Accepted Manuscript

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PII: S0040-4020(18)30396-X

DOI: 10.1016/j.tet.2018.04.017

Reference: TET 29432

To appear in: *Tetrahedron*

Received Date: 20 February 2018

Revised Date: 4 April 2018

Accepted Date: 5 April 2018

Please cite this article as: Gupton JT, Shimozono A, Crawford E, Ortolani J, Clark E, Mahoney M, Heese C, Noble J, Mandry CP, Kanters R, Dominey RN, Goldman EW, Sikorski JA, Fisher DC, Further studies on the application of vinylogous amides and β-halovinylaldehydes to the regiospecific synthesis of unsymmetrical, polyfunctionalized 2,3,4- and 1,2,3,4- substituted pyrroles, *Tetrahedron* (2018), doi: 10.1016/j.tet.2018.04.017.

Further studies on the application of vinylogous amides and β-halovinylaldehydes to the regiospecific synthesis of unsymmetrical, polyfunctionalized 2,3,4- and 1,2,3,4-substituted pyrroles

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Abstract- Highly functionalized pyrroles with appropriate regiochemical functionality represent an important class of marine natural products and potential drug candidates. We describe herein a detailed study of the reaction of α-aminoacid esters with vinylogous amides and also β-halovinylaldehydes for the regiospecific synthesis of 2,3,4-trisubstituted and 1,2,3,4-tetrasubstituted pyrroles. Since the vinylogous amides and β-halovinylaldehydes are readily available precursors, rapid access to a wide variety of unsymmetrically substituted pyrroles is accomplished via this methodology.

1. Introduction

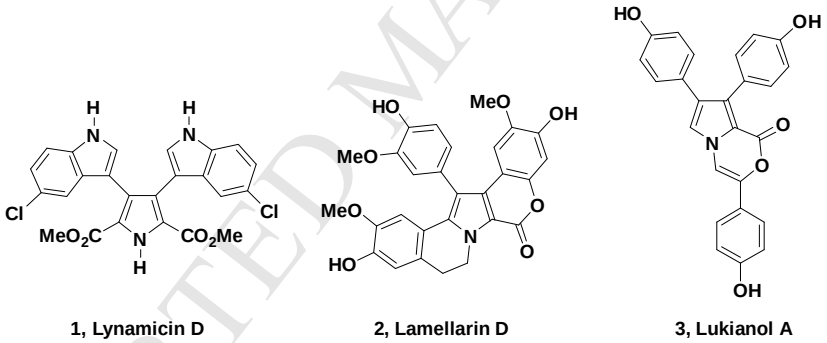

Figure 1. Pyrrole Containing Natural Products

Our previous studies have established that vinamidinium salts[1] and related compounds are useful building blocks for the construction of five and six membered heterocyclic compounds and in particular highly functionalized, unsymmetrical pyrroles. The presence of the pyrrole core in a large number of natural (Fig. 1) and synthetic products has attracted the attention of many others and as a result, various synthetic approaches are currently available[2]. The attention given to such pyrrole containing natural products arises from their very important biological properties[3]. Such properties include potent anti-proliferative activity of lamellarin D[4] (2, Fig. 1) and lukianol A[5] (3, Fig. 1) on various cancer cell lines including those, which exhibit multidrug-resistance. Lynamicin D[6] (1, Fig. 1) and related compounds have demonstrated good antibiotic activity against *Staphylococcus aureus* ATCC 43300-MRSA and *Haemophilus influenzae* ATCC 49247. Consequently, short and efficient methods for the regiocontrolled synthesis of symmetrical and unsymmetrical, polyfunctionalized pyrroles are of some importance.

Keywords: Vinylogous Amide; β-Halovinylaldehyde; Pyrrole; Marine Natural Products.
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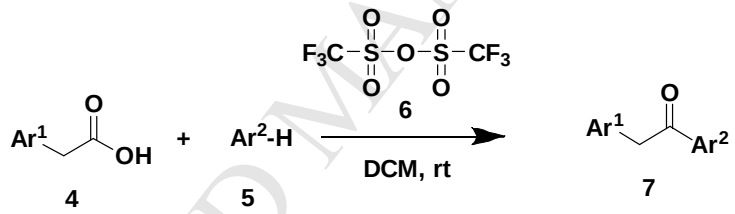
The ideal method for synthesizing polyfunctionalized pyrroles should allow for a high yielding, regiospecific preparation from readily available starting materials in as few synthetic steps as possible. In 1999 we reported[7] a short and efficient synthesis of the Furstner pyrrole intermediate, which had been converted to the marine natural product Lukianol A (3, Fig. 1). The key pyrrole core for this intermediate was prepared by the condensation reaction of a single vinylogous amide or it's corresponding β-halovinylaldehyde with several glycine derivatives. These early results suggested that both vinylogous amides and β-halovinylaldehydes could meet the general requirements of ideal building blocks for the high yielding, regiospecific preparation of appropriately functionalized pyrroles. We now report a thorough investigation of vinylogous amides and β-halovinylaldehydes as efficient precursors for unsymmetrical 1,2,3,4-tetrasubstituted and 2,3,4-trisubstituted pyrroles.

2. Results and Discussions

Since a significant number of the important bioactive pyrroles[3] contain aryl groups at the C-3 and C-4 positions of the pyrrole, we decided to define optimum conditions for the construction of a variety of aryl benzyl ketones as starting materials for our work. Although many Friedel-Craft acylation conditions[8] are available, we liked the idea of using one equivalent of triflic anhydride, (Scheme 1 and Table 1) to mediate[9] such reactions due to high yields, and very clean and mild reaction conditions. These reactions were typically run overnight at room temperature, required minimum work up and the crude products were exceptionally pure and could be used in subsequent steps without further purification.



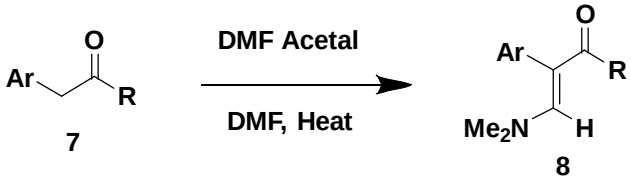
Scheme 1. Triflic Anhydride Mediated Acylation with Aryl Acetic Acids

Table 1. Preparation of Aryl Benzyl Ketones

Compound Number	Ar^1	Ar^2	% Yield
7a	4-MePh	2,4-$(MeO)_2$Ph	94
7b	4-MePh	2,3,4-$(MeO)_3$Ph	71
7c	4-MePh	3,4-$(MeO)_2$Ph	89
7d	Ph	4-MeOPh	98
7e	4-BrPh	4-MeOPh	81
7f	4-MePh	4-MeOPh	98
7g	4-ClPh	4-MeOPh	90
7h	2,3,4-$(MeO)_3$Ph	4-MeOPh	71
7i	3,4-$(MeO)_2$Ph	4-MeOPh	79

The preparation of vinylogous amides from active methylene compounds is well known[10] and with a variety of benzyl ketones in hand we employed N,N-dimethylformamide dimethyl acetal in refluxing DMF for this transformation. Nearly all reactions proceeded in high yield with little or no purification of the crude products required after concentration of the reaction mixtures.

The only exception was in the case of compound **8d** (Table 2) in which case the product yield was lower and this could be due to steric issues.

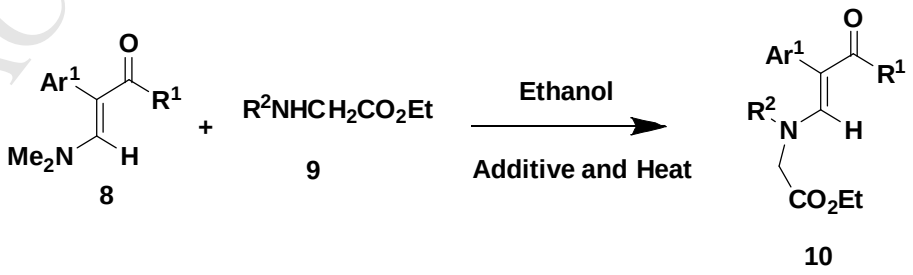


Scheme 2. Preparation of Vinylogous Amides from Benzyl Ketones

Table 2. Preparation of Vinylogous Amides

Compound Number	Ar	R	% Yield
8a	4-MeOPh	Me	99
8b	4-MeOPh	4-MeOPh	99
8c	4-MePh	4-MeOPh	96
8d	4-MePh	2,3,4-$(MeO)_3$Ph	54
8e	4-MePh	3,4-$(MeO)_2$Ph	91
8f	4-MePh	2,4-$(MeO)_2$Ph	95
8g	4-BrPh	4-MeOPh	91
8h	4-ClPh	4-MeOPh	99
8i	Ph	4-MeOPh	85
8j	2,3,4-$(MeO)_3$Ph	4-MeOPh	83
8k	3,4-$(MeO)_2$Ph	4-MeOPh	85

In our previous studies of pyrrole forming reactions[1] with glycine derivatives and vinamidinium salts, we proposed that the amino acid ester undergoes an amine exchange reaction with one of the amine groups at the vinamidinium salt terminus followed by base-mediated cyclization. Consequently we decided to see if we could accomplish the same exchange process with a vinylogous amide and N-methyl glycine ethyl ester and actually isolate and characterize the suggested intermediate (Scheme 3 and Table 3). A number of examples were evaluated and they gave good yields by refluxing the reactants in ethanol. Because N-methyl glycine was purchased and used as the hydrochloride salt, we employed trifluoroacetic acid as an additive for the N-benzyl glycine exchange process, since it was purchased as the free base. The presence of one equivalent of acid clearly facilitated the exchange reaction. In addition NOESY NMR analysis of one of the reaction products (**10a**) indicated that when R^1 was an aryl group the E configuration of the amine exchanged product was obtained as shown in Scheme 3.

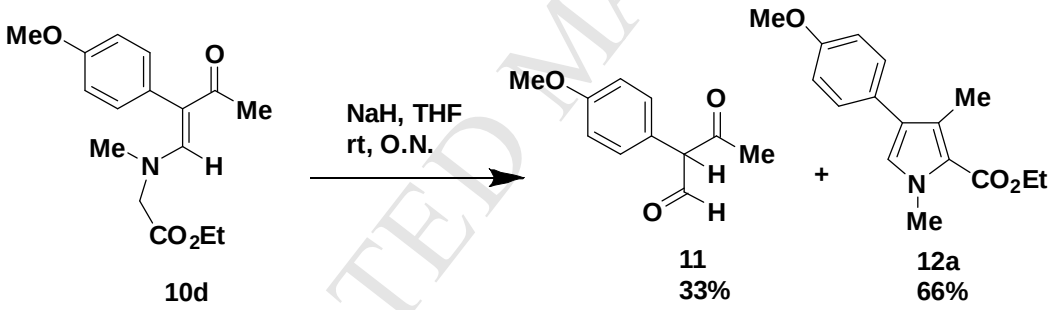


Scheme 3. The Amine Exchange Reaction

Table. 3 Amine Exchange Reaction of Vinylogous Amides with Glycine Derivatives

Compound Number	Ar^1	R^1	R^2	Additive	% Yield
10a	4-MePh	4-MeOPh	Me	None	64
10b	4-MePh	3,4-$(MeO)_2$Ph	Me	None	54
10c	4-MeOPh	4-MeOPh	Me	None	100
10d	4-MeOPh	Me	Me	None	89
10e	4-MePh	2,3,4-$(MeO)_3$Ph	Me	None	93
10f	4-MePh	4-MeOPh	Bn	CF_3CO_2H	75
10g	4-MeOPh	4-MeOPh	Bn	CF_3CO_2H	84

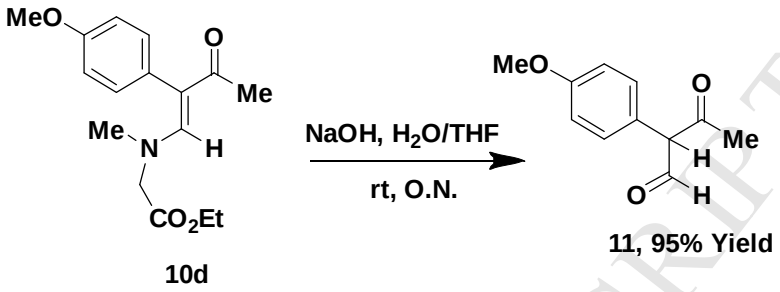
Our previous cyclization studies with vinamidinium salts and glycine derivatives employed base mediated conditions[1] for pyrrole formation. We therefore selected sodium hydride in THF at room temperature for our intitial cyclization studies with the amino acid ester exchanged vinylogous amide (**10d**) and the results are depicted in Scheme 4.



Scheme 4. Base Mediated Pyrrole Formation from Sarcosine Exchanged Vinylogous Amide

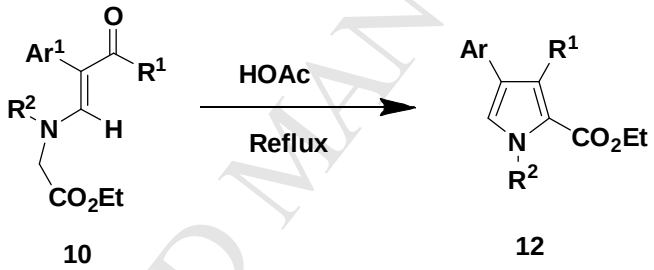
We were pleased to obtain a 66% yield of the desired pyrrole (**12a**) based on ^{1}H NMR analysis of the crude product and comparison with an authentic sample[11].The product regiochemistry was established by NOESY NMR analysis of **12a**[11] (Table 4). Given the E stereochemistry of the starting material **(10d)** it was clear that isomerization about the double bond occurred prior to the cyclization step. We were also able to determine that the side product (**11**) formed in the reaction (in 33% yield) was a ketoaldehyde (**11**), which we assumed was formed by hydrolysis of the sarcosine exchanged vinylogous amide (**10d**). Since water was generated in the cyclization step, this presented an obvious problem. To further verify our assumptions the sarcosine exchanged vinylogous amide (**10d**) was treated with aqueous sodium hydroxide in THF at room temperature overnight in which case the keto aldehyde (**11**) was produced in 95% yield (Scheme 5) and was identical by ^{1}H NMR to the material obtained in the base mediated cyclization (Scheme 4) to form the pyrrole (**12a**).Although the keto aldehyde (**11**) could in principle react with sarcosine to regenerate the exchanged vinylogous amide (**10d**) and then cyclize, the basic reaction conditions should cause deprotonation of the keto aldehyde (**11**) and

make it unavailable for such a process. It should be noted that an attempt was made to remove water during the dehydration step by running the cyclization reaction (as described in Scheme 4) in toluene with azeotropic removal of water. Interestingly, these conditions did not result in a meaningful improvement in the yield of the desired pyrrole versus the reaction in THF at room temperature.



Scheme 5. Hydrolysis of Sarcosine Exchanged Vinylogous Amide

Because of the issues associated with the base mediated cyclization conditions we turned our attention to an acid mediated process as described in Scheme 6 and Table 4.



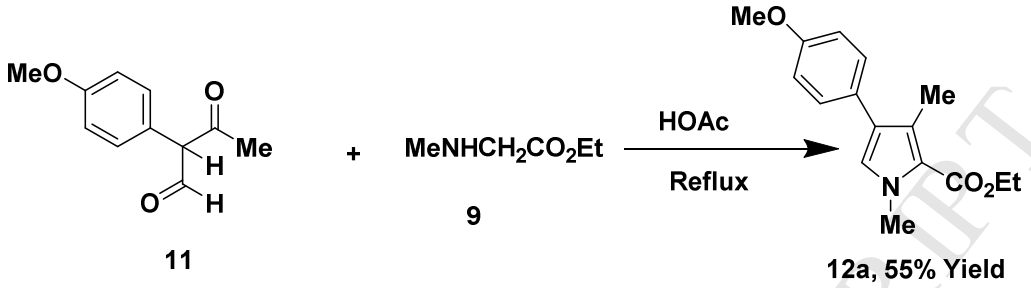
Scheme 6. Acid Mediated Formation of 1,2,3,4-Tetrasubstituted Pyrroles from Sarcosine Exchanged Vinylogous Amides

Table 4. Acid Mediated Formation of 1,2,3,4-Tetrasubstituted Pyrroles

Compound Number	Ar	R^1	R^2	% Yield
12a	4-MeOPh	Me	Me	94
12b	4-MeOPh	4-MeOPh	Me	95
12c	4-MePh	4-MeOPh	Me	81
12d	4-MePh	3,4-$(MeO)_2$Ph	Me	88
12e	4-MeOPh	4-MeOPh	Bn	80
12f	4-MePh	4-MeOPh	Bn	88

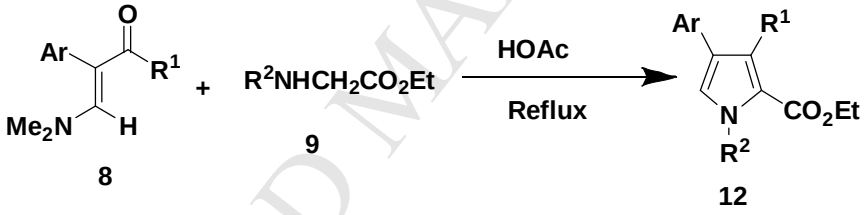
For the six examples studied (Scheme 6, Table 4), refluxing the respective vinylogous amide (**10**) in glacial acetic acid gave relatively clean pyrrole (**12a-12f**) with little if any keto aldehyde (**11**) formed from the hydrolytic side reaction. Any hydrolysis, which may have occurred, would still allow for the reaction of the N-substituted glycine with the keto aldehyde (**11**) thereby reproducing the exchanged vinylogous amide (**10**) and subsequently forming the pyrrole (**12**) in an irreversible cyclization step. Therefore, no discernible yield loss of pyrrole would be expected given the deprotonation of the keto aldehyde (**11**) in an acidic environment would not

be possible. Upon reaction of the keto aldehyde **(11)** with N-methyl glycine ethyl ester hydrochloride in refluxing acetic acid (Scheme 7) a 55% yield of the respective pyrrole (**12a**) was obtained after normal reaction work up thereby verifying its (**11**) viability as a pyrrole precursor.



Scheme 7. Acetic Acid Mediated Cyclization of Ketoaldehyde (11) to Pyrrole (12a).

Given the success of the acid-mediated reaction conditions, we decided to evaluate a one pot reaction where the N-substituted glycine derivative **(9**) would undergo exchange with the vinylogous amide **(8)** *in situ* followed by cyclization to the respective pyrrole (**12**) in refluxing glacial acetic acid (Scheme 8). A total of 13 examples were evaluated (Table 5) and very respectable yields of 1,2,3,4-tetrasubstituted pyrrole (**12a-12m**) products were obtained in all cases.



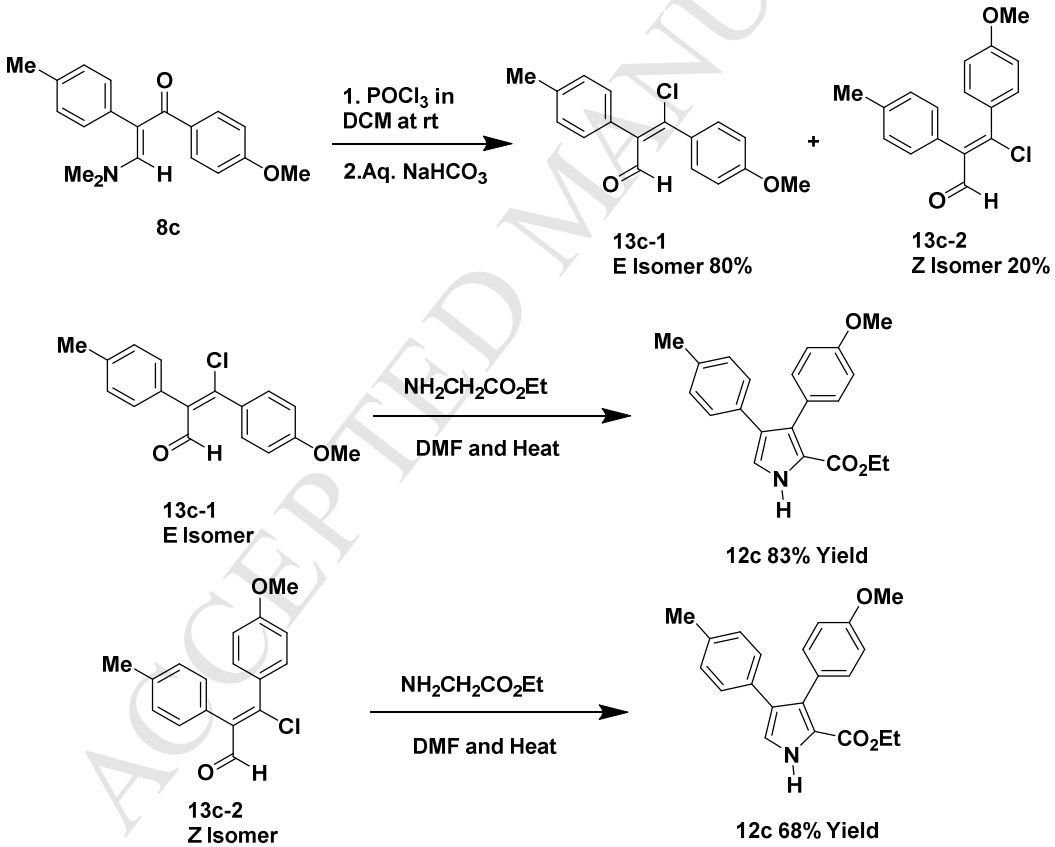
Scheme 8. Acetic Acid Mediated One Pot Cyclization of Vinylogous Amides to 1,2,3,4-Tetrasubstituted Pyrroles

Table 5. One Pot Cyclization of Vinylogous Amides to 1,2,3,4-Tetrasubstituted Pyrroles

Compound Number	Ar	R^1	R^2	% Yield
12a	4-MeOPh	Me	Me	81
12b	4-MeOPh	4-MeOPh	Me	73
12c	4-MePh	4-MeOPh	Me	86
12d	4-MePh	3,4-$(MeO)_2$Ph	Me	87
12g	Ph	4-MeOPh	Me	72
12h	4-BrPh	4-MeOPh	Me	87
12i	4-ClPh	4-MeOPh	Me	87
12j	3,4-$(MeO)_2$Ph	4-MeOPh	Me	91
12k	2,3,4-$(MeO)_3$Ph	4-MeOPh	Me	91
12l	4-MeOPh	Me	Bn	61
12m	4-MePh	3,4-$(MeO)_2$Ph	Bn	60
12e	4-MeOPh	4-MeOPh	Bn	58
12f	4-MePh	4-MeOPh	Bn	67

It is proposed that the above cyclization occurs after isomerization of the E-vinylogous exchanged amides (**10**) to the Z isomers. This isomerization would be followed by enolization of the ester group and then an acid mediated intramolecular condensation with subsequent dehydration should yield the desired tetrasubstituted pyrroles (**12**).

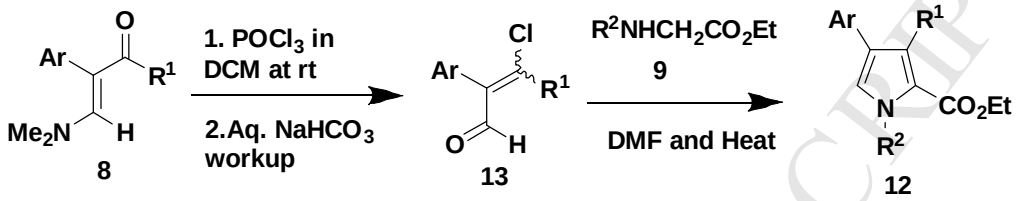
It is important to note that a significant number of bioactive[3], pyrrole natural products and their synthetic counterparts require the nitrogen of the pyrrole to be unsubstituted. Attempts to use glycine ester hydrochloride in place of N-substituted glycines under the previously described conditions showed no indication of pyrrole formation. We have previously had success[7] in converting vinylogous amides (**8**) to β-halovinylaldehydes[12] (**13**) in high yield and we anticipated that such substances would offer an alternative three-carbon building block for successful condensation with glycine ester hydrochloride. After preparation of a model β-halovinylaldehyde (**13c**) as a mixture of E (**13c-1**) and Z (**13c-2**) isomers, the isomeric products were separated chromatographically and individually characterized along with NOESY NMR analysis. The isomers (**13c-1** and **13c-2**) were then separately reacted with glycine ester hydrochloride in refluxing DMF (Scheme 9) whereby the desired N-unsubstituted pyrrole (**12c**, Table 6) was produced in both reactions in generally good yields (83% for the E isomer and 68% for the Z isomer).



Scheme 9. Formation of N-H-2,3,4-Trisubstituted Pyrrole (12c) from Individual β-Chlorovinyl Aldehyde Isomers (13c-1 and 13c-2)

Since both individual isomers were converted to the respective pyrrole (Scheme 9), a variety of chlorovinyl aldehydes (**13**) were prepared and the crude isomeric products were subjected to reaction with glycine ethyl ester in refluxing DMF. The respective unsymmetrical 2,3,4-trisubstituted pyrroles (**12n-12t**) were subsequently obtained in generally good yields (Table 6).

Interestingly, similar reactions with either N-methylglycine ethyl ester or N-benzylglycine ethyl ester also produced pyrroles (**12b,12c,12d,12g,12h,12f** and**12m**) in good yield as well and the pyrrole products were identical to those prepared by the previously described vinylogous amide/acetic acid route (Scheme 8, Table 5). It is also worth noting that no added acid or base was required to initiate the amine exchange or the cyclization processes in refluxing DMF. It is assumed that trace amounts of acid from the salts of the amino acid esters or from elimination of HCl during the elimination step could facilitate the observed process. It is also assumed that the amine group of the amino acid ester would react preferentially with the aldehyde group and not the chlorovinyl group for steric reasons.



Scheme 10. Formation of Unsymmetrical 2,3,4-Trisubstitutedpyrroles and Unsymmetrical 1,2,3,4-Tetrasubstitutedpyrroles via β-Chlorovinyl Aldehydes

Table 6. Unsymmetrical 2,3,4-Trisubstitutedpyrroles and Unsymmetrical 1,2,3,4-Tetrasubstitutedpyrroles via β-Chlorovinyl Aldehydes

Compound Number	Ar	R^1	R^2	% Yield
12n	4-MeOPh	4-MeOPh	H	84
12o	4-MePh	3,4-$(MeO)_2$Ph	H	59
12p	4-MePh	4-MeOPh	H	85
12q	4-MeOPh	Me	H	45
12r	Ph	4-MeOPh	H	86
12s	4-BrPh	4-MeOPh	H	85
12t	3,4-$(MeO)_2$Ph	4-MeOPh	H	66
12b	4-MeOPh	4-MeOPh	Me	80
12c	4-MePh	4-MeOPh	Me	82
12g	Ph	4-MeOPh	Me	67
12h	4-BrPh	4-MeOPh	Me	73
12d	4-MePh	3,4-$(MeO)_2$Ph	Me	81
12m	4-MeOPh	3,4-$(MeO)_2$Ph	Bn	60
12f	4-MePh	4-MeOPh	Bn	69

3.Conclusions

In summary we have described a two-step process for regiospecifically preparing unsymmetrical 1,2,3,4-tetrasubstituted pyrroles (**12**) in good yield from benzyl ketones via acetic acid mediated condensation of the corresponding vinylogous amides (**8**) with N-substituted glycine derivatives (**9**). Additionally, a step wise process involving the reaction of the vinylogous amide exchanged materials (**10**) with refluxing acetic acid was found to produce the respective pyrroles thereby helping to clarify the nature of the one pot, pyrrole forming reaction. Since N-unsubstituted pyrroles could not be made by the acetic acid mediated route, the vinylogous amides (**8**) were converted to an isomeric mix of β-halovinylaldehydes (**13**) via reaction with phosphorous oxychloride. Subsequent reaction of the crude isomeric β-halovinylaldehydes (**13**) with both N-unsubstituted and N-substituted glycines in refluxing DMF produced unsymmetrical 2,3,4-trisubstituted pyrroles (**12**)

and unsymmetrical 1,2,3,4-tetrasubstituted pyrroles (**12**), repectively in good yield. The isolation, characterization and individual conversion of E and Z chloroenals to a 2,3,4-trisubstituted pyrrole (**12c**) establishes viability of both isomers to be successfully converted to the desired product. In an overall sense a very compact sequence of reactions was shown to regiospecifically produce functionalized, unsymmetrical, polysubstututed pyrroles thereby making it possible for rapid generation of various libraries of compounds bearing the pyrrole scaffold.

4. Experimental

4.1 General

All chemicals were used as received from the manufacturer (Aldrich Chemicals and Fisher Scientific). All solvents were dried over 4 angstrom molecular sieves prior to their use. NMR spectra were obtained on either a Bruker 300 MHz spectrometer, or a Bruker 500 MHz spectrometer in either $CDCl_3$, d_6-DMSO or d_6-acetone solutions. IR spectra were recorded on a Nicolet Avatar 320 FT-IR spectrometer with an HATR attachment. High resolution mass spectra were obtained on a Shimadzu IT-TOF 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. Chromatographic purifications were carried out on a Biotage SP-1 instrument or a Biotage Isolera instrument (both equipped with a silica cartridge). Gradient elution with ethyl acetate/hexane was accomplished in both instances. The reaction products were normally eluted within the range of 4-8 column volumes of eluant with a gradient mixture of 60-80% ethyl acetate in hexane. TLC analyses were conducted on silica plates with hexane/ethyl acetate as the eluant. All purified reaction products gave TLC results, flash chromatograms, and ^{13}C NMR spectra consistent with a sample purity of >95%.

4.1.1 1-(2,4-Dimethoxyphenyl)-2-*p*-tolylethanone (7a). Into a 100 mL round bottom flask equipped with magnetic stirring was placed 4-tolylacetic acid (0.524 g, 3.61 mmol) along with 15 mL of dry dichloromethane (DCM). To this mixture with ice bath cooling was added 1,3-dimethoxybenzene (0.542 g, 3.61 mmol) and 4.33 mL (4.33 mmol) of a 1.00 M solution of triflic anhydride in anhydrous DCM. The resulting mixture was stirred overnight, diluted with 20 mL of saturated aqueous bicarbonate and extracted with DCM (3 x 20 mL). The DCM solution was dried over anhydrous sodium sulfate, filtered through a fritted glass funnel and the filtrate was then passed through a short plug of silica gel and the plug was then washed with 50 mL of ethyl acetate. The combined filtrates were concentrated *in vacuo* to yield a dark grey solid (0.918 g, 94% yield), which exhibited the following physical properties: mp 63-65 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.7 Hz, 1H), 7.12 (broad s, 4H), 6.53 (dd, *J* = 8.7 Hz, *J* = 2.3 Hz, 1H), 6.47 (d, *J* = 2.3 Hz, 1H), 4.25 (s, 2H), 3.91 (s, 3H), 3.87 (s, 3H) and 2.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.0, 164.5, 160.6, 135.9, 133.1, 132.6, 129.5, 129.0, 121.0, 105.2, 98.4, 55.5, 55.4, 49.5 and 21.0; IR (neat) 1665 cm^{-1}; HRMS (ES, M+Na) *m/z* calcd for $C_{17}H_{18}O_3Na$ 293.1148, found 293.1158.

4.1.2 2-*p*-Tolyl-1-(2,3,4-trimethoxyphenyl)ethanone (7b). This material was prepared in a manner identical to the previous example **(7a)** with the exception that 1,2,3-trimethoxybenzene was used as the aromatic hydrocarbon component instead of 1,3-dimethoxybenzene in which case a dark oil (0.379 g, 71% yield) was obtained. This material exhibited the following physical properties: bp 146-147 °C at 0.54 torr; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, *J* = 9.0 Hz, 1H), 7.12 (broad s, 4H), 6.70 (d, *J* = 9.0 Hz, 1H), 4.25 (s, 2H), 3.96 (s, 3H), 3.91 (s, 3H), 3.89 (s, 3H) and 2.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.6, 157.3, 153.8, 142.1, 136.1, 132.1, 129.5, 129.1, 126.0, 125.8, 107.2, 61.6, 60.9, 56.1, 48.9 and 21.1; IR (neat) 1680 cm^{-1}; HRMS (ES, M+Na) *m/z* calcd for $C_{18}H_{20}O_4Na$ 323.1254, found 323.1236.

4.1.3 1-(3,4-Dimethoxyphenyl)-2-*p*-tolylethanone (7c). This material was prepared in a manner identical to the previous example **(7a)** with the exception that 1,2-dimethoxybenzene was used as the aromatic hydrocarbon component instead of 1,3-dimethoxybenzene in which case a dark oil (89% yield) was obtained, which exhibited a ^{1}H NMR spectrum identical to the reported values[13]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 8.3 Hz, *J* = 2.0 Hz, 1H), 7.58 (d, *J* = 2.0 Hz, 1H), 7.18 (d, *J* = 8.1 Hz, 2H), 7.14 (d, *J* = 8.1 Hz, 2H), 6.89 (d, *J* = 8.3 Hz, 1H), 4.22 (s, 2H), 3.95 (s, 3H), 3.93 (s, 3H) and 2.34 (s, 3H).

4.1.4 1-(4-Methoxyphenyl)-2-phenylethanone (7d). This material was prepared in a manner identical to the previous example **(7a)** with the exception that methoxybenzene was used as the aromatic hydrocarbon component and phenyl acetic acid was used as the acyl component. A solid (98% yield) was obtained, which exhibited a ^{1}H NMR spectrum identical to the reported values[14]. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 10.0 Hz, 2H), 7.31 (m, 5H), 6.95 (d, *J* = 10.0 Hz, 2H), 4.26 (s, 2H) and 3.88 (s, 3H).

4.1.5 2-(4-Bromophenyl)-1-(4-methoxyphenyl)ethanone (7e). This material was prepared in a manner identical to the previous example **(7a)** with the exception that 4-bromophenyl acetic acid was used as the acyl component. A solid (81% yield) was obtained, which exhibited a ^{1}H NMR spectrum identical to the reported values[14]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.9 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 6.95 (d, *J* = 8.9 Hz, 2H), 4.20 (s, 2H) and 3.89 (s, 3H).

4.1.6 1-(4-Methoxyphenyl)-2-*p*-tolylethanone (7f). This material was prepared in a manner identical to the previous example **(7a)** with the exception that 4-tolyl acetic acid was used as the acyl component. A solid (98% yield) was obtained, which exhibited a ^{1}H NMR spectrum identical to the reported values[14]. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.8 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 7,14 (d, *J* = 8.1 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 4.21 (s, 2H), 3.88 (s, 3H) and 2.34 (s, 3H).

4.1.7 2-(4-Chlorophenyl)-1-(4-methoxyphenyl)ethanone (7g). This material was prepared in a manner identical to the previous example **(7a)** with the exception that 4-chlorophenyl acetic acid was used as the acyl component. A solid (90% yield) was obtained, which exhibited a ^{1}H NMR spectrum identical to the reported values[15]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.9 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 2H), 7.21 (d, J = 8.5 Hz, 2H), 6.95 (d, J = 8.9 Hz, 2H), 4.22 (s, 2H) and 3.89 (s, 3H**).**

4.1.8 1-(4-Methoxyphenyl)-2-(2,3,4-trimethoxyphenyl)ethanone (7h). This material was prepared in a manner identical to the previous example **(7a)** with the exception that 2,3,4-trimethoxyphenyl acetic acid was used as the acyl component. A solid (71% yield) was obtained after flash purification on A Biotage Isolera instrument with a silica column. This material exhibited the following physical properties: mp 55-56 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 9.0 Hz, 2H), 6.96 (d, *J* = 9.0 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 1H), 6.65 (d, *J* = 8.5 Hz, 1H),4.20 (s, 2H), 3.89 (s, 6H), 3.87 (s, 3H) and 3.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.6, 163.4, 152.9, 151.7, 142.3, 130.7, 129.9, 124.9, 121.6, 113.7, 107.4, 60.8, 60.7, 56.0, 55.4, and 39.2; IR (neat) 1680 cm^{-1}; HRMS (ES, M+Na) *m/z* calcd for $C_{18}H_{20}O_5Na$ 339.1203 found 339.1200.

4.1.9 2-(3,4-Dimethoxphenyl)-1-(4-methoxyphenyl)ethanone (7i). This material was prepared in a manner identical to the previous example **(7a)** with the exception that 3,4-dimethoxyphenyl acetic acid was used as the acyl component. A dark oil (79% yield) was obtained, which exhibited a ^{1}H NMR spectrum identical to the reported values[16]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.8

Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.85-6.80 (m, 3H), 4.19 (s, 2H), 3.89 (s, 3H), 3.88 (s, 3H) and 3.87 (s, 3H).

4.1.10 4-Dimethylamino-3-(4-methoxyphenyl)-but-3-en-2-one (8a). Into a 20 mL microwave vial equipped with a magnetic stir bar and crimping cap was added 4-methoxyphenylacetone (0.545 g, 3.32 mmol), N,N-dimethylformamide dimethyl acetal (3.18 g, 26.6 mmol), and dimethylformamide (5 mL). The reaction mixture was heated in a microwave reactor for 2 hours at 100 °C. The solvent was removed *in vacuo*, the crude mixture was diluted with water (30 mL), and the aqueous solution was extracted with ethyl acetate (3 x 15 mL). The combined organic phases were washed with aqueous lithium chloride (20 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo* to yield an orange solid (0.721 g, 99% yield), which exhibited the following properties: mp 51-53 °C; ^{1}H NMR ($CDCl_3$; 500 MHz) δ 7.60 (s, 1H), 7.11 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 3.85 (s, 3H), 2.72 (s, 6H), 1.95 (s, 3H); ^{13}C NMR ($CDCl_3$; 75 MHz) δ 27.41, 42.91, 55.11, 110.51, 113.27, 130.27, 133.03, 149.03, 158.36, and 196.77; IR (neat) 1647 cm^{-1}; HRMS (ES, M+H) *m/z* calcd for $C_{13}H_{17}NO_2$ 220.1332 found 220.1300.

4.1.11 4-Dimethylamino-3-(4-methoxyphenyl)-but-3-en-2-one (8a). Into a 200 mL round bottom flask equipped with a magnetic stir bar and reflux condenser was added 4-methoxyphenylacetone (3.10 g, 18.9 mmol), N,N-dimethylformamide dimethyl acetal (13.56 g, 113 mmol), and dimethyl-formamide (15 mL). The reaction mixture was heated to reflux for 6 hours, cooled to room temperature, and the solvent was removed *in vacuo*. The reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic phases were washed with aqueous lithium chloride (20 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo* to yield a substance (3.78 g, 91% yield), which was identical by ^{1}H NMR to 4-dimethylamino-3-(4-methoxyphenyl)-but-3-en-2-one **(8a)** prepared via microwave irradiation.

4.1.12 3-Dimethylamino-1,2-bis-(4-methoxyphenyl)-propenone (8b). This material was prepared in a manner identical to the previous reflux example **(8a)** with the exception that desoxyanisoin was used as the ketone in which case a yellow solid was obtained (2.39 g, 99% yield), which was identical by ^{1}H NMR analysis to a previously prepared sample[7].

4.1.13 3-Dimethylamino-1-(4-methoxyphenyl)-2-*p*-tolyl-propenone (8c). This material was prepared in a manner identical to the previous reflux example **(8a)** with the exception that 1-(4-methoxyphenyl)-2-p-tolyl-ethanone was used as the ketone in which case an orange solid (1.31 g, 96 % yield) was obtained. An analytical sample was prepared via a Biotage Isolera flash chromatography system, which displayed the following properties: mp 60-62°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.8 Hz, 2H), 7.34 (s, 1H), 7.08-6.97 (m, 4H), 6.75 (d, *J* = 8.8 Hz, 2H), 3.77 (s, 3H), 2.71 (s, 6H), 2.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.89, 160.61, 153.06, 135.62, 134.64, 134.27, 131.87, 130.93, 128.36, 112.77, 111.73, 55.19, 43.42, 21.18; IR (neat) 1629 cm^{-1} HRMS (ES, M+H) *m/z* calcd for $C_{19}H_{21}NO_2$ 296.1645 found 296.1640.

4.1.14 3-Dimethylamino-2-*p*-tolyl-1-(2,3,4-trimethoxyphenyl)-propenone (8d). This material was prepared in a manner identical to the previous reflux example **(8a)** with the exception that 2-p-tolyl-1-(2,3,4-trimethoxyphenyl)ethanone was used as the ketone. The crude material was dissolved in a minimal amount of ethyl acetate and filtered through a short plug of silica with a 3:2 mixture of hexane/ethyl acetate (100 mL) followed by ethyl acetate (75 mL) and acetonitrile (25 mL). The solvent from the second fraction was removed *in vacuo* to yield an orange solid (0.614g, 54 % yield). An analytical sample was prepared via a Biotage Isolera flash chromatography system which displayed the following properties: mp 62-64°C; 1H NMR (300 MHz, $CDCl_3$) δ 7.16 (s, 1H), 7.10 (broad s, 4H), 6.94 (d, J = 8.5 Hz, 1H), 6.63 (d, J = 8.5 Hz, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.86

(s, 3H), 2.70 (s, 6H), 2.33 (s, 3H); 13C NMR (75 MHz, $CDCl_3$) δ 193.02, 154.14, 153.74, 150.79, 141.82, 135.70, 133.48, 131.81, 129.82, 128.19, 123.37, 113.32, 106.95, 61.76, 60.84, 55.98, 43.32, 21.14; IR (neat) 1636; HRMS (ES, M+H) *m/z* calcd for $C_{21}H_{25}NO_4$ 356.1856 found 356.1850.

4.1.15 1-(3,4-Dimethoxyphenyl)-3-dimethylamino-2-*p*-tolylpropenone (8e). this material was prepared in a manner identical to the previous reflux example **(8a)** with the exception that 1-(3,4-dimethoxyphenyl)-2-p-tolyl-ethanone was used as the ketone in which case an orange solid (1.12 g, 91 % yield) was obtained. An analytical sample was prepared via a Biotage Isolera flash chromatography system, which displayed the following properties: mp 128-129 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.12 (dd, *J* = 8.3 Hz, *J* = 2.0 Hz, 1H), 7.05 (broad s, 4H), 6.98 (d, *J* = 2.0 Hz, 1H), 6.74 (d, *J* = 8.3 Hz, 1H), 3.87 (s, 3H), 3.72 (s, 3H), 2.77 (s, 6H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.41, 152.82, 150.15, 147.81, 135.67, 134.90, 134.18, 131.92, 128.40, 122.73, 112.70, 111.42, 109.72, 55.80, 55.65, 43.49, 21.13; IR (neat) 1622; HRMS (ES, M+H) *m/z* calcd for $C_{20}H_{23}NO_3$ 326.1751 found 326.1765.

4.1.16 1-(2.4-Dimethoxyphenyl)-3-dimethylamino-2-*p*-tolyl-propenone (8f). This material was prepared in a manner identical to the previous reflux example **(8a)** with the exception that 1-(2,4-dimethoxyphenyl)-2-p-tolyl-ethanone was used as the ketone in which case an orange solid (1.29 g, 95 % yield) was obtained. An analytical sample was prepared via a Biotage Isolera flash chromatography system, which displayed the following spectral properties: 134-135°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (s, 1H), 7.10 (d, *J* = 8.2 Hz, 1H), 7.05-6.95 (m, 4H), 6.38 (dd, *J* = 8.2 Hz, *J* = 2.3 Hz, 1H), 6.32 (d, *J* = 2.3 Hz, 1H), 3.73 (s, 3H), 3.65 (s, 3H), 2.64 (s, 6H), 2.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.64, 160.94, 157.47, 153.09, 135.40, 133.88, 131.91, 129.78, 127.91, 125.19, 113.31, 104.15, 98.60, 55.57, 55.29, 43.34, 21.16; IR (neat) 1622 cm^{-1}; HRMS (ES, M+H) *m/z* calcd for $C_{20}H_{23}NO_3$ 326.1751 found 326.1695.

4.1.17 2-(4-Bromophenyl)-3-dimethylamino-1-(4-methoxyphenyl)-propenone (8g). This material was prepared in a manner identical to the previous reflux example **(8a)** with the exception that 2-(4-bromophenyl)-1-(4-methoxyphenyl)-ethanone was used as the ketone in which case an orange solid (1.29 g, 95 % yield) was obtained. An analytical sample was prepared via a Biotage Isolera flash chromatography system, which displayed the following properties: 103-104°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.8 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.30 (s, 1H), 7.01 (d, *J* = 8.4 Hz, 2H), 6.77 (d, *J* = 8.9 Hz, 2H), 3.77 (s, 3H), 2.70 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.58, 160.81, 153.61, 136.82, 133.86, 133.61, 130.86, 130.68, 120.04, 112.97, 110.52, 55.25, 43.65; IR (neat) 1629 cm^{-1}; HRMS (ES, M+H) *m/z* calcd for $C_{18}H_{18}NO_2Br$ 360.0594 found 360.0600.

4.1.18 2-(4-Chlorophenyl)-3-dimethylamino-1-(4-methoxyphenyl)-propenone (8h). This material was prepared in a manner identical to the previous reflux example **(8a)** with the exception that 2-(4-chlorophenyl)-1-(4-methoxyphenyl)-ethanone was used as the ketone in which case a yellow solid (1.20 g, 99 % yield) was obtained. An analytical sample was prepared via a Biotage Isolera flash chromatography system, which displayed the following properties: mp 113-116°C; ^{1}H NMR (300 MHz, Acetone-d_6) δ 7.44 (d, *J* = 8.8 Hz, 2H), 7.33-7.26 (m, 3H), 7.17 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 3.82 (s, 3H), 2.77 (s, 6H); ^{13}C NMR (75 MHz, Acetone-d_6) δ 192.23, 160.83, 153.30, 137.29, 134.44, 133.64, 131.02, 130.63, 127.22, 112.83, 110.01, 54.74, 42.87; IR (neat) 1629; HRMS (ES, M+H) *m/z* calcd for $C_{18}H_{18}NO_2Cl$ 316.1099 found 316.1099.

4.1.19 3-Dimethylamino-1-(4-methoxyphenyl)-2-phenylpropenone (8i). This material was prepared in a manner identical to the previous reflux example **(8a)** with the exception that 1-(4-methoxyphenyl)-2-phenylethanone was used as the ketone in which case an 85 % yield of a

semisolid was obtained, which displayed an identical ^{1}H NMR spectrum to the reported values[15] ;^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.9 Hz, 2H), 7.41 (s, 1H), 7.31 – 7.13 (m, 5H), 6.77 (d, *J* = 8.9 Hz, 2H), 3.80 (s, 3H), 2.75 (s, 6H).

4.1.20 3-Dimethylamino-1-(4-methoxyphenyl)-2-(2,3,4-trimethoxyphenyl)-propenone (8j). This material was prepared in a manner identical to the previous reflux example **(8a)** with the exception that 1-(4-methoxyphenyl)-2-(2,3,4-trimethoxyphenyl)-ethanone was used as the ketone in which case an orange solid (2.29 g, 83 % yield) was obtained. An analytical sample was prepared via a Biotage Isolera flash chromatography system, which displayed the following properties: mp 85-86 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.7 Hz, 2H), 7.31 (s, 1H), 6.87-6.78 (m, 3H), 6.64 (d, *J* = 8.7 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.76 (s, 3H), 2.75 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.17, 160.67, 153.78, 152.80, 152.37, 142.15, 134.50, 130.65, 127.69, 124.27, 112.87, 107.33, 106.77, 60.73, 60.37, 55.93, 55.25, 42.78; IR (neat) 1630; HRMS (ES, M+H) *m/z* calcd for $C_{21}H_{25}NO_5$ 372.1805 found 372.1824.

4.1.21 3-Dimethylamino-2-(3,4-dimethoxyphenyl)-1-(4-methoxyphenyl)propenone (8k). This material was prepared in a manner identical to the previous reflux example **(8a)** with the exception that 2-(3,4-dimethoxyphenyl)-1-(4-methoxyphenyl)-ethanone was used as the ketone in which case an orange solid (1.06 g, 85 % yield) was obtained. An analytical sample was prepared via a Biotage Isolera flash chromatography system, which displayed the following properties: mp 68-70 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.7 Hz, 2H), 7.37 (s, 1H), 6.82 – 6.77 (m, 3H), 6.72 (dd, *J* = 8.1, 1.9 Hz, 1H), 6.69 (d, *J* = 1.9 Hz, 1H), 3.89 (s, 4H), 3.82 (s, 4H), 3.81 (s, 4H), 2.77 (s, 7H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.95, 160.64, 152.99, 148.18, 147.54, 134.20, 130.86, 130.27, 124.44, 115.50, 112.81, 111.56, 110.53, 55.85, 55.79, 55.21, 43.35.; IR (neat) 1628; HRMS (ES, M+H) *m/z* calcd for $C_{20}H_{23}NO_4$ 342.1700 found 342.1716.

4.1.22 {[2-(4-Methoxyphenyl)-3-oxo-but-1-enyl]methylamino}acetic acid ethyl ester (10d). Into a 100 mL round bottom flask equipped with a magnetic stir bar and a reflux condenser was added 4-dimethylamino-3-(4-methoxyphenyl)-but-3-en-2-one (2.86 g, 13.0 mmol), sarcosine ethyl ester hydrochloride (5.01 g, 32.6 mmol) and ethanol (30 mL). The reaction mixture was heated at reflux for 4 hours. The solvent was removed *in vacuo*, the crude reaction mixture was diluted with water (50 mL), and the aqueous solution was extracted with ethyl acetate (3 x 20 mL). The combined organic phases were washed with brine (20 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo* to yield a dark orange oil (3.44 g, 91%), which exhibited the following properties: bp 104-105 °C at 0.45 torr; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.52 (s, 1H), 7.11 (d, J = 8.6 Hz, 2H) 6.87 (d, J=8.6 Hz, 2H), 4.13 (q, 7.1 Hz, 2H), 3.83 (s, 3H), 3.69 (s, 2H), 2.78 (s, 3H), 1.95 (s, 3H), 1.25 (t, J= 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$; 75 MHz) δ 13.94, 27.35, 42.56, 55.05, 55.50, 61.08, 112.02, 113.42, 129.29, 132.76, 148.47, 158.56, 168.61, and 197.28; IR (neat) 1742 and 1658 cm^{-1}; HRMS (ES, M+H) *m/z* calcd for $C_{16}H_{21}NO_4$ 292.1543 found 292.1513.

4.1.23 {[2-(4-Methoxyphenyl)-3-oxo-but-1-enyl]methylamino}acetic acid ethyl ester via microwave heating (10d). Into a 20 mL microwave vial equipped with a magnetic stir bar and a crimping cap was added 4-dimethylamino-3-(4-methoxyphenyl)-but-3-en-2-one (0.652 g, 2.97 mmol), sarcosine ethyl ester hydrochloride (1.14 g, 7.42 mmol), and ethanol (10 mL). The reaction mixture was heated in a microwave reactor for 2 hours at 100 °C. The solvent was removed *in vacuo*, the crude mixture was diluted with water (30 mL) and the aqueous solution was extracted with ethyl acetate (3 x 20 mL). The combined organic phases were washed with brine (20 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo* to yield a dark orange oil (0.774 g, 89 % yield), which was identical by ^{1}H NMR ($CDCl_3$, 300 MHz) 7.52 (s, 1H), 7.11 (d, J=8.6 Hz, 2H) 6.87 (d, J=8.6 Hz, 2H), 4.13 (q, 7.1 Hz, 2H), 3.83 (s, 3H), 3.69 (s, 2H), 2.78 (s, 3H), 1.95 (s,

3H), 1.25 (t, J= 7.1 Hz, 3H)] to {[2-(4-methoxyphenyl)-3-oxo-but-1-enyl]-methylamino}acetic acid ethyl ester prepared via normal heating.

4.1.24 {[3-(4-Methoxyphenyl)-3-oxo-2-*p*-tolylpropenyl]methylamino}acetic acid ethyl ester (10a). This material was prepared in a manner identical to the reflux exchange example **(10d)** with the exception that 3-dimethylamino-1-(4-methoxyphenyl)-2-p-tolylpropenone was used as the vinylogous amide in which case the crude product was passed through a short plug of silica using 100 mL of a 30:70 ethyl acetate:hexane mix followed by two 100 mL portions of ethyl acetate. The second 100 mL fraction was concentrated *in vacuo* yield to yield an orange oil (1.00 g, 64% yield). An analytical sample was prepared on a Biotage Isolera flash chromatography system to yield a yellow oil, which displayed the following properties: bp 160-161°C @ 0.285 torr; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.8 Hz, 2H), 7.23 (s, 1H), 7.07 (s, 4H), 6.78 (d, *J* = 8.8 Hz, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.78 (s, 3H), 3.70 (s, 2H), 2.74 (s, 3H), 2.32 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 3H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.47, 168.80, 160.91, 152.44, 136.06, 133.84, 133.81, 131.58, 131.07, 128.57, 113.59, 112.87, 61.26, 56.38, 55.22, 42.77, 21.20, 14.09; IR (neat) 1737 and 1586 cm^{-1}; HRMS (ES, M+H) *m/z* calcd for $C_{22}H_{25}NO_4$ 368.1858 found 368.1856.

4.1.25 {[3-(3,4-Dimethoxyphenyl)-3-oxo-2-*p*-tolylpropenyl]methylamino}acetic acid ethyl ester (10b). This material was prepared in a manner identical to the previous reflux example **(10d)** with the exception that 1-(3,4-dimethoxyphenyl)-3-dimethylamino-2-*p*-tolylpropenone was used as the vinylogous amide in which case the crude product was purified using a Biotage Isolera flash chromatography system to yield a yellow solid (0.509 g, 54% yield), which displayed the following properties: mp 87-88 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (s, 1H), 7.17 (dd, *J* = 8.3 Hz , *J* = 2.0 Hz, 1H), 7.09 (s, 4H), 7.05 (d, *J* = 2.0 Hz, 1H), 6.78 (d, *J* = 8.3 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.89 (s, 3H), 3.77 (s, 3H), 3.75 (s, 2H), 2.78 (s, 3H), 2.34 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.06, 168.79, 152.34, 150.43, 147.92, 136.06, 134.05, 133.76, 131.59, 128.57, 122.82, 113.27, 112.61, 109.75, 61.26, 55.80, 55.67, 42.72, 21.15, 14.07.; IR (neat) 1740 and 1556 cm^{-1}; HRMS (ES, M+H) *m/z* calcd for $C_{23}H_{27}NO_5$ 398.1962 found 398.1961.

4.1.26 {[2,3-Bis(4-methoxyphenyl)-3-oxopropenyl]methylamino}acetic acid ethyl ester (10c). This material was prepared in a manner identical to the previous reflux example **(10d)** with the exception that 3-dimethylamino-1,2-bis(4-methoxyphenyl)propenone was used as the vinylogous amide in which case a dark orange solid (1.46 g, 99% yield) was obtained. An analytical sample was prepared via a Biotage Isolera flash chromatography system yielding a yellow solid, which displayed the following properties: mp 98-99 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.6 Hz, 2H), 7.19 (s, 1H), 7.07 (d, *J* = 8.6 Hz, 2H), 6.74-6.79 (m, 4H), 4.10 (q, *J* = 7.1Hz, 2H), 3.74 (s, 6H), 3.68 (s, 2H), 2.70 (s, 3H), 1.20 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.53, 168.82, 160.90, 158.30, 152.60, 133.81, 132.72, 131.01, 129.05, 113.33, 113.16, 112.89, 61.24, 56.33, 55.20, 55.11, 42.67, 14.07; IR (neat) 1746 and 1625 cm^{-1} ; HRMS (ES, M+H) *m/z* calcd for $C_{22}H_{25}NO_5$ 384.1805 found 384.1832.

4.1.27 {Methyl-[3-oxo-2-p-tolyl-3-(2,3,4-trimethoxyphenyl)propenyl]amino}acetic acid ethyl ester (10e). This material was prepared in a manner identical to the previous reflux example **(10d)** with the exception that 3-dimethylamino-2-p-tolyl-1-(2,3,4-trimethoxyphenyl)propenone was used as the vinylogous amide in which case a dark orange solid (1.41g, 93%) was obtained. An analytical sample was prepared via a Biotage Isolera flash chromatography system, which exhibited the following properties: 54-56 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (broad s, 4H), 6.96 (d, *J* = 8.6 Hz, 1H), 6.64 (d, *J* = 8.6 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.91 (s, 3H), 3.88 (s, 3H), 3.87 (s, 3H), 3.66 (s, 2H), 2.77 (s, 3H), 2.34 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.78, 168.55, 154.01, 153.42, 151.01, 141.89, 136.25, 132.78, 131.59, 129.41, 128.51, 123.57,

115.11, 106.90, 61.87, 61.25, 60.93, 56.04, 21.21, 14.04.; IR (neat) 1742 and 1578 cm^{-1}; HRMS (ES, M+H) *m/z* calcd for $C_{24}H_{29}NO_6$ 428.2068 found 428.2110.

4.1.28 Benzyl-[3-(4-methoxyphenyl)-3-oxo-2-p-tolyl-propenyl]amino}acetic acid ethyl ester (10f). Into a 100 ml round bottom flask equipped with a reflux condenser and a stir bar was added (3-dimethylamino-1-(4-methoxyphenyl)-2-p-tolylpropenone (0.755 g, 2.56 mmol), N-benzyl glycine ethyl ester (.985 g, 5.12 mmol), ethanol (20 ml), and trifluoroacetic acid (0.329 ml, 5.12 mmol). The reaction mixture was heated to reflux overnight, cooled to room temperature, and the solvent was removed *in vacuo* to yield a crude yellow oil. Purification on a Biotage Isolera automated flash chromatography system (hexane/ethyl acetate gradient) produced a yellow solid (0.820 g, 72% yield), which displayed the following properties: 92-93 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.7 Hz, 2H), 7.44 (s, 1H), 7.40-7.30 (m, 3H), 7.19 (dd, *J* = 7.7, 1.8 Hz, 2H), 7.09 (s, 4H), 6.81 (d, *J* = 8.8 Hz, 2H), 4.31 (s, 2H), 4.08 (q, *J* = 7.2 Hz, 2H), 3.83 (s, 3H), 3.58 (s, 2H), 1.20 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.74, 168.75, 160.98, 152.27, 136.34, 135.94, 133.77, 133.67, 131.41, 131.04, 128.91, 128.84, 128.07, 127.98, 113.92, 113.03, 112.96, 61.13, 59.63, 55.24, 51.39, 21.23, 14.02.; IR (neat) 1737 and 1586 cm^{-1}; HRMS (ES, M+H) *m/z* calcd for $C_{28}H_{29}NO_4$ 444.2169 found 444.2136.

4.1.29 {Benzyl-[2,3-bis(4-methoxyphenyl)-3-oxo-propenyl]amino}acetic acid ethyl ester (10g). This material was prepared in a manner identical to the previous example **(10f)** with the exception that 3-dimethylamino-1,2-bis-(4-methoxyphenyl)-propenone was used as the vinylogous amide in which case a yellow solid (0.637 g, 84% yield) was obtained, which displayed the following properties: 89-91 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, *J* = 9.0 Hz, 2H), 7.44 (s, 1H), 7.40-7.29 (m, 3H), 7.17 (d, *J* = 9.0, 2H), 7.12 (d, *J* = 9.0 Hz, 2H), 6.82 (d, *J* = 9.0 Hz, 2H), 6.79 (d, *J* = 9.0 Hz, 2H), 4.31 (s, 2H), 4.08 (q, *J* = 7.2 Hz, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 3.61 (s, 2H), 1.21 (t, *J* = 7.2 Hz, 3H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.85, 168.78, 160.99, 158.52, 152.36, 135.96, 133.77, 132.60, 131.04, 128.85, 128.83, 128.08, 127.97, 113.62, 113.57, 112.98, 61.16, 59.52, 55.24, 55.14, 51.45, 14.02. IR (neat) 1749 and 1586 cm^{-1}. HRMS (ES, M+H) calcd for $C_{28}H_{29}NO_5$ 460.2118 found 460.2128.

4.1.30. 4-(4-Methoxyphenyl)-1,3-dimethyl-1*H*-pyrrole-2-carboxylic acid ethyl ester (12a) and 2-(4-methoxyphenyl)-3-oxo-butyraldehyde (11) under base mediated conditions. Into a 100 mL three neck round bottom flask equipped with a magnetic stir bar and reflux condenser under an inert atmosphere was placed dry THF (30 mL) sodium hydride (0.137 g, 3.40 mmol) and {[2-(4-methoxyphenyl)-3-oxo-but-1-enyl]methylamino}acetic acid ethyl ester (0.500 g, 1.72 mmol). The reaction mixture was stirred at room temperature overnight, brought to neutral pH with acetic acid and diluted with water (50 mL). The aqueous phase was extracted with ethyl acetate (3 x 20 mL) and the combined organic phases were washed with brine (20 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo* to yield a dark oil, which by ^{1}H NMR analysis was suggestive of a 60:40 mixture of 4-(4-methoxyphenyl)-1,3-dimethyl-1*H*-pyrrole-2-carboxylic acid ethyl ester[7] and 2-(4-methoxyphenyl)-3-oxo-butyraldehyde **(11)**[17].

4.1.31. 2-(4-Methoxyphenyl)-3-oxobutyraldehyde (11). Into a 100 mL round bottom flask equipped with a magnetic stir bar and a rubber septum was placed {[2-(4-methoxyphenyl)-3-oxo-but-1-enyl]-methylamino}-acetic acid ethyl ester (1.41 g, 4.85 mmol), 25 % by weight aqueous sodium hydroxide (2 mL), THF (15 mL) and water (15 mL). The reaction mixture was stirred overnight at room temperature, brought to neutral pH with acetic acid, and diluted with water (50 mL). This mixture was then extracted with ethyl acetate (3 x 20 mL) and the combined organic phases were washed with brine (20 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo* to yield a dark oil (0.886 g, 95 %). An analytical sample was prepared via a Biotage Isolera

flash chromatography system and it displayed the following properties: mp. 43-45 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 15.33 (d, *J* = 6.5 Hz, 1H), 8.20 (d, *J* = 6.5 Hz, 1H), 7.14 (d, *J* = 8.7 Hz, 2H), 6.94 (d, *J* = 8.7 Hz, 2H), 3.85 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.40, 178.98, 159.05, 131.33, 127.37, 116.94, 114.08, 55.28, 24.68; IR (neat) 2559 cm^{-1}, 1645 cm^{-1}; HRMS (ES, M+H) *m/z* calcd for $C_{11}H_{12}O_3$ 193.0859 found 193.0841.

4.1.32. 4-(4-Methoxyphenyl)-1,3-dimethyl-1*H*-pyrrole-2-carboxylic acid ethyl ester (12a) in a stepwise reaction. Into a 100 mL round bottom flask equipped with a magnetic stir bar and a reflux condenser was placed {[2-(4-methoxyphenyl)-3-oxo-but-1-enyl]methylamino}acetic acid ethyl ester (0.500 g, 2.28 mmol) and glacial acetic acid (15 mL). The reaction mixture was heated at reflux overnight. The crude reaction mixture was diluted with ethyl acetate (35 mL), washed with saturated aqueous sodium bicarbonate solution (3 x 20 mL) and brine (20 mL), and dried over anhydrous sodium sulfate. The organic phases were combined and concentrated *in vacuo* to yield a brown oil (0.440 g, 94% yield). From this material, an analytical sample was prepared via flash chromatography on a Biotage Isolera system using a hexane/ethyl acetate gradient, which yielded a yellow solid that displayed the following properties: mp 49-51°C; ^{1}H NMR (300 MHz, Acetone-d_6) δ 7.27 (d, *J* = 8.8 Hz, 2H), 6.99-6.91 (m, 3H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.90 (s, 3H), 3.81 (s, 3H), 2.36 (s, 3H), 1.37 (t, *J* = 7.1 Hz, 3H) ; ^{13}C NMR (75 MHz, Acetone-d_6) δ 161.58, 158.30, 129.49, 127.71, 126.98, 125.82, 124.30, 120.41, 113.77, 59.16, 54.62, 36.79, 13.93, 11.82; IR (neat) 1685 cm^{-1}; HRMS (ES, M+H) *m/z* calcd for $C_{16}H_{19}NO_3$ 274.1438 found 274.1412.

4.1.33. 3,4-Bis(4-methoxyphenyl)-1-methyl-1*H*-pyrrole-2-carboxylic acid ethyl ester (12b) in a stepwise reaction. This material was prepared in a manner identical to the previous example **(12a)** with the exception that {[2,3-bis(4-methoxyphenyl)-3-oxo-propenyl]methylamino}acetic acid ethyl ester was used as the exchanged vinylogous amide in which case a brown oil (0.451 g, 95%) was obtained. An analytical sample was prepared via automated flash chromatography on a Biotage Isolera system using a hexane/ethyl acetate gradient, which yielded a yellow solid that was identical by ^{1}H analysis to 3,4-bis-(4-methoxyphenyl)-1-methyl-1*H*-pyrrole-2-carboxylic acid ethyl ester previously prepared by our group.[1]

4.1.34. 3-(4-Methoxyphenyl)-1-methyl-4-*p*-tolyl-1*H*-pyrrole-2-carboxylic acid ethyl ester (12c) in a stepwise reaction. This material was prepared in a manner identical to the previous example **(12a) w**ith the exception that {[3-(4-methoxyphenyl-3-oxo-2-*p*-tolyl-propenyl]-methylamino}acetic acid ethyl ester was used as the exchanged vinylogous amide and the crude reaction mixture was filtered through a short plug of silica using a 1:1 solution of ethyl acetate:hexane (120 ml) in which case a brown-orange solid (0.349 g, 81% yield) was obtained. An analytical sample was prepared via automated flash chromatography to yield a yellow solid, which displayed the following properties: mp 102-103 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (d, *J* = 8.7 Hz, 2H), 7.03-6.96 (m, 4H), 6.93 (s, 1H), 6.84 (d, *J* = 8.7 Hz, 2H), 4.10 (q, *J* = 7.2 Hz, 2H), 3.99 (s, 3H), 3.84 (s, 3H), 2.29 (s, 3H), 1.03 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.88, 158.34, 135.28, 131.74, 131.69, 130.66, 128.83, 128.34, 127.96, 126.68, 124.11, 120.70, 112.90, 59.60, 55.18, 37.53, 21.02, 13.84; IR (neat) 1686 cm^{-1}; HRMS (ES, M+Na) *m/z* calcd for $C_{22}H_{23}NO_3$ 372.1570 found 372.1579.

4.1.35. 3-(3,4-Dimethoxyphenyl)-4-*p*-tolyl-1-methyl-1*H*-pyrrole-2-carboxylic acid ethyl ester (12d) in a stepwise reaction. This material was prepared in a manner identical to the previous example **(12a)** with the exception that {[3-(3,4-dimethoxyphenyl-3-oxo-2-*p*-tolyl-propenyl]-methylamino}acetic acid ethyl ester was used as the exchanged vinylogous amide in which case a brown solid (0.378 g, 88%) was obtained. An analytical sample was prepared via flash chromatography on a Biotage Isolera system using a hexane/ethyl acetate gradient, which yielded a yellow solid that displayed the following properties: mp 114-117 °C; ^{1}H NMR (300 MHz, $CDCl_3$)

δ 6.98 (s, 4H), 6.90 (s, 1H), 6.83-6.73 (m, 3H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.95 (s, 3H), 3.88 (s, 3H), 3.74 (s, 3H), 2.27 (s, 3H), 1.03 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.79, 148.01, 147.79, 135.26, 131.65, 130.64, 128.81, 128.67, 127.91, 126.63, 124.09, 123.06, 120.67, 114.46, 110.49, 59.57, 55.78, 55.73, 37.43, 20.99, 13.94; IR (neat) 1687 cm^{-1}; HRMS (ES, M+Na) *m/z* calcd for $C_{23}H_{25}NO_4$ 402.1676 found 402.1693.

4.1.36. 1-Benzyl-3,4-bis-(4-methoxyphenyl)-1H-pyrrole-2-carboxylic acid ethyl ester (12e) in a stepwise reaction. This material was prepared in a manner identical to the previous example **(12a)** with the exception that {benzyl-[2,3-bis-(4-methoxyphenyl)-3-oxo-propenyl]amino}acetic acid ethyl ester was used as the exchanged vinylogous amide in which case a light yellow solid was obtained (0.367 g, 80% yield), which displayed the following properties: mp 128-129 °C; (500 MHz, $CDCl_3$) δ 7.36 (t, *J* = 10.0 Hz, 2H), 7.31 (t, *J* =10.0 Hz, 1H), 7.25 (d, *J* = 10.0 Hz, 2H), 7.16 (d, *J* = 10.0 Hz, 2H), 7.02 (d, *J* = 10.0 Hz, 2H), 6.99 (s, 1H), 6.85 (d, *J* = 10.0 Hz, 2H), 6.74 (d, *J* = 10.0 Hz, 2H), 5.61 (s, 2H), 4.03 (q, *J* = 7.1 Hz, 2H), 3.84 (s, 3H), 3.77 (s, 3H), 0.96 (t, *J* = 7.1 Hz, 3H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.70, 158.36, 157.88, 138.20, 131.80, 130.99, 129.18, 128.66, 128.30, 127.49, 127.13, 125.80, 124.37, 120.33, 113.60, 112.92, 59.67, 55.19, 55.15, 52.72, 13.73; IR (neet) 1689 cm^{-1}; HRMS (ES, M+Na) *m/z* calcd for $C_{28}H_{27}NO_4$ 464.1832 found 464.1854.

4.1.37. 1-Benzyl-3-(4-methoxyphenyl)-4-*p*-tolyl-1H-pyrrole-2-carboxylic acid ethyl ester (12f) in a stepwise reaction. This material was prepared in a manner identical to the previous procedure **(12a)** with the exception that {benzyl-[3-(4-methoxyphenyl)-3-oxo-2-p-tolyl-propenyl]amino}acetic acid ethyl ester was used as the exchanged vinylogous amide in which case an orange solid (0.598, 88% yield) was obtained. This material displayed the following properties: mp 89-91^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.29 (m, 3H), 7.31(d, *J* = 10.0 Hz, 2H), 7.25 (d, *J* = 9.0 Hz, 2H), 7.01 (s, 1H), 6.99 (s, 4H), 6.84 (d, *J* = 9.0 Hz, 2H), 5.60 (s, 2H), 4.02 (d, *J* = 7.1 Hz, 2H), 3.83 (s, 3H), 2.28 (s, 3H), 0.95 (t, *J* = 7.1 Hz, 3H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.70, 158.38, 138.17, 135.36, 131.77, 131.63, 131.11, 128.82, 128.66, 128.30, 127.97, 127.49, 127.13, 126.07, 124.64, 120.41, 112.91, 59.68, 55.19, 52.75, 21.03, 13.73; IR (neat) 1693 cm^{-1}; HRMS (ES, M+Na) calcd for $C_{28}H_{27}NO_3$ 448.1883 found 448.1848.

4.1.38 4-(4-Methoxyphenyl)-1,3-dimethyl-1*H*-pyrrole-2-carboxylic acid ethyl ester (12a) by a one-pot reaction. Into a 100 mL round bottom flask equipped with a magnetic stir bar and a reflux condenser was placed 4-dimethylamino-3-(4-methoxyphenyl)-but-3-en-2-one (0.500 g, 2.28 mmol), sarcosine ethyl ester hydrochloride (0.876 g, 5.70 mmol), and glacial acetic acid (15 mL). The reaction mixture was heated at reflux overnight and the crude reaction mixture was diluted with ethyl acetate (35 mL), washed with saturated aqueous sodium bicarbonate (3 x 20 mL) and brine (20 mL), and dried over anhydrous sodium sulfate. After filtration the organic phase was concentrated *in vacuo* to yield a brown oil (0.507 g, 81%). An analytical sample was prepared via flash chromatography on a Biotage Isolera system using a hexane/ethyl acetate gradient, which yielded a yellow solid, which was identical by ^{1}H NMR to 4-(4-methoxyphenyl)-1,3-dimethyl-1*H*-pyrrole-2-carboxylic acid ethyl ester **(12a)** prepared via the stepwise route.

4.1.39 3,4-Bis-(4-methoxyphenyl)-1-methyl-1*H*-pyrrole-2-carboxylic acid ethyl ester by a one-pot reaction (12b). This material was prepared in a manner identical to the previous example **(12a)** with the exception that 3-dimethylamino-1,2-bis-(4-methoxyphenyl)propenone was used as the vinylogous amide in which case automated flash chromatography yielded a yellow solid (0.426 g, 73 %), which was identical by ^{1}H NMR to a sample of 3,4-bis-(4-methoxyphenyl)-1-methyl-1*H*-pyrrole-2-carboxylic acid ethyl ester **(12b)** previously prepared by our group.[1]

4.1.40 3-(4-Methoxyphenyl)-4-*p*-tolyl-1-methyl-1*H*-pyrrole-2-carboxylic acid ethyl ester by a one-pot reaction (12c). This material was prepared in a manner identical to the previous example **(12a)** with the exception that 3-dimethylamino-1-(4-methoxyphenyl)-2-p-tolyl-propenone was used as the vinylogous amide in which case an orange solid (0.530 g, 86% yield) was obtained. An analytical sample was prepared via automated flash chromatography to yield a yellow solid, which was identical by ^{1}H NMR to 3-(4-methoxyphenyl)-4-p-tolyl-1-methyl-1*H*-pyrrole-2-carboxylic acid ethyl **(12c)** prepared via the stepwise route.

4.1.41 3-(3,4-Dimethoxyphenyl)-4-*p*-tolyl-1-methyl-1*H*-pyrrole-2-carboxylic acid ethyl ester (12d) by a one-pot reaction. This material was prepared in a manner identical to the previous example **(12a)** with the exception that 3-dimethylamino-1-(3,4-dimethoxyphenyl)-2-p-tolyl-propenone was used as the vinylogous amide in which case a brown solid (0.464 g, 87% yield) was obtained. An analytical sample was prepared via flash chromatography on a Biotage Isolera system using a hexane/ethyl acetate gradient yielding a yellow solid, which was identical by ^{1}H NMR to 3-(3,4-dimethoxyphenyl)-4-p-tolyl-1-methyl-1*H*-pyrrole-2-carboxylic acid ethyl ester **(12d)** prepared via the stepwise route.

4.1.42 3-(4-Methoxyphenyl)-1-methyl-4-phenyl-1*H*-2-carboxylic acid ethyl ester in a one-pot reaction (12g). This material was prepared in a manner identical to the previous example **(12a)** with the exception that 3-dimethylamino-1-(4-methoxyphenyl)-2-phenyl-propenone (0.689 g, 2.45 mmol) was used as the vinylogous amide in which case an oily solid (0.591 g, 72%) was obtained. An analytical sample was prepared via flash chromatography on a Biotage Isolera system using a hexane/ethyl acetate gradient in which case a yellow solid was obtained and displayed the following properties: : mp 85-87 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 – 7.06 (m, 7H), 6.95 (s, 1H), 6.84 (d, *J* = 8.8 Hz, 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 4.00 (s, 3H), 3.83 (s, 3H), 1.03 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.87, 158.45, 134.74, 131.81, 130.76, 128.27, 128.13, 126.89, 125.77, 124.17, 120.85, 112.97, 59.66, 55.17, 37.56, 13.89; IR (neat) 1689 cm^{-1}; HRMS (ES, M+Na) *m/z* calcd for $C_{21}H_{21}NO_3$ 358.1414 found 358.1432.

4.1.43 4-(4-Bromophenyl)-3-(4-methoxyphenyl)-1-methylpyrrole-2-carboxylic acid ethyl ester (12h) in a one-pot reaction. This material was prepared in a manner identical to the previous example **(12a)** with the exception that 2-(4-bromophenyl)-3-dimethylamino-1-(4-methoxyphenyl) propenone was used as the vinylogous amide in which case a brown solid (0.500 g, 87%) was obtained. An analytical sample was prepared via flash chromatography on a Biotage Isolera system using a hexane/ethyl acetate gradient, yielding a pale yellow solid, which displayed the following properties: mp 148-149 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.7 Hz, 2H), 7.11 (d, *J* = 8.7 Hz, 2H), 6.99-6.90 (m, 3H), 6.85 (d, *J* = 8.7 Hz, 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.99 (s, 3H), 3.84 (s, 3H), 1.03 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.73, 158.51, 133.67, 131.68, 131.20, 130.60, 129.60, 127.82, 126.61, 122.95, 121.02, 119.66, 113.04, 59.72, 55.19, 37.60, 13.83; IR (neat) 1685 cm^{-1}; HRMS (ES, M+Na) *m/z* calcd for $C_{21}H_{20}NO_3Br$ 436.0519 found 436.0488.

4.1.44 4-(4-Chlorophenyl)-3-(4-methoxyphenyl)-1-methylpyrrole-2-carboxylic acid ethyl ester (12i) by a one-pot reaction. This material was prepared in a manner identical to the previous example **(12a)** with the exception that 2-(4-chlorophenyl)-3-dimethylamino-1-(4-methoxyphenyl)-propenone was used as a the vinylogous amide in which case a brown solid (0.535 g, 91%) was obtained. An analytical sample was prepared via flash chromatography on a Biotage Isolera system using a hexane/ethyl acetate gradient, which yielded a yellow solid, which displayed the following properties: mp 134-135 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19-7.08 (m, 4H), 7.00 (d, *J* = 8.5 Hz, 2H), 6.93 (s, 1H), 6.85 (d, *J* = 8.5 Hz, 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.98 (s, 3H), 3.83 (s, 3H), 1.03 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.74, 158.50, 133.20, 131.68, 131.55, 130.63,

129.25, 128.26, 127.85, 126.64, 122.96, 120.98, 113.03, 59.71, 55.19, 37.59, 13.82; IR (neat) 1685 cm^{-1}; HRMS (ES, M+Na) *m/z* calcd for $C_{21}H_{20}NO_3Cl$ 392.1024 found 392.1037.

4.1.45 4-(3,4-Dimethoxyphenyl)-3-(4-methoxyphenyl)-1-methylpyrrole-2-carboxylic acid ethyl ester (12j) in a one-pot reaction. This material was prepared in a manner identical to the previous example **(12a)** with the exception that 3-dimethylamino-2-(3,4-dimethoxyphenyl)-2-(4-methoxyphenyl)-propenone was used as the vinylogous amide in which case a brown solid (0.450 g, 91%) was obtained. An analytical sample was prepared via flash chromatography on a Biotage Isolera system using a hexane/ethyl acetate gradient, which yielded a yellow solid, which displayed the following properties: mp 102-104 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (d, *J* = 8.7 Hz, 2H), 6.94 (s, 1H), 6.86 (d, *J* = 8.7 Hz, 2H), 6.75 (broad s, 2H), 6.52 (broad s, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 4.00 (s, 3H), 3.85 (s, 3H), 3.82 (s, 3H), 3.55 (s, 3H), 1.03 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.82, 158.40, 148.33, 147.18, 131.79, 130.53, 128.55, 127.49, 126.29, 123.85, 120.68, 119.81, 113.00, 111.80, 111.08, 59.61, 55.78, 55.35, 55.26, 37.51, 13.82; IR (neat) 1680 cm^{-1}; HRMS (ES, M+Na) *m/z* calcd for $C_{23}H_{25}NO_5$ 418.1625 found 418.1656.

4.1.46 4-(2,3,4-Dimethoxyphenyl)-3-(4-methoxyphenyl)-1-methylpyrrole-2-carboxylic acid ethyl ester (12k) in a one pot reaction. This material was prepared in a manner identical to the previous example **(12a)** with the exception that 3-dimethylamino-2-(2,3,4-dimethoxyphenyl)-2-(4-methoxyphenyl)propenone (0.323g, 0.87 mmol) was used as the vinylogous amide in which case an orange solid (0.280 g, 76%) was obtained. An analytical sample was prepared via flash chromatography on a Biotage Isolera system using a hexane/ethyl acetate gradient and a yellow solid was obtained, which displayed the following properties: mp 58-60 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (d, *J* = 8.9 Hz, 2H), 6.98 (s, 1H), 6.79 (d, *J* = 8.9 Hz, 2H), 6.59 (d, *J* = 8.6 Hz, 1H), 6.46 (d, *J* = 8.6 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.98 (s, 3H), 3.84 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H), 3.60 (s, 3H), 1.06 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.89, 158.19, 152.22, 151.67, 142.19, 131.67, 128.55, 128.41, 125.99, 121.18, 119.79, 119.36, 112.68, 106.78, 60.78, 60.40, 59.59, 55.85, 55.15, 37.58, 13.89; IR (neat) 1685 cm^{-1}; HRMS (ES, M+Na) *m/z* calcd for $C_{24}H_{27}NO_6$ 448.1731 found 448.1725.

4.1.47 1-Benzyl-4-(4-methoxyphenyl)-3-methylpyrrole-2-carboxylic acid ethyl ester (12l) by a one-pot reaction. Into a 100 mL round bottom flask equipped with magnetic stir bar and reflux condenser was added 4-dimethlamino-3-(4-methoxyphenyl)-but-3-en-2-one (0.500 g, 2.23 mmol), N-benzylglycine ethyl ester (0.881 g, 4.56 mmol), and acetic acid (20 mL). The reaction mixture was heated at reflux overnight, cooled, and the solvent was removed *in vacuo*. The crude mixture was then filtered through a short plug of silica with a 20:80 mixture of ethyl acetate:hexane. The solvent was removed *in vacuo* to yield a brown oil (0.489 g, 61% yield). An analytical sample was prepared via automated flash chromatography to yield a brown solid, which exhibited the following properties: mp 54-56˚C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (t, *J* = 10.0 Hz, 2H), 7.26-7.30 (m, 3H), 7.15 (d, *J* = 10.0 Hz, 2H), 6.95 (d, *J* = 10.0 Hz, 2H), 6.87 (s, 1H), 5.56 (s, 2H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.85 (s, 3H), 2.42 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.99, 158.22, 138.55, 129.76, 128.55, 127.58, 127.35, 127.28, 126.82, 126.37, 125.21, 120.10, 113.84, 59.68, 55.29, 52.72, 14.37, 12.51; IR (neat) 1693 cm^{-1}; HRMS (ES, M+Na) *m/z* calcd for $C_{22}H_{23}NO_3$ 372.1570 found 372.1581.

4.1.48 1-Benzyl-3-(3,4-dimethoxyphenyl)-4-*p*-tolylpyrrole-2-carboxylic acid ethyl ester (12m) by a one-pot reaction. This material was prepared in a manner identical to the previous example **(12l)** with the exception that 1-(3,4-dimethoxyphenyl)-3-dimethylamino-2-p-tolyl-propenone was used as the vinylogous amide in which case a yellow solid (0.440 g, 60% yield) was obtained, which displayed the following properties: mp 44-46 ˚C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (t, *J* =

7.4 Hz, 2H), 7.31 (d, *J* = 7.4 Hz, 1H), 7.26 (d, *J* = 7.4 Hz, 2H), 7.03 (s, 1H), 7.00 (broad s, 4H), 6.85 – 6.78 (m, 3H), 5.61 (s, 2H), 4.05 (q, *J* = 7.1 Hz, 2H), 3.91 (s, 3H), 3.77 (s, 3H), 2.29 (s, 3H), 0.98 (t, *J* = 7.1 Hz, 3H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.68, 147.99, 147.78, 138.09, 135.41, 131.56, 131.09, 128.81, 128.66, 128.57, 127.92, 127.52, 127.19, 125.96, 124.65, 123.06, 120.36, 114.41, 110.43, 59.69, 55.81,52.72, 29.70, 21.02, 13.82; IR (neat) 1693 cm^{-1}. HRMS (ES, M+Na) *m/z* calcd for $C_{29}H_{29}NO_4$ 478.1989 found 478.2026.

4.1.49 1-Benzyl-3,4-bis-(4-methoxyphenyl)-1H-pyrrole-2-carboxylic acid ethyl ester (12e) by a one-pot reaction. This material was prepared in a manner identical to the previous example **(12l)** with the exception that 3-dimethylamino-1,2-bis-(4-methoxyphenyl)-propenone was used as the vinylogous amide in which case a yellow solid (0.340 g, 58 % yield) was obtained and displayed a proton NMR spectrum identical to the pyrrole prepared by the stepwise process: (500 MHz, $CDCl_3$) δ 7.36 (t, *J* = 10.0 Hz, 2H), 7.31 (t, *J* =10.0 Hz, 1H), 7.25 (d, *J* = 10.0 Hz, 2H), 7.16 (d, *J* = 10.0 Hz, 2H), 7.02 (d, *J* = 10.0 Hz, 2H), 6.99 (s, 1H), 6.85 (d, *J* = 10.0 Hz, 2H), 6.74 (d, *J* = 10.0 Hz, 2H), 5.61 (s, 2H), 4.03 (q, *J* = 7.1 Hz, 2H), 3.84 (s, 3H), 3.77 (s, 3H), 0.96 (t, *J* = 7.1 Hz, 3H).

4.1.50 1-Benzyl-3-(4-methoxyphenyl)-4-*p*-tolylpyrrole-2-carboxylic acid ethyl ester (12f) in a one-pot fashion. This material was prepared in a manner identical to the previous example **(12l) (12l)** with the exception that 3-dimethylamino-1-(4-methoxyphenyl)-2-p-tolyl-propenone was used as the vinylogous amide in which case a yellow solid (0.502 g, 67% yield) was obtained, which was identical by ^{1}H NMR analysis to 1-benzyl-3-(4-methoxyphenyl)-4-p-tolyl-1-1*H*-pyrrole-2-carboxylic acid ethyl ester prepared via the stepwise process: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.29 (m, 3H), 7.25 (d, *J* = 7.2 Hz, 2H), 7.17 (d, *J* = 8.6 Hz, 2H), 7.01 (s, 1H), 6.99 (s, 4H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.61 (s, 2H), 4.03 (q, *J* = 7.1 Hz, 2H), 3.84 (s, 3H), 2.29 (s, 3H), 0.96 (t, *J* = 7.1 Hz, 3H).

4.1.51. 4-(4-Methoxyphenyl)-1,3-dimethylpyrrole-2-carboxylic acid ethyl ester (12a) from 2-(4-methoxyphenyl)-3-oxo-butyraldehyde (11). Into a 100 mL round bottom flask equipped with a magnetic stir bar and a reflux condenser was placed 2-(4-methoxyphenyl)-3-oxo-butyraldehyde (0.482 g, 2.51 mmol), sarcosine ethyl ester hydrochloride (0.963 g, 6.27 mmol), and glacial acetic acid (15 mL). The reaction mixture heated at reflux overnight and the crude reaction mixture was diluted with ethyl acetate (35 mL), washed with saturated aqueous sodium bicarbonate (3 x 20 mL) and brine (20 mL), and dried over anhydrous sodium sulfate. The organic phase was concentrated *in vacuo* and then filtered through a short plug of silica using a 35:65 mixture of ethyl acetate:hexane (100 mL). The eluent was concentrated *in vacuo* to yield a brown oil (0.377 g, 55%) and an analytical sample was prepared via flash chromatography on a Biotage Isolera system using a hexane/ethyl acetate gradient, which yielded a yellow solid. This material was identical by ^{1}H NMR to 4-(4-methoxyphenyl)-1,3-dimethyl-1*H*-pyrrole-2-carboxylic acid ethyl ester **(12a)** prepared via the stepwise route.

4.1.52 (E/Z) 3-Chloro-3-(4-methoxyphenyl)-2-*p*-tolyl-propenal (13c). Into a 100 ml round bottom flask equipped with a magnetic stir bar was placed 3-dimethylamino-1-(4-methoxyphenyl)-2-p-tolyl-propenone (3.69 g, 12.5 mmol), anhydrous dichloromethane (30 ml) and phosphorous oxychloride (1.17 ml, 12.5 mmol) was added dropwise to the stirred solution and the reaction mixture was stirred overnight at room temperature. The reaction mixture was quenched by addition of saturated aqueous, sodium bicarbonate (20 ml) and the biphasic mixture was stirred for 30 minutes. The phases were separated and the aqueous phase was extracted with additional dichloromethane (2 x 15 ml) and the combined organic phases were filtered through a short plug of silica with a 30:70 mixture of ethyl acetate:hexane. The organic phase was then concentrated *in vacuo* to yield an orange solid (3.362 g, 94 % yield), which by ^{1}H NMR was a 4:1 mixture of E:Z

isomers. The crude product was separated into the two isomers by flash chromatography with a hexane/ethyl acetate gradient in which case the following materials were obtained: (E isomer, **13c-1**): white solid; 117-118 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.69 (s, 1H), 7.54 (d, *J* = 8.8 Hz, 2H), 7.28 (d, *J* = 8.3 Hz, 2H), 7.20 (d, *J* = 8.3 Hz, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 3.91 (s, 3H), 2.42 (s, 3H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.06, 161.87, 154.98, 140.03, 138.19, 132.14, 131.39, 129.76, 129.00, 128.11, 113.99, 55.53, 21.38.; IR (neat) 1665 cm^{-1}. HRMS (ES, M+Na) calcd for $C_{17}H_{15}O_2Cl$ 309.0653 found 309.0657. (Z isomer, **13c-2**): yellow oil; bp 109-110 °C @ 0.300 torr; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.58 (s, 1H), 7.27 (d, *J* = 8.3 Hz, 2H), 7.08 (d, *J* = 8.3 Hz, 2H), 6.90 (d, *J* = 8.9 Hz, 2H), 6.73 (d, *J* = 8.9 Hz, 2H), 3.79 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.58, 160.82, 150.27, 137.69, 136.37, 131.58, 131.25, 130.46, 129.52, 129.09, 113.37, 55.28, 21.24.; IR (neat) 1676 cm^{-1}; HRMS (ES, M+Na) calc for $C_{17}H_{15}O_2Cl$ 309.0653 found 309.0647.

4.1.53 3-(4-Methoxyphenyl)-4-*p*-tolyl-1H-pyrrole-2-carboxylic acid ethyl ester (12c) from the E-chloroenal isomer (13c-1). Into a nitrogen flushed 3-neck, round bottom flask equipped with a magnetic stir bar, and a reflux condenser was placed (E)-3-chloro-3-(4-methoxyphenyl)-2-p-tolylpropenal (0.500 g, 1.65 mmol), glycine ethyl ester HCl (.346 g, 2.48 mmol), 4A molecular sieves (10 g), and anhydrous DMF (60 ml). The reaction mixture was heated at reflux for 4 hours, cooled to room temperature, and the solvent was removed *in vacuo*. The crude solid was dissolved in a minimal amount of dichloromethane and filtered through a short plug of silica with a 50:50 mixture of ethyl acetate:hexane. The solvent was removed *in vacuo* to yield a brown solid (0.488 g, 83% yield), which exhibited the following properties:82-83 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.16 (s, 1H), 7.22 (d, *J* = 8.7 Hz, 2H), 7.08 (d, *J* = 3.1 Hz, 1H), 7.03 (s, 4H), 6.86 (d, *J* = 8.7 Hz, 2H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.84 (s, 3H), 2.31 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.43, 158.55, 135.51, 131.97, 131.83, 129.06, 128.92, 128.21, 126.83, 126.57, 120.46, 119.85, 113.02, 60.16, 55.16, 21.09, 14.20.; IR (neat) 3346 and 1689 cm-1; HRMS (ES, M+Na) calcd for $C_{21}H_{21}NO_3$ 358.1414 found 358.1424.

4.1.54 3-(4-Methoxyphenyl)-4-*p*-tolyl-1H-pyrrole-2-carboxylic acid ethyl ester (12c) from the Z-chloroenal isomer (13c-2). This material was prepared in a manner identical to the previous example **(13c-1)** with the exception that (Z)-3-chloro-3-(4-methoxyphenyl)-2-p-tolyl-propenal was used as the starting material in which case a brown solid (0.062 g, 68 % yield) was obtained, which was identical by ^{1}H NMR to 3-(4-methoxyphenyl)-4-p-tolyl-1H-pyrrole-2-carboxylic acid ethyl ester prepared from (E) 3-chloro-3-(4-methoxyphenyl)-2-p-tolyl-propenal.

4.1.55 3,4-Bis(4-methoxyphenyl)-1*H*-pyrrole-2-carboxylic acid ethyl ester (12n) from the chloroenal isomer mix. Into a 100 ml round bottom flask equipped with a magnetic stir bar was added 3-dimethylamino-1,2-bis-(4-methoxyphenyl)propenone (0.800 g, 2.57 mmol) and anhydrous dichloromethane (20 ml). To the stirred solution was added phosphorusoxy chloride (0.251 mL, 2.70 mmol) dropwise. The reaction mixture was stirred at room temperature overnight and quenched by addition of saturated aqueous sodium bicarbonate (20 mL). The biphasic mixture was stirred for 30 minutes, the phases were separated and the aqueous phase was extracted with dichloromethane (2 x 15 mL). The combined organic phases were filtered through a short plug of silica using a 30:70 mixture of ethyl acetate:hexane (100 ml). The eluent was concentrated *in vacuo* to yield a white solid (0.705 g, 91% yield). A portion of this crude material (0.604 g, 2.00 mmol), glycine ethyl ester hydrochloride (0.418 g, 3.00 mmol), 4A molecular sieves (10 g) and anhydrous DMF (60 ml) were added to a nitrogen flushed 250 mL, 3-neck round bottom flask equipped with a reflux condenser and a magnetic stir bar. The mixture was heated at reflux overnight before, cooled to room temperature and the solvent was removed *in vacuo*. This crude material was then filtered through a short plug of silica using a 50:50 mixture of ethyl acetate:hexane and the eluent was concentrated *in vacuo* to yield a brown solid (0.494 g, 84% yield), which was identical by ^{1}H NMR

to 3,4-bis-(4-methoxyphenyl)-1*H*-pyrrole-2-carboxylic acid ethyl ester previously prepared by our group[1] by a different procedure.

4.1.56 3-(3,4-Dimethoxyphenyl)-4-*p*-tolyl-1*H*-pyrrole-2-caboxylic acid ethyl ester (12o) from the chloroenal isomer mix. This material was prepared in a manner identical to the previous example **(12n)** with the exception that 3-dimethylamino-1-(3,4-dimethoxyphenyl)-2-p-tolylpropenone was used as the vinylogous amide. The crude reaction product was dissolved in ethyl acetate and passed through a short plug of diatomaceous earth. After concentration of the filtrate *in vacuo* an orange solid (.307 g, 59% yield) was obtained, which displayed the following properties: 60-62 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.25 (s, 1H), 7.08 (d, *J* = 5.0 Hz, 1H), 7.03 (s, 4H), 6.87 (dd, *J* = 5.0 Hz, *J* = 1.0 Hz, 1H), 6.83 (s, 1H), 6.81(d, *J* = 1.0 Hz, 1H) , 4.23 (q, *J* = 7.1 Hz, 2H), 3.91 (s, 3H), 3.73 (s, 3H), 2.34 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.07, 147.93, 135.62, 131.61, 129.49, 129.03, 128.85, 128.20, 127.61, 126.80, 123.26, 119.94, 119.78, 114.45, 110.42, 60.11, 55.75, 55.69, 21.03, 14.25.; IR (neat) 1683 cm^{-1}; HRMS (ES, M+Na) calcd for $C_{22}H_{23}NO_4$ 388.1534 found 388.1519.

4.1.57 3-(4-Methoxyphenyl)-4-*p*-tolyl-1H-pyrrole-2-carboxylic acid ethyl ester (12p) from the chloroenal isomer mix. This material was prepared in a manner identical to the previous example **(12n)** with the exception that 3-dimethylamino-1-(4-methoxyphenyl)-2-p-tolyl-propenone was used as the vinylogous amide in which case a brown solid (0.504 g, 85% yield) was obtained, which displayed the following properties: 82-83 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.16 (s, 1H), 7.22 (d, *J* = 8.7 Hz, 2H), 7.08 (d, *J* = 3.1 Hz, 1H), 7.03 (s, 4H), 6.86 (d, *J* = 8.7 Hz, 2H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.84 (s, 3H), 2.31 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.43, 158.55, 135.51, 131.97, 131.83, 129.06, 128.92, 128.21, 126.83, 126.57, 120.46, 119.85, 113.02, 60.16, 55.16, 21.09, 14.20.; IR (neat) 1689 cm-1; HRMS (ES, M+Na) calcd. for $C_{21}H_{21}NO_3$ 358.1414 found 358.1424.

4.1.58 4-(4-Methoxyphenyl)-3-methyl-1*H*-pyrrole-2-carboxylic acid ethyl ester (12q) from the chloroenal isomer mix. This material was prepared in a manner identical to the previous example **(12n)** with the exception that 4-dimethylamino-3-(4-methoxyphenyl)-but-3-en-2-one was used as the vinylogous amide in which case a viscous brown solid (0.219 g, 45% yield) was obtained. An analytical sample was prepared via a Biotage Isolera automated flash chromatography system in which case a tan solid was obtained and exhibited the following properties: mp 157-159˚C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.10 (s, 1H), 7.34 (d, *J* = 8.7 Hz, 2H), 6.99 (d, *J* = 2.8 Hz, 1H), 6.96 (d, *J* = 8.7 Hz, 2H), 4.35 (q, *J* = 7.1 Hz, 2H), 3.86 (s, 3H), 2.43 (s, 3H), 1.39 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.52, 157.96, 130.07, 128.76, 128.42, 123.44, 120.39, 115.19, 113.96, 60.20, 55.29, 14.50, and 12.71; IR (neat) 1671 cm^{-1}; HRMS (ES, M+Na) *m/z* calcd for $C_{15}H_{17}NO_3$ 282.1101 found 282.1113.

4.1.59 3-(4-Methoxyphenyl)-4-phenyl-1*H*-pyrrole-2-carboylic acid ethyl ester (12r) from the chloroenal isomer mix. This material was prepared in a manner identical to the previous example **(12n)** with the exception that 3-dimethylamino-1-(4-methoxyxphenyl)-2-phenylpropenone was used as the vinylogous amide. After purification of the crude product via a Biotage Isolera automated flash chromatography system a white solid (0.509 g, 86% yield) was obtained, which displayed the following properties: mp 133-134˚C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.19 (s, 1H), 7.27 – 7.11 (m, 7H), 7.10 (d, *J* = 3.1 Hz, 1H), 6.85 (d, *J* = 8.8 Hz, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.84 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.36, 158.58, 134.74, 131.95, 129.11, 128.33, 128.16, 126.66, 126.62, 125.98, 120.49, 119.94, 113.02, 60.19, 55.17, and 14.18; IR (neat) 1663 cm^{-1}; HRMS (ES, M+Na) *m/z* calcd for $C_{20}H_{19}NO_3$ 344.1252 found 344.1257.

4.1.60 4-(4-Bromophenyl)-3-(4-methoxyphenyl)-1*H*-pyrrole-2-carboxylic acid ethyl ester (12s) from the chloroenal isomer mix. This material was prepared in a manner identical to the previous example **(12n)** with the exception that 2-(4-bromophenyl)-3-dimethylamino-1-(4-methoxyphenyl)-propenone was used as the vinylogous amide in which case a brown solid (0.578 g, 85% yield) was obtained. An analytical sample was prepared via a Biotage Isolera automated flash chromatography system to yield a tan solid, which displayed the following properties: 141-142 °C; ^{1}H NMR (300 MHz, $CDCl_3$)) δ 9.41 (s, 1H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.7 Hz, 2H), 7.08 (d, *J* = 3.1 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.84 (s, 3H), 1.20 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.14, 158.71, 133.68, 131.85, 131.28, 129.85, 128.95, 126.15, 125.52, 120.18, 119.95, 113.13, 60.26, 55.17, 14.15.; IR (neat) 1661 cm^{-1}; HRMS (ES, M+Na) calcd for $C_{20}H_{18}NO_3Br$ 422.0362 found 422.0411.

4.1.61 4-(3,4-Dimethoxyphenyl)-3-(4-methoxyphenyl)-1*H*-pyrrole-2-carboxylic acid ethyl ester (12t) from the chloroenal isomer mix. This material was prepared in a manner identical to the previous example **(12n)** with the exception that 3-dimethylamino-1-(3,4-dimethoxyphenyl)-2-p-tolyl-propenone was used as the vinylogous amide in which case a red-brown solid (0.413 g, 66% yield) was obtained. An analytical sample was prepared via a Biotage Isolera automated flash chromatography system to yield a light orange solid which displayed the following properties: 51-53 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.25 (s, 1H), 7.23 (d, *J* = 8.7 Hz, 2H), 7.05 (d, *J* = 3.0 Hz, 1H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.80-6.73 (m, 2H), 6.57 (d, *J* = 1.7 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.86 (s, 3H), 3.83 (s, 3H), 3.58 (s, 3H), 1.21(t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.34, 158.56, 148.38, 147.34, 131.95, 128.87, 127.57, 126.98, 126.28, 120.10, 120.01, 119.84, 113.07, 112.01, 111.18, 60.13, 55.80, 55.39, 55.22, 14.15.; IR (neat)1685 cm^{-1}; HRMS (ES, M+Na) calcd for $C_{22}H_{23}NO_5$ 404.1468 found 404.1492.

4.1.62 3,4-Bis-(4-methoxyphenyl)-1-methylpyrrole-2-carboxylic acid ethyl ester (12b) via a chloroenal intermediate. Into a 100 ml round bottom flask equipped with a magnetic stir bar was added 3-dimethylamino-1,2-bis-(4-methoxyphenyl)-propenone (0.800 g, 2.57 mmol) and anhydrous dichloromethane (20 ml). To the stirring solution was added phosphorousoxy chloride (0.251 ml, 0.270 mmol) dropwise. The reaction mixture was stirred at room temperature overnight and quenched by addition of saturated aqueous sodium bicarbonate (20 mL). The biphasic mixture was stirred for 30 minutes before the phases were separated and the aqueous phase was extracted with dichloromethane (2 x 15 mL). The combined organic phases were then filtered through a short plug of silica using a 3:7 mixture of ethyl acetate:hexane (100 ml). The eluent was concentrated *in vacuo* to yield a white solid (0.705 g, 91% yield). A portion of this crude material (0.448 g, 1.48 mmol), and a magnetic stir bar. The mixture was heated to reflux overnight and allowed to cool to room temperature. The solvent was removed *in vacuo,* and the crude material was filtered through a short plug of silica using a 1:1 mixture of ethyl acetate:hexane (120 ml) and the eluent was sarcosine ethyl ester (0.341 g, 2.22 mmol), 4 angstrom molecular sieves (10 g) and anhydrous DMF (60 ml) were added to a nitrogen flushed 250 mL, 3-neck, round bottom flask equipped with a reflux condenser concentrated *in vacuo* to yield an orange solid (0.433 g, 80% yield), which was identical by ^{1}H NMR analysis to 3,4-bis-(4-methoxyphenyl)-1-methylpyrrole-2-carboxylic acid ethyl ester previously prepared by our group.[1]

4.1.63 3-(4-Methoxyphenyl)-4-*p*-tolyl-1-methylpyrrole-2-carboxylic acid ethyl ester (12c) via a chloroenal intermediate. This material was prepared in a manner identical to the previous example **(12b)** with the exception that 3-dimethylamino-1-(4-methoxyphenyl)-2-p-tolyl-propenone was used as the vinylogous amide in which case a brown solid (0.497 g, 82% yield) was obtained, which was identical by ^{1}H NMR analysis to 3-(4-methoxyphenyl)-4-p-tolyl-1-methylpyrrole-2-carboxylic acid ethyl ester prepared via the acetic acid cyclization conditions: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14

(d, *J* = 8.7 Hz, 2H), 7.03-6.96 (m, 4H), 6.93 (s, 1H), 6.84 (d, *J* = 8.7 Hz, 2H), 4.10 (q, *J* = 7.2 Hz, 2H), 3.99 (s, 3H), 3.84 (s, 3H), 2.29 (s, 3H), 1.03 (t, *J* = 7.2 Hz, 3H).

4.1.64 3-(4-Methoxyphenyl)-1-methyl-4-phenylpyrrole-2-carboxylic acid ethyl ester (12g) via a chloroenal intermediate. This material was prepared in a manner identical to the previous example **(12b)** with the exception that 3-dimethylamino-1-(4-methoxyphenyl)-2-phenyl-propenone was used as the vinylogous amide to produce a brown oil (0.589 g, 96% yield) that was purified using a Biotage Isolera flash chromatography system to yield a viscous yellow oil (0.414, 67%), which was identical by ^{1}H NMR to 3-(4-methoxyphenyl)-1-methyl-4-phenylpyrrole-2-carboxylic acid ethyl ester prepared via the acetic acid cyclization conditions: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 – 7.06 (m, 7H), 6.95 (s, 1H), 6.84 (d, *J* = 8.8 Hz, 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 4.00 (s, 3H), 3.83 (s, 3H), 1.03 (t, *J* = 7.1 Hz, 3H)

4.1.65 4-(4-Bromophenyl)-3-(4-methoxyphenyl)-1-methylpyrrole-2-carboxylic acid ethyl ester (12h) via a chloroenal intermediate. This material was prepared in a manner identical to the previous example **(12b)** with the exception that 2-(4-bromophenyl)-3-dimethylamino-1-(4-methoxyphenyl)-propenone was used as the vinylogous amide in which case an orange solid (0.590 g, 73% yield) was obtained, which was identical by ^{1}H NMR analysis to 4-(4-bromophenyl)-3-(4-methoxyphenyl)-1-methyl-1*H*-pyrrole-2-carboxylic acid ethyl ester prepared via the acetic acid cyclization conditions: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.6 Hz, 2H), 7.11 (d, *J* = 8.7 Hz, 2H), 6.99-6.90 (m, 3H), 6.85 (d, *J* = 8.7 Hz, 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.99 (s, 3H), 3.84 (s, 3H), 1.03 (t, *J* = 7.1 Hz, 3H).

4.1.66 3-(3,4-Dimethoxyphenyl)-4-*p*-tolyl-1-methylpyrrole-2-carboxylic acid ethyl (12d) ester via a chloroenal intermediate. This material was prepared in a manner identical to the previous example **(12b)** with the exception that 3-dimethylamino-1-(3,4-dimethoxyphenyl)-2-p-tolyl-propenone was used as the vinylogous amide in which case a red-brown solid was obtained, which was identical by ^{1}H NMR analysis to 3-(3,4-dimethoxyphenyl)-4-p-tolyl-1-methylpyrrole-2-carboxylic acid ethyl ester prepared via the one-pot acetic acid cyclization conditions: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.98 (s, 4H), 6.90 (s, 1H), 6.83-6.73 (m, 3H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.95 (s, 3H), 3.88 (s, 3H), 3.74 (s, 3H), 2.27 (s, 3H), 1.03 (t, *J* = 7.1 Hz, 3H).

4.1.67 1-Benzyl-3-(3,4-dimethoxyphenyl)-4-(4-methoxyphenyl)-pyrrole-2-carboxylic acid ethyl ester (12m). Into a 100 mL round bottom flask equipped with a magnetic stir bar was added 1-(3,4-dimethoxyphenyl)-3-dimethylamino-2-*p*-tolyl-propenone (2.642 g, 8.12 mmol) and anhydrous dichloromethane (32 ml). To the stirred solution was added phosphorous oxychloride (0.805 mL, 1.324 mmol) dropwise. The reaction mixture was stirred at room temperature overnight and quenched by addition of saturated aqueous sodium bicarbonate solution (34 mL). The biphasic mixture was stirred for 30 minutes before the phases were separated and the aqueous phase was extracted with dichloromethane (3 x 15 mL). The combined organic phases were then filtered through a short plug of silica using a 3:7 mixture of ethyl acetate:hexane (100 mL). The eluent was concentrated *in vacuo* to yield an orange solid (1.894 g, 73% yield). A portion of this crude material (0.490 g, 1.70 mmol), N-benzyl glycine ethyl ester (0.787 g, 4.07 mmol), 4 angstrom molecular sieves (10 g) and anhydrous DMF (50 ml) were added to a nitrogen flushed 250 mL, 3-neck round bottom flask equipped with a reflux condenser and a magnetic stir bar. The mixture was heated to reflux overnight and allowed to cool to room temperature. The solvent was removed *in vacuo*, the crude material was diluted with ethyl acetate (20 mL) and then filtered through a short plug of silica using a 1:1 mixture of ethyl acetate:hexane (150 mL). The eluent was concentrated *in vacuo* to yield material, which was dissolved in ethyl acetate (20 mL) and washed with 10% aqueous hydrochloric acid (1 x 15 mL). The organic phase was dried and concentrated *in vacuo* to yield a dark yellow

solid. The solid product was purified using the Isolera flash chromatography system to yield a yellow solid (0.433 g, 60% yield), which displayed the following properties: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.29 (m, 3H), 7.27 – 7.23 (m, 2H), 7.02 (s, 1H), 6.99 (s, 4H), 6.83 – 6.72 (m, 3H), 5.60 (s, 2H), 4.04 (q, *J* = 7.1 Hz, 2H), 3.91 (s, 3H), 3.76 (s, 3H), 2.28 (s, 3H), 0.97 (t, *J* = 7.1 Hz, 3H) and was identical to the same product obtained via the acetic acid cyclization route.

4.1.68 1-Benzyl-3-(4-methoxyphenyl)-4-*p*-tolyl-1*H*-pyrrole-2-carboxylic acid ethyl ester (12f). This material was prepared in a manner identical to the previous example **(12m)** with the exception that 3-dimethylamino-1-(4-methoxyphenyl)-2-*p*-tolyl-propenone was used as the vinylogous amide. The crude product was passed through a short plug of silica with 1:3 ethyl acetate:hexane (100 mL) in which case a light orange solid (.618 g, 69% yield) was obtained and displayed the following properties: 89-91 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.29 (m, 3H), 7.25 (d, *J* = 1.7 Hz, 1H), 7.22 (s, 1H), 7.19 – 7.11 (m, 2H), 7.01 (s, 1H), 6.99 (s, 4H), 6.84 (d, *J* = 8.7 Hz, 2H), 5.60 (s, 2H), 4.02 (d, *J* = 7.1 Hz, 2H), 3.83 (s, 3H), 2.28 (s, 3H), 0.95 (t, *J* = 7.1 Hz, 3H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.70, 158.38, 138.17, 135.36, 131.77, 131.63, 131.11, 128.82, 128.66, 128.30, 127.97, 127.49, 127.13, 126.07, 124.64, 120.41, 112.91, 59.68, 55.19, 52.75, 21.03, 13.73, 1.03.; IR (neat) 1693 cm^{-1}; HRMS (ES, M+Na) calcd for $C_{28}H_{27}NO_3$ 448.1883 found 448.1848.

Acknowledgements

We gratefully thank the National Institutes of Health (grant no. R15-CA67236) for support of this research. Thanks also to the Floyd D. and Elisabeth S. Gottwald endowment for support to JTG. We are also very appreciative of Mr. Dave Patteson of Advion Inc. for the generous donation of a CMS electrospray mass spectrometer. Previous grants from the MRI program of the National Science Foundation for the purchase of a 500 MHz NMR spectrometer (CHE-0116492) and a high-resolution, electrospray mass spectrometer (CHE-0320669) are also gratefully acknowledged.

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Graphical Abstract

Further studies on the application of vinylogous amides and β-halovinylaldehydes to the regiospecific synthesis of unsymmetrical, polyfunctionalized 2,3,4- and 1,2,3,4-substituted pyrroles. John T. Gupton*, Alex Shimozono, Evan Crawford, Joe Ortolani, Evan Clark, Matt Mahoney, Campbell Heese, Jeffrey Noble, Carlos Perez Mandry, Rene Kanters, Raymond N. Dominey, Emma W. Goldman, James A. Sikorski and Daniel C. Fisher.