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Solid-phase synthesis of lamellarins Q and O

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Abstract—An efficient solid phase synthesis of the pyrrole-based alkaloids lamellarins Q and O using Merrifield resin and *N*-protected methyl 3,4-dibromopyrrole-2-carboxylate as a scaffold is described.

1. Introduction

An important group of marine natural compounds including lamellarins,[1] lukianols, ningalins,[2] and polycytones[3] have a pyrrole ring as a core component of their skeleton. These compounds are important on the basis of their biological activities and the novelty of their structures, which are without precedent. Lamellarins and related compounds have been isolated from invertebrates such as the prosobranch mollusc *Lamellaria* sp., ascidians such as *Didemnum chartaceum* and the sponge *Dendrilla Cactos* collected from different sea areas. The structures of these natural products are related because they probably have a common biogenetic origin. The common structural feature is a pyrrole ring substituted at positions 3 and 4 by polyhydroxy- or methoxyphenyl groups. Lamellarins Q and O (**1**, **2**) are the simplest compounds in this family. The structure is present in more complex molecules such as polycytone A (**3**), which contains a symmetrically substituted pyrrole, and lukianol A (**4**) and ningaline A (**5**), in which new rings condensed to pyrrole are present due to lactonisation processes. Lamellarin A (**6**) possesses the most complex structure and is an example of a pentacyclic lamellarin that is characterised by a lactone and an isoquinoline both condensed to the pyrrole ring. This group of pentacyclic compounds contains the largest number of related natural products.

A considerable number of these natural products possess important cytotoxic activities (Fig. 1). For example, lukianol A exhibits activity against a cell line derived from human epidermatoid carcinoma,[1c] polycytone A inhibits the growth of SV 40 transformed fibroblast[3a] at concentrations of 10 $\mu g\ ml^{-1}$, lamellarins O and P demonstrated antibiotic activity,[1c] lamellarins D and C caused inhibition of cell division[1a] and lamellarin N tested by the NCI in a 60 cell-line panel showed selectivity towards melanoma cell lines.[1f] In addition, a select set of lamellarins exhibit equally potent cytotoxic activity against multidrug-resistant (MDR) cell lines arising over expression of P-glycoprotein and/or reverse MDR at noncyctotoxic concentrations, resensitising the resistant cell lines to conventional therapeutic agents.[4f]

A number of synthetic routes have been described for lamellarins,[4] lukianols,[4a,b,f,5] and ningalins[4f,6] but only one has been developed using the solid-phase approach.[7] Solid-phase combinatorial synthesis is one of the most useful techniques for the preparation of small libraries. This technique provides rapid access to larger collections of products that can possess great diversity and may incorporate optimised physical and pharmacological properties associated with certain structures.

Palladium-catalysed cross-coupling reactions are good methods for the preparation of bisaryl or heteroaryl derivatives. Our previous experience in Pd-catalysed heteroaryl coupling reactions[8] encouraged us to use this methodology for the solid phase preparation of the structurally least complex components of the group of compounds under investigation, namely lamellarins Q and O. The developed methodology will be used in the preparation of compound libraries in which elements of diversity would be introduced in the aromatic substituents at positions 3 and 4 and on the nitrogen of the pyrrole ring. For this reason it was important to develop a synthetic procedure that would be compatible with the sequential introduction of

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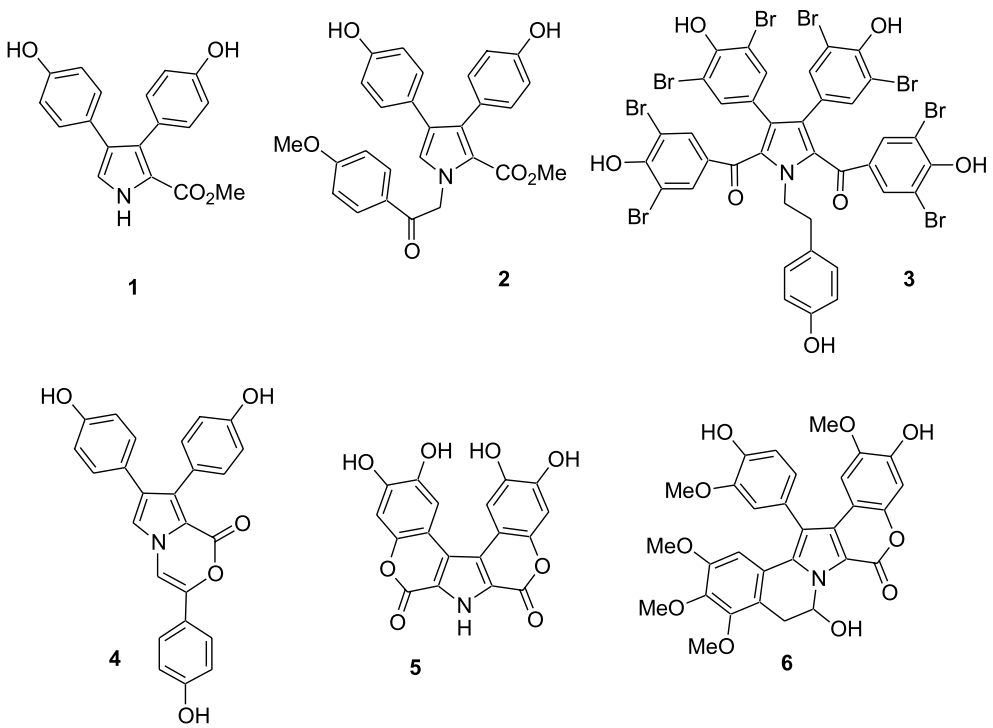


Figure 1.

these aromatic rings into an appropriately functionalised pyrrole ring.

We describe here a solid phase synthesis of lamellarins Q and O using methyl *N*-(triisopropylsilyl)-3,4-dibromo-pyrrole-2-carboxylate (**7a**) as a scaffold. Banwell et al.[4b] used the dibromopyrrole **7a** in an elegant convergent synthesis of several compounds from this family of marine alkaloids. As shown in Figure 2, compound **7** can be attached to the resin at three different positions that could be potentially useful for the preparation of related libraries using coupling methodologies in solid-phase synthesis.

The first strategy (a) involved linking the dibromopyrrole to the resin through the nitrogen to give **8**. However, this strategy was ruled out because it suffers from a serious limitation in that it lacks the flexibility required for the introduction of a nitrogen substituent and therefore loses one avenue to introduce diversity.

The results obtained on linking compounds **9** and **10** to a polystyrene (Merrifield) resin are now described. The formation of an ester linkage between the acid **7b** and hydroxymethyl functionalized Merrifield resin, as in compound **9** (strategy b), was tested for the sequential introduction of three elements of diversity into the pyrrole. Strategy c, on the other hand, involves compound **10** and requires an appropriately substituted iodophenol to be attached to a chloro-functionalised Merrifield resin. A

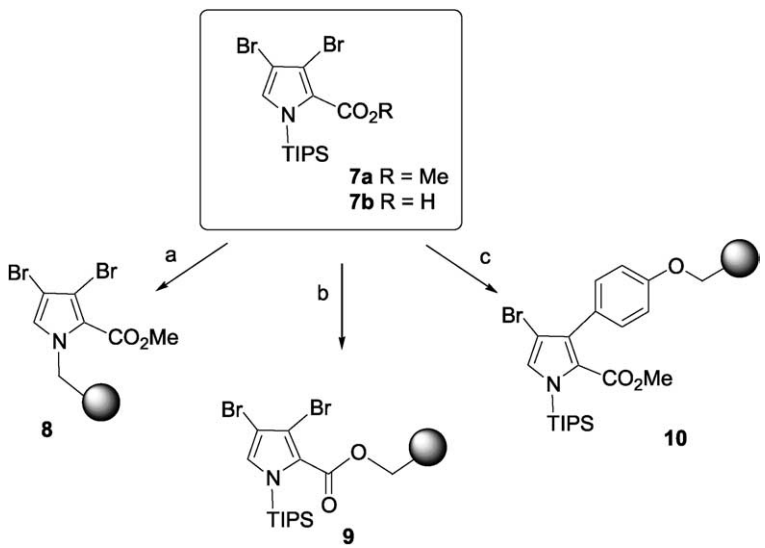


Figure 2.

subsequent Pd-catalysed cross-coupling reaction with a derivative of **7a** would then be used to introduce the scaffold.

2. Results and discussion

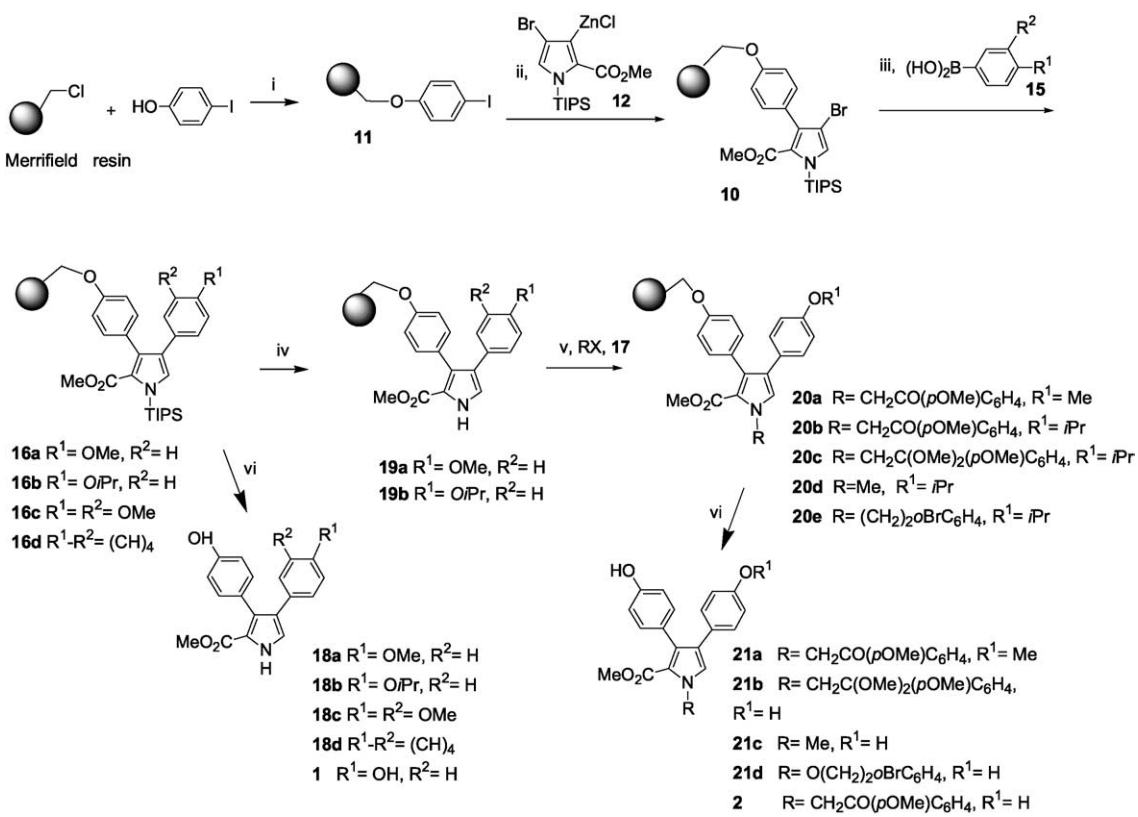
The anchored pyrrole **9** was obtained by reaction of the acid **7b** and hydroxy-functionalised Merrifield resin using DIPCDI as an activating agent and DMF as the solvent. Formation of **9** was confirmed by performing a cleavage reaction and characterising the resulting methyl 3,4-dibromopyrrole-2-carboxylate. Several experiments were performed to assess the regioselective formation of a zinc derivative of **9**, using *n*BuLi and $ZnCl_2$, followed by a Pd-catalysed cross-coupling reaction with *p*-iodoanisole. However, all attempts in this direction were unsuccessful. In all cases the same product, methyl 3,4-dibromopyrrole-2-carboxylate, was obtained after cleavage of the crude coupling reaction product. This result indicates that the bromo-lithium interchange, which occurs prior to formation of the zinc derivative, did not take place. It seems reasonable that this failure is due to steric hindrance caused by the resin being attached close to the reaction site.

As an alternative, strategy c was investigated using compound **10**. The attachment of the *p*-iodophenol to the chloro-functionalised Merrifield resin was achieved under basic conditions (Scheme 1).

4-Iodophenol was attached to the resin under basic conditions using the phenoxy anion, which displaces the Cl of the resin.[9] Treatment with NaOMe was also carried out in order to cap any reactive residual chloromethyl groups.

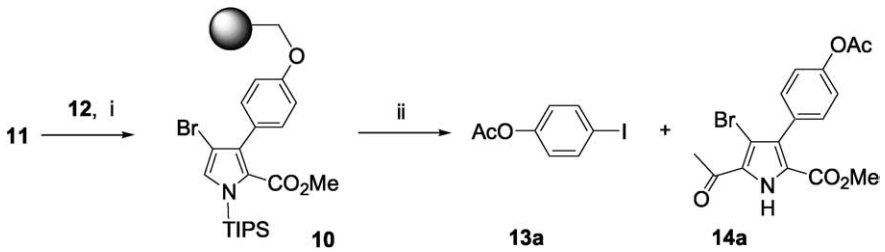
The methyl ester **7a**[10] was used for the chemoselective halogen–metal interchange and preparation of zinc derivative **12**. Compound **12** was obtained by selective *ortho*-directed bromine/lithium interchange at position 3 by treatment of **7a** with *n*-BuLi at low temperature followed by metal–metal interchange using zinc chloride. The organometallic compound **12** was employed in a Pd(0)-catalysed Negishi cross-coupling reaction with the resin-bound iodophenol **11**.

Several experiments were carried out in order to find the optimal conditions for obtaining **10** and the results of these are shown in Table 1. In all the experiments $Pd(PPh_3)_4$ was used as the catalyst and THF as the solvent. Two parameters were changed in an attempt to improve the yield of the coupling reaction; the relative proportion of the reagents and the reaction time. Each reaction was assessed by performing a cleavage reaction using $ZnBr_2$ and acetyl bromide in DCM and the ^1H NMR spectra of the crude product were evaluated. The cleavage using $ZnBr_2$ and AcBr produced several simultaneous reactions in addition to the desired ether cleavage; *O*-acetylation of the resulting phenol occurred along with *N*-desilylation of the pyrrole and acylation at position 5 of the pyrrole. Thus, under these cleavage conditions *O*-acetyl iodophenol **13a**—corresponding to the unreacted starting resin—and



Scheme 1. Reagents: (i) NaOMe, dry DMF, N_2, 80 °C, 24 h; (ii) $Pd(PPh_3)_4$, dry THF, N_2, rt, 24 h; (iii) aq. 2 M Na_2CO_3, $Pd(PPh_3)_4$, dioxane, reflux, 21–48 h; (iv) NH_4F, DCM/MeOH (1:1), reflux, 6 h; (v) NaH (or LDA), dry THF, N_2, −78 °C, 24 h; or 18-crown-6 (2.5 M in DMF), microwave, 100 °C, 30–40 W, 2 min; (vi) $AlCl_3$, dry DCM, rt, 3 h.

Table 1. Solid-phase cross-coupling reaction between the anchored iodophenol **11** and the zinc derivative **12**



Cross-coupling conditions			Products[a]
Entry	**12/11** (equiv.)	Time (h)	**13a/14a**
1	2.5	21	33:66
2	3	18	50:50
3	5	18	50:50
4	10	18	15:85
5	10	24	0:100

Reagents: (i) 15 mol% $Pd(PPh_3)_4$, dry THF, rt; (ii) AcBr (40 equiv.), $ZnBr_2$ (3.5 equiv.), dry DCM.
[a] Proportion of unreacted iodine with respect to the cross-coupling product calculated from the ^1H NMR spectra of the crude cleaved material.

the diacetylarylpyrrole **14a** were obtained. The relative integrations of the doublets at 6.86 and 7.17 ppm, due to the aromatic protons *ortho* to the acetate groups in each compound, indicate the proportion of compound **13a** to **14a**. The anchored arylpyrrole **10**[11] was obtained in quantitative yield (entry 5, Table 1) by treatment of resin **11** with 10 equiv. of **12** at rt for 24 h.

It was envisaged that bisarylpyrrole **16a** would be prepared from **10** by a new Pd(0)-catalysed cross-coupling reaction. Two different alternative procedures could be followed for the formation of the second aryl–pyrrole bond. The first would involve the preparation of the organometallic compound on the resin through a halogen–metal interchange of the bromo-substituent at position 4 of **10** and the second approach would employ an organometallic aryl compound for the cross-coupling reaction with the bromo-containing pyrrole **10** anchored on the resin.

Preparation of the zinc derivative of **10** by bromine/lithium interchange with *n*-BuLi followed by treatment with $ZnCl_2$ and a subsequent coupling reaction with 4-iodoanisole was tried under different catalytic conditions (entries 1–3, Table 2). Unfortunately, all the experiments with zinc derivatives of **10** produced, after cleavage, a crude material that was difficult to manipulate and did not contain either the product corresponding to the coupling or the starting material.[12]

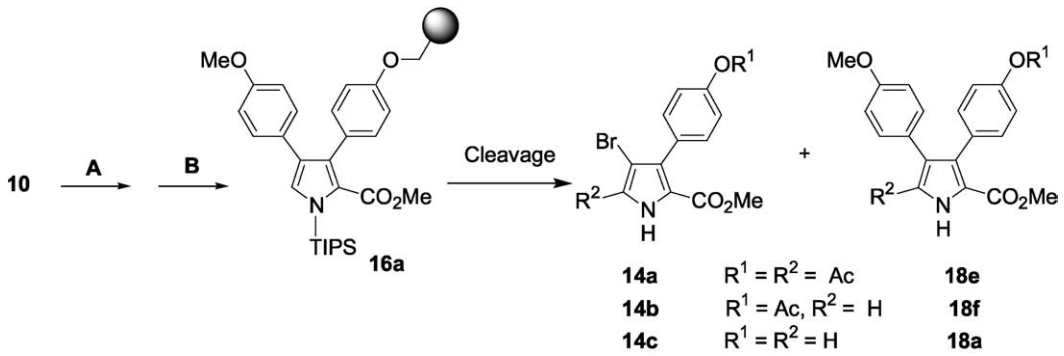
The second option for aryl–pyrrole bond formation was assessed and Suzuki[13] conditions were tried with resin **10**.[14] The different conditions tested for the Suzuki cross-coupling reaction between **10** and 4-methoxyphenylboronic acid are shown in Table 2 (entries 4–10).

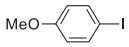
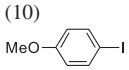
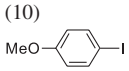
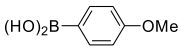
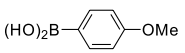
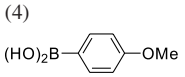
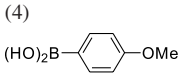
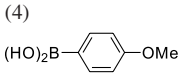
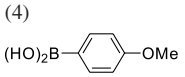
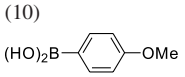
Formation of bisarylpyrrole **16a** was confirmed by gel phase nuclear magnetic resonance (GP ^{13}C NMR). The signal of the methoxy group at 67.0 ppm was indicative of the introduction of the new phenyl ring into the system. The amount of **16a** produced was determined after cleavage from the resin. Cleavage with $ZnBr_2$ and AcBr was used in entries 4–6, Table 2.[15] Under the same reaction conditions it was found that dioxane (entry 8) and dimethoxyethane (DME) (entry 7) gave better yields of **18** than THF (entry 4) as a solvent. Dioxane was the solvent of choice after comparison of yields obtained with these two solvents. $AlCl_3$ in DCM was used as the cleavage reagent (entries 7–9) to avoid the formation of acylated products **14b** and **18e**, which would be produced with $ZnBr_2$ and AcBr. Both cleavage reagents (entries 6 and 7) afforded the same yield but $AlCl_3$ has the advantage of producing cleaner cleavage products without side-reactions such as acetylation. Increasing the amount of boronic acid with respect to resin **10** (entry 8) produced only a small change in the yield, but an increase in the reaction time under these conditions to 21 h improved the yield to 84% (entry 10).

The same reaction conditions were applied to the synthesis of bisarylpyrroles **16b**-**16d**[16] using for the second cross-coupling reaction the appropriate boronic acid **15b**-**d**. Preparation of lamellarins Q and O requires the use of a *p*-hydroxyphenylboronic acid with a suitable hydroxy-protecting group for the introduction of the second aryl substituent. *p*-Isopropoxyphenylboronic acid was used for the cross-coupling reaction with bromide **10** and similar results were obtained as described above.[17] GP ^{13}C NMR was used to assess the success of the cross-coupling reaction, with the signals due to the isopropoxy group at 22.1 and 69.6 ppm (methyl and CH, respectively) confirming the formation of **16b**.

In the case of resin **16b**, the best conditions found for the cleavage of **16a** were used. Cleavage with $AlCl_3$ of a large amount of resin **16** (1 g) afforded only traces of **18** and the resin beads were found to break down under these conditions.[18] A reduction in the amount of $AlCl_3$ and the reaction time allowed the isolation of **18a** in good yield working on a 1 g scale of **16b**. The same results were obtained from the resins **16c** and **16d**, from which the bisarylpyrroles **18c** and **18d** were isolated. As observed previously, *N*-deprotection of pyrrole was concomitant during the cleavage. In addition, the application of these

Table 2. Solid-phase preparation of bisarylpyrrole **16a** and cleavage conditions



Entry	Coupling conditions[a]						Cleav. cond.[b]	Yield[c] (%)	
	Reag. A (equiv.)	Reag. B (equiv.)	Cat., Lig. (%)	Solvent	Temperature	Time (h)		**14**[d]	**18**[e]
1	*n*BuLi (10), $ZnCl_2$ (16)	 (10)	Pd_2dba_3, $AsPh_3$ (15, 40)	THF[f]	37 °C	21	$ZnBr_2$ AcBr		
2	*n*BuLi (10), $ZnCl_2$ (16)	 (10)	$PdCl_2(PPh_3)_2$, PPh_3 (25, 20)	THF[f]	rt	21	$ZnBr_2$ AcBr	Crude material difficult to manipulate	
3	*n*BuLi (10), $ZnCl_2$ (16)	 (10)	$Pd(PPh_3)_4$ (15)	THF[f]	rt	21	*$ZnBr_2$* AcBr		
4	—	 (4)	$Pd(PPh_3)_4$, 2 N Na_2CO_3 (10, 5)	THF	Reflux	19	$ZnBr_2$ AcBr	**a** (30) **b** (16)	**e** (20)
5	—	 (4)	$Pd(PPh_3)_4$, 2 N Na_2CO_3 (10, 5)	DME	Reflux	19	$ZnBr_2$ AcBr	**b** (28)	**e** (15) **f** (16)
6	—	 (4)	$Pd(PPh_3)_4$, 2 N Na_2CO_3 (10, 5)	Dioxane	Reflux	19	*$ZNBR_2$* AcBr	**a** (13) **b** (18)	**e** (22) **f** (10)
7	—	 (4)	$Pd(PPh_3)_4$, 2 N Na_2CO_3 (10, 5)	DME	Reflux	19	$AlCl_3$	**c** (46)	**a** (27)
8	—	 (4)	$Pd(PPh_3)_4$, 2 N Na_2CO_3 (10, 5)	Dioxane	Reflux	19	$AlCl_3$	**c** (32)	**a** (34)
9	—	 (4)	$Pd(PPh_3)_4$, 2 N Na_2CO_3 (10, 10)	Dioxane	Reflux	19	$AlCl_3$	**c** (15)	**a** (37)
10	—	 (10)	$Pd(PPh_3)_4$, 2 N Na_2CO_3 (20, 10)	Dioxane	Reflux	21	$AlCl_3$	(0)	**a** (84)

[a] 30–60 mg of **10** were used.
[b] Dry THF was used.
[c] All cleavage reactions were carried out in dry DCM at rt.
[d] Calculated from the HPLC of the crude cleavage product.
[e] tr **14a** 9.52 min, MS (380, 378); tr **14b** 7.90 min, MS (338, 336); tr **14c** 7.82 min, MS (298, 296).
[f] tr **18a** 8.74 min, MS (325); tr **18e** 10.12 min, MS (408); **18f** 8.82 min, MS (366).

cleavage conditions to resin **16b** also led to deprotection of the *O*-isopropoxy group to give lamellarin Q (**1**). Other Lewis acids, such as $SnCl_4$, reacted with **16b** to produce cleavage from the resin and *N*-deprotection but not the desired *O*-isopropoxy deprotection. This is a new example of how the choice of the appropriate cleavage reaction conditions allows different substituted derivatives to be obtained.[19]

N-Deprotection of **16a** and **16b** by treatment with NH_4F in DCM produced the anchored bisarylpyrroles **19a** and **19b**, respectively. The absence in the GP ^{13}C NMR of

characteristic signals for isopropylsilyl groups provided evidence that *N*-desilylation had occurred.

N-Alkylation of **19a** with *p*-methoxybromoacetylbenzene (**17a**) was investigated under different experimental conditions.[20] The use of excess NaH or LDA as a base[21] in dry THF under reflux gave, after cleavage with $AlCl_3$, moderate yields of the *N*-alkyl derivative **21a**.[22] Similar *N*-alkylation results were obtained starting with the *O*-isopropoxy-protected derivatives **19b** and **17a**.[23] Cleavage of the alkylation product **20b** with $AlCl_3$ afforded mixtures of **1** and **2**, as determined by HPLC and HPLC-MS.[22] The dimethylacetal of *p*-methoxybromoacetylbenzene[24] was prepared to avoid the possibility of enolate formation under the basic alkylation conditions but the N-alkylation process was not improved by this change.

Finally, other alkylating agents—MeI and the tosylate of 2-(2-bromophenyl)ethanol[25]—afforded resins **20d** and **20e**[26] which, after cleavage with $AlCl_3$ and purification by HPLC, produced *N*-methyllamellarin Q (**21c**) in moderate yield. However, **21d** proved impossible to isolate by HPLC.

An efficient solid-phase strategy has been devised for the preparation of the pyrrole-containing alkaloids, lamellarins Q and O. The process involves the incorporation of the appropriately substituted pyrrole ring onto a *p*-alkoxy iodophenyl resin through a Negishi cross-coupling reaction. This step is followed by a Suzuki cross-coupling reaction to introduce the second substituted phenyl ring and *N*-alkylation of the pyrrole. Final cleavage was achieved using a Lewis acid to give the desired product. Diversity can be introduced in each step of the synthetic process as well as during the final cleavage by using the appropriate Lewis acid conditions. GP ^{13}C NMR has proven to be a good method to follow the different steps in the process.

3. Experimental

3.1. General

Melting points were determined in capillary tubes and are uncorrected. TLC was carried out on SiO_2 (silica Gel 60 F_{254}, Merck) and spots were located with UV light. Column chromatography was carried out on SiO_2 (silica Gel 60 SDS 0.035–0.070 mm). Organic extracts were dried over anhydrous Na_2SO_4 and solutions were evaporated under reduced pressure with a rotatory evaporator. IR spectra were obtained using a Thermo Nicolet Nexus spectrophotometer. NMR spectra were acquired with Varian Gemini-200 (200 MHz), Varian Gemini-300 (300 MHz), Mercury-400 (400 MHz) and Varian VXR-500 (500 MHz) spectrometers; data are given on the δ scale referenced to TMS. Mass spectra were measured in the electron impact (EI) mode with a Hewlett–Packard model 5989A spectrometer. High resolution mass spectra were performed on an Auto-Spec/VG by Unidad de Espectrometría de Masas de Santiago de Compostela. HPLC was carried out using a Waters 996 Photodiode Array Detector, a SYMMETRY C_{18} column (4.6×150 mm, 5 μm) and H_2O (0.045% TFA) and AcCN (0.036% TFA) as eluents. HPLC-MS was carried out on a Waters micromass ZQ using a SYMMETRY C_{18} column (3.9×150 mm, 5 μm), Waters 2487 Dual Absorbance Detector and H_2O (0.1% formic acid) and AcCN (0.07% formic acid) as eluents. Purification by HPLC was carried out with Waters 2487 Dual Absorbance Detector, Waters 600 Controller and Waters Fraction Collector II using a SYMMETRY C_{18} (30×100 mm, 5 μm) column and H_2O (0.1% TFA) and AcCN (0.05% TFA) as eluents. Solid-phase reactions were shaken in a Vibromatic SELECTA. Microwave reactions were carried out in a DISCOVER (CEM).

3.1.1. 3,4-Dibromo-1-(triisopropylsilyl)pyrrole-2-carboxylic acid 7b.[4b] *n*BuLi (1.36 ml, 2.17 mmol, 1.6 M) was added dropwise to a cooled (−78 °C) solution of 2,3,4-tribromo-1-trimethylsilanylpyrrole (1 g, 2.17 mmol) in dry THF (15 ml) under N_2 and the mixture was stirred for 15 min at that temperature. Dry CO_2 was bubbled through the mixture at that temperature and the cooling bath was removed. The reaction mixture was stirred at rt for 20 min. The solution was diluted with H_2O, acidified to pH 1 with 1 N HCl and extracted with EtOAc. The organic layer was dried and evaporated under vacuum. The crude product was purified by flash chromatography. Elution with hexane/DCM (8:2) gave **7b** as a white solid (425 mg, 46%). mp 142.3–143.3 °C (hexane/EtOAc). IR (KBr) ν 3272, 1653, 1460, 825; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.14 (d, J=7.7 Hz, 18H, CH_3), 1.41 [m, 1H, $CH(CH_3)_2$], 6.98 (d, J=3.3 Hz, 1H, H5), 9.65 (bs, 1H, CO_2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.3 [q, $(CH_3)_2$], 17.8 [d, $CH(CH_3)_2$], 102.7 (s, C4), 106.3 (s, C3), 121.8 (s, C2), 122.5 (d, C5), 159.4 (s, C=O); MS (EI) m/z 428 (2 $^{81}BrM^+$, 19), 426 ($^{81}BrM^+$, $^{79}BrM^+$, 34), 424 (2 $^{79}BrM^+$, 18), 384 (2 $^{81}BrM^+$, 54), 382 ($^{81}BrM^+$, $^{79}BrM^+$, 100), 380 (2 $^{79}BrM^+$, 50); HRMS (EI) m/z calculated for $C_{13}H_{24}NO_2Br_2Si$: 426.9956; found: 426.9940.

3.1.2. 3,4-Dibromo-1-triisopropylsilylpyrrole-2-carboxylate resin 9. Merrifield-OH resin (1 g, loading 0.68 mmol/g) was swelled in dry DMF and **7b** (289 mg, 1 equiv.) and DMAP (41 mg, 0.5 equiv.) in DMF (0.5 ml) and DIPCDI (106 μl, 1 equiv.) were added. The reaction mixture was stirred at rt for 3 h. The resin was washed with DMF and a second treatment with the same quantities of **7b**, DMAP and DIPCDI was carried out. The reaction mixture was stirred for 3 h at rt. Finally, the resin was washed with DMF, DCM, MeOH and Et_2O and dried under vacuum.

3.1.3. Methyl 3,4-dibromopyrrole-2-carboxylate 7c. Resin **9** (100 mg) was swelled in DCM (5 ml) and LiOH (32.5 mg, 20 equiv.) in MeOH (5 ml) was added. The reaction mixture was shaken at reflux temperature for 2 h. The resin was washed with DCM and the organic layer was evaporated. The crude product was diluted in H_2O, acidified to pH 2 with 1 N HCl and extracted with EtOAc. The organic layer was dried and evaporated under vacuum to give the title compound (3.5 mg of crude material). The spectroscopic data of the product are the same as described previously.[4b] IR (NaCl) ν 3359,31, 1728, 1368; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.91 (s, 3H, CO_2CH_3), 7.00 (d, J=2.8 Hz, 1H, H5); MS (EI) m/z 285 (2 $^{81}BrM^+$, 31), 283 ($^{81}BrM^+$, $^{79}BrM^+$, 63), 281 (2 $^{79}BrM^+$, 33), 253 (2 $^{81}BrM^+$, 50), 251 ($^{81}BrM^+$, $^{79}BrM^+$, 100), 249 (2 $^{79}BrM^+$, 51).

3.1.4. 4-(4-Bromo-2-methoxycarbonyl-1-triisopropylsilylpyrrol-3-yl)phenoxy resin 10. *n*-BuLi (8.13 ml, 10 equiv., 1.6 M) was added dropwise to a cooled (−78 °C) solution of methyl 3,4-dibromo-1-trimethylsilanylpyrrole-2-carboxylate (5.71 g, 10 equiv.) in dry THF (35 ml) under N_2 and the mixture was stirred for 15 min at −78 °C. A solution of $ZnCl_2$ (2.84 g, 16 equiv.) in dry THF (8 ml) was added and the reaction mixture was stirred for 5 min at −78 °C and 25 min at rt. The reaction mixture was transferred using N_2 to a mixture of the swelled resin **11** (2.82 g) with dry THF (15 ml) and $Pd(PPh_3)_4$ (225 mg, 0.15 equiv.). The reaction mixture was shaken for 24 h at rt and, after this time, was washed with THF, DCM, MeOH, Et_2O (3×10 ml, each) and finally was dried in a vacuum oven at 40 °C. IR (KBr) ν 1697 (C═O), 1600, 741, 700; ^{13}C MAS NMR ($CDCl_3$, 125 MHz) δ 13.4 [$CH(CH_3)_2$], 18.3 ($CHCH_3$), 50.9 (CO_2CH_3).

3.1.5. 4-Iodophenoxy-resin 11.[27] Merrifield-Cl resin (4 g, loading 0.5 mmol/g) was swelled in dry DMF (60 ml) for 30 min and 4-iodophenol (2.20 g, 5 equiv.) and NaOMe (22.3 ml, 5 equiv., 4.4 M) in dry DMF were added. The reaction mixture was warmed at 80 °C and shaken for 24 h. The resin was washed with DCM, DMF/DCM (1:1), DMF, DCM, MeOH, Et_2O (3×3 ml, each) and was dried under vacuum. The resin was swelled in dry DMF (60 ml) for 15 min, NaOMe (1.2 ml, 4 equiv., 4.4 M) was added and the mixture was shaken for 3 h at 80 °C. The resin was washed with DMF, DCM, MeOH and Et_2O (3×10 ml) and dried under vacuum. IR (KBr) ν 1943, 1872, 1803, 1599, 743, 698.

3.2. General procedure for cleavage with $ZnBr_2$/AcBr

$ZnBr_2$ (3.5 equiv.) and AcBr (40 equiv.) were added to the swelled resin in DCM under N_2 and the reaction mixture was shaken for 24 h at rt. The resin was filtered off and washed with DCM. The organic solution was washed with 5% aq. $NaHCO_3$, 5% aq. HCl, saturated NaCl, dried and evaporated.

3.2.1. 4-Iodophenol acetate 13a. The general procedure for cleavage with $ZnBr_2$/AcBr on resin **11** (40 mg) gave **13a** (2.5 mg, 50%). ^1H NMR ($CDCl_3$, 200 MHz)[28] δ 2.29 (s, 3H, CH_3), 6.86 (d, J=8.8 Hz, 2H, H2, H6), 7.68 (d, J=8.8 Hz, 2H, H3, H5).

3.2.2. Methyl 3-(4-acetoxyphenyl)-5-acetyl-4-bromopyrrole-2-carboxylate 14a. The general procedure for cleavage with $ZnBr_2$/AcBr on resin **10** (110 mg) gave **14a** (17 mg). HPLC (35–50% ACN in 15 min; tr 12.28 min, 83% purity). ^1H NMR ($CDCl_3$, 200 MHz) δ 2.33 (s, 3H, $COCH_3$), 2.72 (s, 3H, $OCOCH_3$), 3.75 (s, 3H, CO_2CH_3), 7.17 (d, J=8.6 Hz, 2H, H3′, H5′), 7.35 (d, J=8.6 Hz, 2H, H2′, H6′); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 17.7 (q, CH_3), 21.3 (q, CH_3), 52.2 (q, CH_3), 104.9 (s), 120.8 (d), 122.2 (s), 129.4 (s), 130.6 (s), 130.9 (s), 131.6 (d), 150.4 (s), 165.1 (s), 169.2 (s), 188.2 (s). MS(EI) m/z 381 ($^{81}BrM^+$, 11), 379 ($^{79}BrM^+$, 11), 337 (74), 339 (72), 307 (74), 305 (74), 292 (40), 290 (40). HRMS (EI) m/z calculated for $C_{16}H_{14}NO_5Br$: 379.0055; found: 379.0066.

3.3. General procedure for the preparation of 16

Resin **10** was swelled with dioxane for 15 min. 2 M aq. Na_2CO_3 (10 equiv.), boronic acid **15** (10 equiv.) and $Pd(PPh_3)_4$ (0.2 equiv.) were added and the reaction mixture was shaken under reflux between 21 and 48 h. Resin **16** was washed with dioxane, DCM, MeOH, Et_2O (3×4 ml, each) and was dried under vacuum.

3.3.1. 4-[2-Methoxycarbonyl-4-(4-methoxyphenyl)-1-triisopropylsilylpyrrol-3-yl]phenoxy resin 16a. The general diaryl synthesis procedure, with resin **10** (1 g) and 4-methoxyphenylboronic acid, gave resin **16a** after a reaction time of 19 h. IR (KBr) ν 1691 (C═O), 1600, 1450, 746. ^{13}C NMR ($CDCl_3$, Gel Phase, 75 MHz) δ 13.6 [$CH(CH_3)_2$], 18.6 [$CH(CH_3)_2$], 53.4 (CO_2CH_3), 67.0 (OCH_3).

3.3.2. 4-[2-Methoxycarbonyl-4-(4-isopropoxyphenyl)-1-triisopropylsilylpyrrol-3-yl]-phenoxy resin 16b. The general diaryl synthesis procedure, with resin **10** (1 g) and 4-isopropoxyphenylboronic acid,[16] gave resin **16b** after a reaction time of 48 h. IR (KBr) ν 1695 (C═O), 1600, 744. ^{13}C NMR ($CDCl_3$, Gel Phase, 75 MHz) δ 13.6 [$CH(CH_3)_2$], 18.6 [$CH(CH_3)_2$], 22.1 [$OCH(CH_3)_2$], 53.4 (CO_2CH_3), 69.6 [$OCH(CH_3)_2$].

3.3.3. 4-[2-Methoxycarbonyl-4-(3,4-dimethoxyphenyl)-1-triisopropylsilylpyrrol-3-yl]phenoxy resin 16c. The general diaryl synthesis procedure, with resin **10** (1 g) and 3,4-dimethoxyphenylboronic acid, gave resin **16c** after a reaction time of 48 h. IR (KBr) ν 1694 (C═O), 1600, 1492, 744. ^{13}C NMR ($CDCl_3$, Gel Phase, 75 MHz) δ 13.6 [$CH(CH_3)_2$], 18.6 [$CH(CH_3)_2$], 55.2 (−OCH_3), 55.7 (−OCH_3).

3.3.4. 4-[2-Methoxycarbonyl-4-(2-naphthyl)-1-triisopropylsilylpyrrol-3-yl]-phenoxy resin 16d. The general diaryl synthesis procedure, with resin **10** (1 g) and 2-naphthaleneboronic acid, gave resin **16d** after a reaction time of 48 h. IR (KBr) ν 1694 (C═O), 1600. ^{13}C NMR ($CDCl_3$, Gel Phase, 75 MHz) δ 13.6 [$CH(CH_3)_2$], 18.6 [$CH(CH_3)_2$].

3.4. General procedure for cleavage with $AlCl_3$

$AlCl_3$ (3 equiv.) was added to the swelled resin **16** in dry DCM under N_2. The reaction mixture was shaken for 3 h at rt. The resin was washed with DCM. The organic layer was washed with 10% aq. HCl, dried and evaporated to give **18**. The crude material was analysed by HPLC-MS.

3.4.1. Methyl 3-(4-hydroxyphenyl)-4-(4-methoxyphenyl)pyrrole-2-carboxylate 18a. Resin **16a** (600 mg) gave **18a** by following the general procedure for cleavage with $AlCl_3$ (15 equiv.). The crude material was analysed by HPLC-MS (gradient 30–70% ACN in 15 min), **18a** (tr 5.67 min, MS 324, M+1). Purification by HPLC (gradient 20–65% AcCN in 40 min) gave **18a** (1 mg, 2%) as a pale-yellow solid. ^1H NMR ($CDCl_3$, 500 MHz) δ 3.73 (s, 3H, CO_2CH_3), 3.76 (s, 3H, OCH_3), 6.76 (bt, J=8.7 Hz, 4H, H3′, H5′, H3″, H5″), 7.00–7.06 (m, 3H, H2′, H6′, H5), 7.14 (d, J=8.5 Hz, 2H, H2″, H6″), 9.12 (bs, NH/OH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.4 (s, CO_2CH_3), 55.2 (s, OCH_3), 113.8 (d, C3″, C5″), 114.8 (d, C3′, C5′), 129.6 (d, C2′, C6′), 132.2 (d, C2″, C6″). MS (EI) m/z 324 (M+1, 12), 323 (M^+, 9), 292 (18). HRMS (EI) m/z calculated for $C_{19}H_{17}NO_4$: 323.1157; found: 323.1157.

3.4.2. Methyl 3,4-bis(4-hydroxyphenyl)pyrrole-2-carboxylate 1: lamellarin Q. Resin **16b** (500 mg), gave **1** by following the general procedure for cleavage with $AlCl_3$. The crude product was analysed by HPLC-MS (gradient 20–40% ACN in 15 min) and **1** (tr 6.92 min, MS 310, M+1). Purification by HPLC (gradient 20–40% ACN in 20 min) gave **1** (5 mg, 13%) as a pale-yellow gum. ^{1}H NMR (Acetone-d^6, 400 MHz) δ 3.64 (s, 3H, CO_2CH_3), 6.66 (d, J=8.4 Hz, 2H, H3′, H5′), 6.76 (d, J=8.4 Hz, 2H, H3″, H5″), 6.95 (d, J=8.4 Hz, 2H, H2″, H6″), 7.05 (d, J=8.4 Hz, 2H, H2″, H6″), 7.13 (bs, 1H, H5), 8.25 (bs, 2H, OH), 10.91 (bs, 2H, NH). ^{13}C NMR (Acetone-d^6, 100 MHz) δ 50.3 (q, CO_2CH_3), 114.4 (d, C3″, C5″), 115.0 (d, C3′, C5′), 120.5 (d, C5), 120.7 (s, C2), 126.1 (s, C4), 126.2 (s, C3), 126.7 (s, C1″), 129.0 (s, C1), 129.5 (d, C2′, C6′), 132.1 (d, C2″, C6″), 155.8 (s, C4″), 156.3 (s, C4″), 161.2 (s, C=O). MS(EI) *m/z* 310 (M+1, 25), 309 (M$^+$, 22), 278 (100); HRMS (EI) *m/z* calculated for $C_{18}H_{15}NO_4$: 309.1001; found: 309.1012.

3.4.3. Methyl 3-(4-hydroxyphenyl)-4-(4-isopropoxyphenyl)pyrrole-2-carboxylate 18b. Resin **16b** (100 mg) was swelled in DCM for 10 min, $SnCl_4$ (10 equiv.) was added and the mixture was shaken at rt for 12 h. The resin was washed with DCM and the organic layer was washed with 10% aq. HCl, dried and evaporated. The crude material was analysed by HPLC-MS (gradient 20–40% ACN in 15 min) and **18b** (tr 10.09 min, MS 352) was obtained. Purification by HPLC (gradient 50–70% ACN in 20 min) gave **18b** (1 mg, 11%) as a white solid. ^{1}H NMR (Acetone-d^6, 500 MHz) δ 1.27 [d, J=6 Hz, 6H, $(CH_3)_2$], 3.65 (s, 3H, CO_2CH_3), 4.55 [h, J=6 Hz, 1H, $CH(CH_3)_2$], 6.73 (d, J=8.7 Hz, 2H, H3′, H5′), 6.76 (d, J=8.7 Hz, 2H, H3″, H5″), 7.03 (d, J=8.7 Hz, 2H, H2′, H6′), 7.06 (d, J=8.7 Hz, 2H, H2″, H6″), 7.17 (d, J=3 Hz, 1H, H5). ^{13}C NMR (Acetone-d^6, 100 MHz) δ 22.1 [q, $(CH_3)_2$], 50.3 (q, CO_2CH_3), 69.4 [d, $CH(CH_3)_2$], 114.5 (d, C3″, C5″), 115.5 (d, C3′, C5′), 120.8 (d, C5), 125.8 (s, C1″), 125.9 (s, C1′),128.8 (s, C3), 129.4 (d, C2′, C6′), 131.8 (s, C4), 132.1 (d, C2″, C6″), 156.1 (s, C4′), 156.3 (s, C4″), 162.6 (s, C=O). MS (EI) *m/z* 352 (M+1, 15), 351 (M$^+$, 11), 320 (38). HRMS (EI) *m/z* calculated for $C_{21}H_{21}NO_4$: 351.1470; found: 351.1465.

3.4.4. Methyl 3-(4-hydroxyphenyl)-4-(3,4-dimethoxyphenyl)pyrrole-2-carboxylate 18c. Resin **16c** (820 mg) gave **18c** by following the general procedure for cleavage with $AlCl_3$. The crude material was analysed by HPLC-MS (gradient 20–40% ACN in 15 min), **18c** (tr 10.09 min, MS 354, M+1). Purification by HPLC (gradient 25–40% ACN in 30 min) gave **18c** (10 mg, 14%) as a white solid. ^{1}H NMR (Acetone-d^6, 500 MHz) δ 2.98 (bs, 1H, OH/NH), 3.52 (s, 3H, C4″–OCH_3), 3.65 (s, 3H, CO_2CH_3), 3.75 (s, 3H, C3″–OCH_3), 6.63 (d, J=2 Hz, 1H, H2″), 6.77–6.81 (m, 3H, H5′, H3′, H6″), 7.07 (d, J=8.5 Hz, 2H, H6′, H2′), 7.23 (d, J=3.5 Hz, 1H, H5), 10.96 (bs, 1H, NH/OH). ^{13}C NMR (Acetone-d^6, 100 MHz) δ 50.3 (q, CO_2CH_3), 54.9 (q, OCH_3), 55.4 (q, OCH_3), 112.0 (d, C6″), 112.6 (d, C2″), 114.5 (d, C5′, C3′), 119.4 (s, C2), 120.2 (d, C5″), 120.6 (d, C5), 120.8 (s, C4), 126.4 (s, C1″), 128.3 (s, C3), 129.1 (s, C1′), 132.1 (s, C6′, C2′), 147.9 (s, C3″), 149.1 (s, C4″), 156.4 (s, C4′), 161.2 (s, C=O). MS (EI) *m/z* 354 (M+1, 39), 353 (M$^+$, 31), 322 (100). HRMS (EI) *m/z* calculated for $C_{20}H_{19}NO_5$: 353.1263; found: 353.1261.

3.4.5. Methyl 3-(4-hydroxyphenyl)-4-(2-naphthyl)-pyrrole-2-carboxylate 18d. Resin **16d** (700 mg) gave **18d** by following the general procedure for cleavage with $AlCl_3$. The crude material was analysed by HPLC-MS (gradient 30–70% ACN in 15 min), **18d** (tr 8.6 min, MS 344, M+1). Purification by HPLC (gradient 35–65% AcCN in 30 min) gave **18d** (1 mg, 2%) as a white solid. ^{1}H NMR (Acetone-d^6, 500 MHz) δ 3.67 (s, 3H, CO_2CH_3), 6.76 (d, J=9 Hz, 2H, H3′, H5′), 7.10 (d, J=9 Hz, 2H, H2′, H6′), 7.24 (dd, J=8, 1.5 Hz, 1H, H3″), 7.4 (m, 3H, H5, H5″, H8″), 7.67 (m, 3H, H1″, H6″, H7″), 7.79 (m, 1H, H4″). MS (EI) *m/z* 344 (M+1, 19), 343 (M$^+$, 59). HRMS (EI) *m/z* calculated for $C_{22}H_{17}NO_3$: 343.1208; found: 343.1193.

3.5. General procedure for *N*-desilylation

Resin **16** was swelled in DCM for 10 min and a solution of NH_4F (7 equiv.) in MeOH was added. The mixture was shaken under reflux for 6 h. The resin was washed with DCM and MeOH (5×4 ml, each) and dried.

3.5.1. 4-[2-Methoxycarbonyl-4-(4-methoxyphenyl)-pyrrol-3-yl]phenoxy resin 19a. Resin **16a** (2 g) gave resin **19a** by following the general procedure for desilylation. IR (KBr) ν 3414, 3286, 1690, 1600, 1451, 756, 695. ^{13}C NMR ($CDCl_3$, Gel Phase, 75 MHz) δ 53.4 (CO_2CH_3), 69.8 (OCH_3).

3.5.2. 4-[2-Methoxycarbonyl-4-(4-isopropoxyphenyl)-pyrrol-3-yl phenoxy resin 19b. Resin **16b** (370 mg) gave resin **19b** by following the general procedure for desilylation. IR (KBr) ν 3430, 3287, 1690 (C=O), 1600, 755. ^{13}C NMR ($CDCl_3$, Gel Phase, 75 MHz) δ 22.0 [$OCH(CH_3)_2$], 53.3 (CO_2CH_3), 69.6 [$OCH(CH_3)_2$].

3.5.3. 4-{2-Methoxycarbonyl-4-(4-methoxyphenyl)-1-[2-(4-methoxyphenyl)-2-oxoethyl]pyrrol-3-yl}-phenoxy-resin 20a. LDA (150 μl, 2 equiv.) was added dropwise to swelled resin **19a** (370 mg) in dry THF (10 ml) under N_2 at −78 °C. The resin was shaken for 1 h at this temperature. 2-Bromo-4′-methoxyacetophenone (172 mg, 5 equiv.) was added. The cooling bath was removed and the crude mixture was shaken in a vibromatic at 86 °C for 24 h. After this time the resin was washed with THF, DCM, MeOH and Et_2O (3×5 ml, each) and dried under vacuum. IR (KBr) ν 3400, 2920, 1691, 1600. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.2 (CO_2CH_3), 69.9 (OCH_3).

3.5.4. 4-{2-Methoxycarbonyl-4-(4-isopropoxyphenyl)-1-[2-(4-methoxyphenyl)-2-oxoethyl]pyrrol-3-yl}phenoxy-resin 20b. Resin **19b** (500 mg) was swelled in a solution of 18-crown-6 in DMF (2.5 M, 25 ml) for 10 min. K_2CO_3 (6 equiv.) and 2-bromo-4′-methoxyacetophenone (6 equiv.) were added. The reaction mixture was heated in a microwave oven at 100 °C and 30–40 W during 2 min. The resin was washed with DMF, DMF/H_2O (1:1), DCM, MeOH and Et_2O (3×5 ml, each) and dried under vacuum. **20b** was obtained. IR (KBr) ν 3417, 1724(C=O), 1690 (C=O), 1600. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.1 [$OCH(CH_3)_2$], 59.8 (CO_2CH_3), 69.6 [$OCH(CH_3)_2$].

3.5.5. 4-[2-Methoxycarbonyl-4-(4-isopropoxyphenyl)-1-methylpyrrol-3-yl]phenoxy resin 20d. Resin **19b**

(300 mg) was swelled in a solution of 18-crown-6 in DMF (2.5 M) for 10 min and K_2CO_3 (15 equiv.) and MeI (6 equiv.) were added. The reaction mixture was shaken at rt for 24 h. The resin was washed with DMF, DMF/H_2O (1:1), DCM, MeOH and Et_2O (3×5 ml, each) and dried under vacuum. **20d** was obtained. IR (KBr) ν 1693, 1600, 1492, 743. ^{13}C NMR ($CDCl_3$, Gel Phase, 75 MHz) δ 22.1 [OCH(CH_3)$_2$], 69.6 [OCH(CH$_3$)$_2$].

3.5.6. 4-{2-Methoxycarbonyl-4-(4-isopropoxyphenyl)-1-[2-(2-bromophenethyl)]pyrrol-3-yl}-phenoxy-resin 20e. Resin **19b** (500 mg) was swelled in a solution of 18-crown-6 in DMF (2.5 M, 25 ml) for 10 min and K_2CO_3 (4 equiv.) and 2-bromophenethyl tosylate (4 equiv.) were added. The reaction mixture was shaken at 80 °C for 24 h. After this time, the resin was washed with DMF, DMF/H_2O (1:1), DCM, MeOH and Et_2O (3×5 ml, each) and dried under vacuum. **20e** was obtained. IR (KBr) ν 1642, 610. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.1 [OCH(CH_3)$_2$], 69.6 [OCH(CH$_3$)$_2$].

3.5.7. Methyl 3-(4-hydroxyphenyl)-4-(4-methoxyphenyl)-1-[2-(4-methoxyphenyl)-2-oxoethyl] pyrrole-2-carboxylate 21a. Resin **20a** (300 mg) gave **21a** by following the general procedure for cleavage with $AlCl_3$ (15 equiv.) for 6 h. The crude product was analysed by HPLC-MS (gradient 35–50% ACN in 15 min): **21a** [tr 12.89 min, MS (472, M+1)]. Purification by HPLC (gradient 30–60% ACN in 30 min) gave **21a** (1.0 mg, 2%) as a yellow solid.^1H NMR ($CDCl_3$, 600 MHz) δ 3.45 (s, 3H, CO_2Me), 3.81 (s, 3H, OMe), 3.86 (s, 3H, OMe), 5.72 (s, 2H, CH_2), 6.89 (d, 2H, J=9 Hz, H3″, H5″), 7.00 (s, 1H, H5), 7.05 (d, 2H, J=8.4 Hz, H3‴, H5‴), 7.08 (d, 2H, J=7.6 Hz, H3′, H5′), 7.16 (d, 2H, J=7.6 Hz, H2′, H6′), 7.44 (d, 2H, J=8.4 Hz, H2″, H6″), 8.03 (d, 2H, J=9 Hz, H2‴, H6‴).

3.5.8. Methyl 3,4-bis(4-hydroxyphenyl)-1-methylpyrrole-2-carboxylate 21c. Resin **20d** (500 mg) gave **21c** by following the general procedure for cleavage with $AlCl_3$. The crude product was analysed by HPLC-MS (gradient 30–70% ACN in 15 min): **21c** (tr 5.67 min, MS 324, M+1). Purification by HPLC (gradient 20–70% ACN in 50 min) gave **21c** (1.7 mg, 6%) as a brown solid. ^1H NMR (Acetone-d^6, 500 MHz) δ 2.92 (bs, OH), 3.53 (s, 3H, CO_2CH_3), 3.95 (s, 3H, N–CH_3), 6.64 (d, J=8.5 Hz, 2H, H3′, H5′), 6.75 (d, J=8.5 Hz, 2H, H3″, H5″), 6.91 (d, J=8.5 Hz, 2H, H2′, H6′), 6.97 (d, J=8.5 Hz, 2H, H2″, H6″), 7.10 (s, 1H, H5). ^{13}C NMR (Acetone-d^6, 100 MHz) δ 36.9 (q, CH_3), 50.0 (q, CO_2CH_3), 112.4 (d, C3″, C5″), 115.0 (d, C3′, C5′), 120.6 (s, C2), 124.1 (s, C4), 126.6 (s, C1′), 127.0 (d, C5), 127.4 (s, C1″), 129.4 (d, C2′, C5′), 130.6 (s, C3), 131.9 (d, C2″, C5″), 155.8 (s, C4′), 156.3 (s, C4″), 162.6 (s, C=O). MS(EI) m/z 324 (M+1, 14), 323 (M$^+$, 23), 292 (58). HRMS (EI) m/z calculated for $C_{19}H_{17}NO_4$: 323.1158; found 323.1149.

3.5.9. Methyl 3,4-bis(4-hydroxyphenyl)-1-[2-(2-bromophenyl)ethyl]pyrrole-2-carboxylate 21d. Resin **20c** (500 mg) gave **21d** by following the general procedure for cleavage with $AlCl_3$. The crude product was analysed by HPLC-MS (gradient 30–70% ACN in 15 min): **21d** [tr 12.64 min, MS (492, M+1)].

3.5.10. Methyl 3,4-bis-(4-hydroxyphenyl)-1-[2-(4-methoxyphenyl)-2-oxoethyl]pyrrole-2-carboxylate 2: lamellarin O. Resin **20b** (500 mg) gave **2** by following the general procedure for cleavage with $AlCl_3$. The crude product was analysed by HPLC-MS (gradient 40–80% ACN in 15 min): **2** [tr 11.94 min, MS 458 (M+1)].

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11. Formation of **10** was investigated by ^{13}C MAS NMR and corroborated by characterisation of the diacetyl derivative **14a** obtained by the cleavage reaction of **10** with $ZnBr_2$ and AcBr.
12. The crude cleavage material was analysed by HPLC and HPLC-MS.
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14. Commercial 3-methoxyphenylboronic acid was used to find the best reaction conditions to be applied to the synthesis of lamellarins and derivatives.
15. Mixtures of **18e** and **18f**, as well as of **14a** and **14b**, in different proportions were produced during the cleavage with $ZnBr_2$ in AcBr due to electrophilic acetylation on the pyrrole. Compound **18f** was not isolated but detected by HPLC-MS and its structure postulated on the basis of the ^1H NMR spectrum of the crude mixture by the singlet at 7.29 ppm due to the pyrrole proton 5.
16. GP ^{13}C NMR of bisarylpyrroles **16b**-**16d** were used to corroborate the introduction of the new aromatic ring.
17. The 4-isoproxoxyphenylboronic acid **15b** was not commercial when we started this project. It was prepared from the *p*-iodophenol by protection with 2-iodopropane followed by boronic acid formation via halogen–metal interchange using *n*BuLi followed by reaction with trimethylboronate as described in Chaumeil, H.; Signorella, S.; Le Drian, C. *Tetrahedron* **2000**, *56*, 9655.
18. The stability of chloro-Merrifield resin under the same reaction conditions, i.e. large excess of $AlCl_3$ in DCM at rt during 3 h, was tested and the result was the total breakdown of the resin beads. Less harsh conditions involving an excess of 3 equiv. of $AlCl_3$ over the resin during 3 h allowed total recovery of the resin beads.
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21. 15 equiv. of NaH or 2 equiv. of LDA in dry THF at reflux for 24 h afforded, after cleavage, mixtures of **18a** and **21a** in which the alkylation product was obtained in 25% (NaH) and 30% (LDA) yield (HPLC-MS). Increasing the amount of LDA or the use of other bases did not improve the yield of **21a**.
22. The compound was not isolated after trying different purification procedures on the crude cleavage material by semipreparative HPLC. The loss of material, probably by decomposition in the column.
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