A Paal–Knorr Approach to 3,4-Diaryl-Substituted Pyrroles: Facile Synthesis of Lamellarins O and Q

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Abstract: A very simple, yet efficient synthetic methodology, to obtain 3,4-diaryl-substituted pyrroles is described. The approach is based on the Knoevenagel condensation between arylacetonitriles and substituted aromatic aldehydes, followed by conjugate addition of cyanide to afford succinonitriles in excellent yields. The products thus obtained were subjected to DIBAL-H reduction, followed by cyclization under acidic conditions to produce the corresponding pyrroles in good overall yields. The utility of this protocol is exemplified by the synthesis of the marine alkaloids lamellarins O and Q.

Key words: pyrroles, Paal–Knorr, lamellarins, heterocycles, natural products

Lamellarins are a vast group of alkaloids of marine origin, first isolated by Faulkner[1] in 1985 from the mollusk *Lamellaria sp*. Thereafter, several members of the family have been isolated from other marine sources.[2–5] Currently, more than 50 members of this family are known,[6] which display a variety of biological activities such as bactericidal, antiviral, antioxidant, and cytotoxic. A comprehensive review on the synthesis and biological activity of lamellarin alkaloids has been recently published.[7] The basis for the mechanism of action of these compounds are not clearly understood, but it has been established that the cytotoxic activity is caused by the inhibition of the enzyme Topoisomerase-I,[8,9] and some members of the family inhibit the development of the HIV virus through the inhibition of the HIV-I integrase enzyme.[10] Hence, the availability of efficient synthetic protocols to have access to sufficient amounts of lamellarins required for bioassays would be highly desirable.

Lamellarins are polyoxygenated aromatic compounds containing a 3,4-diaryl-substituted pyrrole nucleus, which in some cases is fused to an isoquinoline ring, with the simplest members of this family being lamellarins O, P, Q and R (Figure 1).

As a consequence of the growing interest on these kind of compounds, several elegant syntheses have been reported. For instance, three syntheses have been reported for lamellarin D,[11–13] which shows the highest cytotoxicity.

For lamellarins Q and O, the aromatic rings on C-3 and C-4 were installed using a palladium-mediated cross coupling reaction,[14–18] which requires the preparation of the corresponding 3,4-dihalogenated pyrroles as the substrates using cumbersome procedures.

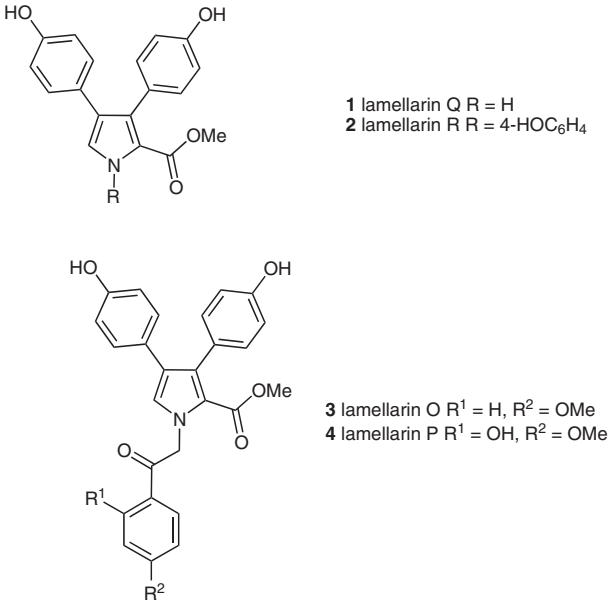

Figure 1 Lamellarins Q (**1**), R (**2**), O (**3**), and P (**4**)

When planning the synthesis of a heterocyclic compound, two approaches can be envisioned: the modification on an existing ring, usually through substitution reactions, and the synthesis of the heterocyclic core from a linear precursor. Even though pyrroles exhibit a readiness to undergo electrophilic substitution, this process takes place preferentially or exclusively at C-2/C-5, and some extra manipulations might be required to selectively introduce substituents at C-3/C-4.

Among the arsenal of methods to obtain pyrroles, the Paal–Knorr reaction[19] (the condensation between 1,4-dicarbonyl compounds and ammonia or primary amines), enjoys an excellent reputation, mainly because of its scope and simplicity of execution. Depending on the availability of the dicarbonyl compound, it can be the best choice to prepare 1,5-disubstituted pyrroles. However, when a different substitution pattern is required, such as C-3 or C-3 and C-4, the difficulties to prepare the 1,4-dialdehyde precursor, and its inherent instability, might represent a serious limitation to be considered during the use of this reaction.

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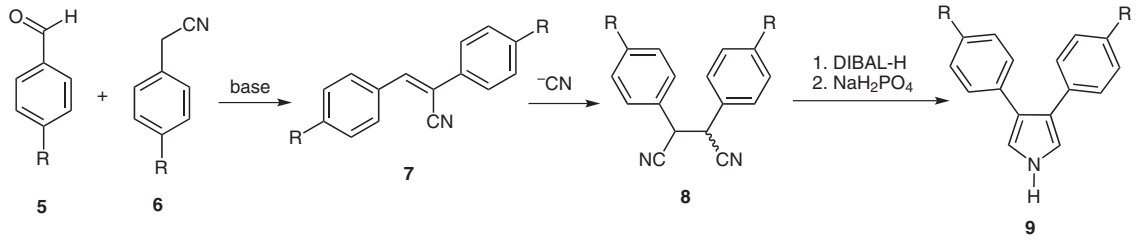


Scheme 1 Synthetic strategy to assemble 3,4-diarylsubstituted pyrroles

To the best to our knowledge, the Paal–Knorr approach has not been used to synthesize 3,4-diaryl-substituted pyrroles, and only two examples of the use of nitriles as masked carbonyl compounds to prepare substituted pyrroles have been reported.[20] In one of those examples, our group used this strategy for the synthesis of danaidone, a semiochemical of Danaid butterflies.[21]

Herein, we would like to disclose our findings on the use of succinonitriles as surrogates for the synthesis of 3,4-diaryl-substituted pyrroles. The potential of the method is further illustrated by the synthesis of lamellarins O and Q.

The general strategy for the construction of the pyrrole moiety is depicted in Scheme 1. Knoevenagel condensation between substituted benzaldehydes **5** and the corresponding phenylacetonitriles **6** would afford the acrylonitriles **7**, which upon conjugate addition of cyanide should produce a stereoisomeric mixture of succinonitriles **8**. DIBAL-H reduction of **8**, followed by heating the mixture with NaH_2PO_4 would yield the corresponding 3,4-diaryl-substituted pyrroles **9**.

Indeed, acrylonitriles **7a**–**d** and **7f** were obtained in 85–93% yields via a Knoevenagel condensation between benzaldehydes **5** and phenylacetonitriles **6** in the presence of NaOMe (1.15 equiv) in MeOH at ambient temperature. Only in the case of **7e**, heating the reaction mixture at reflux temperature was required (Table 1). When 4-nitrobenzaldehyde was used as the starting material, the corresponding dimethylacetal was obtained in almost quantitative yield under the conditions employed for the condensation.

Conjugate addition of cyanide in the presence of NH_4Cl afforded succinonitriles **8** in good yields. After some experimentation, it was established that a 3:1 ratio of DMF–H_2O was crucial to obtain the best results (Table 2). In the case of **8b**, no desired product was detected, instead a mixture of compounds was obtained, consisting of the starting material and the S_NAr products (Figure 2).

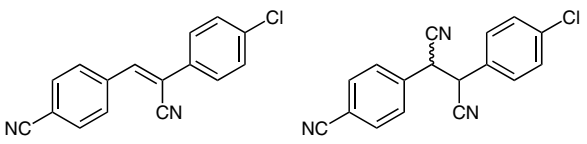
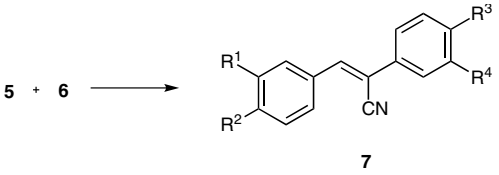


Figure 2 Products obtained from **8b**

Table 1 Knoevenagel Condensation to Obtain Acrylonitriles[a]



7	R^1	R^2	R^3	R^4	Yield (%)
a	H	OMe	OMe	H	85
b	H	Cl	Cl	H	90
c	OMe	OMe	OMe	OMe	90
d	H	H	H	H	90
e[b]	H	OBn	OBn	H	93
f	H	H	Cl	H	93
g	H	H	Me	H	99
h	H	H	OMe	H	87

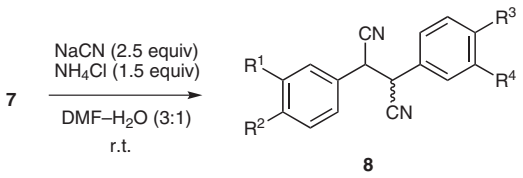
[a] Reaction conditions: NaOMe (1.15 equiv), MeOH (0.5 M), 6 h, r.t.
[b] At reflux temperature.

All succinonitriles thus obtained showed a very low solubility in the common organic solvents, including DMF and DMSO. As a matter of fact, the products precipitated from the reaction mixture upon cooling to ambient temperature.

For the formation of the pyrrole ring, it was found that the use of 2.5 equivalents of a 1.0 M DIBAL-H solution, followed by acidic treatment (aq 1.5 M NaH_2PO_4) at 100 °C produced the corresponding pyrroles **9** in good yields (Table 3). These results can be considered as excellent in the context of pyrrole synthesis, and the mild reaction conditions employed strongly suggest that the process is amenable to scaling up.

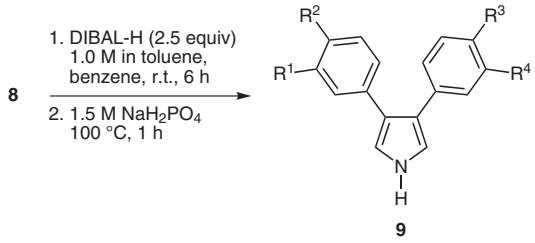
Acylation of 3,4-diaryl-substituted pyrroles such as **9a** has been reported in the literature,[22] however, when we tried to reproduce the conditions described, only starting material was observed. When trichloroacetyl chloride in the presence of DMAP was employed, pyrrole **9a** was smoothly acylated (Scheme 2). Since the methyl ester was the target product, the trichloromethyl ketone was not isolated and the crude mixture was treated with NaOMe in

Table 2 Succinonitrile Formation via Conjugate Addition



8	R^1	R^2	R^3	R^4	Yield (%)
a	H	OMe	OMe	H	90
b	H	Cl	Cl	H	–
c	OMe	OMe	OMe	OMe	77
d	H	H	H	H	90
e	H	OBn	OBn	H	95
f	H	H	Cl	H	95
g	H	H	Me	H	89
h	H	H	OMe	H	94

Table 3 Pyrrole Formation



9	R^1	R^2	R^3	R^4	Yield (%)
a	H	OMe	OMe	H	63
c	OMe	OMe	OMe	OMe	60
d	H	H	H	H	58
e	H	OBn	OBn	H	70
f	H	H	Cl	H	65
g	H	H	Me	H	60
h	H	H	OMe	H	73

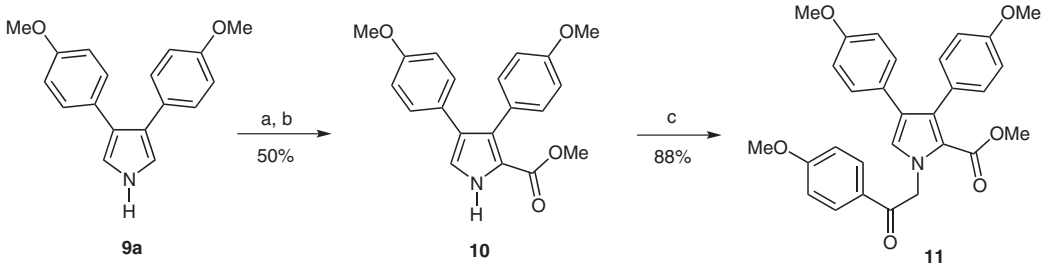
MeOH[23] to produce the Fürstner intermediate[14] **10** in 50% (two steps).

With pyrrole **10** in hand, the next step was the N-alkylation with 2-bromo-4′-methoxyacetophenone using K_2CO_3 in refluxing acetone (3 h), which allowed to obtain the methyl ether of lamellarin O in 88% yield. In order to remove the methyl groups, the use of $Me_2S{\cdot}BCl_3$ failed, and when BBr_3 was employed, in addition to the ether functionalities, the methyl ester was also deprotected. When the conditions reported by Iwao were used,[18] lamellarin O was obtained in moderate yield, along with the corresponding carboxylic acid. To overcome this obstacle, the benzyl ether analogue of the Fürstner intermediate **12** was prepared from **9e** according to the procedure described for the synthesis of **10**. N-Alkylation of **12** under standard conditions (K_2CO_3, acetone, reflux, 10 h) afforded compound **13** in 85% yield (Scheme 3). When the same reaction was performed under microwave heating (K_2CO_3, DMF, MW 40 W, 100 °C, 30 min) **13** was obtained in 88% yield.

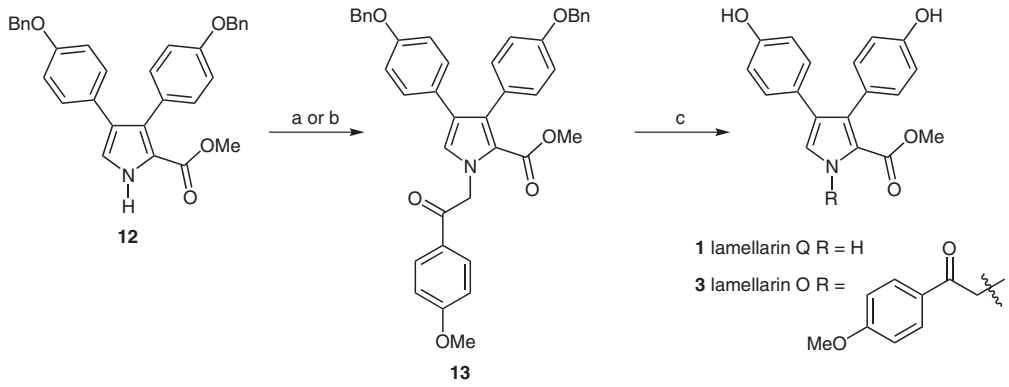
Finally, removal of the benzyl ethers from **12** was achieved with $Pd(OH)_2$ and MeOH as the solvent to afford lamellarin Q (**1**, Scheme 3) in 90% yield. Using the same conditions on the N-alkylated product **13** provided lamellarin O (**3**, Scheme 3) in >95% yield. All the intermediates were fully characterized in accordance to literature reports.

In conclusion, we have developed a simple and convenient synthetic procedure to assemble 3,4-diaryl-substituted pyrroles in very good yields. The procedure relies on the use of succinonitriles as surrogates for 1,4-dialdehydes required in the Paal–Knorr synthesis. The potential of this method was illustrated by the synthesis of lamellarins O and Q in good overall yields.

We believe that this approach can be employed for the synthesis of other members of this interesting family of alkaloids, and would allow the preparation of multigram amounts of some lamellarins. Studies to explore the scope of this method are currently underway and the results will be published elsewhere.



Scheme 2 Acylation and N-alkylation of pyrroles. *Reagents and conditions*: a) $ClCOCCl_3$ (1.5 equiv), DMAP (1.6 equiv), 25 °C, 3 h; b) NaOMe (4 equiv), MeOH, 25 °C, 24 h; c) K_2CO_3 (8 equiv), 2-bromo-4′-methoxyacetophenone (2 equiv), acetone, reflux, 3 h.



Scheme 3 N-Alkylation of pyrrole **12**. *Reagents and conditions*: a) 2-bromo-4′-methoxyacetophenone, K_2CO_3 (5 equiv), acetone, reflux, 10 h (method A), 85%; b) 2-bromo-4′-methoxyacetophenone K_2CO_3 (5 equiv), DMF, 18-crown-6 (0.1 equiv), MW 40 W, 100 °C, 30 min (method B), 88%; c) H_2, $Pd(OH)_2$/C, MeOH, r.t., >95%.

Commercial reagents were purchased from Sigma-Aldrich and were used without purification. Solvents were purified by distillation and were dried using Na/benzophenone when required. All reactions were monitored by TLC. Crude mixtures purifications were performed by flash column chromatography (FCC) on silica gel 60 mesh. NMR measurements were performed on a Varian Inova 300 MHz instrument using Me_4Si as internal standard. IR spectra were recorded on a Perkin-Elmer IR-FT with ATR Spectrum 400 spectrophotometer. Mass spectrometry was carried out on a JEOL SMX-102a spectrometer. Melting points were obtained on a Melt-Temp apparatus and are uncorrected.

2,3-Bis[4-(benzyloxy)phenyl]acrylonitrile (7e); Typical Procedure

A 30% solution of NaOMe in MeOH (488 μL, 2.71 mmol) was added to a mixture of 4-(benzyloxy)phenylacetonitrile (500 mg, 2.24 mmol) and 4-(benzyloxy)benzaldehyde (475 mg, 2.24 mmol) in MeOH (5 mL) and the mixture was refluxed for 12 h. The reaction mixture was cooled to r.t. and diluted with 50% EtOAc–hexanes (50 mL). The two layers were separated and the organic phase was washed successively with H_2O (3 × 20 mL) and brine (20 mL), dried (Na_2SO_4), and the solvent removed in vacuo. The residue was fractionated by FCC (SiO_2, 30% EtOAc–hexanes) to afford 870 mg (93%) of the desired product as a yellow solid; mp 130–131 °C (CH_2Cl_2–hexanes).

IR (KBr): 3063, 3032, 2216, 1248 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 9 Hz, 2 H), 7.57 (d, *J* = 9 Hz, 2 H), 7.45–7.33 (m, 11 H), 7.02 (d, *J* = 9 Hz, 2 H), 7.00 (d, *J* = 9 Hz, 2 H), 5.11 (s, 2 H), 5.09 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.2, 159.2, 157.7, 139.9, 136.5, 136.3, 130.9, 128.6, 128.2, 128.1, 127.5, 127.4, 127.0, 126.9, 118.6, 115.3, 115.3, 115.1, 108.4, 70.1, 70.0.

MS: *m*/*z* = 417 (M^+).

2,3-Bis[4-(benzyloxy)phenyl]succinonitrile (8e); Typical Procedure

A solution of KCN (700 mg, 10.75 mmol) and NH_4Cl (345 mg, 6.45 mmol) in H_2O (10 mL) was added dropwise to a solution of 2,3-bis(4-benzyloxyphenyl)acrylonitrile (**7e**; 1.8 g, 4.3 mmol) in DMF (30 mL) at r.t. After completion of the addition, the resultant mixture was heated at 100 °C (oil bath) for 6 h. The reaction mixture was then poured into ice-water (ca. 150 mL) to precipitate the product. The solid was filtered and rinsed with H_2O (100 mL). After removal of most of the H_2O by suction, the product was dried under vacuum to afford the desired succinonitrile as a yellow-brownish solid (1.8 g, 95%); mp 240–244 °C (acetone).

IR (KBr): 3070, 3032, 2936, 2880, 2244, 1514, 1247 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.35 (m, 10 H), 7.13 (d, *J* = 8.7 Hz, 4 H), 6.96 (d, *J* = 8.7 Hz, 4 H), 5.07 (s, 4 H), 4.16 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152, 136.4, 129.7, 128.7, 128.2, 127.5, 122.9, 117.5, 115.4, 70.1.

MS: *m*/*z* = 444 (M^+).

3,4-Bis[4-(benzyloxy)phenyl]-1*H*-pyrrole (9e)

A 1 M solution of DIBAL-H in toluene (10 mL, 10 mmol) was added dropwise to a suspension of **8e** (1.8 g, 4 mmol) in anhyd benzene (27 mL). After completion of the addition, the mixture was stirred at r.t. for 6 h and then quenched with aq 1.5 M NaH_2PO_4 (70 mL). The resulting heterogeneous mixture was stirred at 100 °C for an additional period of 1 h; cooled to r.t., diluted with 50% EtOAc–hexanes (150 mL) and filtered through Celite. The two layers were separated and the organic phase was washed with H_2O (2 × 30 mL), brine (30 mL), and dried (Na_2SO_4). After removal of the solvent in vacuo, the residue was fractionated by FCC (SiO_2, 30% EtOAc–hexanes) to obtain 1.29 g (70%) of a yellowish solid; mp 120–140 °C (dec.; CH_2Cl_2–hexanes).

IR (KBr): 3443, 3061, 3030, 2883, 2852, 2549, 1696, 1593, 1497, 1247 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.19 (br s, 1 H), 7.45–7.31 (m, 10 H), 7.19 (d, *J* = 9 Hz, 4 H), 6.88 (d, *J* = 9 Hz, 4 H), 6.81 (d, *J* = 3 Hz, 2 H), 5.03 (s, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.1, 137.2, 129.6, 128.6, 128.5, 127.9, 127.6, 123.0, 116.8, 114.5, 69.9.

MS: *m*/*z* = 431 (M^+).

Methyl 3,4-Bis(4-methoxyphenyl)-1*H*-pyrrole-2-carboxylate (10) (Fürstner Intermediate)

A solution of trichloroacetyl chloride (230 μL, 2.06 mmol) in anhyd THF (2 mL) was added dropwise to a mixture of pyrrole **9a** (381 mg, 1.36 mmol) and DMAP (268 mg, 2.2 mmol) in anhyd THF (2 mL) at 0 °C. After completion of the addition, the resultant mixture was stirred at r.t. for 6 h. The reaction was quenched by the addition of 30% NaOMe in MeOH (1 mL, 5.5 mmol) and MeOH (7 mL) and the stirring continued overnight. The mixture was diluted with 50% EtOAc–hexanes (50 mL) and washed successively with H_2O (3 × 20 mL) and brine (20 mL), dried (Na_2SO_4), and the solvent evaporated in vacuo. The residue was fractionated by FCC (SiO_2, 30% EtOAc–hexanes) to afford 230 mg (50%) of the desired product as a pale-yellow solid; mp 166–168 °C (CH_2Cl_2–hexanes). The recovered unreacted pyrrole **9a** (57 mg, 15%) was recycled.

IR (KBr): 3307, 3000, 2947, 2832, 1674, 1246 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.24 (br s, 1 H), 7.16 (d, *J* = 9 Hz, 2 H), 7.00–7.03 (m, 3 H), 6.81 (d, 2 H, *J* = 9 Hz), 6.72 (d, *J* = 9 Hz, 2 H), 3.79 (s, 3 H), 3.73 (s, 3 H), 3.69 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.5, 158.5, 158.0, 131.8, 129.5, 127.1, 126.5, 120.0, 119.4, 113.7, 113.1, 55.2, 55.1, 51.2.

MS: *m*/*z* = 337 (M^+).

Methyl 3,4-Bis(4-methoxyphenyl)-1-[2-(4-methoxyphenyl)-2-oxoethyl]-1*H*-pyrrole-2-carboxylate (11, Lamellarin *O*-Dimethyl Ether)

A mixture of **10** (223 mg, 0.7 mmol), anhyd K_2CO_3 (773 mg, 5.6 mmol) 2-bromo-4′-methoxyacetophenone (321 mg, 1.4 mmol) in anhyd acetone (50 mL) was heated under reflux for 3 h. The reaction was cooled to r.t., followed by the addition of Celite, and removal of the solvent. The supported crude mixture was fractionated by FCC (SiO_2, 30% EtOAc–hexanes) to afford 300 mg (88%) of the desired product as yellow crystals; mp 68–72 °C (CH_2Cl_2–hexanes).

IR (KBr): 3000, 2937, 2836, 2039, 1685, 1598, 1234, 1168 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 9 Hz, 2 H), 7.15 (d, *J* = 9 Hz, 2 H), 6.99 (d, *J* = 9 Hz, 2 H), 6.98 (d, *J* = 9 Hz, 2 H), 6.92 (s, 1 H), 6.82 (d, *J* = 9 Hz, 2 H), 6.71 (d, *J* = 9 Hz, 2 H), 5.72 (s, 2 H), 3.88 (s, 3 H), 3.81 (s, 3 H), 3.73 (s, 3 H), 3.47 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 50.7, 55.1, 55.4, 55.5, 112.8, 113.5, 114.1, 119.7, 124.6, 126.9, 127.1, 127.8, 127.9, 129.4, 130.3, 131.1, 131.8, 157.8, 158.2, 162.3, 163.9, 191.8.

MS: *m*/*z* = 485 (M^+).

Methyl 3,4-Bis(4-benzyloxyphenyl)-1*H*-pyrrole-2-carboxylate (12)

This compound was prepared from the dibenzyl ether **9e** according to the procedure described for the synthesis of **10**, to afford the analogous Fürstner intermediate **12** in 53% yield; foam.

IR (KBr): 3410, 3300, 3062, 3032, 2949, 2927, 1638, 1672, 1239 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.25 (br s, 1 H), 7.47–7.30 (m, 10 H), 7.19 (d, *J* = 9 Hz, 2 H), 7.04–6.99 (m, 3 H), 6.92 (d, *J* = 9 Hz, 2 H), 6.82 (d, *J* = 9 Hz, 2 H), 5.05 (s, 2 H), 4.99 (s, 2 H), 3.71 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.5, 157.8, 157.2, 137.1, 137, 131.9, 129.5, 129.4, 129.0, 128.5, 127.9, 127.6, 127.5, 127.3, 126.7, 126.4, 120.1, 119.2, 114.6, 114.0, 70.0, 69.9, 51.2.

MS: *m*/*z* = 489 (M^+).

Methyl 3,4-Bis(4-benzyloxyphenyl)-1-[2-(4-methoxyphenyl)-2-oxoethyl]-1*H*-pyrrole-2-carboxylate (13, Lamellarin *O*-Dibenzyl Ether)

Method A: Lamellarin *O*-dibenzyl ether was prepared from **12** in 85% yield according to the procedure described for compound **11**.

Method B: A mixture of **12** (150 mg, 0.3 mmol), K_2CO_3 (207 mg, 1.5 mmol), 18-crown-6 (80 mg, 0.03 mmol) and 2-bromo-4′-methoxyacetophenone (138 mg, 0.6 mmol) in anhyd DMF (2 mL) was heated at 100 °C under microwave irradiation (40 W, CEM-Discovery 300 oven) for 30 min. After this time, the reaction was cooled to r.t., diluted with 50% EtOAc–hexanes (150 mL), and washed successively with H_2O (5 × 30 mL), aq 10% LiCl (30 mL), brine (30 mL), and dried (Na_2SO_4). The solvent was removed in vacuo, and the residue was purified by FCC (SiO_2, 30% EtOAc–hexanes) to afford 169 mg (88%) of a white-yellowish powder; mp 119–122 °C (CH_2Cl_2–hexanes).

IR (KBr): 3034, 2930, 1692, 1601, 1532, 1237, 1171 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 9 Hz, 2 H), 7.47–7.30 (m, 10 H), 7.17 (d, *J* = 8.7 Hz, 2 H), 7.02–6.97 (m, 4 H), 6.91 (s, 1 H), 6.90 (d, *J* = 8.7 Hz, 2 H), 6.79 (d, *J* = 9 Hz, 2 H), 5.72 (s, 2 H), 5.06 (s, 2 H), 4.99 (s, 2 H), 3.88 (s, 3 H), 3.45 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.8, 163.9, 162.3, 157.5, 157.1, 137.1, 137.0, 131.8, 131.0, 130.3, 129.4, 128.5, 128.2, 127.9, 127.6, 127.5, 127.2, 124.6, 119.8, 114.4, 114.1, 113.8, 69.9, 55.5, 50.8.

MS: *m*/*z* = 637 (M^+).

Removal of the Benzyl Group from 12 and 13; General Procedure

A mixture of **12** (20 mg, 0.04 mmol) or **13** (12 mg, 0.019 mmol) and $Pd(OH)_2$ (10 mol%) in MeOH (0.5 M solution) was stirred overnight under H_2 atmosphere. After that, the resulting mixture was filtered through Celite and the solvent was evaporated under reduced pressure to afford the desired product in almost quantitative yield. No further purification was performed.

Methyl 3,4-Bis(4-hydroxyphenyl)-1*H*-pyrrole-2-carboxylate (Lamellarin Q, 1)

Yield: 12.2 mg (quant); unstable yellow solid; mp 220–222 °C (dec.).

IR (KBr): 3288, 3023, 2949, 1895, 1683, 1438, 1245 cm^{-1}.

^{1}H NMR (300 MHz, acetone-d_6): δ = 10.91 (br s, 1 H), 8.25 (br s, 2 H), 7.14 (d, *J* = 3 Hz, 1 H), 7.05 (d, *J* = 8.7 Hz, 2 H), 6.95 (d, *J* = 8.7 Hz, 2 H), 6.75 (d, *J* = 8.7 Hz, 2 H), 6.66 (d, *J* = 8.7 Hz, 2 H), 3.64 (s, 3 H).

Note: When the ^{1}H NMR spectra for compound **1** was acquired using a diluted sample (<10 mg), the signal at 8.25 ppm corresponding to phenolic OH groups appeared as two simple signals at 8.25 and 8.18 ppm, and each signal integrated for 1 H (see spectra of compound **1** in the Supporting Information).

^{13}C NMR (75 MHz, acetone-d_6): δ = 161.9, 157.0, 156.5, 132.8, 130.2, 129.7, 127.4, 127.0, 126.8, 121.4, 120.0, 115.8, 115.2, 51.0.

MS: *m*/*z* = 309 (M^+).

Methyl 3,4-Bis(4-hydroxyphenyl)-1-[2-(4-methoxyphenyl)-2-oxoethyl]-1*H*-pyrrole-2-carboxylate (Lamellarin O, 3)

Yield: 8.5 mg (quant); unstable yellow solid; mp 255–260 °C (dec.).

IR (KBr): 3385, 3124, 3029, 2916, 2847, 2478, 1752, 1679, 1659, 1594, 1166 cm^{-1}.

^{1}H NMR (300 MHz, acetone-d_6): δ = 8.24 (s, 1 H), 8.18 (s, 1 H), 8.08 (d, *J* = 9 Hz, 2 H), 7.18 (s, 1 H), 7.09 (d, *J* = 9 Hz, 2 H), 7.03 (d, *J* = 8.7 Hz, 2 H), 6.95 (d, *J* = 9 Hz, 2 H), 6.78 (d, *J* = 8.7 Hz, 2 H), 6.66 (d, *J* = 8.7 Hz, 2 H), 5.88 (s, 2 H), 3.91 (s, 3 H), 3.39 (s, 3 H).

^{13}C NMR (75 MHz, acetone-d_6): δ = 192.5, 164.7, 162.6, 156.8, 156.3, 132.5, 131.3, 130.9, 130.0, 129.0, 128.1, 127.9, 127.0, 124.9, 120.5, 115.6, 115.0, 114.7, 56.3, 55.9, 50.6.

MS: *m*/*z* = 457 (M^+).

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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