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Formyl group activation of bromopyrrole suzuki cross-coupling: application to a formal synthesis of lamellarin g trimethyl ether

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Formyl Group Activation of Bromopyrrole Suzuki Cross-Coupling: Application to a Formal Synthesis of Lamellarin G trimethyl ether

by

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Table of Contents

Abstract

Many biologically interesting compounds have been isolated from marine natural products, many of which contain characteristic pyrroles. Compounds such as polycitones, storniamides, ningalins, and lamellarins have been of particular interest for synthesis due to their vast pharmaceutical potential including the ability to fight tumors as well as induce cytolysis of drug resistant cancer cell lines.[1] Previous studies on the synthesis of Lamellarin G trimethyl ether by the Gupton Group have relied upon vinylogous amide derivatives as building blocks.[2] A new pathway utilizing a formylated pyrrole ring provides an interesting method for the synthesis of Lamellarin G trimethyl ether. Regioselective Suzuki cross-coupling of the pyrrole leads to relay synthesis of the marine alkaloid yet the possibilities of generated compounds from the activated pyrrole building block are numerous.

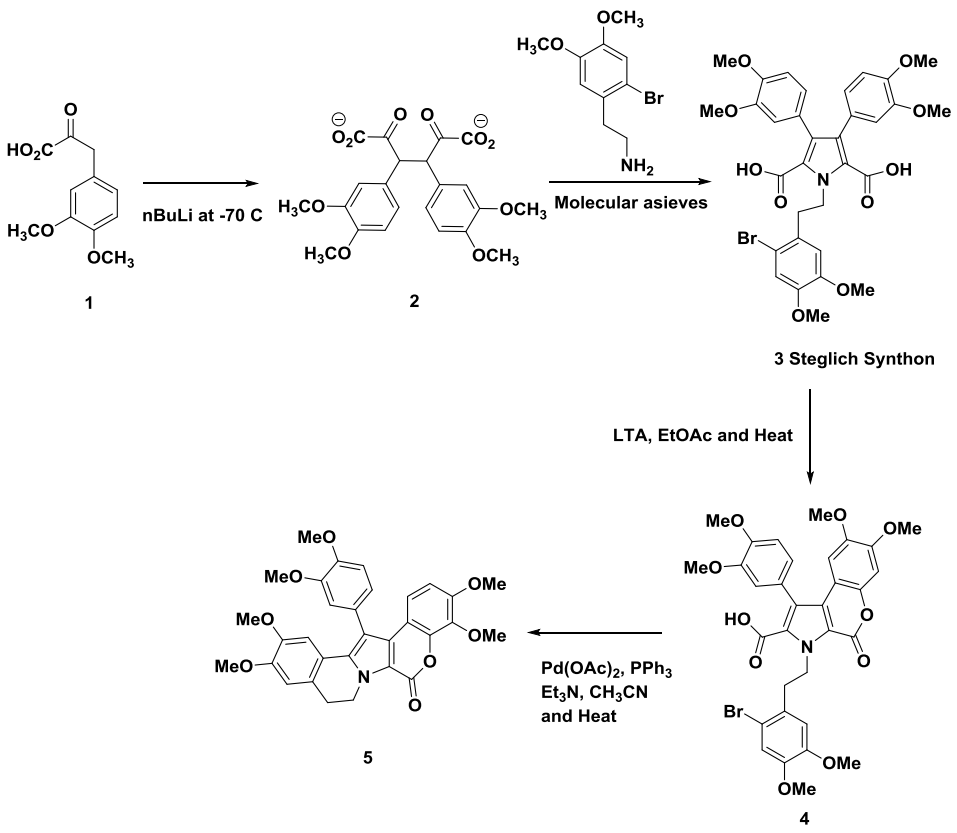
1. Introduction

Many marine natural products have been found to have potent pharmaceutical properties.[1] Derivatives and analogs of these molecules have therefore been extensively studied and utilized as potential, and active, medicines. One such class of compounds is the Lamellarin family which has drawn significant interest from the scientific community.[2] This marine alkaloid family is very diverse, and has demonstrated several medicinal purposes including antiproliferation properties.[3]

Members of the Lamellarin family were first isolated in 1985[4] from the *Lamellaria* prosobranch mollusk. Since then the family has grown to include over 30 members deriving from not only the original mollusk but also from invertebrates such as ascidians and sponges.[3] Cytotoxic affects that have been attributed to the Lamellarins include inhibition of topoisomerase I[5,3] as well as many kinases[6], and multi-drug resistance reversal[7].

While many of the Lamellarins do show potent biological activity, Lamellarin G does not necessarily show the same level of activity as others.[8] However, it is still heavily researched for synthetic routes because it can be considered a foundation for most of the other compounds. In other words, the synthesis of Lamellarin G trimethyl ether is considered a standard for the synthesis of the Lamellarin family of compounds.[9]

First derived by Steglich[10] in 1997, Lamellarin G trimethyl ether has been synthesized by many other groups[11-14], with varying schemes, including Gupton[15]. The Steglich methodology (Scheme 1) relies on a pentasubstituted pyrrole as the key intermediate for synthesis of Lamellarin G trimethyl ether. This molecule is prepared by a condensation reaction to form a symmetrical bis-ketoacid (1) which then undergoes cyclization to create the substituted pyrrole ring (3). After the formation of the pyrrole, the compound undergoes lactonization proceeded by a cross-coupling reaction which results in decarboxylation and the completion of the Lamellarin G trimethyl ether (5).

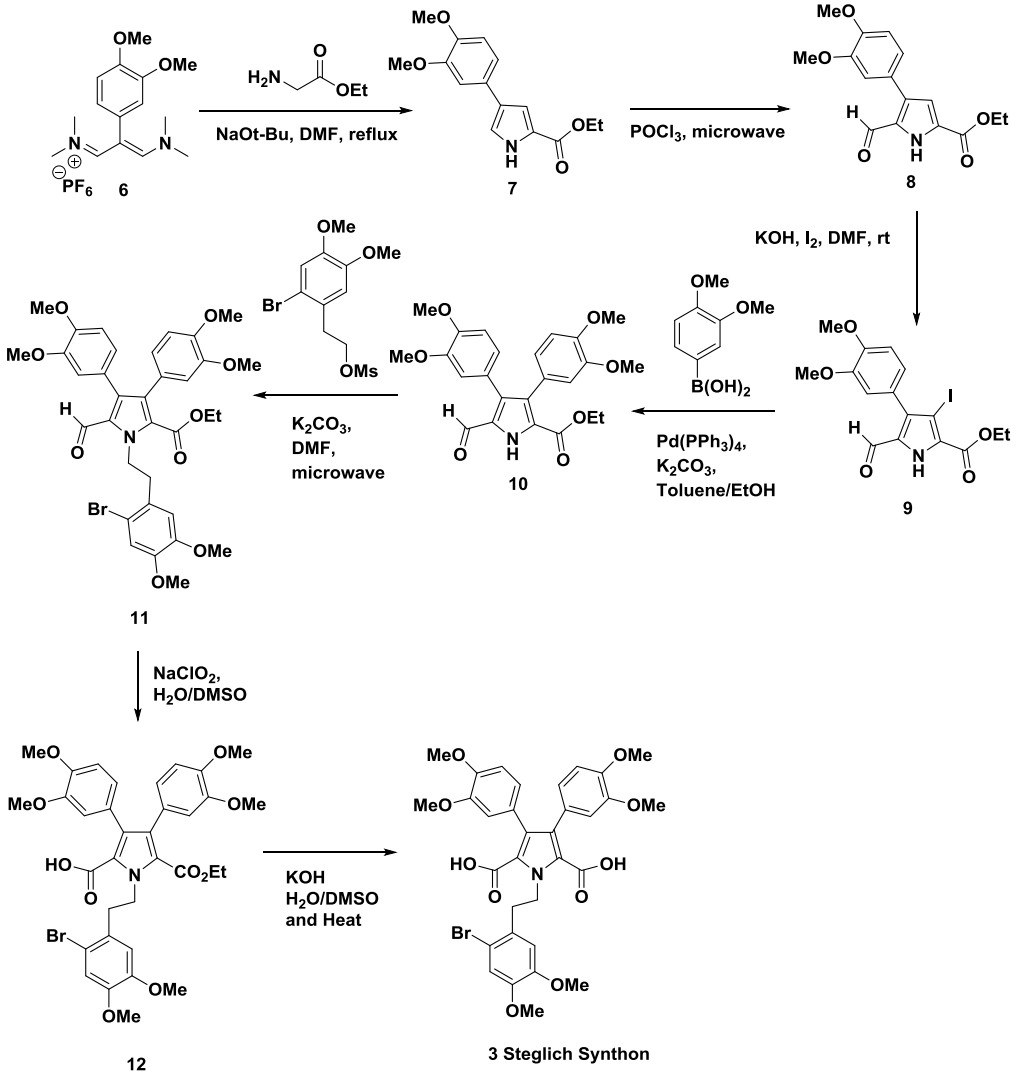


Scheme 1[10]: Steglich Synthesis of Lamellarin G trimethyl ether

Previous Gupton Group syntheses[15] were accomplished by the use of either vinamidinium salts or β-chloroenals. Both routes converged at a common intermediate on the way to constructing the Steglich Synthon (3). The vinamidinium salt method (Scheme 2) results in an overall ten step pathway while synthesis from a β-chloroenal pathway leads to a highly substituted pyrrole in a total of nine steps.[9]

Preparation of Lamellarin G trimethyl ether via vinamidinium salt (6) is described as a modular process of synthesis, which makes it ideal for the study of potential analog compounds. Following the formation of the 2,4-disubstituted pyrrole (7), formylation at the C-5 position (8) occured by Vilsmeier-Haack-Arnold conditions. The pyrrole ring then undergoes iodination (9) which allows for the substitution of the second aromatic ring (10) through Suzuki cross-coupling. After alkylating the pyrrole

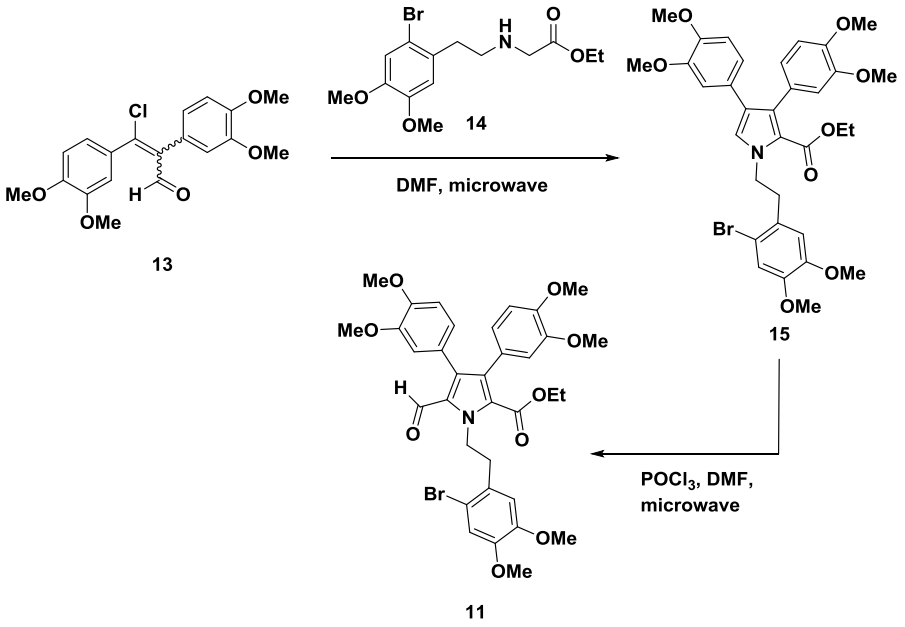
nitrogen (11), forming the carboxylic acid (12), and hydrolyzing the ester the Steglich Synthon (3) was reached.



Scheme 2[9, 15]**:** Gupton Group Modular Synthesis of Lamellarin G trimethyl ether

In addition to the modular pathway of synthesis there is the convergent method (Scheme 3) which employs the β-chloroenal. The (E,Z)-3-chloro-2,3-bis(3,4-dimethoxyphenyl)chloroenal (13) underwent a condensation reaction with N-2-(3,4-dimethoxyphenyl-ethyl)glycine ethyl ester[14] (14) which led to the formation of the tetrasubstituted pyrrole (15). The pyrrole was then formylated with

Vilsmeier-Haack-Arnold conditions to produce a known precursor (12) to the pentasubstituted Steglich Synthon.



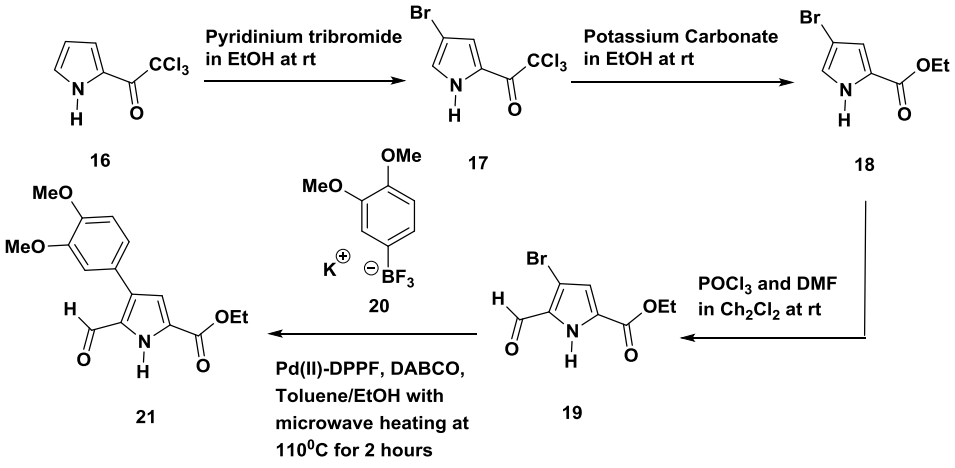
Scheme 3[9]: Convergent Pathway to Lamellarin G

Outlined in this paper is an alternative route to the synthesis of Lamellarin G trimethyl ether which is founded upon the utilization of an ethyl 3-bromo-2-formylpyrrole-5-carboxylate for Suzuki Cross-Coupling.

2. Results and Discussion

Production of the formylated pyrrole (Scheme 4) begins with the bromination of the widely available trichloro-2-acetylpyrrole (16) through the use of pyridinium tribromide as the halogenating agent. Bromination occurs selectively at the C-4 position (17) with no overbromination as long as the reaction is kept in absence of light and quenched after five hours. The power of this result is that aromatic appendage through cross-coupling will also occur in a regioselective fashion. Esterification is facilitated with potassium carbonate and ethanol to produce the 3-bromo-pyrrole ethyl ester (18).

Vilsmeier-Haack-Arnold formylation then generates the formlyated pyrrole (19). Of note is the fact that all of these reactions demonstrate high yields and the products are sufficiently clean as to be reacted, in succession, without the need for purification. Also, rigorous care was taken in determining conditions to be used for formylation (Table 1) which would produce such a clean reaction. Two of the most important aspects of this were in finding the timeframe for the formation of the Vilsmeier-Haack-Arnold reagent as well as the selection of the solvent (Trials 1-5, Table 1) in which the reaction took place. Variations on either of these aspects resulted in the reaction not achieving completion. Suzuki cross-coupling with (3,4)-dimethoxyphenyl trifluoroborate (20) appends the aromatic ring to the C-3 position of the pyrrole (21) by replacing the bromine in 70% yield.



Scheme 4: Production of the Formylated Pyrrole for Suzuki Cross-Coupling

Table 1: Optimization Study of Vilsmeier-Haack Formylation

Trial	Solvent	Ratio of $POCl_3$ to DMF	% Yield by HPLC (Isolated)
1	CH_2Cl_2	2.0/2.5	82 (81)
2	$CHCl_3$	2.0/2.5	79 (80)
3	CH_3CCl_3	2.0/2.5	67 (56)
4	DMF	2.0/2.5	0 (NI)
5	THF	2.0/2.5	0 (NI)
6	CH_2Cl_2	3.0/3.5	87 (86)

NI – not isolated; HPLC analysis was performed on a Water Alliance 2695 instrument with an Inertsil ODS-2 column using a 1:1 methanol:acetonitrile eluent at a flow rate of 0.25 mL per minute.

Appendage of aryl groups to the pyrrole is the cornerstone of this research. Previous studies[15] with Suzuki cross-coupling have employed $Pd(PPh_3)_4$, a boronic acid, toluene, K_2CO_3, EtOH, and heat. To increase the efficiency of the synthesis Lamellarin G trimethyl ether the Suzuki cross-coupling reaction was optimized (Table 2). Utilization of the best reaction conditions also strengthens the general applicability of cross-coupling for a large variety of boronic acid derivatives. During the study, *in situ* yields were determined by HPLC analysis. The reaction showed no preference for a range of solvents (Trials 1-4, Table 2) yet seemed to require an organic base for better completion (Trials 5-8, Table 2). Ligand studies on the paladium catalyst (Trials 10-13, Table 2) were also conducted using the optimized solvent and base conditions. Usage of Pd(II)DPPF resulted in the highest isolated yield which led future reactions to use the optimized conditions as outlined in Trial 13.

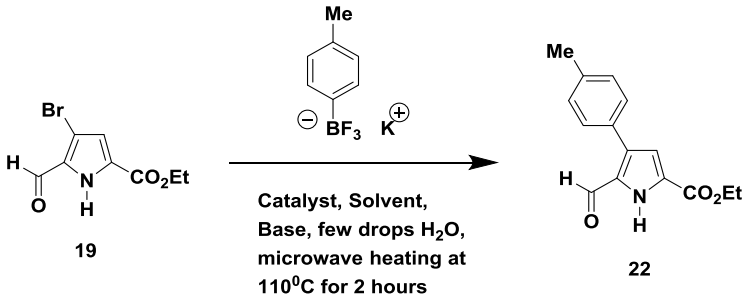


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Table 2: Optimization Study of Suzuki Cross-Coupling

Trial	Solvent	Base	Catalyst	% Yield via HPLC (Isolated)
1	Toluene/EtOH	DIPEA	$Pd(PPh_3)_4$	86
2	THF	DIPEA	$Pd(PPh_3)_4$	86
3	CH_3CN	DIPEA	$Pd(PPh_3)_4$	86
4	EtOH	DIPEA	$Pd(PPh_3)_4$	86
5	Toluene/EtOH	Cs_2CO_3	$Pd(PPh_3)_4$	72
6	Toluene/EtOH	K_2CO_3	$Pd(PPh_3)_4$	73
7	Toluene/EtOH	Na_2CO_3	$Pd(PPh_3)_4$	83
8	Toluene/EtOH	DABCO	$Pd(PPh_3)_4$	91
9	Toluene/EtOH	DABCO	$Pd(OAc)_2$	84
10	Toluene/EtOH	DABCO	$PdCl_2$	98
11	Toluene/EtOH	DABCO	PdDBA	53 (42)
12	Toluene/EtOH	DABCO	$PdCl_2(PPh_3)_4$	100 (89)
13	Toluene/EtOH	DABCO	$PdDPPF(Cl_2)$	95 (99)

HPLC analyses were performed on a Waters Alliance 2695 instrument with an Inertsil ODS-2 column using a 1:1 methanol/acetonitrile eluent at a flow rate of 0.25 mL per minute.

Generality studies (Table 3) for the application of Suzuki cross-coupling with the ethyl 3-bromo-2-formylpyrrole-5-carboxylate were also performed to demonstrate the ability to append varyingly functionalized phenyl rings. Respectable yields were found for all of the tested compounds, some of the lower yields are thought to have been caused by loss of product during purification. Nonetheless, a wide variety of boronic acid derivatives were shown to be compatible with the Suzuki cross-coupling reaction. Most notably, perhaps, are the oxygenated species which are abundantly found in marine natural products.

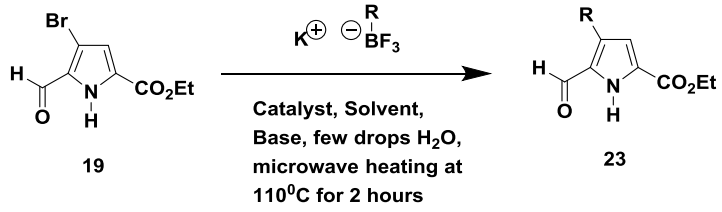
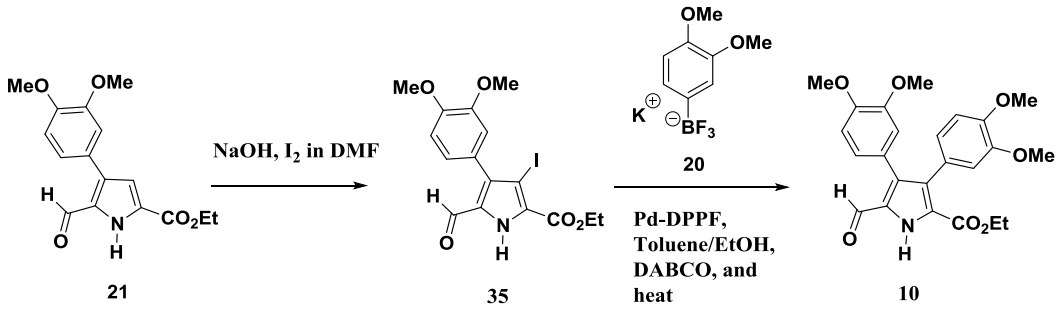


Table 3: Applicability of Suzuki Cross-Coupling with ethyl 3-bromo-2-formylpyrrole-5-carboxylate

Trial	Compound	R-Group	% Isolated Yield
1	22	4–MePh	99
2	24	4–MeOPh	86
3	25	4–ClPh	69
4	21	3,4–$(MeO)_2$Ph	70
5	26	3,4,5–$(MeO)_3$Ph	64
6	27	Ph	78
7	28	4-MeSPh	63
8	29	4-PPh	51 (69)*
9	30	Benzo(3,4)dioxolyl	99
10	31	3,4-$(Cl)_2$Ph	90*
11	32	4-HOPh	66*
12	33	4-CF_3OPh	96*
13	34	N-Phenylsulfonyl-3-indolyl	55

*These reactions utilized the corresponding boronic acids while the other reactions used the corresponding trifluoroborate.



Scheme 5[15]**:** Gupton Group Approach to the Lamellarin G Synthon

In order to reach the Gupton Group common intermediate (13) for the synthesis of Lamellarin G trimethyl ether the ethyl 2-formyl-3-(3,4-dimethoxyphenyl)pyrrole-5-carboxylate (22) must undergo iodination (Compound 23, Scheme 5). This reaction takes place cleanly, with an isolated yield of 82%, at the C-4 position of the pyrrole due its electrophilicity and relatively mild conditions. Subsequent cross-coupling, utilizing the optimized conditions, leads to the formation of ethyl 2-formyl-3,4-bis-(3,4-dimethoxyphenyl)pyrrole-5-carboxylate (13) in 61% yield. Due to the pyrrole ring's high degree of substitution the cross-coupling reaction is thought to be sterically hindered which explains the lower yield in comparison with the first Suzuki cross-coupling (22). This compound was spectrally identical to the key intermediate found in route to the synthesis of the Steglich Synthon in the previous Gupton studies[14] (Scheme 2) thereby completing the formal synthesis of Lamellarin G trimethyl ether.

3. Conclusion

Based on these results it can be seen that the use of the formylated pyrrole for cross-coupling is not only a rapid route to the synthesis of Lamellarin G trimethyl ether but also a clean method which requires relatively little purification along the way. Respectable yields that either meet or exceed those achieved through previous routes demonstrate the efficiency of this pathway. This ease-of-use can obviously be of great benefit as it relates to the production of medicinal chemicals at a manufacturing scale. Another significant benefit of this synthesis route is its flexibility and generality. The study shows

that a wide variety of substituted aromatic rings can be appended to the pyrrole via cross-coupling in a regiospecific way which allows for an almost infinite possibility of products, Lamellarin G being just one. In short, after three steps a commercially available molecule can be chemically altered to become a powerful intermediate for a multitude of medicinally important compounds. Future research will delve further into the vast array of possibilities that this method presents, be they in marine natural product synthesis or the study of their analogs.

4. Experimental

4.1. General

All chemicals were used as received from Aldrich Chemicals and Fisher Scientific. All solvents were dried over 4 Â molecular sieves prior to use. NMR spectra were obtained on either a 300 MHz, or 500 MHz spectrometer in $CDCl_3$, DMSO-d_6, or acetone-d_6 as noted. IR spectra were taken on a Nicolet Avatar 320 FT-IR spectrometer with an HATR attachment. High resolution mass spectra were taken at the University of Richmond on a Shimadzu IT-TOF mass spectrometer while low resolution GC-MS spectra were obtained on a Shimadzu QP 5050. Melting and boiling points are uncorrected. Chromatographic purifications were carried out on a Biotage SP-1 or Isolera instrument (equipped with silica cartridge) and gradient elution was completed with ethyl acetate/hexane in both instances. The reaction products generally eluted within a range of 4-8 column volumes of eluant with a gradient mixture of 60:40 ethyl acetate/hexane. TLC analyses were performed on silica plates with ethyl acetate/hexane as the eluant. All purified reaction products gave TLC results, flash chromatograms, and ^{13}C NMR spectra consistent with a sample purity of >95%.

4.1.1. *Ethyl 3-bromo-2-formylpyrrole-5-carboxylate (19)*. Into a 100 mL round bottom flask equipped with magnetic stirring and a rubber septum cap was placed 10 mL of anhydrous dichloromethane, 4.83 g (0.0661 mol) of dry DMF, 8.69 g (0.0566 mol) of phosphorus oxychloride, and the resulting mixture was stirred for 10 min. To this flask was then added 4.12 g (1.89 mmol) of ethyl 4- bromopyrrole-2-carboxylate in 15 mL of anhydrous dichloromethane and the resulting mixture was stirred overnight at room temperature. The reaction was worked up by the addition of 80 mL of water and separation of the two phases. The aqueous phase was extracted with additional dichloromethane (3x20 mL) and the combined dichloromethane phases were washed with brine (1x15 mL), dried over anhydrous sodium sulfate, and concentrated in vacuo to yield 4.01 g (86% yield) of a brown solid. This material was of sufficient purity to be used in subsequent experiments but an analytical sample was prepared by purification via flash chromatography on a Biotage Isolera system in which case a light colored solid was obtained, which exhibited the following physical properties: mp 91-92 °C; ^1H NMR ($CDCl_3$) δ 9.74 (s, 1H), 6.96 (d, J=1.2 Hz, 1H), 4.40 (q, J=7.2 Hz, 2H), and 1.39 (t, J=7.2 Hz, 3H); ^{13}C NMR (acetone-d_6) δ 179.0, 159.1, 131.0, 128.4, 117.5, 106.0, 61.1, and 13.6; IR (neat) 1711 and 1671 cm^{-1}; HRMS (ES, M+) m/z calcd for $C_8H_8BrNO_3$ 244.9688, found 244.9057.

4.1.2. *Ethyl 2-formyl- 3-(3,4-dimethoxyphenyl)pyrrole-5-carboxylate (21)*. Into a 20 mL microwave reaction tube was placed a magnetic stir bar, ethyl 3-bromo-2-formylpyrrole-5-carboxylate (0.250 g,

1.02 mmol), potassium 3,4-dimethoxyphenyltrifluoroborate (0.316 g, 1.32 mmol), and DABCO (0.229 g, 2,04 mmol). A mixture of 3:1 toluene/ethanol (12 mL) was added to the microwave reaction tube along with 20 drops of water. After stirring for several minutes dichloro[1,10-bis-(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct (0.037 g, 0.051 mmol) was added to the reaction mixture and the tube was capped and sealed with a crimping tool. The reaction mixture was heated in a Biotage Initiator microwave system for 2 h at 110 °C. After cooling to room temperature, the reaction mixture was filtered through a short plug of silica gel and the silica was subsequently washed with 2x30 mL of ethyl acetate and the combined organic materials were concentrated in vacuo to give a dark solid. The crude material was purified by flash chromatography on a Biotage Isolera system in which case a light colored solid was obtained (0.300 g, 70% yield). We have previously described[16] the synthesis of this substance by a different synthetic route and the spectral properties exhibited by this reaction product were identical to those reported earlier: ^{1}H NMR ($CDCl_3$) δ 9.79 (s, 1H), 7.04 (dd, J=2.0, 8.5 Hz, 1H). 7.00-7.02 (m, 3H), 4.42 (q, J=7.2 Hz, 2H), 3.95 (s, 6H), and 1.42 (t, J=7.2 Hz, 3H).

4.1.3. *Ethyl 2-formyl- 3-(4-methylphenyl)pyrrole-5-carboxylate (22)*. This material was prepared in a manner identical to the previous example with the exception that potassium 4-methoxyphenyltrifluoroborate was used as the coupling agent. Work up of the reaction mixture produced a dark solid (0.260 g, 99% yield). This material was quite pure by TLC and HPLC analysis but an analytical sample was prepared by flash chromatography on a Biotage Isolera system in which case a light colored solid was obtained. We have previously described[16] the synthesis of this substance by a different synthetic route and the spectral properties exhibited by this reaction product were identical to those reported earlier: ^{1}H NMR ($CDCl_3$) δ 9.78 (s, 1H), 7.40 (d, J=8.1 Hz, 2H), 7.29 (d, J=8.1 Hz, 2H), 7.02 (d, J=2.4 Hz, 1H), 4.41 (q, J=7.2 Hz, 2H), 2.43 (s, 3H), and 1.42 (t, J=7.2 Hz, 3H). It should be noted that a control experiment was run on 4-bromo-2-carbethoxypyrrole (the compound minus the 2- formyl group) under conditions as described above in which case a gross mixture of products was obtained.

4.1.4. *Ethyl 2-formyl- 3-(4-methoxyphenyl)pyrrole-5-carboxylate (24)*. This material was prepared in a manner identical to the previous example with the exceptions that diisopropylethylamine (DIPEA) was used as the base instead of DABCO and tetrakis(-triphenylphosphine)palladium (0) was used as the catalyst and potassium 4-methoxyphenyltrifluoroborate was used as the coupling agent. Work up of the reaction mixture produced a dark solid, which was purified by flash chromatography on a Biotage Isolera system in which case a light colored solid was obtained (0.280 g, 72% yield). We have previously described[16] the synthesis of this substance by a different synthetic route and the spectral properties exhibited by this reaction product were identical to those reported earlier: ^{1}H NMR ($CDCl_3$) d 9.76 (s, 1H), 7.43 (d, J=9.0 Hz, 2H), 7.00-7.02 (m, 3H), 4.41 (q, J=6.9 Hz, 2H), 3.88 (s, 3H), and 1.42 (t, J=6.9 Hz, 3H).

4.1.5. *Ethyl 2-formyl- 3-(4-chlorophenyl)pyrrole-5-carboxylate (25)*. This material was prepared in a manner identical to the previous example with the exception that potassium 4-chlorophenyltrifluoroborate was used as the coupling agent. Work up of the reaction mixture produced a dark solid, which was purified by flash chromatography on a Biotage Isolera system in which case a light colored solid was obtained (0.116 g, 69% yield). We have previously described[16] the synthesis of this substance by a different synthetic route and the spectral properties exhibited by this reaction product were identical to those reported earlier: ^{1}H NMR ($CDCl_3$) δ 9.76 (s, 1H), 7.45 (d, J=8.5 Hz, 2H), 7.44 (d, J=8.5 Hz, 2H), 7.02 (d, J=2.9 Hz, 1H), 4.42 (q, J=7.2 Hz, 2H), and 1.42 (t, J=7.2 Hz, 3H).

4.1.6. *Ethyl 2-formyl- 3-(3,4,5-trimethoxyphenyl)pyrrole-5-carboxylate (26)*. This material was prepared in a manner identical to the previous example with the exception that potassium 3,4,5-trimethoxyphenyltrifluoroborate was used as the coupling agent. Work up of the reaction mixture produced a dark solid, which was purified by flash chromatography on a Biotage Isolera system in which case a light colored solid was obtained (0.110 g, 64% yield). We have previously described[16] the synthesis of this substance by a different synthetic route and the spectral properties exhibited by this reaction product were identical to those reported earlier: ^{1}H NMR ($CDCl_3$) δ 9.82 (s, 1H), 7.28 (d, J=2.4 Hz, 1H), 6.68 (s, 2H), 4.40 (q, J=6.9 Hz, 2H), 3.91 (s, 6H), 3.90 (s, 3H), and 1.41 (t, J=6.9 Hz, 3H).

4.1.7. *Ethyl 2-formyl- 3-phenylpyrrole-5-carboxylate (27)*. This material was prepared in a manner identical to the previous example with the exception that potassium phenyltrifluoroborate was used as the coupling agent. Work up of the reaction mixture produced a dark solid, which was purified by flash chromatography on a Biotage Isolera system in which case a light colored solid was obtained (0.256 g, 78% yield). We have previously described[16] the synthesis of this substance by a different synthetic route and the spectral properties exhibited by this reaction product were identical to those reported earlier: ^{1}H NMR (acetone-d_6) δ 9.83 (s, 1H), 7.63 (d, J=7.5 Hz, 2H), 7.49 (t, J=7.5 Hz, 2H), 7.42 (t, J=7.5 Hz, 1H), 7.07 (s, 1H), 4.38 (q, J=7.5 Hz, 2H), and 1.38 (t, J=7.5 Hz, 3H).

4.1.8. *Ethyl 2-formyl- 3-(4-methylthiophenyl)pyrrole-5-carboxylate (28)*. This material was prepared in a manner identical to the previous example with the exception that DABCO was used as the base, dichloro[1,10-bis-(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct was used as the catalyst, and potassium 4-methylthiophenyltrifluoroborate was used as the coupling agent. Work up of the reaction mixture produced a dark solid, which was purified by flash chromatography on a Biotage Isolera system in which case a light colored solid was obtained (0.184 g, 63% yield), which exhibited the following physical properties: mp 123e124 °C; ^{1}H NMR ($CDCl_3$) δ 9.78 (s, 1H), 7.42 (d, J=8.4 Hz, 2H), 7.35 (d, J=8.4 Hz, 2H), 7.02 (d, J=2.7 Hz, 1H), 4.42 (q, J=7.2 Hz, 2H), 2.55 (s, 3H), and 1.42 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 180.7, 160.3, 139.1, 135.5, 130.2, 129.4, 129.2, 127.8, 126.6, 115.2, 61.5, 15.6, and 14.3; IR (neat) 1701 and 1685 cm^{-1}; HRMS (ES, M+H) m/z calcd for $C_{15}H_{16}NO_3S$ 290.0851, found 290.0837.

4.1.9. *Ethyl 2-formyl- 3-(4-fluorophenyl)pyrrole-5-carboxylate (29)*. This material was prepared in a manner identical to the previous example with the exception that 4-fluorophenylboronic acid was used as the coupling agent. Work up of the reaction mixture produced a dark solid, which was purified by flash chromatography on a Biotage Isolera system in which case a light colored solid was obtained (0.219 g, 69% yield), which exhibited the following physical properties: mp 95-96 °C; ^{1}H NMR ($CDCl_3$) δ 9.75 (s, 1H), 7.47 (dd, J=5.4, 8.7 Hz, 2H), 7.17 (t, J=8.7 Hz, 2H), 7.01 (d, J=2.4 Hz, 1H), 4.42 (q, J=7.2 Hz, 2H), and 1.42 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 180.4, 162.9 (d, J=248.4 Hz), 160.2, 134.9, 130.7 (d, J=8.0 Hz), 103.2, 128.7 (d, J=3.5 Hz), 127.7, 115.9 (d, J=82.3 Hz), 115.3, 61.5, and 14.3; IR (neat) 1686 and 1655 cm^{-1}; HRMS (ES, M+H) m/z calcd for $C_{14}H_{13}FNO_3$ 262.0879, found 262.0868.

4.1.10. *Ethyl 2-formyl- 3-[benzo(3,4)dioxolylphenylpyrrole]-5-carboxylate (30)*. This material was prepared in a manner identical to the previous example with the exception that potassium benzo[1,3]dioxolyltrifluorofluoroborate was used as the coupling agent. Work up of the reaction mixture produced a dark solid (0.300 g, 99% yield). This material was quite pure by TLC and HPLC and was not purified further. This material exhibited the following physical properties: mp 140-141 °C; ^{1}H NMR (acetone-d_6) δ 9.81 (s, 1H), 7.15 (d, J=1.5 Hz, 1H), 7.10 (dd, J=1.5, 8.0 Hz, 1H), 7.01 (s, 1H), 6.95 (d, J=8.0 Hz, 1H), 6.08 (s, 2H), 4.36 (q, J=7.0 Hz, 2H), and 1.37 (t, J=7.0 Hz, 3H); ^{13}C NMR (acetone-d_6) δ 180.1, 159.9, 148.2, 147.7, 134.6, 130.6, 127.7, 127.0, 123.0, 115.0, 109.3, 108.4, 101.4, 60.7, and 13.6; IR (neat) 1704 and 1644 cm^{-1}; HRMS (ES, M+H) m/z calcd for $C_{15}H_{14}NO_5$ 288.0872, found 288.0873.

4.1.11. *Ethyl 2-formyl- 3-(3,4-dichlorophenyl)pyrrole-5-carboxylate (31)*. This material was prepared in a manner identical to the previous example with the exception that 3,4-dichlorophenylboronic acid was used as the coupling agent. Work up of the reaction mixture produced a dark solid, which was purified by flash chromatography on a Biotage Isolera system in which case a light colored solid was obtained (0.340 g, 90% yield) and this material exhibited the following physical properties: mp 160-161 °C; ^{1}H NMR ($CDCl_3$) δ9.77 (s, 1H), 7.60 (d, J=2.1 Hz, 1H), 7.55 (d, J=8.1 Hz, 1H), 7.33 (dd, J=2.1, 8.1 Hz, 1H), 7.02 (d, J=2.4 Hz, 1H), 4.42 (q, J=7.2 Hz, 2H), and 1.42 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 179.9, 159.9, 133.2, 133.0, 132.7, 132.6, 130.9, 130.7, 130.1, 128.2, 127.9, 115.2, 61.6, and 14.3; IR (neat) 1717 and 1668 cm^{-1}; HRMS (ES, M+H) m/z calcd for $C_{14}H_{12}Cl_2NO_3$ 312.0194, found 312.0182.

4.1.12. *Ethyl 2-formyl- 3-(4-hydroxyphenyl)pyrrole-5-carboxylate (32)*. This material was prepared in a manner identical to the previous example with the exception that potassium 4-hydroxyphenylboronic acid was used as the coupling agent. Work up of the reaction mixture produced a dark solid, which was purified by flash chromatography on a Biotage Isolera system in which case a light colored solid was obtained (0.173 g, 66% yield) and this material exhibited the following physical properties: mp 158-159 °C; ^{1}H NMR ($CDCl_3$) δ 9.76 (s, 1H), 7.38 (d, J=8.7 Hz, 2H), 6.99 (d, J=2.7 Hz, 1H), 6.94 (d, J=8.7 Hz, 2H), 4.41 (q, J=7.2 Hz, 2H), and 1.42 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 180.7, 160.3, 155.9, 135.8, 130.5, 130.1, 127.7, 125.3, 115.9, 115.1, 61.5, and 14.3; IR (neat) 3254, 1701, and 1634 cm^{-1}; HRMS (ES, M+H) m/z calcd for $C_{14}H_{14}NO_4$ 260.0923, found 260.0908.

4.1.13. *Ethyl 2-formyl- 3-(4-trifluoromethoxyphenyl)pyrrole-5-carboxylate (33)*. This material was prepared in a manner identical to the previous example with the exception that potassium 4-trifluoromethoxyphenylboronic acid was used as the coupling agent. Work up of the reaction mixture produced a dark solid (0.320 g, 96% yield), which did not require additional purification. This material exhibited the following physical properties: mp 52-54 °C; ^{1}H NMR ($CDCl_3$) δ 9.77 (s, 1H), 7.53 (d, J=8.0 Hz, 2H), 7.33 (d, J=8.0 Hz, 2H), 7.03 (d, J=2.5 Hz, 1H), 4.42 (q, J=7.0 Hz, 2H), and 1.43 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 180.3, 160.2, 149.3, 134.3, 131.4, 130.4, 130.2, 127.8,121.4,120.5 (q, J=251.6 Hz),115.3, 61.9, and 14.3; IR (neat) 1718 and 1661 cm^{-1}; HRMS (ES, M+H) m/z calcd for $C_{15}H_{13}F_3NO_4$ 328.0797, found 328.0796.

4.1.14. *Ethyl 3-(1-benzenesulfonyl-1H-indol-3-yl)-2-formylpyrrole-5-carboxylate (34)*. This material was prepared in a manner identical to the previous example with the exceptions that DIPEA was used as the base instead of DABCO and potassium 1-benzenesulfonyl-1H-indol-3-trifluoroborate was used as the coupling agent. Work up of the reaction mixture produced a dark orange solid, which was purified by flash chromatography on a Biotage Isolera system in which case a bright orange solid was obtained (0.470 g, 55% yield) and this material exhibited the following physical properties: mp 164-166 °C; ^{1}H NMR ($CDCl_3$) δ 9.94 (s, 1H), 8.10 (d, J=8.0 Hz, 1H), 7.97 (d, J=8.5 Hz, 2H), 7.70 (s, 1H), 7.65 (d, J=8.0 Hz, 1H), 7.60 (t, J=8.5 Hz, 1H), 7.51 (t, J=8.5 Hz, 2H), 7.44 (t, J=8.5 Hz, 1H), 7.36 (t, J=8.5 Hz, 1H), 7.13 (d, J=3.0 Hz, 1H), 4.43 (q, J=7.0 Hz, 2H), and 1.43 (t, J=7.0 Hz, 3H); ^{13}C NMR (acetone-d_6) δ 179.8, 159.8, 137.9, 135.1, 134.5, 131.7, 130.0, 129.7, 128.3, 127.0, 125.6, 125.3, 124.2, 124.0, 120.3, 115.6, 115.0, 113.7, 60.8, and 13.7; IR (neat) 1714 and 1659 cm^{-1}; HRMS (ES, M+H) m/z calcd for $C_{22}H_{18}N_2O_5S$ 423.1009, found 423.1003.

4.1.15. *Ethyl 2-formyl-3-(3,4-dimethoxyphenyl) 4-iodopyrrole-5-carboxylate (35)*. Into a 100 mL round bottom flask equipped with magnetic stirring was placed ethyl 2-formyl-3-(3,4-dimethoxyphenyl)pyrrole-5-carboxylate (0.140 g, 0.513 mmol), potassium hydroxide (0.0575 g, 1.03 mmol) and 15 mL of DMF. The mixture was stirred for 15 min and N-bromosuccinimide (0.0913 g, 0.513

mmol) was added to the reaction flask and the resulting reaction mixture was allowed to stir overnight at room temperature. The reaction mixture was subsequently quenched with 45 mL of water and extracted with ethyl acetate (3x20 mL). The combined organic phases were washed with a saturated, aqueous solution of lithium chloride and this was followed by drying the organic phase over anhydrous sodium sulfate. The drying agent was removed by filtration and the filtrate was concentrated in vacuo to give a solid product. This material was subjected to flash chromatography on a Biotage Isolera system with a hexane/ethyl acetate gradient in which case a tan solid (0.148 g, 82% yield) was obtained. We have previously described[16] the synthesis of this substance by a different synthetic route and the spectral properties exhibited by this reaction product were identical to those reported earlier: ^{1}H NMR (d_6-DMSO). δ 13.19 (broad s, 1H), 9.49 (s, 1H), 7.04 (d, J=8.0 Hz, 1H), 7.00 (d, J=2.0 Hz, 1H), 6.93 (d of d, J=2.0 Hz, J=8.0 Hz, 1H), 4.33 (q, J=7.0 Hz, 2H), 3.82 (s, 3H), 3.79 (s, 3H), and 1.36 (t, J=7.0 Hz, 3H).

4.1.16. *Ethyl 2-formyl-3,4-bis-(3,4-dimethoxyphenyl)pyrrole-5-carboxylate (10*). Into a 20 mL microwave reaction tube equipped with a magnetic stir bar was placed ethyl 4-bromo-2- formyl-3-(3,4-dimethoxyphenyl)pyrrole-5-carboxylate (0.150 g, 0.446 mmol), potassium 3,4-dimethoxyphenyltrifluoroborate (0.124 g, 0.580 mmol), and DABCO (0.100 g, 0.892 mmol). A mixture (12 mL) of 3:1 of toluene/ethanol was added to the reaction tube along with 20 drops of water followed by dichloro[1,10-bis-(diphenylphosphino) ferrocene]palladium(II) dichloromethane adduct (0.016 g, 0.022 mmol). The reaction tube was capped and sealed with a crimping tool and the reaction mixture was heated in a Biotage Initiator microwave system for 2 h at 110 °C. After cooling to room temperature, the reaction mixturewas filtered through a short plug of silica gel and the silica was subsequently washed with 2x30 mL of ethyl acetate and the combined organic materials were concentrated in vacuo to give a dark solid. This material was subjected to flash chromatography on a Biotage Isolera system with a hexane/ethyl acetate gradient in which case a light brown solid (0.145 g, 61% yield) was obtained. We have previously described[16] the synthesis of this substance by a different synthetic route and the spectral properties exhibited by this reaction product were identical to those reported earlier: ^{1}H NMR (d_6-DMSO). δ 12.71 (broad s, 1H), 9.61 (s, 1H), 6.88 (d, J=8.4 Hz, 1H), 6.83 (d, J=8.4 Hz, 1H), 6.76 (d of d, J=2.1 Hz, J=8.4 Hz, 1H), 6.73 (d, J=2.1 Hz, 1H), 6.70 (d, J=2.1 Hz, 1H), 6.63 (d of d, J=2.1 Hz, J=8.4 Hz, 1H), 4.15 (q, J=7.1 Hz, 2H), 3.72 (s, 3H), 3.723 (s, 3H), 3.57 (s, 3H), 3.52 (s, 3H), 1.13 (t, J=7.2 Hz, 3H).

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5. References

1. Munro, et al. "The Discovery And Development Of Marine Compounds With Pharmaceutical Potential." *Journal of Biotechnology* 70.1-3 (1999): 15-25. *Research Gate*. Web. 15 Oct. 2013.
2. Pla, D.; Albericio, F.; Alvarez, M. "Recent Advances in Lamellarin Alkaloids: isolation, synthesis and activity." *Anti-Cancer Agents Med. Chem.* 2008, 8, 746.
3. Bailly, C. Curr. "Lamellarins A to Z: a family of anticancer marine pyrrole alkaloids." *Med. Chem.dAnti-Cancer Agents* 2004, 363.
4. Andersen, Raymond J., D. John Faulkner, Cun Heng He, Gregory D. Van Duyne, and Jon Clardy. "Metabolites Of The Marine Prosobranch Mollusk Lamellaria Sp." *Journal of the American Chemical Society* 107.19 (1985): 5492-5495.
5. "Lamellarin D: a novel potent inhibitor of topoisomerase I." *Cancer Res* 63, 7392-7399 (2003).
6. Baunbæk, et al. "Anticancer Alkaloid Lamellarins Inhibit Protein Kinases." *Marine Drugs* 6.4 (2008): 514-527.
7. Quesada, A.; Gravalos, M.; Puentes, J. Br. *J. Cancer* 1996, 74, 677.
8. Chittchang, et al. "Cytotoxicities And Structure-Activity Relationships Of Natural And Unnatural Lamellarins Toward Cancer Cell Lines." *ChemMedChem* 4.3 (2009): 457-465. *Wiley Online Library*. Web. 23 Oct. 2013.
9. Giglio, Benjamin. "Relay Total Synthesis of Lamellarin G Trimethyl Ether." *University of Richmond* (2009). https://dspace.lasrworks.org/bitstream/handle/10349/697/09CHEM-GiglioBenjamin.pdf?sequence=1. Web. 26 Oct. 2013.
10. Heim, Alexander, Andreas Terpin, and Wolfgang Steglich. "Biomimetic Synthesis Of Lamellarin G. Trimethyl Ether." *Angewandte Chemie International Edition in English* 36.12 (1997): 155-156.
11. Liermann, JC, and T. Opatz. "Synthesis of Lamellarin U and Lamellarin G Trimethyl Ether by Alkylation of a Deprotonated r-Aminonitrile." *J.Org. Chem* 73.12 (2008): 4526-31.
12. Handy, S.; Zhang, Y.; Bregman, H. "A Modular Synthesis of the Lamellarins: total synthesis of Lamellarin G trimethyl ether." *J. Org. Chem*. 2004, 69, 2362.
13. Iwao, M.; Takeuchi, T.; Fujikawa, N.; Fukuda, T.; Ishibashi, F. "Short and Flexible Route to 3,4-diarylpyrrole Marine Alkaloids." *Tetrahedron* 2003, 44, 4443.
14. Ruchirawat, S.; Mutarapat, T. "An efficient synthesis of lamellarin alkaloids: synthesis of lamellarin G trimethyl ether." *Tetrahedron* 2001, 42, 1205.
15. Gupton, John T., Jonathan E. Hempel, Lauren T. Firich, Peter J. Barelli, Matthew J. Keough, Kristin L. Smith, Elizabeth A. Rieck, James E. Eaton, Benjamin C. Giglio, and Timothy M. Smith. "The Application Of Vinylogous Iminium Salt Derivatives To Efficient Formal Syntheses Of The Marine Alkaloids Lamellarin G Trimethyl Ether And Ningalin B." *Tetrahedron* 65.22 (2009): 4283-4292.
16. Gupton, J.; Banner, E.; Sartin, M.; Coppock, M.; Hempel, J.; Kharlamova, A.; Fisher, D.; Giglio, B.; Smith, K.; Keough, M.; Smith, T.; Kanters, R.; Dominey, R.; Sikorski, J. "The application of vinylogous iminium salt derivatives and microwave accelerated Vilsmeier–Haack reactions to efficient relay syntheses of the polycitone and storniamide natural products." *Tetrahedron* 2008, 64, 5246.