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The application of vinylogous iminium salt derivatives to an efficient synthesis of the pyrrole containing alkaloids Rigidin and Rigidin E

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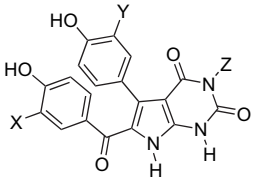
Dedicated to Professor Hiroki Yamanaka on the occasion of his retirement

Abstract—Studies directed on the synthesis of the pyrrole containing marine natural products Rigidin and Rigidin E via vinylogous iminium salts are described. The successful strategy relies on the formation of a 2,4-disubstituted pyrrole from a vinamidinium salt followed by acylation at the 5-position of pyrrole. Halogenation and aminocarbonylation at the 3-position of pyrrole followed by hydrolysis of the ester group at C-2 and subsequent Curtius rearrangement generates the pyrrolopyrimidine skeleton. A final deprotection step completes the synthesis of Rigidin and Rigidin E.

1. Introduction

Marine natural products[1] continue to attract significant attention as a result of their diverse and interesting biological properties. Consequently, synthetic organic chemists continue to develop and explore new synthetic strategies[2] for the efficient and selective preparation of such substances. The pyrrolo[2,3-*d*]pyrimidine skeleton is often encountered in important pharmacologically active substances and more recently it has been observed in a class of marine natural products known as Rigidins[3] (Fig. 1). These alkaloids have been obtained from tunicates obtained near Okinawa and New Guinea and they have been shown to exhibit very significant calmodulin antagonist activity. Edstrom and Wei[4] were the first to report a total synthesis of the parent Rigidin (**1**) and his synthetic sequence is outlined in Scheme 1.



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

Figure 1.

Edstrom route begins with the displacement of a 6-chloro group of a 1,3-dibenzyl protected uracil (**6**) by an *N*-benzyl protected glycine to yield the corresponding aminouracil (**7**). Heating this compound (**7**) with acetic anhydride causes cyclization to the acetoxypyrrolopyrimidine (**8**). Base mediated hydrolysis followed by reaction with triflic anhydride

Keywords: Vinamidinium salt; Pyrrole; Marine natural product; Microwave acceleration.
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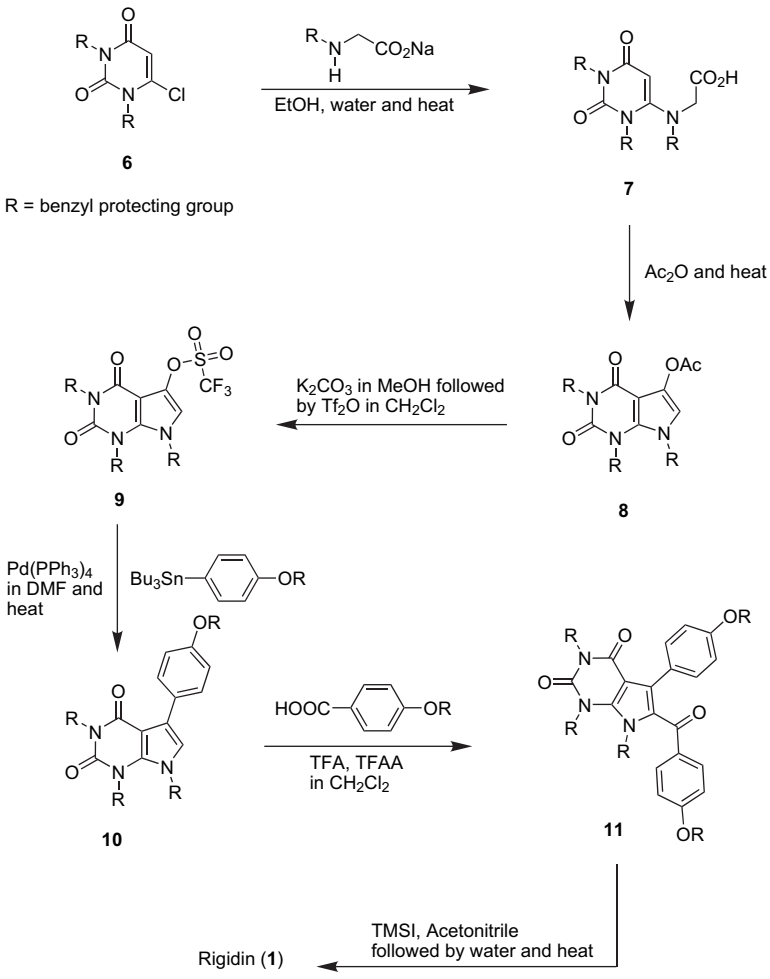


Scheme 1.

produces the triflate derivative (**9**), which then undergoes Stille cross-coupling to give the corresponding arylpyrrolopyrimidine (**10**). Acylation of compound **10** in the presence of trifluoroacetic anhydride/trifluoroacetic acid yields Rigidin analog **11**, which is then deprotected with TMSI to produce Rigidin (**1**) in an overall yield of 26%. Sakamoto and co-workers[5] have reported the only other synthesis of Rigidin (**1**) to date and it is described in Scheme 2.

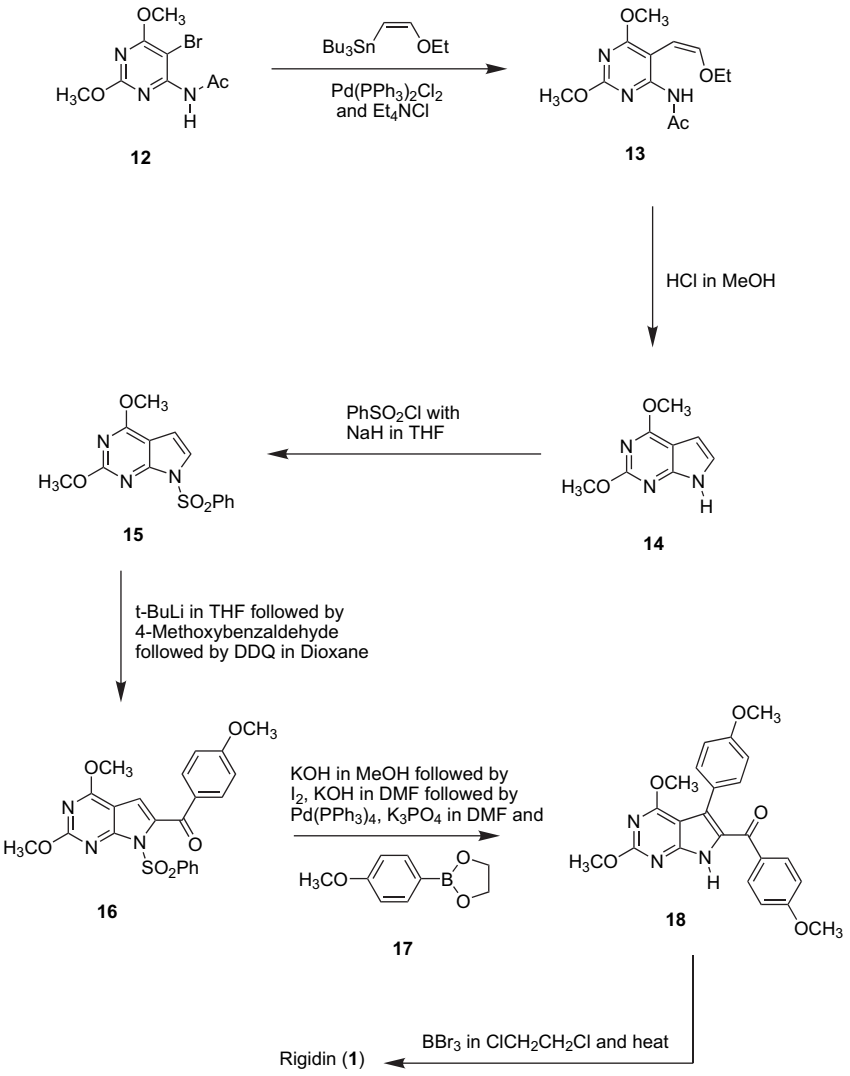
The Sakamoto synthesis begins with a Stille cross-coupling reaction of a highly functionalized bromopyrimidine (**12**) with a vinylstannane, which produces an intermediate (**13**) that is deprotected and cyclized under acidic conditions to yield pyrrolopyrimidine **14**. This pyrrolopyrimidine (**14**) is *N*-protected as the phenylsulfonyl derivative, treated with *t*-butyl lithium at −78 °C, quenched with 4-methoxybenzaldehyde, and oxidized with DDQ in dioxane to yield the corresponding acylated derivative (**16**). Removal of the phenylsulfonyl group from **16** followed by iodination, Suzuki cross-coupling, and deprotection with boron tribromide yielded Rigidin (**1**) in less than 10% overall yield.

2. Results and discussion

In the past several years we have utilized disubstituted β-chloroenals[6] (**19**) as building blocks for the preparation of 2,3,4-trisubstituted pyrroles (**20**), which served as precursors (Scheme 3) for the pyrrole containing natural products Lamellarin O (**21**), Lukianol A (**22**), and Ningalin B (**23**). A key reaction[7] involved the condensation of amino acid esters with the disubstituted β-chloroenals to produce the desired highly functionalized pyrroles.

More recently we have opted for a different strategy, which utilizes 2,4-disubstituted pyrroles[8] as the key building blocks for the preparation of pyrrole containing natural products Polycitone A and B.[9] We now describe our efforts toward the synthesis of Rigidin and Rigidin E as they relate to these two related pathways. Our initial approach was conceived a number of years ago and is depicted in Scheme 4. An aryl keto ester (**24a**) was converted in good yield (95%) to the corresponding vinylogous amide (**25a**) with DMF acetal. The initial studies were carried out with the aryl groups being phenyl. This vinylogous amide (**25a**) was then treated with either the hydrochloride salt or PTSA salt of an α-aminoketone in which case an amine exchange reaction occurred in good yield (92%) to produce the corresponding vinylogous amide (**26**).

This vinylogous amide (**26**) was then subjected to a variety of acid mediated cyclization conditions and these trials are described in Table 1. It was observed that PTSA in EtOH gave reasonable yields (56%) of the desired



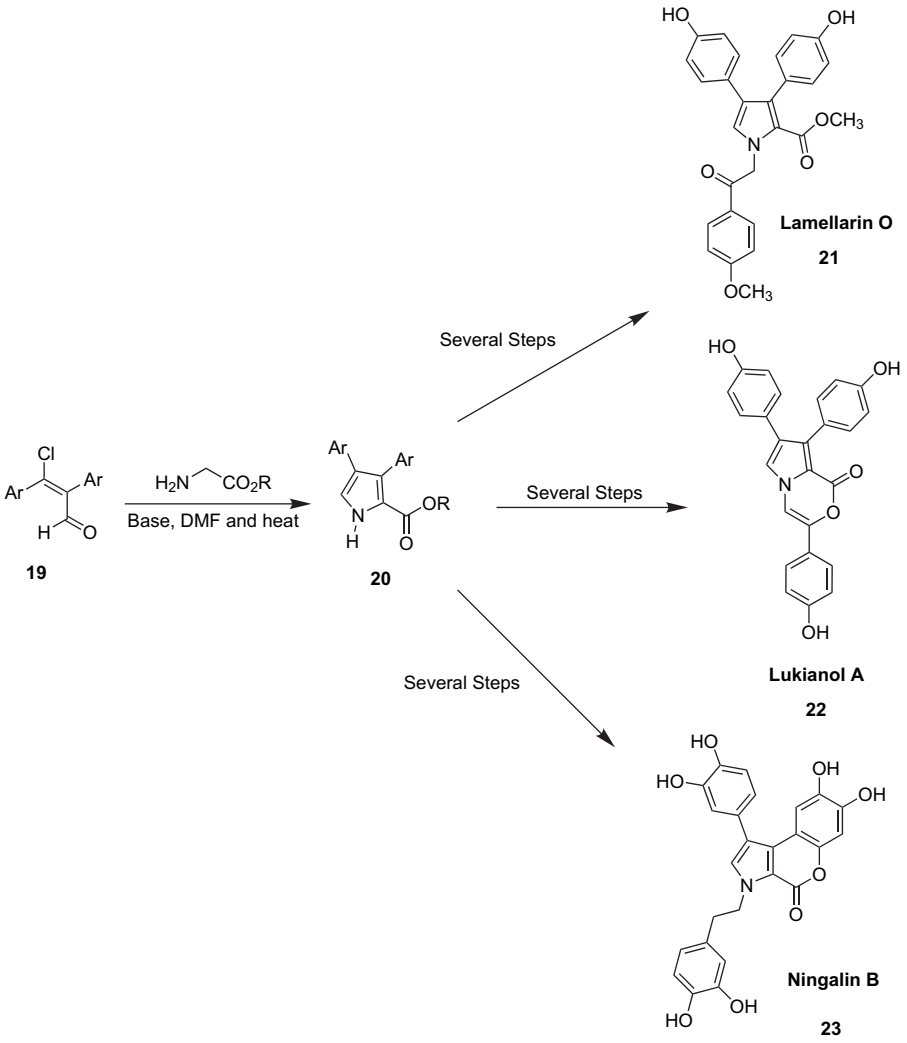
Scheme 2.

2,3,4-trisubstituted pyrrole (**27a**) and that the primary reaction byproduct (keto ester **24a**) resulted from hydrolysis of the vinylogous amide (**26**) starting material. The 2,3,4-trisubstituted pyrrole (**27a**) was then *N*-methylated under basic conditions to produce pyrrole **29**, which was subjected to NMR NOE studies that verified the indicated regiochemistry (see Section 4 for details). The 2,3,4-trisubstituted pyrrole (**27a**) was then nitrated in 35% yield at the 5-position and also brominated in 85% yield at the 5-position. It was anticipated that this tetrasubstituted pyrrole (**28a**) containing the 5-nitro group could then be converted to the pyrrolopyrimidine skeleton by reduction of the nitro group to an amino group followed by reaction with TMS isocyanate.

During the course of these studies, we developed an alternative route to the desired trisubstituted pyrrole (**27b**) and this is presented in Scheme 5.

The vinylogous amide (**25b**) was prepared in the usual manner (79% yield) with DMF acetal and this material was then treated with phosphorous oxychloride in dichloromethane followed by hydrolysis with water/THF to give a β-chloroenal (**30**) as a mixture of *E*- and *Z*-stereoisomers (87% yield) as reported for a similar case in our synthesis[6b] of Ningalin B hexamethyl ether. The crude mixture of isomers (**30**) could be used for the next step involving condensation with the PTSA salt of α-amino-4-methoxyacetophenone to yield the desired 2,3,4-trisubstituted pyrrole (**27b**) in 48% yield. Interestingly, this reaction can be carried out somewhat more efficiently under microwave accelerated conditions to produce the desired material (**27b**) in about the same yield (45%). It should be noted that this condensation reaction is carried out in the absence of external base. When the reaction was repeated using sodium hydride and DMF, a different isomeric trisubstituted pyrrole (**31**) was obtained (Scheme 6) in good yield (86%).

Both compounds **31** and **27b** were subjected to appropriate NOE NMR experiments (see Section 4 for details) to verify the regiochemical assignments. It appears that under neutral conditions an imine is formed by reaction of β-chloroenal (**30**) with glycine in the first step followed by cyclization, whereas under basic conditions the displacement of the chlorine of β-chloroenal (**30**) by the amino group of the aminoketone takes place first followed by ring closure. The ability to tune this regiochemical outcome by the presence or

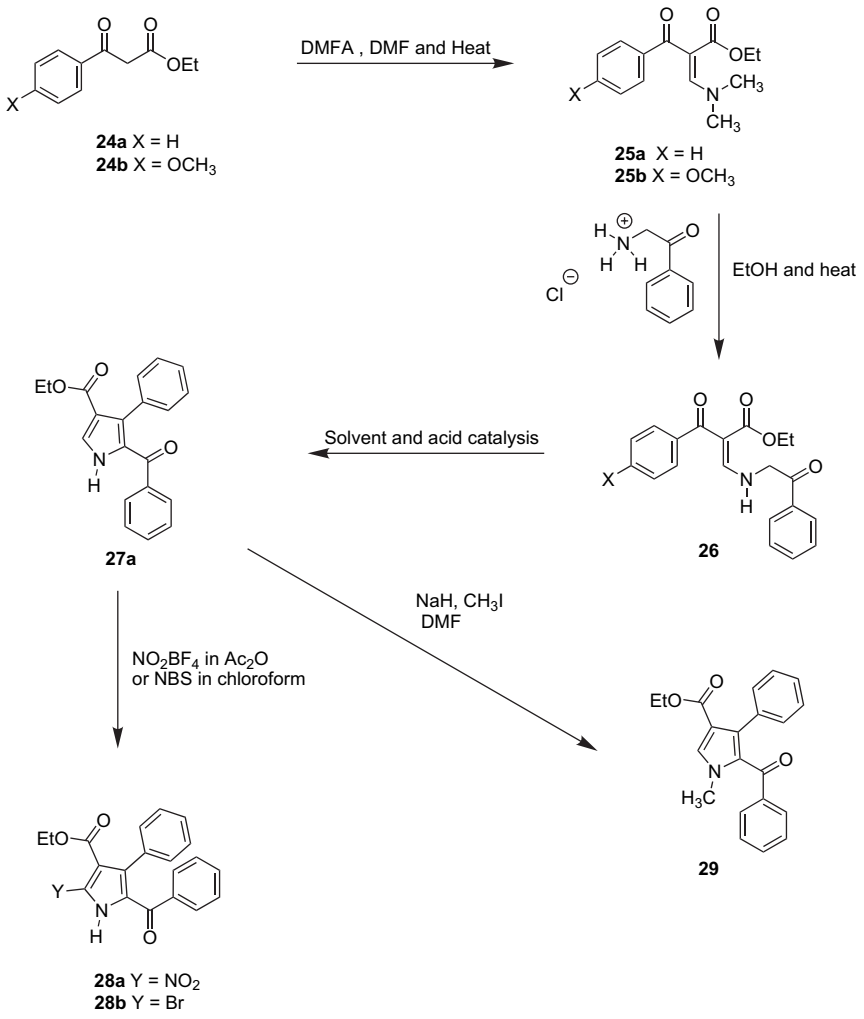


Scheme 3.

absence of strong base is quite remarkable. With the ability to generate a significant amount of the desired 2,3,4-trisubstituted pyrrole (**27b**), we turned our attention to the nitration at the 5-position of the pyrrole. After the examination of many nitration conditions including those described in Scheme 4 for the nitration of the phenyl analog, no 5-nitro analog of compound **27b** could be obtained. NMR analysis of the crude reaction products suggested that preferential nitration of the methoxyphenyl group at C-3 of the pyrrole was occurring as the primary reaction pathway.

More recently, we have successfully utilized a somewhat different strategy[9] to construct an efficient relay synthesis of the marine natural products Polycitone A and B, which is presented in Scheme 7. Pyrrole **37** was the key intermediate prepared by Steglich and co-workers[10] for the synthesis of the Polycitone natural products. Our strategy involved the use of a symmetrical vinamidinium salt (**32**) for the preparation of 2,4-disubstituted pyrrole (**33**), which could be acylated at the 5-position with 4-methoxybenzoic acid to produce 2,3,5-trisubstituted system (**34**). Bromination or iodination of this pyrrole (**34**) produced the 4-halogenated compound (**35a** or **35b**). Subsequent Suzuki cross-coupling of this halopyrrole (**35a** or **35b**) followed by ester hydrolysis and Friedel–Crafts acylation yielded the 'Steglich synthon' (**37**) for Polycitone A and B in very good overall yield (42%) with each of the individual steps being high yield reactions (>75%).

We recently recognized that pyrroles **35a** or **35b** should be well suited for the preparation of Rigidins if a carboxamide group could be introduced at the halogen bearing carbon from which a uracil ring could be constructed. This strategy is represented in Scheme 8. Upon subjecting our tetrasubstituted pyrrole (**35a**) from the Polycitone synthesis to conditions described by Larhed and Wannenberg[11] for microwave accelerated aminocarbonylation reactions, it was possible to produce either an *N*-2,4-dimethoxybenzylamide (80% yield) or an *N*-methyl amide (65% yield) depending upon which amine trapping agent was used. Both amidoesters (**38a** and **38b**) could be efficiently hydrolyzed to the desired carboxylic acids (**39a** in 89% yield and **39b** in 80% yield). The resulting acids (**39a** and **39b**) were subjected to Curtius rearrangement conditions[12] whereby the carboxylic acid groups were converted to an isocyanate followed by trapping with the neighboring amide group to generate the uracil skeleton (**40a** in 69% yield or **40b** in 53% yield). Removal of the *O*-methyl and *N*-benzyl groups from the respective pyrrolopyrimidines (**40a** or **40b**) via boron tribromide produced products, which were spectroscopically identical to Rigidin (**1** in 96% yield) and Rigidin E (**5** in 41% yield)



Scheme 4.

thereby completing a total synthesis of these pyrrole containing marine natural products.

3. Conclusions

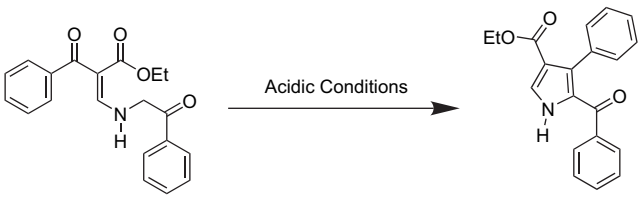
In summary, we have demonstrated a new, 'pyrrole first approach' to an important family of bioactive, pyrrole containing marine natural products. This was accomplished by constructing 2,4-disubstituted pyrroles from vinamidinium salts, electrophilically substituting the 5-position of the pyrrole followed by halogenation and a microwave accelerated, palladium mediated, aminocarbonylation reaction at the 3-position. The resulting amide group, which is proximate to the 2-carboxyl group, is transformed to a uracil via a Curtius rearrangement. A subsequent deprotection step leads to the desired natural products. It is important to note that each pyrrole substituent is introduced independently and can be easily varied so as to accommodate in depth SAR studies for Rigidin analogs. The seven-step syntheses of Rigidin and Rigidin E, from the readily available 2,4-disubstituted pyrrole (**33**) was accomplished in 40 and 10% overall yields, respectively. 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 either on a GE Omega 300 MHz spectrometer, a Bruker 500 MHz spectrometer or a Varian Gemini 200 MHz spectrometer either in $CDCl_3$, DMSO-d_6 or acetone-d_6 solutions. IR spectra were recorded on a Nicolet Avatar 320 FTIR spectrometer with an HATR attachment or a Perkin–Elmer 1600 series FTIR spectrometer. 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 electrospray mass spectrometer. 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 or SP-1 instrument, which had been equipped

Table 1. Acid mediated cyclization results



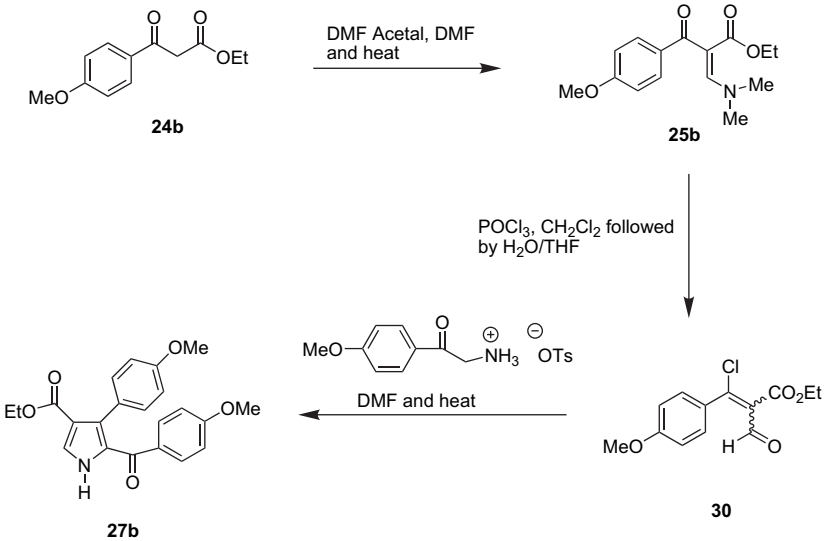
26 **27a**

Trial	Acid	Solvent	Yield (%)	Determination
1	Acetic acid	Acetic acid	48	Isolated yield
2	PTSA	$CHCl_3$	43	Isolated yield
3	PTSA	EtOH	56	Isolated yield
4	PTSA	CH_3CN	50	Isolated yield
5	PTSA	Dioxane	46	Isolated yield
6	PTSA/TFA	TFAA/$CHCl_3$	42	Isolated yield
7	$POCl_3$	$CHCl_3$	39	Isolated yield
8	Amberlyst	$CHCl_3$	Trace	NMR, TLC
9	$ZnCl_2$	$CHCl_3$	Trace	NMR, TLC
10	PPA	$CHCl_3$	Trace	NMR, TLC
11	TFA	TFAA/$CHCl_3$	Trace	NMR, TLC
12	TFA	TFAA/EtOH	Trace	NMR, TLC
13	TFA	EtOH	Trace	NMR, TLC
14	Nafion	$CHCl_3$	0	NMR, TLC
15	$AlCl_3$	$CHCl_3$	0	NMR, TLC
16	$MeO_3{}^+BF_4{}^-$	$CHCl_3$	0	NMR, TLC
17	BF_3Et_2O	$CHCl_3$	0	NMR, TLC

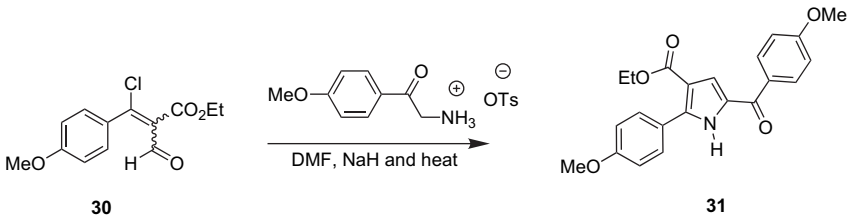
with a silica cartridge, and ethyl acetate/hexane was used as the eluant. TLC analyses were conducted on silica plates with hexane/ethyl acetate as the eluant. Vinamidinium salts utilized for pyrrole formation were prepared according to standard procedures.[7] All purified reaction products gave TLC results, GC–MS spectra, flash chromatograms, and ^{13}C NMR spectra consistent with a sample purity of >95%.

4.1.1. 2-Benzoyl-3-dimethylaminoacrylic acid ethyl ester (25a). A 250-mL, three-neck, round-bottom flask was equipped with a stir bar and a reflux condenser. Into the flask were placed 8.00 g (0.0416 mol) of ethyl benzoyl acetate, 14.70 g (0.167 mol) of *N*,*N*-dimethylformamide dimethyl acetal (DMFA), and 150 mL of DMF. The reaction mixture was heated at 75–80 °C overnight. The DMF and unreacted DMFA were removed in vacuo, yielding a yellow oil (9.76 g, 95% yield). An analytical sample was obtained by radial chromatography using an 80:20 mixture of hexane/ethyl acetate as eluent. After removal of solvent, a light yellow oil was obtained, which exhibited the following physical properties: bp 30 °C at 0.1 mm of Hg; ^1H NMR ($CDCl_3$) δ 7.60–7.80 (m, 3H), 7.30–7.50 (m, 3H), 3.95 (q, J=7.0 Hz, 2H), 2.60–3.20 (br s, 6H), and 0.87 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 15.9, 32.9, 61.7, 129.9, 130.4, 130.5, 130.8, 133.7, 157.9, 170.8, and 196.2; IR (CCl_4) 1740 and 1688 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{14}H_{17}NO_3$ 247.1208, found 247.1204.

4.1.2. 2-Benzoyl-3-(2-oxo-2-phenylethylamino)acrylic acid ethyl ester (26). A one-neck, 500-mL round-bottom flask was equipped with a stir bar and a reflux condenser. Into the flask were placed 5.00 g (20.2 mmol) of 2-benzoyl-3-dimethylaminoacrylic acid ethyl ester (**25a**), 3.82 g (22.2 mmol) of α-aminoacetophenone hydrochloride, and 200 mL of ethanol. The mixture was refluxed overnight. The solvent was removed in vacuo and the residue was taken up in 100 mL of chloroform and washed with 2×50 mL of water. The chloroform phase was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo, yielding 6.53 g (96% yield) of a yellow solid. The product was purified by dissolving it in 50 mL of ethyl acetate and passing through a short plug of silica gel, followed by recrystallization with an 80:20 mixture of hexane/ethyl acetate, yielding 6.26 g (92% yield) of a white solid. This material exhibited the following physical properties: mp 148–149 °C; ^1H NMR ($CDCl_3$) δ 10.75 (br s, 0.5H), 9.50 (br s, 0.5H), 7.86–8.20 (m, 3H), 7.31–7.70 (m, 8H), 4.88–4.91 (m, 2H), 3.96–4.1 (m, 2H), and 0.94 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 15.7, 15.8, 56.3, 56.6, 61.6, 61.7, 103.4, 103.7, 129.2, 129.5, 129.6, 129.9, 130.2, 131.1, 131.9, 132.6, 136.0, 136.1, 136.3, 143.6, 144.4, 161.0, 162.0, 169.9, 170.7, 194.2, 194.5, 196.2, and 198.1; IR (CCl_4) 1678 and



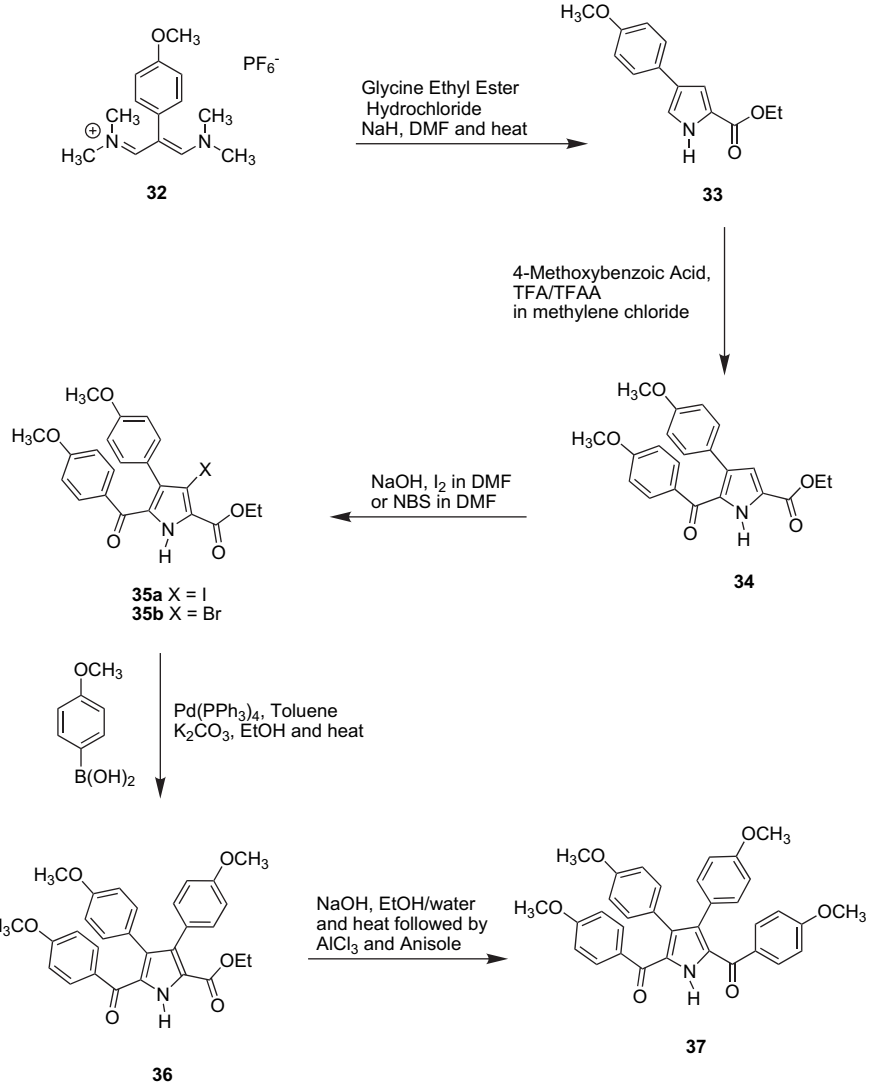
Scheme 5.



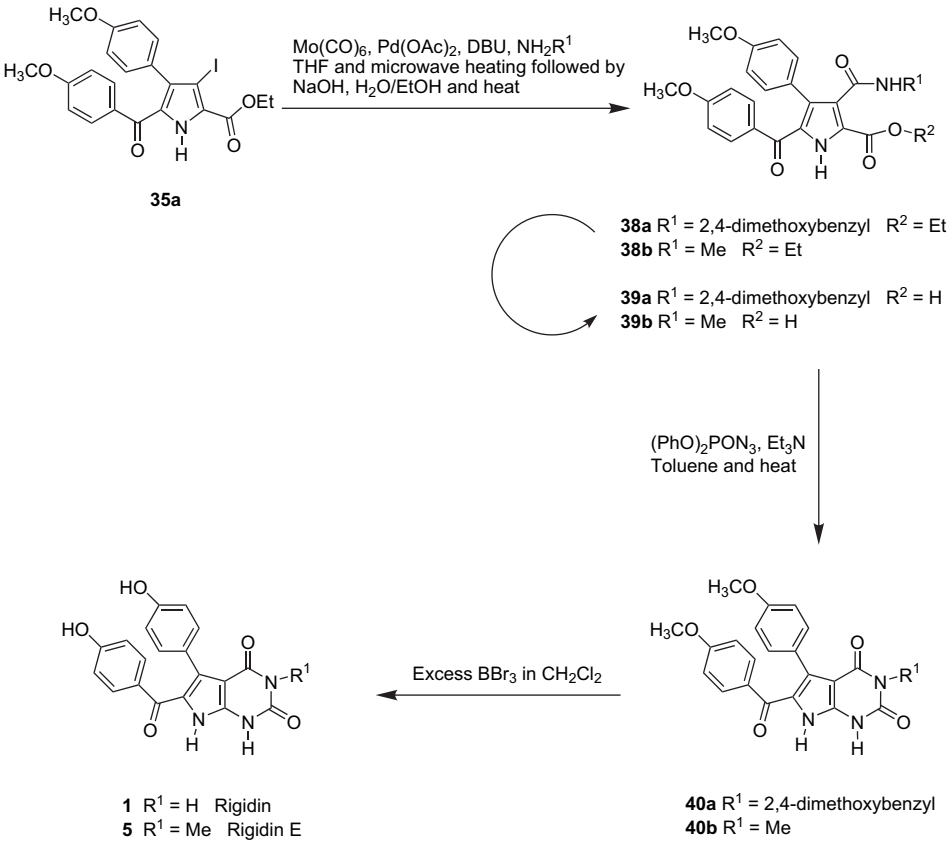
Scheme 6.

1620 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{20}H_{19}NO$ 337.1314, found 337.1292.

4.1.3. 2-Benzoyl-3-phenylpyrrole-4-carboxylic acid ethyl ester (27a). Into a one-neck, 200-mL round-bottom flask were placed 0.800 g (2.37 mmol) of 2-benzoyl-3-(2-oxo-2-phenylethylamino)acrylic acid ethyl ester (**26**), 0.368 g (2.37 mmol) of phosphorous oxychloride, and 80 mL of dry chloroform. The reaction mixture was refluxed for 1 h. The solvent was removed in vacuo and the residue was partitioned between chloroform (50 mL) and saturated aqueous sodium bicarbonate solution (50 mL). The chloroform phase was dried over anhydrous magnesium sulfate, filtered, and concentrated, yielding 0.730 g of a brown semi-solid. The crude material was dissolved in ethyl acetate (30 mL) and eluted through a short plug of silica gel. The product was further purified by radial chromatography using an 80:20 mixture of hexane/ethyl acetate as eluent. A 0.318 g sample (42% yield) of a light yellow solid was obtained, which exhibited the following properties: mp 141–142 °C; ^{1}H NMR (DMSO-d_6) δ 12.58 (br s, 1H), 7.73 (d, J=3.5 Hz, 1H), 7.2–7.40 (m, 3H), 7.00–7.18 (m, 7H), 4.06 (q, J=7.1 Hz, 2H), and 1.11 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 16.2, 62.0, 118.9, 129.0, 129.1, 129.4, 130.8, 130.9,



Scheme 7.



Scheme 8.

131.7, 133.1, 133.4, 135.0, 135.4, 139.1, 165.9, and 190.0; IR (CCl_4) 3246, 1718, and 1610 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{20}H_{17}NO_3$ 319.1208, found 319.1194.

4.1.4. 2-Benzoyl-1-methyl-3-phenylpyrrole-4-carboxylic acid ethyl ester (29). A 100-mL, three-neck, round-bottom flask was equipped with a magnetic stir bar and placed under a nitrogen atmosphere. Into the flask was placed 0.291 g (7.27 mmol) of a 60% mineral oil dispersion of sodium hydride. The dispersion was washed with hexane and the hexane was removed via cannula. To the flask were added 40 mL of dry DMF, 0.400 g (1.25 mmol) of 2-benzoyl-3-phenylpyrrole-4-carboxylic acid ethyl ester (**27a**), and 2.890 g (20.4 mmol) of iodomethane. The mixture was stirred overnight at room temperature. The solvent was removed by Kugelrohr distillation and the residue was taken up in 50 mL of chloroform and washed with 2×30 mL of water. The chloroform phase was dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was dissolved in 50 mL of ethyl acetate and passed through a short plug of silica gel. After removal of solvent, 0.409 g of a light yellow solid (98% yield) was obtained, which exhibited the following properties: mp 146–147 °C; ^{1}H NMR (DMSO-d_6) δ 7.91 (s, 1H), 7.42 (d, J=7.0 Hz, 2H), 7.30 (t, J=7.2 Hz, 1H), 6.96–7.18 (m, 7H), 4.08 (q, J=7.1 Hz, 2H), 3.85 (s, 3H), and 1.13 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 16.2, 39.3, 61.8, 115.4, 128.9, 129.5, 131.6, 132.2, 133.1, 133.9, 135.3, 135.7, 140.1, 165.8, and 191.0; IR (CCl_4) 1706 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{21}H_{19}NO_3$ 333.1365, found 333.1353. NOEDIF ($CDCl_3$): irradiating at 3.96 ppm (*N*-methyl hydrogens), an NOE was observed at 7.56 ppm (α-pyrrole hydrogen); irradiating at 7.56 ppm (α-pyrrole hydrogen), an NOE was observed at 3.96 ppm (*N*-methyl hydrogens).

4.1.5. 2-Benzoyl-5-bromo-3-phenylpyrrole-4-carboxylic acid ethyl ester (28b). A one-neck, 250-mL, round-bottom flask was equipped with a stir bar and a reflux condenser. Into the flask were placed 0.600 g (1.88 mmol) of 2-benzoyl-3-phenylpyrrole-4-carboxylic acid ethyl ester (**27a**), 0.336 g (1.88 mmol) of *N*-bromosuccinimide, and 120 mL of dry chloroform. The reaction mixture was refluxed for 6 h. The solvent was removed in vacuo and the residue was partitioned between chloroform (60 mL) and saturated aqueous sodium bicarbonate (30 mL) solution. The chloroform phase was dried over anhydrous magnesium sulfate and the solvent was removed in vacuo yielding 0.690 g (92% yield) of a solid. The crude material was dissolved in ethyl acetate and eluted through a short column of silica gel. The chromatographed material was further purified by recrystallization with a mixture of 80:20 hexane/ethyl acetate yielding a bright yellow solid (0.64 g, 85% yield), which exhibited the following properties: mp 155–156 °C; ^{1}H NMR (DMSO-d_6) δ 7.37 (d, J=7.9 Hz, 2H), 7.20–7.32 (m, 1H), 6.90–7.19 (m, 7H), 4.01 (q, J=7.0 Hz, 2H), and 0.96 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 15.8, 62.4, 114.5, 118.4, 129.1, 129.3, 129.4, 130.8, 131.8, 132.8, 133.5, 135.0, 136.0, 138.6, 165.0, and 188.8; IR (CCl_4) 3210, 1717, and 1612 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{20}H_{17}BrNO_3$ 397.0313, found 397.0301.

4.1.6. 2-Benzoyl-5-nitro-3-phenylpyrrole-4-carboxylic acid ethyl ester (28a). A 100 mL, three-neck, round-bottom flask was equipped with a magnetic stir bar, chilled to −78 °C in an isopropanol/dry ice slurry, and placed under a nitrogen atmosphere. Into the flask were placed 0.200 g (0.630 mmol) of 2-benzoyl-3-phenylpyrrole-4-carboxylic acid ethyl ester (**27a**) and 5 mL of acetic anhydride. Subsequently, 0.443 g (3.34 mmol) of nitronium tetrafluoroborate was dissolved in 15 mL of cold acetic anhydride solution and added dropwise to the reaction flask through an addition funnel. The mixture was stirred for 2 h at −78 °C, followed by room temperature stirring for 4 h. The reaction mixture was then diluted with water with cooling. The resulting reaction mixture was stirred for 2 h at room temperature and was then extracted with chloroform (3×30 mL). The combined chloroform extracts were washed with saturated aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was dissolved in ethyl acetate and eluted through a short plug of silica gel. The product was further purified by radial chromatography using a 70:30 mixture of hexane/ethyl acetate as eluent. After removal of solvent from the chromatography fractions, 0.090 g (35% yield) of a light yellow solid was obtained, which exhibited the following properties: mp 132–133 °C; ^{1}H NMR ($CDCl_3$) δ 12.58 (br s, 1H), 7.47 (dd, J=8.0, 1.1 Hz, 2H), 7.22–7.35 (m, 1H), 7.00–7.18 (m, 7H), 4.30 (q, J=7.1 Hz, 2H), and 1.21 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 15.8, 64.3, 119.6, 129.9, 130.1, 130.2, 131.2, 131.5, 132.0, 132.2, 132.8, 135.0, 137.3, 137.5, 164.5, and 189.1; IR (CCl_4) 3410, 1739, and 1638 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{20}H_{16}N_2O_5$ 364.1059, found 364.1070.

4.1.7. 2-Benzoyl-3-phenylpyrrole-4-carboxylic acid ethyl ester (acetic acid catalysis) (27a). Into a one-neck, 50 mL, round-bottom flask were placed 0.200 g (0.594 mmol) of 2-benzoyl-3-(2-oxo-2-phenylethylamino)acrylic acid ethyl ester (**26**) and 20 mL of acetic acid. The reaction mixture was refluxed overnight and then acetic acid was removed in vacuo. The residue was partitioned between chloroform and a saturated aqueous sodium bicarbonate solution and the chloroform phase was dried over anhydrous magnesium sulfate, filtered, and concentrated. The crude material was dissolved in ethyl acetate and purified by radial chromatography using hexane/ethyl acetate yielding 0.091 g (48% yield) of a light yellow solid (48% yield), which exhibited identical physical properties to the 2-benzoyl-3-phenylpyrrole-4-carboxylic acid ethyl ester reported in Section 4.1.3.

4.1.8. 2-Benzoyl-3-phenylpyrrole-4-carboxylic acid ethyl ester (PTSA catalysis) (27a). Into a one-neck, 50 mL, round-bottom flask were placed 0.200 g (0.594 mmol) of 2-benzoyl-3-(2-oxo-2-phenylethylamino)acrylic acid ethyl ester (**26**), 0.110 g (0.653 mmol) of PTSA, and 20 mL of anhydrous ethanol. The reaction mixture was refluxed overnight and the solvent was removed in vacuo. The residue was then partitioned between water and chloroform. The chloroform layer was dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was dissolved in ethyl acetate and purified by radial chromatography using hexane/ethyl acetate yielding a light yellow solid (0.106 g, 56% yield), which exhibited identical physical properties to the 2-benzoyl-3-phenylpyrrole-4-carboxylic acid ethyl ester reported in Section 4.1.3.

4.1.9. 2-(4-Methoxybenzoyl)-3-dimethylaminoacrylic acid ethyl ester (25b). A 100 mL, one-neck, round-bottom flask was charged with 30 mL of DMF, 3-oxo-3-(4-methoxyphenyl)propionic acid ethyl ester (**24b**) (2.22 g, 0.0100 mol), and *N*,*N*-dimethylformamide dimethyl acetal (4.77 g, 0.0400 mol). The reaction mixture was heated at reflux with stirring for 24 h and subsequently cooled to room temperature. The reaction mixture was diluted with 100 mL of ethyl acetate and 50 mL of water. The aqueous layer was extracted with additional ethyl acetate (3×50 mL) and the combined ethyl acetate phases were washed with brine (3×20 mL) and dried over anhydrous magnesium sulfate. After removal of the drying agent by vacuum filtration, the filtrate was concentrated in vacuo leaving a dark oil (2.18 g, 79% yield), which could be used without further purification. An analytical sample was prepared by taking 1.00 g of the reaction product and subjecting it to chromatographic separation on a Biotage Horizon flash chromatography system with a gradient elution of ethyl acetate/hexanes. A yellow oil was obtained, which exhibited the following properties: bp 79–80 °C at 0.1 mm of Hg; ^{1}H NMR ($CDCl_3$) δ 7.60–7.85 (m, 3H), 6.88 (d, J=8.8 Hz, 2H), 3.98 (q, J=7.0 Hz, 2H), 3.84 (s, 3H), 2.91 (br s, 6H), and 0.96 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 14.1, 55.4, 59.6, 99.7, 113.2, 131.3, 133.7, 154.7, 162.7, 168.7, and 193.1; IR (neat) 1683 and 1601 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{15}H_{19}NO_4$ 278.1392, found 278.1440.

4.1.10. 3-Chloro-2-formyl-3-(4-methoxyphenyl)acrylic acid ethyl ester (30). A round-bottom flask was charged with 2-(4-methoxybenzoyl)-3-dimethylaminoacrylic acid ethyl ester (**25b**) (2.00 g, 7.22 mmol) dissolved in 50 mL of dry methylene chloride. To the stirred solution was added phosphorous oxychloride (1.68 g, 10.9 mmol) and the resulting mixture was heated at reflux for 1 h. The reaction mixture was cooled to room temperature and the solvent was removed in vacuo. The residue was then taken up in 50 mL of a 50:50 mixture of water/THF and stirred for 4 h in a round-bottom flask equipped with a stopper. The reaction mixture was subsequently diluted with 100 mL of water and extracted with 3×50 mL of ethyl acetate. The combined organic layers were then washed with brine (2×50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo yielding a dark viscous oil (1.68 g, 87% yield). An analytical sample was prepared by taking a 1.30 g sample of the crude product and subjecting it to flash chromatography using an ethyl acetate/hexane gradient elution in which case 0.75 g (50% yield) of a yellow oil was obtained. This oil exhibited the following properties: (major isomer) bp 107–109 °C at 0.3 mm of Hg; ^{1}H NMR ($CDCl_3$) δ 9.34 (s, 1H), 7.46 (d, J=9.0 Hz, 2H), 6.98 (d, J=9.0 Hz, 2H), 4.35 (q, J=7.0 Hz, 2H), 3.89 (s, 3H), and 1.38 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 14.2, 55.7, 62.2, 114.4, 126.3, 130.4, 132.2, 155.5, 162.9, 164.5, and 186.7; IR (neat) 1730, 1670, and 1600 cm^{-1}; HRMS (ES, M+H) *m/z* calcd for $C_{13}H_{14}O_4Cl$ 269.0581, found 269.0591.

4.1.11. 2-(4-Methoxybenzoyl)-3-(4-methoxyphenyl)pyrrole-4-carboxylic acid ethyl ester (27b). Method A: a round-bottom flask was equipped with a reflux condenser and magnetic stir bar and was placed under a nitrogen atmosphere. The flask was charged with 200 mL of DMF and

5.41 g (20.18 mmol) of 3-chloro-2-formyl-3-(4-methoxyphenyl)acrylic acid ethyl ester (**30**). 2′-Amino-4-methoxyacteophenone *p*-toluenesulfonic acid salt[9] (6.90 g, 20.57 mmol) was then added and the reaction mixture was stirred at room temperature for 30 min and then heated at reflux for 20 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. The crude residue was chromatographed on a silica gel column using ethyl acetate/hexane gradient elution in which case 3.64 g (48% yield) of a tan solid was obtained. This solid exhibited the following physical properties: mp 151–152 °C; ^{1}H NMR ($CDCl_3$) δ 10.10 (br s, 1H), 7.72 (d, J=3.3 Hz, 1H), 7.37 (d, J=9.0 Hz, 2H), 7.03 (d, J=9.0 Hz, 2H), 6.61 (d, J=9.0 Hz, 2H), 6.52 (d, J=9.0 Hz, 2H), 4.19 (q, J=7.0 Hz, 2H), 3.72 (s, 3H), 3.70 (s, 3H), and 1.21 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 14.4, 55.3, 55.4, 56.0, 112.9, 113.0, 116.7, 125.8, 128.7, 129.7, 130.1, 131.7, 132.6, 132.7, 159.0, 162.6, 164.3, and 187.1; NOEDIF ($CDCl_3$): irradiating at 7.37 ppm (*o*-benzoyl hydrogen), NOEs were observed at 10.10 ppm (pyrrole N–H) and 7.03 ppm (*o*-methoxyphenyl hydrogen); IR (KBr) 3280 and 1680 cm^{-1}; HRMS (ES, M+H) *m*/*z* calcd for $C_{22}H_{22}NO_5$ 380.1498, found 380.1517.

Method B: a 7 mL microwave reaction vessel equipped with a stir bar was charged with 6 mL of DMF, 0.220 g (0.821 mmol) of 3-chloro-2-formyl-3-(4-methoxyphenyl)-acrylic acid ethyl ester (**30**), and 0.331 g (0.982 mmol) of 2′-amino-4-methoxyacteophenone *p*-toluenesulfonic acid salt.[9] The reaction vessel was sealed (Crymper-seal) and heated under 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, concentrated in vacuo, and subjected to flash chromatography using an ethyl acetate/hexane gradient yielding 0.140 g (45% yield) of a tan solid, which was identical by NMR and TLC comparison with the material prepared by method A.

4.1.12. 5-(4-Methoxybenzoyl)-2-(4-methoxyphenyl)pyrrole-3-carboxylic acid ethyl ester (31). A three-neck round-bottom flask was placed under a nitrogen atmosphere and sodium hydride (0.47 g, 1.96 mmol) mineral oil dispersion was placed in the flask along with 80 mL of dry DMF. A mixture of 3-chloro-2-formyl-3-(4-methoxyphenyl)acrylic acid ethyl ester (**30**) (0.966 g, 3.60 mmol) and 2′-amino-4-methoxyacteophenone *p*-toluenesulfonic acid salt (1.286 g, 3.82 mmol) in 80 mL of dry DMF was prepared in a second flask and this mixture was stirred for 30 min. The 3-chloro-2-formyl-3-(4-methoxyphenyl)acrylic acid ethyl ester (0.966 g, 3.60 mmol)/2′-amino-4-methoxyacteophenone *p*-toluenesulfonic acid salt mixture in DMF was added dropwise to the reaction vessel containing sodium hydride/DMF and the resulting mixture was refluxed for 12 h. After cooling to room temperature, the reaction mixture was quenched with 5 mL of methanol and concentrated in vacuo. The residue was partitioned between water (50 mL) and methylene chloride (3×40 mL) and the combined methylene chloride extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The resulting residue was dissolved in a minimum amount of ethyl acetate and placed on a short plug of silica gel. The plug was washed with several portions of ethyl acetate and the combined washings were concentrated in vacuo to give a tan solid (1.174 g, 86% yield), which exhibited the following properties: mp 208–209 °C; ^{1}H NMR ($CDCl_3$) δ 9.66 (br s, 1H), 7.95 (d, J=8.0 Hz, 2H), 7.63 (d, J=8.0 Hz, 2H), 7.37 (d, J=2.6 Hz, 1H), 7.01 (d, J=8.0 Hz, 2H), 6.97 (d, J=8.0 Hz, 2H), 4.25 (q, J=8.0 Hz, 2H), 3.91 (s, 3H), 3.86 (s, 3H), and 1.28 (t, J=8.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 14.3, 55.3, 55.5, 60.0, 113.6, 113.7, 114.1, 121.5, 123.0, 129.7, 130.2, 130.7, 131.3, 142.2, 160.4, 163.1, 164.2, and 183.4; NOEDIF ($CDCl_3$): irradiating at 7.87 ppm (*o*-benzoyl hydrogen), NOEs were observed at 9.66 ppm (pyrrole N–H) and 7.37 ppm (pyrrole C-4 hydrogen); IR (Nujol) 3250 and 1705 cm^{-1}; HRMS (ES, M+H) *m*/*z* calcd for $C_{22}H_{22}NO_5$ 380.1498, found 380.1499.

4.1.13. 3-(2,4-Dimethoxybenzylcarbamoyl)-5-(4-methoxybenzoyl)-4-(4-methoxyphenyl)pyrrole-2-carboxylic acid ethyl ester (38a). Into a 7 mL microwave reaction vessel, which had been equipped with a magnetic stir bar, was placed molybdenum hexacarbonyl (0.261 g, 0.99 mmol), palladium(II) acetate (0.066 g, 0.099 mmol), 3-iodo-5-(4-methoxybenzoyl)-4-(4-methoxyphenyl)pyrrole-2-carboxylic acid ethyl ester[9] (**35a**) (0.500 g, 0.99 mmol), and tetrahydrofuran (6 mL). Then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.445 mL, 2.97 mmol) and 2,4-dimethoxybenzylamine (0.446 mL, 2.97 mmol) were quickly added and the vial was capped. The reaction mixture was stirred for 5 min and subjected to microwave irradiation for 40 min at 100 °C (15–20 W). The reaction mixture was filtered through a plug of sand, silica, and Celite and then the plug was washed with tetrahydrofuran (50 mL). The filtrate was concentrated in vacuo to give a viscous red oil. The residue was adsorbed onto silica gel and purified by flash chromatography (gradient elution with ethyl acetate/hexanes) to provide 0.456 g (80% yield) of a solid, which exhibited the following properties: mp 162–164 °C; ^{1}H NMR ($CDCl_3$) δ 9.75 (br s, 1H), 7.45 (d, J=9.0 Hz, 2H), 7.04 (d, J=8.0 Hz, 1H), 6.97 (d, J=9.0 Hz, 2H), 6.56 (d, J=9.0 Hz, 2H), 6.50 (d, J=9.0 Hz, 2H), 6.35 (d of d, J=2.5, 8.0 Hz, 1H), 6.31 (d, J=2.5 Hz, 1H), 4.41 (d, J=6.0 Hz, 2H), 4.32 (q, J=7.0 Hz, 2H), 3.79 (s, 3H), 3.73 (s, 3H), 3.70 (s, 3H), 3.64 (s, 3H), and 1.32 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 14.2, 38.9, 55.0, 55.1, 55.2, 55.3, 61.5, 98.2, 103.8, 113.1, 113.3, 118.6, 122.4, 124.8, 125.9, 129.1, 129.5, 129.6, 130.2, 131.2, 131.9, 158.4, 158.8, 159.8, 160.3, 162.9, 164.1, and 186.1; IR (neat) 3346, 3276, 1695, and 1667 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{32}H_{32}N_2O_8$ 572.2158, found 572.2167.

4.1.14. 3-(2,4-Dimethoxybenzylcarbamoyl)-5-(4-methoxybenzoyl)-4-(4-methoxyphenyl)pyrrole-2-carboxylic acid (39a). A one-necked, round-bottom flask was equipped with a magnetic stir bar and a reflux condenser. Into the flask were placed 3-(2,4-dimethoxybenzylcarbamoyl)-5-(4-methoxybenzoyl)-4-(4-methoxyphenyl)pyrrole-2-carboxylic acid ethyl ester (**38a**) (0.521 g, 0.900 mmol), potassium hydroxide (0.173 g, 3.00 mmol), and 60 mL of a 50:50 mixture of ethanol/water. The mixture was refluxed for 24 h, cooled to room temperature, and then placed in an ice/water bath. Hydrochloric acid (6 M) was added dropwise to a pH of 2 and

a few drops of water were added to induce crystallization. The precipitate was collected by suction filtration and dried in vacuo (Kugelrohr) to yield a fine white powder (0.436 g, 89% yield), which exhibited the following properties: mp 157–158 °C; ^{1}H NMR ($CDCl_3$) δ 7.56 (d, J=9.0 Hz, 2H), 7.16 (d, J=9.0 Hz, 2H), 7.04 (d, J=8.0 Hz, 1H), 6.82 (d, J=9.0 Hz, 2H), 6.75 (d, J=9.0 Hz, 2H), 6.46 (d, J=2.5 Hz, 1H), 6.45 (dd, J=2.5, 8.0 Hz, 1H), 4.30 (d, J=5.0 Hz, 2H), 3.82 (s, 3H), 3.81 (s, 3H), 3.76 (s, 3H), and 3.67 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 39.2, 54.6, 54.7, 54.9, 55.0, 98.1, 104.3, 113.3, 114.1, 116.6, 123.6, 127.8, 130.0, 130.5, 131.6, 132.1, 158.5, 159.7, 159.9, 161.3, 163.3, 165.5, and 185.5; IR (neat) 3403, 3244, 1707, and 1621 cm^{-1}; HRMS (EI) m/z calcd for $C_{30}H_{28}N_2O_8$ 544.1846, found 544.1846.

4.1.15. 3-(2,4-Dimethoxybenzyl)-6-(4-methoxybenzoyl)-5-(4-methoxyphenyl)-1,7-dihydropyrrolo[2,3-*d*]pyrimidine-2,4-dione (40a). Into an argon blanketed, three-neck, round-bottom flask equipped with a thermometer, condenser, septa, and magnetic stir bar were placed 3-(2,4-dimethoxybenzylcarbamoyl)-5-(4-methoxybenzoyl)-4-(4-methoxyphenyl)pyrrole-2-carboxylic acid (**39a**) (0.355 g, 0.65 mmol) and toluene (12 mL). Triethylamine (0.14 mL, 1.00 mmol) was added dropwise followed by diphenylphosphorylazide (0.22 mL, 1.00 mmol). The reaction mixture was then refluxed for 9 h and then stirred at room temperature for 16 h. The solvent was removed in vacuo and the residue was subjected to flash chromatography (gradient elution with EtOAc/hexanes) to provide a light yellow solid (0.242 g, 69% yield), which exhibited the following properties: mp 196–200 °C; ^{1}H NMR ($CDCl_3$) δ 10.43 (br s, 1H), 10.10 (br s, 1H), 7.41 (d, J=9.0 Hz, 2H), 7.15 (d, J=9.0 Hz, 2H), 6.96 (d, J=8.0 Hz, 1H), 6.59 (d, J=9.0 Hz, 2H), 6.55 (d, J=9.0 Hz, 2H), 6.46 (d, J=2.4 Hz, 1H), 6.39 (d of d, J=2.4, 8.0 Hz, 1H), 5.18 (s, 2H), 3.84 (s, 3H), 3.74 (s, 6H), and 3.70 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 38.9, 55.1, 55.2, 55.3, 55.7, 98.7, 99.3, 104.3, 112.8, 112.9, 117.6, 123.8, 125.5, 127.3, 129.5, 130.9, 131.5, 132.6, 139.5, 151.4, 157.9, 159.1, 159.6, 159.9, 162.4, and 186.5; IR (neat) 1712 and 1663 cm^{-1}; HRMS (EI) m/z calcd for $C_{30}H_{27}N_3O_7$ 541.1849, found 541.1836.

4.1.16. Rigidin (1). A solution of 3-(2,4-dimethoxybenzyl)-6-(4-methoxybenzoyl)-5-(4-methoxyphenyl)-1,7-dihydropyrrolo[2,3-*d*]pyrimidine-2,4-dione (**40a**) (0.190 g, 0.350 mmol) in methylene chloride (25 mL) was prepared in a three-neck 50 mL round-bottom flask equipped with a condenser, thermometer, septa, and magnetic stir bar. The solution was placed under an argon atmosphere and cooled to −78 °C in an acetone/dry ice bath. A 1 M solution of boron tribromide in methylene chloride (7 mL, 7.00 mmol) was added to the reaction mixture slowly over 5 min and the reaction set-up was protected from the light. The reaction mixture was allowed to slowly equilibrate to room temperature over 8 h and then stirred for 60 h. After cooling the reaction mixture to −78 °C an additional amount of boron tribromide solution (2.5 mL) was added slowly over 3 min and the reaction mixture was allowed to equilibrate to room temperature and stirred for 20 h. The reaction mixture was cooled in an ice/water bath and quenched with slow addition of methanol to a total of 40 mL. This mixture was stirred in an ice bath for 5 h and 20 mL of water was added followed by the careful addition of 5% aqueous NaOH (30 mL) to a pH of 6. This solution was allowed to warm to room temperature and stirred for 16 h. The solvents were removed in vacuo and the resulting aqueous mixture was transferred to a separatory funnel and extracted with ethyl acetate (3×50 mL). The combined organic extracts were filtered through a cotton plug and concentrated in vacuo followed by drying in vacuo (Kugelrohr) to give a reddish brown solid (0.157 g). HPLC analysis of the crude product on a C-18 reverse phase column with a methanol/water gradient indicated that the material was 77.8% Rigidin (96% in situ yield). A 50 mg sample of the crude product was subjected to flash chromatography on a C-18 reverse phase column with a methanol/water gradient and this resulted in 0.030 g of a light yellow solid, which exhibited physical properties[3a,4,5] identical to those reported for Rigidin: mp>325 °C (lit.[3]>300 °C); ^{1}H NMR (DMSO-d_6) δ 11.73 (br s, 1H), 11.17 (br s, 1H), 10.62 (br s, 1H), 9.99 (br s, 1H), 9.72 (br s, 1H), 7.30 (d, J=9.0 Hz, 2H), 6.95 (d, J=9.0 Hz, 2H), 6.48 (d, J=9.0 Hz, 2H), and 6.45 (d, J=9.0 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 98.6, 114.3, 114.8, 123.2, 125.4, 128.5, 129.1, 132.0, 132.7, 141.6, 151.1, 156.9, 160.2, 161.2, and 185.7; IR (neat) 3215, 1695, 1568, 1434, 1413, and 1258 cm^{-1}; HRMS (ES, M−H) m/z calcd for $C_{19}H_{12}N_3O_5$ 362.0777, found 362.0774.

4.1.17. 3-Methylcarbamoyl-5-(4-methoxybenzoyl)-4-(4-methoxyphenyl)pyrrole-2-carboxylic acid ethyl ester (38b). Into a 7 mL microwave reaction vessel, which had been equipped with a magnetic stir bar, were placed molybdenum hexacarbonyl (0.228 g, 0.865 mmol), palladium(II) acetate (.058 g, 0.087 mmol), 3-iodo-5-(4-methoxybenzoyl)-4-(4-methoxyphenyl)pyrrole-2-carboxylic acid ethyl ester[9] (**35a**) (0.437 g, 0.865 mmol), and tetrahydrofuran (4 mL). Then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.39 mL, 2.60 mmol) was added and the reaction vessel was capped. Through the septum was added 1.30 mL (2 M in THF, 2.60 mmol) of *N*-methyl amine. The reaction mixture was stirred for 5 min and subjected to microwave irradiation for 45 min at 100 °C (15–20 W). The reaction mixture was filtered through a plug of sand, silica, and Celite and the plug was washed with tetrahydrofuran (50 mL). The filtrate was concentrated in vacuo and the residue was adsorbed onto silica gel and purified by flash chromatography (gradient elution with ethyl acetate/hexanes) to yield 0.240 g (64.5% yield) of a yellow solid, which exhibited the following properties: mp 85–86 °C; ^{1}H NMR ($CDCl_3$) δ 9.89 (br s, 1H), 7.48 (d, J=9.0 Hz, 2H), 7.08 (d, J=9.0 Hz, 2H), 6.64 (d, J=9.0 Hz, 2H), 6.59 (d, J=9.0 Hz, 2H), 6.29 (broad absorption, 1H), 4.43 (q, J=7.0 Hz, 2H), 3.76 (s, 3H), 3.73 (s, 3H), 2.87 (d, J=5.0 Hz, 3H), and 1.42 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 14.3, 26.6, 55.2, 55.4, 61.7, 113.1, 113.4, 122.2, 125.0, 125.6, 129.0, 129.8, 130.1, 131.5, 131.9, 158.9, 159.9, 163.0, 164.9, and 186.2; IR (neat) 3266, 1704, and 1627 cm^{-1}; HRMS (ES, M+H) m/z calcd for $C_{24}H_{25}N_2O_6$ 437.1707, found 437.1712.

4.1.18. 3-Methylcarbamoyl-5-(4-methoxybenzoyl)-4-(4-methoxyphenyl)pyrrole-2-carboxylic acid (39b). Into a round-bottom flask equipped with reflux condenser and magnetic stir bar were placed 0.254 g (0.582 mmol) of 3-methylcarbamoyl-5-(4-methoxybenzoyl)-4-(4-methoxyphenyl)pyrrole-2-carboxylic acid ethyl ester (**38b**), 0.098 g (1.75 mmol) of potassium hydroxide, and 30 mL of a 1:1

mixture of ethanol/water. The mixture was heated at reflux for 24 h, cooled to room temperature, and acidified with 6 M hydrochloric acid to a pH of 2. The reaction mixture was placed in a freezer for 16 h, and the resultant precipitate was collected by vacuum filtration and dried in vacuo. The filtrate was placed back in the freezer for 24 h and a second crop of solid was obtained. Combination of the two crops yielded 0.190 g (79.8% yield) of a white solid, which exhibited the following properties; mp 176–178 °C; ^{1}H NMR (acetone-d_6) δ 7.55 (d, J=8.7 Hz, 2H), 7.24 (d, J=8.7 Hz, 2H), 6.87 (d, J=8.7 Hz, 2H), 6.82 (d, J=8.7 Hz, 2H), 3.82 (br s, 3H), 3.78 (br s, 3H), and 2.76 (s, 3H); ^{13}C NMR (acetone-d_6) δ 26.0, 54.7, 55.0, 113.3, 116.6, 114.2, 123.7, 127.8, 128.1, 130.0, 131.2, 131.6, 132.3, 159.8, 160.0, 163.3, 166.9, and 185.6; IR (neat) 3394, 1701, and 1569 cm^{-1}; HRMS (ES, M−H) m/z calcd for $C_{22}H_{19}N_2O_6$ 407.1238, found 407.1234.

4.1.19. 3-Methyl-6-(4-methoxybenzoyl)-5-(4-methoxyphenyl)-1,7-dihydropyrrolo[2,3-*d*]pyrimidine-2,4-dione (40b). Into an argon blanketed, three-neck, round-bottom flask equipped with a thermometer, condenser, septa, and magnetic stir bar were placed 0.175 g (0.429 mmol) of 3-methylcarbamoyl-5-(4-methoxybenzoyl)-4-(4-methoxyphenyl)pyrrole-2-carboxylic acid (**39b**) and 15 mL of toluene. To this mixture were added 0.10 mL (0.75 mmol) of triethylamine and 0.16 mL (0.75 mmol) of diphenylphosphorylazide. The reaction mixture was heated at 75 °C for 9 h, cooled to room temperature, and stirred for an additional 24 h at room temperature. The solvent was then removed in vacuo, and the residue was purified by automated flash chromatography using a gradient elution of hexanes/ethyl acetate to yield 0.092 g (53% yield) of a yellow solid, which exhibited the following properties: mp 300 °C; ^{1}H NMR (DMSO-d_6) δ 11.94 (br s, 1H), 7.36 (d, J=9.0 Hz, 2H), 7.05 (d, J=9.0 Hz, 2H), 6.65 (d, J=9.0 Hz, 2H), 6.62 (d, J=9.0 Hz, 2H), 3.70 (s, 3H), 3.67 (s, 3H), and 3.15 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 27.2, 55.5, 55.8, 98.3, 112.9, 113.4, 124.8, 125.7, 128.7, 130.7, 131.6, 132.7, 140.1, 151.2, 158.8, 159.5, 162.3, and 185.7; IR (neat) 3180, 1709, and 1658 cm^{-1}; HRMS (ES, M+H) m/z calcd for $C_{22}H_{19}N_2O_6$ 406.1397, found 406.1412. It should also be noted that the three-step process of aminocarbonylation, ester hydrolysis, and uracil formation has also been carried out in an overall 30% yield with only a purification (flash chromatography) being required for the last step.

4.1.20. Rigidin E (5). A three-neck, round-bottom flask was equipped with a condenser and magnetic stir bar and was placed under a nitrogen atmosphere. Into the flask were placed 0.100 g (0.247 mmol) of 3-methyl-6-(4-methoxybenzoyl)-5-(4-methoxyphenyl)-1,7-dihydropyrrolo[2,3-*d*]-pyrimidine-2,4-dione (**40b**) and 12 mL of methylene chloride. The mixture was cooled to −78 °C in an acetone/dry ice bath and 5.0 mL of a 1.0 M (5.00 mmol) boron tribromide in methylene chloride was slowly added over 5 min. The reaction mixture was protected from light, stirred, and allowed to equilibrate to room temperature for 72 h. The reaction mixture was again cooled to −78 °C in an acetone/dry ice bath and an additional 1.6 mL (1.6 mmol) of boron tribromide was added. The reaction mixture was stirred and allowed to equilibrate to room temperature over 18 h. The reaction mixture was cooled to 0 °C, slowly quenched with methanol (45 mL), and stirred at 0 °C for 6 h. Water (25 mL) was subsequently added, followed by the dropwise addition of 5% NaOH such that the pH of the solution reached 7. This solution was then stirred overnight at room temperature and the solvents were removed in vacuo. The residue was diluted with 50 mL of ethyl acetate and the aqueous phase was extracted with 3×30 mL portions of ethyl acetate. The organic layers were combined and concentrated in vacuo to give 0.182 g of a light brown solid, which was adsorbed onto silica gel and purified by flash chromatography (gradient elution with ethyl acetate/hexanes) to yield 0.170 g of a light brown solid. Trituration of this material with acetone yielded 0.038 g (40.8% yield) of a solid, which exhibited spectral properties[3c] identical to those reported for Rigidin E: mp>330 °C; ^{1}H NMR (DMSO-d_6) δ 11.90 (br s, 1H), 10.00 (br s, 1H), 9.25 (br s, 1H), 7.30 (d, J=9.0 Hz, 2H), 6.96 (d, J=9.0 Hz, 2H), 6.48 (d, J=9.0 Hz, 2H), 6.46 (d, J=9.0 Hz, 2H), and 3.16 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 27.2, 98.2, 114.2, 114.7, 123.3, 125.4, 128.6, 129.2, 132.0, 132.8, 139.9, 151.7, 156.9, 159.7, 161.1, and 185.7; IR (neat) 3200, 1689, and 1646 cm^{-1}; HRMS (ES, M+H) m/z calcd for $C_{20}H_{16}N_3O_6$ 378.1084, found 378.1100.

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