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Formation of 3,4-Diarylpyrrole- and Pyrrolocoumarin Core of Natural Marine Products via Barton-Zard Reaction and Selective O-demethylation

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ABSTRACT

A metal-free approach to 3,4-diarylpyrrole-2-carboxylate and pyrrolocoumarin cores of lamellarins and related natural products based on Barton-Zard reaction of nitrostilbenes with ethyl isocyanoacetate was developed. In the case of diarylpyrrole-2-carboxylates with a 3-(*o*-methoxyphenyl) fragment, treatment with 1 eq. BBr_3 resulted in selective O-demethylation of the *ortho*-methoxy group, while other methoxy groups in the molecule remained intact. The resulting 3-(2-hydroxyphenyl)pyrrole-2-carboxylates underwent base-induced lactonization to form the target pyrrolocoumarins.

INTRODUCTION

Since the first isolation of lamellarins in 1985, about 100 related naturally occurring pyrrole-based alkaloids (in particular, ningalins and lukianols), have been isolated from diverse marine organisms until 2012.[1] Almost all these compounds share a common 2-carboxy-3,4-diarylpyrrole core, and most of them feature a pyrrolocoumarin fragment with multiple hydroxy or methoxy substituents in benzene rings (Figure 1).

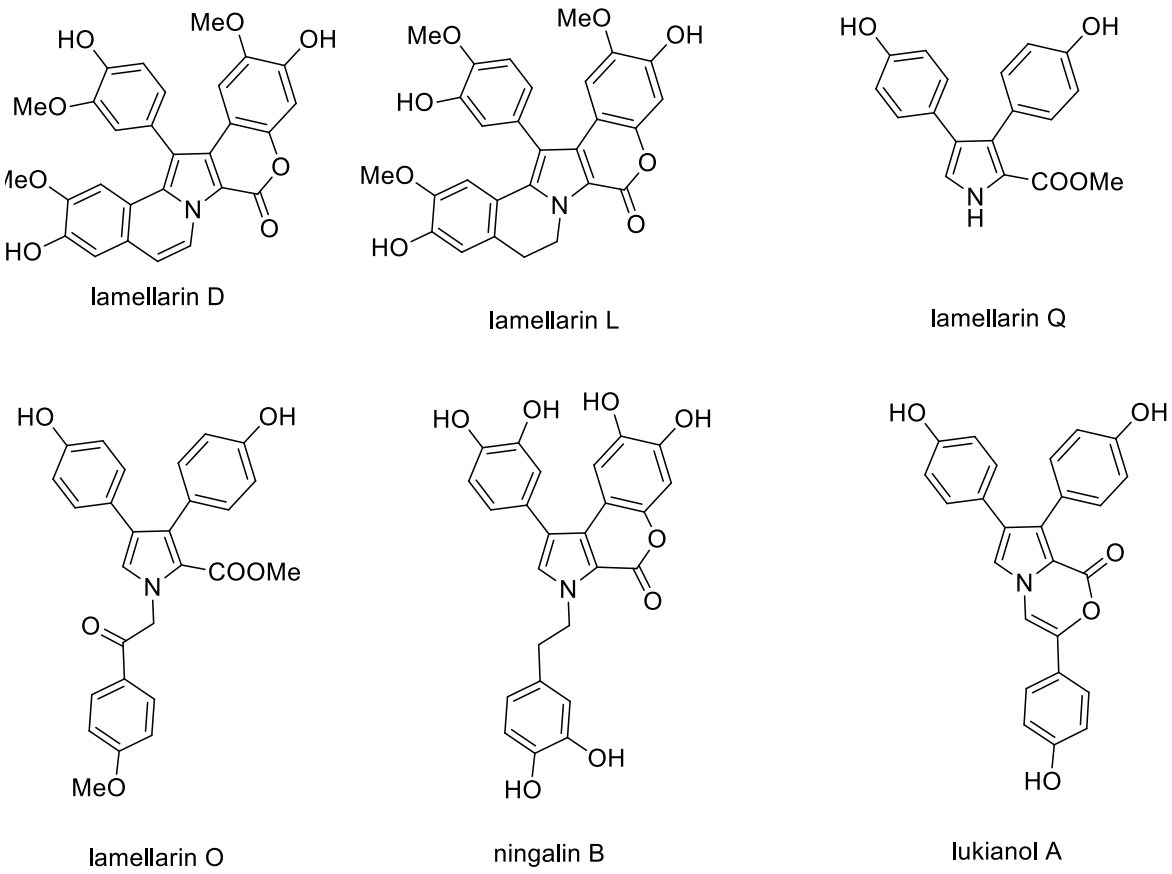


Figure 1. Some natural marine products with 3,4-diarylpyrrole and pyrrolocoumarin cores

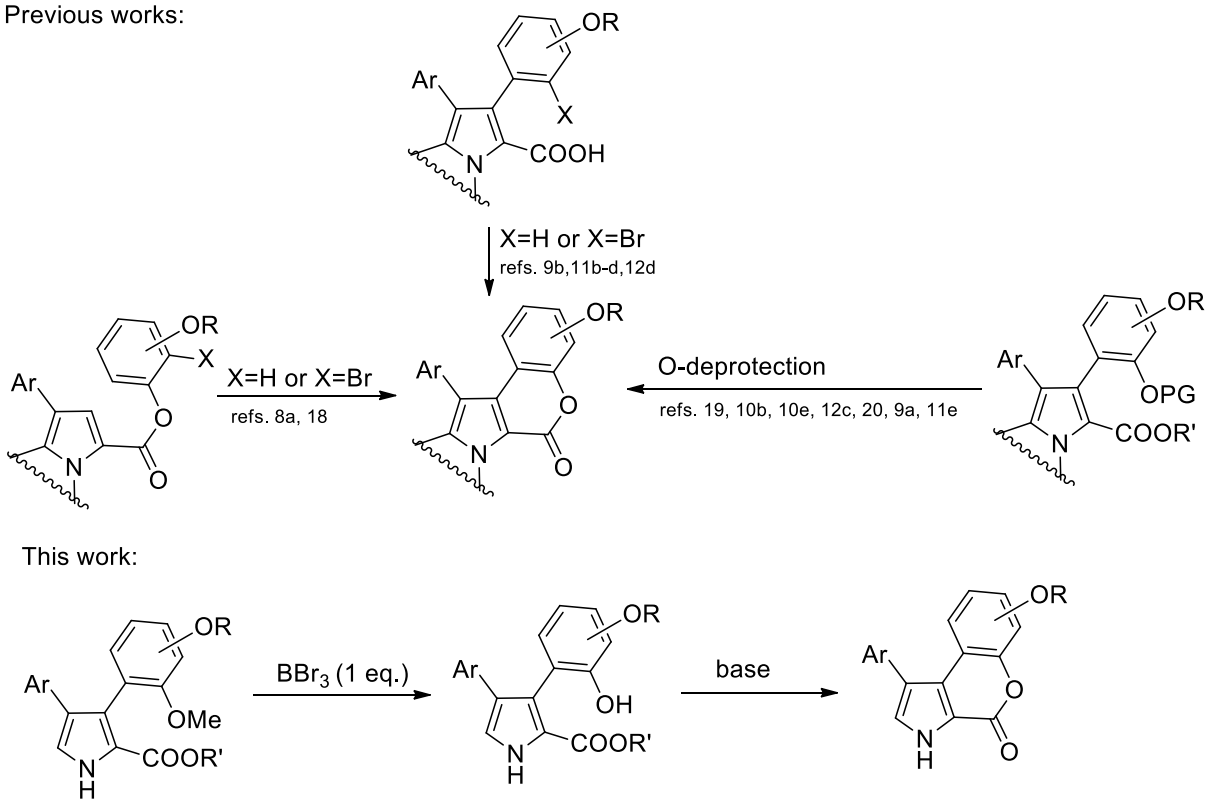
These lamellarin alkaloids have been found to exhibit a variety of biological activities such as antitumor activity,[2] reversal of multidrug resistance;[3] as well as inhibiting HIV-1 integrase,[4] topoisomerase,[5] and various kinases.[6] Due to their novel molecular structures and promising biological activity, the synthesis of lamellarins and their analogues continues to attract considerable interest of chemists and was extensively reviewed during the last decade.[1,2,7]

These syntheses can be divided into two categories: one is the functionalization of a pre-existing pyrrole, and the other is the formation of the pyrrole core as the key step. Syntheses of the first category include successive introduction of aryl substituents into positions 3/4/5 of the pyrrole ring (mostly by metal-catalyzed coupling reactions)[8] and introduction of a carboxy group into position 2.[9] In the second approach the pyrrole ring is formed by various methods such as Grob cyclization,[10] Paal-Knorr and Hantsch reactions,[11] interaction of α-aminoester or α-aminonitrile with α,β-unsaturated carbonyl compounds,[12] [3+2] dipolar cycloaddition,[13] metal-catalyzed [3+2] annulation,[14] or the reductive recyclization of pyridazines.[15]

The coumarin (lactone) fragment might be present in the molecule before the pyrrole ring formation;[16] in some cases these two rings are closed simultaneously,[13,17] but more often the lactone fragment is formed later than the pyrrole one – either from of O-aryl pyrrole-2-carboxylates (by intramolecular oxidative coupling[8a] or Heck reaction[18]), or by intramolecular

nucleophilic substitution of Br in 3-(2-bromophenyl)pyrrole-2-carboxylic acids,[9c,10c,12a] or by intramolecular C-H/O-H oxidative coupling of 3-arylpyrrole-2-carboxylic acids.[9b,11b-d,12d] However, the most ubiquitous approach consists in lactonization of 3-(2-hydroxyphenyl)pyrrole-2-carboxylates, prepared from their O-protected derivatives (PG = MOM,[19] Bn,[10b,10e] *i*-Pr,[12c,20] Ac,[9a] Ms[11e] (Scheme 1) (this usually implies an introduction of the protective group as a separate step).

Scheme 1. Formation of the lactone fragment.



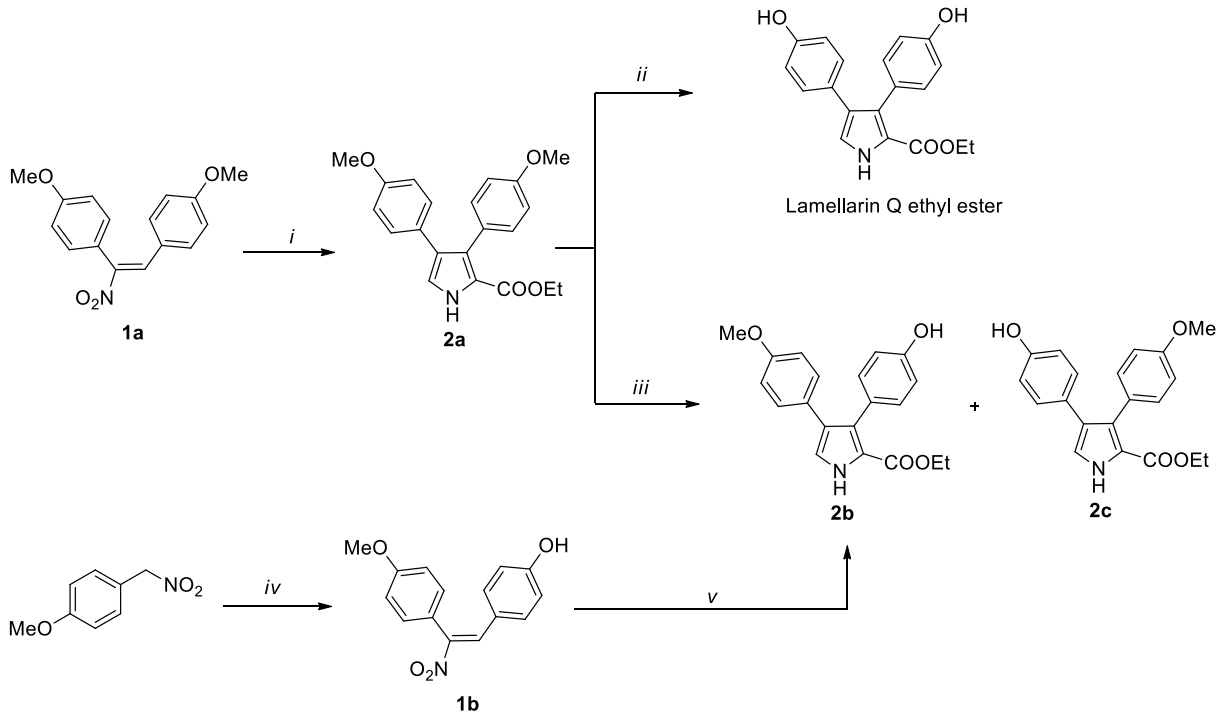
RESULTS AND DISCUSSION

An Approach to 3,4-Diarylpyrrole Core. Surprisingly, a Barton-Zard reaction[21] (that is, base-catalyzed reaction of nitroalkenes with alkyl isocyanoacetate) has not yet been reported for synthesis of the pyrrole core of lamellarins and related compounds,[22] though such reaction with 1,2-diaryl-1-nitroethylenes should be a straightforward way of accessing 3,4-diarylpyrrole-2-carboxylates as key structural fragments of the lamellarins, ningalins and lukianols.

Recently, we reported a useful modification of the reaction conditions which enabled an efficient synthesis of 3,4-diarylpyrrole-2-carboxylates from nitrostilbenes and helped us to overcome a problem of low yields in this reaction in the case of highly oxygenated Ar substituents.[23] This modification (that is, carrying out the reaction in ethanol as a solvent and using K_2CO_3 as a base) was now applied for a synthesis of the target products.

Thus, ethyl 3,4-bis(4-methoxyphenyl)pyrrole-2-carboxylate **2a** was prepared by this method from nitrostilbene **1a** and then demethylated under the action of BBr_3 (3 eq.) to afford lamellarin Q Et ester (Scheme 2):

Scheme 2. Synthesis of Lamellarin Q Et ester.

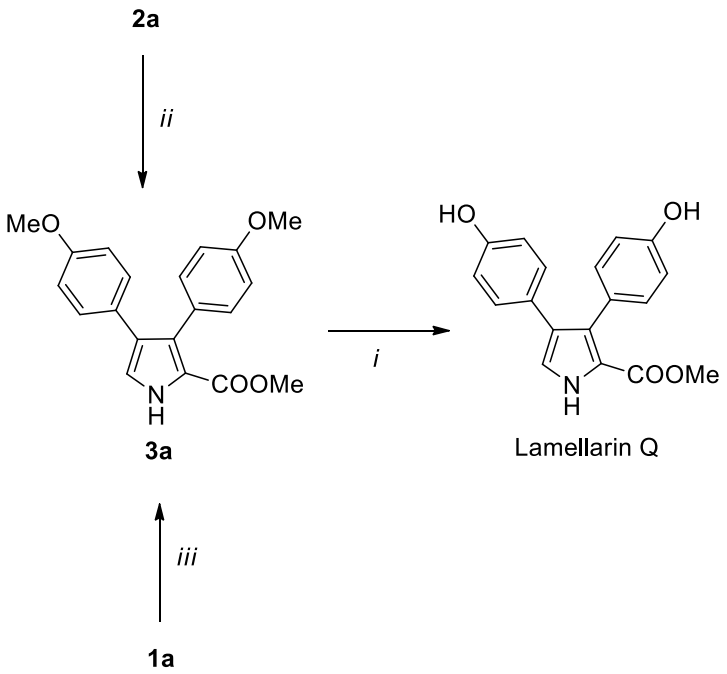


i: $CNCH_2COOEt$, EtOH, K_2CO_3, 87%; *ii*: BBr_3 (3 eq.), CH_2Cl_2, 0°C, 85%; *iii*: BBr_3 (2 eq.), CH_2Cl_2, 0°C, 63%; *iv*: 4-HOC_6H_4CHO, MeOH, $MeNH_2$•HCl, $NaHCO_3$; *v*: $CNCH_2COOEt$, EtOH, K_2CO_3

Noteworthy, the reaction in the presence of 2 eq.BBr_3[24] demonstrated a pronounced selectivity: it produced a mixture of partially demethylated products **2b** and **2c** in ca. 1:4 ratio. The structure of a minor product (**2b**) was confirmed by its alternative synthesis from 2-(4-hydroxyphenyl)-1-(4-methoxyphenyl)-1-nitroethene **1b** (Scheme 2) (the latter was, in turn, prepared by condensation of 4-methoxyphenylnitromethane and 4-hydroxybenzaldehyde).

Demethylation of methyl 3,4-bis(4-methoxyphenyl)pyrrole-2-carboxylate **3a** with excess BBr_3 (3 eq.) furnished lamellarin Q (Scheme 3, Figure 2):

Scheme 3. Synthesis of Lamellarin Q.



i: BBr_3 (3 eq.), CH_2Cl_2, 0°C, 84%; *ii*: MeONa, reflux, 84%; *iii*: $CNCH_2COOEt$, MeOH, K_2CO_3, 89%

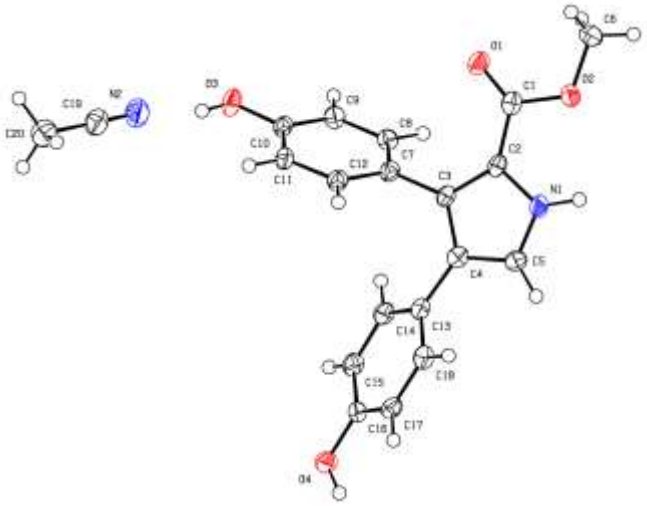


Figure 2. Molecular structure of **Lamellarin Q** • MeCN (50% ellipsoids).

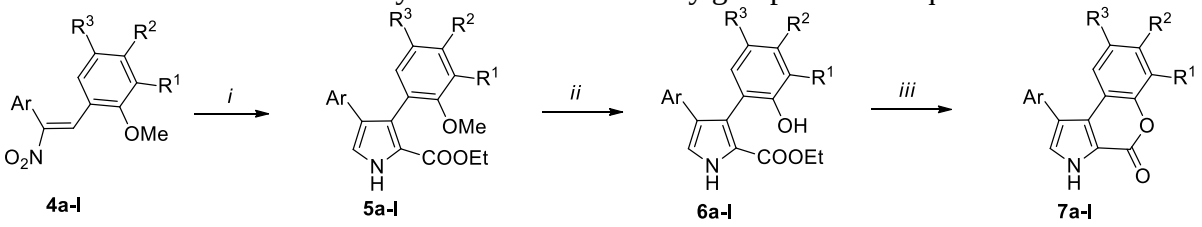
Methyl ester **3a** could be prepared either by transesterification of the ethyl ester **2a**, or directly from the nitrostilbene **1a** by reacting it with ethyl isocyanoacetate in MeOH instead of EtOH. The latter approach gives lamellarin Q in only 3 steps (starting from 4-methoxyphenylnitromethane and *p*-anisaldehyde) and total yield 35% (this is quite comparable with the known syntheses of this compound, [25] cf. the most recent work[25a] – 20% in 7 steps).

An Approach to the Pyrrolocoumarin Core. Further experiments showed that Barton-Zard reaction of nitrostilbene **4a (**prepared by condensation of phenylnitromethane and 2-methoxybenzaldehyde) furnished 3-(2-methoxyphenyl)pyrrole **5a**, and demethylation of the

latter with 1 eq. BBr_3 produced 3-(2-hydroxyphenyl) derivative **6a** in almost quantitative yield (Table 1, entry 1). An attempt of preparing **6a** directly from salicylaldehyde via the corresponding nitrostilbene failed.

More careful investigation of this reaction revealed that various 3,4-diarylpyrrole-2-carboxylates **5**, containing an *ortho*-methoxy group in the 3-Ar moiety, upon treatment with 1 eq. BBr_3 underwent selective O-demethylation *of this particular group* to afford 3-(2-hydroxyphenyl) derivatives **6** in high yields, while *other alkoxy groups* present in the molecule **5** *remained intact* (Scheme 4, Table 1):

Scheme 4. Selective O-demethylation of an *o*-methoxy group and subsequent lactonization.



i: $CNCH_2COOEt$, EtOH, K_2CO_3; *ii*: BBr_3 (1 eq.), CH_2Cl_2, 0°C; *iii*: NaOH, EtOH

Yields are somewhat lower for the compounds **5e,f,j,k** – probably, methylenedioxy fragment was attacked in these cases.

Obviously, this is a rare and interesting example of a selective O-demethylation induced by a substituent remote from the reacting methoxy group – in this case by COOEt fragment in the pyrrole ring (to the best of our knowledge, no such examples were reported for aryl-substituted pyrrole carboxylates).[26,27] Moreover, such an approach allows one to avoid a separate step of introducing O-protective groups, as discussed above (cf. Scheme 1).

Upon treatment with ethanolic NaOH at room temperature hydroxy derivatives **6** readily undergo cyclization into lactones **7** in high yields (Table 1).

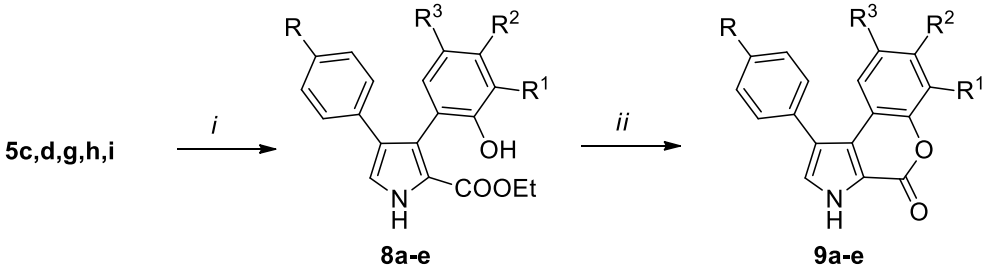
Table 1. Yields of selective demethylation products **6** and cyclization products **7**

Entry	Starting compound	Ar	R^1	R^2	R^3	Product **6** (yield, %)	Product **7** (yield, %)
1	**5a**	Ph	H	H	H	**6a** (96)	**7a** (82)
2	**5b**	Ph	OMe	H	H	**6b** (82)	**7b** (80)
3	**5c**	Ph	H	OMe	H	**6c** (98)	**7c** (83)
4	**5d**	Ph	H	H	OMe	**6d** (89)	**7d** (74)
5	**5e**	Ph	OCH_2O		OMe	**6e** (61)	**7e** (78)
6	**5f**	Ph	OMe	OCH_2O		**6f** (55)	**7f** (80)
7	**5g**	4-$MeOC_6H_4$	H	H	H	**6g** (78)	**7g** (71)
8	**5h**	4-$MeOC_6H_4$	H	OMe	H	**6h** (81)	**7h** (80)
9	**5i**	4-$MeOC_6H_4$	H	H	OMe	**6i** (81)	**7i** (71)
10	**5j**	4-$MeOC_6H_4$	OCH_2O		OMe	**6j** (68)	**7j** (83)
11	**5k**	4-$MeOC_6H_4$	OMe	OCH_2O		**6k** (51)	**7k** (81)
12	**5l**	2-MeO-5-MeC_6H_3	H	H	Me	**6l** (78)	**7k** (82)

Noteworthy, demethylation of an "almost symmetrical" pyrrole **5l**[28] with two identical 2-methoxy-5-methylphenyl fragments in positions 3 and 4 selectively afforded 3-(2-hydroxy-5-methyl)phenylpyrrole **6l**, which produced lactone **7l** upon treatment with the base (Table 1, entry 12). This control experiment provided additional evidence for a crucial role of COOEt as a directing group in the selective O-demethylation process.

If the molecule **5** contains more than one methoxy group, treatment with an excess BBr_3 could result in a complete O-demethylation[29] to produce the corresponding hydroxy derivatives **8** and **9** (Scheme 5, Table 2):

Scheme 5. Complete O-demethylation of methoxy groups and lactonization.



i: BBr_3 (3-4 eq.), CH_2Cl_2, 0°C; *iii*: NaOH, EtOH

Table 2. Yields of products of complete demethylation **8** and cyclization products **9**

Starting compound	R	R^1	R^2	R^3	Product **8** (yield, %)	Product **9** (yield, %)
5c	H	H	OH	H	**8a** (74)	**9a** (80)
5d	H	H	H	OH	**8b** (87)	**9b** (84)
5g	OH	H	H	H	**8c** (79)	**9c** (76)
5h	OH	H	OH	H	**8d** (79)	**9d** (79)
5i	OH	H	H	OH	**8e** (83)	**9e** (81)

Structure of the compound **9a** was confirmed by X-ray diffraction study (see ESI):

CONCLUSION

Thus, an approach to 3,4-diarylpyrrole-2-carboxylate core of lamellarins and related natural products via Barton-Zard reaction of 1,2-diaryl-1-nitroethenes with ethyl isocyanoacetate was developed, and lamellarin Q was prepared by this method. In the case of pyrrole-2-carboxylates with a 3-(2-methoxyphenyl) fragment, treatment with 1 eq. BBr_3 resulted in selective O-demethylation of the *ortho*-methoxy group, while other methoxy groups in the molecule remained intact. Lactonization of the 3-(2-hydroxyphenyl)pyrrole-2-carboxylates thus formed produced the target pyrrolocoumarin system. We hope that these results could serve as a useful supplement to the known methods of lamellarin synthesis.

EXPERIMENTAL SECTION

General Experimental

Melting points were measured on a Boetius melting point apparatus and were uncorrected. Reaction mixtures were stirred magnetically. ^{1}H NMR spectra were recorded on a Bruker AM-300 (300.13MHz), Bruker DRX-500 (500.13 MHz) and Bruker AV-600 (600.13 MHz) instruments. Chemical shifts are stated in parts per million (ppm) and referenced to the appropriate NMR solvent peak(s). Spin-spin coupling constants (*J*) were reported in hertz (Hz). ^{13}C NMR spectra were recorded on a Bruker DRX-500 (125.76 MHz) and Bruker AV-600 (150.9 MHz) instruments. Chemical shifts are stated in parts per million (ppm). Spin−spin coupling constants were reported in hertz (Hz). Low resolution mass spectra (*m/z*) were recorded on a Finnigan MAT/INCOS 50 mass spectrometer at 70 eV using direct probe injection. Elemental analysis was performed on the automated PerkinElmer 2400 CHN microanalyzer. Flash chromatography was carried out on silica gel (Acros, 0.035−0.070 mm, 60 Å). TLC was performed on Merck 60 F254 plates. Anhydrous CH_2Cl_2 was obtained by distillation with P_2O_5. The preparation and characteristics of nitrostilbenes **1a**,[30a] **4e**,[30b], **4j**[23] and 3,4-diarylpyrrole-2-carboxylates[23] **2a**, **5e**, **5j** were identical to those reported earlier.

General Procedure for the Synthesis of 1,2-diarylnitroethylenes 1a, 4a-k. A mixture of arylnitromethane (4.5 mmol), arylaldehyde (5 mmol), MeOH (7 ml), $MeNH_2$•HCl (27 mg, 0.4 mmol), and $NaHCO_3$ (17 mg, 0.2 mmol) was stirred at room temperature for 3-5 days (TLC control). The resulting suspension was filtered, washed twice with cold methanol (3 ml) and d/ried.

1-Nitro-1-(4-methoxyphenyl)-2-(2,5-dimethoxyphenyl)ethylene (4i): 700 mg, 61% yield, yellow crystals, m.p. 121-122 °C. H NMR (500 MHz, $CDCl_3$): δ = 8.56 (s, 1H; H-2), 7.26 (d, *J* = 8.8 Hz, 2H; Ar), 6.98 (d, *J* = 8.8 Hz, 2H; Ar), 6.85 (dd, *J* = 9.1 Hz, *J* = 2.9 Hz, 1H; Ar), 6.82 (d, *J* = 9.1 Hz, 1H; Ar), 6.30 (d, *J* = 2.8 Hz, 1H; Ar), 3.86 (s, 3H; OCH_3), 3.84 (s, 3H; OCH_3), 3.34 ppm (s, 3H; OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.2, 154.0, 153.2, 149.8, 132.6, 129.5, 123.5, 121.2, 119.5, 115.0, 114.4, 112.6, 56.6, 55.8, 55.6 ppm; MS (70 eV): *m/z* (%): 316 (6) [M /+ H]$^+$, 315 (36) [M]$^+$, 254 (55), 239 (22), 211 (9), 168 (11), 152 (10), 139 (10), 127 (8), 121 (100), 77 (6), 28 (7), 15 (25); elemental analysis calcd (%) for $C_{17}H_{17}NO_5$ (%): C 64.75, H 5.43, N 4.44; found: C 64.55, H 5.29, N 4.58.

1-Nitro-1,2-bis(2-methoxy-5-methylphenyl)ethylene (4l). A suspension of $AgNO_2$ (616 mg, 4 mmol) and iodine (1.027 g, 4 mmol) in THF (20 ml) was stirred for 45 min. and a solution of 2,2'-dimethoxy-5,5'-dimethylstilbene[31] (536 mg, 2 mmol) and pyridin (0.5 ml) in THF (10 ml) was added. The mixture was stirred for 5 h, a resulting precipitate was filtered off and washed with THF (3 ml). To the filtrate, Et_3N (1 ml) was added, the solution was kept for 2 h and evaporated to dryness. The residue was dissolved in CH_2Cl_2 (10 ml), washed successively with

5% aq. $Na_2S_2O_3$, 5% HCl and water, dried, and the solvent removed in vacuo. Column chromatography of the residue on silica gel (eluent hexane-EtOAc 5:1) afforded 0.29 g of the nitrostilbene **4l**. 288 mg, 46% yield, yellow crystals, m.p. 106-107 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.54 (s, 1H; H-2), 7.25 (dd, *J* = 8.4 Hz, *J* = 2.0 Hz, 1H; Ar), 7.07 (dd, *J* = 8.4 Hz, *J* = 2.1 Hz, 1H; Ar), 6.93 (d, *J* = 2.1 Hz, 1H; Ar), 6.91 (d, *J* = 8.4 Hz, 1H; Ar), 6.77 (d, *J* = 8.4 Hz, 1H; Ar), 6.56 (d, *J* = 2.0 Hz, 1H; Ar), 3.85 (s, 3H; OCH_3), 3.76 (s, 3H; OCH_3), 2.23 (s, 3H; CH_3), 1.97 ppm (s, 3H; CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.9, 156.1, 147.3, 132.6, 132.0, 131.9, 130.5, 130.4, 129.6, 129.3, 120.4, 120.3, 111.3, 110.7, 55.9, 55.8, 20.4, 20.3 ppm; MS (70 eV): *m/z* (%): 314 (18) $[M + H]^+$, 313 (100) $[M]^+$, 267 (18), 252 (34), 237 (7), 165 (10), 145 (10), 135 (60), 119 (7), 105 (27); elemental analysis calcd (%) for $C_{18}H_{19}NO_4$: C 68.99, H 6.11, N 4.47; found: C 69.24, H 6.01, N 4.63.

Ethyl 3,4-bis(4-hydroxyphenyl)-1H-pyrrole-2-carboxylate (lamellarin Q ethyl ester). To a stirred solution of ethyl 3,4-bis(4-methoxyphenyl)-1*H*-pyrrole-2-carboxylate **2a**[23a] (175 mg, 0.5 mmol) in anhydrous CH_2Cl_2 (2 ml), BBr_3 (1.5 ml 1M in CH_2Cl_2) was added dropwise at -5 °C. The resulting solution was stirred for 90 min (TLC control), quenched with $NaHCO_3$ (756 mg, 9 mmol) in H_2O (5 ml), stirred for 1 min, diluted with water (25 ml), extracted with ethyl acetate (3×7 ml). The extract was washed with water (2×5 ml), dried by filtration through cotton wool, and evaporated in vacuo. Pure product was obtained after column chromatography (ethyl acetate – heptane 1:2): 137 mg, 85% yield, white solid, m.p. 176-177 °C; ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 11.75 (s, 1H; NH), 9.24 (s, 1H; OH), 9.17 (s, 1H; OH), 7.07 (d, *J* = 3.2 Hz, 1H; H-5), 6.93 (d, *J* = 8.5 Hz, 2H; Ar), 6.86 (d, *J* = 8.6 Hz, 2H; Ar), 6.65 (d, *J* = 8.5 Hz, 2H; Ar), 6.56 (d, *J* = 8.6 Hz, 2H; Ar), 4.06 (q, *J* = 7.1 Hz, 2H; CH_2), 1.09 ppm (t, *J* = 7.1 Hz, 3H; CH_3); ^{13}C NMR (125 MHz, [D_6]DMSO): δ = 160.6, 155.9, 155.4, 131.7, 128.9, 128.4, 125.7, 125.5, 125.1, 120.8, 118.9, 114.9, 114.3, 59.1, 14.1 ppm; MS (70 eV): *m/z* (%): 324 (12) $[M + H]^+$, 323 (53) $[M]^+$, 277 (100), 248 (7), 220 (10), 190 (5), 165 (17), 152 (6), 139 (8), 105 (7), 77 (6), 51 (5), 29 (28); elemental analysis calcd (%) for $C_{19}H_{17}NO_4$: C 70.58, H 5.30, N 4.33; found: C 70.21, H 5.17, N 4.67.

Partial O-demethylation of 2a. To a stirred solution of ethyl 3,4-bis(4-methoxyphenyl)-1*H*-pyrrole-2-carboxylate **2a** (175 mg, 0.5 mmol) in anhydrous CH_2Cl_2 (2 ml), BBr_3 (1 ml 1M in CH_2Cl_2) was added dropwise at -5 °C. The resulting solution was stirred for 90 min (TLC control), quenched with $NaHCO_3$ (504 mg, 6 mmol) in H_2O (5 ml), stirred for 1 min, diluted with water (25 ml), extracted with ethyl acetate (3×7 ml). The extract was washed with water (2×5 ml), dried by filtration through cotton wool, and evaporated in vacuo. The residue was chromatographed (ethyl acetate – heptane 1:2) to furnish an inseparable mixture of **2b** and **2c** in

ca. 1:4 ratio (total yield 106 mg, 63%), as well as some amounts of the starting **2a** (10 mg, 6%) and lamellarin Q Et ester (21 mg, 13%).

Ethyl 3-(4-hydroxyphenyl)-4-(4-methoxyphenyl)-1H-pyrrole-2-carboxylate (2b), minor component of the mixture: ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 11.8 (s, 1H; NH), 9.26 (s, 1H; OH), 7.13 (d, J = 3.1 Hz, 1H; H-5), 6.99 (d, J = 8.6 Hz, 2H; Ar), 6.94 (d, J = 8.4 Hz, 2H; Ar), 6.74 (d, J = 8.6 Hz, 2H; Ar), 6.66 (d, J = 8.4 Hz, 2H; Ar), 4.07 (q, J = 7.1 Hz, 2H; CH_2), 3.68 (s, 3H; OCH_3), 1.09 ppm (t, J = 7.1 Hz, 3H; CH_3).

Ethyl 3-(4-methoxyphenyl)-4-(4-hydroxyphenyl)-1H-pyrrole-2-carboxylate (2c), major component of the mixture: ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 11.8 (s, 1H; NH), 9.18 (s, 1H; OH), 7.09 (d, J = 3.2 Hz, 1H; H-5), 7.06 (d, J = 8.6 Hz, 2H; Ar), 6.86 (d, J = 8.6 Hz, 2H; Ar), 6.83 (d, J = 8.3 Hz, 2H; Ar), 6.56 (d, J = 8.6 Hz, 2H; Ar), 4.07 (q, J = 7.1 Hz, 2H; CH_2), 3.75 (s, 3H; OCH_3), 1.09 ppm (t, J = 7.1 Hz, 3H; CH_3) (signals at 11.8, 4.07 and 1.09 coincide).

Alternative synthesis of the compound 2b. A mixture of 4-methoxyphenylnitromethane (388 mg, 2.3 mmol), 4-hydroxybenzaldehyde (312 mg, 2.6 mmol), MeOH (2 ml), $MeNH_2$•HCl (13 mg, 0.2 mmol), and $NaHCO_3$ (8 mg, 0.1 mmol) was stirred at room temperature for 5 days (TLC control). The reaction mixture was diluted with water (30 ml) and extracted with ethyl acetate (3×5 ml). The extract was washed with water (2×3 ml), dried by filtration through cotton wool, and evaporated in vacuo. Crude 1-nitro-1-(4-methoxyphenyl)-2-(4-hydroxyphenyl)ethylene **1b** (206 mg) was isolated by column chromatography (toluene) as an oil and used without further purification.

Freshly calcined potassium carbonate (204 mg, 1.45 mmol) was added to a solution of the above crude **1b** (200 mg, 0.74 mmol) and ethyl isocyanoacetate (84 mg, 0.74 mmol) in ethanol (1 ml) and the mixture stirred at room temperature until the disappearance of the starting nitrostilbene (12 h, TLC control). The reaction mixture was diluted with water (up to 30 ml), neutralized with HCl, extracted with ethylacetate (3×5 ml). The extract was washed with water (2×3 ml), dried by filtration through cotton wool, and evaporated in vacuo. Pure product **2b** (15 mg, 2% in 2 steps) was obtained after column chromatography (ethyl acetate – hexane 1:3).

1-Nitro-1-(4-methoxyphenyl)-2-(4-hydroxyphenyl)ethylene (1b) (crude): yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.16 (s, 1H; H-2), 7.24 (d, J = 8.5 Hz, 2H; Ar), 7.00-7.05 (m, 4H; Ar), 6.69 (d, J = 8.2 Hz, 2H; Ar), 5.45 (s, 1H; OH), 3.88 ppm (s, 3H; OCH_3).

Ethyl 3-(4-hydroxyphenyl)-4-(4-methoxyphenyl)-1H-pyrrole-2-carboxylate (2b): white solid; m.p. 152-153 °C; ^{1}H NMR spectrum is identical to that of the minor product in the mixture of **2b** and **2c** (see above); MS (70 eV): *m/z* (%): 338 (10) $[M + H]^+$, 337 (46) $[M]^+$, 291 (100), 276 (21), 220 (17), 190 (9), 165 (18), 110 (13), 96 (9), 89 (9), 29 (33), 15 (13); elemental analysis calcd (%) for $C_{20}H_{19}NO_4$: C 71.20, H 5.68, N 4.15; found: 70.95; H 5.61; N 4.36.

Methyl 3,4-bis(4-methoxyphenyl)-1H-pyrrole-2-carboxylate (3a). *Method 1*. Solution of Na (33 mg, 1.4 mmol) in methanol (2.5 ml) was added to suspension of ethyl 3,4-bis(4-methoxyphenyl)-1*H*-pyrrole-2-carboxylate **2a** (50 mg, 0.14 mmol) in methanol (2 ml) and refluxed for 90 min. The reaction mixture was neutralized with aq. HCl, filtered, washed with water (2×3 ml) and dried. The resulting pyrrole was obtained in 84% yield. White solid, m.p. 175-176 °C (lit.[22a] 176-177 °C); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.13 (s, 1H; NH), 7.19 (d, J = 8.6 Hz, 2H; Ar), 7.02 (m, Ar, 3H; H-5), 6.84 (d, J = 8.7 Hz, 2H; Ar), 6.75 (d, J = 8.7 Hz, 2H; Ar), 3.82 (s, 3H; OCH_3), 3.76 (s, 3H; OCH_3), 3.73 ppm (s, 3H; OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ =161.5, 158.5, 157.9, 131.8, 129.4, 129.0, 127.1, 126.4, 120.0, 119.3, 113.6, 113.1, 55.1, 55.0, 51.2 ppm; MS (70 eV): *m/z* (%): 338 (18) $[M + H]^+$, 337 (81) $[M]^+$, 305 (100), 290 (21), 191 (21), 164 (15), 152 (16), 117 (12), 102 (12), 95 (12), 88 (13), 15 (60).

Method 2. Freshly calcined potassium carbonate (552 mg, 4 mmol) was added to a suspension of 1,2-bis(4-methoxyphenyl)-nitroethylene **1a**[30a] (570 mg, 2 mmol) and ethyl isocyanoacetate (226 mg, 2 mmol) in methanol (4 ml) and the mixture stirred at room temperature until the disappearance of the starting nitrostilbene (12 h, TLC control). The reaction mixture was diluted with water (up to 30 ml), neutralized with HCl, filtered, washed wish water (3×5 ml) and dried. The resulting pyrrole **3a** was obtained in 89% yield.

Methyl 3,4-bis(4-hydroxyphenyl)-1H-pyrrole-2-carboxylate (lamellarin Q). To a stirred solution of anhydrous CH_2Cl_2 (2 ml) and methyl 3,4-bis(4-methoxyphenyl)-1*H*-pyrrole-2-carboxylate **3a** (168 mg, 0.5 mmol) was added BBr_3 (1.5 ml 1M in CH_2Cl_2) dropwise at -5 °C. The resulting solution was stirred for 90 min (TLC control), quenched with $NaHCO_3$ (756 mg, 9 mmol) in H_2O (5 ml), stirred for 1 min, diluted with water (5 ml), extracted with ethyl acetate (3×7 ml). The extract was washed with water (2×5 ml), dried by filtration through cotton wool, and evaporated in vacuo. Pure product was obtained after column chromatography (ethyl acetate – heptane 1:2): 84% yield, white solid, m.p. 226-227 °C (lit.[8d] 227-228 °C); ^{1}H NMR (500 MHz , [D_6]DMSO): δ = 11.80 (s, 1H; NH), 9.26 (s, 1H; OH), 9.18 (s, 1H; OH), 7.07 (d, J = 3.2 Hz, 1H; H-5), 6.93 (d, J = 8.5 Hz, 2H; Ar), 6.85 (d, J = 8.6 Hz, 2H; Ar), 6.65 (d, J = 8.5 Hz, 2H; Ar), 6.56 (d, J = 8.6 Hz, 2H; Ar), 3.60 ppm (s, 3H; CH_3); ^{13}C NMR (125 MHz, [D_6]DMSO): δ =160.9, 155.9, 155.4, 131.6, 128.9, 128.5, 125.7, 125.3, 125.2, 120.9, 118.4, 114.9, 114.4, 50.7 ppm; MS (70 eV): *m/z* (%): 310 (12) $[M + H]^+$, 309 (60) $[M]^+$, 277 (100), 248 (9), 220 (13), 165 (19), 138 (8), 88 (9), 15 (5).

General Procedure for the Synthesis of Ethyl Pyrrole-2-carboxylates 2a, 5a-l. Freshly calcined potassium carbonate (552 mg, 4 mmol) was added to a suspension of 1,2-diarylnitroethylene **1a, 4a-l** (2 mmol) and ethyl isocyanoacetate (226 mg, 2 mmol) in ethanol (4

ml) and the mixture stirred at room temperature until the disappearance of the starting nitrostilbene (12-36 h, TLC control). The reaction mixture was diluted with water (up to 30 ml), neutralized with HCl, filtered, washed wish water (3×5 ml) and dried. **5a, 5c, 5d** were extracted with ethyl acetate (3×5 ml), the extract was washed with water (2×3 ml), dried by filtration through cotton wool, and evaporated in vacuo.

Ethyl 3-(6,7-dimethoxy-2H-1,3-benzodioxol-5-yl)-4-phenyl-1H-pyrrole-2-carboxylate (5f): 727 mg, 92% yield, yellowish solid, m.p. 149-150 °C; ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 11.99 (s, 1H; NH), 7.30 (d, J = 3.2 Hz, 1H; H-5), 7.19 (m, 4H; Ar), 7.10 (m, 1H; Ar), 6.30 (s, 1H; Ar), 6.01 (s, 1H; OCH$_2$O), 5.98 (s, 1H; OCH$_2$O), 4.05 (m, 2H; C$\underline{H}_2$CH$_3$), 3.89 (s, 3H; OCH$_3$), 3.30 (s, 3H; OCH$_3$), 1.06 ppm (t, J = 7.1 Hz, 3H; CH$_2$C$\underline{H}_3$); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 160.3, 144.5, 143.5, 136.9, 136.7, 135.0, 128.1, 126.7, 125.5, 124.8, 124.1, 122.2, 121.1, 120.3, 104.6, 101.2, 59.8, 59.7, 59.1, 13.9 ppm; MS (70 eV): *m/z* (%): 396 (25) [M + H]$^+$, 395 (100) [M]$^+$, 364 (4), 349 (22), 334 (9), 307 (12), 276 (7), 177 (3), 165 (5), 150 (3), 139 (3), 29 (19), 15 (6); elemental analysis calcd (%) for C$_{22}$H$_{21}$NO$_6$: C 66.83, H 5.35, N 3.54; found: C 66.61, H 5.42, N 3.64.

General Procedure for the Synthesis of 3-(2-Hydroxyaryl)-4-Arylpyrrole-2-carboxylates 6a-l. To a stirred mixture of anhydrous CH$_2$Cl$_2$ (2 ml) and ethyl 3-(2-methoxyaryl)-4-aryl-1H-pyrrole-2-carboxylate **5a-l** (0.5 mmol) was added BBr$_3$ (0.5 ml 1M in CH$_2$Cl$_2$) dropwise at -5 °C. The resulting solution was stirred for 30 min (TLC control), quenched with NaHCO$_3$ (252 mg, 3 mmol) in H$_2$O (5 ml), stirred for 1 min, diluted with water (25 ml), extracted with ethyl acetate (3×7 ml). The extract was washed with water (2×5 ml), dried by filtration through cotton wool, and evaporated in vacuo. Pure products were obtained after column chromatography (ethyl acetate – heptane 1:2).

Ethyl 3-(2-hydroxy-5-methylphenyl)-4-(2-methoxy-5-methylphenyl)-1H-pyrrole-2-carboxylate (6l): 142 mg, 78% yield, yellowish oil; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 9.29 (s, 1H; NH), 7.18 (d, J = 3.1 Hz, 1H; H-5), 6.97 (dd, J = 8.3 Hz, J = 1.7 Hz, 1H; Ar), 6.93 (dd, J = 8.3 Hz, J = 1.9 Hz, 1H; Ar), 6.88 (d, J = 1.9 Hz, 1H; Ar), 6.82 (d, J = 8.3 Hz, 1H; Ar), 6.72 (d, J = 1.7 Hz, 1H; Ar), 6.67 (d, J = 8.3 Hz, 1H; Ar), 5.52 (s, 1H; OH), 4.21 (q, J = 7.1 Hz, 2H; CH$_2$), 3.52 (s, 3H; OCH$_3$), 2.17 (s, 3H; CH$_3$), 2.12 (s, 3H; CH$_3$), 1.16 ppm (t, J = 7.1 Hz, 3H; CH$_3$); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 161.4, 154.6, 151.5, 131.9, 131.7, 129.4, 129.2, 128.6, 128.5, 125.1, 123.9, 122.7, 122.6, 122.2, 120.2, 115.5, 110.6, 60.7, 55.2, 20.5, 20.4, 14.1 ppm; MS (70 eV): *m/z* (%): 366 (24) [M + H]$^+$, 365 (100) [M]$^+$, 319 (86), 304 (16), 290 (10), 276 (14), 149 (7), 29 (29); elemental analysis calcd (%) for C$_{22}$H$_{23}$NO$_4$: C 72.31, H 6.34, N 3.83; found: C 72.62, H 6.19, N 3.63.

General Procedure for the Synthesis of Polyhydroxyarylpyrrole-2-carboxylates 8a-e. To a stirred mixture of anhydrous CH_2Cl_2 (2 ml) and ethyl polymethoxyaryl-*1H*-pyrrole-2-carboxylate **5c, d, g, h, i** (0.5 mmol) was added BBr_3 (1.5 ml for **5d,c**; 2 ml for **5g,h,i** 1M in CH_2Cl_2) dropwise at -5 °C. The resulting solution was stirred for 30 min (TLC control), quenched with $NaHCO_3$ (756 mg (9 mmol) for **5d,c**; 1008 mg (12 mmol) for **5g,h,i**) in H_2O (5 ml), stirred for 1 min, diluted with water (25 ml), extracted with ethyl acetate (3×7 ml). The extract was washed with water (2×5 ml), dried by filtration through cotton wool, and evaporated in vacuo. Pure products were obtained after column chromatography (ethyl acetate – heptane 1:2).

Ethyl 3-(2,4-dihydroxyphenyl)-4-(4-hydroxyphenyl)-1H-pyrrole-2-carboxylate (8d): 134 mg, 79% yield, white solid, m.p. 221-222 °C; ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 11.65 (s, 1H; NH), 9.11 (s, 1H; OH), 9.02 (s, 1H; OH), 8.65 (s, 1H; OH), 7.08 (d, *J* = 3.1 Hz, 1H; H-5), 6.96 (d, *J* = 8.5 Hz, 2H; Ar), 6.61 (d, *J* = 8.2 Hz, 1H; Ar), 6.54 (d, *J* = 8.5 Hz, 2H; Ar), 6.26 (d, *J* = 2.2 Hz, 1H; Ar), 6.11 (dd, *J* = 8.2 Hz, *J* = 2.2 Hz, 1H; Ar), 4.01 (m, 2H; CH_2), 1.05 ppm (t, *J* = 7.1 Hz, 3H; CH_3); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 160.7, 157.1, 156.1, 155.2, 132.1, 128.0, 126.5, 125.4, 124.9, 120.1, 114.8, 113.7, 105.7, 102.3, 58.9, 14.1 ppm; MS (70 eV): *m/z* (%): 340 (19) $[M + H]^+$, 339 (74) $[M]^+$, 293 (100), 273 (3), 265 (6), 236 (4), 29 (7); elemental analysis calcd (%) for $C_{19}H_{17}NO_5$: C 67.25, H 5.05, N 4.13; found: C 67.51, H 5.14, N 3.83.

General Procedure for the Synthesis of Benzo[c]chromen-6-ones 7a-l, 9a-e. Solution of 3-(2-hydroxyaryl)-4-aryl-*1H*-pyrrole-2-carboxylate (0.5 mmol) **6a-l**, **8c**,**d**,**g**,**h**,**i** in ethanol and 10% NaOH (0.1 ml) was stirred at room temperature for 3 h, evaporated, diluted with water (20 ml), filtered, washed with water (3×5 ml) and CH_2Cl_2 (3 ml) and dried.

1-(2-Methoxy-5-methylphenyl)-8-methylchromeno[3,4-b]pyrrole-4(3H)-one (7l): 131 mg, 82% yield, white solid, m.p. 247-248 °C; ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 12.77 (s, 1H; NH), 7.46 (s, 1H; H-2), 7.31 (d, *J* = 8.3 Hz, 1H; Ar), 7.26 (d, *J* = 8.0 Hz, 1H; Ar), 7.18 (m, 2H; Ar), 7.12 (s, 1H; Ar), 7.07 (d, *J* = 8.3 Hz, 1H; Ar), 3.64 (s, 3H; OCH_3), 2.32 (s, 3H; CH_3), 2.18 ppm (s, 3H; CH_3); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 155.1, 154.5, 148.7, 132.6, 132.2, 129.6, 129.2, 129.0, 128.2, 125.6, 123.2, 122.7, 118.3, 117.2, 116.5, 116.4, 111.1, 55.2, 20.6, 20.1 ppm; MS (70 eV): *m/z* (%): 320 (21) $[M + H]^+$, 319 (100) $[M]^+$, 304 (6), 276 (6), 233 (2), 212 (2), 189 (2); elemental analysis calcd (%) for $C_{20}H_{17}NO_3$: C 75.22, H 5.37, N 4.39; found: C 75.03, H 5.30, N 4.53.

1-(4-Hydroxyphenyl)-8-hydroxychromeno[3,4-b]pyrrole-4(3H)-one (9e): 119 mg, 81% yield, white solid, m.p. 327-328 °C; ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 12.69 (s, 1H; NH), 9.55 (s, 1H; OH), 9.43 (s, 1H; OH), 7.38 (s, 1H; H-2), 7.28 (d, *J* = 8.0 Hz, 1H; Ar), 7.23 (d, *J* = 8.9 Hz, 1H; Ar), 7.04 (s, 1H; Ar), 6.88 (d, *J* = 8.0 Hz, 2H; Ar), 6.78 ppm (d, *J* = 8.9 Hz, 1H; Ar); ^{13}C

NMR (125 MHz, [D_6]DMSO) δ 156.8, 154.6, 153.3, 144.0, 130.7, 128.4, 124.6, 124.2, 121.5, 118.8, 117.8, 116.8, 115.5, 115.3, 108.1 ppm; MS (70 eV): *m/z* (%): 294 (18) $[M + H]^+$, 293 (100) $[M]^+$, 264 (6), 236 (6), 152 (8), 89 (5), 63 (7), 55 (9), 39 (7), 28 (17); elemental analysis calcd (%) for $C_{17}H_{11}NO_4$: C 69.62, H 3.78, N 4.78; found: C 69.87, H 3.82, N 4.56.

X-ray structural study

X-ray diffraction data for **Lamellarin Q** and **9a** were collected on a three-circle Bruker D8 QUEST PHOTON-III CCD diffractometer (λ(MoK$_\alpha$)-radiation, T = 100 K, graphite monochromator, φ and ω scan mode) and corrected for absorption using the SADABS program.[32] The data were indexed and integrated using the SAINT program.[33]. The structures were determined by direct methods and refined by full-matrix least squares technique on F^2 with anisotropic displacement parameters for non-hydrogen atoms. In the crystal of **Lamellarin Q**, a solvate acetonitrile molecule was found in the asymmetric unit. The hydrogen atoms of the amino and hydroxy groups were localized in the difference-Fourier map and refined isotropically with fixed displacement parameters [U_{iso}(H) = 1.2U_{eq}(N) and 1.5U_{eq}(O)]. The other hydrogen atoms were placed in calculated positions and refined within riding model with fixed isotropic displacement parameters [U_{iso}(H) = 1.5U_{eq}(C) for the CH_3-groups and 1.2U_{eq}(C) for the other groups]. All calculations were carried out using the SHELXTL[34] program suite.

Crystallographic data for **Lamellarin Q** • MeCN and **9a** have been deposited with the Cambridge Crystallographic Data Center, CCDC 1964758 and CCDC 1964759, respectively. Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or www.ccdc.cam.ac.uk).

Crystal structure determination was performed in the Department of Structural Studies of Zelinsky Institute of Organic Chemistry, Moscow, Russia.

[†]Electronic supplementary information (ESI) available: X-ray data for **Lamellarin Q** • MeCN and compound **9a**; characterization and spectra for the compounds **4-9**; copies of ^{1}H and ^{13}C NMR spectra for all new compounds.

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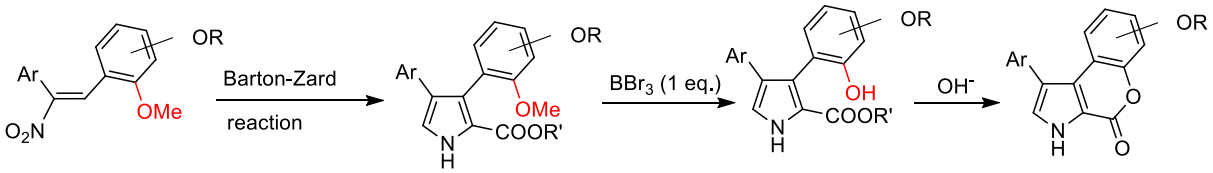

A metal-free approach to pyrrolocoumarin cores of lamellarins and related natural products based on Barton-Zard reaction of nitrostilbenes with ethyl isocyanoacetate was developed. Treatment of diarylpyrrole-2-carboxylates with 1 eq. BBr_3 resulted in selective O-demethylation of the *ortho*-methoxy group, while other methoxy groups remained intact. Subsequent base-induced lactonization give target pyrrolocoumarins.

Keywords: lamellarin Q, natural products, Barton-Zard reaction, O-demethylation, total synthesis
Key Topic: lamellarin synthesis