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Sythetic flexibility of a bromopyrrole ester intermediate : toward novel biologically active compounds

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Synthetic Flexibility of a Bromopyrrole Ester Intermediate: Toward Novel Biologically Active Compounds

By

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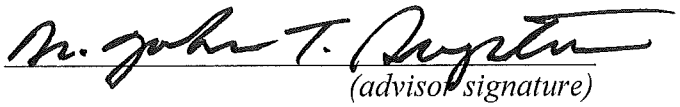

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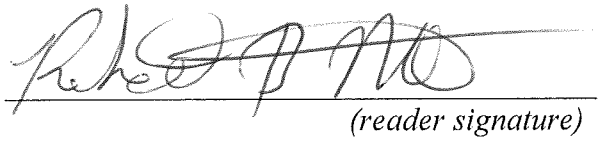

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Acknowledgments

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Abstract

Compounds containing the pyrrole ring as a core structural motif continue to show significant biological activity, and both natural product derivatives and novel chemical scaffolds show potential for use as pharmaceuticals in treating a variety of cancers, infections, and inflammation. Given the widespread and important applications of compounds containing this motif, novel, rapid, and selective methods for the synthesis of multifunctional pyrroles is of some importance. Previous work in our group has utilized palladium-mediated Suzuki cross-coupling as a powerful tool for functionalizing activated bromopyrrole esters, generating structural analogues of bioactive natural products. We have also used a similar approach to synthesize a novel class of microtubule polymerization inhibitors that have potential as future antitumor agents. Herein we describe methods for the selective modification of the C3 and C5 positions on the pyrrole ring, which have modified and expanded upon the previous work using cross-coupling and other common methods, to improve synthetic flexibility and broaden the scope of these reactions. I also show application to the synthesis of new derivatives of Lycogarubin C natural product, as well as preparation of novel microtubule-inhibiting agents as part of a structure-activity relationship study (SAR) for development of new cancer chemotherapeutics.

Introduction

Highly substituted heterocycles are common chemical motifs that are at the core of numerous essential pharmaceuticals and a number of naturally occurring molecules, which themselves have interesting biological activity or which have been chemically modified for commercial use. Consequently, the preparation of substituted heterocyclic compounds is of great interest to synthetic chemists. Compounds containing the pyrrole motif, a five-membered, nitrogen-containing aromatic heterocycle, are of particular interest due to the large number of bioactive pyrrole-containing natural products, including the Polycitones (**1**) (which exhibit anti-HIV-1 integrase activity)[1], Lycogarubin C (**2**) (a biosynthetic precursor to the protein kinase inhibitor rebeccamycin)[2], and the Rigidins (**3**) (calmodulin antagonists)[3]. Some examples of pyrrole natural products are shown in Figure 1.

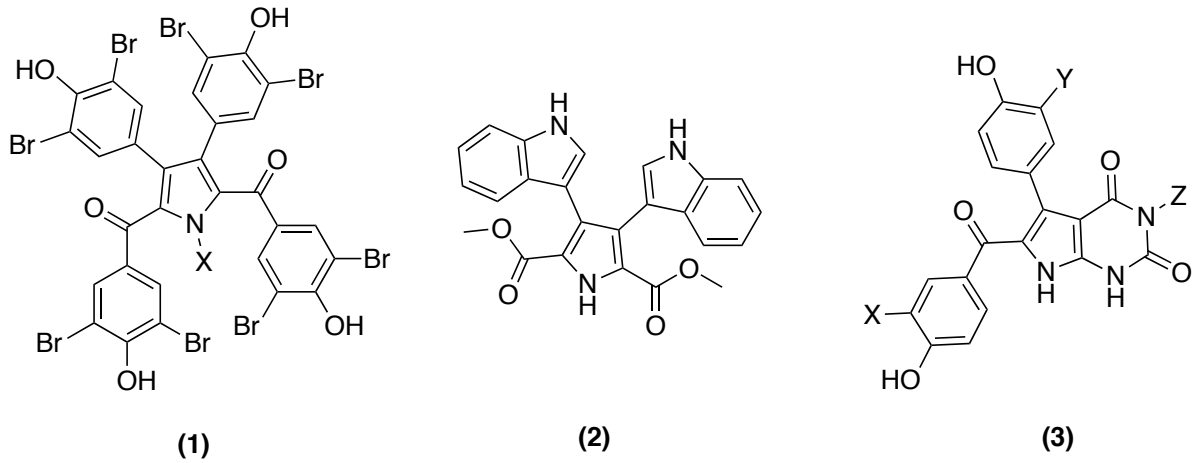
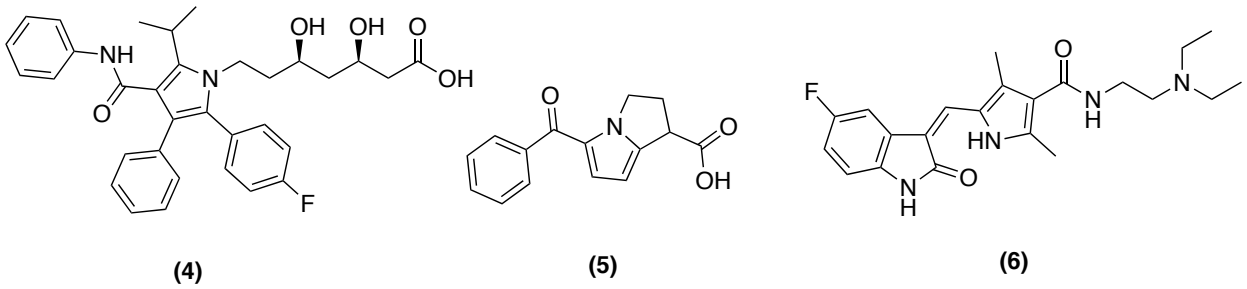


Figure 1. Polysubstituted pyrrole natural products include the Polycitones **(1)** A (X=*p*-OH-phenethyl) and B (X=H); Lycogarubin C **(2)**; and the Rigidins **(3)** A-E (X=Y=H or MeO, Z=H or Me).

Additionally, commercial drugs, such as those in Figure 2, that contain a pyrrole ring as a core structural element include the cholesterol treatment atorvastatin (aka Lipitor) **(4)**, as well as the cyclooxygenase-2 (COX2) inhibitor ketorolac **(5)**, and sunitinib **(6)**, a receptor tyrosine kinase inhibitor used in the treatment of renal and gastrointestinal cancer.

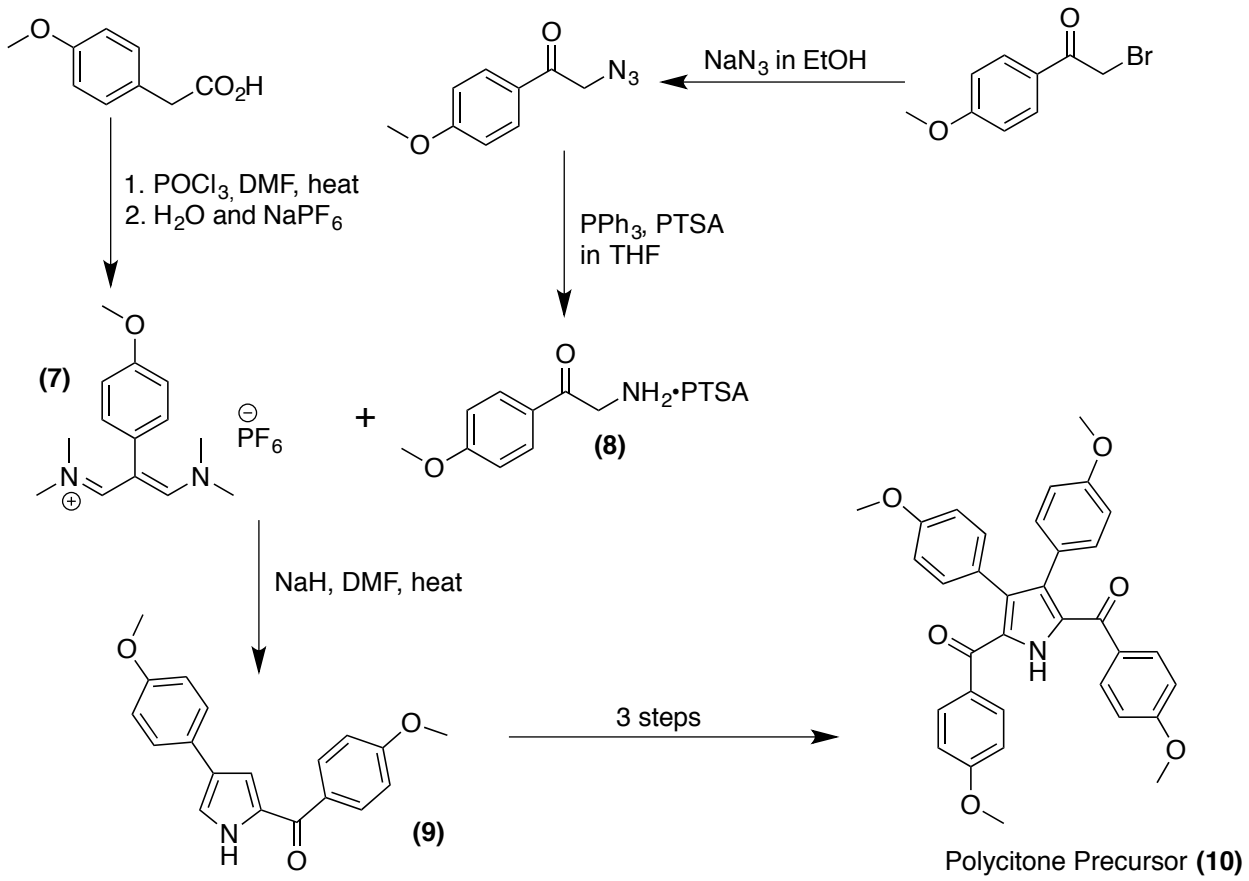
Given the importance of these and other pyrrole-containing compounds, synthetic methods that generate large quantities of pure material and that are stereoselective, require inexpensive reagents, and utilize mild reaction conditions and minimal purification are key to the rapid production and study of these compounds. The multi-step nature of these syntheses, however, frequently results in methods that require purification at each stage of preparation and low overall yields, where several grams of starting materials yield only a few milligrams of pure product. In addition, the need to selectively modify one functional group while leaving the rest of the molecule unchanged leads to the use of protecting groups, which both increases the total number of stages in the synthesis and the amount of waste generation.



(4) **(5)** **(6)**

Figure 2. Cholesterol-lowering atorvastatin (Lipitor) **(4)**, COX-2 inhibitor ketorolac **(5)**, and cancer therapeutic sunitinib **(6)** are all pyrrole-containing pharmaceuticals.

One way to reduce the waste associated with long multistep syntheses is to build smaller pieces of the overall structure separately and them bring them together in the middle of the synthetic process to generate the core target structure. When using such an approach, individual components, some of which might be commercially available, are faster and easier to prepare with minimal waste, and only small modifications may need to be made after the components are brought together to afford the compound of interest. The Gupton group has previously employed such a strategy to prepare Polycitones A and B, wherein an aromatic vinylogous quaternary iminium salt **(7)** and an α-aminoketone **(8)** are used to generate a compound **(9)** that in a few steps was converted **(10)** to a natural product precursor (Scheme 1)[4].

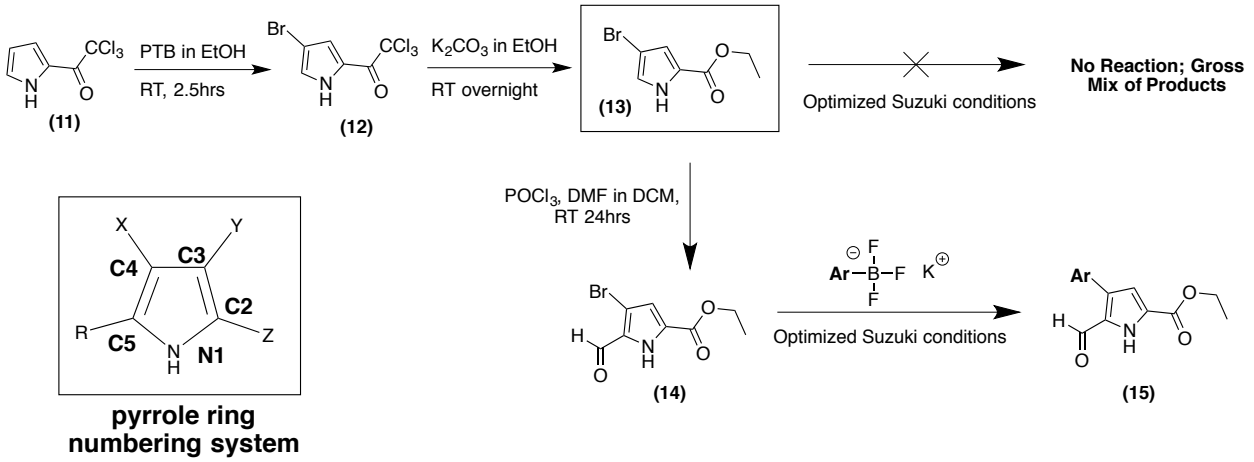


Scheme 1. Previous work[4] in the Gupton group utilized the reaction of a vinylogous iminium salt **(7)** and α-aminoketone **(8)** to generate a disubstituted pyrrole **(9)**, which was readily converted to a Polycitone precursor.

The individual components are synthesized in 1 and 2 steps, respectively, from readily available materials in high yield, and the variety of different aromatic starting materials available means that analogous molecules with different substituents could be prepared.[4] Similar methods have also been employed by the Gupton group to prepare Rigidin A and E[3], and in both cases the natural products (or their precursors) were generated with regioselectivity and in fair overall yield.

While this approach does have some advantages, it is limited in a key component of synthetic strategy: flexibility. Since the individual components are prepared from starting materials containing the groups present in the final product, for each desired change in the final product, a new starting material must be prepared and the entire synthetic process must be

carried out. This time-consuming process is particularly problematic in structure-activity relationship (SAR) studies, where small quantities of many different molecules, each containing slight modifications to the same core structure, are desired for biological screening. By using a highly flexible, easily synthesized intermediate that is several steps into the synthetic pathway, individual modifications can be made in smaller quantities without the need to restart the synthesis for each new analogue. This reduces both chemical waste and time needed to prepare such biologically active compounds, both of which translate into more economical syntheses.



Scheme 2. The key intermediate ethyl 4-bromopyrrole 2-carboxylate **(13)** is easily prepared by 1) Bromination of 2-trichloroacetylpyrrole **(11)** and 2) Esterification of the brominated starting material **(12)**. While **(13)** does not undergo Suzuki cross coupling, the formylated BPE **(14)** is readily coupled with a variety of aromatic and heteroaromatic trifluoroborates to give disubstituted pyrroles **(15)**. **Optimized Suzuki conditions, as reported[5], are 1 eq. **(14)**, 1.2 eq. organoboron (boronic acid or trifluoroborate), 1.4 eq. DABCO, 5mol% Pd(II)dppf catalyst, and 2mL water in a 9:3 toluene:ethanol solvent mix under microwave heating for 2hrs at 110°C.*

Recently the Gupton group has been interested in the applications of a flexible pyrrole building block, ethyl 4-bromopyrrole 2-carboxylate **(13)** (abbreviated "bromopyrrole ester" or BPE), as an intermediate in the synthesis of natural products and the generation of novel compounds with important biological activity. This intermediate, which can be prepared in multi-gram quantities from the commercially available 2-trichloroacetylpyrrole in a simple 2 step process requiring no purification (compounds **11** and **12**), has already been shown[5], when activated via formylation **(14)**, to be an excellent substrate for Suzuki cross coupling. While the

unmodified BPE gave a gross mixture of materials under Suzuki conditions, the addition of the aldehyde group adjacent to the carbon-bromine bond (labeled C4 by convention, see Scheme 2) allowed the pyrrole to efficiently cross-couple with a variety of aromatic and heteroaromatic boronic acids in high yields (Scheme 2).

In the Suzuki reaction mechanism, a bond is formed between an sp^2-hybridized carbon with an attached leaving group (typically a halide) and the sp^2-carbon on an organoboron species, such as a boronic acid, boronic acid ester, or trifluoroborate salt, through a palladium-catalyzed cycle. The first step in this process, the oxidative addition of the palladium (Pd^0 to $Pd^{(II)}$) between the carbon and its attached leaving group, requires polarization of the carbon-halogen bond. In an electron-rich ring system such as a pyrrole, the additional electron density lowers the polarization of this bond, reducing reactivity. Through the addition of an electron-withdrawing group, such as an aldehyde, on the adjacent carbon, that electron density is pulled away from the carbon-halogen bond, restoring the reactivity and allowing the pyrrole to undergo oxidative addition. This first step in the mechanism is rate-determining[6], so once the oxidative addition has occurred, the remaining steps, transmetallation of the $Pd^{(II)}$ complex with the organoboron (which transfers the carbon-containing group from the boron to the $Pd^{(II)}$ complex) and reductive elimination of the palladium (which forms the new carbon-carbon sigma bond and restores the catalyst to Pd^0) can proceed to completion.

Not only does the aldehyde group serve to activate the BPE toward cross coupling, but it is also a highly reactive group that can be modified in numerous ways to introduce a wide variety of functional groups at that position (C5) on the pyrrole ring. Since this formylbromopyrrole ester intermediate has flexibility at both the C4 (via cross coupling) and C5 (via aldehyde modification), it has the potential to be a powerful tool in SAR studies. Furthermore, many of the

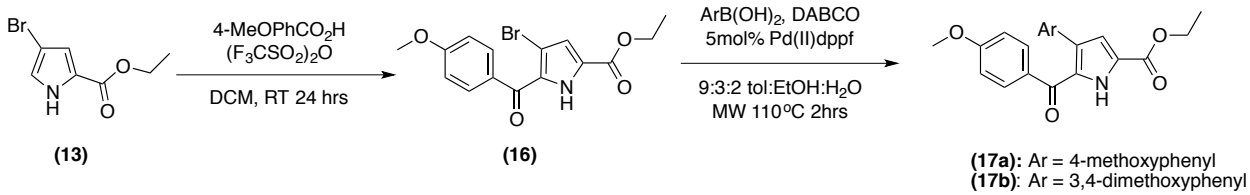
important natural products have carbonyl groups at C5 and aromatic or heteroaromatic groups at C4, meaning that this intermediate also has the potential to be used in the development more efficient syntheses of these compounds.

Since previous members of the Gupton group had shown the application of aldehydes as activating groups for pyrrole cross coupling, the aim of the present research was two-fold. First, to examine the ability of other electron withdrawing groups to activate BPE toward cross coupling, increasing the potential of such methods for natural product synthesis. Second, to determine the synthetic flexibility of the C5 and C3 positions of the pyrrole, with the aim of generating novel pyrrole-containing compounds for biological SAR study. Throughout this work, we examined the scope of reactivity of our BPE intermediate and limitations relevant to commercial or biological application, including improved yield, simplified purification, and reduced waste.

Results and Discussion

Electron Withdrawing Group Activation in Suzuki Cross Coupling

In an effort to expand the range of activating groups used in Suzuki coupling of BPE, two chemically and structurally distinct groups were examined first for their ease of synthesis, and second, for their ability to activate the pyrrole toward coupling. The first group installed was a aromatic ketone, containing a motif common in some pyrrole-containing natural products. Initial attempts to acylate BPE with p-methoxyphenylbenzoic acid, trifluoroacetic acid, and trifuoroacetic anhydride proved complicated and did to go to completion. Since the formation of the acylium cation requires the formation of a mixed acid anhydride, followed by loss of trifluoroacetate (a good leaving group), we decided to see if using an acid anhydride that would generate a stronger leaving group might improve the conversion of this reaction (Scheme 3).



Scheme 3. Acylation of BPE results in activation of BPE towards Cross Coupling. Acylation with 2 eq. of benzoic acid and 4 eq. of triflic anhydride gave high-yielding p-methoxybenzoylpyrrole **(16)** that required no further purification prior to cross coupling. Using previously described Suzuki cross coupling conditions, the acylpyrroles were coupled to a range of aromatic boronic acids to give trisubstituted pyrroles **(17a-b)**.

Trifluoromethanesulfonic (triflic) anhydride, which generates the much stronger triflate ($^{-}$OTf) leaving group, was used in place of the TFAA and TFA reagents. Although pure triflic anhydride can be quite difficult to work with due to its violent reactivity with water and corrosive properties, it is readily available in an easy-to-handle 1M solution in dichloromethane, allowing us to store it and use it safely, with minimal additional waste.

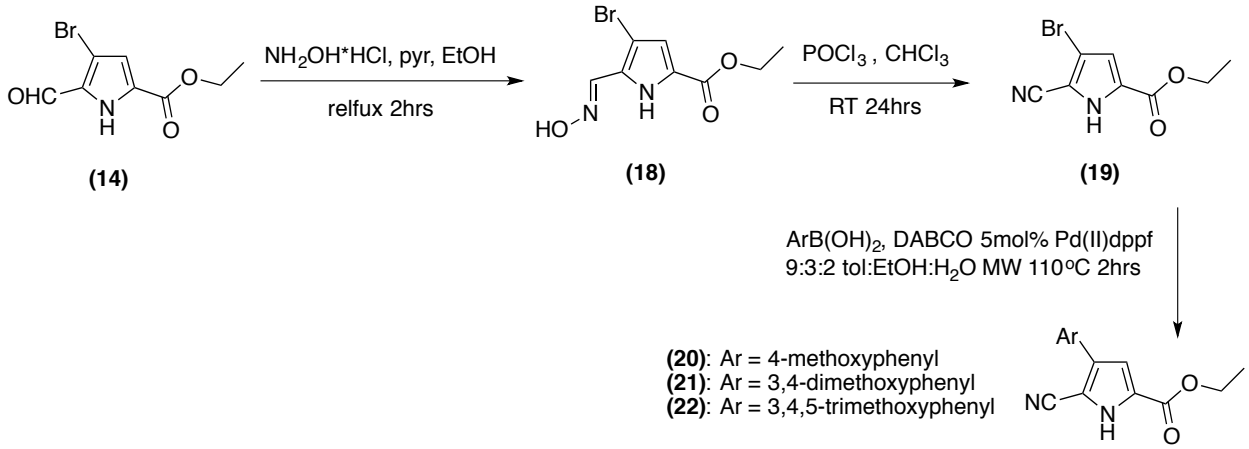
Reacting one equivalent of the BPE starting material with two of the p-methoxyphenyl benzoic acid and for of the anhydride in dichloromethane overnight at room temperature yielded a dark colored solid that appeared by NMR to be the acylated bromo pyrrole ester at near analytical purity. As such, it was used in forthcoming cross coupling reactions without further purification. Two analogues were tested for their ability to be coupled to acylated BPE using the standard conditions previously determined for the aldehyde. In both cases the analogues (4-methoxyphenyl and 3,4-dimethoxyphenyl) were chosen because highly oxygenated phenyl groups are common motifs in

Entry	C5 Group	C4 Group	Isolated Yield (%)
16	*p*-methoxybenzoyl	bromine	58
17a	*P*-methoxybenzoyl	*p*-methoxyphenyl	50
17b	*p*-methoxybenzoyl	3,4-dimethoxyphenyl	63
18	Oxime (syn/anti)	bromine	98 (39/43)
19	nitrile	bromine	71
20	nitrile	*p*-methoxyphenyl	91
21	nitrile	3,4-dimethoxyphenyl	99
21	nitrile	3,4,5-trimethoxyphenyl	70

Table 1. Both the acylated and nitrile BPE compounds underwent cross coupling with boronic acids containing highly oxygenated phenyl rings in good to excellent yield.

naturally-occurring compounds that are biologically active. In both cases, cross coupling proceeded in good yield after purification by flash chromatography (see Table 1).

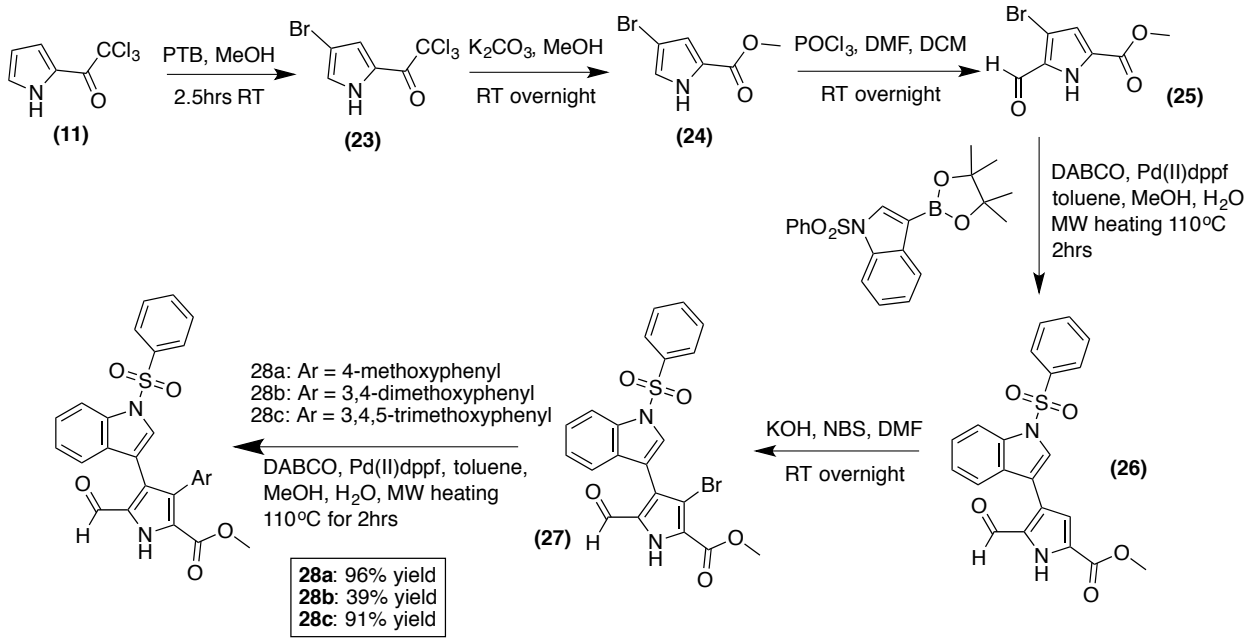
After establishing the feasibility of acyl ketones as activating groups, we examined how a nitrile, also electron withdrawing but with vastly different steric properties, would act in coupling (Scheme 4). Taking the formylated bromopyrrole ester **(14)** and refluxing it for 2 hours with hydroxylamine hydrochloride in pyridine and ethanol yielded a mixture of oxime isomers, which were easily separated by chromatography. The crude mixture of the oximes was dehydrated by addition of phosphorus (V) oxychloride in chloroform at room temperature yielding nitrile **(19)**, which was not purified prior to cross coupling reactions, again with three highly oxygenated phenyl coupling agents **(20-22)**. These reactions, summarized in Table 1, all proceeded in good to excellent yield, and were purified by flash chromatography to remove a small amount of side product, which was identified as the reduction product of the bromine to hydrogen. Currently we are exploring the optimization of these activating groups in cross coupling reactions of pyrroles as well as the viability of new electron withdrawing groups, to show the scope and versatility of the BPE as a flexible synthetic tool.



Scheme 4. Nitrile groups are easily added to the BPE intermediate and activate it in Suzuki coupling. An oxime intermediate allows for the simple preparation of nitrile **(18)** from the formylated BPE without the need for purification between steps. The same optimized coupling conditions used for the original aldehyde paper and acyl group cross coupling.

Natural Product Analogues – Towards Structure-Activity Relationship Studies

One of the pyrrole-containing natural products of synthetic interest to the Gupton group is Lycogarubin C **(2)**, a symmetric, tetrasubstituted pyrrole with indole rings and C3 and C4 and methyl esters at C2 and C5. Derived from the slime mold *Lycogala epidendrum*, Lycogarubin C is believed to be a biological precursor to the important bioactive alkaloids rebeccamycin and staurosporine[2], and as such has a core structure that may be of interest in potential structure-activity relationship (SAR) studies. In the previous study[5] of formyl-group activation of BPE, an analogue with an *N*-phenyl-sulfonyl-3-indolyl moiety at C4 of the pyrrole was prepared; this reaction was again utilized in a Gupton group formal synthesis of the natural product.



Scheme 5. Synthesis of asymmetric Lycogarubin C analogues, for potential use in SAR studies. The methyl ester intermediate was utilized since this functionality is present in the natural product. Three different aromatic analogues **(28a-c)** were prepared on small scale in fair to excellent yield.

The initial steps of the synthetic pathway, as shown in Scheme 5, are very similar to the preparation of BPE **(13)**, except that the methyl ester was prepared, mimicking the native structure of Lycogarubin C. Formylation **(25)** and Suzuki cross coupling were conducted as previously described, except that instead of the boronic acid, the more readily available *N*-

phenyl-sulfonyl-3-indolyl pinacol borane was used. (This compound gets converted to the boronic acid *in situ*). This cross-coupled aldehyde **(26)**, which, in the total synthesis was converted to the methyl diester prior to further modification, became my substrate for examination of flexibility at the C3 position of the pyrrole.

Bromination of the pyrrole **(26)** at the C3 position was achieved under basic conditions using *N*-bromosuccinimide (NBS), a shelf-stable, easier-to-use source of bromine than liquid Br_2. Under basic conditions, the amine proton of the pyrrole ring is abstracted, generating an enamine that has a significant resonance form at C3 with a formal charge of -1. This negative character to C3 means that Br^+ is most likely to form a bond at this position, resulting in a highly selective reaction that produces no over-bromination byproducts. Bromoaldehyde **(27)** was then cross-coupled with three highly oxygenated phenylboronic acids (4-methoxyphenyl, 3,4-dimethoxyphenyl, and 3,4,5-trimethoxyphenyl) to determine what chemical modularity can be achieved at the C3 position of the pyrrole ring.

While cross-coupled products of **(27)** with 4-methoxyphenylboronic acid **(28a)** and 3,4,5-trimethoxyphenylboronic acid **(28c)** showed excellent yields greater than 90%, the 3,4-dimethoxyphenylboronic acid cross coupling **(28b**) had a significantly lower yield, 39%. This reaction, which was repeated under identical conditions to give almost an identical yield, was inexplicably lower than the other two couplings. Since all three examples had similar electronic characteristics (electron-rich) and since 3,4,5-trimethoxyphenylboronic acid is bulkier than 3,4-dimethoxyphenylboronic acid, it seems unlikely that the difference in yield is due to differences in the structures. However, since these reactions were conducted on a small scale, it is possible that a small mistake in material transfer could lead to a significant effect in the final yield. Regardless of isolated yield, these experiments show how a bromopyrrole ester intermediate can

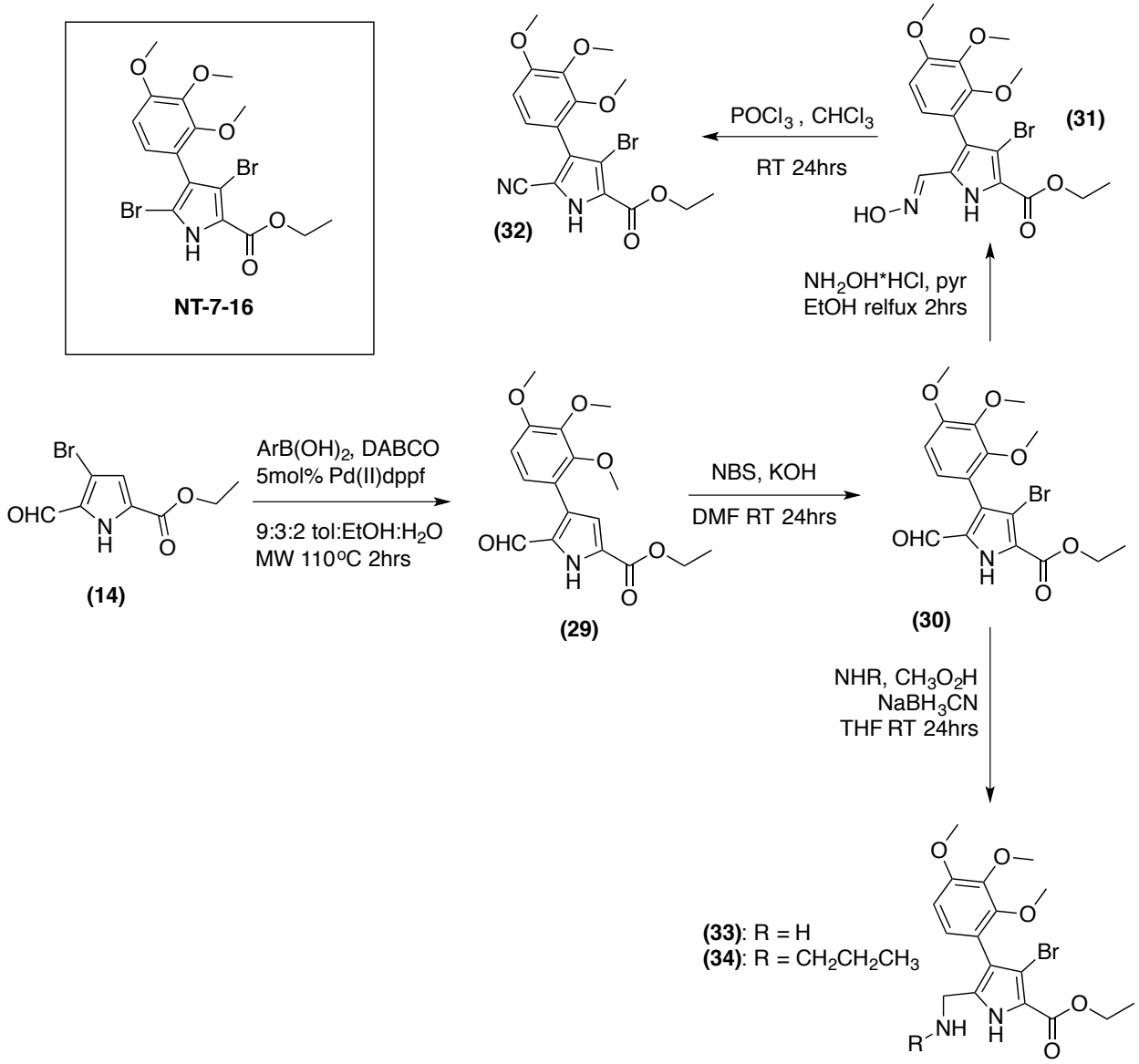
be used not only in an additional natural product synthesis, but also how the inherent flexibility of the BPE intermediate makes it perfectly suited for the generation of small amounts of many different analogues with the same core structure, a feature that proves invaluable during SAR study[7]. By using a bromopyrrole ester intermediate, the Polycitone, Rigidin, and Lycogarubin C natural products and associated analogues can be more easily and efficiently prepared.

Modifications of a Biologically Active Pyrrole – Towards Structure-Activity Relationship Studies

For several years the Gupton group, in collaboration with computational chemists at Virginia Commonwealth University (Kellogg group) and pharmacologists at The University of Texas Health Science Center at San Antonio (Mooberry group), have been developing and examining the biological activity of a class of novel pyrrole-based antitubulin agents using an SAR approach. These agents, which prevent the polymerization of tubulin into microtubules (cellular substructures essential to, among other processes, cell division), show promise as potential antitumor agents for the treatment of cancer. As previously mentioned, ethyl 4-bromo-2-pyrrole carboxylate **(13)** is an ideal candidate for SAR due to its ease of preparation and high degree of synthetic flexibility, and recently the Gupton group has used BPE as a key building block in the preparation of new pyrrole-based antitubulin agents.

Previous SAR studies on Gupton group compounds have shown that the optimum groups at C2[8] and C4[9] positions are, respectively, an ethyl ester and a 2,3,4-trimethoxyphenyl group. These studies gave rise to a parent compound, NT-7-16, which has bromine at both C3 and C5 and exhibits inhibition of cancer cell growth at nanomolar concentrations. Based on computational modeling of these pyrroles in the colchicine binding site, it appears that C5 sticks out into the aqueous environment of the cell, which suggests that modifications at C5 that improve the hydrogen bonding capability of the molecule might help lock the pyrrole into a

high-affinity orientation, while simultaneously improving the overall water solubility of the compound.



Scheme 6. 4 C5 analogues of NT-7-16 were prepared from a common intermediate prepared from BPE. Oxime (mix of isomers), nitrile, and 2 amines were all prepared in fair to good yield, as part of ongoing SAR study as potential microtubule inhibitors.

Four compounds with potential water-solubilizing compounds have been synthesized **(Scheme 6)** and are currently undergoing biological testing. An oxime **(31)** was introduced by reaction of aldehyde **(30)** with hydroxylamine hydrochloride and pyridine in ethanol, in a high yield transformation that gave two distinct stereoisomers. The oxime mixture was dehydrated

with phosphorus (V) oxychloride to give the nitrile **(32)**, also in good yield. In both these cases, the compounds did not require further purification prior to characterization, but were purified by chromatography to ensure purity for biological testing. A reductive amination strategy, using the same aldehyde starting material, was employed to add hydrogen-donating amine groups at C5 attached by a one carbon linker. Since amines are typically protonated at physiological pH, it was hypothesized that introduction of these groups might greatly improve water solubility of these compounds. In a one-pot reaction, primary amines reacted with the aldehyde under mildly acidic conditions to generate an imine *in situ*, which as then reduced by sodium cyanoborohydride. This reducing agent was used due to its lower reactivity, to prevent reduction of the bromine at C3. Aminomethylene **(33)** and propylaminomethylene **(34)** compounds were prepared in modest yield. Upon purification, another product, identified as the reduced aldehyde, was isolated, indicating that the direct reduction of the aldehyde competes with the imine formation. Current work continues to optimize the reaction conditions for the preparation of the aminomethylene compounds, as well as to expand the range of groups substituted on the amine.

Compound	C5 Group	Isolated Yield (%)
31	Oxime (cis/trans)	68 (30/34)
32	nitrile	89
33	aminomethylene	35
34	propylaminomethylene	76

Table 2. Four analogues of NT-7-16 were prepared with modifications at C5 in an effort to improve water solubility. Fair to good yields were obtained for all compounds.

All of these new compounds (Table 2) are undergoing the same range of biological testing that initially identified NT-7-16 as a key therapeutic target. Dr. Susan Mooberry and colleagues have reported[9] typical procedures used for bioassay of these and other compounds, ranging from cell toxicity assays to microtubule binding and longer-term examinations of these compounds biological effects.

Conclusions

The bromopyrrole ester (BPE) intermediate has already been shown to be a highly flexible tool in Suzuki cross coupling, and herein I have described how two additional electron withdrawing groups can serve to activate this intermediate toward cross coupling, further showing the utility of the BPE building block in both potential natural product synthesis and pharmaceutical development. A further extension of these ideas showed how the rapid ability to generate analogues of the bioactive pyrrole natural product Lycogarubin C would prove useful during SAR studies, and this flexibility was employed in the preparation of novel analogues of NT-7-16, a potent microtubule inhibitor with potential as a cancer chemotherapeutic. In each of these cases the ease of preparation of the intermediate, and the flexible synthetic nature of the compound have revealed its efficacy as a powerful chemical tool for synthetic preparation of polysubstituted pyrroles.

Experimental

All chemicals were obtained from the manufacturer (Aldrich Chemicals or Fisher Scientific) and were used without modification. All solvents were dried over 4Å molecular sieves prior to use. NMR spectra were collected on either a Bruker 300MHz or 500MHz spectrometer in either $CDCl_3$, DMSO-d_6 or d_6-acetone solutions. IR spectra were recorded on a Nicolet 320 FTIR spectrometer with HATR attachment. High resolution mass spectra were obtained on an LCMS-IT-TOF mass spectrometer at the University of Richmond. Low resolution GC-MS data were collected on a Shimadzu QP 5050 instrument. Melting points and boiling points are uncorrected. Chromatographic purifications were carried out on a Biotage Isolera or SP-1 instrument, both equipped with a silica gel cartridge. Gradient elution with ethyl acetate/hexanes was used on both instruments. TLC analyses were conducted on silica plates

with ethyl acetate/hexanes as the eluent. All purified reaction products gave TLC results, flash chromatograms, and ^{13}C NMR spectra consistent with greater than 95% sample purity. Presented in this experimental section are representative procedures and spectral data for each type of reaction presented in the text.

4-bromo-5-(4-methoxybenzoyl)-1H-pyrrole 2-carboxylic acid ethyl ester (16): To a 100 mL round bottom flask was added 1.67 g p-anisic acid (11.0 mmol) and 30 mL of dry dichloromethane. To the flask was then added 22 mL triflic anhydride solution, 1 M in DCM (22.0 mmol) and the reaction stirred on ice bath 45 minutes. To the mixture was then added 1.20 g of bromopyrrole ester (5.503 mmol). The reaction mixture was stirred at room temperature for 20 hours. The reaction mixture was quenched with saturated sodium bicarbonate (100 mL) and the pH of this mixture was confirmed to be basic. This mixture was then extracted three times with dichloromethane. The organic layer was washed twice with brine, dried over magnesium sulfate, and concentrated in vacuo to give 1.11g of a dark solid (57.3% yield) which exhibited the following properties: m.p. 109-110°C; ^1H NMR (acetone-d_6, 300 MHz) δ 1.31 (t, J = 9 Hz, 3H), 3.93 (s, 3H), 4.30 (q, J = 9 Hz, 2H), 6.98 (s, 1H), 7.07 (d, J = 6 Hz, 2H), 7.81 (d, J = 6 Hz, 2H); ^{13}C NMR (acetone-d_6) δ 184.30, 164.60, 163.87, 159.24, 132.11, 129.91, 125.74, 117.79, 113.73, 100.83, 60.67, 55.13, 13.65; IR (neat) 3249, 2363 and 1717 cm^{-1}; HRMS (ES) calcd for $C_{15}H_{14}NO_4Br$ 350.0033 and 352.0015, found 350.0030 and 352.0014.

5-(4-methoxybenzoyl)-4-(4-methoxyphenyl)-1H-pyrrole 2-carboxylic acid ethyl ester (17a): Bromo pyrrole ester (0.530 mmol, 0.187g), paramethoxyphenyl boronic acid (0.630mmol, 0.0970 g), and 1,4-diazabicyclo[2.2.2]octane (DABCO; 0.740 mmol, 0.0833 g) were added to a 20 mL, microwave vial fitted with a magnetic stir bar. To the reaction mixture was added toluene (9 mL) and ethanol (3 mL), after which dichloro-1,1,-bis(diphenylphosphino)ferrocene palladium (II) (0,027mmol, 0,0194g) was stirred into the solution. Twenty drops of reverse osmosis water were then added to the microwave vial which was then capped and microwaved for 2 hours at 110°C with 30 seconds of pre-stirring. After the reaction was completed and allowed to cool, the reaction mixture was poured through a silica plug and rinsed with 3x20 ml of ethyl acetate and the filtrate was evaporated in vacuo. The resulting light brown solid had a mass of 0.252g (125%). The crude product was flash purified twice on a 10g silica column with a 50:50 gradient of hexane/ethyl acetate yielding a product with a mass of .105g (49.8% yield), with the following properties: m.p. 96-97°C; ^1H NMR (acetone-d_6, 300 MHz) δ 1.31 (t, J = 9 Hz, 3H), 3.70 (s, 3H), 3.90 (s, 3H), 4.30 (q, J = 9 Hz, 2H), 6.98 (s, 1H), 6.74 (d, J = 9 Hz, 2H), 6.78 (d, J = 9 Hz, 2H) 7.18 (d, J = 9 Hz, 2H), 7.61 (d, J = 9 Hz, 2H); ^{13}C NMR (acetone-d_6) δ 185.93, 163.21, 160.02, 158.72, 131.88, 130.32, 130.23, 130.17, 130.13, 127.10, 125.11, 115.05, 113.47, 113.25, 60.31, 54.97, 54.58, 13.75; IR (neat) 1709 and 1614 cm^{-1}; HRMS (ES) calcd for $C_{22}H_{21}NO_5$ 402.1312, found 402.1294.

4-bromo-5-(hydroxyiminomethyl)-1H-pyrrole 2-carboxylic acid ethyl ester (18): To a 100ml round-bottomed flask fitted with magnetic stirring bar and reflux condenser were added 4-bromo-5-formyl-1H-pyrrole-2-carboxylic acid ethyl ester (0.05 g, 2.03 mmol), hydroxylamine hydrochloride (0.14 g, 2.03 mmol), pyridine (0.2 mL) and ethanol (20 ml). The mixture was

heated at reflux for 2 hours, cooled to room temperature, and the solvent removed by rotary evaporation. The crude residue was dissolved in deionized water (15 mL) and extracted 3 times with 10 mL portions of ethyl acetate. The combined organic layer was washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and the solvent removed *in vacuo* to give 0.51 g (a 98% yield) of a brown solid identified as 4-bromo-5-(hydroxyimino methyl)-1Hpyrrole-2-carboxylic acid ethyl ester. While this material was pure enough for further synthesis, an analytical sample was prepared via flash chromatography yielding the syn (0.21 g, a 39% yield, fractions 8-10) and anti (0.22 g, a 43% yield, fractions 5-7) isomers, which exhibited the following spectral properties: *syn*-isomer: m.p. 115-117°C, ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.36 (t, J = 9 Hz, 3H), 4.34 (q, J = 9 Hz, 2H), 6.94 (d, J = 3 Hz), 8.14 (s, 1H), 9.91 (s br, 1H); ^{13}C NMR ($CDCl_3$) δ 160.11, 140.71, 125.89, 124.56, 118.07, 102.20, 61.56, 14.37, 14.25; IR (neat) 3217, 2990 and 1682 cm^{-1}. HRMS (ES) calcd for $C_8H_9N_2O_3Br$ 260.9869 and 262.9850; found 260.9874 and 262.9841. *anti*-isomer: m.p. 105-107°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.39 (J = 6 Hz, 3H), 4.35 (q, J = 6 Hz, 2H), 6.93 (d, J = 3 Hz, 1H), 7.53 (s, 1H), 10.81 (s br, 1H); ^{13}C NMR ($CDCl_3$) δ 160.17, 135.85, 125.14, 124.52, 116.84, 102.72, 61.39, 61.35, 14.28; IR (neat) 3440, 3133 and 1709 cm^{-1}; HRMS (ES) calcd for $C_8H_9N_2O_3Br$ 260.9869 and 262.9850; found 260.9874 and 262.9841.

4-bromo-5-cyano-1H-pyrrole 2-carboxylic acid ethyl ester (19): To a round bottom flask equipped with magnetic stirring bar, addition funnel and rubber septum was added 4-bromo-5-(hydroxyimino-methyl)-1H-pyrrole-2-carboxylic acid ethyl ester (0.50 g, 1.92 mmol) dissolved in anhydrous chloroform (20 mL), and stirred on an ice bath for 5 minutes. Phosophorus (V) oxychloride (0.29 g, 1.92 mmol) was dissolved in a further 10 mL of anhydrous chloroform, and added dropwise to the stirring solution over a period of 10 minutes. The addition funnel and ice bath were removed, and the reaction allowed to stir at room temperature overnight, The mixture was quenched with deionized water (30 ml), the phases were separated, and the organic layer was washed with brine (15 mL), dried over anhydrous sodium sulfate, and filtered. The solvent was removed in vacuo to give 0.370g of a red solid, which was further purified on a Biotage Isolera flash chromatography system (hexanes/ethyl acetate gradient) to give 0.329g (71% yield) of a yellow solid, 4-bromo-5-cyano-1H-pyrrole-2 carboxylic acid ethyl ester, which exhibited the following properties: m.p. 131-133°C ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.42 (t, J = 6 Hz, 3H), 4.43 (q, J = 6 Hz, 2H), 6.94 (d, J = 6 Hz, 1H), 10.91 (s br, 1H); ^{13}C NMR ($CDCl_3$) δ 159.83, 127.06, 117.16, 111.29, 107.95, 107.02, 62.48, 14.18; IR (neat) 3189, 3126, 2230 and 1692 cm^{-1}; HRMS (ES) calcd for $C_8H_7N_2O_2Br$ 240.9600, found 240.9618.

5-cyano-4-(4-methoxyphenyl)-1H-pyrrole 2 carboxylic acid ethyl ester (20): Into a 20ml, microwave vial equipped with a magnetic stirring bar and a crimping cap was added 4-bromo-5-cyano-1Hpyrrole-2-carboxylic acid ethyl ester (0.823 mmol, 200 mg), 4-methoxyphenyl boronic acid (0.987 mmol, 150 mg), 1,4diazabicyclo[2.2.2]octane (1.15 mmol, 130 mg), dichloro-1,1,-bis(diphenylphosphino)ferrocene palladium (II) (0.042 mmol, 31 mg) along with toluene (9 mL), ethanol (3 mL) and water (2 mL). The reaction mixture was heated for 2 hours at 110°C in a Biotage Initiator microwave system. The reaction mixture was filtered through a short silica gel plug in vacuo with ethyl acetate (25 mL), dried over anhydrous sodium sulfate and concentrated in vacuo to give a dark brown crude residue (0.39 g, 178% yield).The crude residue was subjected to flash chromatographic purification on a Biotage isolera system with a SNAP 25 g silica column in which case a light yellow solid was obtained (0.20 g, 91% yield). It had the

following properties: m.p. 105-106°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.42 (t, J = 6 Hz, 3H), 3.87 (s, 3H), 4.39 (q, J = 6 Hz, 2H), 6.98 (d, J = 9 Hz, 2H), 7.07 (d, J = 3 Hz, 1H), 7.62 (d, J = 9 Hz, 2H), 9.61 (s br, 1H); ^{13}C NMR ($CDCl_3$) δ 160.08, 159.75, 135.42, 128.03, 127.14, 124.18, 114.47, 113.75, 112.90, 101.17, 61.82, 55.36, 14.29; IR (neat) 3240 and 2214 cm^{-1}; HRMS (ES) calcd for $C_{15}H_{14}N_2O_3$ 269.0932, found 269.0979.

4.1.1 Methyl 3-Bromo-2-formylpyrrole-5-carboxylate (24): Into a 100 mL round bottom flask equipped with magnetic stirring and a rubber septum cap was placed 10 mL of anhydrous dichloromethane, 1.61 g (0.022 mol) of dry DMF, 2.90 g (0.019 mol) of phosphorus oxychloride and the resulting mixture was stirred in an ice bath for 10 mins. To this flask was then added 1.28 g (0.0063 mol) of methyl 4-bromopyrrole-2-carboxylate in 10 mL of anhydrous dichloromethane and the resulting mixture was stirred overnight at room temperature. The reaction was worked up by the addition of 50 mL of water and separation of the two phases. The aqueous phase was extracted with additional dichloromethane (3 x 15 mL) and the combined dichloromethane phases were washed with brine (1 x 15 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to yield 1.20 g (82% yield) of a light brown solid. This material was of sufficient purity to be used in subsequent experiments but an analytical sample was prepared by purification via flash chromatography on a Biotage Isolera system in which case a light colored solid was obtained, which exhibited the following physical properties: mp 169-172 °C; ^{1}H NMR ($CDCl_3$) δ 9.75 (s, 1H), 6.97 (d, J = 3.0 Hz, 1H) and 3.94 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 179.3, 159.9, 130.7, 127.5, 117.9, 107.8 and 52.5; IR (neat) 1704 and 1663 cm^{-1}; HRMS (ES) calcd for $C_7H_7BrNO_3$ 231.9609, found 231.9609.

4.1.2 4-(1-Benzenesulfonyl-1H-indol-3-yl)-5-formyl-1H-pyrrole-2-carboxylic acid methyl ester (25): Into a 20 mL microwave reaction tube containing a stir bar was placed methyl 3-bromo-2-formylpyrrole-5-carboxylate (0.250 g, 1.22 mmol), 1-(phenylsulfonyl)-3-indolylboronic acid pinacol ester (0.468 g, 1.22 mmol), DABCO (0.160 g, 1.43 mmol) along with 9 mL of toluene and 3 mL of ethanol. After stirring the resulting mixture for several minutes, dichloro[1,1'-bis-(diphenyl-phosphino)ferrocene]palladium(II) dichloromethane adduct (0.037 g, 0.031 mmol) was added to the microwave reaction tube followed by the addition of 20 drops of water and the tube was capped and sealed with a crimping tool. The reaction mixture was heated in a Biotage Initiator microwave system for 2 hrs at 110 °C. After cooling to room temperature, the reaction mixture was filtered through a short plug of silica gel and the silica was subsequently washed with 3 x 20 mL of ethyl acetate and the combined organic materials were concentrated *in vacuo* to give a dark solid (0.598 g). The solid was subjected to flash chromatographic purification on a Biotage Isolera system with a SNAP 25 g silica column in which case an orange-red solid was obtained (0.374 g, 90% yield). This material exhibited the following physical properties: mp 160-162 °C; ^{1}H NMR (acetone-d_6) δ 9.85 (s, 1H), 8.10-8.14 (m, 4H), 7.68-7.73 (m, 2H), 7.62 (t , J = 6.3 Hz, 2H), 7.45 (t , J = 6.9 Hz, 1H), 7.36 (t , J = 6.9 Hz, 1H), 7.20 (s, 1H) and 3.91 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 185.0, 165.4, 143.1, 140.3, 139.6, 136.9, 135.2, 134.9, 133.1, 132.2, 130.8, 130.4, 129.3, 129.2, 125.5, 120.9, 120.2, 118.9 and 56.6; IR (neat) 1720 and 1658 cm^{-1}; HRMS (ES) calcd for $C_{21}H_{16}N_2NaO_5S$ 431.0678 found 431.0641.

4.1.7 4-(1-Benzenesulfonyl-1H-indol-3-yl)-3-bromo-5-formyl-1H-pyrrole-2-carboxylic acid methyl ester (26): Into a 100 mL round bottomed flask equipped with a magnetic stir bar was

placed 4-(1-benzenesulfonyl-1H-indol-3-yl)-5-formyl-1H-pyrrole-2-carboxylic acid methyl ester (.100 g, 0.245 mmol), KOH (0.014 g, 0.245 mmol) and 10 mL of DMF. The resulting mixture was stirred for 45 minutes and N-bromosuccinimide (0.087 g, 0.45 mmol), which had been dissolved in 5 mL of DMF, was added in one portion. The flask was covered with aluminum foil and the reaction mixture was stirred overnight at room temperature. The reaction was subsequently worked up by dilution with water (40 mL) and a 10% aqueous solution of sodium thiosulfate (20 mL) followed by extraction with ethyl acetate (3 x 15 mL). The combined organic phases were washed with brine (1 x 30 mL) and dried over anhydrous magnesium sulfate. After removal of the drying agent by filtration, the organic phase was concentrated in vacuo to yield a solid (0.340 g). This material was purified via flash chromatography on a Biotage Isolera system in which case a white solid (0.105 g, 89% yield) resulted. This material exhibited the following physical properties: mp 211-213 °C; ^{1}H NMR (acetone-d_6) δ 9.57 (1H), 8.10-8.12 (m, 3H), 8.02 (s, 1H), 7.71 (t, J = 7.2 Hz, 1H), 7.63 (t, J = 7.2 Hz, 2H), 7.40-7.48 (m, 2H), 7.31 (t, J = 8.7 Hz, 1H) and 1.98 (s, 3H); ^{13}C NMR (acetone-d_6) δ 179.7, 158.3, 137.7, 134.9, 134.5, 131.5, 130.4, 129.7, 129.6, 127.1, 127.0, 125.2, 125.1, 125.0,123.8, 121.0, 113.6, 113.0 and 51.5; IR (neat) 1713 1672 cm^{-1}; HRMS (ES) m/z calcd for $C_{21}H_{15}N_2NaO_5SBr$ 508.9777 found 508.9729.

4.1.8 4-(1-Benzenesulfonyl-1H-indol-3-yl)-5-formyl-3-(4-methoxyphenyl)-1H-pyrrole-2-carboxylic acid methyl ester (28a): Into a 20 mL microwave reaction tube containing a stir bar was placed 4-(1-benzenesulfonyl-1H-indol-3-yl)-3-bromo-5-formyl-1H-pyrrole-2-carboxylic acid ethyl ester (0.080 g, 0.164 mmol), 4-methoxyphenylboronic acid (0.030 g, 0.197 mmol), DABCO (0.026 g, 0.230 mmol), dichloro[1,1'-bis-(diphenyl-phosphino)ferrocene]palladium(II) dichloromethane adduct (.006 g, 0.008 mmol), toluene (9 mL), methanol (3 mL) and water (5 drops). The resulting mixture was stirred and heated in a Biotage Initiator microwave system for 2 hrs at 110 °C. After cooling to room temperature, the reaction mixture was filtered through a short plug of silica gel and the silica was subsequently washed with ethyl acetate (25 mL) and the combined organic phases were concentrated in vacuo to yield an orange solid. The crude product was purified via flash chromatography on a Biotage Isolera system in which case a yellow-orange solid (0.081 g, 96% yield) was obtained and exhibited the following physical properties: mp 75-78 °C; ^{1}H NMR (acetone-d_6) δ 9.61 (s, 1H), 7.98 (d, J = 6.0 Hz, 1H), 7.90 (d, J = 8.4 Hz, 2H), 7.75 (s, 1H), 7.72 (t, J = 7.5 Hz, 1H), 7.59 (t, J = 6.9 Hz, 2H), 7.28 (t, J = 8.1 Hz 1H), 7.07-7.16 (m, 4H), 6.68 (d, J = 8.7 Hz, 2H), 3.77 (s, 3H) and 3.74 (s, 3H); ^{13}C NMR (acetone-d_6) δ 180.5, 160.4, 158.8, 137.7, 134.8, 134.3, 131.4, 131.3, 131.0, 129.7, 129.6, 127.0, 126.8, 126.7, 125.0, 124.5, 123.9, 123.6, 120.5, 114.6, 113.4, 112.8, 54.5 and 51.1; IR (neat) 1714 and 1666 cm^{-1}; HRMS (ES) m/z calcd for $C_{28}H_{22}N_2NaO_6S$ 537.1091 found 537.1054.

4-(2,3,4-trimethoxyphenyl)-5-formyl-1H-pyrrole 2-carboxylic acid ethyl ester (29): To a 20mL microwave vial was added 4-bromo-5-formyl pyrrole 2-carboxylic acid ethyl ester (0.5 g, 2.032 mmol), 2,3,4-trimethoxyphenyl trifluoroborate (0.723 g, 2.64 mmol), Pd tetrakis(triphenylphosphine) (0.023 g, 0.02 mmol), Hunig's base (0.341 g, 2.664 mmol) in toluene (9 mL) and ethanol (3 mL) with 20 drops of water. The reaction mixture was microwaved at 110°C for 2 hours. After cooling the reaction to room temperature, it was filtered through a short silica plug and the resulting mixture was evaporated in vacuo. The crude product was dried using a Kugelrohr apparatus to give a reddish brown solid (0.75 g, 110%). The crude residue was subjected to flash chromatography on a Biotage SP-1 instrument with silica column in which case 0.51 g (75% yield) of a dark brown solid was obtained upon elution with seven

column volumes of hexane/ethyl acetate gradient. This solid exhibited the following properties: m.p. 138-140°C; ^{1}H NMR (acetone-d_6, 500 MHz) δ 1.36 (t, J = 7.2 Hz, 3H), 3.66 (s, 3H), 3.88 (s, 3H), 3.91 (s, 3H), 4.36 (q, J = 7.2 Hz, 2H), 6.89 (d, J = 8.5 Hz, 1H), 6.96 (s, 1H), 7.11 (d, J = 8.5 Hz, 1H), 9.63 (s, 1H); ^{13}C NMR (acetone-d_6) δ 180.3, 159.0, 154.6, 152.0, 142.4, 130.9, 130.7, 126.7, 124.6, 117.1, 107.5, 104.9, 60.9, 60.4, 60.2, 55.5, 13.6; IR (neat) 1709 and 1660 cm^{-1}; HRMS (ES) m/z calcd for $C_{17}H_{19}NO_6$ 356.1105, found 356.1077.

3-bromo-4-(2,3,4-trimethoxyphenyl)-5-formyl-1H-pyrrole 2-carboxylic acid ethyl ester (30): To a 100 mL round bottom flask equipped with a stir bar, was added 4-(2,3,4-tri methoxyphenyl)-5-formyl pyrrole 2-carboxyic acid ethyl ester (0.100 g, 0.300 mmol) and potassium hydroxide (0.034 g, 0.6 mmol) in 15 mL of DMF. The reaction mixture was allowed to stir for 15 minutes at room temperature, after which *N*-bromosuccinimide (0.053 g, 0.33 mmol) was added and the reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with 30 mL water and 15 mL of sodium thiosulfate solution was added to the reaction mixture. The reaction misture extracted with ethyl acetate (3 x 15 mL). The combined ethyl acetate layers were dried over anhydrous sodium sulfate, filtered and concentrated to give a dark brown solid (0.12 g, 96%). This solid exhibited the following properties: m.p. 158–160 °C; ^{1}H NMR ($CDCl_3$) δ 1.43 (t, J = 7.2 Hz, 3H), 3.68 (s, 3H), 3.93 (s, 3H), 3.94 (s, 3H), 4.45 (q, J = 7.2 Hz, 2H), 6.81 (d, J = 8.5 Hz, 1H), 7.04 (d, J = 8.5 Hz, 1H), 9.45 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 181.0, 159.5, 154.5, 151.8, 142.3, 131.2, 130.2, 126.7, 124.6, 116.7, 107.2, 105.3, 61.6, 60.2, 56.0, 14.2; IR (neat) 1708 and 1660 cm^{-1}; HRMS (ES) m/z calcd for $C_{17}H_{18}NNaBrO_6$ 434.0210, 436.0192 found 434.0199, 436.0186.

***cis/trans*-3-bromo-4-(2,3,4-trimethoxyphenyl)-5-oximino-1H-pyrrole 2-carboxylic acid ethyl ester (31):** To a 100 mL round bottom flask equipped with a stir bar, was added 4-(2',3',4' trimethoxyphenyl)-5-formyl-pyrrole-2-ethyl ester (0.13 g, 0.315 mmol), hydroxyl amine hydrochloride (0.022 g, 0.315 mmol), 0.1 mL of pyridine in 15 mL of ethanol. The reaction mixture was allowed to reflux for 2 hours. The reaction mixture was cooled and evaporated to give a crude residue. Water (10 mL) was added to the residue and the solution was cooled in an ice bath and stirred until the oxime crystallized. The solid was filtered and washed with water (2 x 15 mL) and dried to give cis/trans-3-Bromo-4-(2,3,4-trimethoxyphenyl)-5 oximino-1H-pyrrole 2-carboxylic acid ethyl ester, as an orange solid (0.091 g, 68 %): This solid mixture was subjected to flash chromatography on Biotage Isolera instrument with a silica column in which case 0.04 g (30% yield) of the cis isomer and 0.045 g (34% yield) of the trans isomer.

(cis-3-Bromo-4-(2,3,4-trimethoxyphenyl)-5-oximino-1H pyrrole 2-carboxylic acid ethyl ester) exhibited the following properties: m.p. 141 143 °C; ^{1}H NMR (acetone-d_6) δ 1.39 (t, J = 7.2 Hz, 3H), 3.64 (s, 3H), 3.86 (s, 3H), 3.91 (s, 3H), 4.39 (q, J = 7.2 Hz, 2H), 6.87 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H), 7.03 (s, 1H); ^{13}C NMR (acetone-d_6) δ 159.1, 1542, 1522, 1424, 1394, 127.0, 126.69, 124.7, 120.9, 1184, 107.4, 105.2, 60.2, 60.1, 55.4, 13.7; IR (neat) 1710 cm^{-1}; HRMS (ES) m/z calcd for $C_{17}H_{19}NNaBrO_3$ 449.0319, 451.0301; found 449.0314, 451.0296.

(trans-3-Bromo-4-(2,3,4-trimethoxyphenyl)-5 oximino-1H-pyrrole 2-carboxylic acid ethyl ester) exhibited the following properties: m.p. 125–126 °C; ^{1}H NMR (acetone-d_6) δ 1.39 (t, J = 7.2 Hz, 3H), 3.64 (s, 3H), 3.86 (s, 3H), 3.91 (s, 3H), 4.39 (q, J = 7.2 Hz, 2H), 6.88 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H), 7.74 (s, 1H); ^{13}C NMR (acetone-d_6) δ 159.1, 154.2, 152.2, 142.4,

139.4, 127.1, 126.7, 124.8, 121.0, 118.4, 107.5, 105.2, 60.3, 60.1, 55.4, 13.7; IR (neat) 1710 cm^{-1}; HRMS (ES) m/z calcd for $C_{17}H_{19}NNaBrO_3$ 449.0319, 451.0301; found 449.0313, 451.0297.

3-bromo-5-cyano-4-(2,3,4-trimethoxyphenyl)-1H-pyrrole 2-carboxylic acid ethyl ester (32): To a 100 mL round bottom flask equipped with a magnetic stir bar, was added 4 (2,3,4 trimethoxyphenyl)-5-oximino-1H-pyrrole-2-carboxylic acid ethyl ester (0.100 g, 0.234 mmol) dissolved in 20 mL of anhydrous chloroform. The reaction mixture was allowed to cool in an ice bath for 5 minutes. Phosphorus oxychloride (0.036 g, 0.234 mmol) was dissolved in 10 mL of anhydrous chloroform and the resulting mixture was added dropwise to the reaction mixture. The reaction mixture was stirred in an ice bath for 30 minutes and overnight at room temperature. The reaction mixture was diluted with 30 mL of water. The organic layer was washed with water (3 x 25 mL) and brine (1x 15 mL), dried over anhydrous sodium sulfate, filtered, evaporated and dried to give a light brown solid. The crude product was purified using a s silica plug and eluting with 30 mL of hexane/ethyl acetate (1:1), evaporated and dried to give a golden solid (0.085g, 89%). This solid exhibited the following properties: m.p. 173–176 °C; ^{1}H NMR ($CDCl_3$) δ 1.45 (t, J = 7.2 Hz, 3H), 3.83 (s, 3H), 3.93 (s, 6 H), 4.45 (q, J = 7.2 Hz, 2H), 6.75 (d, J = 8.4 Hz, 1H), 6.97 (d, J = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 159.2, 154.8, 152.0, 1422, 133.0, 126.0, 1242, 116.3, 111.9, 106.9, 104.9, 104.8, 62.1, 61.2, 61.2, 56.0, 14.2; IR (neat) 2221 and 1729 cm^{-1}; HRMS (ES) m/z calcd for $C_{17}H_{17}N_2O_5Br$ 409.0230 found 409.0283.

3-bromo-5-(*N*-propylaminomethylene)-4-(2,3,4-trimethoxyphenyl)-1H-pyrrole 2-carboxylic acid ethyl ester (34): To a 100 mL round bottom flask equipped with a magnetic stir bar, was added 3 bromo-5-formyl-4-(2,3,4-trimethoxyphenyl)-1H-pyrrole 2-carboxylic acid ethyl ester (0.300 g, 0.73 mmol) and n-propyl amine (0.36 mL, 4.34 mmol) in 15 mL of THF. The reaction mixture was stirred for 1 hour after which sodium cyanoborohydride (0.068g, 1.095 mmol) and glacial acetic acid (0.5 mL) were added. The reaction mixture was stirred for 24 hours at room temperature after which the reaction mixture was diluted with 50 mL of water and was extracted with ethyl acetate (3 x 15 mL). The organic layers were combined, dried over anhydrous sodium sulfate and evaporated in vacuo. The crude product was dried using a Kulgelrohr apparatus to give 0.356 g of dark brown solid. The crude residue was subjected to flash chromatography on a Biotage SP-1 instrument with a silica column in which case 0.25 g (76%) of a pale yellow solid was obtained upon elution with 19 column volumes of hexane/ethyl acetate gradient. This solid exhibited the following properties: m.p. 143-145 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.91 (t, J = 7.5 Hz, 3H), 1.41 (t, J = 7 Hz, 3H), 1.49 (hex, J = 7 Hz, 2H), 2.57 (t, J = 7 Hz, 2H), 3.60 (s, 3H), 3.68 (m, 2H), 3.92 (s, 3H), 3.93 (s, 3H), 4.39 (q, J = 7.2 Hz, 2H), 6.75 (d, J = 8.7 Hz, 1H), 6.95 (d, J = 8.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 160.1, 153.3, 152.3, 1422, 126.9, 119.7, 118.7, 107.1, 104.9, 61.2, 61.1, 60.5, 55.9, 51.3, 44.93, 22.4, 14.4, 11.6; IR (neat) 1727 cm^{-1}; HRMS (ES) m/z calcd for $C_{20}H_{29}N_2BrO_5$ 479.1152, 481.1134; found 479.1837, 481.2068.

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Appendix

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List of Schemes

List of Abbreviations

BPE: brompyrrole ester = 4-bromo-1H-pyrrole 2-carboxylic acid ethyl ester
BFPE: bromoformylpyrrole ester = 4-bromo-5-formyl-1H-pyrrole 2-carboxylic acid ethyl ester
DABCO: 1,4-diazabicyclo[2.2.2]octane
DCM: dichloromethane
DMF: dimethylformamide
NBS: *N*-bromosuccinimide
Pd(II)-dppf: dichloro-1,1,-bis(diphenylphosphino)ferrocene palladium (II)
Triflic anhydride: trifluoromethanesulfonic anhydride