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The application of vinylogous iminium salt derivatives to an efficient relay synthesis of the pyrrole containing alkaloids polycitone A and B

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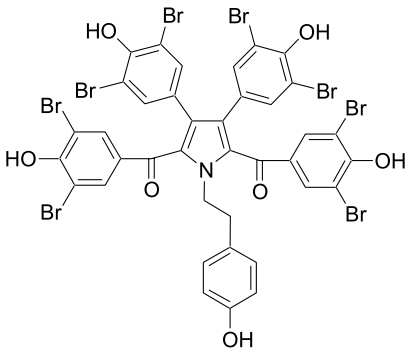
Abstract—A new and efficient relay synthesis of the marine natural products polycitone A and B is described. The new strategy relies on the formation of 2,4-disubstituted pyrroles from a vinamidinium salt followed by electrophilic substitution at the 5-position of the pyrrole and Suzuki coupling at the 4-position to produce the tetrasubstituted heterocycle efficiently and with complete control of regiochemistry.

1. Introduction

Polycitone A (**1a**) and B (**1b**) (Fig. 1) represent novel members of a growing class of pyrrole-containing marine natural products, which exhibit significant bioactivity[1] as inhibitors of retroviral reverse transcriptases and cellular DNA polymerases. These substances were first isolated and reported by Kashman[2] and co-workers and the first total synthesis was recently accomplished by Steglich[3] and co-workers. The Steglich synthesis (Scheme 1) employs a very elegant biomimetic approach involving the ammonia promoted cyclodehydration of an appropriate 1,4-diketone **2**



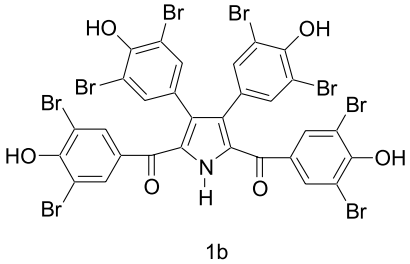


Figure 1.

Keywords: Vinamidinium salt; Pyrrole; Marine natural product.
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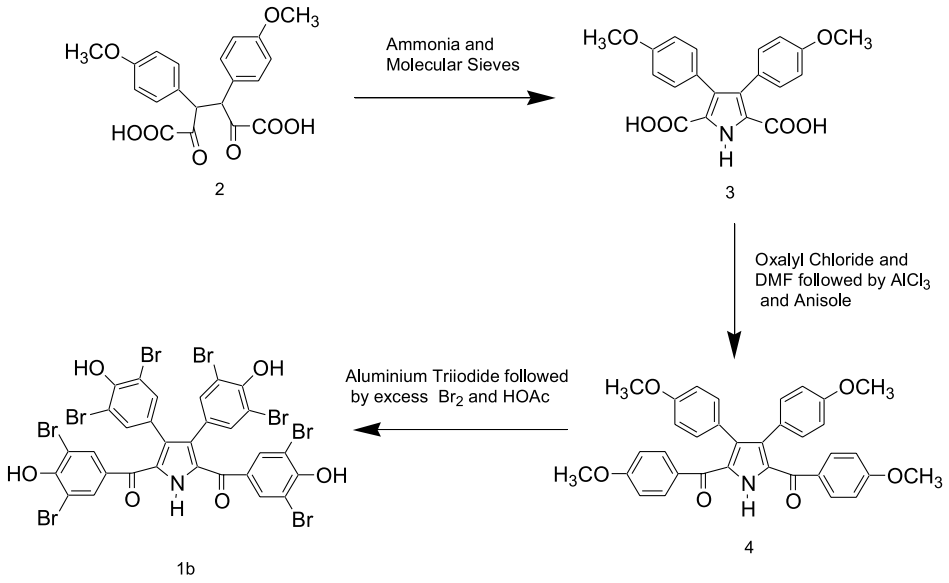


Scheme 1.

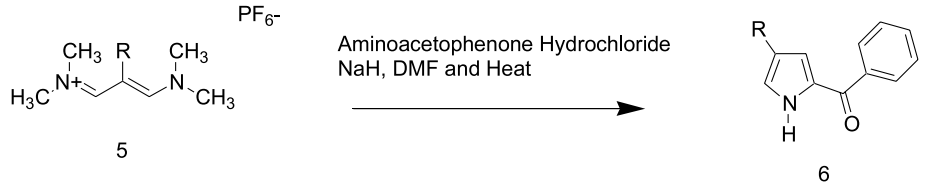
to form a 3,4-diarylpyrrole-2,5-dicarboxylic acid **3**. This 3,4-diarylpyrrole-2,5-dicarboxylic acid is then reacted with anisole under Friedel–Crafts conditions to produce the corresponding 2,5-dibenzoyl derivative **4**, which is O-dealkylated and brominated to produce polycitone B (**1b**) in 55% overall yield. By subsequent O-protection, N-alkylation and O-deprotection, polycitone B (**1b**) was converted to polycitone A (**1a**) in three steps and 39% yield.

It is clear from the work of Steglich and co-workers that symmetrical diketone **4** is a key synthetic intermediate for the polycitone natural products and also for analogs. Since SAR studies have yet to be accomplished for this class of alkaloids, new synthetic approaches, which provide substantial structural and functional group diversity, are required. We have previously reported the preparation of diaryl substituted chloropropeniminium salts and their corresponding β-chloroenals. Reacting either of these materials with glycinate esters efficiently produced 2,3,4-trisubstituted pyrroles[4] and these substances served as key synthons for the preparation of the pyrrole containing alkaloids lukianol A, lamellarin O[5] and ningalin B.[6] For the synthesis of polycitone A and B we have opted for a somewhat different approach, which allows for the incorporation of much greater structural diversity. This new strategy begins with the initial reaction of a 2-arylvinamidinium hexafluorophosphate with an α-aminoacetophenone in order to construct a 2-aroyl-4-arylpyrrole. Our initial studies of such a reaction are reported in Table 1.

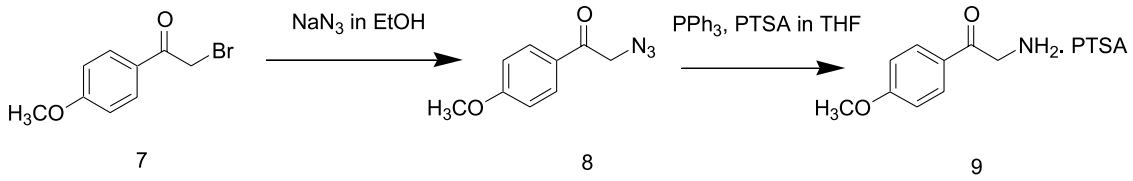
2. Results and discussion

α-Aminoketones are considerably less well behaved for pyrrole formation as compared to α-aminoesters due to self-condensation reactions. However, treatment of a series of 2-arylvinamidinium hexafluorophosphates **5**, which are readily available from the corresponding aryl acetic acids, with α-aminoacetophenone hydrochloride in refluxing DMF in the presence of sodium hydride (Table 1) results in quite reasonable yields of the desired 4-aryl-2-benzoylpyrroles **6**. The α-aminoketones can be easily and efficiently prepared according to Scheme 2 by conversion of an α-bromoketone **7** to the α-azidoketone **8** followed by reduction to the amine by triphenylphosphine and crystallization as the PTSA salt **9**. Consequently, reaction of

Table 1. Reaction of aminoacetohenone with 2-arylvinamidinium salts



Compound	R	% Yield
a	4-MeOPh	81
b	3,4-$(MeO)_2$Ph	55
c	4-MePh	77
d	Ph	85
e	4-BrPh	79
f	4-ClPh	73
g	4-FPh	63



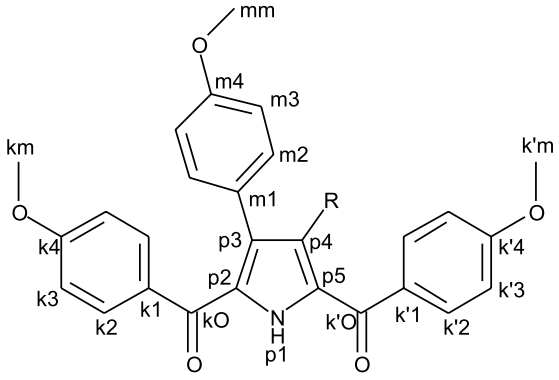
Scheme 2.

aminoketone **9** (Scheme 3) with the 4-methoxyphenyl vinamidinium salt **11** (obtained from aryl acetic acid **10**) under base mediated conditions produced the desired polycitone precursor **12** in 77% yield. This substance was then acylated with 4-methoxybenzoic acid in the presence of trifluoroacetic anhydride/trifluoroacetic acid (TFAA/TFA) according to the conditions of Edstrom[7] and co-workers in which case the 5-(4-methoxybenzoyl)-4-(4-methoxyphenyl)-2-carbethoxypyrrole (**13**) was obtained in 97% yield.

The regiochemistry of this trisubstituted pyrrole **13** was determined by NOESY, DQF-COSY and HMBC experiments, which allowed for the assignment of all signals in the proton and carbon NMR spectra (Table 2). Iodination of this pyrrole **13** with NaOH/I_2 in DMF yielded the 3-iodo derivative **14a** in 91% yield and this compound was also subjected to a NOESY NMR experiment, which confirmed the indicated regiochemical assignments (Table 2). The 3-iodopyrrole **14a** was then subjected to standard Suzuki cross-coupling conditions[8] with conventional heating (Method A) in which case a 21% yield of the 'Steglich synthon' **4** was obtained. A substantial amount of starting material was observed in this experiment thereby suggesting this transformation to be rather sluggish, which may be due to the steric congestion surrounding the iodine bearing carbon.

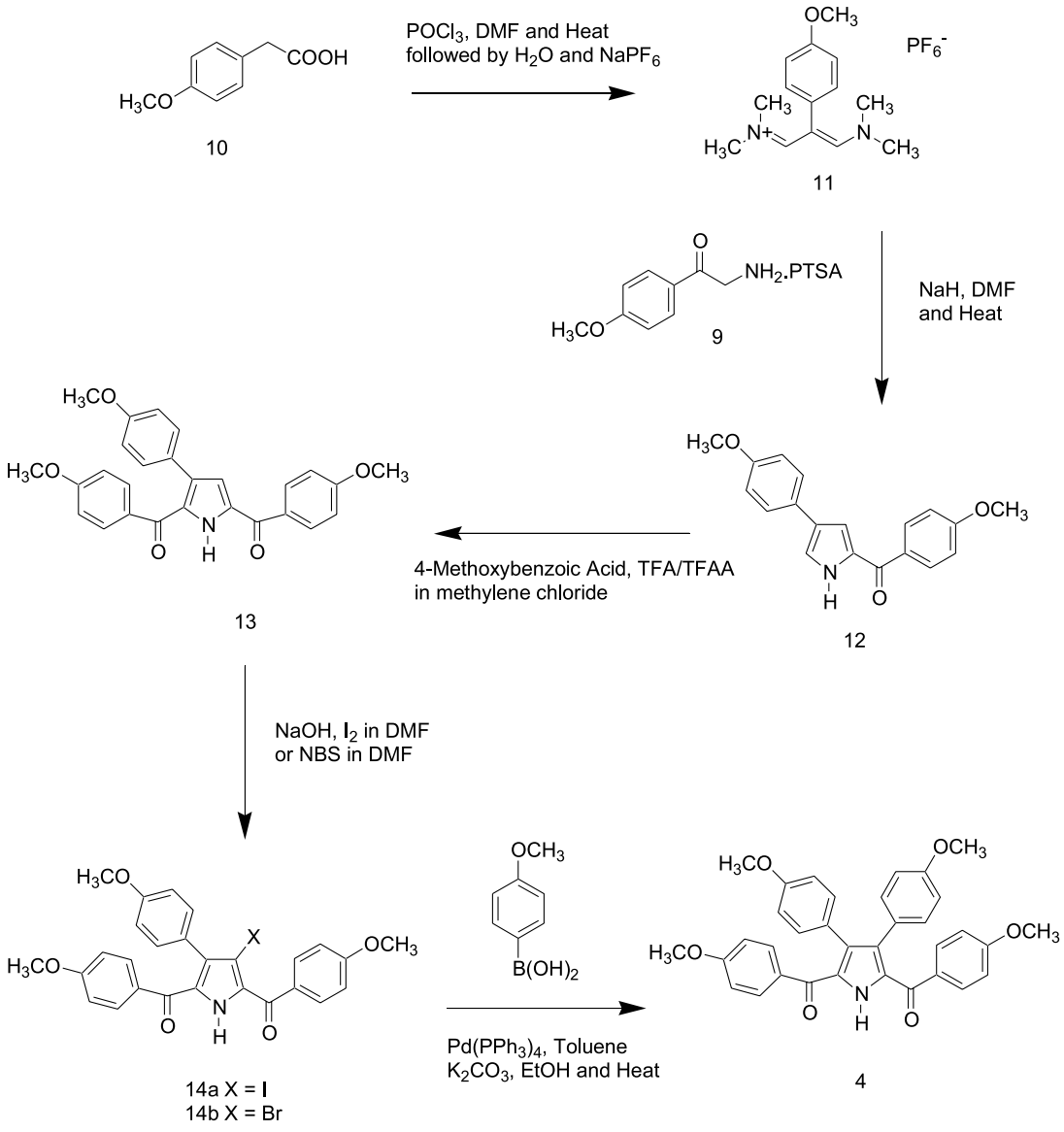
Microwave accelerated heating has become an important tool[9] to facilitate many types of organic reactions and we

Table 2. NMR Chemical shift assignments for compounds **13** and **14a** via NOESY, HMBC and DQF-COSY studies[a]



Label	R=H **13**		R=I **14a**	
	^{13}C NMR	^{1}H NMR	^{13}C NMR	^{1}H NMR
p1		10.103		10.150
p2	132.65		132.21	
p3	131.61		135.30	
p4	118.24	6.958	130.76	
p5	130.51		133.70	
kO	186.31		185.56	
k1	129.67		128.95	
k2	132.04	7.640	131.73	7.478
k3	113.31	6.701	113.04	6.602
k4	163.11		162.87	
km	55.40	3.801	55.37	3.769
k′O	183.80		185.70	
k′1	130.27		129.43	
k′2	131.45	8.031	132.41	7.923
k′3	113.89	7.033	114.00	7.032
k′4	163.88		163.79	
k′m	55.53	3.927	55.57	3.928
m1	127.02		126.50	
m2	130.53	7.139	132.33	7.083
m3	113.65	6.720	113.36	6.721
m4	158.77		159.12	
mm	55.29	3.771	55.22	3.767

[a] Carbon NMR shifts are reported to 2 decimal places and proton NMR shifts are reported to 3 decimal places so as to differentiate signals, which were extremely close to one another. NMR spectra were obtained in $CDCl_3$ solutions at room temperature.

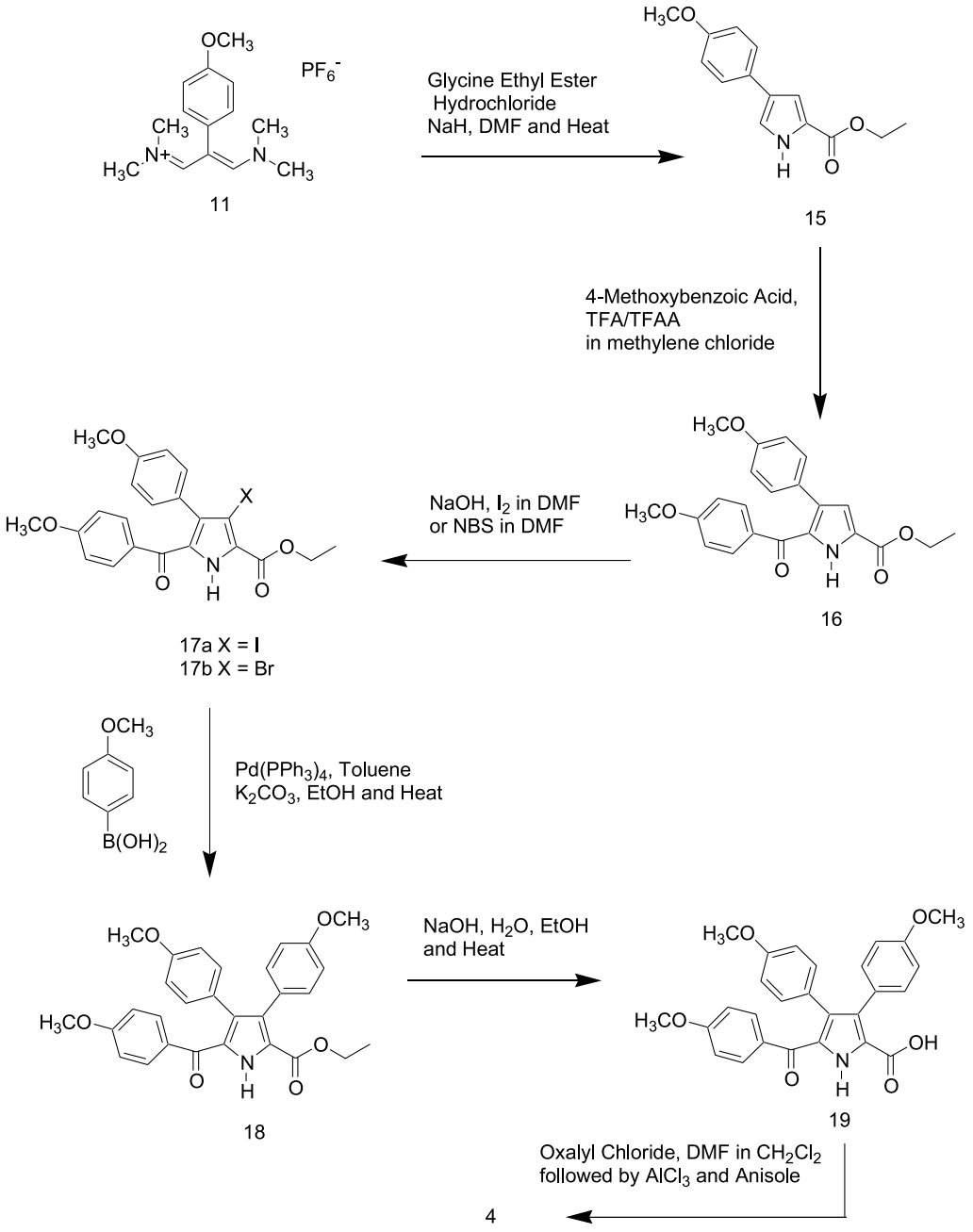


Scheme 3.

opted to repeat the cross-coupling process with the aid of a Personal Chemistry Emrys Liberator US microwave reaction system (Method B) for 2 h at 110 °C and 50 W in which case a 64% yield of the Steglich synthon was obtained. The product **4** of both reaction sequences (Methods A and B) exhibited mass spectra, proton and carbon NMR chemical shifts and NMR coupling constants identical to the values reported by Steglich[3,10] and co-workers (Scheme 1).

In addition, the symmetrical nature of **4** greatly facilitates the unambiguous assignment of its structure. It is of interest to note that the material **4** prepared in our laboratory had a melting point of 163–164 °C while the compound prepared by the Steglich group[10] had a melting point of 131–132 °C. In addition to studying the Suzuki cross-coupling reaction of the 3-iodopyrrole **14a**, the 3-bromo analog **14b** was prepared in 68% yield by reaction of **13** with NBS in DMF. When the 3-bromo analog (**14b**) was subjected to Suzuki cross-coupling conditions (both conventional and microwave accelerated), none of the desired Steglich synthon **4** could be observed. Although the bromo analog **14b** failed to cross-couple, the five step synthesis of the Steglich synthon **4** via the 3-iodopyrrole **14a** proved to be highly efficient (43% overall yield from the vinamidinium salt), convenient and very amenable to creating a variety of analogs late in the synthetic sequence.

We have previously reported[11] the preparation of 2-carbethoxy-4-(4-methoxyphenyl)pyrrole (**15**) (87% yield) by the base mediated condensation of glycine ethyl ester with the 4-methoxyphenyl vinamidinium salt (**11**). We anticipated applying a series of reactions (Scheme 4) analogous to those represented in Scheme 3 to this compound **15** and this would allow for the formation of tetrasubstituted pyrrole **18**, which could also be an appropriate precursor to the Steglich synthon **4** albeit via a few additional steps. Consequently, reaction of 2-carbethoxy-4-(4-methoxyphenyl)pyrrole (**15**) with 4-methoxybenzoic acid and TFA/TFAA produced a 94% yield of 2-carbethoxy-5-(4-methoxybenzoyl)-4-(4-methoxyphenyl)pyrrole (**16**), which was subjected



Scheme 4.

to NOEDIF NMR analysis thereby confirming the 2,3,5-trisubstitution pattern. This pyrrole **16** was subjected to both iodination and bromination conditions as previously described in which case the 3-iodo analog **17a** and 3-bromo analog **17b** were obtained in 89 and 99% yields, respectively. Exposure of the 3-bromopyrrole or the 3-iodopyrrole to Suzuki cross-coupling conditions with 4-methoxyphenyl boronic acid yielded the corresponding pyrrole ester **18** in 89 and 79% yields, respectively. It is of interest to note that both reactions were accomplished using conventional heating methods as opposed to microwave acceleration thereby suggesting a greater reactivity of the pyrrole ester **17a** and **17b** over the pyrrolo ketone **14a** and **14b** under Suzuki cross-coupling conditions. The resulting pyrrole ester **18** was then converted to the corresponding carboxylic acid **19** in 77% yield by base mediated hydrolysis. Conversion of the carboxylic acid to the acid chloride and subsequent acylation with anisole to yield the Steglich synthon **4** was accomplished in 75% yield. The overall yield for the preparation of **4** by this method from the 2,4-disubstituted pyrrole **15** was 42%.

3. Conclusions

In summary, we have demonstrated a new synthetic approach to an important family of bioactive, pyrrole containing marine natural products. This is accomplished by constructing 2,4-disubstituted pyrroles from vinamidinium salts, electrophilically substituting the 5-position of the pyrrole followed by halogenation and a microwave accelerated Suzuki coupling at the 3-position and ultimately

yielding the tetrasubstituted heterocycle. It is important to note that each pyrrole substitutent (e.g. compound **18**) is introduced independently and can be easily varied so as to accommodate in depth SAR studies for polycitone A and B analogs. We are currently in the process of applying this same strategy to other important pyrrole containing marine natural products.

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, a Bruker 500 MHz spectrometer or a Varian Gemini 200 MHz spectrometer in either $CDCl_3$ or d_6-DMSO solutions. IR spectra were recorded on a Nicolet Avatar 320 FT-IR spectrometer with an HATR attachment or a Perkin–Elmer 1600 series FT-IR spectrometer. High-resolution mass spectra were provided by the Midwest Center for Mass Spectrometry at the University of Nebraska at Lincoln. Low resolution GC–MS spectra were obtained on a Shimadzu QP 5050 instrument. Melting points and boiling points are uncorrected. Radial chromatographic separations were carried out on a Harrison Chromatotron using silica gel plates of 2 mm thickness with a fluorescent backing using ethyl acetate/hexane as the eluant. Flash chromatographic separations were carried out on a Biotage Horizon HFC instrument, which had been equipped with a #1542-2 silica cartridge, and ethyl acetate/hexane was used as the eluant. 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.[12] 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. 2-Benzoyl-4-(4-methoxyphenyl)pyrrole (6a). Into a 250 mL, round bottom flask was placed 1.0 g (2.64 mmol) of vinamidinium salt (**5a**) and 0.454 g (2.64 mmol) of α-aminoacetophenone hydrochloride. After a magnetic stir bar and dry DMF (60 mL) were added to the flask, the mixture was stirred at room temperature for 3 h. Another 250 mL, round-bottom flask was equipped with a magnetic stir bar, a reflux condenser, and placed under a nitrogen atmosphere. To this flask was added 0.158 g (0.66 mmol) of a 60% mineral oil dispersion of sodium hydride. The sodium hydride was washed twice with dry hexane and the washings were removed via cannula. Dry DMF (20 mL) was slowly added to the flask and the resulting mixture was allowed to stir for several minutes. The vinamidinium salt solution was added dropwise to the sodium hydride solution and the resultant mixture was stirred for 1 h at room temperature followed by refluxing for 2 h. The reaction was quenched with methanol and the solvent was removed in vacuo and the residue was partitioned between water (50 mL) and chloroform (50 mL) and the aqueous phase was extracted with additional portions of chloroform (2×50 mL). The combined chloroform extracts were dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was dissolved in ethyl acetate (50 mL) and passed through a 4 g plug of 200 mesh silica gel. The silica gel was washed with a mixture of 80:20 hexane/ethyl acetate and the solvent was removed in vacuo from the filtrate. The product was purified by radial chromatography using a mixture of 80:20 hexane/ethyl acetate as eluent. After removal of solvent from the chromatography fractions, 0.594 g (81% yield) of a light yellow solid was obtained, which exhibited the following properties: mp 200–201 °C; ^1H NMR ($CDCl_3$) δ 3.83 (s, 3H), 6.92 (d, $J=8.7$ Hz, 2H), 7.09 (m, 1H), 7.38 (m, 1H), 7.40–7.65 (m, 5H), 7.95 (d, $J=8.3$ Hz, 2H) and 9.78 (broad s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 57.4, 116.3, 118.1, 123.5, 128.5, 129.0, 129.2, 130.4, 131.0, 133.6, 134.0, 140.3, 160.4 and 186.9 ppm; IR (CCl_4) 3260, 1613 and 1247 cm^{-1}; HRMS (EI, M+) *m/z* for $C_{18}H_{15}NO_2$ calcd 277.1103, found 277.1106.

4.1.2. 2-Benzoyl-4-(3,4-dimethoxyphenyl)pyrrole (6b). This compound was prepared from **5b** by the same procedure as previously described affording a 55% purified yield of a light yellow solid, which exhibited the following properties: mp 163–164 °C; ^1H NMR ($CDCl_3$) δ 3.90 (s, 3H), 3.94 (s, 3H), 6.89 (d, $J=8.2$ Hz, 1H), 6.98–7.12 (m, 3H), 7.37 (m, 1H), 7.46–7.66 (m, 3H), 7.95 (d, $J=8.2$ Hz, 2H) and 9.58 (broad s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 58.0, 111.0, 113.6, 118.1, 119.8, 123.6, 129.4, 129.5, 130.5, 131.0, 133.6, 134.0, 140.2, 150.0, 151.2 and 186.8 ppm; IR (CCl_4) 3212 and 1612 cm^{-1}; HRMS (EI, M+) *m/z* for $C_{19}H_{17}NO_3$ calcd 307.1208, found 307.1208.

4.1.3. 2-Benzoyl-4-(4-methylphenyl)pyrrole (6c). This compound was prepared from **5c** by the above procedure affording a 77% purified yield of a light yellow solid, which exhibited the following properties: mp 190–191 °C; ^1H NMR ($CDCl_3$) δ 2.36 (s, 3H), 7.12 (m, 1H), 7.18 (d, $J=8.0$ Hz, 2H), 7.40–7.65 (m, 6H), 7.95 (d, $J=8.2$ Hz, 2H) and 9.80 (broad s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 23.1, 118.3, 123.8, 127.3, 129.5, 130.4, 131.0, 131.5, 133.4, 133.6, 134.0, 138.2, 140.3 and 186.9 ppm; IR (CCl_4) 3256 and 1610 cm^{-1}; HRMS (EI, M+) *m/z* for $C_{18}H_{15}NO$ calcd 261.1154, found 261.1163.

4.1.4. 2-Benzoyl-4-phenylpyrrole (6d). This compound was prepared from **5d** by the above procedure affording a 85% purified yield of a light yellow solid, which exhibited the following properties: mp 191–192 °C; ^1H NMR ($CDCl_3$) δ 7.15 (m, 1H), 7.20–7.61 (m, 9H), 7.95 (d, $J=8.3$ Hz, 2H) and 9.80 (broad s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 118.4, 124.1, 127.4, 128.5, 129.4, 130.5, 130.8, 131.0, 133.7, 134.0, 136.3, 140.2 and 187.0 ppm; IR (CCl_4) 3256 and 1614 cm^{-1}; HRMS (EI, M+) *m/z* for $C_{17}H_{13}NO$ calcd 247.0997, found 247.1001.

4.1.5. 2-Benzoyl-4-(4-bromophenyl)pyrrole (6e). This compound was prepared from **5e** by the above procedure affording a 79% purified yield of a light yellow solid, which exhibited the following properties: mp 226–227 °C; ^1H NMR ($CDCl_3$) δ 7.10 (m, 1H), 7.37–7.7 (m, 8H), 7.94 (d, $J=8.2$ Hz, 2H) and 9.88 (broad s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 122.9, 125.8, 131.1, 131.7, 134.2, 135.7, 135.9, 138.6, 138.7, 139.1, 140.9, 145.4 and 191.0 ppm; IR (CCl_4)

3250 and 1616 cm^{-1}; HRMS (EI, M+) *m/z* for $C_{17}H_{12}BrNO$ calcd 325.0102, found 325.0118.

4.1.6. 2-Benzoyl-4-(4-chlorophenyl)pyrrole (6f). This compound was prepared from **5f** by the above procedure affording a 73% purified yield of a light yellow solid, which exhibited the following properties: mp 208–209 °C; ^1H NMR ($CDCl_3$) δ 7.11 (m, 1H), 7.28–7.65 (m, 8H), 7.95 (d, $J=8.1$ Hz, 2H) and 9.88 (broad s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 118.2, 124.1, 128.2, 128.6, 130.5, 130.9, 133.9, 134.1, 134.2, 134.8, 140.1 and 187.0 ppm; IR (CCl_4) 3259 and 1617 cm^{-1}; HRMS (EI, M+) *m/z* for $C_{17}H_{12}ClNO$ calcd 281.0607, found 281.0606.

4.1.7. 2-Benzoyl-4-(4-flurophenyl)pyrrole (6g). This compound was prepared from **5g** by the above procedure followed by recrystallization with a mixture of 70:30 hexane/ethyl acetate and affording a 63% purified yield of a light yellow solid, which exhibited the following properties: mp 177–178 °C; ^1H NMR ($CDCl_3$) δ 6.98–7.15 (m, 3H), 7.37 (m, 1H), 7.40–7.65 (m, 5H), 7.94 (d, $J=8.3$ Hz, 2H) and 9.65 (broad s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 122.6 (d, $J=20.6$ Hz), 123.0, 130.7, 132.0, 134.0 (d, $J=7.8$ Hz), 135.7, 136.0, 138.1 (d, $J=3.0$ Hz), 138.5, 139.0, 145.5, 167.9 (d, $J=245.6$ Hz) and 190.9 ppm; IR (CCl_4) 3266 and 1613 cm^{-1}; HRMS (EI, M+) *m/z* for $C_{17}H_{12}FNO$ calcd 265.0903, found 265.0904.

4.1.8. 2′-Amino-4-methoxyacetophenone *p*-toluenesulfonic acid salt (9). Into a 3000 mL flask was placed 20.0 g (87.3 mmol) of 2′-bromo-4-methoxyacetophenone along with dry ethanol (500 mL). Once the solution became homogeneous, 5.70 g (87.3 mmol) of sodium azide was added in one portion. The reaction mixture was allowed to stir at room temperature for 24 h and the ethanol was removed in vacuo to give a yellow, oily solid. The solid was dissolved in chloroform (150 mL) and the organic layer was washed with water (3×100 mL), brine (100 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to give an amber oil. This oil was dissolved in THF (400 mL) and to the solution was added 22.9 g (87.3 mmol) of triphenylphosphine. Once the solution was homogeneous, 49.6 g (261 mmol) of PTSA was added in small portions and the reaction mixture was allowed to stir for 24 h. The resulting product was filtered and allowed to dry under vacuum to give 24.7 g (80%) of a white solid, which was suitable for further reactions and exhibited the following properties: mp 188–189 °C; ^1H NMR (d_6-DMSO) δ 2.27 (s, 3H), 3.85 (s, 3H), 4.52 (s, 2H), 7.10 (d, $J=8.0$ Hz, 4H), 7.46 (d, $J=8.0$ Hz, 2H), 7.98 (d, $J=8.0$ Hz, 2H) and 8.08 (broad s, 3H) ppm; ^{13}C NMR (d_6-DMSO) δ 20.7, 44.9, 55.7, 114.3, 125.6, 126.7, 128.1, 130.7, 137.7, 145.9, 164.3 and 191.4 ppm; IR (KBr) 3100 (broad absorption) and 1690 cm^{-1}; HRMS (EI, M+) *m/z* calcd for $C_9H_{12}NO_2$ 166.0868, found 166.0875.

4.1.9. 2-(4-Methoxybenzoyl)-4-(4-methoxyphenyl)pyrrole (12). Into a 250 mL erylenmyer flask was placed 2.00 g (5.29 mmol) of 4-methoxyphenyl vinamidiniun hexafluorophosphate (**11**), 2.07 g (5.82 mmol) of 2′-amino-4-methoxyacetophenone *p*-toluenesulfonic acid salt (**9**), 0.593 g (5.29 mmol) of DABCO and DMF (50 mL). The mixture was allowed to stir for 1 h at room temperature and subsequently added over a 1 h period to a 250 mL 3-neck round bottom flask containing 0.381 g (15.8 mmol) of sodium hydride (60% by wt. mineral oil dispersion) in 75 mL of DMF. The reaction mixture was heated at reflux for 18 h, cooled to room temperature, quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate (3×50 mL). The organic layers were combined, washed with brine (50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to give 1.24 g (77% yield) of a dark solid which was suitable for further transformations. An analytical sample was prepared by purification of a 0.500 g sample by automated flash chromatography on silica gel using a gradient elution of hexane/ethyl acetate to give 0.213 g of a yellow solid, which exhibited the following properties: mp 153–154 °C; ^1H NMR ($CDCl_3$) δ 3.85 (s, 3H), 3.92 (s, 3H), 6.94 (d, $J=9.0$ Hz, 2H), 7.03 (d, $J=9.0$ Hz, 2H), 7.10 (m, 1H), 7.36 (m, 1H), 7.48 (d, $J=9.0$ Hz, 2H), 8.00 (d, $J=9.0$ Hz, 2H) and 9.88 (broad s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 55.3, 55.5, 113.7, 114.3, 115.4, 121.0, 126.5, 127.0, 127.2, 130.9, 131.2, 131.7, 158.4, 162.9 and 183.7 ppm; FTIR (neat) 3250 and 1588 cm^{-1}; HRMS (EI, M+) *m/z* calcd for $C_{19}H_{17}NO_3$ 307.1208, found 307.1207.

4.1.10. 2,5-Bis(4-methoxybenzoyl)-3-(4-methoxyphenyl)-pyrrole (13). Into a 250 mL 3-neck flask was placed 5.22 g (34.4 mmol) of 4-methoxybenzoic acid and methylene chloride (35 mL). To the stirring suspension was added 7.22 g (34.4 mmol) of trifluroacetic anhydride. After 5 min the solution became homogeneous and 9.16 g (80.4 mmol) of trifluroacetic acid was added in one portion. To the stirring solution was added 2.35 g (7.65 mmol) of 2-(4-methoxybenzoyl)-4-(4-methoxyphenyl)pyrrole and the reaction mixture was allowed to stir overnight. After 17 h the reaction mixture was carefully quenched with saturated, aqueous sodium bicarbonate, diluted with ethyl acetate (200 mL), washed with 10% aqueous sodium hydroxide (3×50 mL), brine (50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to give 3.26 g (97% yield) of a black solid. An analytical sample was prepared by automated flash chromatography of a 0.500 g sample of crude material on silica gel using a gradient elution of hexane/ethyl acetate to give 0.325 g of a yellow solid which exhibited the following properties: mp 148–150 °C; for detailed ^1H and ^{13}C NMR analysis of compound **13** see Table 2; FTIR (neat) 3242 and 1592 cm^{-1}; HRMS (EI, M+) *m/z* calcd for $C_{27}H_{23}NO_5$ 441.1576, found 441.1578.

4.1.11. 2,5-Bis(4-methoxybenzoyl)-3-iodo-4-(4-methoxyphenyl)pyrrole (14a). Into a 100 mL flask was placed 0.750 g (1.70 mmol) of 2,5-bis(4-methoxybenzoyl)-3-(4-methoxyphenyl)pyrrole along with DMF (40 mL). To the stirring solution was added 0.285 g (5.07 mmol) of potassium hydroxide and after 5 min 0.560 g (2.21 mmol) of iodine was added. The reaction mixture was allowed to stir overnight (18 h) and was then quenched with 20% aqueous sodium thiosulfate (50 mL) with stirring. The reaction mixture was extracted with ethyl acetate (3×50 mL). The organic layers were combined and washed once with brine (50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to give 0.880 g (91% yield) of a dark oil. An analytical sample (0.500 g

sample of crude material) was prepared by automated flash chromatography of a on silica using a gradient elution of hexane/ethyl acetate to give 0.350 mg of yellow solid, which exhibited the following properties: mp 77–79 °C; For detailed ^{1}H and ^{13}C NMR analysis of compound **14a** see Table 2; FTIR (neat) 3215 and 1596 cm^{-1}; HRMS (EI, M+) *m/z* calcd for $C_{27}H_{22}NO_5I$ 567.0543, found 567.0564.

4.1.12. 2,5-Bis(4-methoxybenzoyl)-3-bromo-4-(4-methoxyphenyl)pyrrole (14b). Into a 50 mL flask was placed 0.430 g (1.21 mmol) of 2,5-bis(4-methoxybenzoyl)-3-(4-methoxyphenyl)pyrrole along with DMF (30 mL). To the stirring solution was added 0.324 g (1.82 mmol) of NBS in one portion and the resulting reaction mixture was allowed to stir at room temperature overnight. Subsequently, the DMF was removed in vacuo and the resulting residue was dissolved in ethyl acetate (100 mL) and the organic layer was washed with water (3×50 mL), with brine (50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to give 0.430 g (68% yield) of a brown solid. An analytical sample was prepared by automated flash chromatography on silica gel using a gradient elution of hexane/ethyl acetate to give a yellow solid, which exhibited the following properties: mp 147–149 °C (recrystallized from MeOH/H_2O); ^{1}H NMR ($CDCl_3$) δ 3.77 (s, 3H), 3.78 (s, 3H), 3.93 (s, 3H), 6.62 (d, J=9.0 Hz, 2H), 6.72 (d, J=9.0 Hz, 2H), 7.03 (d, J=9.0 Hz, 2H), 7.11 (d, J=9.0 Hz, 2H), 7.51 (d, J=9.0 2H), 7.94 (d, J=9.0 Hz, 2H) and 9.97 (broad s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 55.2, 55.4, 55.5, 113.1, 113.4, 113.8, 124.8, 128.9, 129.5, 130.1, 131.0, 131.3, 131.6, 131.8, 132.2, 132.3, 159.1, 162.9, 163.7, 185.1 and 185.5 ppm; FTIR (neat) 3231 and 1584 cm^{-1}; HRMS (EI, M+) *m/z* calcd for $C_{27}H_{22}NO_5Br$ calcd for 519.0681, found 519.0674.

4.1.13. 2,5-Bis(4-methoxybenzoyl)-3,4-bis(4-methoxyphenyl)pyrrole (4) (Method A). Into a 250 mL, 3-neck flask was placed 0.225 g (0.396 mmol) of 2,5-bis(4-methoxybenzoyl)-3-iodo-4-(4-methoxy-phenyl)pyrrole and 50 mL of a 3:1 mixture, respectively, of toluene/ethanol. The solution was allowed to become homogeneous and then 0.072 g (0.475 mmol) of 4-methoxyphenylboronic acid and 0.076 g (0.554 mmol) of potassium carbonate were added. The system was purged with Ar and to the stirring suspension was added 0.004 g (0.0039 mmol) of $Pd(PPh_3)_4$. The reaction mixture was heated at 80 °C overnight. After 18 h the reaction mixture was allowed to cool and was filtered through a plug of sand/silica/celite. The cake was washed with ethyl acetate (50 mL) and the resulting organic layer was washed with 10% aqueous sodium hydroxide (3×50 mL), with brine (50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to give 0.280 g of a brown solid. The crude material was subjected to automated flash chromatography on silica gel using a gradient elution of hexane/ethyl acetate to give 0.048 g (21% yield) of a yellow solid,[12] which exhibited the following properties: mp 163–164 °C (lit.[3] 131–132 °C); ^{1}H NMR ($CDCl_3$) δ 3.69 (s, 6H), 3.76 (s, 6H), 6.53 (d, J=8.8 Hz, 4H), 6.60 (d, J=9.0 Hz, 4H), 6.78 (d, J=8.8 Hz, 4H), 7.53 (d, J=9.0 Hz, 4H) and 10.03 (broad s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 55.1, 55.3, 113.0, 113.2, 125.8, 129.7, 129.9, 130.5, 131.8, 132.2, 158.3, 162.7 and 186.7 ppm; FTIR (neat) 3289 and 1596 cm^{-1}; MS (EI, M+) *m/z* 547.

4.1.14. 2,5-Bis(4-methoxybenzoyl)-3,4-bis(4-methoxyphenyl)pyrrole (4) (Method B). Into a 7 mL test tube (microwave reaction vessel) was placed 0.100 g (0.176 mmol) of 2,5-bis(4-methoxybenzoyl)-3-iodo-4-(4-methoxyphenyl)pyrrole along with 5 mL of 3:1 toluene/ethanol and a stir bar. To the solution was added 0.079 g (0.529 mmol) of 4-methoxyphenylboronic acid 0.082 g (0.598 mmol) of potassium carbonate and 0.002 g (0.00176 mmol) of $Pd(PPh_3)_4$. The reaction mixture was subjected to the following microwave conditions: 5 min initial stir time; 100 W power setting; 110 °C; 2 h run time. After 2 h the reaction mixture was filtered through a plug of sand/silica/celite and the cake was washed with ethyl acetate (50 mL). The organic filtrate was washed with 10% aqueous sodium hydroxide (3×25 mL), with brine (50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to give 0.250 g of a brown-yellow semi-solid. The crude mixture was purified by automated flash chromatography on silica gel using a gradient elution of hexane/ethyl acetate to give 0.061 g (64% yield) of a yellow solid, which exhibited ^{1}H NMR and ^{13}C NMR spectra and TLC behavior identical to the compound prepared by Method A.

4.1.15. 2-Carbethoxy-5-(4-methoxybenzoyl)-4-(4-methoxyphenyl)pyrrole (16). To a solution of 3.13 g (20.57 mmol) of 4-methoxybenzoic acid in dry methylene chloride (25 mL) was added 4.32 g (20.5 mmol) of trifluoroacetic anhydride and the resulting solution was stirred for 15–20 min at room temperature. This was followed by the addition of 5.48 g (48.0 mmol) of trifluoroacetic acid and the resulting mixture was stirred for an additional 5 min. Subsequently, 1.68 g (6.86 mmol) of 2-carbethoxy-4-(4-methoxyphenyl)pyrrole[11] was added to the reaction mixture in which case the solution darkened immediately. The resulting solution was then stirred at room temperature for 3 days and the reaction was carefully quenched with saturated, aqueous sodium bicarbonate. The reaction mixture was then diluted with ethyl acetate (100 mL), washed with 10% aqueous sodium hydroxide (3×50 mL), brine (50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The crude residue was subjected to radial chromatography using hexane/ethyl acetate as the eluant in which case 2.45 g (94% yield) of brown solid was obtained, which exhibited the following properties: mp 145–147 °C; ^{1}H NMR ($CDCl_3$) δ 1.39 (t, J=7.1 Hz, 3H), 3.73 (s, 3H), 3.75 (s, 3H), 4.39 (q, J=7.1 Hz, 2H), 6.63 (d, J=8.9 Hz, 2H), 6.66 (d, J=8.9 Hz, 2H), 6.99 (d, J=2.9 Hz, 1H), 7.06 (d, J=8.9 Hz, 2H), 7.54 (d, J=8.9 Hz, 2H) and 9.86 (broad s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 16.4, 31.7, 57.2, 57.3, 63.1, 115.1, 115.5, 118.1, 127.5, 129.1, 131.5, 131.6, 132.5, 133.7, 134.1, 160.6, 162.4, 164.9 and 188.1 ppm; IR (KBr) 3309, 1711 and 1597 cm^{-1}; HRMS (EI, M+) *m/z* for $C_{22}H_{21}NO_5$ calcd 379.1420, found 379.1421.

4.1.16. 2-Carbethoxy-3-iodo-5-(4-methoxybenzoyl)-4-(4-methoxyphenyl)pyrrole (17a). To a stirred solution of 2-carbethoxy-5-(4-methoxybenzoyl)-4-(4-methoxyphenyl)-pyrrole (1.00 g, 2.64 mmol) in DMF (60 mL) was added potassium hydroxide (0.44 g, 7.90 mmol). After 10 min, iodine (0.87 g, 3.43 mmol) was added in one portion and the reaction mixture was stirred for 18 h while protecting it

from light. The reaction mixture was quenched with 20% aqueous sodium thiosulfate (70 mL) and extracted with ethyl acetate (3×100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to give 1.18 g (89% yield) of a brown oil. An analytical sample was prepared by automated flash chromatography on silica gel using a gradient elution of hexane/ethyl acetate to give a dark yellow solid, which exhibited the following properties: mp 123–125 °C; ^{1}H NMR ($CDCl_3$) δ 1.46 (t, J=6.9 Hz, 3H), 3.75 (s, 3H), 3.76 (s, 3H), 4.46 (q, J=6.9 Hz, 2H), 6.59 (d, J=9.0 Hz, 2H), 6.71 (d, J=9.0 Hz, 2H), 7.04 (d, J=9.0 Hz, 2H), 7.45 (d, J=9.0 Hz, 2H) and 10.15 (broad s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 14.4, 55.2, 55.4, 61.5, 75.1, 113.0, 113.3, 125.8, 126.4, 128.4, 130.8, 131.7, 132.3, 135.1, 159.1, 159.5, 162.9 and 185.5 ppm; FTIR (neat) 3310, 1714 and 1594 cm^{-1}; HRMS (EI, M+) *m/z* calcd for $C_{22}H_{20}NO_5I$ 505.0386, found 505.0395.

4.1.17. 3-Bromo-2-carbethoxy-5-(4-methoxybenzoyl)-4-(4-methoxyphenyl)pyrrole (17b). Into a 100 mL round bottom flask was placed 0.250 g (0.660 mmol) of 2-carbethoxy-5-(4-methoxybenzoyl)-4-(4-methoxyphenyl)pyrrole along with DMF (50 mL). To the reaction mixture was added 0.176 g (0.990 mmol) of NBS and the resulting solution was stirred for 23 h at room temperature. The solvent was removed in vacuo and the remaining residue was dissolved in ethyl acetate (100 mL), washed with water (3×50 mL), brine (50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to give 0.300 g (99% yield) of a brown solid. An analytical sample was prepared by automated flash chromatography on silica using a gradient elution of hexane/ethyl acetate to give a solid, which exhibited the following properties: mp 128–130 °C; ^{1}H NMR ($CDCl_3$) δ 1.43 (t, J=7.2 Hz, 3H), 3.78 (s, 6H), 4.44 (q, J=7.2 Hz, 2H), 6.58 (d, J=9.0 Hz, 2H), 6.70 (d, J=9.0 Hz, 2H), 7.06 (d, J=9.0 Hz, 2H), 7.46 (d, J=9.0 Hz, 2H) and 10.10 (broad s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 14.3, 55.2, 55.3, 61.4, 104.9, 113.0, 113.4, 123.0, 124.7, 128.9, 129.9, 131.1, 131.8, 132.1, 159.0, 159.5, 162.9 and 185.5 ppm; FTIR (neat) 3256, 1678 and 1592 cm^{-1}; HRMS (EI, M+) *m/z* calcd for $C_{22}H_{20}NO_5Br$ 457.0525, found 457.0529.

4.1.18. 3,4-Bis-(4-methoxyphenyl)-2-carbethoxy-5-(4-methoxybenzoyl)pyrrole (18) (Method C). In an Ar purged 100 mL flask was placed 0.427 g (0.280 mmol) of 4-methoxyphenylboronic acid, 0.452 g (0.327 mmol) of potassium carbonate, and 50 mL of a 3:1 toluene/ethanol mixture. To the stirring suspension was added 1.07 g (2.34 mmol) of 3-bromo-2-carbethoxy-5-(4-methoxybenzoyl)-4-(4-methoxy-phenyl)pyrrole. Once the pyrrole dissolved, 0.0270 g (0.0234 mmol) of $Pd(PPh_3)_4$ was added and the reaction mixture was heated at reflux for 22 h. The reaction mixture was allowed to cool to room temperature, filtered through a plug of sand/silica/celite and the cake was washed with ethyl acetate (100 mL). The filtrate was washed with 10% aqueous sodium hydroxide (3×50 mL), brine (50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to give 0.990 g (87% yield) of a brown semi-solid. An analytical sample was prepared by automated flash chromatography on silica using a gradient elution of hexane/ethyl acetate to give a soild, which exhibited the following properties: mp 151–153 °C; ^{1}H NMR ($CDCl_3$) δ 1.26 (t, J=7.2 Hz, 3H), 3.68 (s, 3H), 3.75 (s, 3H), 3.80 (s, 3H), 4.28 (q, J=7.2 Hz, 2H), 6.50 (d, J=9.0 Hz, 2H), 6.59 (d, J=9.0 Hz, 2H), 6.73 (d, J=9.0 Hz, 2H), 6.80 (d, J=9.0 Hz, 2H), 7.10 (d, J=9.0 Hz, 2H), 7.50 (d, J=9.0 Hz, 2H) and 9.93 (broad s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 14.2, 55.0, 55.1, 55.3, 60.8, 112.9, 113.0, 113.1, 122.1, 125.4, 125.7, 129.6, 129.7, 130.7, 131.7, 131.8, 132.0, 132.2, 158.3, 158.6, 160.4, 162.7 and 186.5 ppm; FTIR (neat) 2963, 1693 and 1600 cm^{-1}; HRMS (EI, M+) *m/z* calcd for $C_{29}H_{27}NO_6$ 485.1838, found 485.1833.

4.1.19. 3,4-Bis-(4-methoxyphenyl)-2-carbethoxy-5-(4-methoxybenzoyl)pyrrole (18) (Method D). Into a nitrogen purged round bottom flask was placed 4-methoxyphenyl boronic acid (0.896 g, 5.9 mmol), potassium carbonate (0.816 g, 5.9 mmol), 200 mL of a toluene/ethanol solution (3:1) and a stir bar. To the stirred suspension was added 2-carbethoxy-3-iodo-5-(4-methoxybenzoyl)-4-(4-methoxyphenyl)pyrrole (1.93 g, 3.8 mmol). Once the pyrrole became dissolved in solution, $Pd(PPh_3)_4$ (0.066 g, 0.057 mmol) was added and the reaction mixture was heated to reflux. Upon reflux, 8 drops of water were added to the reaction mixture. Reflux was continued and after 24 h additional boronic acid (0.40 g, 2.6 mmol) and Pd catalyst (0.04 g, 0.034 mmol) were added and reflux was continued for another 24 h. The reaction mixture was cooled to room temperature, filtered through a plug of sand/silica gel/celite and the plug was washed with ethyl acetate (100 mL). The filtrate was extracted with 10% aqueous sodium hydroxide (3×50 mL), with brine (50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo, to yield 1.45 g of a dark yellow solid (79% yield), which exhibited physical properties identical to the product described in the above reaction. This material was sufficiently pure by spectroscopic characterization and TLC for direct use in subsequent reactions.

4.1.20. 3,4-Bis-(4-methoxyphenyl)-5-(4-methoxybenzoyl)-2-pyrrolecarboxylic acid (19). Into a 100 mL flask was placed 0.300 g of 3,4-bis-(4-methoxyphenyl)-2-carbethoxy-5-(4-methoxybenzoyl)pyrrole and 50 mL of a 50/50 mixture of ethanol/water. To the stirring suspension was added 0.100 g (2.47 mmol) of aqueous sodium hydroxide and the reaction mixture was heated at reflux for 22 h. Subsequently, the reaction mixture was allowed to cool to room temperature and was acidified with 6 M hydrochloric acid. An appropriate amount of water was added to induce crystallization and the resulting solid was collected by vacuum filtration and dried in vacuo to give 0.217 g (77% yield) of a brown solid, which exhibited the following properties: mp 212–215 °C (dec.); ^{1}H NMR ($CDCl_3$) δ 3.68 (s, 3H), 3.75 (s, 3H), 3.81 (s, 3H), 6.51 (d, J=9.0 Hz, 2H), 6.60 (d, J=9.0 Hz, 2H), 6.74 (d, J=9.0 Hz, 2H), 6.81 (d, J=9.0 Hz, 2H), 7.12 (d, J=9.0 Hz, 2H), 7.52 (d, J=9.0 Hz, 2H) and 10.13 (broad s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 55.1, 55.3, 113.1, 113.2, 120.9, 124.9, 125.5, 129.4, 130.7, 130.8, 131.6, 131.9, 132.0, 132.2, 158.3, 158.7, 162.9, 164.1 and 186.5 ppm; FTIR (neat) 3231, 1681 and 1588 cm^{-1}; HRMS (EI, M+) *m/z* calcd for $C_{27}H_{23}NO_6$ 457.1525, found 457.1521.

4.1.21. 2,5-Bis(4-methoxybenzoyl)-3,4-bis(4-methoxyphenyl)pyrrole (4) (Method E). To a stirred suspension of 3,4-bis-(4-methoxyphenyl)-5-(4-methoxybenzoyl)pyrrole-2-carboxylic acid (0.370 g, 0.800 mmol) in dichloromethane (20 mL) at 0 °C were added oxalyl chloride (0.80 mL, 1.60 mmol) and a catalytic amount (3.0 μL) of DMF. The reaction mixture was warmed to room temperature, stirred for 2 h and the volatile materials were removed in vacuo. The residue was taken up in methylene chloride (20 mL) and cooled to 0 °C. With stirring under a nitrogen atmosphere, aluminum trichloride [2.80 mL (2.80 mmol) of a 1 M solution in nitrobenzene] and anisole (4.0 mmol) were added to the methylene chloride solution and the resulting reaction mixture was stirred overnight at room temperature. The reaction was quenched by pouring it into ice water (100 mL) and this was followed by extraction with aqueous sodium bicarbonate (3×50 mL), drying the organic phase over anhydrous magnesium sulfate, filtering and concentrating in vacuo to yield 0.597 g of a brown semi-solid. This material was purified by automated flash chromatography on silica using a gradient elution of hexane/ethyl acetate to give 0.330 g (75% yield) of yellow solid (**4**), which exhibited ^{1}H NMR and ^{13}C NMR spectra and TLC behavior identical to the material prepared by methods A and B.

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