81}BrNO_4Na$: 483.9558; found: 483.9543.

Halogen–magnesium exchange of trihalopyrroles (Scheme 2)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with dibromoiodopyrrole **16** (177.5 mg, 0.30 mmol, 1.0 equiv) and anhydrous THF (3.0 mL). After *i*-PrMgCl·LiCl (1.3 M in THF, 0.30 mL, 0.39 mmol, 1.3 equiv) was added dropwise to the Schlenk tube, the reaction mixture was stirred at room temperature for 10 min, at the which time the reaction mixture was treated with water (3 mL). After being partitioned, the aqueous layer was extracted twice with Et_2O (3 mL). The combined organic extracts were washed with brine (5 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product. The yields of dibromopyrroles **10** and **19** were determined by ^1H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard by comparing relative values of integration for the peaks observed at 7.03 ppm (1 proton for **10**) and 6.46 ppm (1 proton for **19**) with that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm.

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with tribromopyrrole **18** (164.5 mg, 0.31 mmol, 1.0 equiv) and anhydrous THF (3.1 mL). After *i*-PrMgCl·LiCl (1.3 M in THF, 0.31 mL, 0.40 mmol, 1.3 equiv) was added dropwise to the Schlenk tube, the reaction mixture was stirred at room temperature for 10 min, at the which time the reaction mixture was treated with water (3 mL). After being partitioned, the aqueous layer was extracted twice with Et_2O (3 mL). The combined organic extracts were washed with brine (5 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product. The yields of dibromopyrroles **10** and **19** were determined by ^1H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard by comparing relative values of integration for the peaks observed at 7.03 ppm (1 proton for **10**) and 6.46 ppm (1 proton for **19**) with that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm.

1-(Benzyloxy)-4-iodo-2-methoxybenzene (12)

A 300-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was charged with 2-methoxyphenol (2.777 g, 22.4 mmol, 1.0 equiv), NaOH (1.690 g, 42.2 mmol, 1.9 equiv), and MeOH (25 mL). After the solution was cooled to 0 °C, I_2 (5.679 g, 22.4 mmol, 1.0 equiv) in MeOH (31 mL) was added dropwise to the flask at 0 °C. The reaction mixture was allowed to warm to room temperature with stirring over 4 h, at which time the reaction mixture was treated with saturated aqueous sodium thiosulfate (50 mL) and concentrated under reduced pressure to remove MeOH. The residue was dissolved in CH_2Cl_2 (30 mL), and the resulting mixture was washed with saturated aqueous ammonium chloride (30 mL). After being partitioned, the aqueous layer was extracted twice with CH_2Cl_2 (30 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 provide 4-iodo-2-methoxyphenol as a colorless solid (5.464 g), which was used for the next reaction without further purification.

A 100-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was charged with 4-iodo-2-methoxyphenol (5.464 g), K_2CO_3 (6.031 g, 43.6 mmol), benzyl bromide (3.750 g, 21.9 mmol), and MeCN (42 mL). The flask was placed in a preheated oil bath and heated at 80 °C 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 give a crude product, which was purified by silica gel column chromatography (hexane/CH_2Cl_2 = 9:1 to 3:1, gradient) to provide the title product **12** as a colorless solid (4.271 g, 12.6 mmol, 56% over 2 steps), whose ^1H and $^{13}C\{^1H\}$ NMR spectra were identical to those reported in the literature.[45]

Mp 59–60 °C; R_f = 0.21 (hexane/CH_2Cl_2 = 3:1).

IR (ATR): 2923, 1499, 1248, 1219, 1179, 1137, 1023, 838, 793, 735, 697 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, 2H, *J* = 6.8 Hz), 7.39–7.27 (m, 3H), 7.15 (dd, 1H, *J* = 7.6, 2.5 Hz), 7.14 (s, 1H), 6.62 (d, 1H, *J* = 7.6 Hz), 5.12 (s, 2H), 3.86 (s, 3H).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 150.5, 148.3, 136.7, 129.7, 128.6, 128.0, 127.3, 120.9, 115.9, 83.2, 71.0, 56.2.

HRMS (ESI/TOF): *m/z* [M + Na]$^+$ calcd for $C_{14}H_{13}IO_2Na$: 362.9858; found: 362.9846.

Ethyl 3-(4-(benzyloxy)-3-methoxyphenyl)-4,5-dibromo-1-(3,4-dimethoxyphenethyl)-1*H*-pyrrole-2-carboxylate (13)

A flame-dried 100-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with dibromopyrrole **10** (934.2 mg, 2.03 mmol, 1.0 equiv) and anhydrous THF (20 mL). After the solution was cooled to –40 °C, TMPMgCl·LiCl (1.0 M in THF/toluene, 4.7 mL, 4.7 mmol, 2.3 equiv) was added to the Schlenk tube, and the resulting mixture was stirred at –40 °C for 10 min, at which time to the solution was added $ZnCl_2$·TMEDA (664.6 mg, 2.63 mmol, 1.3 equiv) at –40 °C. After the resulting mixture was allowed to warm to room temperature for 20 min, $Pd(PPh_3)_4$ (234.7 mg, 203 μmol, 10 mol%) and aryl iodide **12** (828.6 mg, 2.44 mmol, 1.2 equiv) were added to the Schlenk tube. The Schlenk tube was placed in a preheated oil bath and heated at 60 °C for 15 h, at which time the reaction mixture was treated with 1 M aqueous hydrochloric acid (20 mL). The reaction mixture was extracted twice with Et_2O (20 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 (1st: hexane/methyl acetate = 4:1, 2nd: hexane/ethyl acetate = 17:3) followed by automated flash chromatography system (Yamazen, W-prep 2XY; eluent: hexane/ethyl acetate = 17:3 to 3:2, gradient) to provide the title compound **13** as a yellow solid (923.8 mg, 1.37 mmol, 67%).

Mp 104–105 °C; R_f = 0.30 (hexane/Et_2O = 1:1).

IR (ATR): 2928, 2832, 1698, 1515, 1502, 1462, 1454, 1409, 1383, 1341, 1261, 1237, 1183, 1156, 1139, 1100, 1030 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, 2H, *J* = 7.6 Hz), 7.40–7.27 (m, 3H), 6.88 (d, 1H, *J* = 8.4 Hz), 6.81–6.76 (m, 3H), 6.72 (dd, 1H, *J* = 8.4, 0.8 Hz), 6.65 (s, 1H), 5.20 (s, 2H), 4.66 (t, 2H, *J* = 7.6 Hz), 3.97 (q, 2H, *J* = 7.1 Hz), 3.88 (s, 3H), 3.86 (s, 6H), 2.98 (t, 2H, *J* = 7.6 Hz), 0.87 (t, 3H, *J* = 7.1 Hz).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 160.2, 148.8, 148.6, 147.8, 147.4, 137.1, 132.3, 130.1, 128.5, 127.7, 127.4, 127.2, 122.5, 121.1, 121.0, 114.0, 112.9, 112.0, 111.2, 102.1, 70.8, 60.1, 55.9, 55.8, 55.7, 50.1, 36.6, 13.6 (one aromatic carbon signal is missing because of overlapping).

HRMS (ESI/TOF): *m/z* [M + Na]$^+$ calcd for $C_{31}H_{31}{}^{79}Br^{81}BrNO_6Na$: 696.0395; found: 696.0402.

4-(4-(Benzyloxy)-3-methoxyphenyl)-3-bromo-1-(3,4-dimethoxyphenethyl)-5-(ethoxycarbonyl)-1*H*-pyrrole-2-carboxylic acid (23)

A flame-dried 50-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and rubber septum was charged with dibromopyrrole **13** (506.8 mg, 750 μmol, 1.0 equiv) and anhydrous THF (7.4 mL). After the solution was cooled to –78 °C, *n*-BuLi (1.58 M in hexane, 470 μL, 750 μmol, 1.0 equiv) was added dropwise to the Schlenk tube over 1 min. The mixture was stirred for 10 min, and CO_2 gas was bubbled through the mixture at –78 °C for 30 min. The mixture was allowed to warm to room temperature with stirring for 1 h, at which time the reaction mixture was treated with 1 M aqueous hydrochloric acid (8 mL). The reaction mixture was extracted with Et_2O (8 mL) three times. The combined organic extracts were washed with water (24 mL) and brine (24 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/Et_2O = 1:1, then CH_2Cl_2/MeOH = 20:1) to provide the title compound **23** as a yellow solid (412.7 mg, 646 μmol, 86%).

Mp 129–130 °C; R_f = 0.21 (CH_2Cl_2/MeOH = 20:1).

IR (ATR): 2937, 2901, 2833, 1715, 1673, 1589, 1538, 1516, 1464, 1441, 1409, 1345, 1261, 1238, 1177, 1156, 1139, 1028, 806, 763, 751, 698, 636 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, 2H, *J* = 8.0 Hz), 7.40–7.28 (m, 3H), 6.89 (d, 1H, *J* = 8.4 Hz), 6.76–6.65 (m, 5H), 5.20 (s, 2H), 4.95 (t, 2H, *J* = 7.4 Hz), 3.94 (q, 2H, *J* = 7.1 Hz), 3.89 (s, 3H), 3.85 (s, 3H), 3.82 (s, 3H), 3.05 (t, 2H, *J* = 7.4 Hz), 0.82 (t, 3H, *J* = 7.1 Hz).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.2, 160.7, 148.93, 148.87, 147.9, 147.7, 137.2, 131.5, 130.5, 128.6, 127.9, 127.4, 127.2, 127.0, 122.7, 122.5, 121.1, 114.1, 113.1, 112.1, 111.3, 108.2, 71.0, 61.0, 56.1, 56.0, 55.9, 49.6, 37.9, 13.5.

HRMS (ESI/TOF): *m/z* [M + Na]$^+$ calcd for $C_{32}H_{32}{}^{81}BrNO_8Na$: 662.1189; found: 662.1157.

Ethyl 2-(4-(benzyloxy)-3-methoxyphenyl)-1-bromo-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (24)

A 100-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was charged with carboxylic acid **23** (371.8 mg, 582 μmol, 1.0 equiv), $Pd(OAc)_2$ (148.1 mg, 660 μmol, 1.1 equiv), and anhydrous MeCN (29 mL). The flask was placed in a preheated oil bath and heated at reflux for 13 h, at which time the solution was treated with water (30 mL). The reaction mixture was extracted with ethyl acetate (30 mL) three times. The combined organic extracts were washed with water (90 mL) and brine (90 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 (CH_2Cl_2) to provide the title compound **24** as a yellow solid (112.9 mg, 191 μmol, 33%).

Mp 135–137 °C; R_f = 0.14 (CH_2Cl_2).

IR (ATR): 2934, 1690, 1499, 1464, 1408, 1256, 1228, 1213, 1182, 1132, 1068, 751 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (s, 1H), 7.47 (d, 2H, *J* = 7.6 Hz), 7.40–7.28 (m, 3H), 6.92 (d, 1H, *J* = 8.2 Hz), 6.87 (d, 1H, *J* = 1.8 Hz), 6.79 (dd, 1H, *J* = 8.2, 1.8 Hz), 6.77 (s, 1H), 5.22 (s, 2H), 4.61 (t, 2H, *J* = 6.5 Hz), 4.02 (q, 2H, *J* = 7.1 Hz), 3.94 (s, 3H), 3.93 (s, 3H), 3.90 (s, 3H), 3.01 (t, 2H, *J* = 6.5 Hz), 0.89 (t, 3H, *J* = 7.1 Hz).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 161.1, 148.59, 148.56, 147.5, 147.3, 137.2, 133.1, 130.5, 128.5, 128.0, 127.8, 127.3, 126.3, 122.8, 120.0, 118.8, 114.4, 112.9, 110.8, 108.3, 95.7, 70.8, 59.9, 56.05, 55.96, 55.93, 43.0, 29.1, 13.7.

HRMS (ESI/TOF): *m/z* [M + Na]$^+$ calcd for $C_{31}H_{30}{}^{79}BrNO_6Na$: 614.1154; found: 614.1147.

2-(4-(Benzyloxy)-3-methoxyphenyl)-1-bromo-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylic acid (25)

A 10-mL test tube equipped with a Teflon-coated magnetic stirring bar was charged with compound **24** (112.1 mg, 189 μmol, 1.0 equiv), 18-crown-6 (105.4 mg, 399 μmol, 2.1 equiv), KOH (106.3 mg, 1.89 mmol, 10 equiv), THF (0.6 mL), and water (0.3 mL). The flask was placed in a preheated oil bath and heated at 60 °C for 4 h, at which time the solution was treated with 1 M aqueous hydrochloric acid (3 mL). The crude product was collected by filtration, which was washed with Et_2O (3 mL) to provide the title compound **25** as a colorless solid (96.5 mg, 171 μmol, 90%).

Mp 143–144 °C (decomposition); R_f = 0.58 (CH_2Cl_2/MeOH = 10:1).

IR (ATR): 1654, 1498, 1481, 1465, 1457, 1438, 1417, 1265, 1229, 1215, 1133 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (s, 1H), 7.49 (d, 2H, *J* = 7.2 Hz), 7.42–7.29 (m, 3H), 6.99 (d, 1H, *J* = 8.3 Hz), 6.91 (d, 1H, *J* = 1.9 Hz), 6.88 (dd, 1H, *J* = 8.3, 1.9 Hz), 6.78 (s, 1H), 5.20 (s, 2H), 4.66 (t, 2H, *J* = 6.7 Hz), 3.94 (s, 3H), 3.93 (s, 3H), 3.90 (s, 3H), 3.02 (t, 2H, *J* = 6.7 Hz).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.1, 149.1, 148.9, 147.9, 147.7, 137.3, 135.1, 132.2, 128.7, 128.0, 127.6, 127.4, 126.7, 123.0, 119.8, 117.3, 114.6, 113.0, 110.9, 108.7, 96.7, 71.1, 56.2, 56.12, 56.08, 43.5, 29.2.

HRMS (ESI/TOF): *m/z* [M + Na]$^+$ calcd for $C_{29}H_{26}{}^{79}BrNO_6Na$: 586.0841; found: 586.0847.

2-(4-(Benzyloxy)-3-methoxyphenyl)-1-bromo-10b-hydroxy-8,9-dimethoxy-6,10b-dihydropyrrolo[2,1-*a*]isoquinolin-3(5*H*)-one (26)

A 50-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar and a reflux condenser was charged with carboxylic acid **25** (59.5 mg, 105 μmol, 1.0 equiv) and ethyl acetate (10.5 mL). After $Pb(OAc)_4$ (75.0 mg, 169 μmol, 1.6 equiv) was added to the solution, and the reaction mixture was heated at reflux for 1.5 h. After cooling to room temperature, pinacol (20.5 mg, 173 μmol, 1.6 equiv) was added to the flask, and resulting mixture was treated with water (10 mL). The reaction mixture was extracted with ethyl acetate (10 mL) three times. The combined organic extracts were washed with water (30 mL) and 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 (1st: hexane/Et_2O = 1:1 to Et_2O, gradient, 2nd: hexane/EtOAc = 1:1 to 2:3, gradient) to provide the title product **26** as a yellow solid (21.7 mg, 39.2 μmol, 37%).

Mp 113–115 °C (decomposition); R_f = 0.41 (hexane/ethyl acetate = 1:2).

IR (ATR): 3372, 2927, 2855, 1745, 1686, 1513, 1456, 1408, 1326, 1261, 1208, 1136, 1107, 1025, 864, 822, 806, 755, 697, 627 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 7.74 (s, 1H), 7.43 (d, 2H, *J* = 6.8 Hz), 7.39–7.24 (m, 5H), 6.91 (d, 1H, *J* = 8.7 Hz), 6.63 (s, 1H), 5.18 (s, 2H), 4.43 (dd, 1H, *J* = 13.2, 4.4 Hz), 3.96 (s, 3H), 3.89 (s, 3H), 3.87 (s, 3H), 3.37 (td, 1H, *J* = 12.8, 3.6 Hz), 3.07 (s, 1H), 2.99–2.88 (m, 1H), 2.60 (dd, 1H, *J* = 16.2, 2.2 Hz).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 168.2, 149.5, 149.2, 149.0, 147.7, 138.9, 136.9, 134.1, 128.7, 128.0, 127.3, 125.3, 122.7, 122.0, 113.1, 113.0, 111.3, 111.2, 86.1, 70.9, 56.20, 56.18, 56.0, 36.9, 29.3 (one carbon signal is missing because of overlapping).

HRMS (ESI/TOF): *m/z* $[M + Na]^+$ calcd for $C_{28}H_{26}{}^{79}BrNO_6Na$: 574.0841; found: 574.0850.

7-(Benzyloxy)-1,2-dibromo-3-(3,4-dimethoxyphenethyl)-8-methoxychromeno[3,4-*b*]pyrrol-4(3*H*)-one (14)

A 100-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was charged with compound **13** (1.719 g, 2.55 mmol, 1.0 equiv), 18-crown-6 (1.378 g, 5.21 mmol, 2.0 equiv), KOH (1.448 g, 25.8 mmol, 10 equiv), THF (8.4 mL), and water (4.2 mL). The flask was placed in a preheated oil bath and heated at 60 °C for 4 h, at which time the solution was treated with 1 M aqueous hydrochloric acid (20 mL). The reaction mixture was extracted with Et_2O (20 mL) three times. 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 provide the corresponding carboxylic acid (1.819 g), which was used for the next reaction without further purification.

The crude carboxylic acid (1.819 g) was transferred into a 500-mL round-bottomed flask with the aid of ethyl acetate (250 mL). The flask was equipped with a Teflon-coated magnetic stirring bar and a reflux condenser. After $Pb(OAc)_4$ (1.809 g, 4.08 mmol) was added to the solution, the flask was placed in a preheated oil bath and heated at reflux for 30 min. After cooling to room temperature, pinacol (492.8 mg, 4.17 mmol) was added to the flask, and resulting mixture was treated with water (100 mL). The reaction mixture was extracted with ethyl acetate (50 mL) three times. The combined organic extracts were washed with water (150 mL) and brine (150 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was recrystallized from CH_2Cl_2/MeCN to provide the title compound **14** as a colorless solid (1.236 g, 1.92 mmol, 75% over 2 steps).

Mp 187–188 °C; R_f = 0.47 ($CHCl_3$).

IR (ATR): 2951, 2935, 2835, 1712, 1617, 1591, 1514, 1465, 1456, 1406, 1263, 1233, 1172, 1159, 1124, 1029, 1008, 753 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 8.05 (s, 1H), 7.46 (d, 2H, *J* = 7.2 Hz), 7.42–7.29 (m, 3H), 6.93 (s, 1H), 6.79 (d, 1H, *J* = 9.0 Hz), 6.75 (dd, 1H, *J* = 9.0, 1.4 Hz), 6.73 (d, 1H, *J* = 1.4 Hz), 5.22 (s, 2H), 4.77 (t, 2H, *J* = 7.8 Hz), 4.00 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.00 (t, 2H, *J* = 7.8 Hz).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 153.6, 149.1, 149.0, 148.1, 146.5, 146.1, 136.2, 129.8, 128.8, 128.3, 127.4, 127.3, 121.2, 119.9, 116.0, 112.3, 111.4, 108.8, 104.3, 102.6, 93.5, 71.1, 56.4, 56.0, 55.9, 50.3, 36.9.

HRMS (ESI/TOF): *m/z* $[M + Na]^+$ calcd for $C_{29}H_{25}{}^{79}Br{}^{81}BrNO_6Na$: 665.9926; found: 665.9947.

7-(Benzyloxy)-1-bromo-3-(3,4-dimethoxyphenethyl)-8-methoxy-4-oxo-3,4-dihydrochromeno[3,4-*b*]pyrrole-2-carboxylic acid (27)

A flame-dried 50-mL two-necked flask equipped with a Teflon-coated magnetic stirring bar, rubber septum, and a reflux condenser was charged with dibromopyrrole **14** (609.0 mg, 947 μmol, 1.0 equiv) and anhydrous THF (18.9 mL). After the suspension was heated to 60 °C, to the suspension was added *i*-PrMgCl·LiCl (1.3 M in THF, 1.5 mL, 1.9 mmol, 2.0 equiv). The suspension turned to a yellow solution, which was stirred for 10 min, and CO_2 gas was bubbled through the solution at 60 °C for 1 h, at which time the resulting mixture was treated with 1 M aqueous hydrochloric acid (20 mL). The resulting solid was collected by filtration to provide the title compound **27** as a colorless solid (382.3 mg, 628 μmol, 66%).

Mp 213–214 °C; R_f = 0.21 (CH_2Cl_2/MeOH = 10:1).

IR (ATR): 3365, 1720, 1650, 1620, 1512, 1469, 1462, 1274, 1236, 1160, 1013, 850, 763, 729 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 8.31 (s, 1H), 7.46 (d, 2H, *J* = 7.6 Hz), 7.42–7.32 (m, 3H), 6.94 (s, 1H), 6.80–6.72 (m, 3H), 5.24 (s, 2H), 5.15 (t, 2H, *J* = 7.6 Hz), 4.01 (s, 3H), 3.86 (s, 3H), 3.83 (s, 3H), 3.04 (t, 2H, *J* = 7.6 Hz).

$^{13}C\{^1H\}$ NMR (100 MHz, THF-d_8): δ 154.2, 150.5, 150.1, 149.4, 147.4, 146.9, 137.8, 131.3, 129.0, 128.4, 128.1, 126.3, 121.6, 113.8, 112.9, 109.9, 105.6, 103.1, 71.2, 56.4, 56.0, 55.8, 50.0, 38.3 (four aromatic carbon signals are missing because of overlapping).

HRMS (ESI/TOF): *m/z*:$[M + Na]^+$ calcd for $C_{30}H_{26}{}^{81}BrNO_8Na$: 632.0719; found: 632.0728.

3-(Benzyloxy)-14-bromo-2,11,12-trimethoxy-8,9-dihydro-6*H*-chromeno[4',3':4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (15)

A 100-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was charged with carboxylic acid **27** (304.6 mg, 501 μmol, 1.0 equiv), $Pd(OAc)_2$ (121.4 mg, 541 μmol, 1.1 equiv), and DMF (25 mL). The flask was placed in a preheated oil bath and heated at 60 °C for 13 h. After cooling to 0 °C, NBS (53.5 mg, 301 μmol, 0.60 equiv) was added to the flask. After the resulting mixture was allowed to warm to room temperature, the resulting mixture was stirred for 8 h, at which time the reaction mixture was treated with saturated aqueous sodium thiosulfate (25 mL). The resulting mixture was extracted with ethyl acetate (25 mL) three times. The combined organic extracts were washed with 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/CH_2Cl_2 = 1:9) to provide the title compound **15** as a colorless solid (86.2 mg, 153 μmol, 31%).

Mp 214–216 °C; R_f = 0.28 ($CHCl_3$).

IR (ATR): 1702, 1509, 1485, 1422, 1270, 1240, 1209, 1165, 1040, 1011, 849, 697 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 8.29 (s, 1H), 8.16 (s, 1H), 7.46 (d, 2H, *J* = 7.6 Hz), 7.42–7.29 (m, 3H), 6.95 (s, 1H), 6.82 (s, 1H), 5.23 (s, 2H), 4.77 (t, 2H, *J* = 6.7 Hz), 4.01 (s, 3H), 3.99 (s, 3H), 3.95 (s, 3H), 3.06 (t, 2H, *J* = 6.7 Hz).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 154.8, 149.7, 148.5, 147.8, 146.3, 146.0, 136.3, 135.4, 128.8, 128.3, 127.6, 127.4, 127.2, 119.3, 114.4, 111.2, 110.1, 109.1, 104.8, 102.8, 86.8, 71.1, 56.5, 56.3, 56.1, 42.7, 29.1.

HRMS (ESI/TOF): *m/z* $[M + Na]^+$ calcd for $C_{29}H_{24}{}^{79}BrNO_6Na$: 584.0685; found: 584.0684.

(3-(Benzyloxy)-4-methoxyphenyl)tributylstannane (28)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with 2-benzyloxy-4-bromo-1-methoxybenzene (509.7 mg, 1.74 mmol, 1.0 equiv) and anhydrous THF (8.5 mL). After the solution was cooled to −78 °C, *n*-BuLi (1.57 M in *n*-hexane, 1.11 mL, 1.74 mmol, 1.0 equiv) was added dropwise to the solution. The resulting mixture was stirred at −78 °C for 10 min. To the solution was added tributyltin chloride (564.9 mg, 1.74 mmol, 1.0 equiv) at −78 °C. After stirring at −78 °C for 10 min, the reaction mixture was allowed to warm to room temperature with stirring for 30 min, at which time the reaction mixture was treated with water (10 mL). The reaction mixture was extracted with Et_2O (10 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/CH_2Cl_2 = 3:2) to provide the title product **28** as a colorless oil (795.6 mg, 990 μmol, 57%).

R_f = 0.29 (hexane/CH_2Cl_2 = 3:2).

IR (ATR): 2955, 2927, 1503, 1461, 1454, 1248, 1221, 1142, 1026, 800, 735, 696 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, 2H, *J* = 7.2 Hz), 7.38–7.27 (m, 3H), 6.99 (dd, 1H, *J* = 8.0, 0.8 Hz), 6.94 (d, 1H, *J* = 0.8 Hz), 6.91 (d, 1H, *J* = 8.0 Hz), 5.17 (s, 2H), 3.88 (s, 3H), 1.53–1.43 (m, 6H), 1.35–1.23 (m, 6H), 0.97 (t, 6H, *J* = 8.2 Hz), 0.87 (t, 9H, *J* = 7.2 Hz).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 150.0, 148.0, 137.6, 132.6, 129.9, 128.6, 127.9, 127.4, 122.2, 111.9, 71.4, 55.9, 29.2, 27.5, 13.8, 9.7.

HRMS (DART/TOF): *m/z* $[M + H]^+$ calcd for $C_{26}H_{41}O_2{}^{120}Sn$: 505.2129; found: 505.2141.

(4-(Benzyloxy)-3-methoxyphenyl)tributylstannane (29)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with 1-benzyloxy-4-iodo-2-methoxybenzene (**12**) (577.6 mg, 1.70 mmol, 1.0 equiv) and anhydrous THF (8.5 mL). After the solution was cooled to −78 °C, *n*-BuLi (1.57 M in *n*-hexane, 1.08 mL, 1.70 mmol, 1.0 equiv) was added dropwise to the solution. The resulting mixture was stirred at −78 °C for 10 min. To the solution was added tributyltin chloride (556.3 mg, 1.71 mmol, 1.0 equiv) at −78 °C. After stirring at −78 °C for 10 min, the reaction mixture was allowed to warm to room temperature with stirring for 30 min, at which time the reaction mixture was treated with water (10 mL). The reaction mixture was extracted with Et_2O (10 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/CH_2Cl_2 = 3:2) to provide the title product **29** as a colorless oil (420.6 mg, 836 μmol, 49%), whose spectroscopic data of ^1H and $^{13}C\{^1H\}$ NMR were not in good agreement with those reported in the literature.[46]

R_f = 0.26 (hexane/CH_2Cl_2 = 3:2).

IR (ATR): 2956, 2926, 1502, 1462, 1454, 1379, 1247, 1224, 1143, 1024, 798, 734, 695 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, 2H, *J* = 7.2 Hz), 7.39–7.27 (m, 3H), 6.97 (s, 1H), 6.93 (d, 1H, *J* = 8.2 Hz), 6.89 (d, 1H, *J* = 8.2 Hz), 5.15 (s, 2H), 3.90 (s, 3H), 1.61–1.48 (m, 6H), 1.38–1.27 (m, 6H), 1.03 (t, 6H, *J* = 8.2 Hz), 0.88 (t, 9H, *J* = 7.2 Hz).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 149.4, 148.6, 137.5, 133.4, 129.3, 128.6, 127.9, 127.4, 119.6, 114.0, 70.9, 56.2, 29.2, 27.5, 13.8, 9.8.

HRMS (DART/TOF): *m/z* $[M + H]^+$ calcd for $C_{26}H_{41}O_2{}^{120}Sn$: 505.2129; found: 505.2114.

3-(Benzyloxy)-14-(3-(benzyloxy)-4-methoxyphenyl)-2,11,12-trimethoxy-8,9-dihydro-6*H*-chromeno[4',3':4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (30)

A flame-dried 10-mL test tube equipped with a Teflon-coated magnetic stirring bar, a rubber septum, and a three-way stopcock was charged with bromopyrrole **15** (89.7 mg, 159 μmol, 1.0 equiv), arylstannane **28** (120.6 mg, 240 μmol, 1.5 equiv), $Pd(PPh_3)_4$ (17.9 mg, 15.5 μmol, 10 mol%), and anhydrous toluene (1.6 mL). The flask was placed in a preheated oil bath and heated at 100 °C for 14 h, at which time 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 brine (6 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/$CHCl_3$ = 1:4) followed by preparative SEC–HPLC to provide the title compound **30** as a colorless solid (60.4 mg, 86.8 μmol, 55%).

Mp 227–229 °C; R_f = 0.23 ($CHCl_3$).

IR (ATR): 1698, 1485, 1455, 1440, 1415, 1268, 1243, 1213, 1167, 1137, 1044, 742, 695 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 7.44–7.40 (m, 2H), 7.39–7.33 (m, 4H), 7.33–7.27 (m, 2H), 7.25–7.21 (m, 2H), 7.10–7.08 (m, 3H), 6.90 (s, 1H), 6.74 (s, 1H), 6.62 (s, 1H), 6.60 (s, 1H), 5.18 (s, 2H), 5.14 (d, 1H, *J* = 12.2 Hz), 5.12 (d, 1H, *J* = 12.2 Hz), 4.86–4.77 (m, 1H), 4.76–4.67 (m, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 3.42 (s, 3H), 3.29 (s, 3H), 3.10 (t, 2H, *J* = 6.8 Hz).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 155.6, 149.6, 149.0, 148.9, 147.7, 147.5, 146.1, 145.8, 136.6, 136.4, 136.0, 128.8, 128.7, 128.6, 128.2, 128.1, 128.0, 127.5, 127.3, 126.6, 124.1, 120.1, 116.7, 114.8, 113.8, 112.6, 111.0, 110.7, 108.7, 104.9, 102.6, 71.0, 70.9, 56.5, 56.0, 55.6, 55.2, 42.4, 28.8.

HRMS (ESI/TOF): *m/z* $[M + Na]^+$ calcd for $C_{43}H_{37}NO_8Na$: 718.2417; found: 718.2402.

3-(Benzyloxy)-14-(4-(benzyloxy)-3-methoxyphenyl)-2,11,12-trimethoxy-8,9-dihydro-6*H*-chromeno[4',3':4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (31)

A flame-dried 10-mL test tube equipped with a Teflon-coated magnetic stirring bar, a rubber septum, and a three-way stopcock was charged with bromopyrrole **15** (93.1 mg, 166 μmol, 1.0 equiv), arylstannane **29** (124.7 mg, 248 μmol, 1.5 equiv), $Pd(PPh_3)_4$ (19.1 mg, 16.5 μmol, 10 mol%), and anhydrous toluene (1.7 mL). The flask was placed in a preheated oil bath and heated at 100 °C for 14 h, at which time the reaction mixture was treated with water (2 mL). The resulting mixture was extracted with EtOAc (2 mL) three times. The combined organic extracts were washed with 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/$CHCl_3$ = 1:4) followed by preparative SEC–HPLC to provide the title compound **31** as a colorless solid (48.6 mg, 69.9 μmol, 42%).

Mp 230–232 °C; R_f = 0.35 ($CHCl_3$).

IR (ATR): 1704, 1486, 1462, 1438, 1415, 1269, 1239, 1212, 1166, 1041, 1012, 749, 697 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 7.49–7.44 (m, 2H), 7.43–7.27 (m, 8H), 7.07 (d, 1H, *J* = 8.1 Hz), 7.04 (d, 1H, *J* = 1.7 Hz), 7.01 (dd, 1H, *J* = 8.1, 1.7 Hz), 6.88 (s, 1H), 6.74 (s, 1H), 6.68 (s, 1H), 6.64 (s, 1H), 5.27 (s, 2H), 5.15 (s, 2H), 4.87–4.78 (m, 1H), 4.75–4.66 (m, 1H), 3.879 (s, 3H), 3.875 (s, 3H), 3.37 (s, 3H), 3.27 (s, 3H), 3.13–3.06 (m, 2H).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 155.6, 150.5, 149.0, 147.74, 147.68, 147.5, 146.0, 145.8, 137.0, 136.4, 136.0, 128.80, 128.76, 128.5, 128.19, 128.15, 127.3, 127.1, 126.7, 123.5, 120.1, 114.9, 114.6, 114.5, 113.8, 111.0, 110.7, 108.7, 104.8, 102.7, 71.0, 70.9, 56.3, 56.0, 55.6, 55.2, 42.5, 28.8 (one aromatic carbon signal is missing because of overlapping).

HRMS (ESI/TOF): *m/z* $[M + Na]^+$ calcd for $C_{43}H_{37}NO_8Na$: 718.2417; found: 718.2415.

Lamellarin U

A 10-mL test tube equipped with a Teflon-coated magnetic stirring bar, a rubber septum, and a three-way stopcock was charged with compound

30 (23.8 mg, 34.2 μmol, 1.0 equiv), Pd/C (23.4 mg, 100 wt%), EtOH (0.6 mL), and ethyl acetate (0.6 mL). After the flask was evacuated and backfilled with H_2 three times, the resulting mixture was stirred at room temperature for 16 h. The resulting mixture was filtered through a pad of Celite, and the filter cake was washed with hot MeOH (20 mL). The filtrate was concentrated under reduced pressure to provide lamellarin U as a gray solid (15.0 mg, 29.1 μmol, 85%), whose spectroscopic data of ^{1}H and ^{13}C{^{1}H} NMR were in good agreement with those reported in the literature.[6d,22a]

Mp 230–232 °C (Lit.[22a] 200–204 °C, Lit.[10c] 247–250 °C, Lit.[13a] 198–200 °C, Lit.[6d] 242–243 °C, Lit.[19a] 201–203 °C); R_f = 0.49 (CH_2Cl_2/MeOH = 20:1).

IR (ATR): 1690, 1486, 1462, 1440, 1414, 1273, 1247, 1213, 1163, 1144, 1044, 1024, 758 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13 (d, 1H, *J* = 1.9 Hz), 7.04 (d, 1H, *J* = 8.1 Hz), 7.00 (dd, 1H, *J* = 8.1, 1.9 Hz), 6.95 (s, 1H), 6.75 (s, 1H), 6.72 (s, 1H), 6.70 (s, 1H), 5.74 (s, 1H), 5.71 (s, 1H), 4.88–4.78 (m, 1H), 4.78–4.69 (m, 1H), 3.97 (s, 3H), 3.89 (s, 3H), 3.52 (s, 3H), 3.39 (s, 3H), 3.11 (t, 2H, *J* = 7.0 Hz).

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.69 (s, 1H), 9.31 (s, 1H), 7.15 (d, 1H, *J* = 8.0 Hz), 6.98 (s, 1H), 6.90 (dd, 1H, *J* = 8.0, 2.0 Hz), 6.89 (s, 1H), 6.81 (s, 1H), 6.69 (s, 1H), 6.68 (s, 1H), 4.72–4.63 (m, 1H), 4.63–4.53 (m, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 3.38 (s, 3H), 3.26 (s, 3H), 3.09 (t, 2H, *J* = 7.0 Hz).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 155.8, 149.1, 147.5, 146.6, 146.53, 146.49, 145.6, 143.4, 136.0, 128.8, 128.3, 126.8, 123.2, 120.2, 117.6, 114.7, 113.8, 111.4, 111.1, 110.4, 109.0, 104.3, 103.5, 56.4, 56.1, 55.7, 55.3, 42.5, 28.8.

^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 154.3, 148.9, 147.7, 147.6, 147.0, 146.9, 145.7, 144.5, 135.4, 127.4, 127.2, 127.0, 121.6, 119.2, 117.8, 114.4, 113.5, 112.6, 111.8, 108.7, 108.6, 105.0, 103.6, 56.1, 55.6, 55.1, 54.5, 42.0, 27.7.

HRMS (DART/TOF): *m/z* [M + H]$^+$ calcd for $C_{29}H_{26}NO_8$: 516.1658; found: 516.1654.

Lamellarin A3

A 10-mL test tube equipped with a Teflon-coated magnetic stirring bar, a rubber septum, and a three-way stopcock was charged with compound **31** (20.3 mg, 29.2 μmol, 1.0 equiv), Pd/C (20.3 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 16 h. The resulting mixture was filtered through a pad of Celite, and the filter cake was washed with hot MeOH (40 mL). The filtrate was concentrated under reduced pressure to provide lamellarin A3 as a gray solid (12.1 mg, 23.5 μmol, 80%), whose spectroscopic data of ^{1}H and ^{13}C{^{1}H} NMR were in good agreement with those reported in the literature.[23]

Mp >250 °C (Lit.[6d] 292–294 °C); R_f = 0.39 (CH_2Cl_2/MeOH = 20:1).

IR (ATR): 3368, 1684, 1486, 1438, 1412, 1274, 1247, 1214, 1163, 1043, 759, 668, 640, 615 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13 (d, 1H, *J* = 8.0 Hz), 7.08 (dd, 1H, *J* = 8.0, 1.6 Hz), 6.98 (s, 1H), 6.96 (s, 1H), 6.76 (s, 1H), 6.71 (s, 1H), 6.64 (s, 1H), 5.75 (s, 1H), 5.72 (s, 1H), 4.99–4.89 (m, 1H), 4.70–4.59 (m, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.50 (s, 3H), 3.38 (s, 3H), 3.21–3.04 (m, 2H).

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.39 (br s, 2H), 7.03 (d, 1H, *J* = 2.0 Hz), 7.02 (d, 1H, 7.8 Hz), 6.98 (s, 1H), 6.89 (dd, 1H, *J* = 7.8, 2.0 Hz), 6.80 (s, 1H), 6.70 (s, 1H), 6.61 (s, 1H), 4.63 (t, 2H, *J* = 6.7 Hz), 3.77 (s, 3H), 3.74 (s, 3H), 3.25 (s, 3H), 3.09 (t, 2H, *J* = 6.7 Hz).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 155.8, 149.0, 147.5, 147.3, 146.5, 145.61, 145.58, 143.4, 136.0, 128.4, 127.4, 126.7, 124.4, 120.2, 115.2, 114.9, 113.8, 113.5, 111.1, 110.4, 108.7, 104.1, 103.5, 56.4, 56.1, 55.8, 55.3, 42.5, 28.8.

^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 154.4, 148.9, 148.5, 147.2, 146.9, 146.6, 145.7, 144.6, 135.5, 127.7, 126.9, 125.3, 123.4, 119.4, 116.3, 114.7, 114.6, 112.5, 111.8, 108.6, 105.1, 103.6, 56.0, 55.6, 55.1, 54.5, 42.0, 27.7 (one aromatic carbon signal is missing because of overlapping).

HRMS (DART/TOF): *m/z* [M + H]$^+$ calcd for $C_{29}H_{26}NO_8$: 516.1658; found: 516.1667.

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Supporting Information

YES

Primary Data

NO

Conflict of Interest

The authors declare no conflict of interest.

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