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The application of vinylogous iminium salt derivatives and microwave accelerated Vilsmeier–Haack reactions to efficient relay syntheses of the polycitone and storniamide natural products

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ABSTRACT

Studies directed at the synthesis of polycitone and storniamide natural products via vinylogous iminium salts and microwave accelerated Vilsmeier–Haack formylations are described. The successful strategy relies on the formation of a 2,4-disubstituted pyrrole or a 2,3,4-trisubstituted pyrrole from a vinamidinium salt or vinamidinium salt derivative followed by formylation at the 5-position of the pyrrole. Subsequent transformations of the selectively formylated pyrroles lead to efficient and regiocontrolled relay syntheses of the respective pyrrole containing natural products.

1. Introduction

Pyrrole containing marine natural products and their derivatives continue to be a source of compounds with very interesting biological properties.[1] A number of recent reviews[2] have appeared, which describe synthetic efforts as well as structure–activity relationships and mode of action studies for this large and diverse class of substances.

Our own interest in this area of chemistry has allowed us to develop relay and total syntheses of certain members of this class of alkaloids (Fig. 1) such as rigidin,[3] rigidin E,[3] polycitones A and B,[4] ningalin B,[5] and lukianol A.[6] Edstrom[7] and Sakamoto[8] have successfully synthesized rigidin, while Steglich has synthesized polycitones A and B,[9] ningalin[10] type natural products, and various other members of this class of substances. Boger has also made a major synthetic effort in this area and has completed syntheses of ningalins A and B, lukianol A, and permethylstorniamide A.[11] The research groups of Banwell,[12] Furstner,[13] Handy,[14] Bullington,[15] Iwao,[16] Ishibashi,[17] and Ruchirawat[18] have also made major contributions to this area of chemistry. The majority of the synthetic methods to date rely on the efficient and regiocontrolled preparation of 2-carboalkoxy-3,4-diarylpyrroles (**11**) or 2,5-dicarboalkoxy-3,4-diarylpyrroles (**12**) as key synthetic intermediates (Fig. 2), which are further elaborated to the desired natural products. Interestingly, the conversion of the 2-carboalkoxy-3,4-diarylpyrroles (**11**) to the 2,5-dicarboalkoxy-3,4-diarylpyrroles (**12**) has not been utilized presumably due to the surprising lack of reactivity of these 2,3,4-trisubstituted pyrroles (**11**) at the 5-position with carbon bearing electrophiles. Such a transformation becomes quite significant for the preparation of the 2,3,4,5-tetrasubstituted pyrrole core, which is found in the majority of the natural products that have been previously mentioned. Consequently, any new synthetic methods or strategies, which provide the efficient and regiocontrolled preparation of these two scaffolds (**11** and **12**), are of importance.

2. Results and discussions

Our research efforts have demonstrated the ability to efficiently prepare 4-aryl-2-carbethoxypyrroles,[19] 5-aryl-2-carbethoxypyrroles,[20] 3-aryl-2-carbethoxypyrroles,[21] and 3,4-diaryl-2-carbethoxypyrroles[22] from vinylogous iminium salts (**14** and **18**) and their derivatives (**19**) with regiochemical control. Our general strategy for the synthesis of 4-aryl-2-carbethoxypyrroles (**15**) and 3,4-diaryl-2-carbethoxypyrroles (**20**) is described in Scheme 1.

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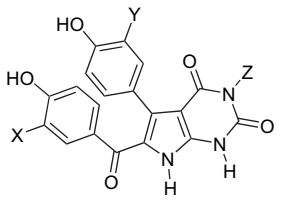
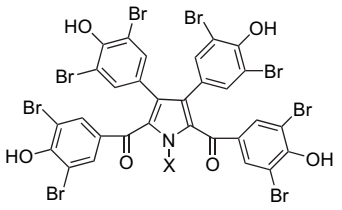
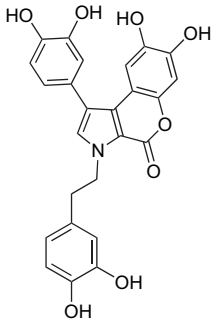


1 X = Y = Z = H Rigidin
2 X = OCH_3 Y = Z = H Rigidin B
3 Y = OCH_3 X = Z = H Rigidin C
4 X = Y = OCH_3 Z = H Rigidin D
5 X = Y = H Z = CH_3 Rigidin E

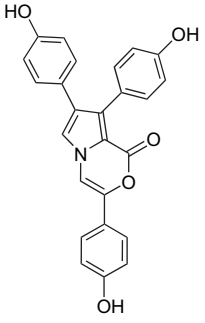


6 Polycitone A X = 4-hydroxyphenethyl

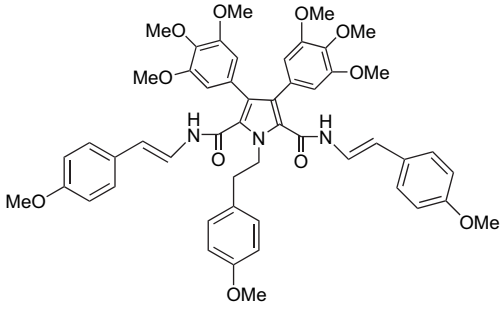
7 Polycitone B X = H



8 Ningalin B

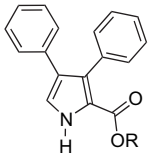


9 Lukianol A



10 Permethyl Storniamide A

Figure 1. Pyrrole containing marine natural products.



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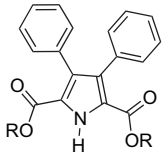


12

Figure 2. General pyrrole natural product motifs.

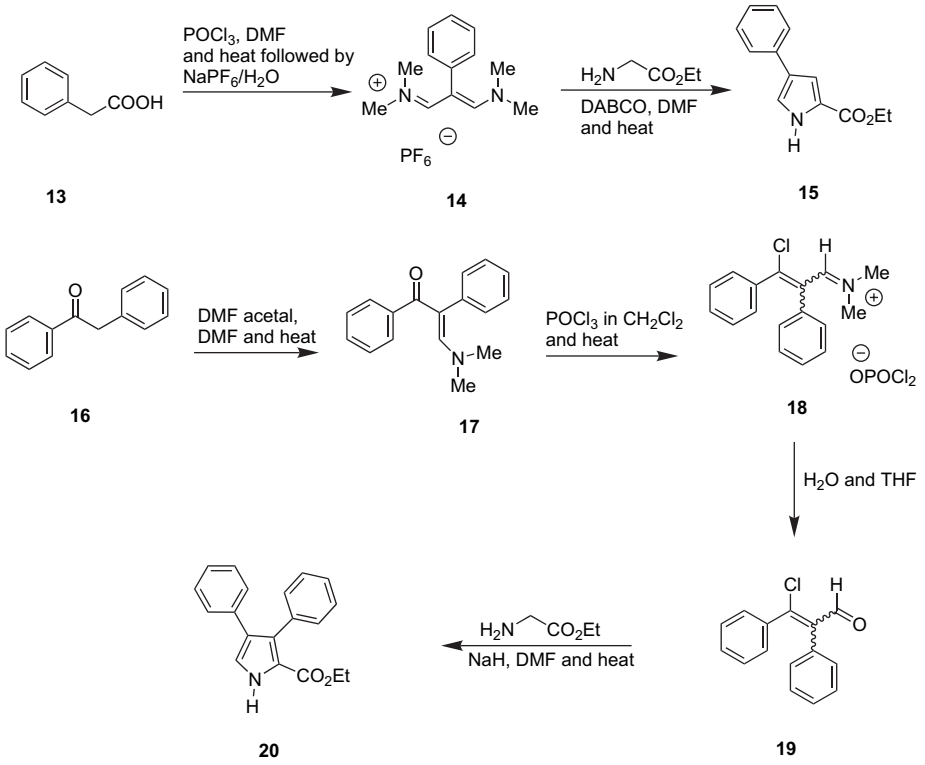
As mentioned previously, the ability to introduce carbon bearing electrophiles at the 5-position (*ortho* to nitrogen) of highly substituted pyrroles is quite significant. The Vilsmeier–Haack reagent[23] has traditionally been a useful means to introduce a formyl group at this position but, at least in the substrates that we have examined (such as **21a**–**21k**, Table 1), traditional heating of the pyrrole with DMF and phosphorous oxychloride does not provide a clean and high yielding method (typically in the 30% range) for the preparation of the desired formylpyrroles. We have had some success in the past in applying microwave acceleration conditions to reactions that appeared sluggish for either electronic or steric reasons. Consequently, we decided to subject some of our representative pyrroles to a microwave accelerated version of the Vilsmeier–Haack reaction and the results are presented in Table 1. To date the only example of microwave acceleration in the presence of the Vilsmeier–Haack reagent is described by Perumal and Dinakaran[24] in their preparation of chloroenals (such as **19** in Scheme 1) from aryl methyl ketones.

The microwave accelerated Vilsmeier–Haack reaction is typically carried out in a microwave reactor at 100 °C for 14 min and produces a near analytically pure product that requires minimal if any purification. In fact, we have found that in most cases the reaction is fully complete within 3–4 min. The regiochemistry of compounds **22b** and **22h** was unambiguously established by the detection of an NOESY signal between the aldehyde hydrogen and the pyrrole hydrogen (**22b**) or pyrrole methyl hydrogens (**22h**). The equivalent NOESY signal could not be detected for compound **22a** due to the close proximity of the signals and broadness of the pyrrole hydrogen signal. NOESY, HSQC, and HMBC spectra for these compounds (**22a**, **22b**, and **22h**) allowed for the assignment of all signals in the proton and carbon NMR spectra (Table 2).

With the ability to achieve high yielding, regioselective, formylations in place, we turned our attention to using this methodology to prepare polycitone- and storniamide-type natural products. We have previously reported[4] a relay synthesis of polycitones A and B based upon a key intermediate (**25**) prepared by the Steglich group[9] in their synthesis of the polycitones (Scheme 2). The precursor to the symmetrical diacylpyrrole (**25**), as developed by Steglich and co-workers, is a symmetrical pyrroledicarboxylic acid (**24**), which also can be viewed as a relay intermediate for the preparation of the polycitones. Consequently, using the appropriate formylated pyrrole (**22k**), we were able to rapidly carry out a synthesis (Scheme 3) of this tetrasubstituted pyrrole (**24**) in two steps and in 62% yield from **22k** and thereby accomplish a second relay synthesis of the polycitones. Interestingly, we also applied microwave acceleration reaction conditions for the preparation of pyrrole **21k** (analogous to the conversion of **19** to **20** in Scheme 1) by reacting the corresponding chloroenal with glycine ethyl ester in which case a 91% yield of the 2,3,4-trisubstituted pyrrole (**21k**) was obtained.

When comparing the spectral data of our material (**24**) with those reported by Steglich, the symmetrical nature of the Steglich intermediate (**24**) made the comparisons very straightforward and we were able to observe an identical match by proton and carbon NMR.

Permethylstorniamide A (**10**) has been an attractive synthetic target by a number of international research groups,[13,16,25] and Boger's efforts[11] in this regard also rely on a symmetrical

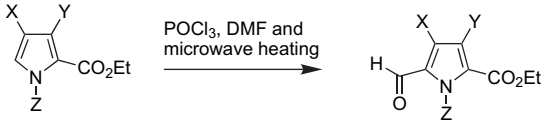


Scheme 1. Gupton group methodology for pyrrole synthesis.

tetrasubstituted pyrrole (**27**) as a key precursor to this natural product (Scheme 4). This pyrrole (**27**) is prepared by Boger via his Diels–Alder/retrograde Diels–Alder strategy coupled with reductive hydrogenolysis chemistry.

Starting from the appropriate formylated pyrrole (**22a**, Table 1), oxidation with sodium chlorite with subsequent basic hydrolysis yields the pyrrole diacid (**29**) very cleanly and in an overall yield of 85% in two steps (Scheme 5). Methylation of both carboxylic acid groups with *N*,*N*-dimethylformamide dimethylacetal followed by iodination yields a tetrasubstituted pyrrole (**31**) in 50% yield in two steps. The bisalkylation step has not been fully optimized (51% yield) so there is substantial room for improvement in this regard. The iodination reaction consistently proceeds in very good yield (97%). The final reaction to make the Boger intermediate (**27**) to permethylstorniamide A[11] (**10**) and thereby complete a relay synthesis involves a Suzuki cross-coupling reaction of the iodopyrrole (**31**) with 3,4,5-trimethoxyphenylboronic acid resulting in a 65% yield of the key synthon (**27**). As was the case for the Steglich polycitone precursor (**24**), the Boger synthon (**27**) is highly symmetrical, which made the spectral comparisons of our material to the data reported by Boger very straightforward, in which case there was an identical match for the proton and carbon NMR.

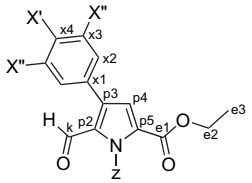
Table 1
Microwave accelerated Vilsmeier–Haack formylation of selected pyrroles



21 22

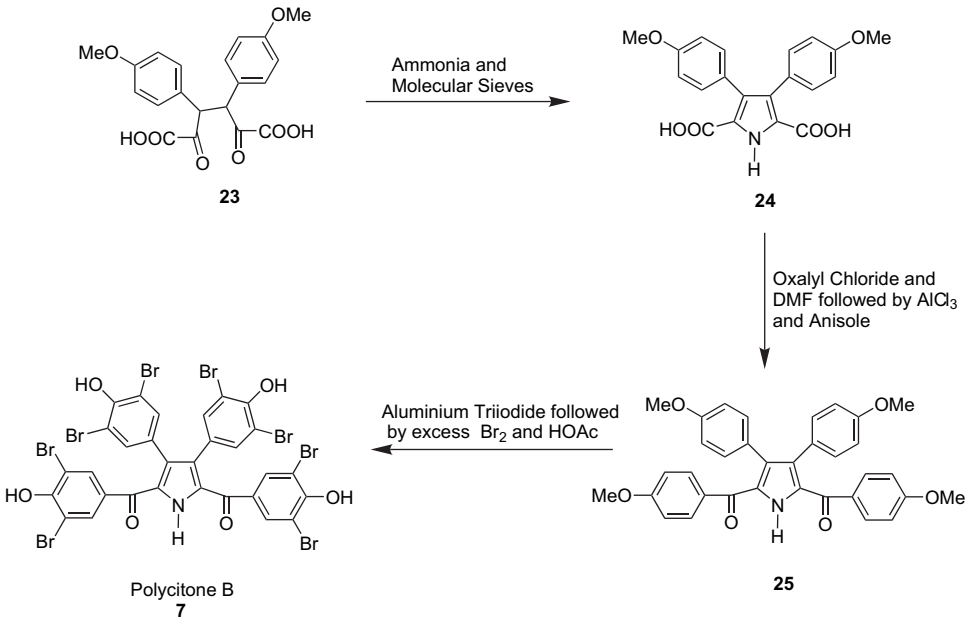
Compound **21**	X	Y	Z	% Yield for **22**
a	3,4,5-Trimethoxyphenyl	H	H	76
b	4-Bromophenyl	H	H	70
c	3,4-Dimethoxyphenyl	H	H	63
d	Phenyl	H	H	91
e	4-Chlorophenyl	H	H	84
f	4-Methylphenyl	H	H	67
g	4-Methoxyphenyl	H	H	81
h	4-Methylphenyl	H	Me	81
i	4-Methoxyphenyl	H	Me	81
j	3,4-Dimethoxyphenyl	H	Me	62
k	4-Methoxyphenyl	4-Methoxyphenyl	H	74

Table 2
NMR chemical shift assignments for compounds **22a**, **22b**, and **22h** via NOESY, HSQC, and HMBC studies

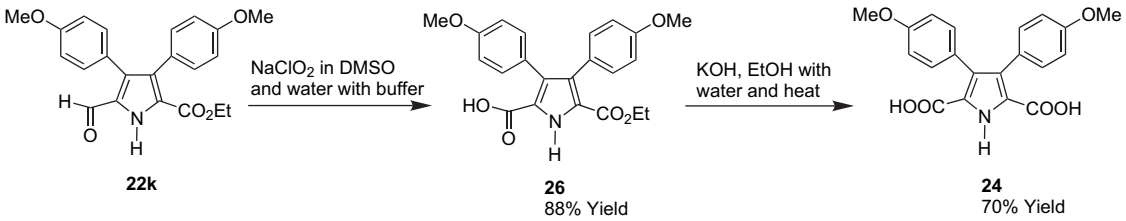


Label	**22a**; X′=X″=OMe, Z=H		**22b**; X′=Br, X″=Z=H		**22h**; X′=Z=Me, X″=H	
	^{13}C NMR	^{1}H NMR	^{13}C NMR	^{1}H NMR	^{13}C NMR	^{1}H NMR
Z		9.8[a]		10.05	34.8	4.35
p2	130.2		130.1		130.7	
p3	136.1		134.6		137.7	
p4	115.2	7.03	115.2	7.02	116.8	6.99
p5	127.6		127.8		128.7	
k	180.6	9.83	180.3	9.75	182.5	9.79
x1	128.2		131.6		130.1	
x2	106.5	6.69	130.5	7.37	129.5	7.31
x3	153.6		132.1	7.60	129.3	7.25
x4	138.5		122.5		137.8	
X′	61.0	3.92			21.2	2.42
X″	56.3	3.93				
e1	160.2		160.1		160.9	
e2	61.5	4.43	61.6	4.42	60.9	4.38
e3	14.3	1.43	14.3	1.42	14.3	1.41

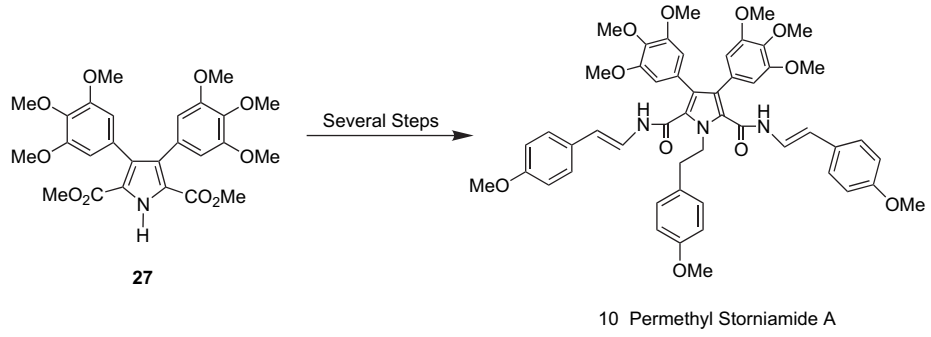
[a] Due to broadness of the NH resonance and overlap with the sharp aldehyde signal, higher precision was not warranted.



Scheme 2. Steglich synthesis of polycitone B.



Scheme 3. Gupton group relay synthesis of polycitone A and B synthon.



Scheme 4. Boger approach to permethylstorniamide A.

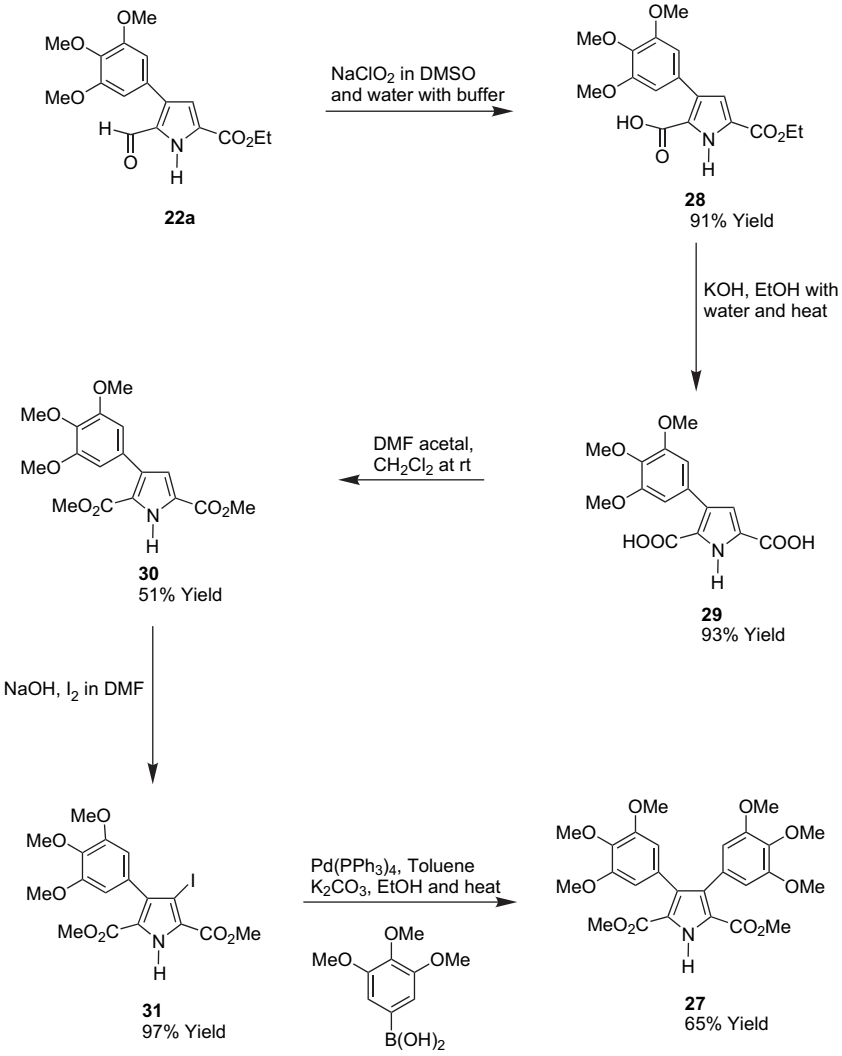
3. Conclusions

In summary, Vilsmeier–Haack formylations of pyrrole substrates can be significantly improved by microwave accelerations. Such formylated pyrroles are key precursors to the ever growing class of pyrrole containing marine natural products such as polycitones A and B as well as permethylstorniamide A. These formylation reactions in combination with our vinylogous iminium salt based approach to highly functionalized pyrroles provide efficient, flexible, and regiocontrolled methodology for the preparation of this important class of natural products and related derivatives. These synthetic strategies and procedures should also provide rapid access to a wide range of highly functionalized pyrroles for subsequent biologically driven SAR studies.

4. Experimental

4.1. General

All chemicals were used as-received from the manufacturer (Aldrich Chemicals and Fisher Scientific) and all reactions were carried out under a nitrogen or argon atmosphere. All solvents were dried over 4 Å molecular sieves prior to their use. NMR spectra were obtained on either a GE Omega 300 MHz spectrometer or a Bruker 500 MHz spectrometer in either $CDCl_3$, DMSO-d_6 or acetone-d_6 solutions. IR spectra were recorded on a Nicolet Avatar 320 FT-IR spectrometer with an HATR attachment. High-resolution mass spectra were provided by the Midwest Center for Mass Spectrometry at the University of Nebraska at Lincoln or on a Biotof Q



Scheme 5. Gupton group relay synthesis of permethylstorniamide A.

electrospray mass spectrometer at the University of Richmond. Low-resolution GC–MS spectra were obtained on a Shimadzu QP 5050 instrument. Melting points and boiling points are uncorrected. Flash chromatographic separations were carried out on a Biotage Horizon HFC or SP-1 instrument, which had been equipped with a silica cartridge, and ethyl acetate/hexane was used as the eluant. Microwave accelerated reactions were carried out in a Biotage Liberator system. Microwave reactions were controlled at a constant temperature whereby the microwave power was allowed to fluctuate so as to maintain a constant temperature and safe pressure limits. TLC analyses were conducted on silica plates with hexane/ethyl acetate as the eluant. Vinamidinium salts utilized for pyrrole formation were prepared according to standard procedures.[19] All purified reaction products gave TLC results, GC–MS spectra, flash chromatograms, and ^{13}C NMR spectra consistent with a sample purity of >95%.

*4.1.1. Ethyl 4-(3,4,5-trimethoxyphenyl)pyrrole-2-carboxylate (**21a**)*

Into a 250-mL flask equipped with a magnetic stirring bar was placed 1.00 g (2.27 mmol) of 3,4,5-trimethoxyphenylvinamidinium hexafluorophosphate along with 0.921 g (6.60 mmol) of ethyl glycinate, 0.740 g (6.58 mmol) of DABCO, and 100 mL of DMF. The resulting mixture was heated at reflux for 3 h, cooled to room temperature, and concentrated in vacuo. The residue was taken up in 100 mL of ethyl acetate and extracted with 3×50 mL of water and one 50 mL portion of brine, and dried over anhydrous magnesium sulfate. The resulting solution was filtered, concentrated in vacuo, which resulted in a tan solid (0.553 g, 80% yield), which exhibited the following properties: mp 140–141 °C; ^1H NMR ($CDCl_3$) δ 9.14 (br s, 1H), 7.28 (s, 2H), 7.20 (dd, J=5.0 Hz and J=2.5 Hz, 1H), 7.16 (d of d, J=5.0 Hz and J=2.5 Hz, 1H), 4.38 (q, J=12 Hz, 2 H), 3.93 (s, 6H) and 3.88 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 161.1, 153.6, 136.9, 130.5, 127.0, 123.7, 119.3, 112.4, 102.8, 61.0, 60.6, 56.2 and 14.5; IR (neat) 3270 and 1670 cm^{-1}; HRMS (ES M+H) m/z calcd for $C_{16}H_{20}NO_5$ 306.1336, found 306.1342.

*4.1.2. Ethyl 2-formyl-3-(3,4,5-trimethoxyphenyl)pyrrole-5-carboxylate (**22a**)*

Method A: a 7-mL microwave reaction vessel was equipped with a stir bar and was charged with 5 mL of DMF and 0.302 g (1.96 mmol) of phosphorous oxychloride and the resulting mixture was allowed to stir in an ice bath for 45 min. To this mixture was then added 0.200 g (0.655 mmol) of ethyl 4-(3,4,5-trimethoxyphenyl)pyrrole-5-carboxylate in 1 mL of DMF. The reaction vessel was sealed (Crymper-seal) and heated by microwaves at 100 °C for 14 min in a Liberator Microwave Reactor. After cooling to room temperature, the reaction mixture was diluted with 20 mL of water and extracted with 3×20 mL of ethyl acetate. The combined organic layers were washed with 3×20 mL of brine and dried over anhydrous magnesium sulfate. The resulting solution was filtered, concentrated in vacuo, which resulted in a tan solid (0.166 g, 76%

yield). This material was of sufficient purity for use in subsequent reactions. However, an analytical sample was prepared by flash chromatography using an ethyl acetate/hexane gradient. The purified product exhibited the following physical properties: mp 110–111 °C; ^{1}H NMR ($CDCl_3$) δ 9.88 (br s, 1H), 9.83 (s, 1H), 7.03 (d, J=2.7 Hz, 1H), 6.69 (s, 2H), 4.43 (q, J=7.1 Hz, 2H), 3.93 (s, 6H), 3.92 (s, 3H) and 1.43 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 180.6, 160.2, 153.6, 138.5, 136.1, 130.2, 128.2, 127.6, 115.2, 106.5, 61.5, 61.0, 56.3 and 14.3; IR (neat) 3256, 1715 and 1642 cm^{-1}; HRMS (EI) m/z calcd for $C_{17}H_{19}NO_6$ 333.1212, found 333.1215.

Method B: into a 50-mL flask, which had been equipped with a condenser and magnetic stirring bar, was placed 10 mL of DMF followed by the addition of 0.901 g (5.89 mmol) of phosphorous oxychloride. The resulting mixture was stirred in an ice bath for 45 min and ethyl 4-(3,4,5-trimethoxyphenyl)pyrrole-5-carboxylate (0.500 g, 1.96 mmol) was added. The resulting mixture was heated at reflux for 2 h. After cooling to room temperature, the reaction mixture was diluted with 30 mL of water and extracted with 3×30 mL of ethyl acetate. The combined organic layers were washed with 3×30 mL of brine and dried over anhydrous magnesium sulfate. The resulting solution was filtered, concentrated in vacuo, which resulted in a tan solid (0.225 g, 34% yield). This material was identical to the product obtained by method A as determined by ^{1}H NMR and TLC comparison.

4.1.3. Ethyl 2-formyl-3-(4-bromophenyl)pyrrole-5-carboxylate (**22b**)

Using a procedure analogous to method A as described in Section 4.1.2, a 70% yield of a solid with the following physical properties was obtained: mp 108–110 °C; ^{1}H NMR ($CDCl_3$) δ 10.05 (br s, 1H), 9.75 (s, 1H), 7.60 (d, J=8.4 Hz, 2H), 7.37 (d, J=8.4 Hz, 2H), 7.02 (d, J=2.7 Hz, 1H), 4.42 (q, J=7.1 Hz, 2H) and 1.42 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 180.3, 160.1, 134.6, 132.1, 131.6, 130.5, 130.1, 127.8, 122.5, 115.2, 61.6 and 14.3; in addition, NOESY (1 s mixing time) cross-peaks were observed between the resonances at 10.05 (pyrrole NH) and 9.75 ppm (aldehyde hydrogen) establishing the location of the formyl group as being *ortho* to the pyrrole nitrogen; IR (neat) 3282, 1712 and 1663 cm^{-1}; HRMS (EI) m/z calcd for $C_{14}H_{12}NO_3Br$ 321.0001, found 320.9995.

4.1.4. Ethyl 2-formyl-3-(3,4-dimethoxyphenyl)pyrrole-5-carboxylate (**22c**)

Using a procedure analogous to method A as described in Section 4.1.2, a 63% yield of a solid with the following physical properties was obtained: mp 107–109 °C; ^{1}H NMR ($CDCl_3$) δ 9.80 (br s, 2H), 7.05 (dd, J=2.0 Hz, J=8.5 Hz, 1H), 7.00–7.02 (m, 2H), 6.97 (d, J=8.5 Hz, 1H), 4.42 (q, J=7.0 Hz, 2H), 3.95 (s, 6H) and 1.42 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 180.7, 160.2, 149.4, 149.3, 136.0, 130.1, 127.6, 125.4, 121.7, 115.1, 112.2, 111.5, 61.5, 56.1, 56.0 and 14.3; IR (neat) 3277, 1711 and 1655 cm^{-1}; HRMS (EI) m/z calcd for $C_{16}H_{17}NO_5$ 303.1107, found 303.1113.

4.1.5. Ethyl 2-formyl-3-phenylpyrrole-5-carboxylate (**22d**)

Using a procedure analogous to method A as described in Section 4.1.2, a 91% yield of a solid with the following physical properties was obtained: mp 110–112 °C; ^{1}H NMR ($CDCl_3$) δ 9.87 (br s, 1H), 9.79 (s, 1H), 7.43–7.52 (m, 5H), 7.05 (d, J=3.0 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 180.8, 160.3, 136.0, 132.7, 130.3, 129.1, 128.9, 128.2, 127.7, 115.3, 61.5 and 14.3; IR (neat) 3269, 1716 and 1663 cm^{-1}; HRMS (EI) m/z calcd for $C_{14}H_{13}NO_3$ 243.0895, found 243.0894.

4.1.6. Ethyl 2-formyl-3-(4-chlorophenylpyrrole)-5-carboxylate (**22e**)

Using a procedure analogous to method A as described in Section 4.1.2, a 84% yield of a solid with the following physical properties was obtained: mp 96–98 °C; ^{1}H NMR ($CDCl_3$) δ 9.97 (br s, 1H), 9.76 (s, 1H), 7.45 (d, J=8.5 Hz, 2H), 7.43 (d, J=8.5 Hz, 2H), 7.02 (d, J=3.0 Hz, 1H), 4.42 (q, J=7.5 Hz, 2H) and 1.42 (t, J=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 180.3, 160.1, 134.5, 132.1, 131.6, 130.5, 130.1, 127.8, 122.6, 115.2, 61.6 and 14.3; IR (neat) 3256, 1719 and 1666 cm^{-1}; HRMS (EI) m/z calcd for $C_{14}H_{12}NO_3Cl$ 277.0506, found 277.0504.

4.1.7. Ethyl 2-formyl-3-(4-methylphenylpyrrole)-5-carboxylate (**22f**)

Using a procedure analogous to method A as described in Section 4.1.2, a 67% yield of a solid with the following physical properties was obtained: mp 104–106 °C; ^{1}H NMR ($CDCl_3$) δ 9.78 (br s, 2H), 7.40 (d, J=8.1 Hz, 2H), 7.29 (d, J=8.1 Hz, 2H), 7.02 (d, J=3.0 Hz, 1H), 4.41 (q, J=6.9 Hz, 2H) and 1.42 (t, J=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 180.8, 160.3, 138.2, 136.1, 130.2, 129.7, 129.6, 128.9, 127.6, 115.2, 61.4, 21.2 and 14.3; IR (neat) 3258, 1697 and 1658 cm^{-1}; HRMS (EI) m/z calcd for $C_{15}H_{15}NO_3$ 257.1052, found 257.1049.

4.1.8. Ethyl 2-formyl-3-(4-methoxyphenylpyrrole)-5-carboxylate (**22g**)

Using a procedure analogous to method A as described in Section 4.1.2, a 81% yield of a solid with the following physical properties was obtained: mp 103–105 °C; ^{1}H NMR ($CDCl_3$) δ 9.84 (br s, H), 9.77 (s, 1H), 7.43 (d, J=9.0 Hz, 2H), 7.00–7.02 (m, 3H), 4.42 (q, J=7.0 Hz, 2H), 3.88 (s, 3H) and 1.42 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 180.7, 160.3, 159.8, 135.9, 130.2, 130.1, 127.7, 125.1, 115.1, 114.4, 61.4, 55.4 and 14.1; IR (neat) 3273, 1703 and 1662 cm^{-1}; HRMS (EI) m/z calcd for $C_{15}H_{15}NO_4$ 273.1001, found 273.0994.

4.1.9. Ethyl N-methyl-2-formyl-3-(4-methylphenylpyrrole)-5-carboxylate (**22h**)

Using a procedure analogous to method A as described in Section 4.1.2, a 81% yield of a solid with the following physical properties was obtained: mp 75–76 °C; ^{1}H NMR ($CDCl_3$) δ 9.79 (s, 1H), 7.31 (d, J=8.0 Hz, 2H), 7.25 (d, J=8.0 Hz, 2H), 6.99 (s, 1H), 4.38 (q, J=7.1 Hz, 2H), 4.35 (s, 3H), 2.42 (s, 3H) and 1.41 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 182.5, 160.9, 137.8, 137.7, 130.7, 130.1, 129.5, 129.3, 128.7, 116.8, 60.9, 34.8, 21.2 and 14.3; in addition, NOESY (3 s mixing time) cross-peaks were observed between the resonances at 4.35 (pyrrole N-CH_3) and 9.78 ppm (aldehyde hydrogen) establishing the location of the formyl group as being *ortho* to the pyrrole nitrogen; IR (neat) 1712 and 1662 cm^{-1}; HRMS (EI) m/z calcd for $C_{16}H_{17}NO_3$ 271.1208, found 271.1209.

4.1.10. Ethyl N-methyl-2-formyl-3-(4-methoxyphenylpyrrole)-5-carboxylate (**22i**)

Using a procedure analogous to method A as described in Section 4.1.2, a 81% yield of a solid with the following physical properties was obtained: mp 73–75 °C; ^{1}H NMR ($CDCl_3$) δ 9.77 (s, 1H), 7.34 (d, J=9.0 Hz, 2H), 6.97–6.99 (m, 3H), 4.36 (q, J=7.0 Hz, 2H), 4.34 (s, 3H), 3.87 (s, 3H) and 1.40 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 182.4, 160.9, 159.6, 137.5, 130.7, 130.6, 128.7, 125.5, 116.7, 114.4, 60.9, 55.4, 34.8 and 14.3; IR (neat) 1706 and 1650 cm^{-1}; HRMS (ES M+H) m/z calcd for $C_{16}H_{18}NO_4$ 288.1230, found 288.1235.

4.1.11. Ethyl N-methyl-2-formyl-3-(3,4-dimethoxyphenylpyrrole)-5-carboxylate (**22j**)

Using a procedure analogous to method A as described in Section 4.1.2, a 62% yield of a solid with the following physical properties was obtained: mp 107–109 °C; ^{1}H NMR ($CDCl_3$) δ 9.80 (s, 1H), 6.98 (s, 1H), 6.93–6.95 (m, 3H), 4.37 (q, J=7.5 Hz, 2H), 4.35 (s, 3H), 3.95 (s, 3H), 3.93 (s, 3H) and 1.41 (q, J=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 182.5, 160.9, 149.1, 149.0, 137.6, 130.8, 128.7, 125.8, 122.3, 116.7, 112.7, 111.2, 61.0, 56.1, 56.0, 34.8 and 14.3; IR (neat) 1711 and 1655 cm^{-1}; HRMS (ES M+H) m/z calcd for $C_{17}H_{20}NO_5$ 318.1336, found 318.1346.

*4.1.12. Ethyl 3,4-bis(4-methoxyphenyl)pyrrole-2-carboxylate (**21k**)*

A 7-mL microwave reaction vessel was equipped with a stir bar and was charged with 6 mL of DMF and 0.200 g (0.660 mmol) of a mixture of *E*- and *Z*-3-chloro-2,3-bis(4-methoxyphenyl)-propenal, 0.277 g (1.98 mmol) of glycine ethyl ester, and 0.222 g (1.98 mmol) of DABCO, and the resulting mixture was allowed to stir for 30 min. The reaction vessel was sealed (Crymper-seal) and heated by microwaves at 150 °C for 14 min in a Liberator Microwave Reactor. After cooling to room temperature, the reaction mixture was diluted with 20 mL of water and extracted with 3×20 mL of ethyl acetate. The combined organic layers were washed with 3×20 mL of brine and dried over anhydrous magnesium sulfate. The resulting solution was filtered and concentrated in vacuo, which resulted in a solid (0.210 g, 91% yield) that was identical by TLC and proton NMR to a sample previously reported by our research group. This material was of sufficient purity to be used in subsequent transformations without additional purification.

*4.1.13. Ethyl 5-formyl-3,4-bis(4-methoxyphenyl)pyrrole-2-carboxylate (**22k**)*

Using a procedure analogous to method A as described in Section 4.1.2, a 74% yield of a solid with the following physical properties was obtained: mp 122–124 °C; ^{1}H NMR ($CDCl_3$) δ 9.88 (br s, 1H), 9.62 (s, 1H), 7.08–7.14 (m, 4 H), 6.84 (d, J=6.0 Hz, 2H), 6.82 (d, J=6.0 Hz, 2H), 4.28 (q, J=6.9 Hz, 2H), 3.82 (s, 6H) and 1.26 (t, J=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 181.4, 160.3, 159.3, 158.8, 134.8, 131.9, 131.8, 130.3, 129.8, 124.6, 123.8, 123.6, 113.8, 113.1, 61.1, 55.2, 55.1 and 14.1; IR (neat) 1675 and 1630 cm^{-1}; HRMS (EI) m/z calcd for $C_{22}H_{21}NO_5$ 379.1420, found 379.1421.

*4.1.14. 5-Carbethoxy-3,4-bis(4-methoxyphenyl)pyrrole-2-carboxylic acid (**26**)*

Ethyl 5-formyl-3,4-bis(4-methoxyphenyl)pyrrole-2-carboxylate (0.200 g, 0.530 mmol) and 50 mL of DMSO were place in a flask equipped with a stirring bar and cooled in an ice-water bath. A solution of sodium dihydrogen phosphate (0.023 g, 0.160 mmol in 10 mL of water) was added to the flask and the reaction mixture was stirred for 15 min. Subsequently, a solution of sodium chlorite (0.146 g, 1.59 mmol in 10 mL of water) was added to the flask dropwise with cooling and the resulting reaction mixture was stirred for 24 h at room temperature. The reaction mixture was then cooled in an ice-water bath and concentrated hydrochloric acid was added dropwise until the mixture reached a pH of approximately 2. The resulting mixture was vacuum filtered and the resulting solid was dried under vacuum thereby producing 0.190 g (88% yield) of material, which exhibited the following physical properties: mp 120–272 °C; ^{1}H NMR ($CDCl_3$) δ 12.62 (s, 1H), 11.95 (s, 1H), 7.00–7.03 (m, 4H), 6.79 (d, J=8.5 Hz, 4H), 4.10 (q, J=7.0 Hz, 2H), 3.71 (s, 6H) and 1.13 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 162.0, 160.4, 158.3, 158.3, 132.3, 132.2, 130.6, 130.1, 126.4, 126.3, 123.0, 121.9, 113.1, 113.0, 60.4, 55.4, 55.3 and 14.4; IR (neat) 3265, 1695 and 1663 cm^{-1}; HRMS (EI) m/z calcd for $C_{22}H_{21}NO_6$ 395.1369, found 395.1367.

*4.1.15. 3,4-Bis(4-methoxyphenyl)pyrrole-2,5-dicarboxylic acid (**24**)*

Into a flask equipped with a stirring bar and reflux condenser were placed 0.064 g (1.10 mmol) of potassium hydroxide and 30 mL of a 50:50 mixture of ethanol/water. The mixture was stirred until all solid materials dissolved and ethyl 5-formyl-3,4-bis(4-methoxyphenyl)pyrrole-2-carboxylate (0.150 g, 0.380 mmol) was added to the flask, and the resulting reaction mixture was refluxed for 20 h. The reaction mixture was then cooled in an ice-water bath and the mixture was adjusted to a pH of 2 by the slow addition of 6 M hydrochloric acid, which resulted in the formation of a white solid. The solid was filtered and dried under vacuum yielding 0.097 g (70% yield) of a solid product, which exhibited identical spectral properties to those reported by Steglich and co-workers: mp 200–202 °C (lit.[9] 268–270 °C); ^{1}H NMR (DMSO-d_6) δ 12.58 (br s, 2H), 11.58 (br s, 1H), 6.96 (d, J=8.5 Hz, 4H), 6.73 (d, J=8.5 Hz, 4H) and 3.70 (s, 6H); ^{13}C NMR (DMSO-d_6) δ 161.9, 158.2, 132.2, 130.2, 126.5, 122.6, 113.1 and 55.3; IR (neat) 3240 and 1683 cm^{-1}; HRMS (EI) m/z calcd for $C_{20}H_{17}NO_6$ 367.1056, found 367.1052.

*4.1.16. 5-Carbethoxy-3-(3,4,5-trimethoxyphenyl)pyrrole-2-carboxylic acid (**28**)*

Ethyl 2-formyl-3-(3,4,5-trimethoxyphenyl)pyrrole-5-carboxylate (0.400 g, 1.20 mmol) was placed in flask equipped with a magnetic stirring bar and to this was added 40 mL of DMSO followed by a solution containing 0.172 g (1.20 mmol) of sodium dihydrogen phosphate in 10 mL of water. The mixture was cooled in an ice-water bath and a solution of sodium chlorite (0.332 g, 3.61 mmol) in 10 mL of water was added in a dropwise fashion to the reaction mixture. After stirring for 24 h at room temperature, the reaction mixture was adjusted to a pH of 2 with 6 M hydrochloric acid while being cooled in an ice-water bath. The resulting mixture was extracted with 3×30 mL of ethyl acetate and the combined organic phases were washed with 30 mL of brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give 0.381 g (91% yield) of a solid, which exhibited the following physical properties: mp 118–120 °C; ^{1}H NMR ($CDCl_3$) δ 10.04 (br s, 1H), 6.98 (d, J=2.5 Hz, 1H), 6.84 (s, 2H), 4.01 (q, J=7.0 Hz, 2H), 3.91 (s, 3H), 3.89 (s, 6H) and 1.41 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 163.8, 160.3, 152.7, 137.7, 133.4, 129.1, 125.6, 120.7, 116.7, 106.9, 61.3, 60.9, 56.2 and 14.3; IR (neat) 3283, 1706 and 1660 cm^{-1}; HRMS (EI) m/z calcd for $C_{17}H_{19}NO_7$ 349.1161, found 349.1160.

*4.1.17. 3-(3,4,5-Trimethoxyphenyl)pyrrole-2,5-dicarboxylic acid (**29**)*

Into a flask equipped with a stirring bar and reflux condenser were placed 0.337 g (6.01 mmol) of potassium hydroxide and 60 mL of a 50:50 mixture of ethanol/water. The mixture was stirred until all solid material dissolved and 5-carbethoxy-3-(3,4,5-trimethoxyphenyl)pyrrole-2-carboxylic acid (0.700 g, 2.04 mmol) was added to the flask and the resulting reaction mixture was refluxed for 24 h. The reaction mixture was then cooled in an ice-water bath, adjusted to a pH of 2 by the slow addition of 6 M hydrochloric acid, and extracted with 3×30 mL of ethyl acetate. The combined organic phases were washed with 1×30 mL of brine and dried over anhydrous magnesium sulfate. After removal of the drying agent, the solution was concentrated in vacuo to give 0.600 g (93% yield) of a solid, which exhibited the following physical properties: mp 178–179 °C (dec); ^{1}H NMR (DMSO-d_6) δ 12.82 (br s, 2H), 11.90 (br s, 1H), 6.91 (d, J=2.5 Hz, 1H), 6.85 (s, 2H), 3.77 (s, 6H) and 3.69 (s, 6H); ^{13}C NMR (DMSO-d_6) δ 162.0, 161.6, 152.6, 137.1, 131.0, 130.3, 126.0, 122.8, 116.7, 107.3, 60.5 and 56.3; IR (neat) 2925, 1690 and 1660 cm^{-1}; HRMS (EI) m/z calcd for $C_{15}H_{15}NO_7$ 321.0848, found 321.0851.

*4.1.18. Dimethyl 3-(3,4,5-trimethoxyphenyl)pyrrole-2,5-dicarboxylate (**30**)*

A flask was equipped with a magnetic stir bar and to it were added 3-(3,4,5-trimethoxyphenyl)pyrrole-2,5-dicarboxylic acid (0.600 g, 1.87 mmol), 60 mL of dry chloroform, and 1.345 g (11.3 mmol) of *N*,*N*-dimethylformamide dimethylacetal. The resulting mixture was stirred at room temperature for 36 h and diluted with 30 mL of water. After separating the two phases, the aqueous phase was extracted with 3×30 mL of ethyl acetate and the combined organic phases were washed with 30 mL of brine and dried over anhydrous magnesium sulfate. After removal of the drying agent, the solution was concentrated in vacuo to give 0.330 g (51% yield) of a solid, which exhibited the following physical properties: mp 118–118 °C; ^{1}H NMR ($CDCl_3$) δ 9.80 (s, 1H), 6.98 (d, J=3.5 Hz, 1H), 6.83 (s, 2H), 3.96 (s, 3H), 3.91 (s, 3H), 3.91 (s, 6H) and

3.87 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 160.6, 160.5, 152.7, 137.7, 132.4, 129.2, 124.7, 121.1, 116.6, 106.8, 60.9, 56.2, 52.1 and 51.9; IR (neat) 3278, 1721 and 1706 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{17}H_{19}NO_7$ 349.1161, found 349.1163.

4.1.19. Dimethyl 3-iodo-4-(3,4,5-trimethoxyphenyl)pyrrole-2,5-dicarboxylate (**31**)

A flask was equipped with a magnetic stir bar and to it were added dimethyl 3-(3,4,5-trimethoxyphenyl)pyrrole-2,5-dicarboxylate (0.150 g, 0.429 mmol), 15 mL of DMF, and 0.072 g (1.29 mmol) of potassium hydroxide. The resulting mixture was stirred for 1 h, iodine (0.142 g, 0.558 mmol) was added to the flask and the resulting reaction mixture was stirred at room temperature for 20 h while being protected from any light. The reaction mixture was then cooled in an ice-water bath and quenched with 20 mL of a 10% by weight aqueous solution of sodium thiosulfate. The reaction mixture was diluted with additional water and extracted with 3×30 mL of ethyl acetate, and the combined organic phases were washed with 30 mL of brine and dried over anhydrous magnesium sulfate. After removal of the drying agent, the solution was concentrated in vacuo to give 0.198 g (97% yield) of a solid, which exhibited the following physical properties: mp 213–216 °C; ^{1}H NMR ($CDCl_3$) δ 10.02 (s, 1H), 6.55 (s, 2H), 3.99 (s, 3H), 3.94 (s, 3H), 3.89 (s, 6H) and 3.79 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 159.8, 159.7, 152.5, 137.8, 136.1, 129.1, 125.3, 122.3, 110.5, 108.1, 60.9, 56.2, 52.2 and 52.1: IR (neat) 3257, 1726 and 1706 cm^{-1}; HRMS (ES M+H) *m*/*z* calcd for $C_{17}H_{19}NO_7I$ 476.0201, found 476.0191.

4.1.20. Dimethyl bis-3,4-(3,4,5-trimethoxyphenyl)pyrrole-2,5-dicarboxylate (**27**)

A 7-mL microwave reaction vessel was equipped with a stir bar and was charged with 5 mL of a 3:1 toluene/ethanol mixture, which was followed by the addition of 0.200 g (0.421 mmol) of dimethyl 3-iodo-4-(3,4,5-trimethoxyphenyl)pyrrole-2,5-dicarboxylate, 0.138 g (0.652 mmol) of 3,4,5-trimethoxyphenylboronic acid, 0.012 g (0.0105 mmol) of palladium tetrakistriphenylphosphine, and 3 drops of water. The reaction vessel was sealed (Crymper-seal) and heated by microwaves at 110 °C for 30 min in a Liberator Microwave Reactor. After cooling to room temperature, the mixture was filtered through a silica gel plug, which was washed with additional ethyl acetate (30 mL). The combined organic filtrates were washed with 20 mL of 10% aqueous sodium hydroxide solution, 30 mL of brine and dried over anhydrous magnesium sulfate. After removal of the drying agent, the solution was concentrated in vacuo to give 0.140 g (65% yield) of a solid. An analytical sample was prepared by flash chromatography using an ethyl acetate/hexane gradient. The purified product exhibited identical spectral properties to those reported by Boger and co-workers: mp 159–160 °C (lit.[11a] 153–155 °C); ^{1}H NMR ($CDCl_3$) δ 9.86 (br s, 1H), 6.40 (s, 4H), 3.85 (s, 12 H) and 3.67 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 160.6, 152.4, 137.4, 131.2, 128.1, 121.0, 108.5, 60.9, 56.1 and 51.9: IR (neat) 3242 and 1696 cm^{-1}; HRMS (ES M+H) *m*/*z* calcd for $C_{26}H_{30}NO_{10}$ 516.1864, found 516.1869.

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