

Study and Development of Synthetic Methodology Towards Pyrrolic Frameworks

by

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Submitted in partial fulfillment of the requirements  
for the degree of Doctor of Philosophy

at

Dalhousie University  
Halifax, Nova Scotia  
November 2019

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To my Mom

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## Abstract

This thesis focuses on the study and development of synthetic methodology towards pyrrolic frameworks. Three projects are discussed: the development of open-air conditions for the synthesis of *F*-BODIPYs, mechanistic studies in the synthesis of symmetrical dipyrrens, and the development of new reactions for the synthesis of sulfur-bridged pyrroles.

The atmospheric effects of water on the synthesis of *F*-BODIPYs were explored. A methodology was developed for the high-yielding synthesis of *F*-BODIPYs involving non-anhydrous reagents and requiring no precautions to exclude moisture. This simple and robust strategy requires the addition of two aliquots of  $\text{NEt}_3$  and  $\text{BF}_3 \cdot \text{OEt}_2$ . The ratio and amounts of  $\text{NEt}_3$  and  $\text{BF}_3 \cdot \text{OEt}_2$  used in each aliquot are critical to success (6 equivalents of  $\text{NEt}_3$  and 9 equivalents of  $\text{BF}_3 \cdot \text{OEt}_2$  per each aliquot). Most important is that the protocol can be completed using air-dried bench-top apparatus, without the need to either purchase anhydrous solvents or achieve and maintain anhydrous solvents and conditions.

The synthesis of symmetric  $\alpha$ -free *meso*-H-dipyrin hydrobromides from 5-unsubstituted 2-formylpyrroles (2-formyl-5-H-pyrroles) was investigated and it was found that the self-condensation produces regioisomeric dipyrrens through adoption of two mechanistic pathways. Through a systematic study involving variously substituted and isotopically labelled 2-formyl-5-H-pyrroles, evidence was provided to suggest that not only does there exist two mechanistic pathways, but that the steric bulk of the substituent adjacent to the 5-unsubstituted position influences which pathway dominates.

There are few synthetic routes to preparing sulfur-bridged dipyrrolyl sulfides, most of which require use of sulfur dichloride, a restricted chemical unavailable within Canada. Towards the preparation of sulfur-bridged di-, tri-, and tetrapyrroles, the first example of electrophilic aromatic substitution of pyrrole using thionyl chloride to produce dipyrrolyl sulfides was developed. The use of thionyl chloride results in an interesting auto-reduction of the sulfoxide centre to produce a sulfide-bridged dipyrrole. The new synthesis was investigated and a mechanism for the auto-reduction reaction was proposed.

## List of Abbreviations and Symbols Used

2-D:	Two-dimensional
2°:	Secondary
48% HBr:	48% Aqueous HBr
Å:	Angstrom
AcOH:	Acetic acid
APCI:	Atmospheric pressure chemical ionization
aq:	Aqueous
Ar:	Arene/Aryl
B:	Base
BF <sub>3</sub> •OEt <sub>2</sub> :	Boron trifluoride diethyl etherate
biPy:	2,2'-bipyridine
Bn:	Benzyl
BOC:	<i>tert</i> -Butoxy carbonyl
BOC <sub>2</sub> O:	Di- <i>tert</i> -butyl dicarbonate
BODIPY:	4-Bora-3a,4a-diaza- <i>s</i> -indacene
br s:	Broad singlet
CAD:	Canadian dollar
CAN:	Ceric ammonium nitrate
cat.:	Catalytic
cm:	Centimetre
CPO:	Coproporphyrinogen oxidase
Cy:	Cyclohexyl

d:	Doublet
DCE:	1,2-Dichloroethane
DDQ:	2,2-Dichloro-5,6-dicyano-1,4-benzoquinone
DIPEA:	N,N-Diisopropylethylamine
DMAP:	4-Dimethylaminopyridine
DMF:	Dimethylformamide
DMSO:	Dimethyl sulfoxide
dOAT:	Deoxygenative O-atom transfer
E:	Energy
Equiv:	Equivalents
ESI:	Electrospray ionization
Et:	Ethyl
Et <sub>2</sub> O:	Diethyl ether
EtOAc:	Ethyl acetate
EtOH:	Ethanol
<i>F</i> -BODIPY:	4,4-Difluoro-4-bora-3a,4a-diaza- <i>s</i> -indacene
FC:	Ferrochelataase
g:	Gram
GP:	General procedure
h:	Hour
HMBC:	Heteronuclear Multiple Bond Correlation
HOMO:	Highest occupied molecular orbital
HPLC:	High-performance liquid chromatography
HRMS:	High-resolution mass spectrometry

HSQC:	Heteronuclear Single Quantum Coherence
HSVM:	High-speed vibration milling
Hz:	Hertz
HZSM-5:	Zeolite Socony Mobil-5, H-form
<sup>i</sup> Pr:	Isopropyl
IUPAC:	International Union of Pure and Applied Chemistry
<i>J</i> :	Coupling constant
kJ:	Kilojoule
KO <sup>t</sup> Bu:	Potassium <i>tert</i> -butoxide
kPa:	Kilopascal
L:	Litre
LCQ:	Liquid Chromatography Quadrupole
LiHMDS:	Lithium bis(trimethylsilyl)amide
M:	Molarity, mol/L
m:	Multiplet
m.p.:	Melting point
<i>m</i> CPBA:	<i>meta</i> -Chloroperoxybenzoic acid
Me:	Methyl
MeOH:	Methanol
Mes:	Mesityl
mg:	Milligram
MHz:	Megahertz
mL:	Millilitre
mmHg:	Millimetre of mercury

mmol:	Millimole
mol:	Mole
mol%:	Mole percent
MSc:	Masters
<i>n</i> -BuLi:	<i>n</i> -Butyl lithium
<i>n</i> -Pn:	<i>n</i> -Pentyl
NBS:	<i>N</i> -Bromosuccinimide
NCS:	<i>N</i> -Chlorosuccinimide
NEt <sub>3</sub> :	Triethylamine
nm:	Nanometre
NMR:	Nuclear Magnetic Resonance
Nu:	Nucleophile
OAc:	Acetate
°C:	Degrees Celsius
<i>p</i> -chloranil:	Tetrachloro-1,4-benzoquinone
Ph:	Phenyl
ppm:	Parts per million
PPO:	Protoporphyrinogen oxidase
<i>p</i> TSA:	<i>p</i> -Toluene sulfonic acid
q:	Quartet
qd:	Quartet of doublets
qs:	Quartet of singlets
quin:	Quintet
s:	Singlet (in context of NMR spectra)

s:	Second
SOCl <sub>2</sub> :	Thionyl chloride
t:	Triplet
<sup>t</sup> Bu:	<i>tert</i> -Butyl
<sup>t</sup> BuCO <sub>2</sub> H:	Pivalic acid, aka trimethylacetic acid
TFA:	Trifluoroacetic acid
THF:	Tetrahydrofuran
TLC:	Thin-layer chromatography
TMOF:	Trimethyl orthoformate
TOF:	Time-of-Flight
Tos/Tosyl:	Toluenesulfonyl
TosMIC:	Toluenesulfonylmethyl isocyanide
UROD:	Uroporphyrinogen decarboxylase
UROS:	Uroporphyrinogen synthase
wt%:	Weight percent
δ:	Chemical shift
Δ:	Heat
δ <sup>(+/-)</sup> :	Partial positive or negative charge
λ <sub>abs</sub> :	Maximum absorbance wavelength
λ <sub>em</sub> :	Maximum emission wavelength
μL:	Microlitre

## Acknowledgments

First and foremost, I would like to thank my supervisor, Dr. Alison Thompson, for her guidance, support, and patience throughout the entirety of this degree. You saw in me many qualities that I never did, and you helped me to grow as an academic, a professional, and a person. Thank you to Dr. Katherine Robertson for her incredible help providing X-Ray crystal structures, Xiao Feng for running the mass spectrometry, and Dr. Mike Lumsden for help with NMR experiments, as well as all of the support staff from the Department of Chemistry. I am incredibly grateful for the financial support provided by Dr. Thompson, the Dalhousie University Faculty of Graduate Studies, the Dalhousie University Department of Chemistry, and the National Science and Engineering Research Council of Canada. I would also like to acknowledge my current and past committee members: Dr. Alex Speed, Dr. Laura Turculet, Dr. Fran Cozens, Dr. Norman Schepp, and Dr. Stephen Bearne.

Thank you to my friends Kate-lyn Lund and Dr. Carlotta Figliola for the endless help in lab and for being good friends. I would also like to thank Dr. Craig Smith for all the help he gave me in the last year of my work and for comradery and friendship in and out of lab. Thank you to Braden Thournout for his kind nature, incredible wit, and for just being a great person, and my closest friend. I would like to acknowledge all of my friends, of whom there are too many to name, but who are all so important.

To Dad, thank you for everything you've done for me, especially for teaching me about hard work and how to be resourceful and able to problem solve. These skills have proved to be incredibly useful throughout my degree and especially in the lab work. Thank you to Bre and Pat, who cautioned me against pursuing chemistry after high

school. That's a joke for my sister and brother; their unconditional love and support has always been a constant in my life and a pillar that I can always lean on for support. Thank you, Mom, for inspiring in me a love of knowledge that has brought me to where I am today. Everything I am and have been able to achieve is a reflection of all that you've done for me throughout my life. For being a kind, caring, and all around wonderful mother, thank you.

And finally, Elise, thank you for everything. Yours is the hardest thanks to describe. Thank you for being there for me through nearly my entire degree and helping me through the toughest parts. Thank you for everything you've done for me, and the happiness you've brought along the way. Contrary to this thesis, I've never been good with words, so I apologize, but I can't string together the right words to come close to describing how much your friendship and love has helped and meant to me over these years.

While this document bears my name alone, it was far from a lone effort. Without my friends and family this would never have been possible, and they all deserve thanks.

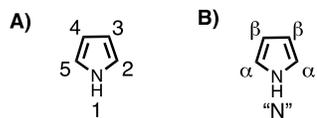
## Chapter 1 – Introduction

### 1.1 Nomenclature of Pyrrole-based Compounds

As with most chemical compounds there exists a number of different naming conventions for pyrroles and pyrrole-based compounds. This body of work deals specifically with pyrroles, dipyrins, and *F*-BODIPYs and as such the nomenclature of each will be discussed in detail below. Naming conventions common to literature that are accepted by the International Union of Pure and Applied Chemistry (IUPAC) for each family of compounds will be discussed, in addition to the systematic IUPAC nomenclature.

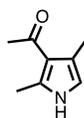
#### 1.1.1 Pyrroles

Numbering of *1H*-pyrrole rings, as recommended by IUPAC,<sup>1</sup> can be seen in Figure 1A. When discussing positions around the pyrrole ring, positions 2- and 5- are commonly referred to as the  $\alpha$ -positions, and positions 3- and 4- are referred to as the  $\beta$ -positions (Figure 1B). When a pyrrole has only hydrogen bound to a given  $\alpha$ - or  $\beta$ -position, it is termed  $\alpha$ - or  $\beta$ -free, respectively. The 1-position, or nitrogen atom, is commonly referred to as the N-position. With a hydrogen atom bound to the nitrogen, the pyrrole of Figure 1 is termed an N-H pyrrole. Following this, substitution with a methyl group on the nitrogen atom would be referred to as an N-Me pyrrole. In this body of work, the use of the described  $\alpha$ -,  $\beta$ -, and N- naming conventions will dominate.



**Figure 1: The IUPAC Defined Numbering and Common Nomenclature of the Pyrrole Ring**

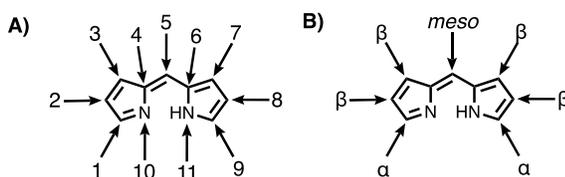
Notwithstanding the different naming conventions for pyrrole itself, the name of pyrrolic heterocycles can change depending on the substituents around the pyrrole ring. For example, Figure 2 shows 1-(2,4-dimethyl-1*H*-pyrrol-3-yl)ethanone, which is named according to systematic IUPAC conventions.<sup>2</sup> However, more common conventions can be used to name the same pyrrole as 3-acetyl-2,4-dimethylpyrrole, or as 2,4-dimethyl-3-acetylpyrrole. The differences arise from consideration of the parent compound as a ketone, a pyrrole, or an acetylpyrrole, respectively. This challenge leads to the notion that this one pyrrole has three possible names. In an effort to unify chemical naming, the systematic IUPAC conventions will be used exclusively within the experimental section of this thesis. Throughout the remainder of the text, pyrrole will be considered as the name of the parent compound and the common pyrrole nomenclature described will be used, e.g. 3-acetyl-2,4-dimethylpyrrole.



**Figure 2: 1-(2,4-Dimethyl-1*H*-pyrrol-3-yl)ethanone, also Known as 3-Acetyl-2,4-dimethylpyrrole or 2,4-Dimethyl-3-acetylpyrrole**

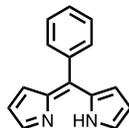
### 1.1.2 Dipyrrins

The numbering of the dipyrrin skeleton (aka dipyrromethene), suggested by IUPAC as an extension from porphyrin nomenclature,<sup>3</sup> is depicted in Figure 3A. However, similar to pyrrole, the  $\alpha/\beta$  nomenclature is commonly used for the carbon atoms that make up each pyrrolic unit of a dipyrrin (Figure 3B). Thus, positions 1- and 9- are  $\alpha$ -positions, and positions 2-, 3-, 7-, and 8- are referred to as  $\beta$ -positions. In addition, the carbon of the methene bridge, the 5-position, is commonly referred to as the *meso*-position, which again originates from porphyrin naming conventions.<sup>3</sup>



**Figure 3: Structure and IUPAC Numbering of the Dipyrrin Skeleton Extended from Porphyrin Nomenclature**

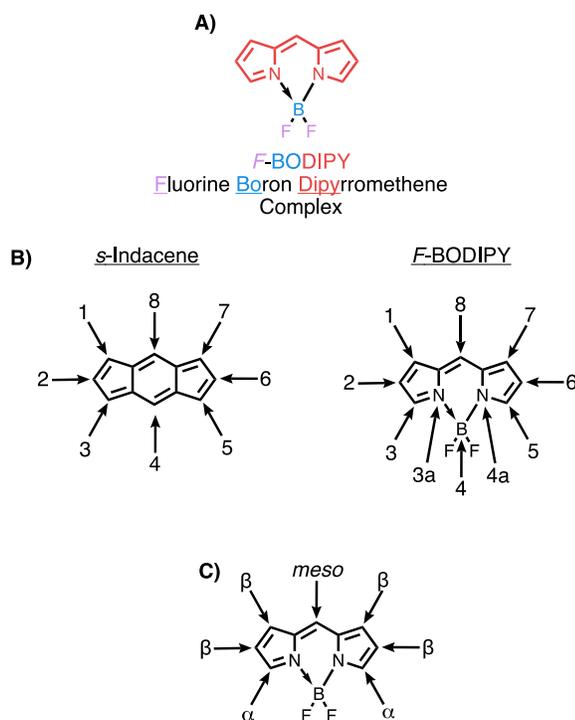
Similar to pyrroles, dipyrrins have multiple naming conventions accepted by IUPAC.<sup>4</sup> Following systematic IUPAC conventions, Figure 4 shows the structure of 2-[phenyl(2*H*-pyrrol-2-ylidene)methyl]-1*H*-pyrrole.<sup>5</sup> Alternatively, dipyrrin or dipyrromethene can be considered as the parent compound and the same molecule could be named 5-phenyldipyrrin or 5-phenyldipyrromethene, respectively. As with pyrroles, the systematic IUPAC conventions for dipyrrins will be used within the experimental section of this thesis. For simplicity, use of dipyrrin and  $\alpha$ -,  $\beta$ -, and *meso*- nomenclature will be used elsewhere.



**Figure 4: 2-[Phenyl(2*H*-pyrrol-2-ylidene)methyl]-1*H*-pyrrole, also Known as 5-Phenyldipyrin or 5-Phenyldipyrromethene**

### **1.1.3 4,4-Difluoro-4-bora-3a,4a-diaza-*s*-indacene (*F*-BODIPYs)**

First discovered in 1968 by Treibs and Kazer,<sup>6</sup> dipyrins complexed to a BF<sub>2</sub> moiety are today known by the chemical name 4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene (Figure 5A), which can be abbreviated as *F*-BODIPY (derived from Fluorine Boron Dipyrromethene complex).<sup>7</sup> The italicized letter before ‘BODIPY’ indicates the atoms bound to the boron centre, with carbon (*C*-BODIPY), oxygen (*O*-BODIPY) and other halogens (e.g. *Cl*-BODIPY) being known.<sup>8-11</sup> Rather than originating from porphyrin conventions, like dipyrins, the numbering scheme for *F*-BODIPYs is analogous to that of *s*-indacene, as shown in Figure 5B. However, despite the relation to *s*-indacene, the α-, β- and *meso*- nomenclature used with dipyrins is also common with *F*-BODIPYs (Figure 5C).

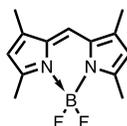


**Figure 5: A) Visual Representation of *F*-BODIPY Naming Convention; B) Numbering of *s*-Indacene and *F*-BODIPYs; C)  $\alpha/\beta$  and *meso* Nomenclature of *F*-BODIPYs**

The first iteration of the term BODIPY was introduced in 1989,<sup>7,12</sup> where it appeared as the all lowercase ‘bodipy’ and was used to abbreviate the compound 3,3',5,5'-tetramethyl-2,2'-pyrromethene-1,1'-borondifluoride (Figure 6). In the following year, uppercase ‘BODIPY’ was trademarked by Molecular Probes, Inc.<sup>13</sup> Following the 1990 trademark, the all uppercase abbreviation BODIPY was widely adopted throughout the literature, with an italicized ‘*F*’ being added to indicate fluorine atoms were bound to the boron centre.<sup>14–19</sup> While Molecular Probes, Inc. made use of the original pyrromethene borondifluoride naming convention<sup>6</sup> for BODIPYs in their 1990 patent, this naming convention was soon succeeded by use of 4,4-difluoro-4-bora-3a,4a-diaza-*s*-

indacene. To the best of our knowledge the *s*-indacene-based convention was first used in 1977,<sup>20</sup> but was not widely adopted until the early 1990s.

As stated above, the simple *F*-BODIPY shown in Figure 6 is known as 3,3',5,5'-tetramethyl-2,2'-pyrromethene-1,1'-borondifluoride, using the original 1968 nomenclature.<sup>6</sup> However, as stated, this naming convention is no longer used and instead the compound would be known as 1,3,5,7-tetramethyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene by modern naming conventions. In addition, using systematic IUPAC conventions the same *F*-BODIPY shown is known as (*T*-4)-difluoro[2-[phenyl(2*H*-pyrrol-2-ylidene- $\kappa$ N)methyl]-1*H*-pyrrolato- $\kappa$ N]boron.<sup>21</sup> As with pyrroles and dipyrins, the systematic IUPAC conventions for *F*-BODIPYs will be used only within the experimental section of this body of work. For clarity, use of *F*-BODIPY and  $\alpha$ -,  $\beta$ -, and *meso*- nomenclature will dominate outside of the experimental section of this thesis.



**Figure 6: 3,3',5,5'-Tetramethyl-2,2'-pyrromethene-1,1'-borondifluoride (1968-1989); 1,3,5,7-Tetramethyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene (2019 IUPAC Accepted Convention); (*T*-4)-Difluoro[2-[(3,5-dimethyl-2*H*-pyrrol-2-ylidene- $\kappa$ N)methyl]-3,5-dimethyl-1*H*-pyrrolato- $\kappa$ N]boron (2019 Systematic IUPAC)**

## 1.2 Pyrrole: Structure and Reactivity

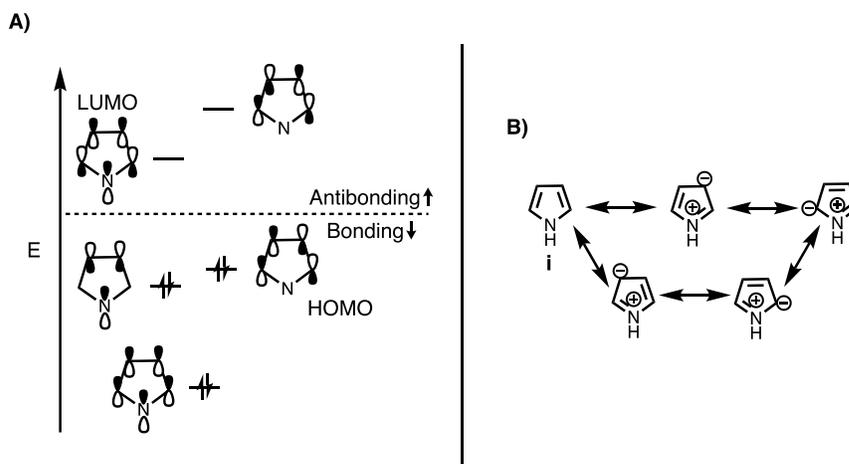
Heterocycles are cyclic compounds containing heteroatoms, i.e. atoms other than carbon (e.g. nitrogen, oxygen, sulfur).<sup>22,23</sup> Molecules containing heterocyclic rings are prevalent throughout nature and in modern pharmaceuticals, representing one of the largest and fastest growing groups of biologically active compounds in present times.<sup>24-26</sup>

Of this vast grouping of chemicals, pyrroles and their derivatives are one of the most important classes.<sup>27</sup> Pyrroles are a diverse and well-studied family of compounds, having been known since the earliest reports of their isolation from coal tar in 1834.<sup>28</sup> Pyrrole-containing compounds have been shown to have antitumor,<sup>29</sup> antibacterial,<sup>30</sup> antiviral,<sup>31</sup> antimicrobial,<sup>32</sup> and anti-inflammatory<sup>33</sup> properties, amongst others.

Pyrroles are known generally as electron-rich aromatic heterocycles and have interesting electronic properties whereby the  $\alpha$ - and  $\beta$ -positions are the most nucleophilic favouring electrophilic addition at those positions rather than the nitrogen atom. In comparison, the nitrogen atom is the most nucleophilic atom in pyridine, the 6-membered heterocyclic and aromatic analogue. In order for pyrrole to be aromatic, the lone-pair of the nitrogen atom must be conjugated to the  $\pi$ -system to create a  $6\pi$ -system (Huckel's rule,  $4n+2$ ). Indeed, looking at the electronic structure<sup>34</sup> of pyrrole (Figure 7A), the  $6\pi$ -electrons occupy the three bonding orbitals, while the antibonding orbitals remain unoccupied, thus making pyrrole decidedly aromatic.<sup>23</sup>

Additionally, the resonance contributors we are capable of depicting for pyrrole (Figure 7B) aid in understanding the aromatic nature, as well as why pyrrole is known as an electron-rich heterocycle, and why the  $\alpha$ - and  $\beta$ -positions are traditionally more nucleophilic. Within the depicted resonance contributors, the nitrogen atom of pyrrole donates its lone-pair into the ring structure, enabling full delocalization of the  $\pi$ -electrons. By donating the lone-pair, the nitrogen atom acts as an electron-donating group, which helps give rise to the electron-rich nature of pyrrole, compared to benzene. It is clear that the main resonance contributor is the structure that features no internal charge separation (i). However, the remaining resonance contributors, with negative charge character across

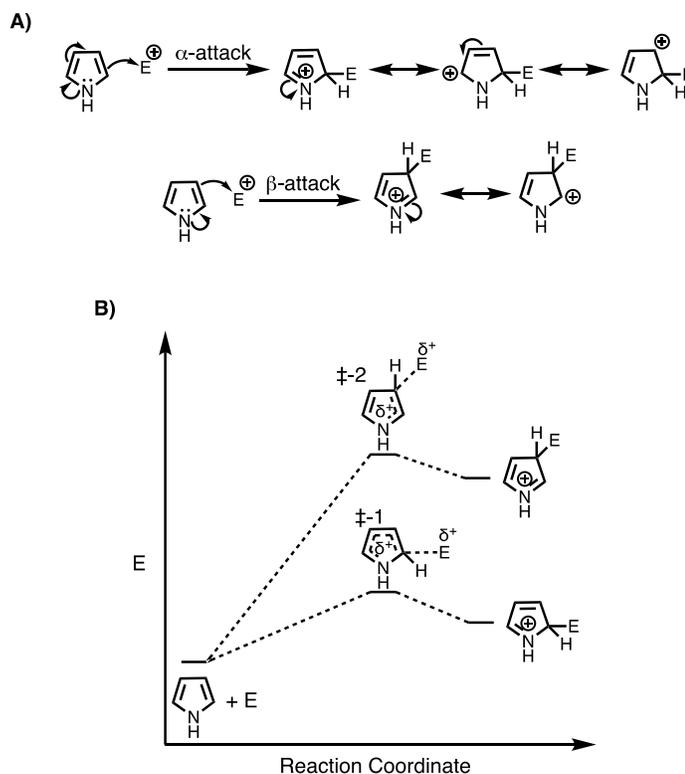
the 4 carbon atoms, lend credence to the strong nucleophilic nature of the  $\alpha$ - and  $\beta$ -positions. Our ability to depict the resonance contributors of pyrrole in this way helps to conceptualize why electrophilic addition to pyrrole at the  $\alpha$ - and  $\beta$ -positions, rather than the nitrogen atom, is favoured.



**Figure 7: A) The Electronic Structure of Pyrrole (Energy Levels are Relative and Not to Scale); B) Pyrrole and its Resonance Contributors**

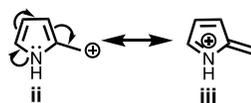
Typically, nucleophilic attack from the  $\alpha$ -position of pyrroles is strongly favoured compared to nucleophilic attack from a  $\beta$ -position. This phenomenon can be explained through calculation of electron densities by theoretical means, finding that the HOMO (Figure 7A) of pyrrole has a larger coefficient in the  $\alpha$ -positions compared to the  $\beta$ -positions.<sup>34,35</sup> Alternatively, when considering the resonance forms one can propose for pyrrole in a general electrophilic addition reaction at either the  $\alpha$ - or  $\beta$ -position (Figure 8), we are able to come to the same conclusion. Nucleophilic attack from the  $\alpha$ -position (Figure 8A, top) would generate an intermediate for which we could propose three contributing resonance forms, while attack from the  $\beta$ -position (Figure 8A, bottom) would generate an intermediate with only two contributing resonance forms. In the case

of an  $\alpha$ -attack, being able to represent the intermediate with three reasonable resonance contributors suggests that the  $\pi$ -electrons can delocalize across the four participating atoms, thus granting increased stability compared to  $\beta$ -attack. The intermediate produced as a result of  $\beta$ -attack would have  $\pi$ -electrons delocalized over just two atoms. In terms of hypothesized transition states (Figure 8B), the greater delocalization of  $\pi$ -electrons that can occur when nucleophilic attack originates from the  $\alpha$ -position would be expected to stabilize the transition state ( $\ddagger$ -1), lowering its energy compared to the  $\beta$ -variant ( $\ddagger$ -2). Therefore, using this argument, functionalization of the pyrrole core would be expected to favour the  $\alpha$ -position.



**Figure 8: A) Pyrrole and its Proposed Resonance Contributors for Electrophilic Addition at the  $\alpha$ - or  $\beta$ -Position; B) Hypothesized Reaction Coordinate Diagram for Pyrrole for Electrophilic Addition at the  $\alpha$ - or  $\beta$ -Position (Energy Levels are Relative and Not to Scale)**

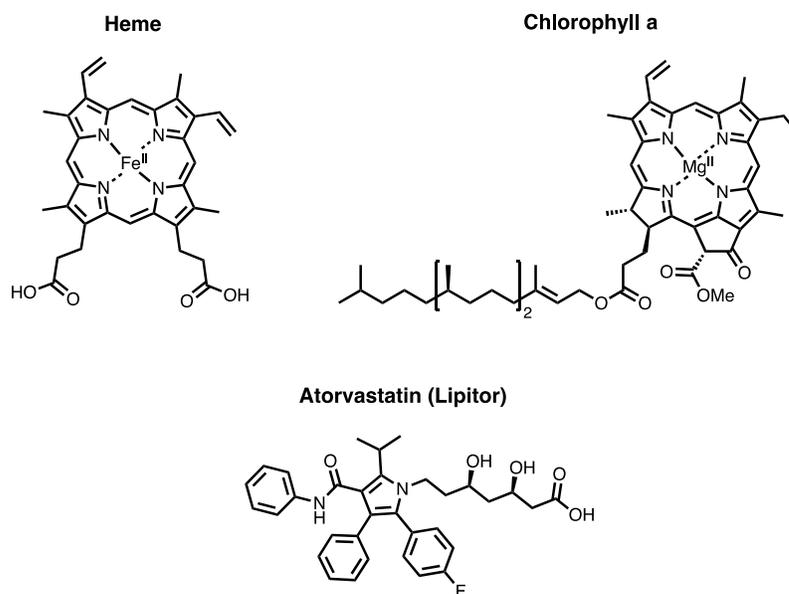
Moreover, the nucleophilic carbon atoms make pyrrole ever prone to ring protonation, and so pyrrole undergoes polymerization under dilute acidic conditions, even readily in water.<sup>36</sup> The electron-rich nature of pyrrole intensifies this nucleophilic reactivity and makes it very prone to oxidation in air, autoxidizing to form polymeric tar-like materials under atmospheric conditions. Substituents with electron donating properties increase the proclivity for autoxidation, ring-protonation, and polymerization. Something as weakly electron donating as an alkyl substituent has a great effect on this reactivity, e.g. 2-methylpyrrole is 24 times more reactive in the 5-position than the corresponding 2/5-position of pyrrole itself.<sup>37</sup> In contrast, electron-withdrawing groups have a significant stabilizing effect on pyrroles, inhibiting ring protonation and dramatically reducing spontaneous polymerization. As such, it is common to append the pyrrolic ring with formyl, acyl, or carboxylate groups, allowing compounds to be stored under bench-top conditions for almost indefinite periods of time. Similar to benzylic carbon atoms, alkyl substituents around the pyrrole framework show enhanced reactivity when compared to simple alkanes. For example, the carbocation in Figure 9 (ii) can be stabilized by donation of electron-density from the adjacent  $\pi$ -system of the pyrrole ring and is known as an azafulvenium ion (iii).



**Figure 9: Azafulvenium Ion Resonance Contributors**

### 1.3 Synthesis of Pyrrole

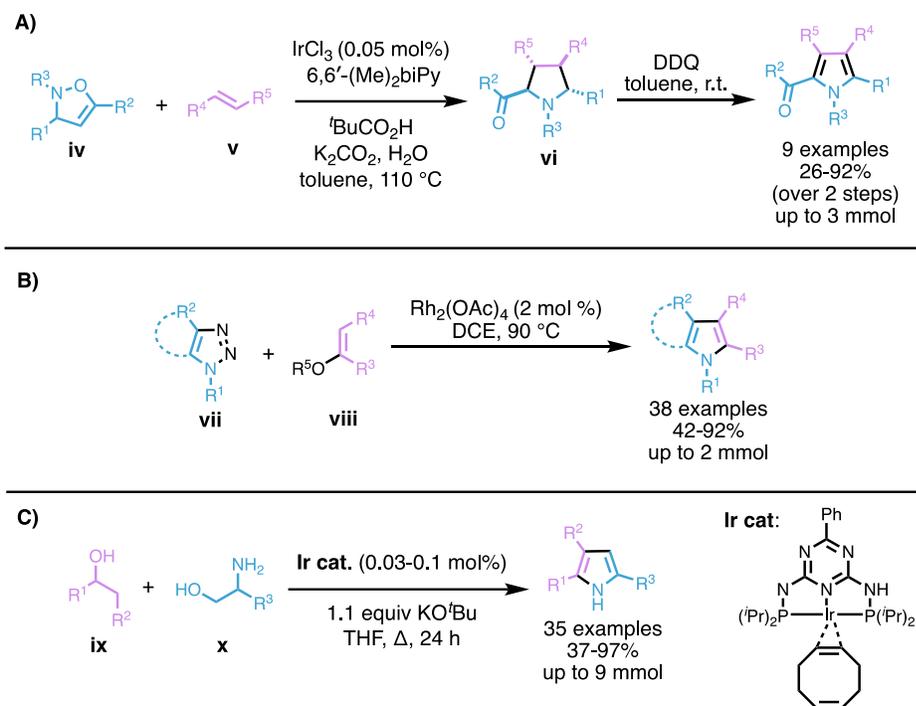
Some of the most well-known natural pyrrole-containing chemical species are heme, vitamin B<sub>12</sub>, and chlorophyll for the vital roles they play within plants and humans (Figure 10). One of the most economically important pyrrole-based compounds has likely been atorvastatin (Figure 10, bottom), a cholesterol lowering pharmaceutical used to help prevent cardiovascular disease. Atorvastatin is most commonly sold under the trade name Lipitor, and as of 2018 was one of the all-time best-selling pharmaceutical drugs, with lifetime sales surpassing \$205 billion CAD in 2018.<sup>38,39</sup> No matter which pyrrolic compound is most well-known, the importance of the small heterocycle to nature, and our well-being, cannot be understated. Investigations into new pyrrolic compounds, and new syntheses, has been a large area of research for decades, and is likely to be for many more. Herein are highlighted three broad categories for the synthesis of pyrroles: transition-metal catalysis, acid catalysis, and stoichiometric synthesis of pyrroles.



**Figure 10: Pyrrole-based Compounds Heme, Chlorophyll, and Atorvastatin**

### 1.3.1 Transition Metal-catalyzed Synthesis of Pyrroles

With thousands of publications available on the topic, there is no shortage of reported methodologies for the transition metal-catalyzed synthesis of pyrroles. The methodologies highlighted herein represent only a small portion of those available but were chosen for their capabilities of furnishing a large number of broadly varied and highly substituted pyrroles in fair to excellent yields from readily available materials. Reported in 2016, Xiao et al.<sup>40</sup> developed an iridium-catalyzed synthesis of pyrroles in a biphasic system (Scheme 1A). The heterogenous iridium catalyst facilitated N–O cleavage and subsequent cyclization of 2,3-dihydroisoxazoles (**iv**) with alkenes (**v**) to give highly substituted pyrrolidines (**vi**), which could be oxidized with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) to furnish pentasubstituted pyrroles. A common oxidant in the pyrrole world, DDQ has been used for decades to furnish pyrrolic compounds via oxidation and aromatization, including pyrroles<sup>41–43</sup> and porphyrins.<sup>44–50</sup> The pyrroles were prepared in 26–92% yield, limited primarily by the DDQ-induced oxidation; the catalytic transformation itself was of moderate efficiency with yields above 60% for each of the pyrrolidine products. The authors bolstered the efficacy of the transformation by countering the high cost of an iridium catalyst with low catalyst loading (0.05 mol%) and catalyst re-use, cycling seven times and returning >80% yields of the chosen pyrrolidine substrate. Using this approach, Xiao et al. prepared nine pentasubstituted pyrroles with a variety of functional groups, including ester, acyl, and aryl moieties. This methodology was utilized to prepare two pyrroles in gram quantities (approximately 3 mmol), thereby demonstrating versatility to moderate scale-up.



**Scheme 1: A) Heterogenous Iridium Catalyzed Synthesis of Pyrroles; B) Rhodium Catalyzed Synthesis of Pyrroles from Readily Available Triazoles and Enol Ethers; C) Sustainable Iridium Catalyzed Synthesis of Pyrroles from Renewable Resources**

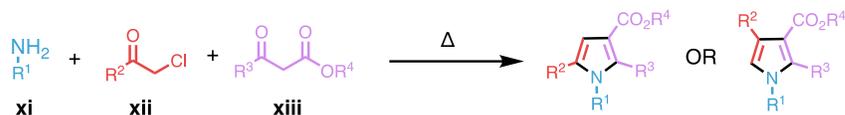
Rajasekar and Anbarasan reported the rhodium-catalyzed synthesis of di-, tri-, and tetrasubstituted pyrroles via the trans-annulation of N-sulfonyl-1,2,3-triazoles (**vii**) with enol ethers (**viii**) (Scheme 1B).<sup>51</sup> Benefiting this work, a number of triazoles and enol ethers are readily available by commercial and synthetic means, and so the rhodium catalyst is likely the largest expense required in order to adopt this method for the synthesis of functionalized pyrroles. Rajasekar and Anbarasan prepared 38 examples of poly-substituted pyrroles featuring a variety of substitution patterns, including  $\alpha,\beta$ -fused pyrroles. By virtue of the N-protected triazole starting material, all synthesized pyrroles were also N-protected, but a handful of pyrroles bearing N-sulfonyl moieties were shown to undergo deprotection to furnish N-H pyrroles in good yields under basic conditions.

Michlik and Kempe developed a sustainable iridium-catalyzed synthesis of pyrroles from secondary alcohols (**ix**) and amino alcohols (**x**) (Scheme 1C).<sup>52</sup> The scope of the reaction was impressive, with incredible variety of functionalization in producing di- and trisubstituted N-H pyrroles, including but not limited to ferrocenyl, aliphatic, fused, heterocyclic and halogenated pyrroles, all produced in fair to excellent yields. It should be noted that this route enables the direct synthesis of N-H pyrroles via use of a transition metal catalyst, a rare feat and one not seen in the previous two catalytic reactions (Scheme 1, A and B). In addition, the reaction was used to prepare bipyrrroles from aliphatic diols, and amino pyrroles from aryl amines, all in good yields. The scope of the reaction was backed by the maximum reported scale of 9 mmol, a comparably large quantity amongst other transition metal catalyzed reactions. Again, the cost of the iridium catalyst is a significant factor to consider, but the draw of simple conditions and renewable starting materials (2° alcohols and amino alcohols) is undeniable.

### 1.3.2 Acid-catalyzed Synthesis of Pyrroles

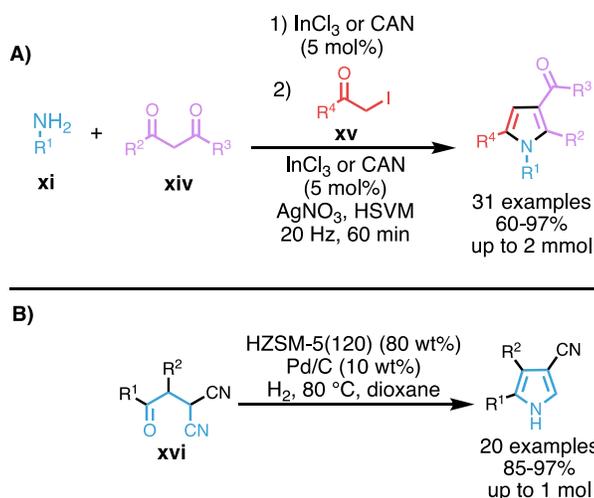
The first multi-component synthesis of pyrroles was reported in 1890 by Hantzsch<sup>53</sup> (Scheme 2) and is now commonly known as the Hantzsch Pyrrole Synthesis. This synthesis furnished tri- and tetrasubstituted pyrroles via the condensation reaction of ammonia, or a primary amine (**xi**), with an  $\alpha$ -halo ketone (**xii**) and a  $\beta$ -keto ester (**xiii**). Despite reaching the status of named reaction, the Hantzsch Pyrrole Synthesis has attracted little attention from researchers,<sup>54</sup> with as few as 30 reported uses in the 129 years since its invention, the majority of which were reported after 1990. However, since

the 1990s, the Hantzsch Pyrrole Synthesis has begun to gain traction, with researchers revisiting and bringing a modern approach to one of the oldest known pyrrole syntheses.



## Scheme 2: Hantzsch Pyrrole Synthesis

Estévez et al. developed a catalytic mechanochemical Hantzsch synthesis of tetrasubstituted pyrroles (Scheme 3A).<sup>55,56</sup> The reaction employed a Lewis-acid catalyst, InCl<sub>3</sub> or ceric ammonium nitrate (CAN), and high-speed vibration milling (HSVM), to achieve the preparation of a number of tetrasubstituted pyrroles from amines (**xi**), diketones (**xiv**), and α-iodo ketones (**xv**) in fair to excellent yields under solvent-free conditions. Five N-H pyrroles were reported, the remaining 26 examples being N-substituted. Furthermore, the methodology was applied to prepare more complex pyrrole-based tricyclic systems, as well as bispyrrole-based macrocycles. The catalytic and mechanochemical methodology presents a unique adaptation of one of the oldest pyrrole syntheses, enabling preparation of pyrroles in fair to excellent yields in the solid state.

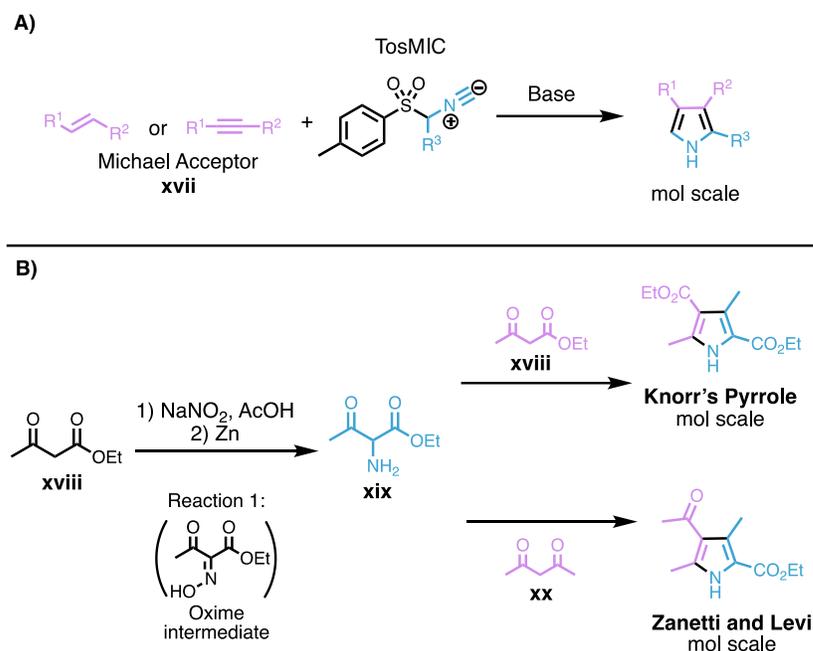


**Scheme 3: A) Lewis Acid-Catalyzed Hantzsch Synthesis of Pyrrole using High Speed Vibrational Milling; B) Single Component Synthesis of Pyrrole Catalyzed by Acidic Zeolite HZSM-5**

Chen et al. developed an acid-catalyzed single-component synthesis of N-H 3-cyanopyrroles (Scheme 3B) from 2-(2-oxo-2-ethyl)malononitriles (**xvi**), using aluminosilicate zeolite HZSM-5 and Pd/C under a  $\text{H}_2$  atmosphere.<sup>57</sup> HZSM-5(120), a zeolite with a  $\text{SiO}_2:\text{Al}_2\text{O}_3$  ratio of 120:1, was found to be the optimal catalyst to prepare a number of 4,5-substituted 3-cyanopyrroles with a variety of substituents including arenes, halogenated and electron-rich/poor furans, and fused-ring substituents. Pd/C-induced hydrogenation of a cyano group of malonitrile **xvi** furnished the imine/enamine tautomer, the intramolecular annulation of which was catalyzed by HZSM-5(120) to furnish the final 3-cyanopyrroles. This synthesis makes use of readily available and reusable hydrogenation and acid catalysts to prepare pyrroles, with 20 examples presented with good to excellent yields, and on a noteworthy scale of up to 1 mol (compare to mmol scale of previously discussed syntheses).

### 1.3.3 Stoichiometric Synthesis of Pyrroles

The reaction of Michael acceptors (**xvii**) and toluenesulfonylmethyl isocyanide (ToSMIC) to prepare di- and trisubstituted pyrroles was first used by van Leusen et al. in 1972<sup>58</sup> (Scheme 4A). Since the original report, the synthesis has been widely used in the preparation of hundreds of disubstituted pyrroles,<sup>59-66</sup> and a smaller number of trisubstituted pyrroles.<sup>67-69</sup> This reaction to prepare pyrroles has proved amenable to a plethora of Michael acceptors bearing a variety of electron-withdrawing groups ( $R^1$ ): cyano,<sup>70</sup> keto,<sup>60</sup> ester,<sup>71</sup> nitro,<sup>72</sup> and electron-withdrawing arenes<sup>73</sup> were all tolerated. With the stipulation that  $R^1$  or  $R^2$  must contain an electron-withdrawing functionality that becomes conjugated to the pyrrole ring, the reaction enabled functionalization around the pyrrole ring to include the aforementioned electron-withdrawing group and more such as aryl,<sup>65</sup> alkyl,<sup>59</sup> acyl,<sup>65</sup> or fused rings<sup>65,74-76</sup> to name just a few. However, the reaction requires deprotonation of TosMIC using a strong base (e.g. NaH), which therefore excludes incorporation of base-sensitive functional groups that may elicit unwanted reactivity. The variability in substitution, relative simplicity of procedure, and scale all make the reaction of TosMIC and various Michael acceptors a useful and versatile synthesis for the preparation of some pyrroles.



**Scheme 4: A) Synthesis of 3,4-Substituted Pyrroles from Michael Acceptors and TosMIC; B) Knorr Pyrrole Synthesis and Zanetti's and Levi's Expansion Using a  $\beta$ -Keto Ester or a 1,3-Diketone, Respectively**

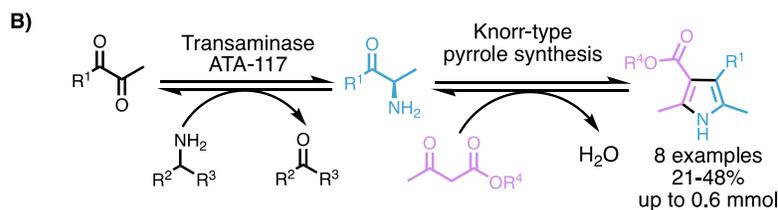
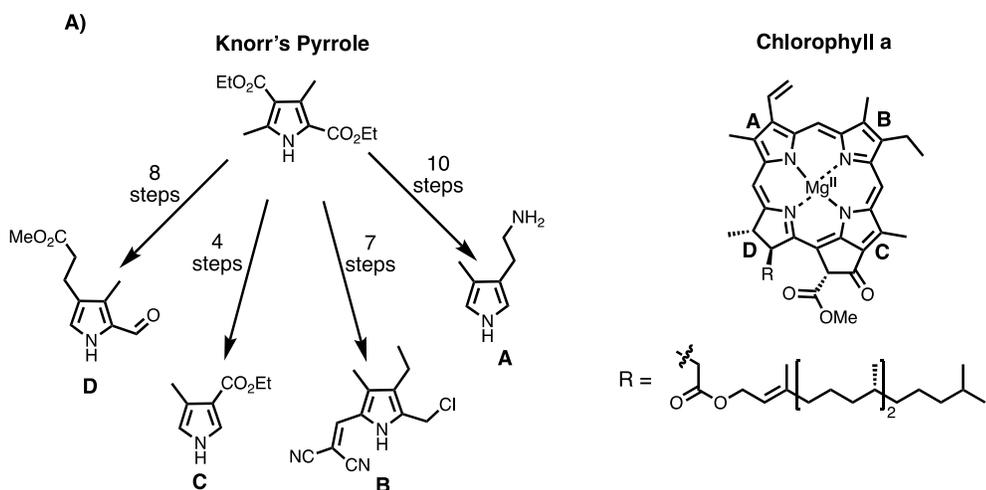
Perhaps one of the most ubiquitous synthetic routes within the field of pyrrole chemistry, and certainly the most used within the Thompson lab, is the Knorr pyrrole synthesis, which produces very stable substituted pyrrole-2-carboxylates (Scheme 4B). First reported in 1884, Knorr<sup>77</sup> found that condensation of ethyl acetoacetate (**xviii**) and ethyl 2-aminoacetoacetate (**xix**), which could be prepared from ethyl acetoacetate (**xviii**), would produce diethyl 2,4-dimethylpyrrole-3,5-dicarboxylate, now commonly known as Knorr's pyrrole. In 1894 Zanetti and Levi<sup>78</sup> expanded Knorr's synthesis, replacing the second equivalent of **xviii** with a 1,3-diketone (**xx**). Indeed, Zanetti and Levi introduced 2,4-pentanedione (**xx**) to give ethyl 4-acetyl-3,5-dimethylpyrrole-2-carboxylate, rather than Knorr's pyrrole. Typically,  $\alpha$ -amino ketones such as **xix** are prepared *in situ* to avoid spontaneous self-condensation,<sup>79</sup> and the Knorr synthesis is no exception.

Thus, in order to prepare  $\alpha$ -amino ketone **xix** while avoiding self-condensation, ethyl acetoacetate is first reacted with aqueous  $\text{NaNO}_2$  in glacial acetic acid to afford the requisite oxime intermediate (Scheme 4B, **xviii** to oxime, reaction 1). The oxime is then reduced, *in situ*, via a zinc-induced exothermic reduction to afford the desired  $\alpha$ -amino ketone **xix**. As discussed, preparing **xix** *in situ* reduces the tendency to self-condense. However, if left unchecked the exothermic reduction required for the *in situ* generation of **xix** can heat the reaction mixture to boiling ( $\sim 118$  °C, boiling point of glacial acetic acid). In fact, sustained reaction temperatures above 70 °C are known to cause a significant reduction in yields of the desired pyrrole,<sup>77,80,81</sup> as higher temperatures are conducive for a variety of unproductive side-reactions including the self-condensation of **xix**. Indeed, the Knorr pyrrole synthesis is a challenging reaction to conduct, the exotherm of which must be carefully controlled via the slow addition of zinc metal dust and external cooling to furnish optimal yields of pyrrole.

Moreover, the Knorr pyrrole can be prepared on the mol scale from inexpensive bulk materials. However, the scale of this reaction is limited with the use of standard laboratory equipment (i.e. multilitre round-bottom and overhead stirrer), primarily by the zinc-induced exothermic reduction required to produce **xix**. While feasible to conduct the Knorr synthesis on the multimol scale using standard equipment, personal experience has taught that a 1 mol scale is best suited to a single researcher wishing to prepare pyrrole via this methodology within the span of a day.

The functional group interconversion of substituents around the core of Knorr's pyrrole, and its derivatives, is incredibly well established<sup>82-89</sup> and is what made the Knorr pyrrole synthesis such a popular methodology over the past decades. The importance and

versatility of the Knorr synthesis, and subsequent functionalization of Knorr's pyrrole, is best represented by the famous total synthesis of Chlorophyll a, reported by Woodward and colleagues (Scheme 5A).<sup>82-85</sup> Beginning with Knorr's pyrrole, and through careful manipulation of functional groups, Woodward et al. were able to prepare the precursors to each of the four pyrrolic rings of chlorophyll a. Beyond Woodward's synthesis of chlorophyll a, the Knorr-type pyrrole synthesis has continued to stand the test of time, and remains pertinent in modern literature as seen in the 2018 chemo-enzymatic synthesis of pyrazines and pyrroles published by Xu et al.<sup>90</sup> In the published synthesis,  $\alpha$ -amino ketones were enzymatically generated and underwent subsequent condensation with  $\beta$ -keto esters to create an enzymatic route to Knorr pyrroles (Scheme 5B). This methodology was used to prepare eight Knorr-type pyrroles in low to fair yields on a small scale (sub-mmol). While the yields and scale are not exceptional, the methodology acted as a proof of concept for preparing Knorr-type pyrroles via *in situ* generation of  $\alpha$ -amino ketones from  $\alpha$ -diketones via an enzymatic transamination reaction.



**Scheme 5: A) Woodward and Colleagues Accessed All Precursors to the Four Pyrrole Rings of Chlorophyll a from Knorr's Pyrrole; B) Xu et al.'s Chemo-Enzymatic Synthesis of Knorr-type Pyrroles**

## 1.4 Dipyrrins: Structure and Reactivity

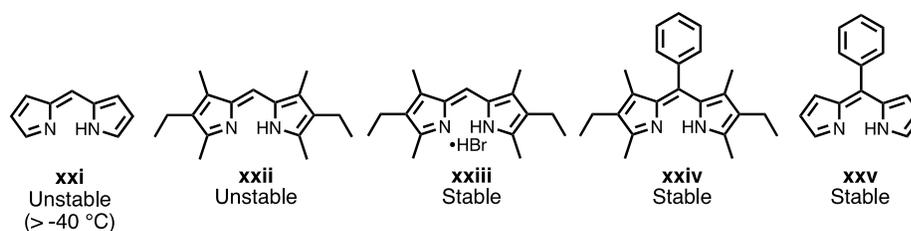
Dipyrrins are fully conjugated planar molecules that consist formally of an azafulvene unit attached to a pyrrole through the 2-position (Figure 11). After their initial discovery in 1914,<sup>91</sup> dipyrrins did not garner much interest until Hans Fischer implicated them in the synthesis of porphyrins – winning the Nobel Prize for such syntheses in 1930. Fischer is responsible for first popularizing the chemistry of dipyrrins, and for decades these compounds found extensive use in the synthesis of porphyrins. In recent years, dipyrrins have found use outside of porphyrin synthesis, and many researchers have begun to look

to dipyrrens as useful ligands with applications in such areas as organometallic catalysis,<sup>92–94</sup> photochemistry,<sup>95–97</sup> and biological labelling.<sup>7,8,98,99</sup>



**Figure 11: A Dipyrren Formally Consists of an Azafulvene Attached to the 2-Position of a Pyrrole**

Dipyrrens share some properties with their parent pyrroles, most notably the nucleophilic properties of ring carbon atoms resulting from the electron-rich pyrrole ring contained within the dipyrren structure. Indeed, fully unsubstituted dipyrren is not stable above  $-40\text{ }^{\circ}\text{C}$  (Figure 12, **xxi**), forming tar-like polymeric materials due to its susceptibility to both nucleophilic and electrophilic attack.<sup>100</sup> Unlike pyrrole, dipyrrens are stabilized by the presence of alkyl substituents in the  $\alpha$ - and  $\beta$ -positions. However, as long as the *meso*-position is unsubstituted (**xxii**), alkyl-substituted dipyrrens remain unstable in air in their free-base forms. Instead, dipyrrens are commonly isolated as hydrobromide (**xxiii**), or hydrochloride, salts which are dramatically more stable.<sup>86</sup> In contrast, aryl substitution in the *meso*-position grants the dipyrren significant stability and such species (**xxiv** and **xxv**) can even be kept as the free-base under ambient conditions, with or without alkyl substituents around the pyrrolic rings.

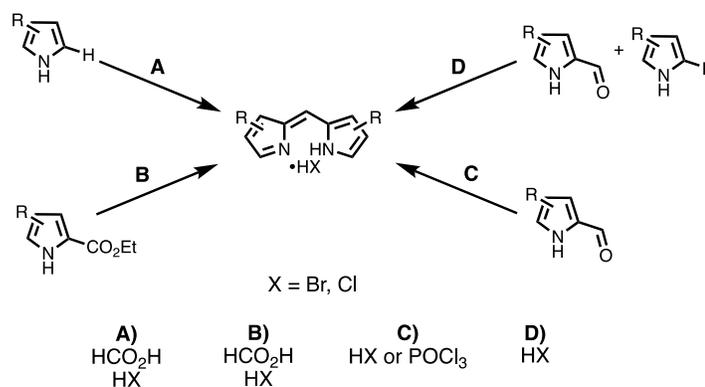


**Figure 12: Alkyl-substituted *meso*-H Free-base, *meso*-H-Dipyrryn Hydrobromide, and *meso*-Phenyl Dipyrrens, and Stabilities at Room Temperature under Ambient Conditions**

## 1.5 Synthesis of Dipyrrens

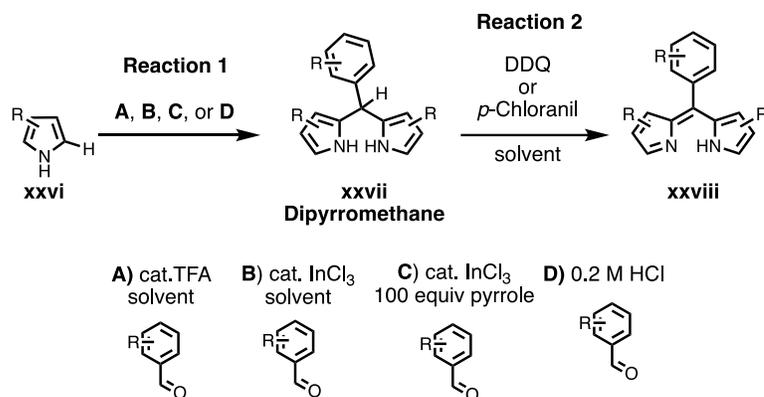
Dipyrrens are a particularly difficult class of compounds to purify,<sup>101,102</sup> likely due to their facile protonation and deprotonation, and column chromatography on silica of such species can be incredibly challenging with minimal improvements in purity. As such, the synthesis of dipyrrens must be highly efficient to enable convenient purification and isolation. *meso*-H-Dipyrrens are generally the ‘best-in-class’ scenario, whereby purification/isolation is often achieved by crystallization of the desired product as a salt. *meso*-H-Dipyrryn salts are commonly prepared via one of four methodologies which are shown in Scheme 6: A) reacting two equivalents of an  $\alpha$ -free pyrrole with formic acid;<sup>103</sup> B) acid-catalyzed hydrolysis, decarboxylation, and condensation of pyrrole-2-carboxylates in formic acid;<sup>104</sup> C) acid-catalyzed self-condensation of a 2-formylpyrrole;<sup>105–107</sup> or D) acid-catalyzed condensation reaction in which an  $\alpha$ -free pyrrole condenses with a 2-formylpyrrole, thus accommodating pyrroles that bear different substitution patterns.<sup>108</sup> Addition of an HX acid (HBr or HCl) within Method A and B enables isolation of the desired dipyrryn salt, while use of HX as the acid catalyst in

Method C and D has the same effect. Methods A, B, and C enable the preparation of symmetric dipyrin salts, while method D is best used to prepare asymmetric dipyrins.



### Scheme 6: Four Common Syntheses of *meso*-H Dipyrin Salts

Another very common type of dipyrin are those bearing *meso*-aryl substituents,<sup>109–114</sup> including but not limited to phenyl, tolyl, or mesityl groups. The popularity of such dipyrins is likely due to their stability, interesting electronic and photophysical properties,<sup>113–117</sup> and how readily available the starting materials are in addition to the relatively simple synthetic procedures required for their preparation. Outlined in Scheme 7 are four common synthetic methods for the preparation of *meso*-aryl dipyrins, each of which requires two-steps to furnish the requisite *meso*-substituted dipyrin (**xxvii**). The first step requires condensation of an  $\alpha$ -free pyrrole (**xxvi**) with an aryl aldehyde to furnish a dipyrromethane (**xxvii**, **Reaction 1**), i.e. two pyrrolic units linked by a methine bridge. The second synthetic step, shared amongst the four highlighted methodologies, is oxidation of the dipyrromethane intermediate to the desired *meso*-substituted dipyrin (**xxviii**, **Reaction 2**). The most common oxidants used to afford dipyrin are DDQ<sup>96,118,119</sup> and *p*-chloranil.<sup>120–122</sup>



### Scheme 7: Four Common Syntheses of *meso*-Aryl Dipyrins, Which Are Applicable to Many Pyrrole and Aryl Aldehyde

Method A,<sup>118</sup> performed in an organic solvent (e.g. CH<sub>2</sub>Cl<sub>2</sub> or THF), employs a catalytic amount of TFA and stoichiometric amounts of the pyrrole and aryl aldehyde. TFA activates the carbonyl group of the aryl aldehyde, which expedites nucleophilic attack by two equivalents of pyrrole **xxvi**, thus furnishing the requisite dipyrromethane, **xxvii**. When performed in the same solvent as required for oxidation of the dipyrromethane, Method A can be used for the one-pot synthesis of dipyrins directly from pyrrole and aryl aldehyde starting materials. The oxidant, DDQ or *p*-chloranil, can be added directly to the reaction vessel immediately following synthesis of the dipyrromethane, thus avoiding its isolation. Similar to A, but with a different acid, dipyrromethane **xxvii** can be prepared via Method B,<sup>123</sup> which employs catalytic amounts of the mild Lewis acid InCl<sub>3</sub> and stoichiometric amounts of pyrrole and aryl aldehyde in an organic solvent. As with Method A, use of the same solvent as required for oxidation enables Method B to be used for the one-pot synthesis of dipyrins. In contrast, Methods C and D are not generally conducted for the one-pot synthesis of dipyrins and require isolation of the dipyrromethane.

Method C<sup>124</sup> makes use of InCl<sub>3</sub> as well, but is unique in that it requires a large excess of pyrrole to function as both reagent and reaction solvent, thus avoiding use of additional organic solvents (e.g. CH<sub>2</sub>Cl or THF). As Method C does not require additional solvents and boasts good recoverability of the catalyst and excess pyrrole, some may consider it to be a ‘greener’ alternative to both Methods A and B. The best application of Method C is in the reaction of a variety of aryl aldehydes with unsubstituted pyrrole, which is commercially available and easily purified via vacuum distillation.<sup>124,125</sup> As Method C employs a very large quantity of the pyrrolic substrate, it is typically not an economically viable choice for use with far more precious substituted pyrroles. Another ‘green’ alternative to Methods A and B, and one that does not require a large excess of pyrrole, is Method D.<sup>126</sup> This methodology avoids organic solvents via the use of a biphasic system of aqueous 0.1 M HCl and stoichiometric amounts of pyrrole/aryl aldehyde. As discussed, both Methods C and D generally require purification and isolation of the dipyrromethane prior to proceeding with oxidation and therefore cannot be used for the one-pot synthesis of dipyrins.

Of the four highlighted methodologies, Method C boasts the most scalable and efficient synthesis of dipyrromethanes, with yields generally >50% and purification via recrystallization.<sup>125</sup> The large excess of pyrrole and use of a mild Lewis acid attenuate the formation of *N*-confused dipyrromethanes (nomenclature extended from porphyrins),<sup>127,128</sup> as well as tripyrromethanes and higher oligo- and polypyrromethanes.<sup>128</sup> The formation of such by-products during the synthesis of dipyrromethanes proves to not only decrease the yield of the dipyrromethane, but also significantly increases the difficulty of purification of the desired dipyrromethane. While

use of Method C typically reduces these unfavourable outcomes, is not amenable to being used with more precious substituted pyrroles for which using 100 equivalents is infeasible. When using more precious substituted pyrroles, dipyrromethanes are best prepared via Methods A, B or D. Of these three methodologies (A, B, and D) each can produce dipyrromethane in yields >50%, however, none present a distinct advantage over the remaining two for the preparation of dipyrromethanes from more precious substituted pyrroles. Each synthetic procedure is relatively simple, requiring a skillset no greater than an undergraduate chemist might possess. However, work-up and purification of the dipyrromethane by any of these methods is far more challenging, often requiring multiple steps and purification attempts.<sup>118–120,124,129</sup>

Methods A and B are certainly attractive methodologies to many researchers<sup>118–120,123</sup> as they avoid the difficult purification of dipyrromethanes by enabling the one-pot synthesis of dipyrins from pyrroles and aryl aldehydes. Nonetheless, this cannot be described as an advantageous method, since avoiding the challenges of dipyrromethane purification is not guaranteed to benefit the synthesis of dipyrins. Oxidation of pure isolated dipyrromethanes, i.e. two-pot, using DDQ or *p*-chloranil, often results in very long and laborious purifications that are more challenging than those involving dipyrromethanes. Due to overoxidation,<sup>130–132</sup> use of either DDQ or *p*-chloranil typically results in beautifully coloured but disastrously troublesome by-products that are incredibly difficult to remove via column chromatography on silica or aluminum oxide. In addition to the previous difficulties, and as described above, dipyrins are generally known to be challenging to purify via chromatography regardless of their method of preparation.<sup>101,102,133</sup>

The one-pot syntheses of dipyrrens has, in our experience, resulted in intractable emulsions during work-up, which typically translates to equally intractable attempts at purification via column chromatography. With a significant amount of experience and sometimes what can only be described as a ‘magic touch’ the work-up and purifications can become manageable. Of methods A, B, and D, each will have its own advantages and disadvantages (e.g. one-pot vs. two-pot reaction, or avoiding use of organic solvents), however, personal experience, and ultimately personal preference, will dictate the ‘best’ way to synthesize and purify dipyrromethanes and the subsequent dipyrrens. Researchers who prefer to dedicate themselves to a single, but incredibly challenging purification, will use methodologies enabling a one-pot reaction to synthesize the final dipyrren (Methods A and B). Other researchers may, author included, choose to purify the dipyrromethane (if possible) prior to oxidation, and thus perform two dreadful, but often less challenging, purifications (Method D).

## 1.6 Thesis Overview

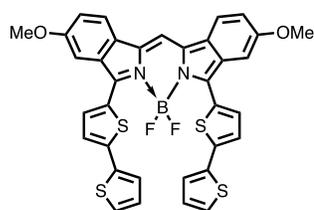
The work described in this thesis builds upon the foundations of fundamental pyrrole and dipyrren chemistry and has focused on the exploration and development of new methodologies towards the synthesis of derivatives of monopyrroles and dipyrrens. Chapter 2 describes the development of a simple and robust open-air synthesis of *F*-BODIPYs from free-base dipyrrens and dipyrren salts. Chapter 3 describes an investigation into the mechanism of dipyrren formation via self-condensation of 2-formylpyrroles, and why a regioisomeric outcome could be observed. Chapter 4 describes

the development, and an exploration, of the reductive formation of sulfide-bridged dipyrroles (-S-) from  $\text{SOCl}_2$  (-SO-), a transformation in which  $\text{SOCl}_2$  acts both as sulfur source and reductant.

## Chapter 2 – A Robust Synthesis of *F*-BODIPYs

### 2.1 Introduction

Compounds built on the 4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene (*F*-BODIPY) framework have a wide range of uses stemming from their highly tunable electronic properties.<sup>134</sup> *F*-BODIPYs have proven to be an incredibly versatile class of compounds due to their high thermal and photochemical stabilities,<sup>10,135,136</sup> a tendency to be laser-excitatable,<sup>137</sup> as well as a high variability in absorption and emission properties. As a result, *F*-BODIPYs have found applications as labels in biological systems,<sup>7,8,98,99</sup> as dyes,<sup>8,98,99</sup> as materials in electroluminescent devices,<sup>121,138–140</sup> and as light harvesting materials.<sup>139–141</sup> *F*-BODIPYs are generally known to be very efficient fluorophores with numerous examples of *F*-BODIPYs with molar absorption coefficients ranging from 40,000 to 150,000 M<sup>-1</sup> cm<sup>-1</sup>,<sup>8–10,142</sup> and quantum yields ranging from 60% to nearly 100%, without internal quenching at play.<sup>8–10</sup> The wavelength at which maximum absorption ( $\lambda_{\text{abs}}$ ) occurs in an *F*-BODIPY is heavily dependent on substitution with the  $\lambda_{\text{abs}}$  of many commercial examples<sup>142–144</sup> typically falling within the range of ~400-600 nm. Similarly, the wavelength at which maximum emission ( $\lambda_{\text{em}}$ ) occurs is equally dependent on substitution, with typical Stokes shifts of as little as 5 nm up to 50 nm, i.e.  $\lambda_{\text{em}}$  ranging from ~405-650 nm.<sup>10,145,146</sup> While the maximum absorption and emission wavelengths for the majority of *F*-BODIPYs fall within the described ranges, there are *F*-BODIPYs that go well beyond with  $\lambda_{\text{abs}}$  nearing 800 nm and  $\lambda_{\text{em}}$  nearing 850 nm.<sup>147–149</sup> For example, Wu et al.<sup>150</sup> patented an *F*-BODIPY (Figure 13) with a  $\lambda_{\text{abs}}$  of 766 nm and a  $\lambda_{\text{em}}$  of 831 nm.



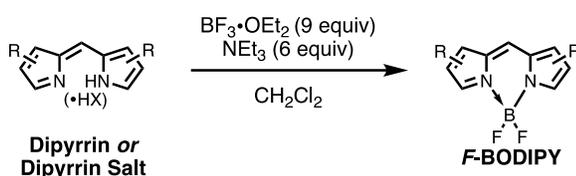
$$\lambda_{\text{abs}} = 766 \text{ nm}; \lambda_{\text{em}} = 831 \text{ nm}$$

**Figure 13: *F*-BODIPY Dye Patented by Wu et al.**<sup>149</sup>

Many *F*-BODIPYs have proven stable under physiological conditions,<sup>151–153</sup> and perhaps as a result, one of the largest areas of application for *F*-BODIPYs is as a fluorescent label within biological systems. As early as the 1980s *F*-BODIPYs became widely used as labels<sup>20,154,155</sup> with some becoming commercialized specifically for biological labelling.<sup>98,99</sup> As of 2019, dozens of *F*-BODIPYs are commercially available for use as fluorescent labels within biological systems<sup>142–144</sup> and over the past 30 years, *F*-BODIPYs have found applications for visualization of dopaminergic receptors,<sup>7</sup> incorporation into and labelling of DNA,<sup>156</sup> and polysaccharide labelling for determination of the disaccharide constitution of polysaccharides.<sup>157</sup>

Perhaps the most common method to prepare *F*-BODIPYs today requires the treatment of a solution of dipyrin (or dipyrin salt) with excess  $\text{NEt}_3$  and  $\text{BF}_3 \cdot \text{OEt}_2$ . The use of  $\text{NEt}_3$  and  $\text{BF}_3 \cdot \text{OEt}_2$  dates back to the first reported synthesis of *F*-BODIPYs, by Treibs and Krauzer in 1968.<sup>6</sup> In their work, Treibs and Krauzer treated dipyrins with  $\sim 13$  equivalents of  $\text{BF}_3 \cdot \text{OEt}_2$  in the presence of  $\sim 9$  equivalents of  $\text{NEt}_3$  to furnish the very first *F*-BODIPYs. Moving into the 1980s and 1990s, DIPEA<sup>158</sup> was used in tandem with  $\text{BF}_3 \cdot \text{OEt}_2$ <sup>98,99,159</sup> as commonly as  $\text{NEt}_3$ . Despite the increase in use of *F*-BODIPYs, there was little consistency in the reported syntheses, other than use of  $\text{NEt}_3$  or DIPEA with  $\text{BF}_3 \cdot \text{OEt}_2$ . An area of large variation between syntheses was the quantity of reagents

used, i.e. of nitrogenous base and  $\text{BF}_3 \cdot \text{OEt}_2$ . The equivalents of base used, with respect to the starting dipyrin, could range from as little as 3 to as much as 180 equivalents, while the use of  $\text{BF}_3 \cdot \text{OEt}_2$  was somewhat more reserved, typically ranging from 2 to 17 equivalents relative to the starting dipyrin.<sup>20,98,99,159</sup> Additionally, the reported isolated yields are as varied as the methodologies themselves, ranging from 10 to 90%. The use of 6 equivalents of  $\text{NEt}_3$ , with respect to the starting dipyrin, followed by the addition of 9 equivalents of  $\text{BF}_3 \cdot \text{OEt}_2$  has been established as an efficient method for furnishing consistently high yields of the requisite *F*-BODIPY (Scheme 8) and deviating from these stoichiometries has been shown to result in decreased yields.<sup>133,160,161</sup>



### Scheme 8: Synthesis of an *F*-BODIPY from the Requisite Dipyrin or Dipyrin Salt

To the best of our knowledge and cognizant of the challenge in tracking down such specifics, the use of a 6:9 ratio of equivalents of  $\text{NEt}_3$  and  $\text{BF}_3 \cdot \text{OEt}_2$ , respectively, arose from preparing *F*-BODIPYs *in situ* immediately following the oxidative formation of a dipyrin, which was driven by either DDQ or *p*-chloranil.<sup>161</sup> This synthetic methodology enabled the synthesis of *F*-BODIPYs from simple, and inexpensive, pyrroles and aryl aldehydes. As well, it avoided the challenging isolation and purification<sup>133</sup> of the dipyrin en route to the *F*-BODIPY. The attractiveness of *F*-BODIPY synthesis using  $\text{NEt}_3$ , or DIPEA, and  $\text{BF}_3 \cdot \text{OEt}_2$  is clear from its widespread use; one only has to search the literature for *F*-BODIPY syntheses to be overwhelmed by the application of these three reagents.<sup>162–170</sup> However, perhaps the most significant

disadvantage to these types of syntheses is the excess of reagents used. Indeed, the large excess of Lewis acid and Lewis base lends itself to the formation of various Lewis adducts,<sup>171-173</sup> such as  $\text{BF}_3 \cdot \text{NEt}_3$  or  $\text{BF}_3 \cdot \text{DIPEA}$ , which can result in intractable emulsions during work-up and detract from the desired *F*-BODIPY formation. Moreover, due to the Lewis acidic nature of  $\text{BF}_3$  and Lewis basic nature of  $\text{H}_2\text{O}$ , even minute amounts of water<sup>174</sup> can cause significant reductions in product yield.

Previously, the Thompson group published a new methodology for the synthesis of *F*-BODIPYs using stoichiometric quantities of LiHMDS and  $\text{BF}_3 \cdot \text{OEt}_2$ .<sup>160</sup> Treatment of a free-base dipyrin with 1.1 equivalent of LiHMDS yielded the corresponding Li salt, which could then be treated with only 1 equivalent of  $\text{BF}_3 \cdot \text{OEt}_2$  to furnish the *F*-BODIPY in modest to excellent yields (60-98%).<sup>160</sup> This method proved equally effective to that invoking the use of excess  $\text{NEt}_3/\text{DIPEA}$  and  $\text{BF}_3 \cdot \text{OEt}_2$ . The simplicity and effectiveness of this methodology is appealing, although it has yet to gain widespread use. While the Thompson group was able to reduce the excess of reagents used, and thus the formation of unwanted Lewis adducts, it remains that the synthesis of *F*-BODIPYs using LiHMDS or  $\text{NEt}_3/\text{DIPEA}$  share a common disadvantage: susceptibility to moisture, i.e. exposure to non-anhydrous conditions. Indeed, over the years, researchers in the Thompson lab have noticed that yields for the formation of *F*-BODIPYs from their corresponding dipyrin HBr salts, using  $\text{BF}_3 \cdot \text{OEt}_2$  and  $\text{NEt}_3$  (Scheme 8),<sup>6,10</sup> can be drastically affected by humidity if the utmost care is not taken in their preparation. This is in spite of the fact that many reports for the synthesis of BODIPYs do not stipulate the use of anhydrous conditions.

Regardless of the synthetic methodology used, if there are any errors in the anhydrous setup of these reactions a reduction in *F*-BODIPY yield will be observed, which can approach a 30% decrease in Nova Scotia's most humid period. The observed reduction in yield is presumably a result of the unproductive interaction of water with  $\text{BF}_3 \cdot \text{OEt}_2$  under the equilibrium reaction conditions. Furthermore, we have recently demonstrated<sup>175</sup> that some *F*-BODIPYs are quantitatively converted into their parent dipyrrens through treatment with  $\text{BF}_3 \cdot \text{OEt}_2$  and subsequent addition of triple the stoichiometric amount of water. Therefore, given the widespread use of  $\text{NEt}_3$  and  $\text{BF}_3 \cdot \text{OEt}_2$ , the need for rigorously anhydrous conditions cannot be overstressed for the preparation of *F*-BODIPYs using this method. Anything less leads to the possibility that successful complexation with boron will be followed by immediate decomplexation, and thus recovery of dipyrren starting material and lower product yields.

## 2.2 Project Goals

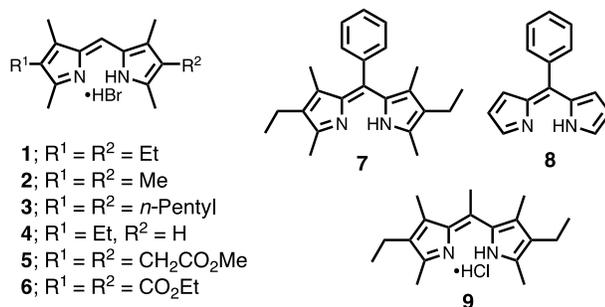
The goal of this project was twofold: to determine a set of conditions to produce high yields of *F*-BODIPYs year-round without need for a double manifold, Schlenk apparatus and Schlenk techniques, or glove box access; and to develop a simple, easy, and reliable procedure that is manageable for these researchers without significant experience in synthetic chemistry. Indeed, as *F*-BODIPYs have a continuously evolving role as fluorescent labels and as materials in systems for energy manipulation, we are cognizant that attempts to prepare such compounds do not always fall to the hands of experienced synthetic chemists. Thus, putting aside considerations of climate, it was important to us to

determine a protocol that would provide high yields when the preparation of *F*-BODIPYs is attempted without proper attention to the rigour required to create and maintain anhydrous reaction conditions. In this way, we strove to develop a reliable procedure amidst the plentiful, varied, and inconsistently described protocols that can be found in the literature.<sup>10,162–170,176,177</sup>

## 2.3 Results and Discussion

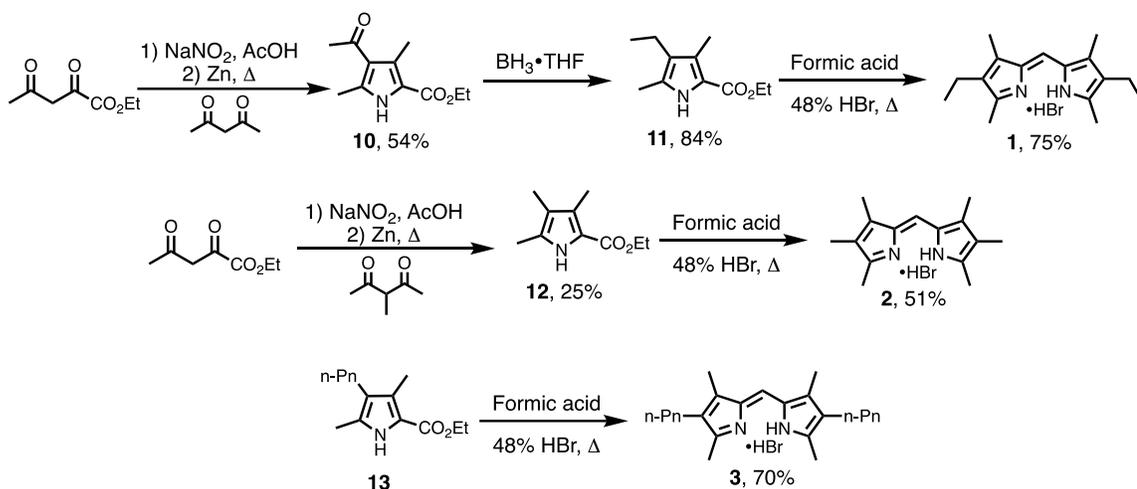
### 2.3.1 Synthesis of Dipyrrins from Requisite Pyrroles

Our goal was to explore the  $\text{BF}_3/\text{NEt}_3$ -based synthesis of *F*-BODIPYs from a variety of dipyrrins, focusing on reagent stoichiometry and overall susceptibility to water. Dipyrrins **1-9** were chosen to showcase a broad range of substituents, including: alkyl chains, both long and short; *meso*-H, *meso*-aryl, and *meso*-alkyl groups; alkyl esters; as well as unsubstituted  $\alpha$ - and  $\beta$ -positions (Figure 14). The requisite dipyrrins were synthesized prior to exploring the synthesis of *F*-BODIPYS. *meso*-Me dipyrrin **9**<sup>178</sup> was readily available within the lab and did not require synthesis.



**Figure 14: Dipyrrins 1 to 9**

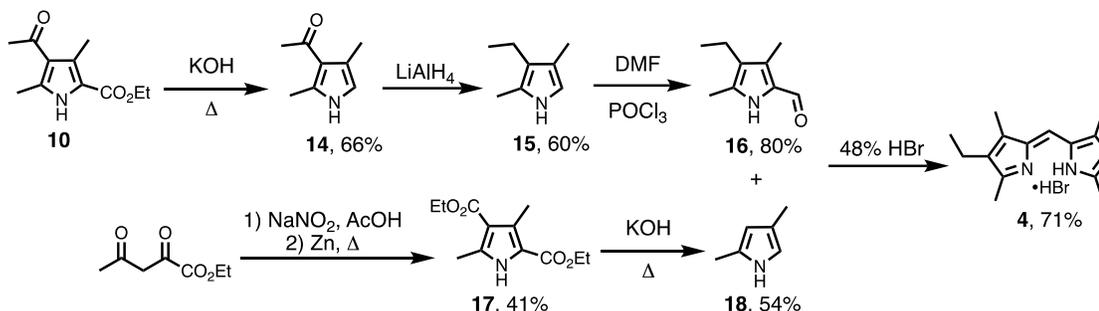
Dipyrrin salts **1**, **2**, and **3** were prepared from ethyl pyrrole-2-carboxylates,<sup>104</sup> **11**, **12**, and **13**, respectively, (Scheme 9) via acid-catalyzed hydrolysis, decarboxylation, and condensation in the presence of formic acid and HBr. Pyrroles **11** and **12** required prerequisite syntheses while pyrrole **13**<sup>179</sup> was already available within the lab. Pyrrole **10**<sup>81</sup> was prepared via the Knorr reaction of ethyl acetoacetate and 2,4-pentanedione, which in turn was reduced with BH<sub>3</sub>•THF to yield pyrrole **11**.<sup>180</sup> Pyrrole **12**<sup>181</sup> was prepared via the Knorr reaction of ethyl acetoacetate and 3-methyl-2,4-pentanedione.



### Scheme 9: Synthesis of Symmetric Dipyrrin Salts **1**, **2**, and **3**

To prepare the asymmetric dipyrrin salt **4**, the two different pyrrole halves were required, i.e. **16** and **18** (Scheme 10). Base-catalyzed hydrolysis and subsequent decarboxylation of **10** yielded **14**.<sup>81</sup> Reduction of the ketone of **14** with LiAlH<sub>4</sub> furnished **15**,<sup>81</sup> which was formylated via a Vilsmeier-Haack reaction to produce **16**.<sup>182</sup> Pyrrole **17**<sup>183</sup> was prepared via the Knorr reaction using only ethyl acetoacetate. Base-catalyzed hydrolysis and decarboxylation of **17** furnished **18**.<sup>184</sup> Finally, cross-condensation of **16** and **18**, via a MacDonald-type<sup>185</sup> reaction, furnished asymmetric dipyrrin salt **4**.<sup>186</sup> The

MacDonald reaction is an acid-catalyzed condensation reaction traditionally used to prepare tetrapyrroles and porphyrins from dipyrrole dialdehydes.<sup>185</sup>

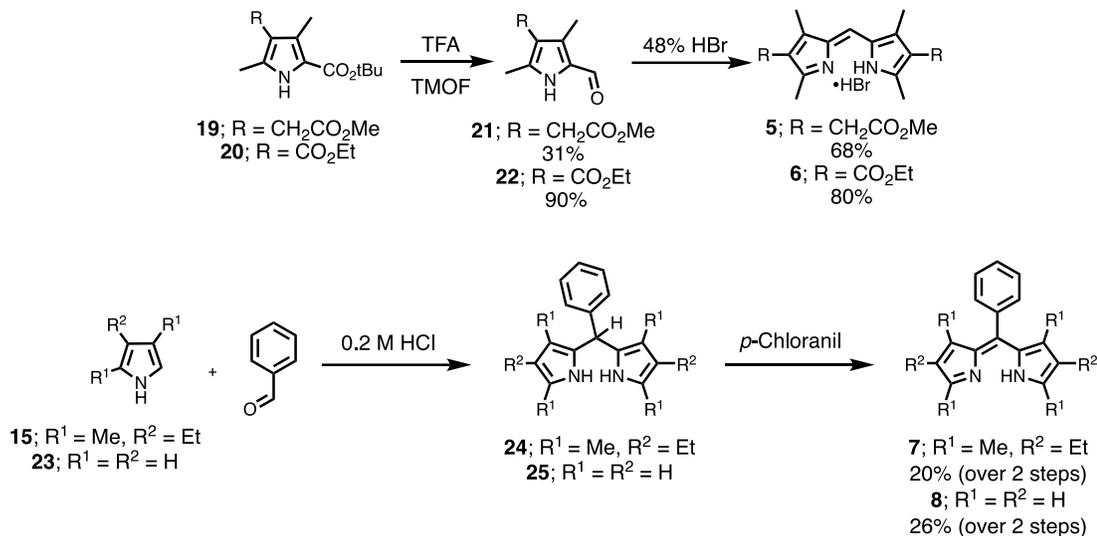


### Scheme 10: Synthesis of Asymmetric Dipyrin Salt 4

The ester-bearing dipyrin salts **5**<sup>105</sup> and **6**<sup>105</sup> were prepared using similar methodologies (Scheme 11, top). One-pot acid-catalyzed hydrolysis, decarboxylation, and formylation of pyrroles **19**<sup>187</sup> and **20**<sup>188</sup> (both available in lab) furnished the 2-formylpyrroles **21**<sup>189</sup> and **22**, respectively.<sup>190</sup> Subsequent self-condensation of each respective pyrrole produced the desired dipyrin salts **5** and **6**.

Next, we prepared the *meso*-phenyl substituted dipyrins **7**<sup>191</sup> and **8**<sup>191</sup> using pyrroles **15** and **23**, respectively, and benzaldehyde (Scheme 11, bottom). The acid-catalyzed condensation of  $\alpha$ -free pyrroles **15** and **23** with benzaldehyde produces dipyrromethanes **24** and **25**, respectively. The methine bridge between the pyrrolic units within **24** and **25** requires oxidation to furnish the fully conjugated dipyrins **7** and **8**, respectively. Typically the synthesis of dipyrromethanes proceeds in fair to high yields (60-90%) and can be performed in an aqueous (0.1 M HCl)<sup>120</sup> or organic medium (CH<sub>2</sub>Cl<sub>2</sub> and cat. InCl<sub>3</sub><sup>192</sup> or cat. TFA<sup>118</sup>). Literature for these three methodologies is plentiful, but also varied, inconsistent, and describes challenging purifications. Each methodology has inherent advantages and disadvantages with no clear ‘best’ choice.

Ultimately, we chose to use the aqueous conditions as they present fewer hazards and an efficient ‘green chemistry’ alternative to using organic solvents. Furthermore, the literature procedure<sup>120</sup> calls for only a slight stoichiometric excess of starting materials.



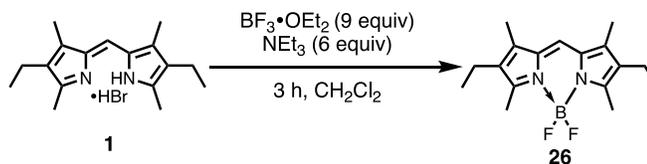
**Scheme 11: Synthesis of Symmetric Dipyrin Salts 5 and 6 (top); Synthesis of Symmetric *meso*-Phenyl Dipyrins 7 and 8 (bottom)**

In contrast, the oxidation of dipyrromethanes is typically a far more troublesome synthesis. The most common oxidants used to enact oxidation of dipyrromethanes are DDQ<sup>96,118,119</sup> and *p*-chloranil.<sup>120–122</sup> Oxidation of dipyrromethanes **24** and **25** with either oxidant produces a number of undesired by-products and will often require very long and laborious purifications as a result. The  $\alpha$ -Me substituents of **24**, and the resulting dipyrin **7**, are known to be susceptible to further reaction.<sup>132</sup> We chose to proceed with *p*-chloranil for the oxidation of the central methine unit to the desired methene unit, a choice which has been shown to result in simplified purification requirements, if only slightly,<sup>130,131</sup> compared to the use of DDQ, the stronger oxidant of the two. In addition,

free-base dipyrrens such as **7** and **8** are known to be challenging to purify via chromatography regardless of their preparation. Even with *p*-chloranil as the oxidant, the synthesis and purification of dipyrrens **7** and **8** proved to be very time-consuming and demanding work.

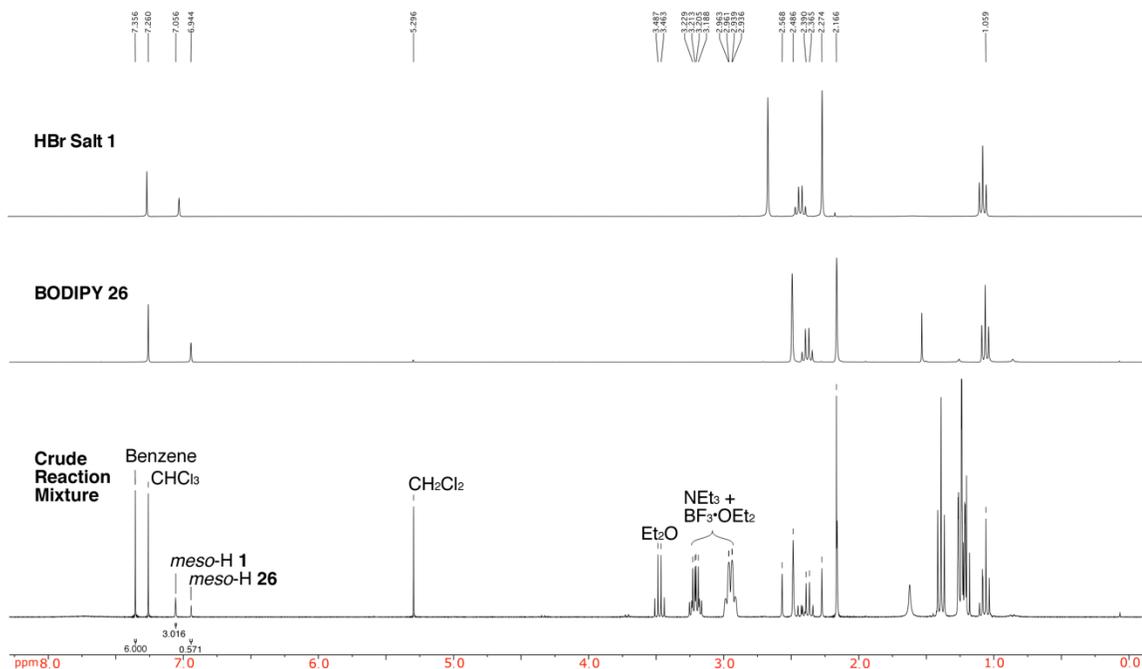
### 2.3.2 Determination of Yield of *F*-BODIPYs Employing $^1\text{H}$ NMR Spectroscopy

In order to explore the effects of humidity on the synthesis of *F*-BODIPYs using the method involving a 6:9 ratio of equivalents of  $\text{NEt}_3$  and  $\text{BF}_3 \cdot \text{OEt}_2$ , respectively, dipyrren salt **1** was chosen as the substrate with which we would begin our investigation (Scheme 12). The goal was to determine a simple and efficient set of conditions to produce high yields of *F*-BODIPYs regardless of interference from atmospheric water. The first challenge was determining to what degree a so-called attempt to use anhydrous reaction conditions could be affected by humid lab conditions. Once this had been determined, the second challenge was to determine how best to move forward with such non-anhydrous reactions in the hopes of developing reaction conditions to counteract the effects of humidity. To begin, the synthesis of the corresponding *F*-BODIPY (**26**) from the HBr salt of the dipyrren (**1**) was studied under various hydration levels.



**Scheme 12: Synthesis of *F*-BODIPY **26** from Dipyrren Salt **1****

We first wanted to maximize efficiency, so a facile and accurate method for determining yield was developed using  $^1\text{H}$  NMR spectroscopic analysis of the crude reaction mixture, thus avoiding the need to isolate the *F*-BODIPY resulting from each trial. In order to isolate the *F*-BODIPY, the crude reaction mixture must be washed with dilute aqueous acid three times, dried over  $\text{Na}_2\text{SO}_4$  and then purified via column chromatography on silica. Avoiding the work-up and isolation of the *F*-BODIPY after each trial helped save time and allowed for simultaneous reactions to be conducted, thus maximizing the number of trials completed in a short amount of time. To determine yield in this way, once the reaction had run for the allotted amount of time (3 h), the reaction solvent was removed *in vacuo* and the residue was dissolved in a known volume of deuterated chloroform ( $\text{CDCl}_3$ ). A known volume of benzene was added as an internal standard. A known aliquot of the new mixture, containing benzene, was added to an NMR tube, and then diluted with a known amount of  $\text{CDCl}_3$  to reach a volume suitable for  $^1\text{H}$  NMR analysis. Figure 15 compares  $^1\text{H}$  NMR spectra for starting material (**1**, top), the corresponding product (**26**, middle) and the crude reaction mixture containing both **1** and **26** (bottom).



**Figure 15:  $^1\text{H}$  NMR Spectra, in  $\text{CDCl}_3$ , of **1**, **26**, and the Crude Reaction Mixture Resulting from the Combination of **1**, **26**,  $\text{NEt}_3$ ,  $\text{BF}_3\cdot\text{OEt}_2$ ,  $\text{CH}_2\text{Cl}_2$ , and Benzene**

To conduct the reaction and analysis, the crude reaction mixture containing 0.160 mmol of dipyrin, either as ligand or BODIPY, was dissolved in 4.0 mL of  $\text{CDCl}_3$  (added using a 5 mL/5000  $\mu\text{L}$  syringe) to which 4  $\mu\text{L}$  of benzene was added using a 10  $\mu\text{L}$  syringe. Cognizant of the number of moles of benzene in the 4 mL solution ( $4.49 \times 10^{-5}$  mol), the molar concentration of benzene in this solution was calculated ( $M_{\text{benz}} = 0.0224$  mol/L). A 200  $\mu\text{L}$  aliquot of this solution ( $V_{\text{NMR}}$ ) was added to an NMR sample tube and diluted to 600  $\mu\text{L}$  for analysis, all using a 500  $\mu\text{L}$  syringe. Using  $M_{\text{benz}}$ , the moles of benzene present in this aliquot ( $n_{\text{benz aliquot}}$ ) could be calculated. The integral value for the *meso*-H signal of **26** ( $\int \mathbf{26}$ ) was calculated when the integration of benzene was set to 6.00. Multiplying  $n_{\text{benz aliquot}}$  by  $\int \mathbf{26}$  allowed us to calculate the moles of **26** in the 200  $\mu\text{L}$  aliquot ( $n_{\text{BF aliquot}}$ ). This then allowed us to calculate the concentration of **26** in the original 4 mL solution ( $M_{\text{BF}}$ ):

$$n_{benz\ aliquot} = M_{benz} * V_{NMR} = 2.24 \times 10^{-6} \text{ mol}$$

$$n_{BF\ aliquot} = n_{benz\ aliquot} * \int \mathbf{26} = 6.75 \times 10^{-6} \text{ mol}$$

$$M_{BF} = \frac{n_{BF\ aliquot}}{V_{NMR}} = 0.0338 \text{ mol/L}$$

We were thus able to calculate the moles of **26** produced during the reaction ( $n_{BF}$ ):

$$n_{BF} = M_{BF} * V_{CDCl_3} = 1.35 \times 10^{-4} \text{ mol}$$

The number of moles of **26** could now be used to calculate the percent conversion of **1** to **26**. In this example (Table 1, entry 1) 0.160 mmol of starting material was used and 0.135 mmol of **26** were present upon completion (3 h) of the reaction, therefore the conversion for this reaction was 84%. In addition, entry 1 of Table 1 indicates that the yield determined using  $^1\text{H}$ NMR analysis of the crude reaction mixture aligns, given reasonable variations when working on a 50 mg scale of starting material, with the isolated yield of 80% obtained subsequent to work-up and purification via chromatography over silica. This reaction was conducted in a period of low relative humidity (0.4-0.5 kPa or 2.9 g/m<sup>3</sup>, according to weather recordings taken at Halifax International Airport).<sup>193</sup> As a comparison, entry 2 reveals NMR-based and isolated yields of **26** obtained when the relative humidity level was much higher (1.3-1.7 kPa or 10.9 g/m<sup>3</sup>).<sup>193</sup> It should be noted that the Thompson lab does not benefit from air-conditioning, and as such ambient humidity would be nearly identical to in-lab humidity. Again, the discrepancy between the NMR-based and isolated yields falls within a reasonable variation expected of a 50 mg-scale reaction (~0.16 mmol). A quartet corresponding to the CH<sub>2</sub> signals of 'free' Et<sub>2</sub>O can be seen in the crude NMR

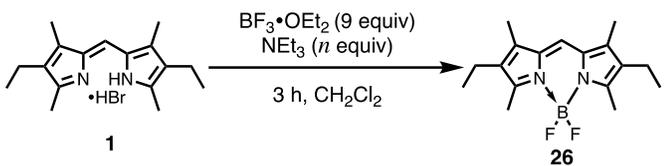
spectrum,<sup>194</sup> and was presumed to arise as a result of Et<sub>2</sub>O becoming trapped within the crude residue during solvent evaporation and thus not being capable of evaporating completely. Nevertheless, this did not affect our determination of product yield.

**Table 1: Efficacy of NMR-based Determination of Yield, According to Scheme 8**

Humidity	Entry	NMR yield of <b>26</b> (%)	Isolated yield of <b>26</b> (%)
Low (0.4-0.5 kPa)	1	84 ± 5	80 ± 5
High (1.3-1.7 kPa)	2	65 ± 5	61 ± 5

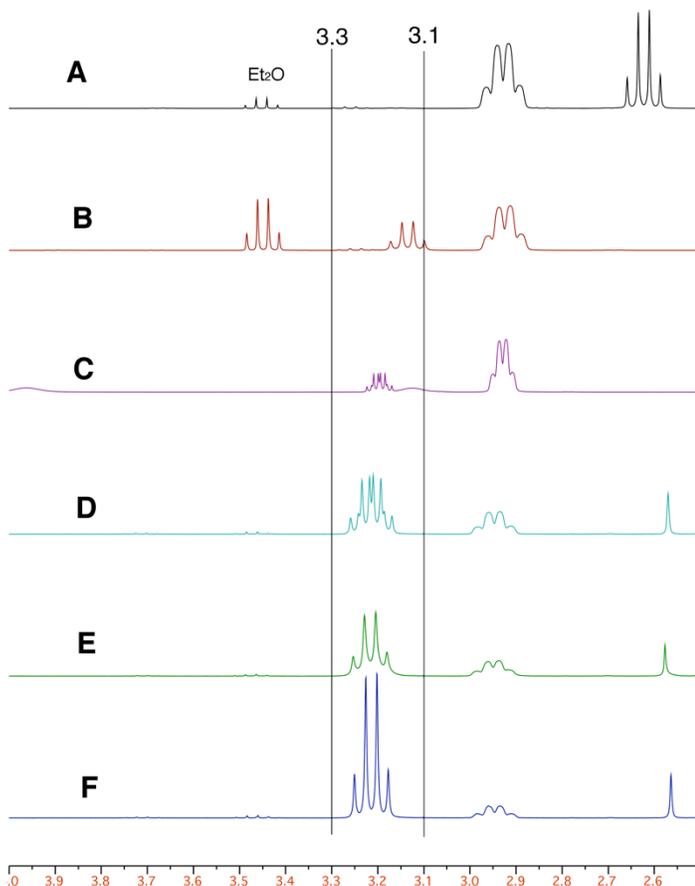
### 2.3.3 Synthesis of *F*-BODIPYs and the Effect of Water

Using the reaction conditions involving BF<sub>3</sub>•OEt<sub>2</sub> and NEt<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub>,<sup>6,10</sup> we investigated the synthesis of *F*-BODIPY **26** from the dipyrin salt **1** (Scheme 8). As of yet, there has been no rationale presented for using the 6:9 ratio of reagents to achieve optimum yields amidst the complex equilibrium in effect between the Lewis acidic boron centre and the various species capable of Lewis basic behaviour (H<sub>2</sub>O, NEt<sub>3</sub>, and Et<sub>2</sub>O). Previously the effect of varying the equivalents of BF<sub>3</sub>•OEt<sub>2</sub>,<sup>160</sup> while the stoichiometry of NEt<sub>3</sub> remained constant, was determined, finding that the 6:9 ratio of NEt<sub>3</sub> and BF<sub>3</sub>•OEt<sub>2</sub> was most effective. Working further, we explored how varying the amount of NEt<sub>3</sub> and keeping BF<sub>3</sub>•OEt<sub>2</sub> constant would affect the yield of **26** (Table 2). Indeed, any variation in equivalents of NEt<sub>3</sub> from the 6:9 ratio of NEt<sub>3</sub> and BF<sub>3</sub>•OEt<sub>2</sub> proved to decrease product yield. We ultimately concluded that the 6:9 ratio of equivalents of NEt<sub>3</sub> and BF<sub>3</sub>•OEt<sub>2</sub>, respectively, was optimal.

**Table 2: Effect of Varying NEt<sub>3</sub> upon the Yield of 26**

Equiv. of NEt <sub>3</sub> ( <i>n</i> )	NMR yield (%)
1	0
3	32 ± 5
5	54 ± 5
6	86 ± 5
7	77 ± 5
12	37 ± 5

A detailed report<sup>174</sup> previously described BF<sub>3</sub>•OEt<sub>2</sub> unsurprisingly becoming less effective in the presence of water during a condensation reaction using BF<sub>3</sub>•OEt<sub>2</sub> as a catalyst. The authors ascribed this observation to the complex equilibrium that must ensue and noted the formation of the less active BF<sub>3</sub>•H<sub>2</sub>O. In our case, several boron-containing byproducts,<sup>172,175</sup> alongside the NEt<sub>3</sub>•BF<sub>3</sub> complex,<sup>195</sup> must inevitably form in solution as the reaction progresses. To shed some light on this complex equilibrium, we collected and analyzed <sup>1</sup>H NMR spectra relating to interactions between NEt<sub>3</sub> and BF<sub>3</sub>•OEt<sub>2</sub> (Figure 16). In each case, samples for analysis were prepared by removing any reaction solvents or residual volatile materials *in vacuo* (~0.03 mmHg) until liquid was no longer visible to the naked eye, followed by dissolving the residue in CDCl<sub>3</sub>. The <sup>1</sup>H NMR spectra presented focus on the ethyl signals originating with NEt<sub>3</sub> and show only the chemical shift range from 4.0-2.5 ppm.



**Figure 16:  $^1\text{H}$  NMR Spectra, Recorded in  $\text{CDCl}_3$ , Showing the Ethyl Signals Arising from the Presence of  $\text{BF}_3\cdot\text{OEt}_2$  and  $\text{NEt}_3$ . (A)  $\text{BF}_3\cdot\text{NEt}_3$  (neat); (B)  $\text{BF}_3\cdot\text{NEt}_3$  Prepared in  $\text{CH}_2\text{Cl}_2$  (1:1 Ratio of  $\text{NEt}_3:\text{BF}_3\cdot\text{OEt}_2$ ); (C)  $\text{BF}_3\cdot\text{NEt}_3$  Prepared in  $\text{CH}_2\text{Cl}_2$  Solution (6:9 Ratio of  $\text{NEt}_3:\text{BF}_3\cdot\text{OEt}_2$ ); (D) Crude Reaction Mixture for Conversion of 1 to 26 (6:9 Ratio of  $\text{NEt}_3:\text{BF}_3\cdot\text{OEt}_2$ ), Spectrum Collected at 26 °C; (E) Crude Reaction Mixture for Conversion of 1 to 26, Spectrum Collected at 50 °C; (F) Crude Reaction Mixture of 1 to 26, Spectrum Collected at 26 °C After Warming to 50 °C and then Cooling**

The spectrum presented in Figure 16A was collected at 26 °C from  $\text{BF}_3\cdot\text{NEt}_3$  prepared by the slow addition of  $\text{NEt}_3$  directly to cooled (dry ice/acetone)  $\text{BF}_3\cdot\text{OEt}_2$  without additional solvent (i.e. neat) and using a 1:1 ratio of reagents. Figure 16B shows the  $^1\text{H}$  NMR spectrum collected at 26 °C from  $\text{BF}_3\cdot\text{NEt}_3$  prepared by the addition of  $\text{NEt}_3$  to a solution of  $\text{BF}_3\cdot\text{OEt}_2$  in  $\text{CH}_2\text{Cl}_2$  using a 1:1 ratio of reagents. The presence of ‘free’

ether signals in both 4A and 4B was presumed to have arisen from unreacted and unevaporated  $\text{BF}_3 \cdot \text{OEt}_2$  separating into  $\text{BF}_3$  and  $\text{OEt}_2$ . The spectrum featured in Figure 16C was collected at 26 °C from  $\text{BF}_3 \cdot \text{NEt}_3$  prepared in  $\text{CH}_2\text{Cl}_2$  using the 6:9 ratio of equivalents of  $\text{NEt}_3$  and  $\text{BF}_3 \cdot \text{OEt}_2$ , respectively. The remaining spectra, Figure 16D-F, were collected from a crude reaction mixture for the conversion of **1** to **26** using the 6:9 ratio of  $\text{NEt}_3$  and  $\text{BF}_3 \cdot \text{OEt}_2$ . Figure 16D was collected at 26 °C, Figure 16E at 50 °C, and Figure 16F after warming the sample to 50 °C and then cooling to 26 °C. In each of the six spectra collected, there are two signals of interest which vary in chemical shift and signal structure. The broad quartet at 3.0 ppm is consistent throughout all spectra and remains relatively unchanged. The second signal of interest appears as a quartet at 2.6 ppm in Figure 16A, but is not present elsewhere, and is instead replaced with a quartet/multiplet at 3.1-3.2 ppm in the remaining spectra (B-F). The quartet at 2.6 ppm (actual chemical shift of 2.63 ppm) was presumed to be a relevant signal, and not ‘free’  $\text{NEt}_3$  as the ethyl signal for  $\text{NEt}_3$  does not typically appear above 2.53 ppm in  $\text{CDCl}_3$ .<sup>194,196</sup>

The characteristics of the equilibrium, as reported through the ethyl signals originating with  $\text{NEt}_3$ , differ based upon the method of preparation (Figure 16, compare A and B), whereby the quartet at 2.5 ppm is absent when  $\text{BF}_3 \cdot \text{NEt}_3$  is prepared in solution, and instead a signal has appeared at 3.15 ppm, which is consistent with the remaining spectra collected from  $\text{BF}_3 \cdot \text{NEt}_3$  prepared in solution. As well, the characteristics of the equilibrium differ based upon the ratio of  $\text{NEt}_3$  and  $\text{BF}_3 \cdot \text{OEt}_2$  used (compare B and C). The simple quartet seen at 3.15 ppm in Figure 16B is replaced by a

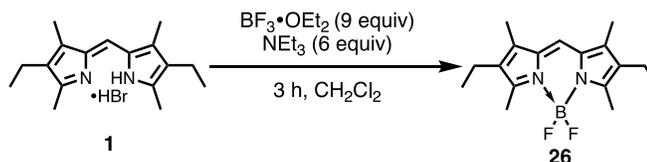
significantly more complex multiplet in Figure 16C as a result of using the 6:9 ratio of  $\text{NEt}_3$  and  $\text{BF}_3 \cdot \text{OEt}_2$ .

The  $^1\text{H}$  NMR spectra corresponding to the crude reaction mixture for the conversion of **1** to **26** reveals an equilibrium involving  $\text{NEt}_3$  that evolves as the reaction progresses (Figure 16, compare D-F). The complex multiplet that first appeared in Figure 16C is present in the initial  $^1\text{H}$  NMR spectrum of the crude reaction mixture (D). The same multiplet is then replaced by a quartet upon heating the sample to  $50\text{ }^\circ\text{C}$  (E), perhaps as a result of evaporating off excess  $\text{Et}_2\text{O}$  that may have contributed to the complex multiplet seen in D. After the sample was heated to  $50\text{ }^\circ\text{C}$ , the spectra remained constant when collected again at  $26\text{ }^\circ\text{C}$  (compare E and F). Evidently, the unproductive interactions of  $\text{BF}_3 \cdot \text{OEt}_2$  and  $\text{NEt}_3$  complicate the conversion of dipyrins to *F*-BODIPYs, yet an optimal 6:9 ratio of  $\text{NEt}_3$  and  $\text{BF}_3 \cdot \text{OEt}_2$  enables the reaction to render maximized yields.

To gauge the effect of moisture content on the synthesis of **26**, the reaction according to Table 3 was performed multiple times with variations in the dedication to securing anhydrous conditions. The reactions were performed in our laboratory (not air-conditioned) during December-March when the relative humidity was low.<sup>193</sup> As benchmark, we established the yield for a control reaction involving rigorously anhydrous and inert conditions secured and maintained using a vacuum/nitrogen manifold, as well as anhydrous reagents – such a control reaction thus ran side-by-side with each reaction(s) of interest. Unless otherwise stated, glassware and stir-bars were pre-dried in an oven ( $110\text{ }^\circ\text{C}$ ) for 18 h and then further heat-dried, using a heat gun, during purge cycles containing the starting material **1**. A dry and inert atmosphere was

assured by equipping the nitrogen line with a flow-through desiccator filled with indicating desiccant. Anhydrous  $\text{BF}_3 \cdot \text{OEt}_2$ ,  $\text{NEt}_3$ , and  $\text{CH}_2\text{Cl}_2$  were used, and transferred using inert and moisture-free methods. The yield for this control reaction, prepared as described, was 86% (Table 3, entry 1). Repeating the reaction with less care given to assuring anhydrous and inert atmospheric conditions detrimentally affected the yield of product. As expected, taking glassware directly from the bench-top and submitting the vessel to a heated purge/fill cycle without any prior drying proved to reduce the yield slightly (entry 2). Following the same conditions but without any heated purge/fill cycles (entry 3) gave equally poor results. The impact of negligence in ensuring rigorous anhydrous conditions can be best appreciated by considering the result when non-anhydrous  $\text{CH}_2\text{Cl}_2$  was used (entry 4, solvent exposed to air overnight before reaction commenced): the desired product, **26**, was not obtained even though the reaction glassware and set-up adhered to strict anhydrous protocols.

**Table 3: Synthesis of 26 Using Varying Set-up Protocols**



Entry	Reaction Conditions	Yield (%) <sup>a</sup>	Control (%) <sup>a</sup>
1	Oven, flame dry, purge	86 ± 5	-
2	No oven; flame dry, purge	78 ± 5	86 ± 5
3	No oven; flame dry	73 ± 5	86 ± 5
4	Non-anhydrous $\text{CH}_2\text{Cl}_2$ ; oven, flame dry, purge	0	86 ± 5

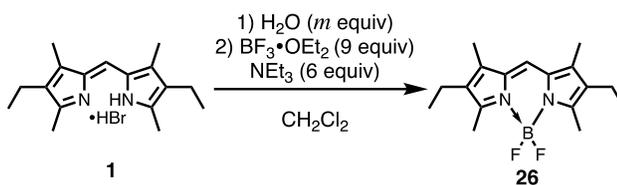
<sup>a</sup>yields determined using the NMR-based method

In an attempt to develop a reliable and simple procedure for the synthesis of *F*-BODIPYs, we first devised a protocol that enabled us to controllably mimic the

detrimental effects of either high laboratory humidity levels or improperly executed anhydrous reaction conditions. Measured amounts of distilled water were thus added to the reaction mixture that had been prepared and was conducted via otherwise rigorously anhydrous conditions (Table 4). Each reaction was prepared as follows: an oven-dried round-bottom equipped with a stir bar was charged with **1**, sealed with a septum, and subjected to three heated purge-fill cycles, filling with N<sub>2</sub>. Once under an N<sub>2</sub> atmosphere, anhydrous CH<sub>2</sub>Cl<sub>2</sub> was added to the reaction vessel to dissolve **1**. A measured amount of water was then added to the solution of **1** in CH<sub>2</sub>Cl<sub>2</sub>. The mixture was stirred for 30-90 min, depending on the amount of water added, so that a uniform emulsion was obtained, and a water droplet was no longer visible to the naked eye. In fact, the waiting period enabling the added water to disperse and uniformly emulsify was essential to determining the true effect of a non-anhydrous environment on the outcome of the reaction. If the reaction were performed while a water droplet was still visible, the influence of the water on the reaction was either diminished or sporadic (sometimes having great effect, other times very little). This experimental detail, i.e. allowing sufficient opportunity for the added water to disperse and uniformly emulsify, was extremely important to ensuring consistency in our work and thus enabling us to compare the outcomes of each experiment. Such concerns had been alluded to previously for experiments involving the formation of BF<sub>3</sub>•H<sub>2</sub>O from using BF<sub>3</sub>•OEt<sub>2</sub> as a catalyst during a condensation reaction.<sup>174</sup> Once the water droplet was no longer visible, the required amounts of NEt<sub>3</sub> and BF<sub>3</sub>•OEt<sub>2</sub> were added, and the reaction mixture stirred for 3 h. Upon removal of the solvent and other volatile materials *in vacuo*, the crude product mixture was analyzed to provide the NMR-based yields through the addition of a measured amount of benzene as

detailed previously. All reactions were set up using strict anhydrous and inert conditions with the addition of water as described above. Moreover, as detailed above, the yields of **26** were recorded alongside a control that was identical in all aspects (excluding addition of water) and run side-by-side with each reaction of interest.

**Table 4: The Effect of Water on the Synthesis of 26**



Entry	Equiv. of water ( <i>m</i> )	Yield (%) <sup>a</sup>	Control (%) <sup>a</sup>	Yield/control <sup>a</sup>
1	0.25	71 ± 5	70 ± 5	1.01
2	0.5	64 ± 5	70 ± 5	0.91
3	1.0	49 ± 5	74 ± 5	0.66
4	1.5	36 ± 5	72 ± 5	0.50
5	2	23 ± 5	74 ± 5	0.31
6	3	0	70 ± 5	0.0

<sup>a</sup>yields determined using NMR-based method

The addition of 0.25 equivalents of water, relative to **1** and equivalent to ~1 μL (added via a 10 μL syringe) on the 0.16 mmol scale of the reactions, made little noticeable difference to the yield (Table 4, entry 1), unsurprising given the small volume and period of high relative humidity at the time (control yield of 70%). However, the addition of increasing amounts of water significantly reduced the yield of **26** (entries 2-6). The addition of 3 equivalents of water (entry 6, 9 μL of H<sub>2</sub>O) proved to be the limit at which product formation was not observed. Remember that *F*-BODIPY **26** was shown to undergo quantitative deprotection to furnish the parent dipyrin (**1**) when treated with 3 equivalents of water in the presence of BF<sub>3</sub>•OEt<sub>2</sub>,<sup>175</sup> matching our observations herein. The addition of 2 equivalents of water (entry 5, 6 μL of H<sub>2</sub>O), however, resulted in the

most significant reduction in yield, while still observing formation of **26**. Thus, the addition of 2 equivalents of water appeared to be a tipping point at which product could still form.

The final column of Table 4 (Yield/Control) shows the yield of each experiment as a ratio of that obtained in the control experiment that was run alongside each trial (period of high laboratory humidity, hence modest yield for the control experiments). For these values, the closer a number is to 1 the more congruent the trial and control experiments were and therefore the less the reaction outcome was affected by the trial conditions, i.e. addition of water for Table 4. In contrast, the greater the difference between the reported value and 1, the more the trial and the control experiments diverged and thus the more the outcome was affected by the trial conditions. Values lower than 1 indicated negative effects and a reduced yield, while values greater than 1 indicated positive effects and an increased yield when compared to the control reaction. For example, addition of 0.25 equivalents of water (entry 1) had no noticeable effect on the outcome of the reaction, as represented by the Yield/Control value of 1.01. In contrast, addition of 2 equivalents of water significantly reduced the product yield, the impact of which is evidenced by the Yield/Control value of 0.31.

It is again clear from these results that the yield for the synthesis of **26** unsurprisingly decreases as the moisture content of the reaction mixture increases. With the observed reduction in yield as laboratory humidity increased, we assumed this a result of atmospheric water slowly poisoning the anhydrous conditions that were achieved using the described methods on a vacuum/nitrogen manifold with a septa-sealed reaction vessel. As well, we expected a slow decrease in quality of the anhydrous reagents used,

which were commercially available and not dried further. It was our intention to observe the effects of ambient atmospheric conditions on a reaction prepared and run under inert and anhydrous conditions. As with any anhydrous conditions, more precautions could have been taken, however this would defeat the purpose of our exploration as we wanted to observe and quantify how atmospheric conditions were affecting our anhydrous reaction conditions.

### **2.3.4 Developing an Open-air Bench-top Synthesis of *F*-BODIPYs**

Once the effect of moisture on the reaction had been established, we took the protocol involving the addition of 2 equivalents of water and used it to mimic reactions inadvertently featuring significant amounts of moisture, i.e. conditions involving rigorously anhydrous conditions, but which had been inadvertently compromised so as to no longer be rigorously anhydrous. This enabled us to develop a procedure to “rescue” reactions such that acceptable yields could be obtained despite the non-anhydrous reaction conditions in effect (Table 5). Our experiments employed the anhydrous set-up described earlier to which water was added. These experiments involved use of the 6:9 ratio of equivalents of  $\text{NEt}_3$  and  $\text{BF}_3 \cdot \text{OEt}_2$ , followed by a second aliquot of  $\text{NEt}_3$  and/or  $\text{BF}_3 \cdot \text{OEt}_2$  added after the reaction had been stirred for half the total reaction time, 1.25 h (total reaction time was 2.5 h). Each reaction mixture was then stirred for a further 1.25 h before removing reaction solvents *in vacuo* and subsequent determination of yield. Attempts featuring the addition of a second full aliquot of *either*  $\text{NEt}_3$  *or*  $\text{BF}_3 \cdot \text{OEt}_2$  to a mixture containing 2 equivalents of uniformly emulsified water

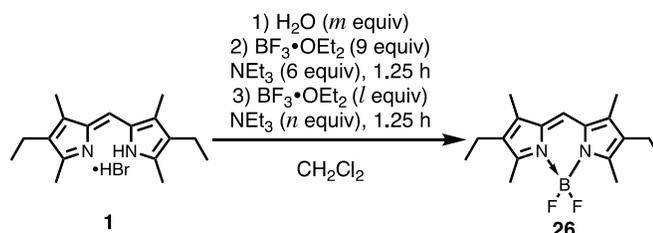
proved ineffective (Table 5, entries 1 and 2). However, a second addition of both  $\text{NEt}_3$  and  $\text{BF}_3 \cdot \text{OEt}_2$  (6:9 ratio of equivalents) proved to be much more successful (entry 3) and resulted in near-quantitative yields despite the presence of 2 equivalents of water.

Curiously, reducing the quantities of the reagents used for the second addition of  $\text{NEt}_3$  and  $\text{BF}_3 \cdot \text{OEt}_2$  was met with only a moderate increase in yield (entry 4). This observation is of significance, as it means that salvage attempts for the synthesis of *F*-BODIPYs should not consist of merely adding *some* additional amount of reagent(s) but rather that the specific ratio of 6:9 equivalents of  $\text{NEt}_3$  and  $\text{BF}_3 \cdot \text{OEt}_2$  is required for optimum results. Entry 5 shows that there was no detriment, in terms of yield, to adding a second aliquot of  $\text{NEt}_3$  and  $\text{BF}_3 \cdot \text{OEt}_2$  to the reaction mixture. This is regardless of moisture levels, as entry 5 did not contain any additional water. Timing of the second aliquot of reagents proved equally important, as addition of 12 and 18 equivalents of  $\text{NEt}_3$  and  $\text{BF}_3 \cdot \text{OEt}_2$ , respectively, at the start of the reaction did not furnish the same increase in yield (75% NMR-based yield in the presence of 2 equivalents of water, compared to 95%).

It should be noted that the use of a second aliquot of 6 and 9 equivalents of  $\text{NEt}_3$  and  $\text{BF}_3 \cdot \text{OEt}_2$ , respectively, is clearly beneficial to yield, although the excess reagents require the implementation of a more thorough work-up procedure so as to remove the large excess of reacted and unreacted reagents (e.g.  $\text{NEt}_3$  salts and unreacted  $\text{NEt}_3$ ). When using only 6 equivalents of  $\text{NEt}_3$  and 9 of  $\text{BF}_3 \cdot \text{OEt}_2$  the work-up and purification typically required three washes with 1 M  $\text{HCl}_{(\text{aq})}$ , subsequent drying over anhydrous  $\text{Na}_2\text{SO}_4$ , and then purification via column chromatography on silica. Indeed, the addition of a second aliquot of 6 of  $\text{NEt}_3$  and 9 of  $\text{BF}_3 \cdot \text{OEt}_2$  required only an additional wash with

5 M HCl<sub>(aq)</sub> after the standard three washes with 1 M HCl<sub>(aq)</sub>; purification was otherwise identical.

**Table 5: The Effect of Additional Aliquots of Reagents upon the Synthesis of 26**



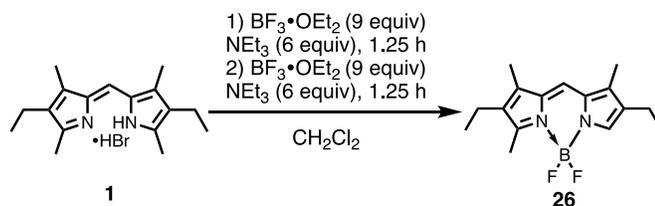
Entry	Equiv. of water ( <i>m</i> )	Second addition (equiv.) <sup>a</sup>	Yield (%) <sup>a</sup>	Control (%) <sup>b</sup>
1	2	NEt <sub>3</sub> ( <i>n</i> = 6)	19 ± 5	21 ± 5 <sup>c</sup>
2	2	BF <sub>3</sub> •OEt <sub>2</sub> ( <i>l</i> = 9)	24 ± 5	21 ± 5 <sup>c</sup>
3	2	NEt <sub>3</sub> :BF <sub>3</sub> •OEt <sub>2</sub> (6:9)	>95 ± 5	23 ± 5 <sup>c</sup>
4	2	NEt <sub>3</sub> :BF <sub>3</sub> •OEt <sub>2</sub> (3:4.5)	82 ± 5	23 ± 5 <sup>c</sup>
5	0	NEt <sub>3</sub> :BF <sub>3</sub> •OEt <sub>2</sub> (6:9)	>95 ± 5 <sup>d</sup>	69 ± 5 <sup>c</sup>

<sup>a</sup>second addition added after reaction mixture stirred for 1.25 h; <sup>b</sup>yields determined using the NMR-based method; <sup>c</sup>control reactions contained 2 equivalents water and only the initial addition of 6 and 9 equivalents of NEt<sub>3</sub>:BF<sub>3</sub>•OEt<sub>2</sub>; <sup>d</sup>isolated yield 90%; <sup>e</sup>control reaction contained 0 equivalents water and only the initial addition of 6 and 9 equivalents of NEt<sub>3</sub>:BF<sub>3</sub>•OEt<sub>2</sub>

After successfully developing a procedure that could achieve high yields even in the presence of 2 equivalents of water, we were curious as to whether the reaction could be performed taking little to no anhydrous precautions, ideally with “wet” lab-grade reagents and solvents (Table 6). Accordingly, yellowed NEt<sub>3</sub> of unknown age (lab grade, long-opened 4 L glass jug with screwcap) and non-anhydrous CH<sub>2</sub>Cl<sub>2</sub> from three different sources were used. Anhydrous SureSeal® BF<sub>3</sub>•OEt<sub>2</sub> was used merely because this is the grade purchased, and we wanted to maintain the integrity of this key reagent. The first CH<sub>2</sub>Cl<sub>2</sub> explored was atmosphere-distilled lab-grade CH<sub>2</sub>Cl<sub>2</sub> (entry 1) and had been stored in a bench-top squeeze-bottle for a minimum of 1 week prior to these experiments. The reaction vessel and stir bar, although clean and naturally air-dried, were

taken directly from the bench-top and used without any special consideration for drying. Each of the experiments was prepared in an open vessel under atmospheric conditions, and the reaction was capped with a septum only after the addition of  $\text{BF}_3 \cdot \text{OEt}_2$ . To our delight, our modified reaction protocol involving the addition of a second aliquot of 6 and 9 equivalents of  $\text{NEt}_3$  and  $\text{BF}_3 \cdot \text{OEt}_2$ , respectively, produced excellent isolated yields of **26** (entries 1-3). Furthermore, the same conditions were employed on a larger scale (2.8 g, 8 mmol), using distilled lab-grade  $\text{CH}_2\text{Cl}_2$ , with equal success (entry 4). Excluding the second aliquot of  $\text{NEt}_3$  and  $\text{BF}_3 \cdot \text{OEt}_2$ , the control reactions were otherwise identical to each reaction of interest. The control yields are an especially important comparison as they give context to the outstanding effect of adding the second aliquot of 6 equivalents of  $\text{NEt}_3$  and 9 of  $\text{BF}_3 \cdot \text{OEt}_2$  no matter the laboratory humidity on the day of the experiment. We again present the yield of each experiment as a ratio of that obtained in the control experiment run alongside each trial (Yield/Control) to emphasize the 2- to 3-fold increase in yield observed compared to the control experiments.

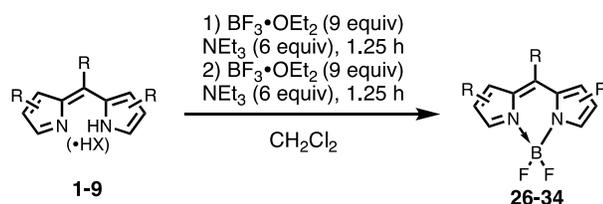
**Table 6: Synthesis of 26 Using Bench-top Conditions**



Entry	Quality of $\text{CH}_2\text{Cl}_2$	Yield (%) <sup>a</sup>	Control (%) <sup>a</sup>	Yield/Control
1	Distilled lab-grade	95 ± 5	35 ± 5 <sup>b</sup>	2.71
2	HPLC-grade	95 ± 5	32 ± 5 <sup>b</sup>	2.97
3	Non-distilled lab-grade	90 ± 5	38 ± 5 <sup>b</sup>	2.37
4	Distilled lab-grade	98 ± 5 <sup>c</sup>	35 ± 5 <sup>b</sup>	2.8

<sup>a</sup>isolated yields; <sup>b</sup>control reactions used the same grade  $\text{CH}_2\text{Cl}_2$  but featured only the initial addition of 6 and 9 equivalents  $\text{NEt}_3$  and  $\text{BF}_3 \cdot \text{OEt}_2$ ; <sup>c</sup>2.8 g starting material, 2.5 g prepared

With such success developing a protocol to produce excellent yields of **26** with a high tolerance for moisture content in the air, and within the reaction mixture, we moved to establish the scope of effectiveness in the production of other *F*-BODIPYs. Eight dipyrrens with varying substitution patterns were used to represent the broad classes of *F*-BODIPYs frequently synthesized. As shown in Scheme 13, our optimized procedure involved an initial addition of 6 and 9 equivalents of NEt<sub>3</sub> and BF<sub>3</sub>•OEt<sub>2</sub>, respectively. After stirring for 1.25 h, the addition of a second aliquot of 6 and 9 equivalents of NEt<sub>3</sub> and BF<sub>3</sub>•OEt<sub>2</sub> was followed by stirring of the reaction mixture for a further 1.25 h before work-up of the reaction. Of note, these reactions featured non-anhydrous solvents and reagents (apart from BF<sub>3</sub>•OEt<sub>2</sub>) and were performed using the bench-top conditions described above, with no attempts made to dry glassware or otherwise ensure moisture-free conditions. In contrast, the control reactions (Table 7) each involved meticulous exclusion of moisture, via oven-drying of glassware, repeated hot purge cycles, inert conditions, one aliquot of NEt<sub>3</sub> and BF<sub>3</sub>•OEt<sub>2</sub> and the use of expensive anhydrous solvents and reagents.

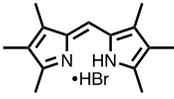
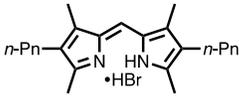
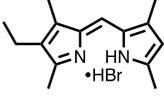
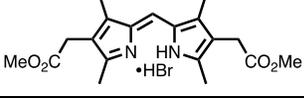
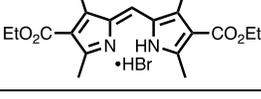
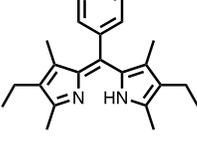
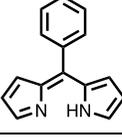
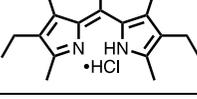


**Scheme 13: Optimized Procedure for the Synthesis of *F*-BODIPYs**

In all cases, our optimized procedure involving two aliquots of NEt<sub>3</sub> and BF<sub>3</sub>•OEt<sub>2</sub> met or exceeded the yields obtained under anhydrous conditions (Table 7). The

revised method, requiring no special set-up, is successful for dipyrrens bearing alkyl substituents (**2** and **3**), as well as those featuring unsubstituted positions about the pyrrolic rings (**4**, **8**). Furthermore, alkanoates (**5**) are tolerated, as are conjugated ester units (**6**). The revised method was also effective in converting *meso*-substituted (phenyl, **7** and **8**; methyl, **9**) dipyrrens into the corresponding *F*-BODIPYs in excellent yield. Dipyrren **8** converts to the widely studied *F*-BODIPY, **33**,<sup>126,197–201</sup> which is used across multiple disciplines, likely due to the availability of the starting materials given that pyrrole and benzaldehyde are commercially available and inexpensive. In the case of **7** and **9**, although our modified protocol gives yields matching those of the anhydrous control reactions run on the same day, the experimental precautions and preparations required to achieve them were significantly less demanding both from physical and monetary viewpoints.

**Table 7: Modified Two-aliquot Protocol for the Synthesis of *F*-BODIPYs According to Scheme 13**

	Dipyrrin	Yield (%) <sup>a,b</sup> Bench-top	Control (%) <sup>c,d</sup> Anhydrous	<i>F</i> -BODIPY
2		92 ± 5	81 ± 5	27
3		87 ± 5	76 ± 5	28
4		98 ± 5	81 ± 5	29
5		85 ± 5	72 ± 5	30
6		96 ± 5	53 ± 5	31
7		92 ± 5	92 ± 5 <sup>a</sup>	32
8		95 ± 5 <sup>c</sup>	70 ± 5 <sup>a</sup>	33
9		96 ± 5	91 ± 5 <sup>a</sup>	34

<sup>a</sup>isolated yields; <sup>b</sup>reactions conducted using non-anhydrous  $\text{NET}_3$  and  $\text{CH}_2\text{Cl}_2$  and two aliquots of 6 and 9 equivalents of  $\text{NET}_3$  and  $\text{BF}_3 \cdot \text{OEt}_2$ ; <sup>c</sup>control reactions conducted under anhydrous conditions with anhydrous reagents and solvent, and using only one addition of 6 and 9 equivalents of  $\text{NET}_3$  and  $\text{BF}_3 \cdot \text{OEt}_2$ ; <sup>d</sup>yields determined using the NMR-based method; <sup>e</sup>prepared 1 g

## 2.4 Conclusions

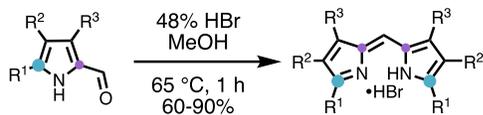
A robust method for the high yielding synthesis of *F*-BODIPYs has been developed that does not rely upon the use or effectiveness of anhydrous conditions. In

light of the complex equilibria<sup>174</sup> that must be present in solution (including  $\text{BX}_n$  complexed to  $\text{Et}_2\text{O}$ ,  $\text{H}_2\text{O}$ , amine, or dipyrin), the focus of this work was on defining an optimized procedure rather than speculating on mechanisms. Certainly, initial thought that further aliquots of  $\text{BF}_3 \cdot \text{OEt}_2$  serve merely to counter the effects of any loss of active  $\text{BF}_3$  upon reaction with water was tantalizing, but unfortunately was refuted by note of the fact that addition of  $\text{BF}_3 \cdot \text{OEt}_2$  alone fails to resurrect the reaction. Indeed, the optimized procedure reported herein involves adding a second aliquot of 6 and 9 equivalents of  $\text{NEt}_3$  and  $\text{BF}_3 \cdot \text{OEt}_2$ , respectively, to the reaction mixture, after a period of initial stirring. The ratio and amounts of the  $\text{NEt}_3$  and  $\text{BF}_3 \cdot \text{OEt}_2$  reagents are critical to producing high yields, both with the initial and second addition. A second aliquot of 6 equivalents of  $\text{NEt}_3$  and 9 equivalents of  $\text{BF}_3 \cdot \text{OEt}_2$  after 1.25 h furnishes excellent yields of *F*-BODIPYs even under non-anhydrous, or “wet” conditions, and even in the presence of 2 equivalents of water (greater than would typically be present after careful reaction set-up in a humid climate). Although the yield can be significantly improved via this protocol, it should be appreciated that the addition of twice the amount of  $\text{NEt}_3$  and  $\text{BF}_3 \cdot \text{OEt}_2$  requires a slightly more thorough work-up procedure. Although deceptively simple in conclusion, we published<sup>202</sup> this work so as to unequivocally document robust and practical conditions to convert dipyrins into *F*-BODIPYs.

## Chapter 3 – Mechanistic Studies in the Synthesis of Symmetrical Dipyrrens

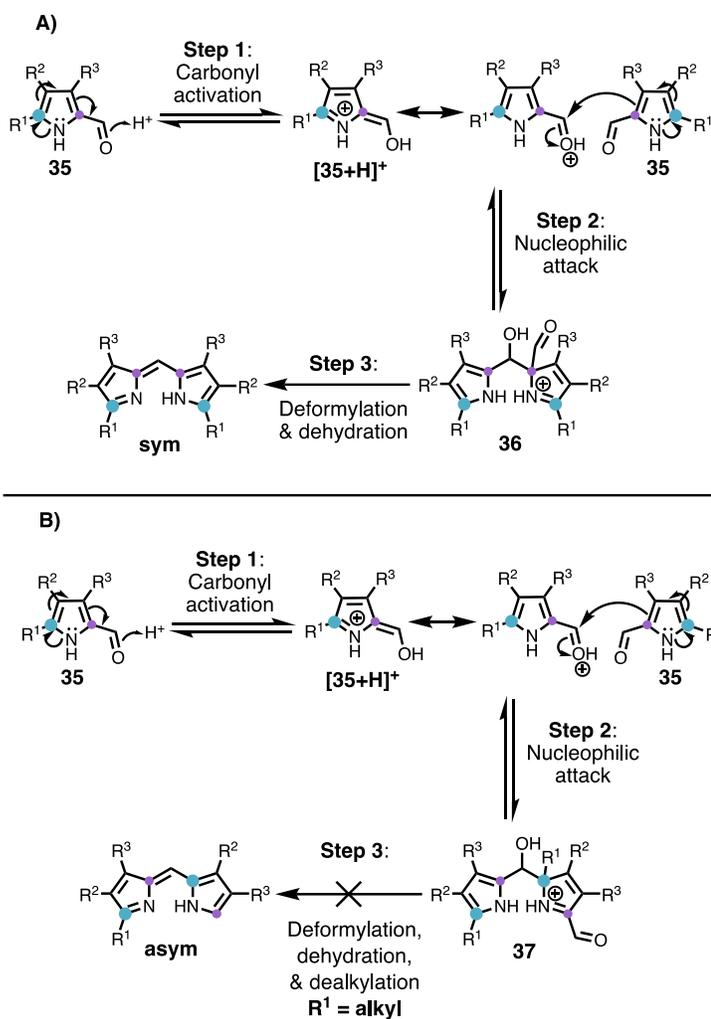
### 3.1 Introduction

Through Chapter 1, and Chapter 2, we have seen how dipyrrens are of interest to the Thompson group, as well as other researchers, with dipyrrens garnering increased attention in recent years as useful ligands with applications in such areas as organometallic catalysis,<sup>92-94</sup> photochemistry,<sup>95-97</sup> and biological labelling.<sup>7,8,98,99</sup> Of important note, the work detailed in Chapter 2, regarding the open-air synthesis of *F*-BODIPYs, relied on access to dipyrrens. Thus, as the use of and applications for dipyrrens increases, developing efficient ways to prepare them is an undeniably important area of research. A previous report<sup>105</sup> by the Thompson group presented the efficient synthesis of symmetric *meso*-H-dipyrrens formed from the self-condensation of fully substituted N-H 2-formylpyrroles in the presence of aqueous hydrobromic acid (Scheme 14). Using methanol as a solvent and heating 2-formylpyrroles at 65 °C for 1 hour in the presence of excess aqueous 48% hydrobromic acid, the requisite symmetric dipyrren hydrobromide salts were produced in moderate-to-high isolated yields (60%-90%). Substituents such as alkyl, keto, alkanoate, and conjugated esters were well tolerated. As well as being convenient and efficient, this strategy complemented existing literature methods by enabling the high-yielding synthesis of symmetric dipyrrens from pyrroles that bear electron withdrawing functional groups.



**Scheme 14: Published Synthesis of Symmetrical *meso*-H Dipyrrens<sup>105</sup>**

While mechanistic work was outside the scope of our previous publication,<sup>105</sup> the self-condensation of 2-formylpyrroles to form dipyrrens was thought to proceed through the reaction mechanism outlined in Scheme 15A, similar to a mechanism proposed for the formation of dipyrrens from 2-formylpyrroles in the presence of POCl<sub>3</sub>.<sup>106</sup> The mechanism begins with activation, via protonation, of the carbonyl group of a 2-formylpyrrole (Scheme 15A, Step 1, **[35+H]<sup>+</sup>**). Following this, the carbonyl carbon atom of **[35+H]<sup>+</sup>** undergoes nucleophilic attack (Step 2) originating from the 2-position of a second equivalent of yet unreacted pyrrole. The resulting intermediate (**36**) is believed to then undergo deformylation<sup>203</sup> and subsequent dehydration (Step 3) to generate the requisite symmetric dipyrren (**sym**). This mechanism was supported by the observed formation of symmetric dipyrrens, and the known ability for formyl pyrroles to undergo deformylation under acidic conditions.<sup>203</sup> However, cognizant that pyrroles typically have nucleophilic 2- and 5-positions,<sup>34,35</sup> we envisioned that nucleophilic attack in Step 2 could originate from the 5-position (Scheme 15B) as well as the 2-position of a 2-formylpyrrole.



**Scheme 15: A) Proposed Formation of Symmetrical Dipyrrens from Fully Substituted 2-Formylpyrroles; B) Proposed Formation of Asymmetrical Dipyrrens, However Nucleophilic Attack From the 5-Position Cannot Produce Dipyrren when R<sup>1</sup> is an Alkyl Group**

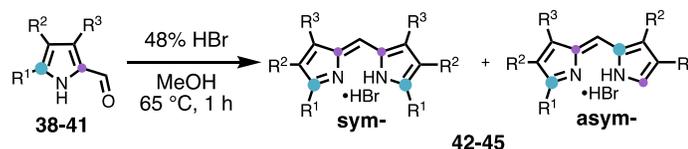
With respect to 2-formylpyrroles and the described mechanistic pathway (Scheme 15B), nucleophilic attack from the 5-position of an unreacted pyrrole unit (Step 2) would result in the formation of intermediate **37**, which is a potential precursor to an asymmetrical dipyrren (**asym**). However, when the 5-position (R<sup>1</sup>) was substituted with an alkyl group only symmetric dipyrrens (**sym**) were observed to form from the self-condensation reaction. According to the mechanism outlined in Scheme 15B, for

nucleophilic attack originating from the 5-position (Step 2) of the pyrrole to furnish an asymmetric dipyrin (**asym**) when  $R^1 = \text{alkyl}$ , it is necessary that formation of intermediate **37** be followed by dealkylation (Step 3, removal of  $R^1$ ) in addition to dehydration, and deformylation. While it is reasonable to believe that intermediate **37** could undergo dehydration and deformylation<sup>203</sup> under the reaction conditions (48% HBr, MeOH, 70 °C), dealkylation is highly unlikely to occur. Dealkylation of pyrroles requires multiple steps, including oxidation, and a carboxylate moiety to be present around the pyrrole ring.<sup>87,204,205</sup> Therefore, with an alkyl group as  $R^1$ , attack from the 5-position would effectively be blocked and asymmetrical dipyrin (**asym**) would not be able to form, in accordance with the observed outcome in our published work.<sup>105</sup> With that said, we still envisioned that coupling of the two pyrroles could proceed via the adoption of two orientations, i.e. 2-attack vs. 5-attack, and thus should be capable of producing symmetrical and asymmetrical dipyrins if  $R^1$  were a more reactive substituent (e.g. H).

Indeed, in our original publication,<sup>105</sup> when subject to the described self-condensation reaction conditions, pyrrole **38** (Table 8, entry 1), bearing a hydrogen atom at the 5-position ( $R^1 = \text{H}$ ), demonstrated regioselective formation of the **sym-42** and **asym-42** dipyrins, in a 9:1 ratio, respectively. We suspected that, by virtue of the unsubstituted 5-position, attack could originate from either the 2- or 5-position of pyrrole **38** to successfully furnish dipyrin. The symmetric product was presumed to form via the mechanism described in Scheme 15A, i.e. identical to the formation of symmetric dipyrin from the self-condensation of fully substituted N-H 2-formylpyrroles. The asymmetric dipyrin was presumed to form via the mechanism outlined in Scheme 16 (adapted from Scheme 15B) wherein nucleophilic attack originates from the 5-position of

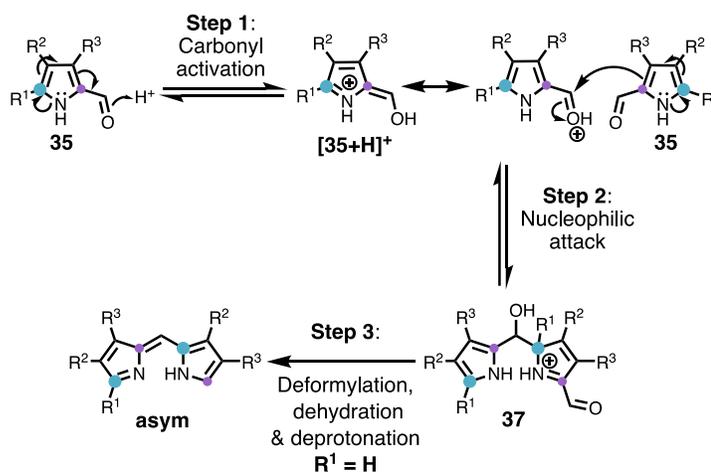
a 2-formylpyrrole (Step 2) to furnish intermediate **37** where  $R^1 = H$ . With a hydrogen atom in the 5-position ( $R^1 = H$ ), intermediate **37** would require deprotonation, rather than dealkylation, to proceed through Step 3 (compare Step 3 of Scheme 15B and Scheme 16) and ultimately furnish asymmetric dipyrin (**asym**).

**Table 8: Symmetrical *meso*-H Dipyrin Formation from 2-Formyl-5-H-pyrroles**



Entry	Pyrrole	$R^1$	$R^2$	$R^3$	Isolated Yield (%)
1	<b>38</b>	H	Et	Me	63 (9:1) <sup>a</sup>
2	<b>39</b>	H	Me	Et	0
3	<b>40</b>	H	Me	Me	0
4	<b>41</b>	H	Et	Et	75

<sup>a</sup>**sym-42** was the major isomer produced

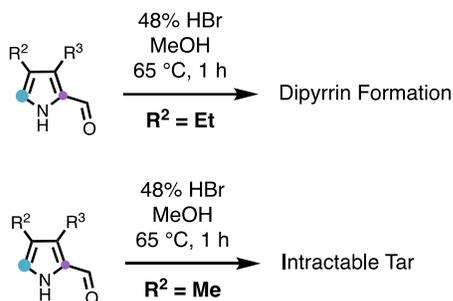


**Scheme 16: Formation of an Asymmetric Dipyrin from the Self-condensation of a 2-Formyl-5-H-pyrrole was Thought to Occur Via Nucleophilic from the 5-H-Position**

Beyond speculation, little focus had been given to earnestly exploring the mechanism of dipyrin formation via the self-condensation and coupling of 2-formylpyrroles. Literature<sup>106</sup> prior to this work did not account for the formation of regioisomers **sym-42** and **asym-42** from pyrrole **38** (Table 8, entry 1). After our initial publication,<sup>105</sup> and to build upon the discussion of potential reaction mechanisms described above, we sought to investigate how the self-condensation of 2-formylpyrroles proceeded, and specifically why pyrrole **38** furnished two regioisomeric dipyrins in a 9:1 ratio. As such, the Thompson group began investigating the reaction pathways for formation of  $\alpha,\alpha'$ -unsubstituted dipyrins from 2-formyl-5-H-pyrroles.

Accordingly, Kate-lyn Lund, MSc, Thompson Lab, prepared several 2-formyl-5-H-pyrroles bearing ethyl and methyl substituents at the 3- and 4-positions, and used NMR spectroscopy to analyze their condensation products (Table 8, entries 1-4). Upon exposure of the 5-H-pyrroles to the published reaction conditions used for dipyrin formation (48% HBr, MeOH, 70 °C, 1 h), evidence of a steric influence emerged. Indeed, when  $R^2 = Et$  (Table 8, entries 1 and 4), dipyrin formation was successful. On the contrary, when  $R^2 = Me$  (entries 2 and 3) dipyrin formation was not observed and the reaction instead produced an intractable tar. These results suggested that an ethyl substituent as  $R^2$  provided sufficient steric bulk to hinder polymerization, while, in contrast, a methyl group at  $R^2$  offered insufficient steric hinderance and permitted polymerization. The nature of how steric bulk from the  $R^2$  substituent affected the reaction remained undetermined. Furthermore, it appeared that increasing steric bulk at  $R^2$  had a more pronounced effect than at  $R^3$  (Scheme 17); note that when  $R^2$  was Me (**39**

and **40**, Table 8, entries 2 and 3), polymeric tars were produced no matter the nature of  $R^3$ .

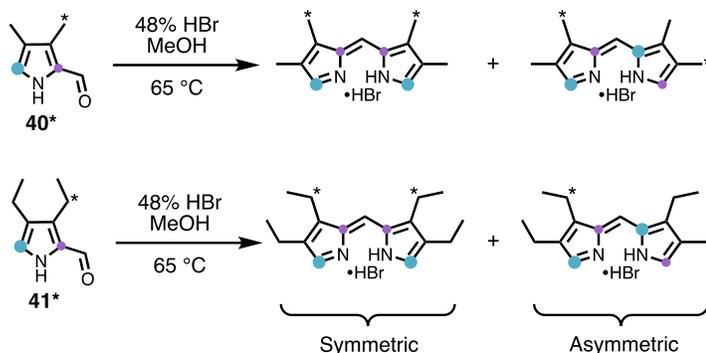


**Scheme 17: Effects of Ethyl and Methyl Alkyl Groups as the  $R^2$  Substituent on the Outcome of the Self-condensation of 2-Formyl-5-H-pyrroles**

### 3.2 Project Goals

The goals of this project were to investigate and to provide evidence for potential mechanisms for the formation of dipyrrins via the self-condensation of 2-formylpyrroles in the presence of aqueous hydrobromic acid. As discussed in the introduction of this chapter, we hypothesized that symmetric dipyrrin could form via the mechanism outlined in Scheme 15A (nucleophilic attack from the 2-position of a 2-formylpyrrole), while asymmetric dipyrrin could form via the mechanism outlined in Scheme 16 (nucleophilic attack from the 5-position of a 2-formylpyrrole). In addition, we had observed that successful dipyrrin formation from 2-formyl-5-H-pyrroles was affected by the substituent at the 4-position ( $R^2$ , Table 8, dipyrrin formation not observed when  $R^2 = \text{Me}$ ). What we lacked was evidence that could explain why **asym-42** had formed from the self-condensation of pyrrole **38**, and why dipyrrin formation was not successful from 2-formyl-5-H-pyrroles when  $R^2 = \text{Me}$ .

The formation of dipyrrens **sym-42** and **asym-42** from the self-condensation of pyrrole **38** suggested that nucleophilic attack was originating from both the 2- and 5-positions of pyrrole **38**. In order to investigate further, we sought to explore the formation of dipyrrens from 2-formyl-5-H-pyrroles **40** and **41** (Table 8, entries 3 and 4) of which the 3- and 4-substituents were identical ( $R^2 = R^3 = \text{Me}$  or  $\text{Et}$ , respectively) within the individual pyrroles. Cognizant that the self-condensation of pyrrole **40** resulted in the formation of an intractable tar (Table 8, entry 3), while **41** (Table 8, entry 4) resulted in dipyrren formation, we were confident that manipulation of the reaction conditions could result in successfully forming an isolable dipyrren product from **40**. As a consequence of identical substituents in the 3- and 4-positions ( $R^2 = R^3$ ), the self-condensation of either pyrrole, **40** or **41**, would result in a symmetric dipyrren regardless of whether nucleophilic attack originated from the 2- or the 5-position. However, if the alkyl groups could be differentiated, and nucleophilic attack was in fact originating from both  $\alpha$ -positions, we would expect to observe a mixture of symmetric and asymmetric dipyrrens. We proposed differentiating the alkyl substituents of **40** and **41** via isotopic labelling to produce labelled analogues **40\*** and **41\*** (Scheme 18). When subject to the self-condensation reaction conditions (48% HBr, MeOH, 70 °C)<sup>105</sup> the isotopic labels of **40\*** and **41\*** would enable us to observe, via NMR spectroscopic analysis, symmetric and asymmetric dipyrren, if present (Scheme 18). Finally, if we were successful in observing the formation of symmetric and asymmetric dipyrrens from the labelled pyrroles, it would provide evidence supporting our hypothesis that nucleophilic attack could, in fact, originate from both  $\alpha$ -positions of a 2-formylpyrrole.

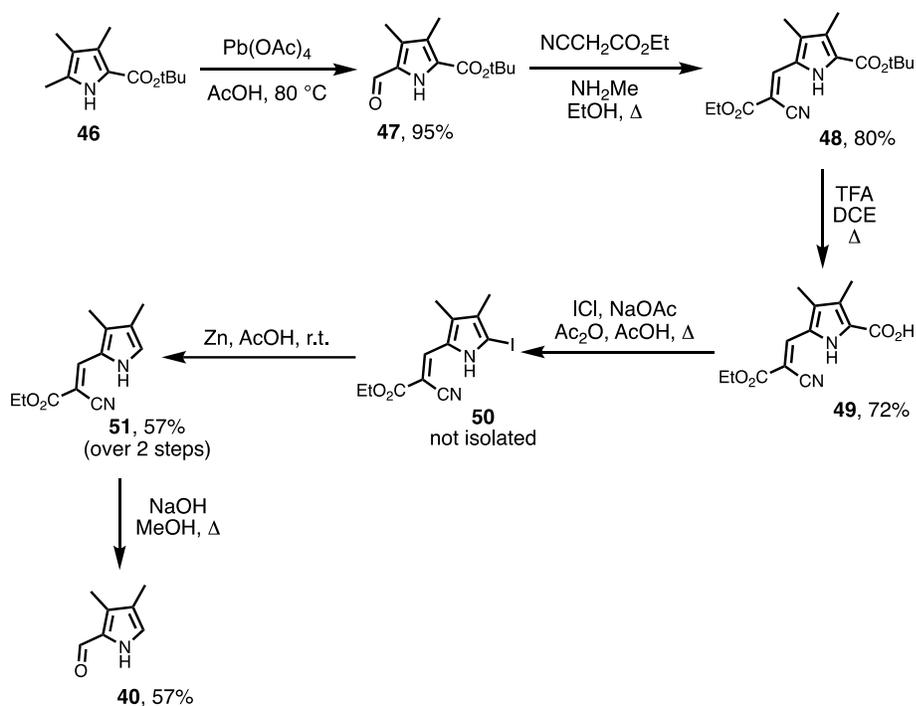


**Scheme 18: Proposed Isotopically Labeled Pyrroles 40\* and 41\* and the Proposed Formation of Isotopically Labeled Symmetric and Asymmetric Dipyrins. The Labeled Group is Indicated by an Asterisk (\*)**

### 3.3 Results and Discussion

#### 3.3.1 Synthesis of 2-Formyl-3,4-dimethylpyrroles 40 and 40\*

To begin our investigations, we first required the unlabelled and deuterium-labelled 2-formylpyrroles **40** and **40\***, respectively. Pyrrole **40** was prepared via a 6-step synthesis in an 18% overall yield (Scheme 19), beginning with pyrrole **46**,<sup>88</sup> which was available in gram quantities within the Thompson lab. Pyrrole **40\*** was prepared via a 9-step synthesis in an overall 0.15% yield (Scheme 20), beginning with pyrrole **52**,<sup>206</sup> which was available in gram quantities within the Thompson lab. The planned synthetic routes to prepare pyrroles **40** and **40\*** converged with the synthesis of **47** and **47\*** (from **46** and **46\***, respectively). Sharing six identical synthetic procedures, all of which focused on manipulation of  $\alpha$ -substituents, pyrroles **40** and **40\*** were easily prepared in tandem once the isotopic label of **46\*** had been installed.



**Scheme 19: Synthesis of Unlabelled 2-Formyl-3,4-dimethylpyrrole 40**

Towards preparing unlabelled pyrrole **40**, the first synthetic step was oxidation of the  $\alpha$ -Me group of pyrrole-2-carboxylate **46** via treatment with lead(IV) acetate,<sup>37</sup> ( $\text{Pb}(\text{OAc})_4$ ). Oxidation of  $\alpha$ -Me groups of pyrrole-2-carboxylates with  $\text{Pb}(\text{OAc})_4$  is a well-established transformation to produce  $\alpha$ -formylpyrroles, and oxidation of **46** in this way successfully gave  $\alpha$ -formylpyrrole **47** in a 95% isolated yield. The same transformation would not be feasible without a carboxylate group in place on the pyrrole ring.<sup>37</sup> Protection of the new aldehyde of **47** with a cyanovinyl protecting group gave  $\alpha$ -cyanovinyl pyrrole **48** in an 80% isolated yield. Protection was necessary in order to mask the aldehyde during the complete removal of the carboxylate group, via hydrolysis (**48** to **49**) and decarboxylation (**49** to **51**). Protection of  $\alpha$ -formylpyrroles using cyanovinyl protecting groups has been known for several decades.<sup>87,88</sup> This is well established as a robust and widely useful protecting group that is easily removed under

basic conditions (4 M aqueous NaOH in MeOH, ~80 °C). Additionally, the choice of a cyanovinyl protecting group was necessary as we were excluded from using protecting groups requiring treatment with acid in order to effect deprotection, due to the instability of the requisite pyrrole aldehyde under acidic conditions.<sup>105,203</sup>

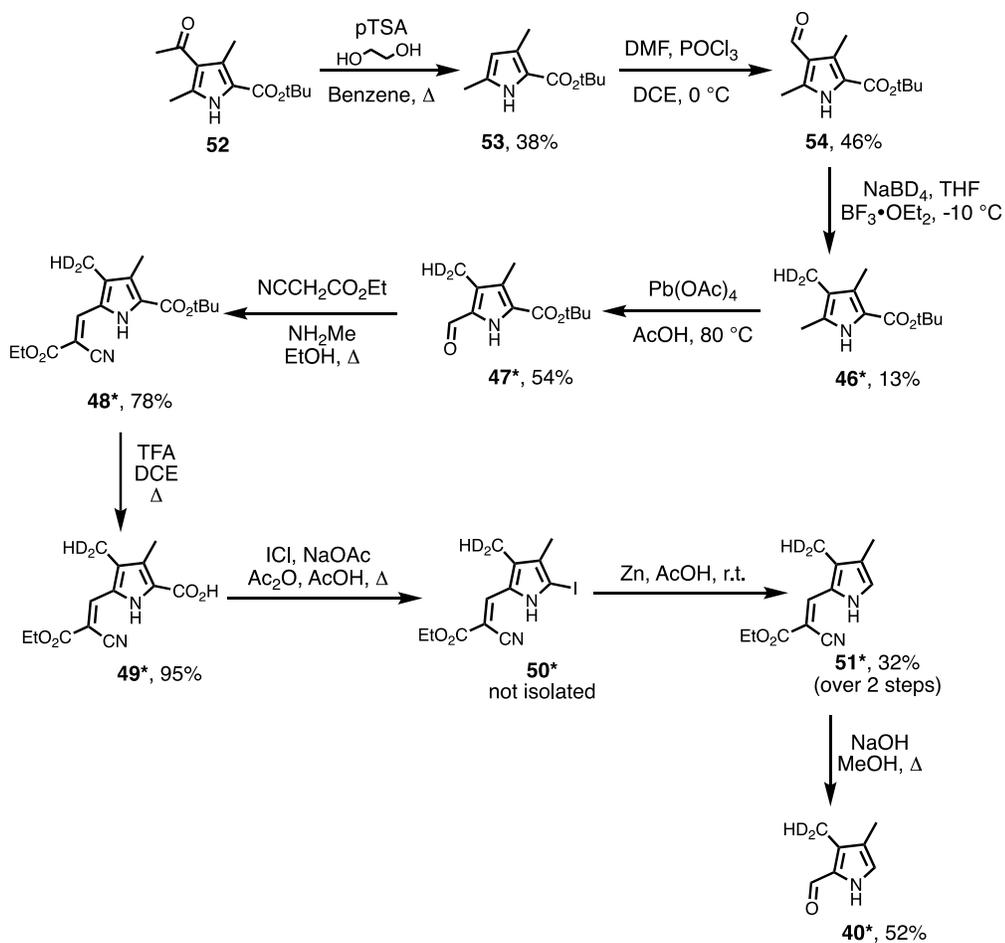
In continuing the synthesis of **40** after introduction of the cyanovinyl protecting group (**47** to **48**, Scheme 19), the *tert*-butyl carboxylate of **48** was hydrolyzed with TFA to yield carboxylic acid **49** (72% isolated yield). Within Knorr pyrrole chemistry<sup>77,86-88</sup> ethyl, benzyl and *tert*-butyl carboxylates are common stabilizing moieties found on pyrroles.<sup>84,87,88</sup> In the decision whether to use an ethyl, benzyl, or *tert*-butyl pyrrole-2-carboxylate for the synthesis of **40**, the only requirement was that hydrolysis and decarboxylation must occur without affecting the cyanovinyl protecting group, which was masking what would become the aldehyde of **40**. With this in mind, ethyl pyrrole-2-carboxylates were not explored, as both the ethanoate and cyanovinyl protecting groups would require basic conditions for removal. Ethyl pyrrole-2-carboxylates are hydrolyzed, and decarboxylated, in a single pot using high temperatures (160 °C) under strongly basic conditions (7 M KOH in ethylene glycol).<sup>184</sup> The cyanovinyl group, however, is removed at a lower temperature (~80 °C) and under less basic conditions (4 M aqueous NaOH in MeOH).<sup>87</sup> The basic conditions required for both meant simultaneous aldehyde deprotection and removal of the carboxylate would likely occur, but was unlikely to proceed efficiently as the deprotected formyl group would not be expected to be stable under the elevated temperature and more basic conditions required for hydrolyzation of the ethyl ester.<sup>203</sup> In addition, once the ester had been hydrolyzed, decarboxylation could present further issues. Pyrrole-2-carboxylic acids stabilized by electron-withdrawing

groups (such as an aldehyde or a cyanovinyl protecting group) are often more difficult to thermally decarboxylate, requiring even higher temperatures which would be of further detriment and likely result in very low product yields, if any.<sup>207,208</sup> Thus, as stated, use of an ethyl pyrrole-2-carboxylate was not explored.

Use of a benzyl pyrrole-2-carboxylate, which was investigated by Kate-lyn Lund, MSc, Thompson Group, was initially proposed to avoid the aforementioned difficulties of using an ethyl pyrrole-2-carboxylate. Rather than effecting a thermally driven hydrolysis under basic conditions, the benzyl ester pyrrole could be converted to the corresponding pyrrole-2-carboxylic acid at room temperature via hydrogenolysis with Pd/C under an atmosphere of H<sub>2</sub>.<sup>87</sup> However, Kate-lyn Lund found that attempted hydrogenolysis of the benzyl ester analogue, with Pd/C and H<sub>2</sub>, resulted in hydrogenation of the vinyl moiety of the cyanovinyl protecting group, in addition to the expected hydrogenolysis of the benzyl ester. Hydrogenation of the double bond unfortunately removed the function of the cyanovinyl group as an efficient protecting group, as there are no known methods for removing the reduced functionality. Thus, having eliminated ethyl and benzyl carboxylates as options, a *tert*-butyl pyrrole-2-carboxylate was used, the ester of which was removed with relative ease,<sup>88</sup> and without affecting the cyanovinyl protecting group.

With the pyrrole-2-carboxylic acid **49** in hand, we looked next to effect decarboxylation. As briefly mentioned above, pyrrole-2-carboxylic acids stabilized with electron-withdrawing groups, such as the cyanovinyl moiety of **49**, are notoriously difficult to thermally decarboxylate, often requiring very high temperatures that are conducive for a variety of unproductive side-reactions, resulting in polymerization, degradation, and very low product yields, if any.<sup>87,207</sup> With this in mind, we chose to

attempt indirect halogenative decarboxylation<sup>87</sup> to produce  $\alpha$ -free pyrrole **51**, with the hopes that it would enable decarboxylation without affecting the cyanovinyl protecting group. Indeed, treatment of **49** with ICl in hot AcOH yielded  $\alpha$ -iodopyrrole (**50**), which was unstable and was immediately reduced with Zn dust in AcOH, at room temperature, to furnish  $\alpha$ -free pyrrole **51** via indirect halogenative decarboxylation. Finally, after hydrolysis and decarboxylation the deprotection of **51** using NaOH in MeOH<sup>88</sup> gave the desired unlabelled 2-formylpyrrole **40** (Scheme 19).



**Scheme 20: Synthesis of <sup>2</sup>D-Labelled 2-Formyl-3,4-dimethyl Pyrrole **40\*****

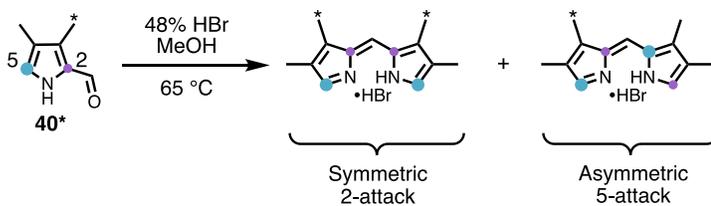
The synthesis of deuterium-labelled pyrrole **40\*** began with pyrrole **52**, the acyl group of which was our gateway to installing the deuterium label (Scheme 20). Deacylation of **52** via treatment with *p*-toluenesulfonic acid (*p*TSA) and ethylene glycol in refluxing benzene furnished  $\beta$ -free pyrrole **53**<sup>203</sup> in a low isolated yield of 38%. In recent years, the deacylation of pyrrole carboxylates has benefited greatly from the development of an efficient microwave assisted reaction (>90%, 15 min).<sup>209</sup> However, the *tert*-butyl carboxylate of **52**, which was vital to the preparation of **40\*** (as described for the synthesis of **40**), was not stable under microwave conditions and the deacylation had to be performed using the less efficient method outlined. With  $\beta$ -free pyrrole **53** in hand, a Vilsmeier-Haack formylation reaction was employed to produce  $\beta$ -formylpyrrole **54**.<sup>182</sup> To install the label, i.e. two deuterium atoms, we planned to reduce the newly installed aldehyde of **54** with a deuteride reducing agent and thus furnish D<sub>2</sub>-labelled pyrrole **46\***. Attempts at incorporating the isotopic label via LiAlD<sub>4</sub>-reduction of **54** did not produce the desired product, which we believed to be a result of the non-selective reduction of both the aldehyde and ester moieties of **54**. Attempting a similar reduction with NaBD<sub>4</sub> was successful in selectively reducing the aldehyde to produce the D<sub>2</sub>-labelled pyrrole **46\***, albeit in a low isolated yield of 13%.<sup>210</sup> Incorporation of two deuterium atoms was clear from the splitting patterns in the <sup>1</sup>H and <sup>13</sup>C NMR spectra (multiplet and quintet, respectively; refer to Appendix B for figures).

Having successfully prepared our first isotopically labelled pyrrole, **46\***, the remaining syntheses required to furnish labelled pyrrole **40\*** were identical to those described above for the synthesis of unlabelled pyrrole **40**. Accordingly, the  $\alpha$ -Me group of **46\*** was oxidized with Pb(OAc)<sub>4</sub> to furnish  $\alpha$ -formylpyrrole **47\***. The aldehyde of **47\***

was then protected with the chosen cyanovinyl protecting group to furnish  $\alpha$ -cyanovinyl pyrrole **48\***. With the protecting group in place, the *tert*-butyl carboxylate of **48\*** was efficiently hydrolyzed with TFA to yield carboxylic acid **49\***. The indirect halogenative decarboxylation of **49\***, via treatment with ICl in hot AcOH, yielded  $\alpha$ -iodopyrrole (**50\***), which was immediately reduced with Zn dust in AcOH, at room temperature, to furnish the  $\alpha$ -free pyrrole **51\***. Finally, removal of the cyanovinyl protecting group of **51\*** via treatment with NaOH in MeOH, gave the desired labelled 2-formylpyrrole **40\***.

### 3.3.2 Mechanistic Insight using 2-Formyl-3,4-dimethylpyrroles

With 2-formylpyrroles **40** and **40\*** in hand, we turned our attention to the formation of dipyrrens via our published self-condensation reaction (48% HBr, MeOH, 70 °C).<sup>105</sup> The goal was to observe whether isotopically labelled pyrrole **40\*** would self-condense to form symmetric and asymmetric dipyrrens (Scheme 21) in order to determine whether the coupling of the two pyrroles proceeded via the adoption of two orientations, i.e. 2-attack vs. 5-attack.



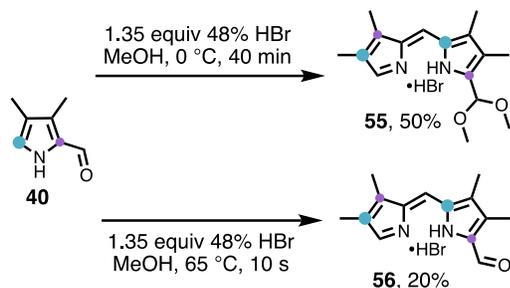
**Scheme 21: Proposed Outcome for the Self-Condensation of Isotopically Labeled Pyrrole **40\*****

Aware that previous exposure of pyrrole **40** to the self-condensation conditions for dipyrren formation<sup>105</sup> had produced a polymeric tar (Table 8, entry 3), and was likely

to do so again with either of the dimethyl pyrroles, **40** or **40\***, we chose to evaluate whether thermal (not acid-catalyzed) deformylation and subsequent condensation of the less precious **40** occurred at the reaction temperature used (70 °C). Despite heating a solution of **40** in MeOH at 70 °C for prolonged periods of time, neither deformylation nor condensation occurred. This indicated that the activation of 2-formylpyrroles using acid was a prerequisite for the reaction to occur under the published conditions, i.e. acid-promoted activation of the aldehyde of 2-formylpyrroles was necessary for successful dipyrin formation.

As reported by Kate-Lyn Lund,<sup>105</sup> when pyrrole **40** was subject to the published reaction conditions (excess 48% HBr, MeOH, 70 °C, 1 h) a polymeric tar was observed to rapidly form (Table 8, entry 3). When the reaction was repeated as a part of this body of work, pyrrole **40** was indeed observed to form an intractable tar within minutes of the addition of excess 48% HBr. However, within seconds of the addition of HBr, the previously colourless reaction mixture was observed to change to a red/brown colour that is typical of dipyrin HBr salts in solution.<sup>202</sup> Based on the assumption that the observed colour change was indicative of dipyrin formation, the reaction conditions were modified such as to attempt to isolate the potential dipyrin prior to polymerization. Introducing a small excess of 48% HBr (1.35 equivalents rather than 7-10) into a solution of pyrrole **40** at 0 °C, rather than 70 °C, resulted in formation and enabled isolation of the new acetal dipyrin **55** (Scheme 22, top, 50%). The acetal moiety of **55** was effectively a masked aldehyde, thus the observed formation of the acetal suggested that nucleophilic attack had originated from the unsubstituted 5-position of 2-formyl-5-H-pyrrole **40**. Additionally, the acetal moiety suggested that deformylation was unsuccessful during

dipyrrin formation, at least at the lower temperature. In order to determine whether the apparent nucleophilic attack from the 5-position of pyrrole **40** was a result of the lowered temperature, we needed to perform the reaction at 70 °C *and* isolate dipyrrin, a feat which had not been accomplished prior.

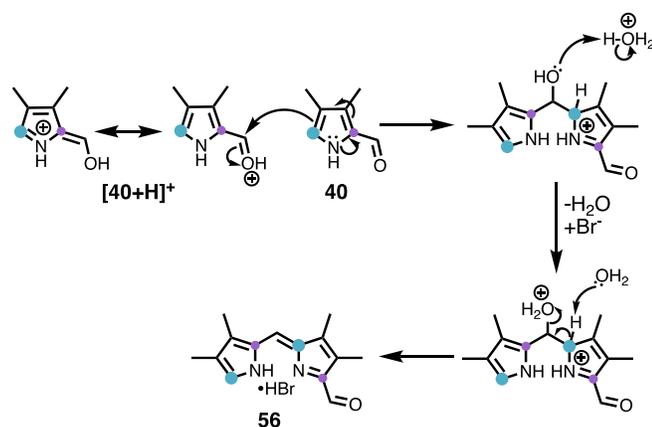


**Scheme 22: Reaction of Pyrrole **40** at 0 °C (Top) and 65 °C (Bottom)**

With this in mind, a solution of pyrrole **40**, in methanol, was warmed to the refluxing temperature via a sand bath heated to a steady temperature of 65 °C. Once the solution of **40** was visibly refluxing, 1.35 equivalents of 48% HBr was added to commence the acid-catalyzed self-condensation reaction. After 10 s, the reaction vessel was immediately plunged into an ice bath ( $\leq 0$  °C) and diluted with diethyl ether to aid in halting any further reaction and assist in rapid cooling. Halting the reaction of pyrrole **40** after just 10 s of heating at 65 °C enabled the isolation of  $\alpha$ -formyldipyrrin **56**, albeit in a 20% yield (Scheme 22, bottom). The low yield of **56** was believed to have been a result of the short reaction time, in conjunction with the previously observed propensity to rapidly polymerize. At the elevated temperature only the  $\alpha$ -formyldipyrrin **56** was observed to form, i.e. no observed formation of  $\alpha$ -acetal dipyrrin. The presence of the aldehyde functionality of **56** further corroborated that attack from the 5-position of **40** dominates, with no evidence of nucleophilic attack from the 2-position nor subsequent

deformylation. In addition, by virtue of the  $\alpha$ -aldehyde of **56** further condensation reactions could occur via nucleophilic attack from remaining unreacted starting material, or other dipyrrens, which we believe could explain why rapid polymerization was observed for the self-condensation of **40** prior to our isolation of **56**. Shortly after the successful self-condensation of **40**, the labelled analogue **40\*** was subject to identical reaction conditions (Scheme 22, bottom). Sadly, no labelled dipyrren was isolated after 10 s of heating at 65 °C and all starting material and product were presumed to have polymerized. It was then clear that there was only a very brief window of opportunity to isolate the formyl dipyrrens. The reaction of **40\*** was not repeated as isolation of unlabelled **55** and **56** had provided us with sufficient information towards better understanding the self-condensation reaction.

Under the conditions used for the formation of **55** and **56**, nucleophilic attack from the 5-position of starting pyrrole was the only observed outcome. We suspected that nucleophilic attack was originating from the unsubstituted 5-position as a result of the 4-methyl group providing little-to-no steric hindrance, thus resulting in relatively unhindered nucleophilicity of the 5-position. In comparison, the nucleophilicity of the 2-position was expected to be more hindered due to direct substitution with an electron-withdrawing formyl group.<sup>211</sup> As a result, we formally propose that the self-condensation of **40** proceeds through the mechanism outlined in Scheme 23, wherein the activated carbonyl carbon atom of  $[\mathbf{40}+\mathbf{H}]^+$  undergoes nucleophilic attack exclusively from the 5-position of yet unreacted starting material **40**, followed by rapid dehydration to furnish the requisite dipyrren **56**.



### Scheme 23: Proposed Mechanism for the Formation of $\alpha$ -Formyldipyrin **56**

Isolation of  $\alpha$ -acetal and  $\alpha$ -formyldipyrins **55** and **56**, respectively, from the self-condensation of **40** confirmed that nucleophilic attack could originate from the unsubstituted 5-position of 2-formyl-5-H-pyrroles, indeed nucleophilic attack from the 5-position was the only observed outcome when  $R^2 = R^3 = \text{Me}$ . From the original work conducted by Kate-lyn Lund, presented in Table 8, it was proposed that the identity of  $R^2$  was the primary factor determining whether dipyrin formation, or polymerization, was favoured during the self-condensation reaction of 2-formyl-5-H-pyrroles **38-41** (Table 8). Provided that  $R^2$  was a methyl group, polymerization was the observed outcome within seconds of HBr addition, despite whether  $R^3$  was a Me or Et group (entry 2 and entry 3). We suspected that when  $R^2 = \text{Me}$ , whether  $R^3 = \text{Et/Me}$  (**39** and **40**) the self-condensation would proceed through a similar pathway with nucleophilic attack originating from the 5-position and resulting in formation of the  $\alpha$ -formyl dipyrin (Scheme 24). The  $\alpha$ -formyl functionality of the dipyrin could then explain the proclivity for polymerization that was originally observed in the self-condensation of pyrrole **39** and **40**.

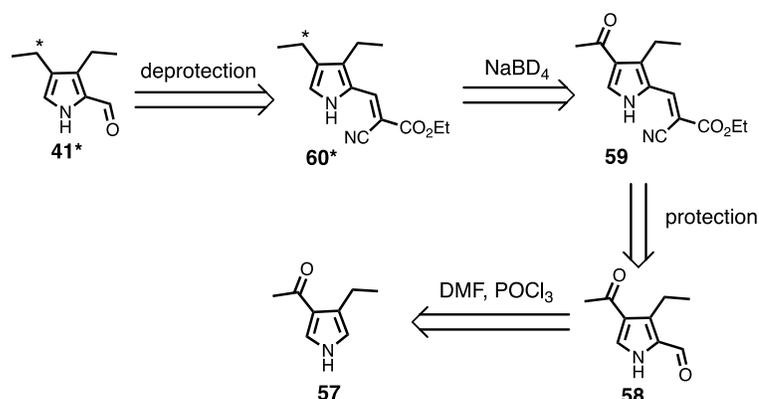


**Scheme 24: Proposed Outcome for the Self-condensation of 2-Formyl-5-H-pyrroles When  $R^2 = \text{Me}$ , and  $R^3 = \text{Me/Et}$**

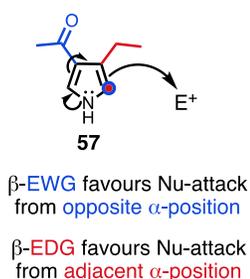
The self-condensation of pyrrole **40** had confirmed that nucleophilic attack could originate from the 5-position of a 2-formyl-5-H-pyrrole. Therefore, cognizant that nucleophilic attack *could* originate from either  $\alpha$ -position, we wished to confirm whether it *would* originate from either  $\alpha$ -position to produce both asymmetric and symmetric dipyrins in line with the self-condensation of pyrrole **38** (Table 8, entry 1). Having learned what we could from the self-condensation of **40**, but not having observed formation of *both* asymmetric and symmetric dipyrins, we next focused on the preparation of the labelled 2-formyl-5-H-pyrrole **41\***, where  $R^2 = R^3 = \text{Et}$  (Scheme 18). Once pyrrole **41\*** had been prepared, our hope was that under the self-condensation conditions (48% HBr, MeOH, 65 °C) the reaction of pyrrole **41\*** would enable us to observe, via NMR spectroscopic analysis, the formation of *both* symmetric and asymmetric dipyrins as a consequence of the bulkier Et groups. If we were capable of observing this, it would provide substantial evidence signifying that nucleophilic attack would, in fact, originate from both  $\alpha$ -positions of the same 2-formyl-5-H-pyrrole. In addition, observation of both symmetric and asymmetric dipyrins from **41\*** would provide evidence towards explaining the formation of regioisomeric dipyrins **sym-42** and **asym-42** in a 9:1 ratio from the self-condensation of pyrrole **38** (Table 8, entry 1).

### 3.3.3 Synthesis of 2-Formyl-3,4-diethylpyrroles **41\*** and **41\*'**

The synthesis of labelled 2-formylpyrrole **41\*** was proposed according to the retrosynthetic strategy outlined in Scheme 25. Beginning with pyrrole **57**, which could be prepared in two steps according to literature procedures,<sup>59,60,62</sup> we proposed an additional 6-step synthesis to prepare isotopically labelled pyrrole **41\***. Formylation of pyrrole **57** via a Vilsmeier-Haack reaction<sup>59</sup> would furnish pyrrole **58** and install the formyl functionality at the  $\alpha$ -position adjacent to the ethyl group. Formylation of pyrrole **57** was expected to proceed selectively as a result of the electronic features of the substituents in the 3- and 4-positions.<sup>211</sup> Pyrroles substituted in the  $\beta$ -positions with electron-withdrawing groups ( $\beta$ -EWG, e.g. acyl group) favour nucleophilic attack from the  $\alpha$ -position opposite to them (Figure 17), while substitution with electron-donating groups ( $\beta$ -EDG, e.g. alkyl group) favours nucleophilic attack from the adjacent  $\alpha$ -position. Thus, the alkyl and acyl groups of **57** work in conjunction to favour production of pyrrole **58** with aldehyde-substitution at the  $\alpha$ -position adjacent to the ethyl group. After formylation, required protection of the aldehyde via use of a cyanovinyl protecting group (**58** to **59**) would enable the selective reduction of the keto moiety via treatment with NaBD<sub>4</sub> (**59** to **60\***). Following protection of the aldehyde and subsequent installation of the isotopic label, removal of the protecting group could then furnish the desired labelled pyrrole **41\*** (**60\*** to **41\***).

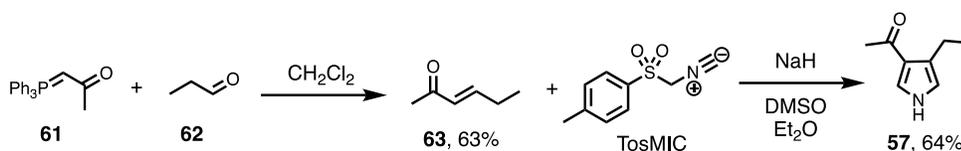


**Scheme 25: Retrosynthetic Strategy for the Synthesis of Labeled Pyrrole 41\***



**Figure 17: Predicting Which  $\alpha$ -Position Nucleophilic Attack is Expected to Originate from in Pyrrole 57, Origin of Nucleophilic Attack is Influenced by the  $\beta$ -Substituents of Pyrroles**

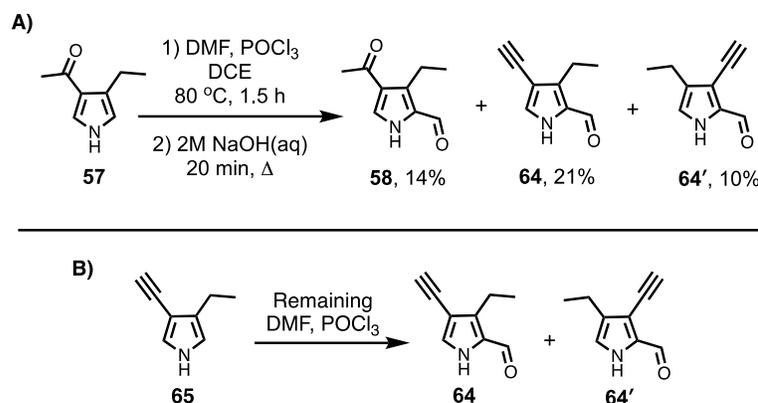
With the intention of following the outlined synthetic strategy (Scheme 25), we moved to prepare pyrrole **57** according to literature procedures. The Wittig reaction of (acetylmethylene)triphenylphosphorane (**61**) and acetaldehyde (**62**) afforded the  $\alpha,\beta$ -unsaturated ketone 3-hexen-2-one (**63**, Scheme 26)<sup>212</sup> in a 63% isolated yield. Subsequent reaction of **63** with TosMIC in the presence of NaH afforded pyrrole **57**, in a 64% isolated yield.<sup>59,60,62</sup> With pyrrole **57** in hand, we turned our attention to the synthesis of **41\*** via our proposed synthetic strategy. All further syntheses discussed within this chapter was performed cooperatively by a previous Thompson lab postdoctoral fellow Dr. Carlotta Figliola and me.



### Scheme 26: Synthesis of Pyrrole 57

When subject to Vilsmeier-Haack formylation conditions suitable for acyl-bearing pyrroles (Scheme 27A),<sup>62,213</sup> **57** was formylated to give the desired 2-formyl-5-H-pyrrole **58** in only a 14% isolated yield. In addition, the two alkynyl regioisomers **64** and **64'** were obtained in 21% and 10% yields, respectively. The position of the aldehyde of **58** and the alkynyl groups of **64** and **64'** (3- or 4-position) was determined using 2-D NMR spectroscopy (HSQC and HMBC); alkynyl pyrroles were analyzed by Dr. Carlotta Figliola. Formation of both acyl pyrrole **58** and alkynyl pyrrole **64** was expected,<sup>213</sup> however **58** was predicted to be the major product, and alkynyl pyrrole **64'** was altogether not expected. The alkynyl groups of **64** and **64'** were assumed to have formed from the enolization of the keto functionality and subsequent elimination reaction affording a triple bond, i.e. dehydration. Pyrrole **64** was rationalized to have formed via formylation of pyrrole **57** and subsequent dehydration of pyrrole **58**. Regioisomer **64'** was rationalized to have formed via the opposite order of events; dehydration of **57** to furnish pyrrole **65** (Scheme 27B) and subsequent non-regioselective formylation to furnish pyrrole **64'** in addition to pyrrole **64**. Indeed, after formation of pyrrole **65**, a mixture of **64** and **64'** could be expected as a consequence of the electronic properties of the ethyl and alkynyl functionalities of pyrrole **65**. As  $\beta$ -electron donating groups favour reaction at the respective adjacent  $\alpha$ -positions,<sup>211</sup> formylation of **65** could then be expected to occur with little regioselectivity for  $\alpha$ -formylation. From the observed mixture of

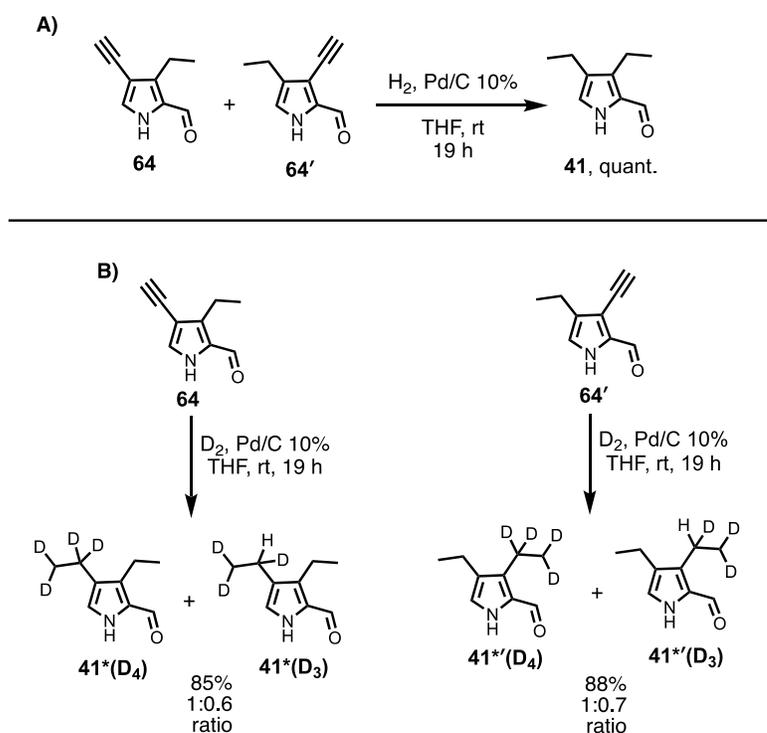
products produced by the formylation of **57** (products **58**, **64**, and **64'**), it is apparent that formylation and dehydration are ongoing throughout the reaction.



**Scheme 27: A) Synthesis of 2-Formyl-5-H-pyrrole **58** and Alkynyl Regioisomers **64** and **64'**; B) Proposed Formylation of Alkynyl Pyrrole **65** which could Result in a Mixture of Products **64** and **64'****

Cognizant that the triple bond would allow for a 1- or 2-step installation of the desired isotopic label, the initial disappointment at not yielding **58** as the major product presented an alternative, and fruitful, opportunity. We thus chose to diverge from the proposed synthetic route for protection and reduction of **58** (Scheme 25) and instead chose to proceed with alkynyl pyrroles **64** and **64'**. An isotopic label could be introduced from either alkynyl pyrrole to furnish a labelled 2-formyl-5-H-pyrrole via two routes: 1) the triple bond could be reduced directly to the corresponding alkyl group using Pd/C under a D<sub>2</sub> atmosphere to produce a D<sub>4</sub>-labelled pyrrole; or 2) the terminal position of the alkynyl group could be deuterated and the triple bond subsequently reduced to produce a D<sub>1</sub>-labelled pyrrole. We initially attempted the latter of the two routes, as we believed introducing a single deuterium atom would greatly simplify all further NMR analysis. Thus, deprotonation of the alkynyl group of a mixture of **64** and **64'** was attempted using nBuLi,<sup>214</sup> followed by quenching with D<sub>2</sub>O to introduce the isotopic label. However, this

treatment failed to produce product and resulted in decomposition. Having not succeeded installing the isotopic label in this way, we moved our attention to testing the reduction of the alkynyl group of either pyrrole regioisomer, **64** or **64'**, using Pd/C under an H<sub>2</sub> atmosphere. To our delight, the hydrogenation of a mixture of **64** and **64'** successfully gave **41**<sup>215,216</sup> in quantitative yields (Scheme 28A). Having successfully prepared pyrrole **41**, we were confident that isotopically labelled pyrrole **41\*** could be prepared using identical methodology but replacing H<sub>2</sub> with D<sub>2</sub> isotopic gas (cylinder of D<sub>2</sub>).



**Scheme 28: A) Synthesis of 3,4-Diethyl-2-formylpyrrole **41**; B) Synthesis of All Deuterium-labelled 3,4-Diethyl-2-formylpyrroles, **41\*** and **41\*'****

In order to obtain labelled pyrrole **41\***, the regioisomers **64** and **64'** were separated using column chromatography on silica and then submitted to the reduction conditions shown in Scheme 28B, using the isotopic gas D<sub>2</sub> instead of H<sub>2</sub>. The two labelled and reduced regioisomers **41\*(D<sub>4</sub>)** and **41''(D<sub>4</sub>)** were obtained, but

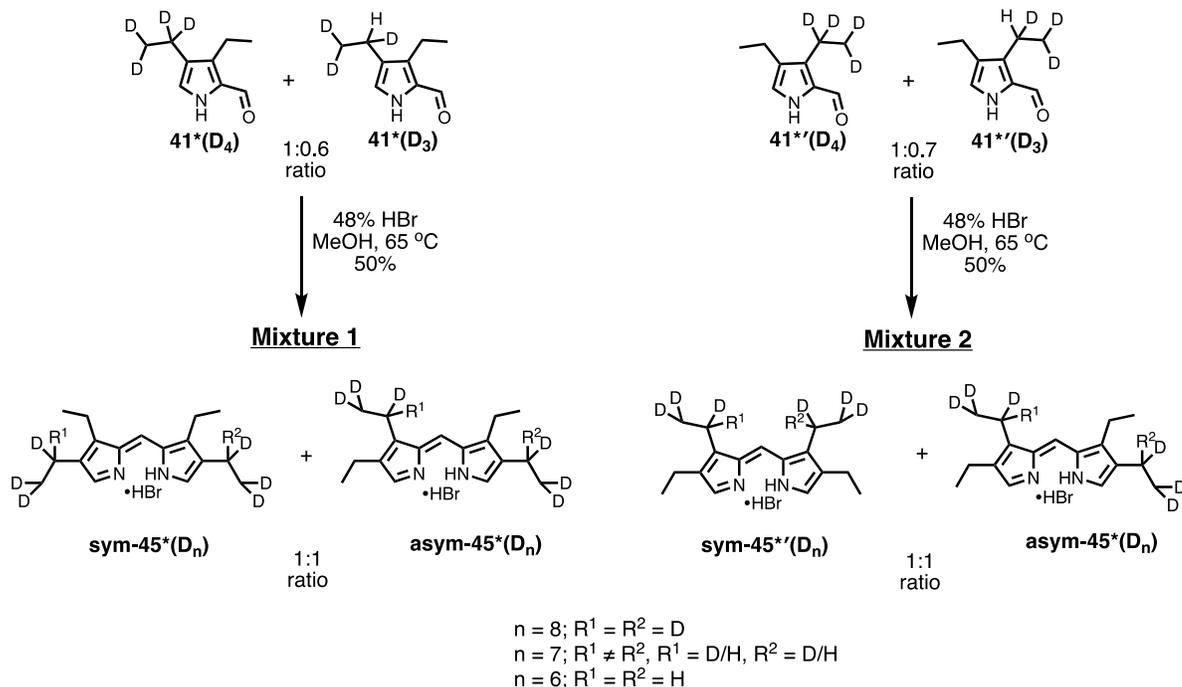
unfortunately, partial deuteration was observed and pyrroles **41\***(D<sub>3</sub>) and **41\*'**(D<sub>3</sub>) were also produced in a 1:0.6 and 1:0.7 ratio to the corresponding D<sub>4</sub>-pyrroles, as observed through <sup>1</sup>H NMR spectroscopic analysis. The origins of the incomplete deuteration are unknown and were not investigated. Nevertheless, we had succeeded in preparing isotopically labelled regioisomeric 2-formyl-5-H-pyrroles, albeit in mixtures of D<sub>4</sub>- and D<sub>3</sub>-isomers (pyrrole mixtures **41\*** and **41\*'**).

We then turned our attention towards the synthesis of the corresponding isotopically labelled dipyrrens. We sought to finally determine whether formation of *both* symmetric and asymmetric dipyrrens could be observed from pyrrole mixtures **41\*** and **41\*'** (via NMR spectroscopic analysis) when subject to the self-condensation reaction conditions (48% HBr, MeOH, 65 °C). If a mixture of symmetric and asymmetric products was observed to form, it would provide substantial evidence confirming that nucleophilic attack will, in fact, originate from both α-positions of the same 2-formyl-5-H-pyrrole. Cognizant that the presence of D<sub>4</sub>- and D<sub>3</sub>-isomers could complicate subsequent NMR analysis, we were confident that it would still be evident if symmetric and asymmetric dipyrrens formed.

### **3.3.4 Mechanistic Insight from the Synthesis of Labelled Tetraethyl Dipyrrens**

Once in hand, pyrrole mixtures **41\*** and **41\*'** (D<sub>4</sub>- and D<sub>3</sub>-isomers) were each submitted to the acid-catalyzed condensation reaction conditions<sup>105</sup> to afford deuterated α-free dipyrrens. According to detailed NMR spectroscopic analysis (<sup>1</sup>H, <sup>13</sup>C, HMBC and HSQC) the condensation of pyrrole mixture **41\*** resulted in a mixture of two D<sub>8</sub>-, three

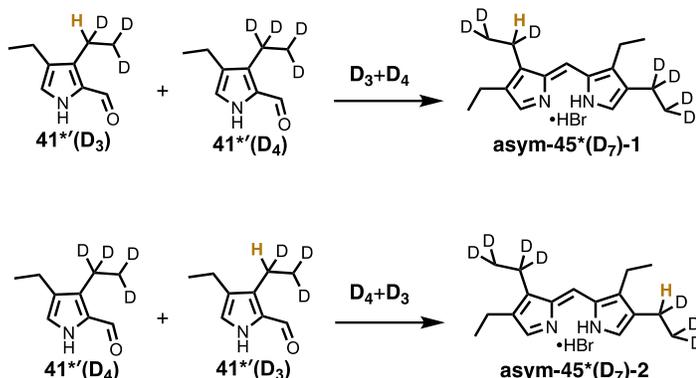
D<sub>7</sub>-, and two D<sub>6</sub>-dipyrin isomers (Scheme 29, Left, **Mixture 1**, **sym-45\*(D<sub>n</sub>)** and **asym-45\*(D<sub>n</sub>)**). Similarly, the condensation of pyrrole mixture **41\*\*'** resulted in a mixture of two D<sub>8</sub>-, three D<sub>7</sub>-, and two D<sub>6</sub>-dipyrin isomers (Scheme 29, Right, **Mixture 2**, **sym-45\*\*'(D<sub>n</sub>)** and **asym-45\*\*'(D<sub>n</sub>)**).



**Scheme 29: Synthesis of Deuterium-labelled  $\alpha$ -Free Dipyrins Sym-45\*, Asym-45\*, and Sym-45\*\*' (D<sub>8</sub>, D<sub>7</sub>, and D<sub>6</sub> Isomers)**

Three D<sub>7</sub>-isomers were believed to be present within each mixture most likely as a result of two possible orientations for the coupling of D<sub>3</sub>- and D<sub>4</sub>-pyrroles (i.e. D<sub>3</sub>+D<sub>4</sub> vs. D<sub>4</sub>+D<sub>3</sub>, Scheme 30), which would result in the formation of two asymmetric D<sub>7</sub>-dipyrin isomers, **asym-45\*(D<sub>7</sub>)-1** and **asym-45\*(D<sub>7</sub>)-2**. According to detailed NMR spectroscopic analysis (<sup>1</sup>H, <sup>13</sup>C, HMBC and HSQC) and based on the ratio between D<sub>4</sub>:D<sub>3</sub> isomers of both pyrrole regioisomers **41\*** (1:0.6) and **41\*\*'** (1.0:7), we determined that, inclusive of all labelled isomers, dipyrins **sym-45\*** and **asym-45\*** were obtained in

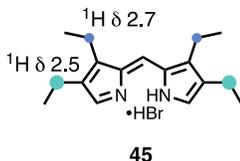
a 1:1 ratio, and **sym-45\*** and **asym-45\*** were obtained in an identical ratio. Henceforth, referring to a labelled dipyrin without specifying the number of deuterium atoms will instead refer to all deuterated isomers of that dipyrin, e.g. **asym-45\*** would refer to the deuterated isomers **asym-45\*(D<sub>8</sub>)**, **asym-45\*(D<sub>7</sub>)-1** and **-2**, and **asym-45\*(D<sub>6</sub>)**.



**Scheme 30: Using Pyrrole 41\*** as an Example, Condensation of D<sub>4</sub>- and D<sub>3</sub>-pyrroles can Occur in Two Different Orientations Resulting in Formation of **Asym-45\*(D<sub>7</sub>)-1** and **Asym-45\*(D<sub>7</sub>)-2**

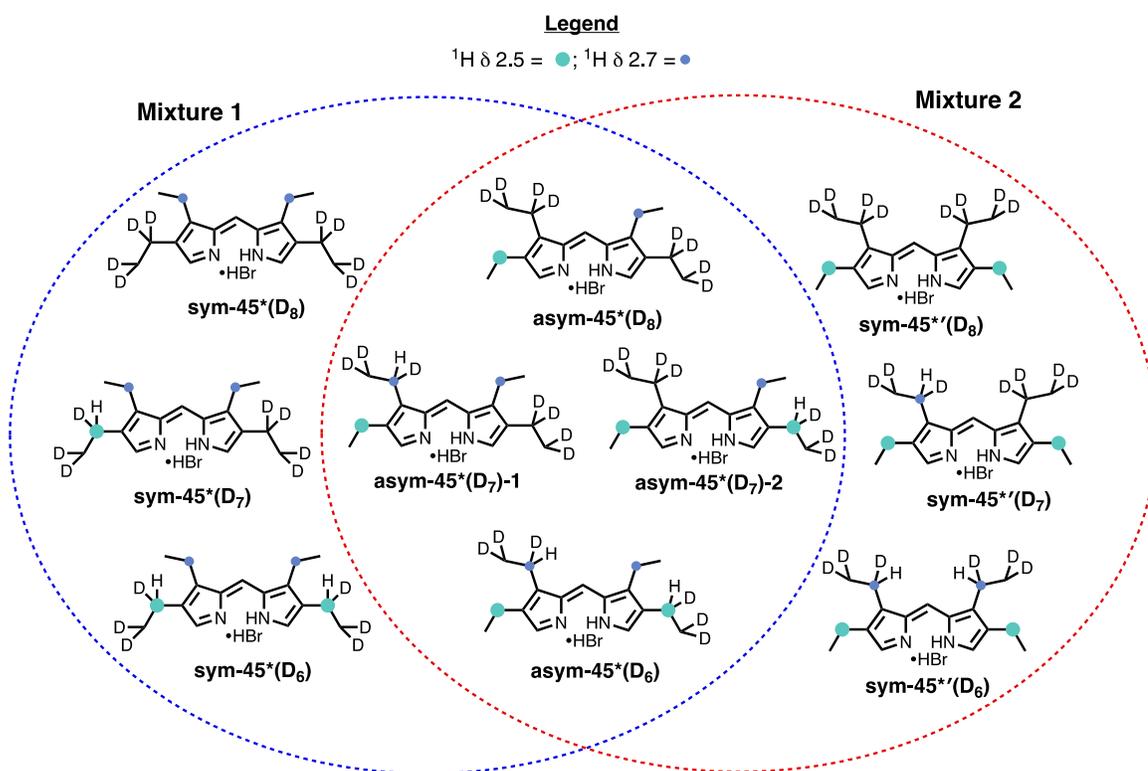
To determine the ratio of symmetric and asymmetric dipyrins for each mixture (**Mixture 1** and **Mixture 2**), we employed <sup>1</sup>H NMR spectroscopy to analyze the <sup>1</sup>H signals corresponding to the ethyl CH<sub>2</sub> hydrogen atoms present in each dipyrin. In order to simplify the analysis of **Mixture 1** and **Mixture 2**, NMR spectroscopic analysis (<sup>1</sup>H, <sup>13</sup>C, HMBC and HSQC) of unlabelled dipyrin **45** was used to determine the <sup>1</sup>H chemical shifts for each of the ethyl CH<sub>2</sub> groups present within **45**. Due to molecular symmetry, dipyrin **45** had two <sup>1</sup>H signals at 2.5 and 2.7 ppm which corresponded to the four CH<sub>2</sub> groups (Figure 18, <sup>1</sup>H δ 2.5 and <sup>1</sup>H δ 2.7). The CH<sub>2</sub> group adjacent to the α-free position (<sup>1</sup>H δ 2.5, large cyan dot) of dipyrin **45** corresponded to the <sup>1</sup>H signal at 2.5 ppm, while the remaining CH<sub>2</sub> group (<sup>1</sup>H δ 2.7, small purple dot) corresponded to the <sup>1</sup>H signal at 2.7 ppm. Having established the <sup>1</sup>H NMR chemical shifts for the ethyl CH<sub>2</sub>-groups of

unlabelled **45**, we were able to use these assignments as a comparison to aid in analyzing the spectra collected ( $^1\text{H}$ ,  $^{13}\text{C}$ , HMBC, and HSQC) for both deuterated dipyrin mixtures.



**Figure 18:  $^1\text{H}$  NMR Signal Assignment for  $^1\text{H}$  Chemical Shifts of Dipyrin **45** Corresponding to the Ethyl  $\text{CH}_2$  Signals of **45****

NMR spectroscopic analysis of **Mixture 1** and **Mixture 2** revealed that the  $^1\text{H}$  signals corresponding to the  $\text{CH}_2$  and  $\text{CHD}$  groups of all labelled **sym-45\***, **asym-45\***, and **sym-45\*' dipyrins** arose at the same chemical shift as seen in dipyrin **45** (Figure 19), i.e. the  $\text{CH}_2/\text{CHD}$  hydrogen atoms adjacent to the  $\alpha$ -free position of a given dipyrin always corresponded to  $^1\text{H } \delta 2.5$ . The presence of a deuterium atom in the  $\text{CHD}$ -groups resulted in a more complex signal in the  $^1\text{H}$  NMR (multiplet vs. quartet) but failed to cause a dramatic change in chemical shift. When fully deuterated, i.e. a  $\text{CD}_2$  group, no signal was observed as a consequence of deuterium not being observed under the  $^1\text{H}$  NMR spectroscopic conditions. Ultimately, we determined that the  $^1\text{H}$  signals at 2.5 and 2.7 ppm comprised all  $\text{CH}_2$  and  $\text{CHD}$  hydrogen atoms present within each individual dipyrin mixture (Figure 19,  $\text{CH}_2$  and  $\text{CHD}$  groups colour-coded according to which  $^1\text{H}$  NMR signal they would contribute to). Thus, we used the integrals of signals  $^1\text{H } \delta 2.5$  and  $^1\text{H } \delta 2.7$  within the  $^1\text{H}$  NMR spectra collected from **Mixture 1** and **Mixture 2** to determine the ratio of asymmetric and symmetric dipyrins within each mixture.

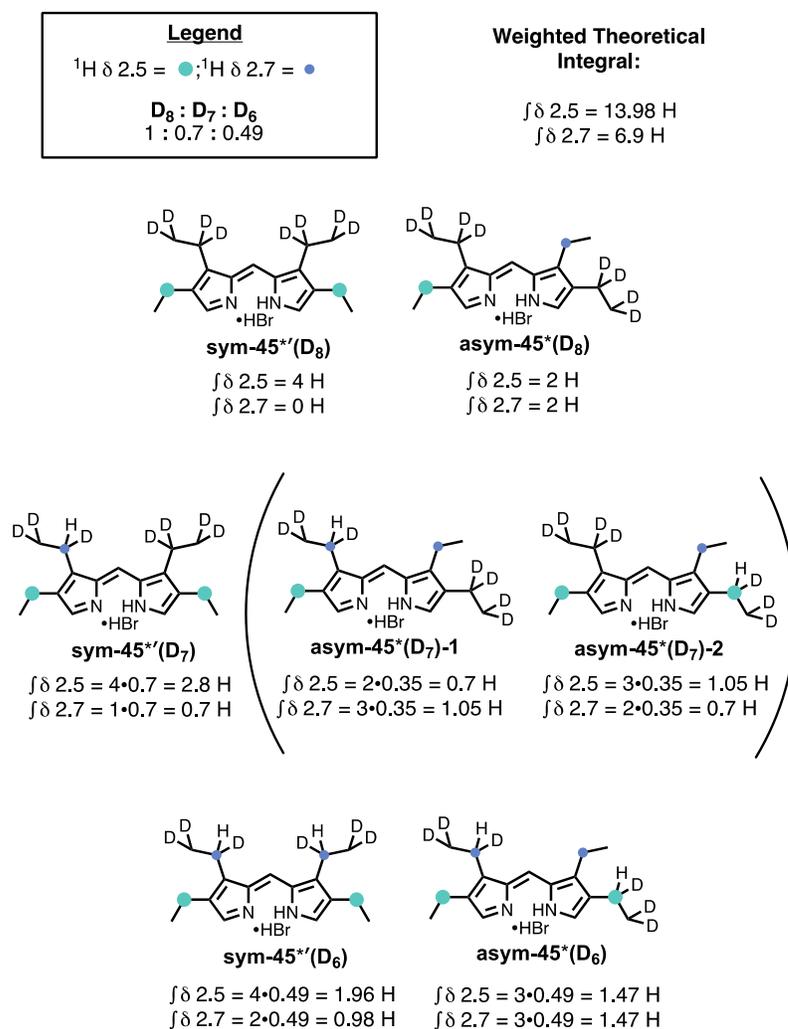


**Figure 19:  $^1\text{H}$  NMR Signal Assignment for  $\text{CH}_2$  and  $\text{CHD}$  Groups of Dipyrriin Mixtures 1 and 2; All  $\text{CH}_2$  and  $\text{CHD}$  Groups Colour-Coded According to the  $^1\text{H}$  NMR Signal to Which They Would Contribute**

Having established that all hydrogen atoms of the ethyl  $\text{CH}_2$  and  $\text{CHD}$  groups were countable through the signals at 2.5 and 2.7 ppm in the  $^1\text{H}$  NMR spectrum, we next determined the theoretical integral of the signals of interest, assuming that a 1:1 mixture of symmetric and asymmetric dipyrriins had formed. Having calculated the theoretical integration, we could then compare to the observed normalized  $^1\text{H}$  NMR signal integrals, and differences between the theoretical and observed values could then be analyzed. For example, if the actual integration of  $^1\text{H } \delta 2.7$  was normalized to the theoretical value, then the observed integration of  $^1\text{H } \delta 2.5$  should match the theoretical integration if and only if there is a 1:1 mixture of products. The choice of calculating integrals for a 1:1 mixture was arbitrary, and initially served only as a starting point for analysis. To determine the

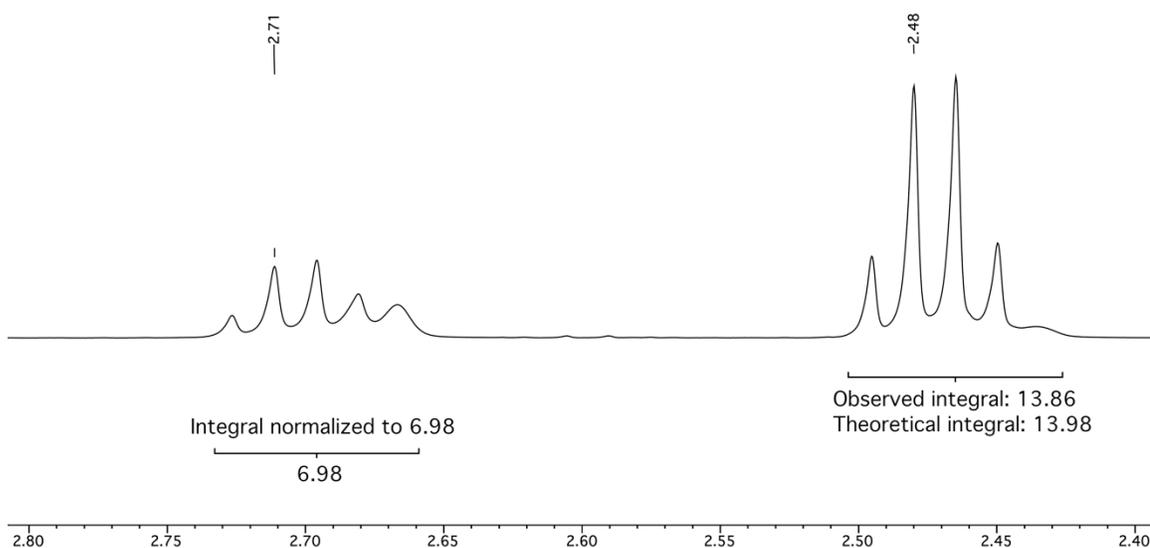


and asymmetric dipyrrens had formed, the weighted theoretical integrals for  $^1\text{H } \delta$  2.5 and  $^1\text{H } \delta$  2.7 were calculated accordingly, and determined to be 13.98 and 6.9, respectively. With the theoretical values calculated, if the observed integral of  $^1\text{H } \delta$  2.7 in the  $^1\text{H}$  spectrum of **Mixture 2** was normalized to the theoretical value (6.9 H), then the observed integration of  $^1\text{H } \delta$  2.5 should be 13.98 if a 1:1 mixture of symmetric and asymmetric products had formed. Any difference could be analyzed to aid in determining the product ratio.



**Figure 20: Weighted Theoretical Integrations of Sym-45\*' and Asym-45\* Within Dipyrren Mixture 2**

To our surprise, when the integral of the  $^1\text{H}$  signal at 2.7 ppm in the  $^1\text{H}$  NMR spectrum of **Mixture 2** was normalized to the theoretical value of 6.9 (Figure 21), the observed integral of the signal at 2.5 ppm closely matched the corresponding weighted theoretical value, 13.86 (observed) vs 13.98 (theoretical). The small difference between values was reasonable given the error expected from manually defining integral ranges. Assignment of integral ranges was performed a number of times by different researchers to determine typical variances as a result of manually defining integral range. In doing so, the observed differences were less than one hydrogen atom regardless of the researcher. We therefore assumed any observed difference of less than one between signal integrations was within reasonable error when manually defining integral ranges.



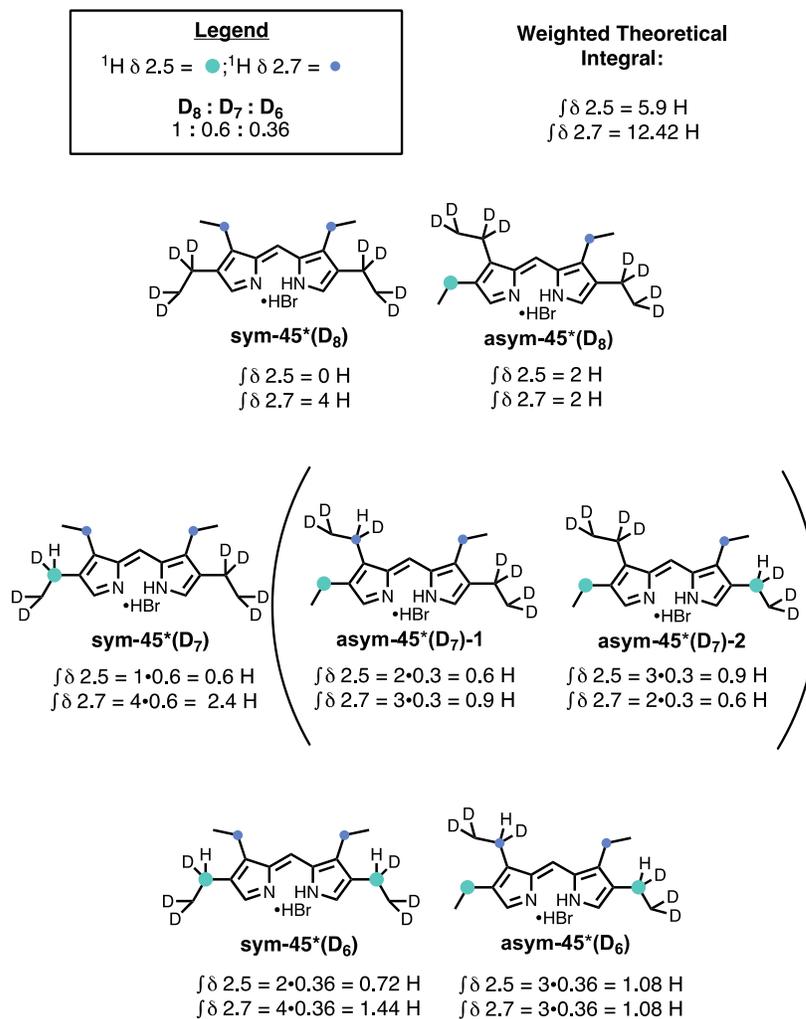
**Figure 21:  $^1\text{H}$  NMR Spectrum Collected from the Mixture of Sym-45\*' and Asym-45\* from 2.8-2.4 ppm Showing Only the  $\text{CH}_2/\text{CHD}$   $^1\text{H}$  Signals Arising at 2.7 and 2.5 ppm**

While not originally anticipated, alignment between the observed and theoretical integrals indicated there was no surplus or deficit of contributing hydrogen atoms, and therefore all dipyrrens were present in quantities predicted from the assumed 1:1 ratio.

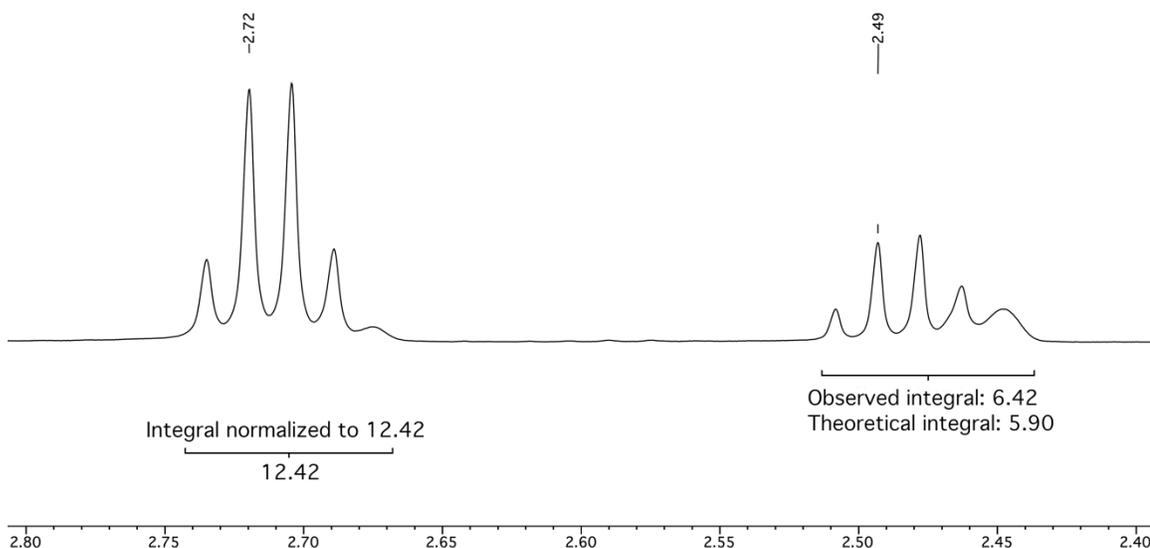
The key to this assertion is that the fully deuterated **sym-45\*(D<sub>8</sub>)** (Figure 20) does not have any contributing hydrogen atoms for signal <sup>1</sup>H δ 2.7. As **sym-45\*(D<sub>8</sub>)** does not contribute to this signal, if the observed ratio of symmetrical and asymmetrical dipyrin isomers varied from the anticipated 1:1 ratio, we should see a notable difference in the observed integrals compared to the theoretical. As we do not see this in the <sup>1</sup>H NMR spectrum collected from **Mixture 2**, we are confident in concluding that a 1:1 ratio of **sym-45\*** and **asym-45\*** dipyrins formed from the condensation of pyrrole mixture **41\***.

**Mixture 1** was analyzed in an identical fashion to **Mixture 2**, and the same conclusion was drawn, i.e. a 1:1 ratio of **sym-45\*** and **asym-45\*** dipyrins formed from the condensation of pyrrole mixture **41\***. The original ratio of D<sub>4</sub> to D<sub>3</sub> isomers of pyrrole mixture **41\*** was 1:0.6, thus, we would expect the D<sub>8</sub>:D<sub>7</sub>:D<sub>6</sub> ratio of deuterated dipyrins for **Mixture 1** to be 1:0.6:0.36. Applying this ratio to contributing hydrogen atoms of D<sub>7</sub> and D<sub>6</sub>-isomers, the weighted theoretical integrals for <sup>1</sup>H δ 2.7 and <sup>1</sup>H δ 2.5 within the <sup>1</sup>H NMR spectrum of **Mixture 1** were calculated to be 12.42 and 5.9, respectively (Figure 22). Normalizing the integral of <sup>1</sup>H δ 2.7 in the corresponding <sup>1</sup>H NMR spectrum (Figure 23) to the theoretical value, 12.42, we observed the integral of <sup>1</sup>H δ 2.5 to be 6.42. The difference between the observed integral of <sup>1</sup>H δ 2.5 (6.42) and the theoretical value (5.9) was 0.52, which falls within our range of reasonable error for manual integration (described above), and therefore we concluded that **sym-45\*** and **asym-45\*** dipyrins were present in a 1:1 ratio. Similar to **Mixture 2**, the key to this assertion arose from the fact that deuterated **sym-45\*(D<sub>8</sub>)** (Figure 22) does not have any contributing hydrogen atoms for signal <sup>1</sup>H δ 2.5. As described previously, if the observed ratio of symmetrical

and asymmetrical dipyrin isomers differed from the assumed 1:1 ratio, we would expect to see a notable difference in the observed integrals compared to the theoretical.



**Figure 22: Weighted Theoretical Integrations of Sym-45\* and Asym-45\* Within Dipyrin Mixture 1**



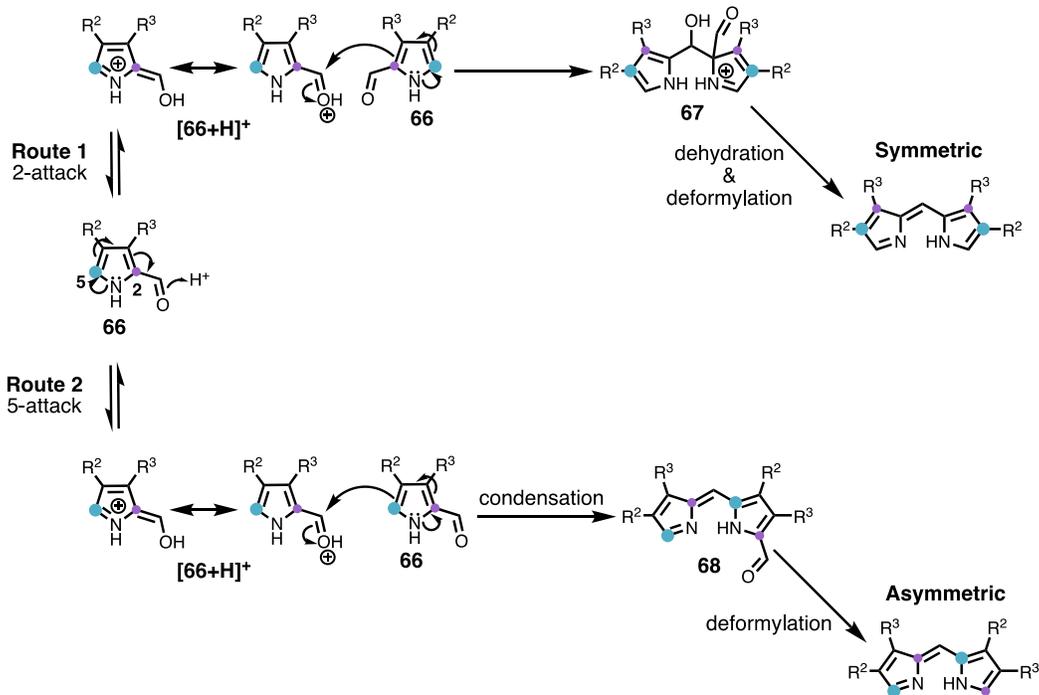
**Figure 23:  $^1\text{H}$  NMR Spectrum Collected from the Mixture of Sym-45\* and Asym-45\* from 2.8-2.4 ppm Showing Only the  $\text{CH}_2/\text{CHD}$   $^1\text{H}$  Signals Arising at 2.7 and 2.5 ppm**

Cognizant that the analysis of products resulting from the condensation of pyrrole mixtures **41\*** and **41\*'** was complicated by the presence of  $\text{D}_3$ - and  $\text{D}_4$ -analogous pyrroles and the resulting  $\text{D}_8$ -,  $\text{D}_7$ -, and  $\text{D}_6$ -dipyrrens, we remain confident in our assertion that a 1:1 ratio of products formed. Nevertheless, placing the analysis of product ratio aside, it is, at minimum, clear from the  $^1\text{H}$  NMR that a mixture of both symmetric and asymmetric dipyrrens formed from the self-condensation reactions of **41\*** and **41\*'.** For example, if only symmetric dipyrren **sym-45\*** was present within **Mixture 1**, then as a result the apparent quartet present as part of signal  $^1\text{H}$   $\delta$  2.5 would not be visible. Dipyrrens **sym-45\*(D<sub>8</sub>)**, **sym-45\*(D<sub>7</sub>)**, and **sym-45\*(D<sub>6</sub>)** have no  $\text{CH}_2$  groups which could contribute to an observable quartet-like signal at 2.5 ppm (Figure 22), and yet such a signal is present within the  $^1\text{H}$  NMR spectrum of **Mixture 1** (Figure 23), thus it is clear that asymmetric product was present. Additionally, if only **asym-45\*** had formed, we would expect to observe signals of approximately equivalent size at 2.5 and 2.7 ppm,

with equivalent integrals (Figure 22). As non-equivalent signals and integrals were observed in the  $^1\text{H}$  NMR spectrum of **Mixture 1** (Figure 23), it was concluded that **sym-45\*** and **asym-45\*** were both present.

At the outset, our goal for the production and reaction of **41\*** was to determine whether a single dipyrin, or a mixture of dipyrins would form, hoping to determine whether nucleophilic attack would originate from both  $\alpha$ -positions of the same pyrrole. Indeed, formation of both symmetric and asymmetric dipyrins was observed, thus confirming nucleophilic attack is capable of originating from both  $\alpha$ -positions of the same 2-formyl-5-H-pyrrole. In addition, we are now confident in the conclusion that self-condensation is capable of proceeding through two separate pathways (Scheme 31), whereby nucleophilic attack originates from either the 2- (Route 1)<sup>106</sup> or 5-position (Route 2) of a 2-formylpyrrole.

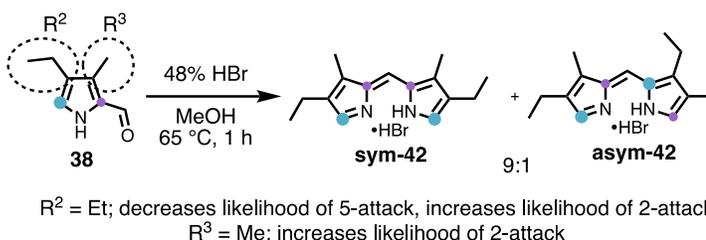
For the self-condensation of **40**, when  $\text{R}^2 = \text{R}^3 = \text{Me}$ , dipyrin formation appeared to be highly regioselective, proceeding only through Route 2 to produce  $\alpha$ -acetal and  $\alpha$ -formyl dipyrins **55** and **56**, respectively (Scheme 22). However, when  $\text{R}^2 = \text{R}^3 = \text{Et}$ , pyrroles **41\*** and **41\*'** , a mixture of symmetric and asymmetric products was observed (1:1 ratio). Formation of both symmetric and asymmetric products suggests that the increased steric bulk of the Et group of **41\*** and **41\*'**  decreased the nucleophilicity of the 5-position to a point where both Routes 1 and 2 are preferred, and thus a mixture was obtained. Further, obtaining a 1:1 ratio of products from both regioisomers, **41\*** and **41\*'** , indicates that the presence of deuterium atoms in the  $\text{R}^2$ - or  $\text{R}^3$ -positions had little effect on the outcome of the reaction.



**Scheme 31: Proposed Mechanistic Routes for Formation of Symmetric and Asymmetric Dipyrins from 2-Formyl-5-H-pyrroles**

Returning to the reaction of **38** (Scheme 32), which spurred our initial investigation, we believe that our findings are capable of rationalizing the 9:1 symmetric:asymmetric product ratio observed. Pyrrole **38** has a methyl group ( $R^2$ ) adjacent to the 2-formyl functionality and an ethyl group ( $R^3$ ) adjacent to the unsubstituted 5-position. As has been shown, when  $R^2 = \text{Et}$  the steric bulk of the ethyl group causes an observable decrease in nucleophilic attack originating from the 5-position, attack from which would furnish **asym-42** (Scheme 31, Route 2). Furthermore, when  $R^2 = \text{Et}$ , we begin to see nucleophilic attack originate from the 2-position, which would furnish **sym-42** (Scheme 31, Route 1). With respect to pyrrole **38**, the methyl group ( $R^3$ ) adjacent to the aldehyde is believed to further increase the likelihood of nucleophilic attack originating from the 2-position, when compared to the ethyl group

(R<sup>3</sup>) of pyrrole **38**. Our previous observations have indicated that the identity of R<sup>3</sup> has a diminished effect compared to R<sup>2</sup>. However, we suspect that the smaller steric presence of the methyl group would be additive with the effects of R<sup>2</sup> = Et. Thus, the combination of the effect of the presence of R<sup>2</sup> = Et and R<sup>3</sup> = Me is what we believe results in the 9:1 ratio of **sym-42:asym-42** that was observed from the self-condensation of pyrrole **38** (Scheme 32).



**Scheme 32: Self-condensation of Pyrrole 38 Resulting in a 9:1 Ratio of Dipyrrens Sym-42 and Asym-42**

### 3.4 Conclusions

In conclusion, the reaction mechanism for formation of *meso*-H-dipyrrens from 2-formyl-5-H-pyrroles was investigated. We were able to shed light on the reaction mechanism through the synthesis of several  $\alpha,\alpha'$ -unsubstituted dipyrrens (Table 8, **38-41**), and isotopically labelled counterparts. We found that nucleophilic attack can originate from the 2-formyl (Scheme 31, Route 1, **66**) or the unsubstituted 5-position (Route 2, **66**) of 2-formyl-5-H-pyrroles, resulting in symmetric or asymmetric regioisomers, respectively. Steric effects from the substituents in the 3- and 4-position appear to play a significant role in determining from which  $\alpha$ -position nucleophilic attack will be favoured, ultimately determining the ratio of symmetric and asymmetric products formed.

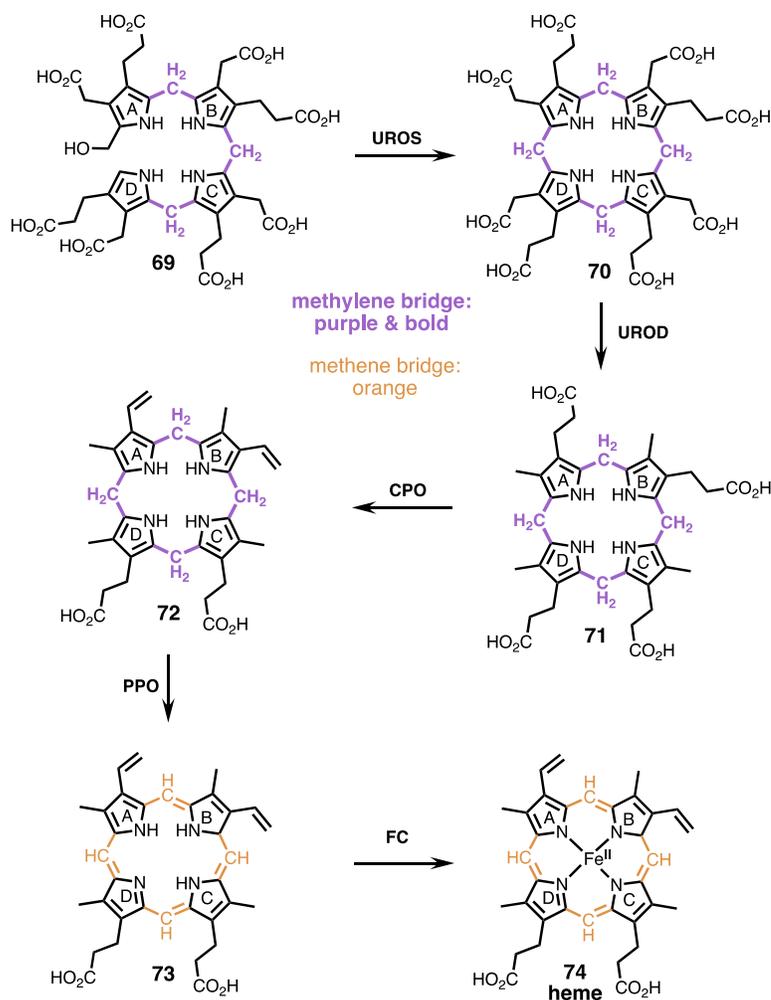
The published<sup>105</sup> self-condensation reaction of 2-formylpyrroles remains an efficient strategy for the synthesis of *meso*-H-dipyrrens, capable of furnishing dipyrrens in good to excellent yields and with good functional group tolerance (e.g. alkyl, keto, alkanoate, and conjugated esters). However, it is clear from our investigation that substitution around the pyrrole ring, or lack thereof, must be carefully considered.

## Chapter 4 – Towards Sulfur-bridged Tetrapyrroles

### 4.1 Introduction

Tetrapyrroles make up five substrates for enzymes in the biosynthesis of heme (Figure 24, **69-73**).<sup>217,218</sup> Of these, four substrates are porphyrinogens with methylene (-CH<sub>2</sub>-) bridges linking the pyrrole rings (**69-72**), and are inherently unstable as a result of the methylene bridges, which are known to undergo spontaneous and rapid oxidation in air.<sup>219</sup> Oxidation of the methylene bridges is driven by aromatization of the porphyrinogens, which furnishes much more stable aromatic porphyrins.<sup>220</sup> The instability of the porphyrinogens presents a challenging obstacle when creating analogues for studying the enzymatic pathway, as many synthetic analogues will be prone to the same spontaneous oxidation and thus will likely have short, non-useful, lifetimes. For example, the puckered tetrapyrrolic substrate linked by methylene bridges, uroporphyrinogen III (**70**, Figure 25, top left), is very susceptible to this oxidation. In the biosynthesis of heme, the four acetate groups of **70** are decarboxylated by uroporphyrinogen decarboxylase (UROD) to furnish **71** (Figure 24). However, oxidation of a single methylene bridge of **70**, to a methene bridge (=CH-), produces porphodimethene **75** (Figure 25, top right), which is the only known tetrapyrrolic inhibitor of heme biosynthesis as it targets the enzyme UROD.<sup>221</sup> Rapid and spontaneous oxidation of the remaining methylene bridges in **75** furnishes planar porphyrin **76** that is no longer an effective inhibitor of UROD, nor an active substrate.<sup>221</sup> The inability of enzymes to act upon such porphyrins is problematic, as the body will not be able to use or remove them easily, and the build-up of porphyrins like **76**, or those from tetrapyrroles **71**

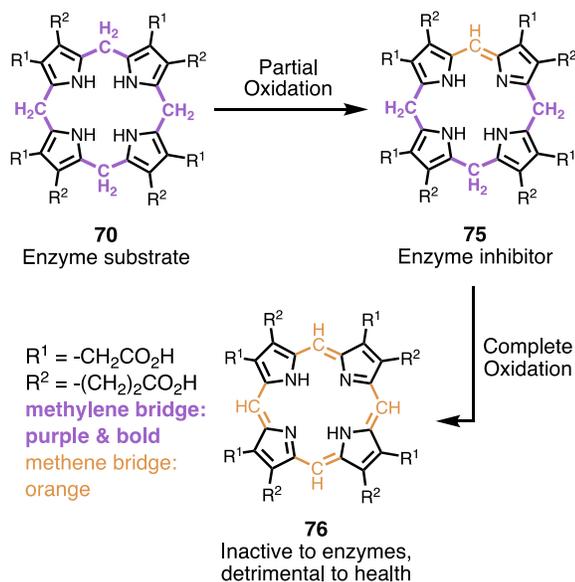
and **72**, can lead to serious health issues, e.g. a significant link between leukemia patients and a deleterious build-up of porphyrins has been identified.<sup>222</sup>



**Figure 24: Tetrapyrrolic Substrates in the Biosynthesis of Heme. Enzymes: Uroporphyrinogen III Synthase (UROS); Uroporphyrinogen III Decarboxylase (UROD); Coproporphyrinogen III Oxidase (CPO); Protoporphyrinogen IX Oxidase (PPO); Ferrochelatase (FC)**

The instability of natural substrates like **70** creates a niche for the utility of analogous air-stable molecules. Access to stable mimics of natural substrates would enable further study of the biosynthesis of heme. Bettering our understanding has long-term potential towards the development of drugs to treat diseases and health problems

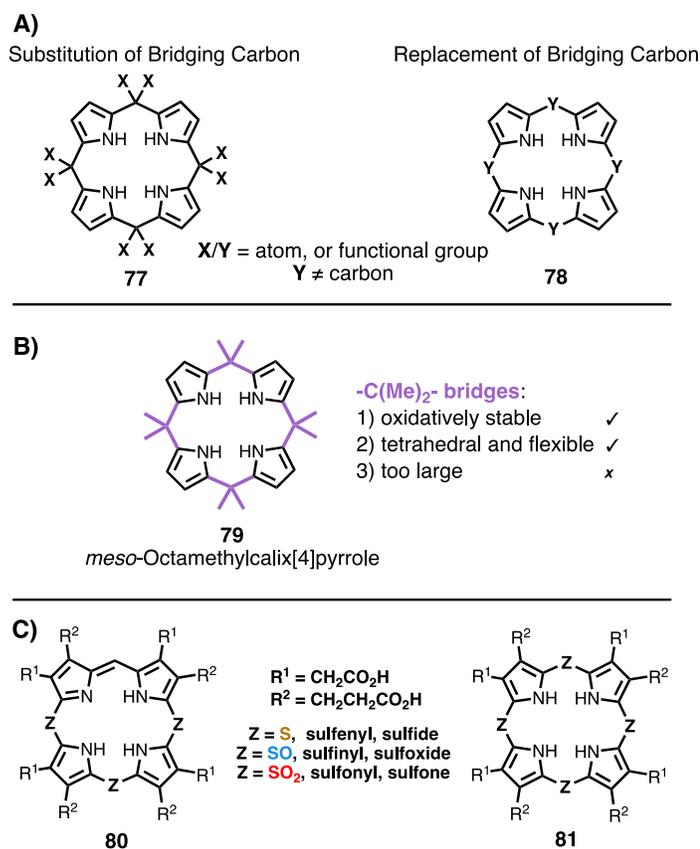
that originate from errors in heme biosynthesis; for example porphyria, cancer, and infections.<sup>221–224</sup>



**Figure 25: Spontaneous Oxidation of Tetrapyrrolic Substrates in the Biosynthesis of Heme**

A persistent area of research in the Thompson group has been the preparation of air-stable tetrapyrrolic substrates analogous to the porphyrinogens found in the biosynthesis of heme (Figure 24). With **70** and **75** (Figure 25) serving as substrate and inhibitor, respectively, of UROD, replacement of the methylene bridge such as to reduce the propensity for oxidation is an attractive strategy to air-stable analogues with inhibiting potential. Indeed, with the desire to create air-stable tetrapyrroles, our work has focused on replacing the methylene bridges of porphyrinogens, like **70**, with more stable and resistant groups of similarly tetrahedral geometry. This could be achieved in one of two ways: substitution of the bridging carbon atom (**77**, Figure 26A), or replacement of the bridging carbon atom in its entirety (**78**, Figure 26A). In order to functionalize or

replace any of the methylene bridges, a new bridge must meet three requirements: 1) it must not be susceptible to oxidation, 2) it must be sufficiently flexible to allow ring-puckering, which is vital for active-site binding<sup>219,221</sup> in enzymes like UROD, and 3) it must be of sufficiently small size to fit in the enzyme active site. As an example, *meso*-octamethylcalix[4]pyrrole (**79**, Figure 26B) meets the first two requirements, but not the third. The methyl substituted  $sp^3$ -bridges are not susceptible to oxidation (requirement 1) and their  $sp^3$ -hybridization infers sufficient flexibility to adapt a puckered ring geometry (requirement 2).<sup>225</sup> However, the methyl groups on the bridging carbon atom provide steric bulk that would inhibit binding within the active site of UROD (requirement 3).<sup>226</sup> When a suitable replacement for the methylene bridges is devised, one that meets these three stipulations, we must then begin exploring methodological approaches for introducing the theorized functionalization between pyrrole units.

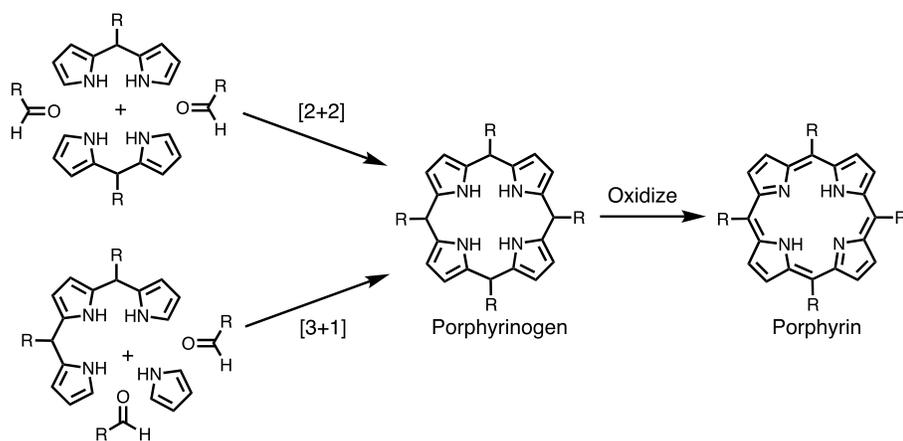


**Figure 26: A) Examples of Substitution and Replacement of Bridging Carbon Atoms of Tetrapyrroles; B) *meso*-Octamethylcalix[4]pyrrole and Comparing it to Our Three Bridge Requirements; C) Targeted Sulfur-bridged Tetrapyrroles**

Previous work in the Thompson lab explored substituting the bridging carbon atom of tetrapyrroles with fluorine atoms, i.e. preparing tetrapyrroles joined with -CF<sub>2</sub>- bridges (Figure 26A, **77** X = F).<sup>227</sup> Fluorine atoms are common bioisosteres for hydrogen atoms, because they are of similar atomic size but the C-F bond is notably stronger than that of a C-H bond (bond dissociation energies of 413 kJ/mol and 485 kJ/mol for C-H and C-F bonds, respectively).<sup>228</sup> Unfortunately this work was unsuccessful in yielding a route to tetrapyrroles. As a continuation of this area of research, we began to explore the synthesis of new analogues to the heme biosynthesis, tetrapyrrolic compounds with sulfur-based bridges linking the four pyrrolic units (Figure 26C). When referring to sulfur

containing organic compounds, common nomenclature used in the literature is based on the oxidation state of the sulfur atom: sulfide (-S-), sulfoxide (-SO-), and sulfone (-SO<sub>2</sub>-).<sup>7229–231</sup> For example, two pyrroles connected via a -SO<sub>2</sub>- bridge is referred to as a dipyrrolyl sulfone. However, when referring to the -SO<sub>2</sub>- moiety specifically, it would be a sulfonyl bridge. The two pyrrole units of a dipyrrolyl sulfoxide are linked by a sulfinyl (-SO-) bridge, and a dipyrrolyl sulfide is connected by a sulfenyl (-S-) bridge.

Sulfur was chosen due to the tetrahedral-like geometries available in the three states of oxidation (i.e. sulfide, sulfoxide, and sulfone). Similar in geometry to the methylene bridge,<sup>232,233</sup> we hypothesized that the sulfur groups would allow such tetrapyrroles to adopt the puckered geometry required for effective binding in the active site of enzymes with tetrapyrrolic substrates, specifically UROD. Computational work, performed in collaboration,<sup>226</sup> supported this hypothesis by showing that a tetrapyrrole with any number of sulfur-bridges (1-4), and at any oxidation state (S, sulfenyl; SO, sulfinyl; or SO<sub>2</sub>, sulfonyl), would be stable and capable of fitting within the active site of optimized model human UROD. Our approach to the synthesis of such tetrapyrroles was adapted from traditional synthetic methodology towards porphyrin; involving the condensation of pyrroles with aldehydes to produce a porphyrinogen (Scheme 33). Subsequent oxidation furnishes the desired porphyrin. The synthesis of porphyrinogens can be approached in two general manners: [2+2], wherein two dipyrrolic ‘halves’ react with two equivalents of aldehyde to furnish a tetrapyrrole; or [3+1], wherein pyrrole reacts with equal amounts of aldehyde and builds sequentially to a tetrapyrrole, i.e. a monopyrrole reacts to form a dipyrrole, which undergoes a subsequent reaction to form a tripyrrole, and the tripyrrole then to a tetrapyrrole.<sup>234</sup>



**Scheme 33: [2+2] and [3+1] Synthetic Approaches to Porphyrin Synthesis**

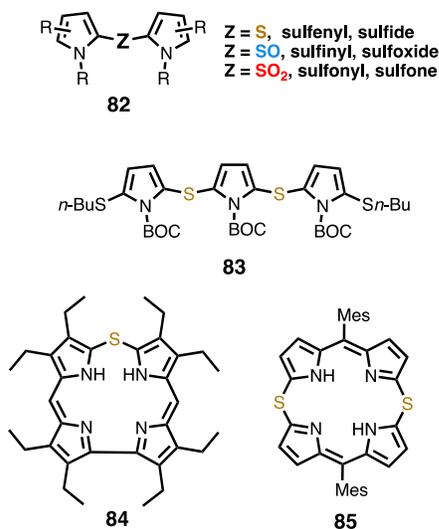
## 4.2 Project Goals

Ultimately, the goal of this project was to replace the bridging carbon atom of compounds like **70** and **75** with sulfur-based groups for the purpose of preparing air-stable mimics of tetrapyrrolic substrates in the biosynthesis of heme, such as **80** and **81** (Figure 26B). The literature regarding such synthetic work is very limited, and as such this project was heavily dependent on fundamental discovery-based synthetic chemistry. The first step, and primary goal driving our efforts, was the development of reliable synthetic methods to sulfur-bridged (poly)pyrroles, i.e. di-, tri-, and tetrapyrroles. Non-polymeric and non-oligomeric compounds made up of multiple pyrroles are commonly referred to as (poly)pyrroles.

To the best of our knowledge there exist only a few reported examples of sulfur-bridged dipyrroles (Figure 27, **82**);<sup>229,235–239</sup> one example of a sulfur-bridged tripyrrole with two bridging sulfur atoms (Figure 27, **83**), and two examples of sulfur-bridged

tetrapyrroles with one, and two, bridging sulfur atoms (Figure 27, **84** and **85**).

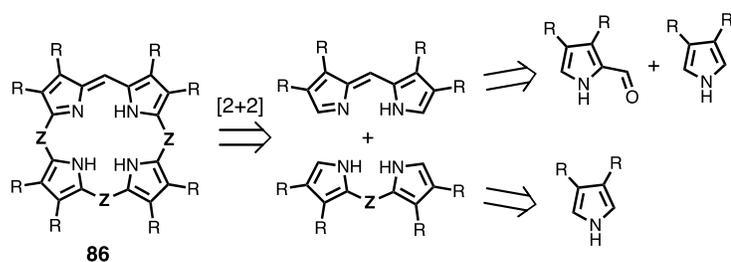
Tetrapyrroles with three or four bridging sulfur atoms are unknown.



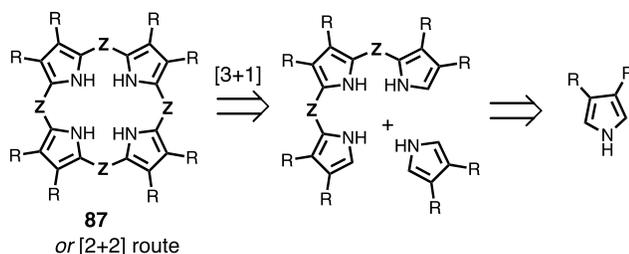
**Figure 27: Examples of Known Sulfur-bridged Pyrroles**

Our synthetic design towards sulfur-bridged tetrapyrroles was analogous to porphyrin chemistry, proposing both the [2+2] and [1+3] methods as potential routes (Scheme 34). Cognizant that no tetrapyrroles with three or four sulfur-bridges were known to exist, we first simplified the targets to bear substituents more readily available in pyrrole chemistry, such as simple alkyl, acyl, or ester groups. Thus, our initial targets became tetrapyrroles **86** and **87** (Scheme 34). We believed the simplest route to tetrapyrrole **86** (Scheme 34, top) would be the [2+2] approach, as it would allow separate syntheses of the dipyrin and sulfur-bridged dipyrrolic halves, with the final step linking the two halves into the desired cyclic tetrapyrrole. We proposed that tetrapyrrole **87** (Scheme 34, bottom) could be prepared from both the [3+1] and [2+2] approach; a [3+1] synthesis analogous to that of calix[4]pyrroles self-assembly,<sup>240–242</sup> or [2+2] via separately prepared sulfur-bridged dipyrrole halves akin to the retrosynthesis of

tetrapyrrole **86**. No matter the route chosen, or the target, the first hurdle was the synthesis of sulfur-bridged dipyrroles. Keeping true to the theme of simplicity, our first synthetic target was to join pyrrole moieties via any of the three sulfur-based bridges (Scheme 34, Z = S, SO, or SO<sub>2</sub>). Literature precedent<sup>235</sup> with pyrroles supports that once a sulfur-bridged dipyrrole is in hand, there is the potential to access the higher or lower oxidation state analogues at the sulfur atom. Aryl sulfides can be selectively oxidized to sulfoxides or sulfones using *m*CPBA.<sup>235</sup> In addition, sulfones and sulfoxides can be reduced to sulfides, non-selectively, via deoxygenative atom transfer to a phosphine, such as triphenyl phosphine (PPh<sub>3</sub>).<sup>243,244</sup>



R = alkyl, acyl, ester  
 Z = S, SO, SO<sub>2</sub>

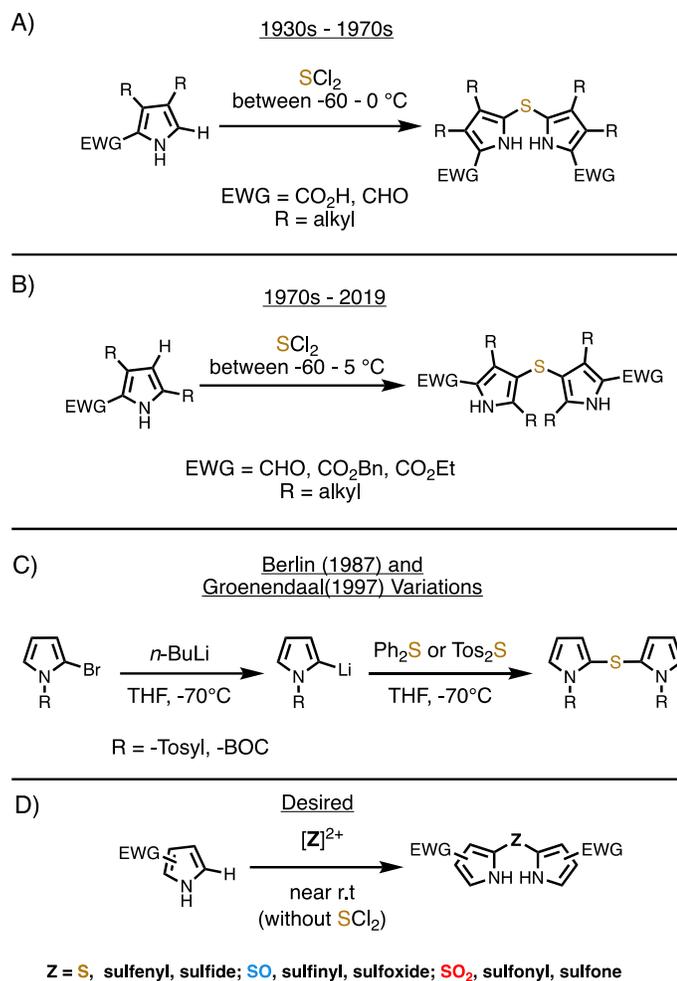


**Scheme 34: Retrosynthetic Approach Towards Sulfur-bridged Tetrapyrroles Containing Three (Top) and Four (Bottom) Sulfur-bridges.**

## 4.3 Results and Discussion

### 4.3.1 Synthesis of Dipyrrolyl Sulfides using Thionyl Chloride

Dipyrrolyl sulfides, two pyrroles linked via a sulfenyl bridge (Figure 28), have been known since the 1930s<sup>245</sup> and are the most prevalent sulfur-bridged pyrroles in the literature. The most common application of dipyrrolyl sulfides involves the preparation of thiacorroles and thiaporphyrinoids, (Figure 27, **84** and **85**, respectively),<sup>246–248</sup> and subsequent metal complexes.<sup>237,249</sup> Since their discovery the synthesis of dipyrrolyl sulfides has remained mostly unchanged and has involved the reaction of a pyrrole with sulfur dichloride (SCl<sub>2</sub>) to produce the desired dipyrrolyl sulfide (Figure 28A & B).<sup>229,230,245,247</sup> From the 1930s to the 1970s (Figure 28A) a variety of  $\alpha$ -free pyrroles, bearing electron-withdrawing formyl or carboxylic acid groups, were reacted with SCl<sub>2</sub> at, or below, 0 °C to furnish the requisite dipyrrolyl sulfides. From the 1970s onwards, using nearly identical conditions, the substrate scope was expanded to include  $\beta$ -free pyrroles appended with electron-withdrawing benzyl or ethyl esters, and formyl groups (Figure 28B).<sup>229</sup> Both pyrroles and sulfenyl groups are electron-rich nucleophilic species, meaning they are chemical species that have a propensity for reacting as a nucleophile. The combination of two electron-rich species such as these would be expected to yield a very electron-rich and nucleophilic product. Thus electron-withdrawing groups, which can attenuate the electron-rich nature of these compounds and control reactivity, would play a significant role in stabilizing the final product.



**Figure 28: Synthesis of Dipyrrolyl Sulfides Throughout History: A) Original Synthesis of 2,2'-Dipyrrolyl Sulfides Using SCl<sub>2</sub>; B) Expansion of Substrate Scope to Include 3,3'-Dipyrrolyl Sulfides using SCl<sub>2</sub> According to Chen et al.; C) SCl<sub>2</sub>-free Variations Reported by Berlin et al. and Groenendaal et al.; D) Desired SCl<sub>2</sub>-free Reaction.**

One variation, and the first example of a 3,4,5-unsubstituted pyrrole being used for the preparation of a dipyrrolyl sulfide, was presented in 1987 by Berlin et al.<sup>239</sup> and involved the preparation of an N,N'-ditosyl dipyrrolyl sulfide (Figure 28C). The reaction of  $\alpha$ -bromo-N-tosyl pyrrole with *n*-BuLi generated the analogous  $\alpha$ -lithiopyrrole, *in situ* via lithium-halogen exchange, which was subsequently reacted with bis(phenylsulfonyl) sulfide to furnish a dipyrrolyl sulfide. This was later expanded upon in 1997, by

Groenendaal et al.,<sup>235</sup> to prepare N,N'-diBOC dipyrrolyl sulfides in the same manner using bis(tosyl) sulfide (Figure 28C). These publications presented an alternative to using SCl<sub>2</sub>, however, the use of the strong base *n*-BuLi precludes use of  $\alpha$ -bromo pyrroles that contain base-sensitive substitution, such as carbonyl, ester, or alkyl moieties. The benzylic-like hydrogen atoms of an alkyl substituted pyrrole are very weakly acidic (pKa ~40-45), rendering *n*-BuLi (pKa ~50) of sufficient strength to effect their deprotonation. Further, deprotection of the pyrrolic nitrogen (i.e. removal of BOC or Tosyl) in the reported dipyrrolyl sulfides proved to be challenging as Groenendaal et al.<sup>235</sup> reported decomposition upon attempted removal of BOC protecting groups. Berlin et al.<sup>239</sup> reported the successful removal of the Tos protecting group of the single reported dipyrrolyl sulfide under basic conditions (MeOH, NaOH, reflux, 90%). While deprotection was successful, Berlin et al reported that the resulting deprotected dipyrrolyl sulfide possessed “only moderate stability to air and light at room temperature”. The described issues with suitably substituted  $\alpha$ -bromo pyrroles and N-deprotection made this methodology unattractive.

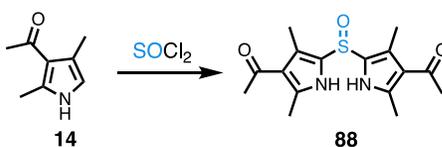
The simplicity of syntheses using SCl<sub>2</sub> were most attractive, although not easily accessible to researchers in Canada. Sulfur dichloride is not commercially available within Canada and producing the chemical in lab on a modest scale is quite challenging and dangerous, as it requires chlorination of sulfur chloride, S<sub>2</sub>Cl<sub>2</sub>, with Cl<sub>2</sub> gas.<sup>250</sup> As such, to avoid use of SCl<sub>2</sub>, we sought to evaluate the utility of other sulfur sources for the purposes of linking two pyrroles via a sulfur-based bridge (Figure 28D). The computational work performed with sulfur-bridged tetrapyrroles<sup>226</sup> showed that sulfur-bridges at any oxidation state (S, sulfenyl; SO, sulfinyl; or SO<sub>2</sub>, sulfonyl) would be

suitable. Thus, in terms of identifying an alternate sulfur source to  $\text{SCl}_2$ , reagents containing sulfur at any of the three oxidation states were considered. The first sulfur source considered was thionyl chloride ( $\text{SOCl}_2$ ), because it contains a suitable sulfoxide centre and two chloro substituents which could act as leaving groups in a substitution reaction with a pyrrole nucleophile.

Reacting arenes, such as benzene or thiophene, with  $\text{SOCl}_2$  in the presence of a catalyst is known to produce sulfinyl bridged diarenes.<sup>251–255</sup> In general, the catalyst activates the S-Cl bond, increasing the electrophilicity of the sulfur centre and thus the rate at which the sulfur centre undergoes substitution by the weakly nucleophilic arenes. A common issue associated with the use of thionyl chloride is production of unwanted chlorinated by-products.<sup>235,253,256,257</sup>  $\text{SOCl}_2$  is a reactive chlorinating agent, and is known to generate equally potent chlorinating agents *in situ*, such as  $\text{Cl}_2$  gas and  $\text{SO}_2\text{Cl}_2$ ,<sup>256,258</sup> and therefore a degree of chlorination is to be expected. We initially hypothesized that the reaction of  $\text{SOCl}_2$  with pyrrole could be a route to sulfinyl bridged pyrroles, and the increased nucleophilicity of pyrrole, compared to benzene and thiophene, would enable catalyst free reactions. To the best of our knowledge, at the outset of this work, there was only one example of a sulfinyl bridged dipyrrole synthesized from  $\text{SOCl}_2$  in the literature, reported by Groenendaal et al. in 1997.<sup>235</sup> In addition to the synthesis of N,N'-diBOC dipyrrolyl sulfides (Figure 28C), Groenendaal and colleagues reported the reaction of  $\alpha$ -bromo-N-BOC pyrrole with *n*BuLi, followed by  $\text{SOCl}_2$ , to prepare the requisite N,N'-diBOC dipyrrolyl sulfoxide. Presumably, the  $\alpha$ -bromo pyrrole underwent lithium halogen exchange with *n*BuLi to prepare the  $\alpha$ -lithio pyrrole, a strong nucleophile. Two equivalents of lithiated pyrrole then react with  $\text{SOCl}_2$  via nucleophilic substitution at the

sulfur centre, with loss of chloride as a leaving group, to furnish the final N,N'-diBOC dipyrrolyl sulfoxide. As previously discussed, use of strong bases, limitations regarding  $\alpha$ -bromo pyrroles bearing substitution sensitive to base deprotection, and N-deprotection made this methodology unattractive. Furthermore, the nitrogen atoms of tetrapyrroles are vital for the binding within enzymes of the biosynthesis of heme,<sup>217,218</sup> and as such pyrroles substituted at the pyrrolic nitrogen are less desirable due to the inevitable requirement to remove the substituents/protecting groups at the nitrogen.

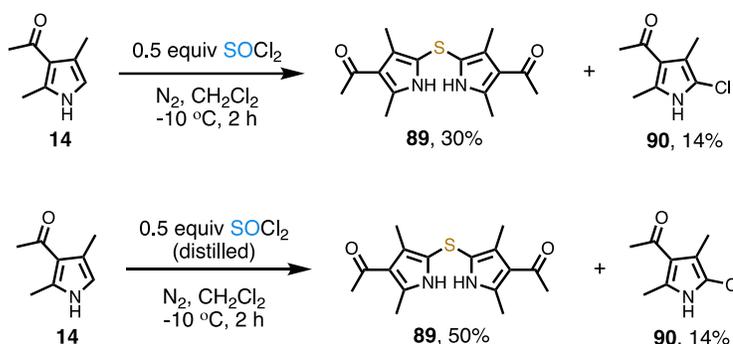
To the best of our knowledge, there are no known examples for the preparation of sulfinyl bridged dipyrroles from  $\text{SOCl}_2$  and N-H pyrroles, i.e. pyrroles unsubstituted at the nitrogen. We sought to explore whether the reaction of an N-H pyrrole and  $\text{SOCl}_2$  could, in the absence of a strong base or catalyst, be a route to sulfinyl bridged dipyrroles. The N-H pyrrole **14** (Scheme 35) was used to explore the reaction of N-H pyrroles with  $\text{SOCl}_2$ . Pyrrole **14** was selected for the stabilizing effects imparted by the electron-withdrawing acyl group, which were anticipated to be beneficial,<sup>229,230</sup> and the ease with which it could be prepared on a large scale.<sup>81</sup>



### Scheme 35: Proposed Reaction of N-H Pyrrole **14** and $\text{SOCl}_2$ as a Route to Dipyrrolyl Sulfoxide **88**

To begin our investigations, pyrrole **14** was reacted with 0.5 equivalents of  $\text{SOCl}_2$  under inert nitrogen atmosphere at  $-10\text{ }^\circ\text{C}$  until complete consumption of starting material was observed via TLC, i.e. 2 h (Scheme 36, top). The reaction temperature and solvent were adapted from Chen and Dolphin's reported reaction of pyrroles with  $\text{SCl}_2$ .<sup>229</sup> The

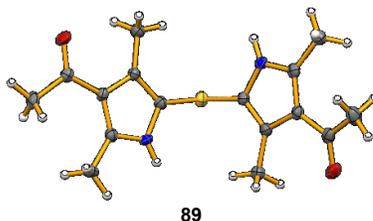
2:1 ratio of **14** to  $\text{SOCl}_2$  was based on the desired product, **88**, containing two pyrrole moieties joined by a sulfinyl bridge. To our surprise, the previously unknown dipyrrolyl sulfide **89** was isolated in 30% yield (Scheme 36, top). Sulfide **89** is stable on benchtop under atmospheric conditions for at least 3 years. In addition, chlorinated pyrrole **90** was isolated in a 14% yield, the presence of which was expected as  $\text{SOCl}_2$  is a known chlorinating agent and is known to generate equally potent chlorinating agents *in situ*, such as  $\text{Cl}_2$  gas and  $\text{SO}_2\text{Cl}_2$ .



**Scheme 36: Synthesis of Dipyrrolyl Sulfide **89** with ‘From the Bottle’ and Freshly Distilled  $\text{SOCl}_2$**

The structure of **89** was elucidated using NMR spectroscopy and HRMS, and confirmed by X-ray crystallographic analysis. Three methyl signals were present in the  $^1\text{H}$  NMR spectrum collected for **89**, but a signal for the  $\alpha$ -H of pyrrole **14** was not, therefore confirming that the isolated product was not still pyrrole starting material. From the  $^1\text{H}$  NMR spectrum alone we could not identify whether a dipyrrolyl sulfoxide, or sulfide, had formed. The HRMS spectrum reported an accurate mass corresponding to two units of pyrrole **14** linked via a sulfenyl (-S-) bridge, indicating **89** was a dipyrrolyl sulfide. Finally, crystals of **89** were grown and then analyzed by Dr. Katherine Robertson, St. Mary’s University, via single crystal X-ray diffraction, fully elucidating

the structure of **89** and unequivocally confirming the presence of the sulfenyl bridge (Figure 29). The fact that a sulfenyl bridge was present in **89** indicated one of two things: either reduction of the sulfur atom of  $\text{SOCl}_2$  had occurred during or subsequent to the reaction, or that a significant impurity was present in the  $\text{SOCl}_2$  that interfered during the reaction.



**Figure 29: Crystal Structure of Dipyrrolyl Sulfide 89 (S = yellow, N = blue, O = red, C = grey, H = white)**

Our first course of action was to rule out any impurities in the  $\text{SOCl}_2$ , as both sulfur dichloride ( $\text{SCl}_2$ ) and sulfur monochloride ( $\text{S}_2\text{Cl}_2$ ) are common impurities,<sup>258</sup> either of which could have been responsible for the formation of the sulfenyl bridge in the isolated product. Thionyl chloride was purified following literature procedure<sup>259</sup> under ambient conditions via two separate fractional distillations with triphenyl phosphite, venting through  $\text{CaCl}_2$ . The second distillation furnished thionyl chloride boiling at 75-76 °C under atmospheric pressure with a faint yellow colour when in large quantity, matching the literature<sup>259</sup> for pure thionyl chloride under atmospheric pressure. Pyrrole **14** was then treated with the freshly distilled (same day)  $\text{SOCl}_2$ . After complete consumption of starting material had been observed via TLC (2 h), **89** was again isolated as the major product, now in a 50% yield (Scheme 36, bottom). The fact that the yield of **89** increased and remained the major product when using freshly distilled  $\text{SOCl}_2$  supported that impurities were not an appreciable source of **89**.

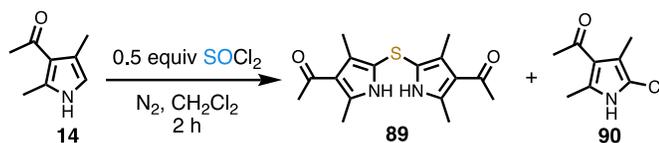
Curiously, the yield of the halogenated pyrrole **90** remained unchanged at 14%. The unchanging yield of **90** from both reactions of **14** with unpurified and distilled SOCl<sub>2</sub> (Scheme 36) made us suspect **90** could potentially be a synthetic intermediate. To investigate the role of **90**, the chlorinated pyrrole was subjected to the same reaction conditions as **14** with distilled SOCl<sub>2</sub> (Scheme 36, bottom). After 2 h at -10 °C, no reaction was observed, which indicated that pyrrole **90** was most likely an unproductive by-product of the reaction, not a synthetic intermediate, and the identical yields were coincidental.

#### **4.3.2 Investigation of the Effects of Temperature and Equivalents of SOCl<sub>2</sub> upon the Synthesis of Dipyrrolyl Sulfides from SOCl<sub>2</sub>**

Having ruled out impurities as the source of dipyrrolyl sulfide **89**, it appeared that an intermediate during the reaction of **14** and SOCl<sub>2</sub> must be undergoing a reduction in order to produce the sulfenyl bridge present in **89**. This prompted us to explore whether we could successfully isolate, or observe the formation of, the dipyrrolyl sulfoxide (**88**, Scheme 35) if the reaction were carried out at a lower temperature (Table 9, entry 1). We found that decreasing the temperature to -76 °C had no noticeable effect compared to the reaction performed at -10 °C (compare entries 1 and 2), both reactions producing **89** in ~50% yield after 2 h. Monitoring the reactions simultaneously via thin-layer chromatography showed only steady consumption of pyrrole **14**, and production of sulfide **89** and chlorinated pyrrole **90** over the 2-h reaction time. At no point during either reaction was formation of sulfoxide **88**, or other intermediates, observed indicating that reduction must be fast on the reaction scale. We now looked to optimize the reaction

conditions, hoping to increase the yield of **89** past 50%. Attempting the synthesis of **89** above -10 °C proved only detrimental, resulting in a notably lower yield at 0 °C (entry 3) and observed production of an intractable tar at room temperature (entry 4). Thus, -10 °C was determined to be the optimal reaction temperature.

**Table 9: Exploring the Effect of Temperature on the Synthesis of **89** from SOCl<sub>2</sub>**

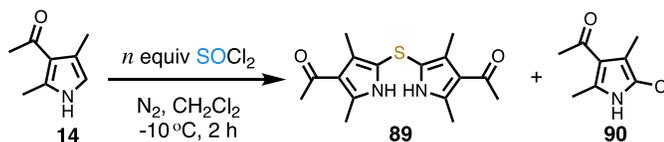


Entry	Temperature (°C)	Yield of <b>89</b> (%)	Yield of <b>90</b> (%)
1	-76	46	16
2	-10	50	14
3	0	23	14
4	23 (rt)	0 <sup>a</sup>	0 <sup>a</sup>

<sup>a</sup>Intractable tar

Without the presence of an obvious reducing agent, we suspected that the SOCl<sub>2</sub> was acting as a sacrificial reductant as well as source of the sulfenyl bridge during the synthesis of **89**. Assuming SOCl<sub>2</sub> was acting as *both* the source of, and reductant for, the production of the sulfenyl bridged **89**, we explored the effect of SOCl<sub>2</sub> equivalents on the yield of **89** and **90** (Table 10). Under this assumption, a 1:1 ratio of pyrrole **14** to SOCl<sub>2</sub> would have been required in order to furnish sulfide **89** in greater than 50% yield, not the 2:1 ratio used previously (Scheme 36). Using 1.0 equivalent of SOCl<sub>2</sub>, with respect to pyrrole **14**, had no positive effect on the isolated yield of **89** or **90** when compared to the same reaction using 0.5 equivalents (compare entry 4 and entry 1). The use of any more than 1.0 equivalent of SOCl<sub>2</sub> was ineffective in promoting an increase in yield of **89** (entries 5-8). Addition of only 0.8 equivalents of SOCl<sub>2</sub> furnished a modest increase, with

**89** being isolated in 60% yield (entry 2). Increasing SOCl<sub>2</sub> equivalents to 0.9 (entry 3) reduced the yield to 50%. The 0.4 mmol scale, with respect to pyrrole **14**, that these reactions were carried out on required the addition of SOCl<sub>2</sub> on the order of microlitres, depending on the equivalents used. On this scale, the difference between 0.8 and 1.0 equivalent was, on average, 6 μL. While the difference between 0.8 and 1.0 equivalents is small, the effects each had were remarkably consistent, and we are confident in the reported results. We believed that the SOCl<sub>2</sub> was in fact acting as a reductant in addition to acting as the source of the sulfur-bridge, evidenced by the 60% yield from the use of 0.8 equivalents. We attributed the decrease in yield of the desired product, and increase in formation of byproducts, when using any more than 0.8 equivalents of SOCl<sub>2</sub> to the inherent reactive and electrophilic nature of SOCl<sub>2</sub>. The use of 0.8 equivalents of SOCl<sub>2</sub> appeared optimal, leading to a reproducible 60% isolated yield of **89** (reaction performed on 3 separate occasions, on different days). As stated, the use of additional SOCl<sub>2</sub> only proved to reduce the yield of **89**, presumably due to unproductive side-reactions as a result of off-target reactivity. Pyrroles are known to polymerize under weakly acidic conditions,<sup>36</sup> of which SOCl<sub>2</sub> can produce via *in situ* generation of hydrochloric acid.<sup>260,261</sup> Both pyrrole **14** and **90** could be subject to this polymerization, and certainly the observed formation of polymer-like tar suggests so.

**Table 10: Effects of SOCl<sub>2</sub> Equivalents on the Synthesis of 89**

Entry	Equiv. of $\text{SOCl}_2$ ( $n$ )	Yield of 89 (%)	Yield of 90 (%)
1	0.5	50	14
2	0.8	60	16
3	0.9	50	20
4	1.0	48	23
5	1.1	43	14
6	3	48	13
7	5	50	13
8	7	37	14

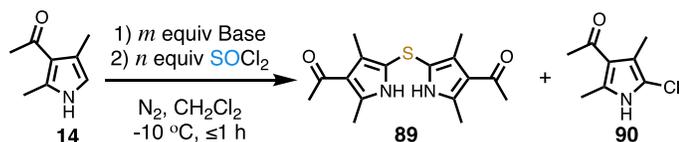
### 4.3.3 Investigation of the Effects of Nitrogenous Bases upon the Synthesis of Dipyrryl Sulfides from $\text{SOCl}_2$

Noting that pyrroles are prone to polymerize under weakly acidic conditions, we looked towards the addition of mild organic nitrogenous bases to the reaction mixture in order to neutralize acids generated *in situ*. Following the assumption that  $\text{SOCl}_2$  is acting as both sulfur source, and reductant, for the synthesis of **89**, we would expect the reaction to have a maximum yield of 80% when using 0.8 equivalents of  $\text{SOCl}_2$  (calculated from pyrrole **14**). It was our hope that addition of an organic base would remove the detrimental effects observed when using larger quantities of  $\text{SOCl}_2$  and thus increase the yield of **89**. Addition of 1.1 equivalents of  $\text{NEt}_3$  ( $\text{pK}_a$  of conjugate acid: 10.8)<sup>262</sup> to a solution of pyrrole **14** in  $\text{CH}_2\text{Cl}_2$ , followed by the addition of 0.8 equivalents of  $\text{SOCl}_2$  (Table 11, entry 1) drastically increased reaction rate. Indeed, consumption of starting material was

observed after 25 min using TLC and the reaction furnished **89** with an increased and reproducible yield of 70% (reaction performed numerous times over the span of several months). Allowing the reaction mixture to stir for 2 h (i.e. length of reaction without adding NEt<sub>3</sub>) did not result in any increase in yield above what was isolated after 25 min (entry 2). The use of 1.1 equivalents of SOCl<sub>2</sub> in the presence of base resulted in a significant decrease in yield of **89** (entry 3). In addition, more equivalents of NEt<sub>3</sub> resulted in similar decreases in yield of **89** (entries 4 and 5). Order of addition proved vital, with NEt<sub>3</sub> being added first to produce best effects (compare entries 1 and 6). Preliminary conclusions indicated the use of base to be advantageous in producing higher yields of **89**. We then looked to different nitrogenous bases to determine if there were any potential improvements in the yield of **89** (entries 7 – 11, starting material was consumed within 25 min as monitored using TLC). Use of amine bases N,N-diisopropylethylamine (DIPEA, pKa: 10.8,<sup>263</sup> entry 7) and diethylamine (pKa: 10.6,<sup>262</sup> entry 8), which were similar in basicity to NEt<sub>3</sub> but with more, or less, steric bulk, resulted in a decreased yield of **89** compared to the 70% achieved with NEt<sub>3</sub> (entry 1). Basicity of the nitrogenous base appeared inconsequential, as use of aniline (pKa: 4.6,<sup>262</sup> entry 9) or 4-dimethylaminopyridine (DMAP, pKa: 9.2,<sup>262</sup> entry 11) furnished only a small decrease in yield, while pyridine (pKa: 5.2,<sup>264</sup> entry 10) furnished **89** in a yield comparable to the use of NEt<sub>3</sub> (entry 1). Finally, use of the significantly more sterically hindered base 2,6-di-tert-butyl-4-methylpyridine (pKa: ~4.4,<sup>265</sup> entry 12) resulted only in a small decrease in yield comparable to that seen from the other amine bases. No significant changes in the yield of chlorinated pyrrole **90** were seen from use of any of the different amine bases. Unfortunately, there were no notable positive changes as a result of any of the chosen

bases, and no apparent significance associated with strength of the base or how sterically hindered they were. Ultimately, the presence of a nitrogenous base was deemed important, as it resulted in an increased reaction rate and yield, with NEt<sub>3</sub> being the best choice, primarily due to its availability.

**Table 11: Exploring the Effects of Organic Bases on the Synthesis of 89**

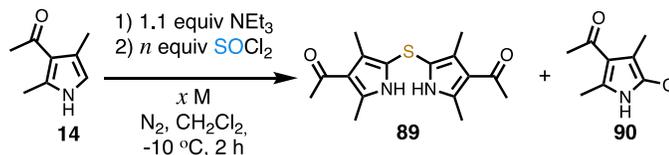


Entry	Base	Protonated pKa	Equiv. of Base ( <i>m</i> )	Equiv. of SOCl <sub>2</sub> ( <i>n</i> )	Yield of 89 (%)	Yield of 90 (%)
1	NEt <sub>3</sub>	10.8	1.1	0.8	70 <sup>a</sup>	14
2	NEt <sub>3</sub>	10.8	1.1	0.8	71 <sup>a,b</sup>	15
3	NEt <sub>3</sub>	10.8	1.1	1.1	28 <sup>a</sup>	18
4	NEt <sub>3</sub>	10.8	2	0.8	30 <sup>a</sup>	22
5	NEt <sub>3</sub>	10.8	5	0.8	23 <sup>a</sup>	3
6	NEt <sub>3</sub>	10.8	1.1	0.8	44 <sup>a,c</sup>	23
7	DIPEA	10.8	1.1	0.8	20	10
8	HNEt <sub>2</sub>	10.6	1.1	0.8	45	19
9	Aniline	4.6	1.1	0.8	50	20
10	Pyridine	5.2	1.1	0.8	68	27
11	DMAP	9.2	1.1	0.8	55	22
12	2,6-Di-tert-butyl-4-methylpyridine	~4.4 <sup>d</sup>	1.1	0.8	48	27

<sup>a</sup>Starting material consumed completely within 25 min, monitoring by TLC; <sup>b</sup>2 h reaction length; <sup>c</sup>SOCl<sub>2</sub> added first, NEt<sub>3</sub> added second; <sup>d</sup>pKa value determined in 50% EtOH, compare to pyridine pKa 4.4 in the same solvent

#### 4.3.4 Investigation of the Effects of Reaction Concentration upon the Synthesis of Dipyrrolyl Sulfides from $\text{SOCl}_2$

Remembering that 0.5 equivalents of  $\text{SOCl}_2$  are required to produce a dipyrrolyl sulfoxide, yet with an apparent need for a reductant, it is presumed that an additional 0.5 equivalents of  $\text{SOCl}_2$  are required to furnish the observed product, dipyrrolyl sulfide **89**. Cognizant that addition of more than 0.8 equivalents of  $\text{SOCl}_2$  was detrimental to the yield of **89**, we sought to determine whether variations in reaction concentration could mitigate this and allow the use of a full equivalent, or more, of  $\text{SOCl}_2$  (Table 12). All prior reactions were conducted at a concentration of 0.1 M with respect to pyrrole **14**. To determine the effects of concentration, we ran reactions at 0.02 M and 0.01 M (5- and 10-times dilution, respectively) in the presence of both 0.8 equivalents and 1.1 equivalents of  $\text{SOCl}_2$ . Not surprisingly, decreasing reaction concentration resulted in an increase in reaction time, back to 2 h (as determined by monitoring starting material consumption via TLC). With the use of 0.8 equivalents of  $\text{SOCl}_2$ , the yields of **89** and **90** remained unchanged at either concentration (entries 1 and 2), compared to those obtained at the original concentration of 0.1 M. At a reaction concentration of 0.02 M (5-times dilution), the use of 1.1 equivalents of  $\text{SOCl}_2$  resulted in a decreased yield of **89** (50%, entry 3). In contrast, at a reaction concentration of 0.01 M (10-times dilution), the use of 1.1 equivalents of  $\text{SOCl}_2$  furnished **89** in a 67% yield, comparable to the prior reactions at 0.1 M and the use of 0.8 equivalents of  $\text{SOCl}_2$ . Decreasing the concentration further was deemed to be impractical, as a reaction concentration of 0.01 M resulted in a notably longer reaction time (2 h vs 25 min) and of course corresponded to 40 mL of solvent required for the 0.4 mmol of pyrrole used in these reactions.

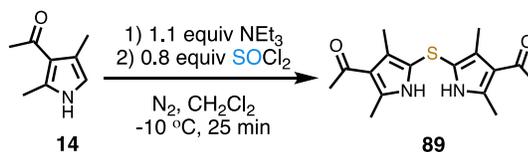
**Table 12: Effect of Concentration on the Synthesis of 89 Using SOCl<sub>2</sub>**

Entry	Equiv of $\text{SOCl}_2$ ( $n$ )	Reaction Concentration ( $x$ , M)	Yield of <b>89</b> (%)	Yield of <b>90</b> (%)
1	0.8	0.02	70	19
2	0.8	0.01	59	22
3	1.1	0.02	50	32
4	1.1	0.01	67	30

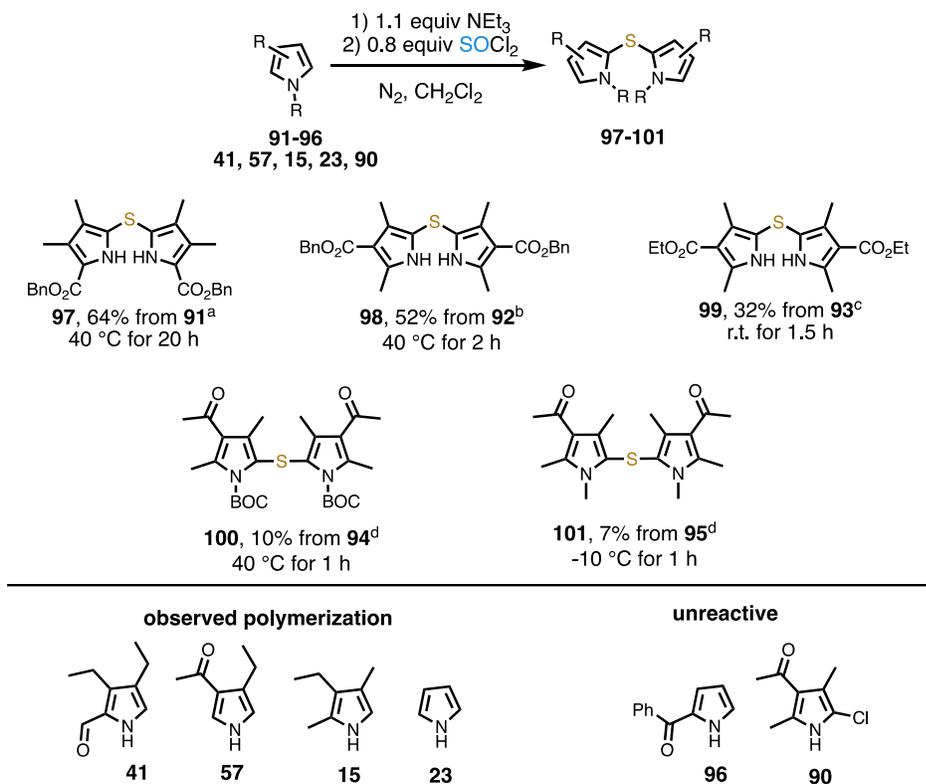
#### 4.3.5 Exploration of Substrate Scope for the Synthesis of Dipyrrolyl Sulfides from $\text{SOCl}_2$

Attempts to optimize yields of **89** through variations in temperature, addition of bases, and reaction concentration resulted in the selection of the final proposed conditions for the synthesis of **89**, as presented in Scheme 37. With the overarching goal of preparing sulfur-linked cyclic (poly)pyrroles to be used as inhibitors in the biosynthesis of heme, we used the reaction conditions outlined in Scheme 37 to explore substrate scope. To our displeasure, the ‘optimized conditions’ were substrate specific, with pyrrole **14** being the ideal substrate (Figure 30) and each additional substrate requiring modified reaction temperature and/or length. Nevertheless, we were successful in preparing a handful of new dipyrrolyl sulfides (**97-101**) in low to modest yields (7-64%). Each pyrrole substrate would presumably have required individual optimization to obtain yields comparable to

that of **89**. Pyrrole **91** was readily available within the Thompson lab, however pyrroles **92-96**, **41**, **57**, **15** and **90** were prepared as needed (refer to Chapter 5 - Experimental).



### Scheme 37: Optimized Conditions for the Synthesis of **89**



<sup>a</sup> $\text{SOCl}_2$  added at  $-10\text{ }^\circ\text{C}$ , reaction mixture warmed to rt, then heated at reflux temperature for 20 h

<sup>b</sup> $\text{SOCl}_2$  added at  $-10\text{ }^\circ\text{C}$ , reaction mixture warmed to rt, then heated at reflux temperature for 2 h

<sup>c</sup> $\text{SOCl}_2$  added at  $-10\text{ }^\circ\text{C}$ , reaction mixture warmed to rt and stirred for 1.5 h

<sup>d</sup>required forcing conditions, monitored by TLC and the reaction was stopped when notable product had appeared to form

**Figure 30: Optimized Conditions for the Synthesis of Dipyrrolyl Sulfide **89** and Substrate Scope**

A curious observation was the difference in reaction length (complete consumption of starting material observed using TLC) required to furnish comparable

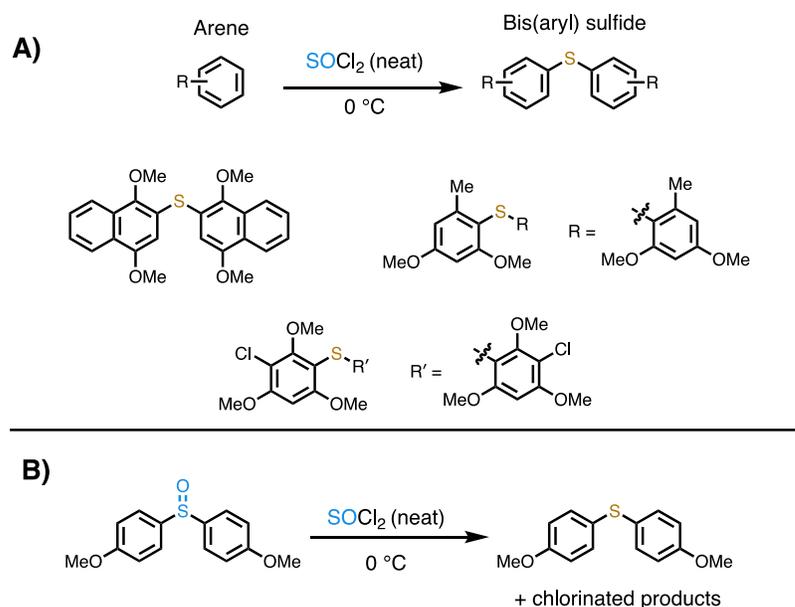
yields of sulfides **97** and **98**, on a 0.4 mmol scale. The reaction of pyrrole **91**,<sup>266</sup> substituted with a benzyl ester in the 2-position, with 0.8 equivalents of SOCl<sub>2</sub> required heating at refluxing temperature in CH<sub>2</sub>Cl<sub>2</sub> for 20 h to furnish **97** in a 64% yield. The reaction of pyrrole **92**,<sup>266</sup> substituted with a benzyl ester in the 3-position, with 0.8 equivalents of SOCl<sub>2</sub> required heating at refluxing temperature in CH<sub>2</sub>Cl<sub>2</sub> for 2 h to furnish **98** in a 52% yield. This trend follows the anticipated reactivity of pyrrole, whereby substitution with an electron-withdrawing group at the  $\alpha$ -position is expected to cause a greater decrease in nucleophilicity of the pyrrole when compared to identical  $\beta$ -substitution.<sup>207</sup> The HOMO of pyrroles such as **91** and **92** bears the greatest electron-density at the  $\alpha$ -positions.<sup>34,35</sup> Substitution with an electron withdrawing benzyl ester at one  $\alpha$ -position, i.e. **91**, should have the most significant impact on decreasing the electron-density at the remaining unsubstituted  $\alpha$ -position.<sup>207</sup> In contrast, substitution with a withdrawing benzyl ester in the  $\beta$ -position of **92** should not cause such significant impact. That is to say that pyrrole **92** is expected to have higher electron density in the unsubstituted  $\alpha$ -position compared to **91**, and as a result pyrrole **92** is more nucleophilic and thus required less time to yield product compared to **91**.

Continuing with substrate scope exploration, a variety of  $\alpha$ -free pyrroles (**41**, **57**, **15**, **23**, and **96**) and chlorinated pyrrole **90** were investigated, and found to not produce the expected dipyrrolyl sulfides. The utility of **41** was explored because if it were successful in yielding sulfide, the formyl group had the potential to enable a condensation reaction to furnish a sulfenyl bridged tetrapyrrole with two sulfide bridges. In a similar vein, **57**, with two  $\alpha$ -free positions was chosen for the potential to lead to a tetrapyrrole bridged with four sulfur atoms. Unfortunately, neither **15** nor **23** reacted with SOCl<sub>2</sub> to

give the desired sulfenyl dipyrroles, believed to be a result of the lack of electron-withdrawing groups, without which would leave the pyrroles remarkably electron-rich and thus reactive. We used substrates **15** and **23** as tests to support that an electron-withdrawing group was required to modulate reactivity for the synthesis of dipyrrolyl sulfides. Pyrroles **96** and **90** were simply unreactive under the reaction conditions.

#### 4.3.6 Proposing a Mechanism for Reductive Formation of Dipyrrolyl Sulfides from SOCl<sub>2</sub>

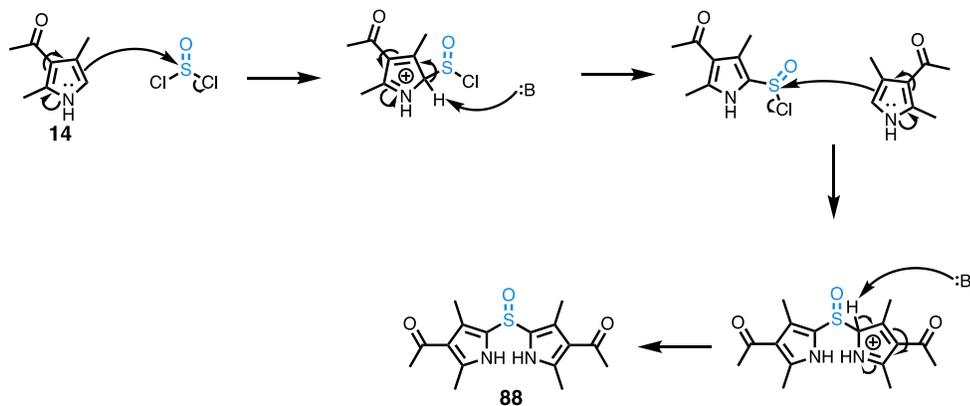
We next explored the reaction mechanism, hoping to better elucidate the challenges encountered thus far, specifically lack of success with >0.8 equivalents of SOCl<sub>2</sub> and limitations with substrate scope. A better understanding of how the reaction proceeds could enable us to devise new approaches by which to overcome or circumvent these challenges. A similar transformation was reported by Kevin Bell in 1985.<sup>256</sup> When arenes bearing 2-3 ethereal substituents were reacted in neat SOCl<sub>2</sub> the resulting bis(aryl) sulfides were isolated (Figure 31A). Bell concluded that the sulfenyl bridge formed as a result of oxygen transfer to another equivalent of SOCl<sub>2</sub>, much like our prior hypothesis regarding the somewhat surprising production of **89**. To determine evidence to support this, Bell treated the isolated di(*p*-anisole) sulfoxide with neat SOCl<sub>2</sub> and observed the formation of sulfenyl bridged products (Figure 31B). This was as far as Bell probed, but it presents an interesting and useful precedent as we began to explore potential mechanisms for our synthesis of **89**.



**Figure 31: A) Diaryl Sulfides Formed in Neat SOCl<sub>2</sub>; B) Treatment of Diaryl Sulfoxide Resulted in Formation of Diaryl Sulfide**

We know that arenes like benzene react with SOCl<sub>2</sub> to produce diaryl sulfoxides (Ar-SO-Ar), but only in the presence of a catalyst.<sup>251–255</sup> Bell showed that suitably substituted and electron-rich benzene-based compounds are capable of spontaneously reacting with SOCl<sub>2</sub> and reductively form diaryl sulfides (Ar-S-Ar). We have observed that pyrrole **14** undergoes a similar reaction with SOCl<sub>2</sub>, analogous to Bell's ethereal arenes, where **14** spontaneously reacted with SOCl<sub>2</sub> to reductively form sulfide **89**. Thus, we propose that pyrrole **14** reacts with SOCl<sub>2</sub> to first form sulfoxide **88** according to Scheme 38. Thionyl chloride undergoes nucleophilic attack from the 5-position of pyrrole **14**, furnishing a pyrrolic sulfinyl chloride. The sulfur atom of this sulfinyl chloride undergoes a second nucleophilic attack from another molecule of pyrrole **14**, forming the desired dipyrrolyl sulfoxide **88**. Remembering that the synthesis of diaryl sulfoxides from benzene and SOCl<sub>2</sub> has been reported<sup>251–255</sup> to occur via nucleophilic substitution at the

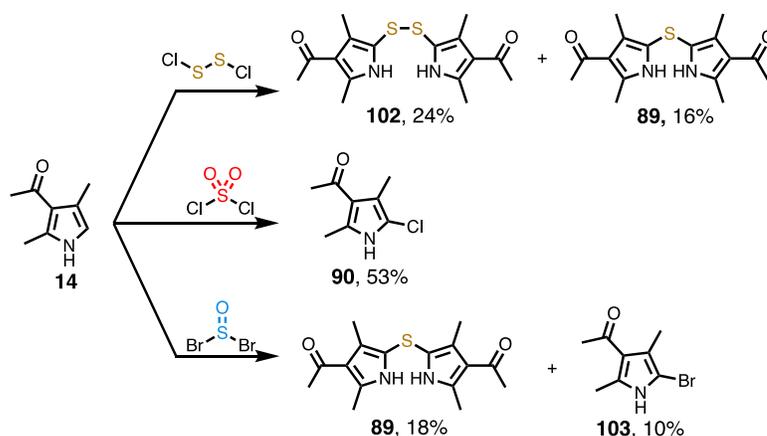
sulfur atom of  $\text{SOCl}_2$ , we are confident in our proposed transformation from **14** to **88**. We hypothesized that sulfoxide **88** was acting as an intermediate product which would react with  $\text{SOCl}_2$  to furnish sulfide **89**, similar to the reduction observed from Bell's electron-rich aryl sulfoxides.<sup>256</sup>



**Scheme 38: Proposed Mechanism for the Formation of Sulfoxide **88** from the Reaction of Pyrrole **14** and  $\text{SOCl}_2$**

With this as our starting point, we began to explore the mechanism behind the reductive formation of sulfide **89**. We sought to determine whether the surprising synthesis of a sulfide, despite the use of a sulfinyl sulfur source, was unique to the use of  $\text{SOCl}_2$ . To do this we first treated **14** with sulfur monochloride ( $\text{S}_2\text{Cl}_2$ , Scheme 39 top), which furnished disulfide **102** as the major product, and sulfide **89** as the minor. Next, treatment of **14** with sulfuryl chloride ( $\text{SO}_2\text{Cl}_2$ , Scheme 39 middle) furnished only the chlorinated pyrrole **90**. The mechanism of chlorination via  $\text{SO}_2\text{Cl}_2$  is entropically driven, whereby removal of both electrophilic chloro groups of  $\text{SO}_2\text{Cl}_2$  results in the evolution of sulfur dioxide gas. Given that treatment of **14** with  $\text{S}_2\text{Cl}_2$  and  $\text{SO}_2\text{Cl}_2$  resulted in the expected formation of disulfide and halogenation, respectively, we concluded that  $\text{SOCl}_2$  was reacting anomalously within the series. Of the three, only the use of  $\text{SOCl}_2$  ( $\text{S}^{4+}$ )

resulted in a redox reaction wherein the sulfur of the product had been reduced ( $S^{2+}$ ). Finally, treatment of **14** with thionyl bromide ( $SOBr_2$ , Scheme 39 bottom) furnished sulfide **89** and the brominated pyrrole **103**, albeit in notably lower yields. Pyrrole **103** proved to possess limited stability under ambient conditions and degraded within hours of its isolation. Indeed, use of  $SOCl_2$  and  $SOBr_2$  resulted in the same outcome, production of a sulfide from a sulfinyl source, indicating that the reductive chemistry was not unique to  $SOCl_2$ , but rather sulfinyl halides.



**Scheme 39: Treatment of Pyrrole 14 with a Series of Sulfur Halides (All Reactions Performed in  $CH_2Cl_2$  at  $-10\text{ }^\circ\text{C}$ )**

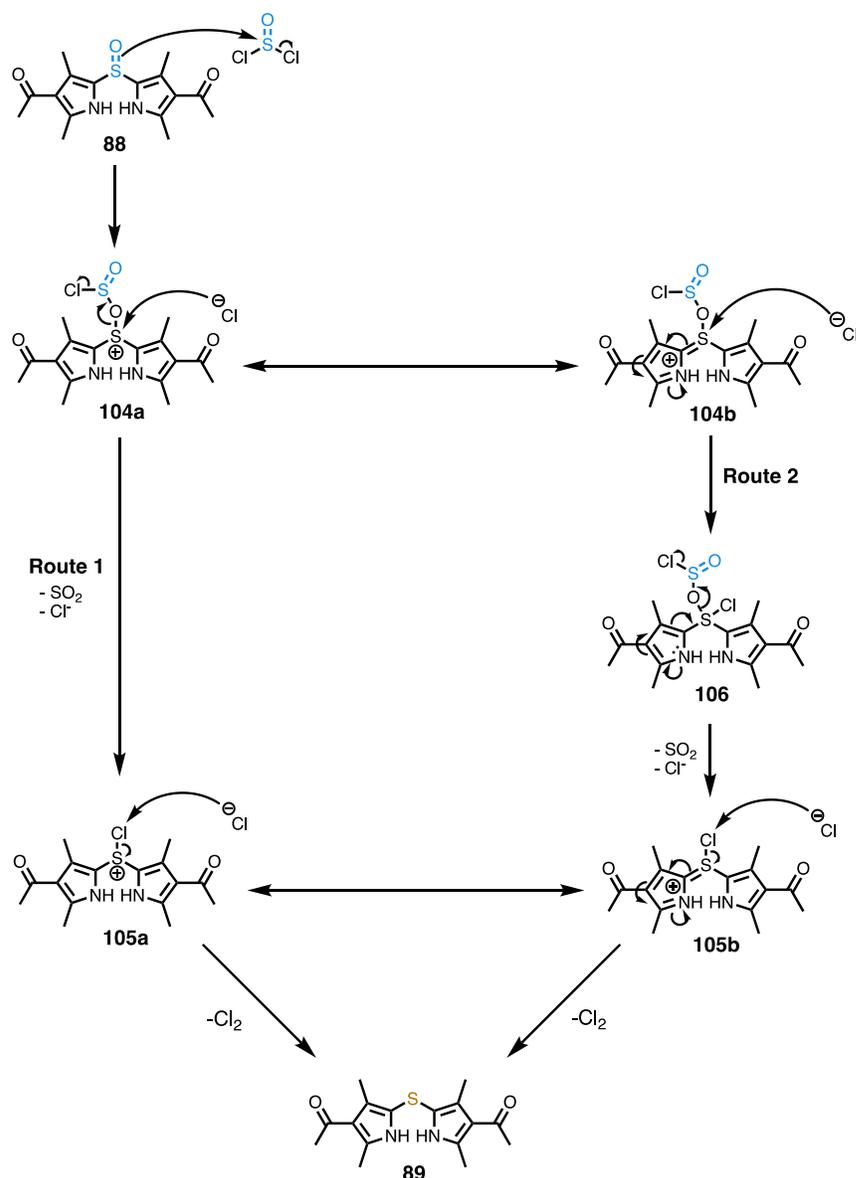
Thus, we propose that sulfide **89** forms according to the transformation outlined in Scheme 40. The proposed pathway from **88** to **89** bears similarities to that of the Swern Oxidation.<sup>267</sup> We were not able to observe sulfoxide **88**, and thus propose reduction involving an additional equivalent of  $SOCl_2$  to produce sulfide **89**. The proposed pathway is presented as two routes, Route 1 and 2, in order to highlight how the transformation from **88** to **89** parallels the Swern Oxidation (Route 1), as well as how the  $\pi$ -system of the pyrrole ring may aid in the reduction of **88** (Route 2), as less electron-rich arenes are known to form diaryl sulfoxides, not sulfides.<sup>251–255</sup>

The reduction of **88** to **89** is proposed to begin with nucleophilic attack at the electrophilic sulfur centre of  $\text{SOCl}_2$ , which originates from the sulfoxide oxygen atom of **88** (Scheme 40, **88** to **104a/b**). Structures **104a** and **104b** are resonance contributors for the same intermediate, **104**. As depicted, resonance contributor **104a** best represents the precursor to the chlorosulphonium ion (**105a**) present during the traditional Swern Oxidation.<sup>267</sup> Remembering that only suitably electron-rich arenes are known to be capable of spontaneously reacting with  $\text{SOCl}_2$  to reductively form diaryl sulfides (Figure 31),<sup>256</sup> resonance contributor **104b** is the best representation of how one could expect the  $\pi$ -system of the electron-rich pyrrole ring to support the reductive formation of sulfide **89**. Suspecting that **104** bears character of both **104a** and **104b**, an evaluation of kinetic parameters would be required before assigning a detailed mechanism.

Focusing first on Route 1, which is directly analogous to the Swern Oxidation,<sup>267</sup> nucleophilic attack of a chloride anion at the electrophilic sulfur atom of **104a** would furnish the chlorosulphonium ion **105a**,  $\text{SO}_2$  gas, and a chloride anion. Subsequent nucleophilic attack by a chloride anion at the electrophilic chloro-substituent of **105a** would furnish the final product, sulfide **89**, and  $\text{Cl}_2$  gas, which is a competent chlorinating agent and could give rise to the observed chlorination during the reaction of pyrrole **14** and  $\text{SOCl}_2$ . We propose that Route 2 could begin similarly, wherein the sulfur centre of **104b** is attacked by a chloride anion to generate intermediate **106**. Next, loss of  $\text{ClS(O)O}^-$  could potentially be supported by the  $\pi$ -system of pyrrole and generates a second protonated pyrrolethione-like intermediate, **105b**, with an electrophilic chloro substituent bound to the sulfur atom. The  $\text{ClS(O)O}^-$  leaving group is presumed to subsequently decompose to generate a chloride anion and  $\text{SO}_2$  gas. Removal of the chloro substituent

of **105b** by a chloride anion would reduce the sulfur atom to give the requisite sulfide, restoring aromaticity to the pyrrole ring and thus generating dipyrrolyl sulfide **89**.

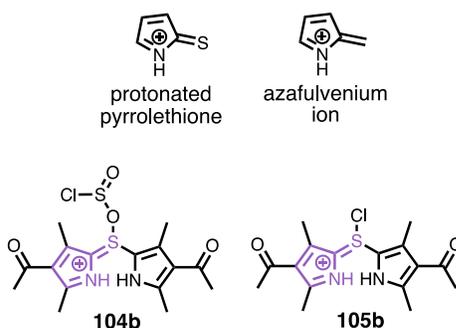
While Bell did not report a proposed mechanism, he observed the same phenomenon, i.e. incorporation and subsequent reduction of thionyl chloride to produce diaryl sulfides. We believe that conjugation of the sulfoxide moiety of **88** to an electron-donating  $\pi$ -system drives the transformation forwards and is the prime reason why no sulfoxide could be observed in our case. This proposed transformation of sulfoxide **88** to sulfide **89** suggests that, if isolated, **88** would undergo a redox reaction in the presence of  $\text{SOCl}_2$  to furnish **89**.



**Scheme 40: Proposed Transformation for the Formation of Dipyrrolyl Sulfide **89** from Sulfoxide **88**.**

The proposed resonance contributors **104b** and **105b** are structurally similar to a protonated pyrrolethione (Figure 32). However, there is minimal literature precedent regarding the reactivity of such species. We propose that the protonated pyrrolethione **104b** would be similar in reactivity to an azafulvenium ion (Figure 32). The azafulvenium ion is electrophilic and readily undergoes nucleophilic attack at the

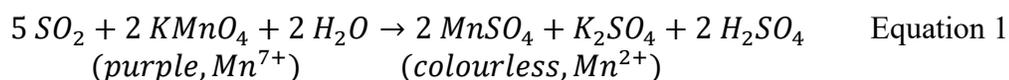
exocyclic carbon atom.<sup>268–270</sup> When comparing the simplest protonated pyrrolothione and azafulvenium ions (Figure 32), the two species are valence-isoelectronic. We could then expect that much like the exocyclic carbon atom of azafulvenium, the exocyclic sulfur of the pyrrolothione could be stabilized by the  $\pi$ -system of the pyrrole moiety while remaining appreciably electrophilic. Comparing this to the highlighted pyrrolothione units of intermediate **104b** and **105b** (Figure 32, purple), we could expect intermediates **104b** and **105b** to be similar in reactivity to an azafulvenium ion, and thus capable of undergoing nucleophilic attack at the bridging sulfur atom.



**Figure 32: Comparison of an Azafulvenium Ion, a Protonated Pyrrolothione, and Intermediate 104b and 105b**

Having proposed that  $\text{SO}_2$  forms as a byproduct of the reaction mechanism (Scheme 40), we sought to indirectly observe the evolution of  $\text{SO}_2$  via a known test, the redox reaction of  $\text{KMnO}_4$  and  $\text{SO}_2$  under aqueous conditions (Equation 1).<sup>271</sup> When dissolved in water, the permanganate ion ( $\text{MnO}_4^+$ ,  $\text{Mn}^{7+}$ ) affords a purple coloured solution. As a strong oxidizing agent,  $\text{MnO}_4^+(\text{aq})$  will readily react with  $\text{SO}_2$ , if present, to afford a colourless solution of  $\text{MnSO}_4$  ( $\text{Mn}^{2+}$ ),  $\text{K}_2\text{SO}_4$ , and sulfuric acid ( $\text{H}_2\text{SO}_4$ ). Thus, if  $\text{SO}_2$  were to evolve during the synthesis of sulfide **89**, we would expect the solution of

KMnO<sub>4</sub> to become colourless as it is reduced to MnSO<sub>4</sub>. In order to determine whether SO<sub>2</sub> was produced during the synthesis of sulfide **89**, a solution of pyrrole **14** and 1.1 equivalents of NEt<sub>3</sub>, in CH<sub>2</sub>Cl<sub>2</sub>, was treated with 0.8 equivalents of SOCl<sub>2</sub> at -10 °C, under a positive flow of N<sub>2</sub> which was vented through an aqueous solution of KMnO<sub>4</sub> (0.005 M, 3 mg in 3.5 mL distilled water). The solution of KMnO<sub>4</sub> was observed to completely decolour within 5 min of the addition of SOCl<sub>2</sub> to the reaction mixture. Once the reaction had reached completion, observed using TLC, it was quenched and purified, furnishing a 73% isolated yield of sulfide **89**.



Using identical experimental setups, two control solutions of SOCl<sub>2</sub> in CH<sub>2</sub>Cl<sub>2</sub>, and NEt<sub>3</sub> with SOCl<sub>2</sub> in CH<sub>2</sub>Cl<sub>2</sub>, were placed under a positive pressures of N<sub>2</sub>. Each of the two solution were vented through separate solutions of aqueous KMnO<sub>4</sub>. The aqueous solutions of KMnO<sub>4</sub> were observed to completely decolour within 10 and 15 minutes of the addition of SOCl<sub>2</sub> (10 and 15 minutes for SOCl<sub>2</sub> and NEt<sub>3</sub> with SOCl<sub>2</sub>, respectively). From these results, it appeared likely that volatile SOCl<sub>2</sub> was venting into the KMnO<sub>4</sub> solutions, at which point the SOCl<sub>2</sub> could undergo oxidation and thus cause the observed decolourization. The question that must be asked was whether the observed decolourization of the aqueous KMnO<sub>4</sub> solution during the reaction of pyrrole **14** and SOCl<sub>2</sub> to produce dipyrrolyl sulfide **88** was a result of the production of SO<sub>2</sub> gas or simply due to the venting of SOCl<sub>2</sub>. Given that pyrrole **14** and SOCl<sub>2</sub> reacted to produce **88** in a 73% isolated yield, it would be unlikely that appreciable decolourization could have been caused by SOCl<sub>2</sub>. Such an isolated yield of **88** would correspond to consumption of 95% of SOCl<sub>2</sub> in the reaction mixture. In addition, decolourization of the

KMnO<sub>4</sub> solution during the reaction of pyrrole **14** and SOCl<sub>2</sub> was complete after 5 min, while the control setups required 10 minutes, and 15 minutes in the presence of NEt<sub>3</sub>, for complete decolourization to occur. Thus, based on the high yield of **88** and the comparatively fast decolourization of the solution of KMnO<sub>4</sub>, we believe it would be most likely that SO<sub>2</sub> gas was produced as a byproduct of the reaction of **14** and SOCl<sub>2</sub>.

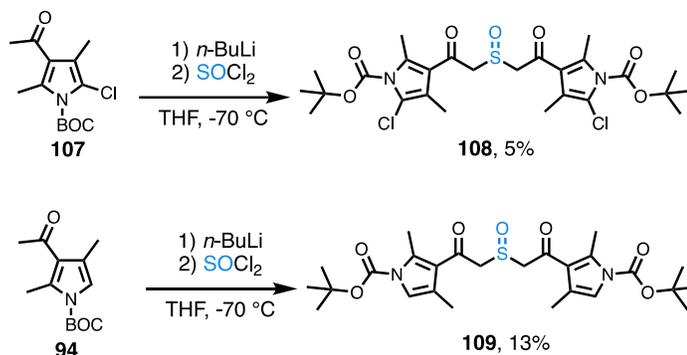
#### 4.3.7 Further Investigations into the Reductive Formation of Dipyrrolyl Sulfides from SOCl<sub>2</sub>

As previously mentioned, sulfoxide **88** was not observed during the formation of **89**. When **89** was synthesized in the presence of NEt<sub>3</sub>, starting material was completely consumed within 25 min at -10 °C (Table 11). Without NEt<sub>3</sub>, the reaction time increased to approximately 2 h (Table 10), but again, no sulfoxide was observable. Only starting material **14**, sulfide **89**, and baseline impurities were noted at any time-point during the reaction. We believe that the rate-limiting step is nucleophilic attack by pyrrole **14**, which leads to the formation of **88**. Once sulfoxide **88** has been formed it immediately and rapidly undergoes reduction to **89**. The belief is based on the proposed mechanism, not on the inability to isolate **88**. Unable to observe formation of sulfoxide **88** during the reaction of **14** and SOCl<sub>2</sub>, we sought to prepare **88** separately and treat it with SOCl<sub>2</sub>. If under these conditions sulfide **89** was produced, it would bolster the proposed role of **88** as a synthetic intermediate in the mechanism and help to explain why sulfoxide **88** was not observable *in situ*.

The preparation of **88** was approached using two concurrent methods, the first involving synthesis from pyrrole **107** (Scheme 41), and the second involving the

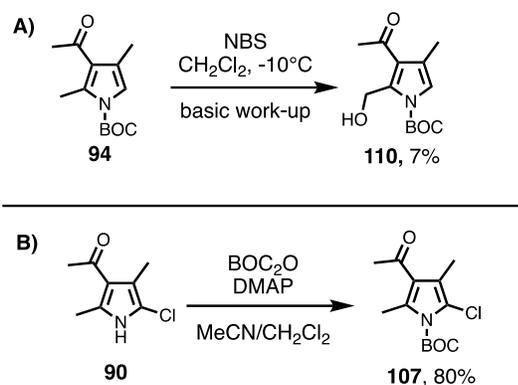
synthesis of **88** from **89** (Scheme 43). According to the procedure outlined by Groenendaal,<sup>235</sup> an N-BOC protected  $\alpha$ -bromo pyrrole could be treated with *n*-BuLi followed by SOCl<sub>2</sub> at -70 °C to furnish the corresponding sulfoxide. Interestingly, under the reaction conditions reported by Groenendaal,<sup>235</sup> chlorinated pyrrole **107** furnished a dipyrrolyl sulfoxide connected through the terminal carbon atom of the  $\beta$ -acetyl group (Scheme 41 top, **108**). While unexpected, production of sulfoxide **108** is not entirely surprising. The  $\alpha$ -hydrogen atoms of the acetyl group are comparable to the  $\alpha$ -hydrogens of an ester or amide. Where esters and amides have donating O and N atoms, respectively, the acetyl group has a donating pyrrole moiety instead. Thus, the acetyl group  $\alpha$ -hydrogens would be expected to have a pKa comparable to esters and amides (pKa of ~25-30), which is significantly lower than that of *n*-BuLi (pKa ~50). In order to confidently conclude that deprotonation of the  $\beta$ -acetyl group was dominant, the reaction was repeated with non-halogenated pyrrole **94**, from which the analogous  $\beta$ -acetyl bridged dipyrrolyl sulfoxide **109** was isolated. Evidently, deprotonation of the  $\beta$ -acetyl groups of **107** and **94** dominated over lithium-halogen exchange. Thus, sulfoxides **108** and **109** presumably arose from enolization of the  $\beta$ -acetyl group, the resulting anion attacked the sulfur atom of SOCl<sub>2</sub> to produce a pyrrole sulfinyl chloride. A second such attack on the electrophilic sulfur atom of the pyrrole sulfinyl chloride would then generate dipyrrolyl sulfoxides **108** and **109**. What was most interesting to us was that the sulfur atom of both **108** and **109** were separated from the pyrrole ring by an aliphatic carbon, and remained in the +4 oxidation state, i.e. sulfoxide, rather than reducing to the +2 of the sulfide in **89**. While not unequivocal, this certainly appears to support our proposition that conjugation to an electron-donating  $\pi$ -system (increasing the

nucleophilicity of the sulfoxide) enables the reduction of the sulfinyl bridge under the conditions explained involving  $\text{SOCl}_2$ .



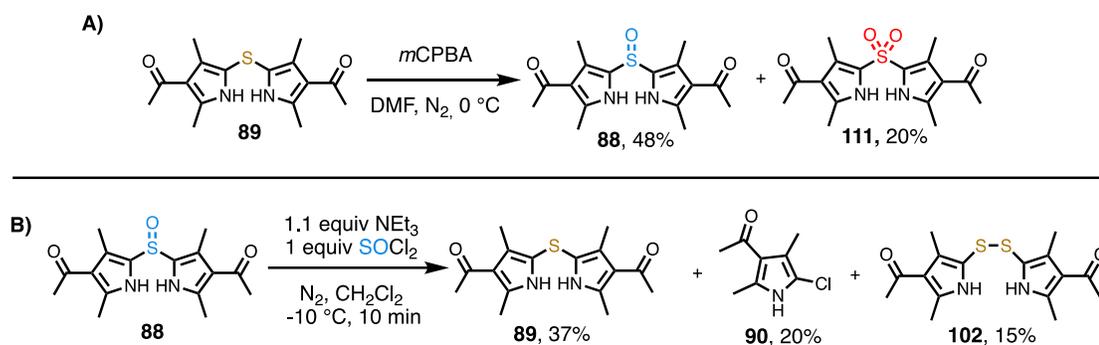
#### Scheme 41: Groenendaal's Literature Conditions Applied to Pyrrole **107** and **94** Towards the Synthesis of Symmetric Sulfoxide-bridged Pyrroles

We initially attempted the synthesis of the N-BOC protected  $\alpha$ -bromo analogue of **107**, via NBS bromination of **94** (Scheme 42A), however treatment with NBS, and subsequent basic work-up, afforded pyrrole alcohol **110** instead of the desired  $\alpha$ -bromo pyrrole. Adapting our approach, we turned our attention to the BOC-protection of  $\alpha$ -halogenated N-H pyrroles. Having previously observed that N-H  $\alpha$ -bromo pyrrole **103** (Scheme 39) possessed limited stability under ambient conditions we opted to proceed with pyrrole **90**, which was easily protected to afford the aforementioned N-BOC protected  $\alpha$ -chloro pyrrole **107** (Scheme 42B).



**Scheme 42: A) NBS Bromination of 94 Furnished pyrrole alcohol 110; B) BOC-protection of Pyrrole 90 to Afford 107**

Sulfoxide **88** was ultimately prepared from **89** via oxidation with *m*CPBA, furnishing **88** in a 48% isolated yield (Scheme 43A), alongside sulfone **111** isolated in a 20% yield. With **88** in hand we were able to test our hypothesis regarding the proposed mechanism indicated in Scheme 40. For the proposed mechanism (Scheme 40) to have merit, sulfoxide **88** would react with  $\text{SOCl}_2$  to produce sulfide **89**. Treatment of **88** with  $\text{SOCl}_2$  resulted in rapid consumption of starting material and production of **89** (Scheme 43B, monitored via TLC). The fact that **89** was the major product supports our mechanism, showing that sulfoxide **88** is not only capable of reacting with  $\text{SOCl}_2$  but does so in a reductive fashion to furnish **89**. Furthermore, this supports that **88** is a synthetic intermediate, one that reacts very rapidly with  $\text{SOCl}_2$ , thus giving strong justification to our proposed mechanism (Scheme 40).



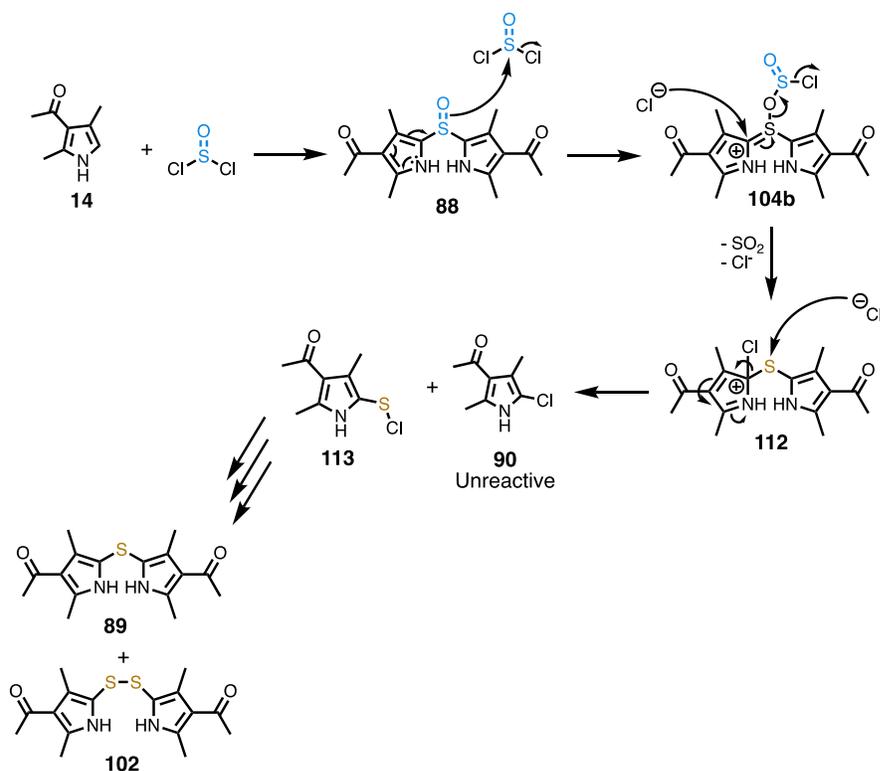
**Scheme 43: A) Synthesis of Sulfoxide **88** and Sulfone **111** from **89**; B) Reduction of Sulfoxide **88** in the Presence of  $\text{SOCl}_2$**

To our surprise, chlorinated pyrrole **90** and disulfide **102** were also isolated from the reaction of **88** with  $\text{SOCl}_2$ . The formation of both these products suggests that cleavage of the C-S bonds of **88**, or a later intermediate, occurs. If this were the case, it was not beyond reason that **89** could have been produced as a result of cleavage and subsequent recombination. Up to this point, it had been presumed that production of the chlorinated pyrrole **90** was simply a by-product of using  $\text{SOCl}_2$ , a reagent with significant chlorinating potential, and which could produce other chlorinating agents *in situ* (e.g.  $\text{Cl}_2$ , or  $\text{SO}_2\text{Cl}_2$ ).

In order to investigate the formation of **90** and **102** from the reaction of **88** with  $\text{SOCl}_2$ , we hypothesized the transformation outlined in Scheme 44. Reaction of sulfoxide **88** with  $\text{SOCl}_2$  produces **104b**. Analogous to the Pummerer rearrangement of chlorosulphonium chlorides,<sup>272</sup> nucleophilic attack by a chloride anion on the carbon atom of the C-S bond of **104b** would furnish intermediate **112**. We believed this plausible based on the known precedent of chlorosulphonium chloride Pummerer rearrangements, as well as production of **112** involving the favourable evolution of  $\text{SO}_2$  gas. A final nucleophilic attack by a chloride anion could then cleave the C-S bond of **112**, generating

pyrrole **90** and the more reactive counterpart, pyrrole sulfenyl chloride **113**. Pyrrole **113** would then have the potential to react with itself, or other intermediates to produce sulfide **89** and disulfide **102**.

To support the proposed mechanism for Route 2, and that cleavage of intermediate **112** was occurring as described, we sought to confirm the formation of sulfenyl chloride pyrrole **113**. When sulfoxide **88** was reacted with  $\text{SOCl}_2$  at  $-10\text{ }^\circ\text{C}$ , **88** was consumed and the reaction completed within 5 min. Given the rapid rate of the reaction, we attempted to observe **113** indirectly, via formation of a characteristic derivative. The chosen method was treatment of sulfoxide **88** with  $\text{SOCl}_2$  in the presence of a large excess of an additional pyrrole, which we hoped would intercept pyrrole **113** and produce an asymmetric dipyrrolyl sulfide. We selected pyrrole **95** (Scheme 45) as the pyrrole to be present in a large excess for two reasons: the structural similarity to **14**, and the rate at which **95** had been shown to react with  $\text{SOCl}_2$  (Figure 30). If pyrrole **95** were successful at intercepting sulfenyl chloride **113**, the N-Me group of pyrrole **95** would be easily identifiable using  $^1\text{H}$  NMR spectroscopy. The slow rate at which **95** had been shown to react with  $\text{SOCl}_2$  (7% product produced in 1 h) was ideal, as it suggested that the reduction of **88** by  $\text{SOCl}_2$  (complete within 5 min) would dominate, and thus cleavage of **112** should occur, even in the presence of 10 equivalents pyrrole **95**.



**Scheme 44: Proposed, but Ultimately Believed to be Disproven, Formation of 89, 90, and 102 from Reaction of 88 and  $\text{SOCl}_2$ .**

Treatment of sulfoxide **88** with  $\text{SOCl}_2$  in the presence of a large excess of **95**, resulted in the formation of the asymmetric dipyrrolyl sulfide **114** and chlorinated pyrrole **115** (Scheme 45). No other products were observed via  $^1\text{H}$  NMR spectroscopy, nor by HRMS of the crude reaction mixture. The formation of asymmetric sulfide **114** confirmed that during the reduction of **88** by  $\text{SOCl}_2$ , C-S bond cleavage does occur. Asymmetric dipyrrolyl sulfide **114** was detected via HRMS in the crude reaction mixture and in order to isolate it an extremely challenging purification was required (multiple byproducts with similar  $R_f$  values), likely contributing to the low yield of 8%. Despite the low yield, the structure of **114** was confirmed following analysis of both HRMS and NMR spectra corresponding to the purified sample.



The formation of dipyrrolyl disulfide **102** from the reaction of **88** with  $\text{SOCl}_2$  (Scheme 43B) further supports the view that C-S bond cleavage is a competing non-productive mechanism. The reaction of **88** with  $\text{SOCl}_2$  was repeated three times on separate days, all of which resulted in formation of disulfide **102**. Dipyrrolyl sulfide **89** and chlorinated pyrrole **90** were both stable when subjected to the reaction conditions used for the reduction of **88** (Scheme 43B), i.e. treatment with  $\text{SOCl}_2$  in the presence of  $\text{NEt}_3$  at  $-10\text{ }^\circ\text{C}$ . This led us to believe that the formation of **102** was a direct result of C-S bond cleavage and does not involve derivatization of **89** or **90**. Therefore, we believe the absence of disulfide **102** under the original reaction conditions used to synthesize **89** from **14** (Scheme 37) suggests that, although cleavage is possible, as seen from Scheme 45, it is not a significant reaction pathway. To summarize, when synthesizing **89** according to Scheme 37, we believe cleavage can occur, but it is a competing and non-productive mechanism. There was never any observed formation of sulfoxide **88** nor of disulfide **102**, and as such we believe the proposed mechanism outlined in Scheme 40 to be the leading pathway for the formation of **89**.

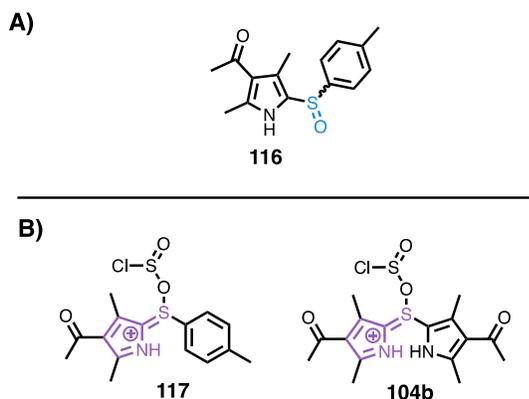
Returning to the reaction mechanism proposed in Scheme 40, we remain confident in the first half of the mechanism. Transformations analogous to that of **14** to **88** have been reported to proceed via nucleophilic substitution at the sulfur atom of  $\text{SOCl}_2$ .<sup>251–255</sup> We are now confident **88** proceeds to **89** as outlined in Scheme 40; forming *in situ* as a synthetic intermediate. Sulfoxide **88** rapidly undergoes reduction in the presence of additional  $\text{SOCl}_2$ , as shown in Scheme 43B. Having investigated the formation of chlorinated pyrrole **90** and dipyrrolyl disulfide **102**, we conclude that while C-S bond cleavage can occur, it is not a significant contributor to the production of **89**. In

addition, we feel confident concluding that chlorinated pyrrole **90**, observed to form in the presence of SOCl<sub>2</sub> under all reported reaction conditions, is merely a result of the chlorination properties of SOCl<sub>2</sub>, or from chlorinating reagents generated *in situ* from SOCl<sub>2</sub>.

#### 4.3.8 Investigating the Reduction of Pyrrolyl Sulfoxides in the Presence of SOCl<sub>2</sub>

When Bell reported the synthesis of diaryl sulfides from SOCl<sub>2</sub> (Figure 31),<sup>256</sup> the reductive formation of a sulfide was only observed in ethereal arene substrates with at least one ether, suggesting electron-donating  $\pi$ -systems directly conjugated to the sulfur atom cause facile auto-reduction. Appreciating the correlation between the work of Bell, and our work involving the synthesis of sulfenyl bridged pyrroles, we investigated whether a sulfinyl bridged pyrrole arene could undergo a similar reduction in the presence of SOCl<sub>2</sub>. To evaluate the reaction of such a sulfoxide with SOCl<sub>2</sub>, we investigated pyrrolyl tolyl sulfoxide **116** (Figure 33A). This compound contains the single desired pyrrole moiety and a tolyl moiety; tolyl was chosen as ditolyl sulfoxides have been shown to not undergo reduction to the analogous ditolyl sulfide in the presence of SOCl<sub>2</sub>.<sup>251–254</sup> Therefore, if compound **116** underwent oxidation in the presence of SOCl<sub>2</sub>, it could be assumed to be a result of the pyrrole moiety. With convincing evidence in hand to support the proposed mechanism for the formation of **89** (Scheme 40), we suspected that a sulfoxide with a single pyrrole moiety would be capable of reacting with SOCl<sub>2</sub> to form the pyrrolethione intermediate **117**, which is analogous to the previously discussed pyrrolethione **104b** (Figure 33B). That is to say, **117** is expected

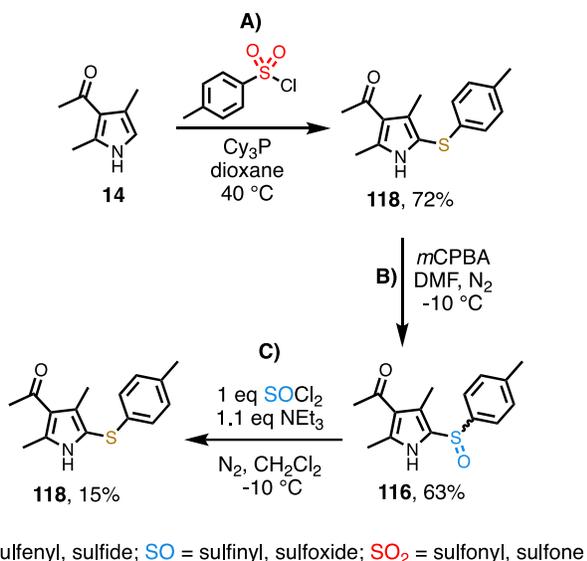
to form via nucleophilic attack from the sulfoxide oxygen of **116** to the sulfur atom of  $\text{SOCl}_2$ , which is aided by the  $\pi$ -system of pyrrole, as seen in the formation of **104b** (Scheme 40). In this way, we expected the sulfinyl bridge of **116** to undergo reduction with  $\text{SOCl}_2$ , thus producing the requisite pyrrolyl tolyl sulfide.



**Figure 33: A) Pyrrolyl Tollyl Sulfoxide 116; B) Comparison of Pyrrolethione Intermediates 117 and 104b**

In order to prepare **116**, we first synthesized pyrrole **118** via deoxygenative O-atom transfer (dOAT) methodology using pyrrole **14** and tosyl chloride in the presence of  $\text{Cy}_3\text{P}$  (Scheme 46, reaction A).<sup>243</sup> With sulfide **118** in hand, oxidation with *m*CPBA furnished pyrrolyl tolyl sulfoxide **116** (Scheme 46, reaction B). **116** was then subjected to the same reaction conditions as dipyrrolyl sulfoxide **88** (Scheme 43B) to observe whether sulfoxide **116** would undergo reduction with  $\text{SOCl}_2$ ; sulfoxide **116** furnished sulfide **118**, the only isolable product, in 15% yield (Scheme 46; reaction C). The marked decrease in yield compared to the  $\text{SOCl}_2$ -induced reduction of **89** (37%, Scheme 43B) may have arisen from the weaker electron-donating tolyl group compared to the second pyrrole group of **89**. Nevertheless, formation of sulfide **118** confirms that reduction of the sulfinyl moiety can occur with only one linked pyrrole moiety, and further supports the

notion that conjugation to an electron-donating  $\pi$ -system helps to enable the auto-reduction of the sulfinyl bridge with  $\text{SOCl}_2$ .



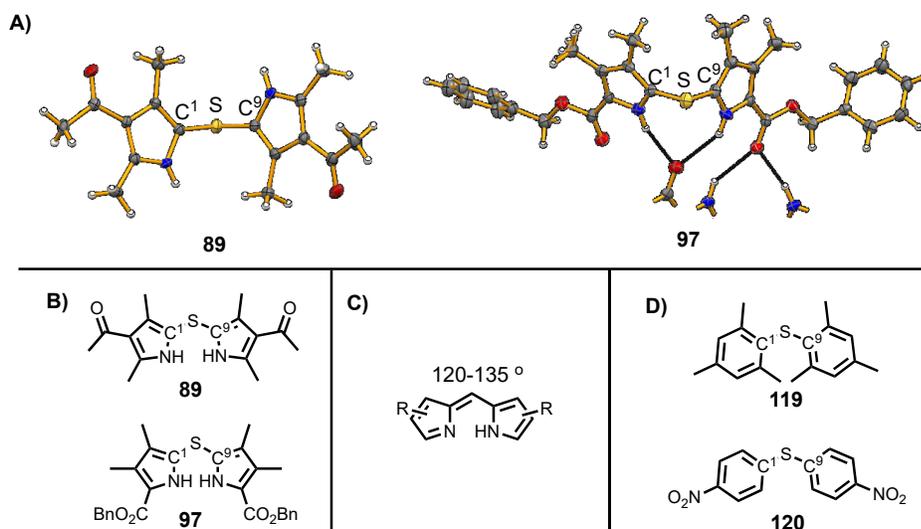
**Scheme 46: A) Synthesis of Sulfide 118 from Pyrrole 14 via dOAT Methodology; B) *m*CPBA Oxidation of Sulfide 118 to Sulfoxide 116; C)  $\text{SOCl}_2$  Reduction of Sulfoxide 116 to Sulfide 118**

#### 4.3.9 Comparisons of Dipyrrolyl Sulfide Crystal Structures and Known Diaryl Sulfides

During investigations in to preparing dipyrrolyl sulfides from  $\text{SOCl}_2$ , the crystal structures of **89** and **97** were solved. The slow evaporation of separate solutions of **89** and **97** in methanol furnished clear light pink clear crystals, and clear colourless crystals, respectively, that were suitable for analysis via x-ray diffraction (Figure 34A). Dr. Katherine Robertson, Saint Mary's University, solved the structures and revealed that **89** crystallizes in the orthorhombic space group  $\text{Pbca}$ , and **97** crystallizes in the monoclinic space group  $\text{P2}_1/\text{n}$ . The  $\text{C}^1\text{-S}$  and  $\text{C}^9\text{-S}$  bond lengths of **89** are similar to each other, at  $1.755(3) \text{ \AA}$  and  $1.744(2) \text{ \AA}$ , respectively. The  $\text{C}^1\text{-S}$  and  $\text{C}^9\text{-S}$  bond lengths of **97** are

similar to those of **89**, at 1.757(5) Å and 1.740(5) Å. The dimeric nature of **97** and the identity and position of the electron-withdrawing group (acyl vs. benzyl ester) does not appear to have a significant effect on the length of the C-S bonds. However, a notable difference can be seen in the C<sup>1</sup>-S-C<sup>9</sup> bond angles of **89** and **97**, i.e. 105.8(1)° and 101.4(2)°, respectively. The narrowing of the bond angle from **89** to **97** may be a result of the dimeric nature of **97**, where the hydrogen bonding between two molecular units forces the sulfide bond angle to narrow. Given that the central bond angles between the pyrrole units of **89** and **97** are comparable with sp<sup>3</sup> and higher hybridized atoms containing lone pairs (e.g. bent, ~104.5 °; see-saw, ~101.6 °),<sup>273,274</sup> it is fair to conclude that the pyrrole units are not conjugated through the sulfur atom. We would expect there to be little electronic communication between the two aryl substitutions of the sulfide. Further evidence to support this can be seen when compared to the analogous conjugated system of a dipyrromethene, a pyrrole linked to an azafulvene via the sp<sup>2</sup> bridging carbon, with central bond angles in the range of 120-135 ° (Figure 34C).<sup>175,275,276</sup> To the best of our knowledge these are the first examples of solved dipyrrolyl sulfide crystal structures.

The sulfide bond lengths of **89** and **97** are slightly shorter (~0.02-0.05 Å) than those seen in similar aryl sulfides **119** and **120** (Figure 34D). The length of the C<sup>1</sup>-S and C<sup>9</sup>-S bonds of **119** are 1.782(1) Å and 1.787(1) Å, respectively. The length of the C<sup>1</sup>-S and C<sup>9</sup>-S bonds are 1.768(1) Å and 1.777(2) Å, respectively. The C<sup>1</sup>-S-C<sup>9</sup> bond angle of **89** is similar to that of the electron-rich **119** (106.43(6)°), while that of **97** is similar to that of electron-poor **120** (100.8(1)°).



**Figure 34: (A) X-Ray Crystal Structure of Dipyrrolyl Sulfide 89 and One Half of Dimeric 97 (see Appendix A for Full Crystal Structure); (B) Structure of Dipyrrolyl Sulfide 89 and 97; (C) Analogous Conjugated Dipyrromethene (D) Related Literature Compounds with Published Solved Crystal Structures**

## 4.4 Conclusion

The synthesis of sulfur-bridged (poly)pyrroles has been explored via electrophilic aromatic substitution around the pyrrolic core. A synthesis for dipyrrolyl sulfides was developed, using  $\text{SOCl}_2$  as the sulfur source. While the reaction was optimized for substrate **14** it proved to have limited scope, with other substrates requiring further optimization. Functional group tolerance to treatment with  $\text{SOCl}_2$  unsurprisingly proved extremely limited. Nevertheless, five new dipyrrolyl sulfides were synthesized and isolated, and the mechanism for the reaction, involving reduction of sulfur from the +4 to +2 oxidation states, was explored alongside a mechanistic rationale.

## Chapter 5 – Experimental

### 5.1 General Experimental

All chemicals were used as received unless indicated otherwise. Moisture and air-sensitive reactions were performed in flame-dried glassware under a positive pressure of nitrogen unless indicated otherwise. Moisture- and air-sensitive compounds were introduced via gas-tight oven-dried syringe or cannula through a rubber septum. Thionyl chloride was purified via fractional distillation, using a 20 cm Vigreux column, according to Fieser & Fieser's *Reagents in Organic Chemistry*.<sup>259</sup> Sulfuryl chloride was purified via fractional distillation, using a 20 cm Vigreux column, according to Perrin & Armarego's *Purification of Laboratory Chemicals*.<sup>258</sup> Flash chromatography was performed using Silicycle ultra-pure silica (230-400 mm). NMR spectra were recorded using 500 or 300 MHz spectrometers. All <sup>1</sup>H, <sup>13</sup>C, <sup>11</sup>B, <sup>19</sup>F, <sup>15</sup>N NMR chemical shifts (δ) are expressed in parts per million (ppm). The solvent signal was used as the internal reference for <sup>1</sup>H and <sup>13</sup>C spectra [ $\text{CDCl}_3$  (<sup>1</sup>H 7.16 ppm; <sup>13</sup>C 77.16 ppm);  $\text{CD}_2\text{Cl}_2$  (<sup>1</sup>H 5.31 ppm; <sup>13</sup>C 53.84 ppm);  $\text{DMSO}-d_6$  (<sup>1</sup>H 2.50 ppm; <sup>13</sup>C 128.06 ppm)]. For <sup>11</sup>B, the 0 ppm position corresponds to the chemical shift of  $\text{BF}_3 \cdot \text{OEt}_2$  (15% in  $\text{CDCl}_3$ ); for <sup>19</sup>F, the 0 ppm position corresponds to the chemical shift of  $\text{CFCl}_3$ ; and for <sup>15</sup>N, the 0 ppm position corresponds to the chemical shift of pure nitromethane. Splitting patterns are indicated as follows: br s, broad singlet; s, singlet; d, doublet; t, triplet; q, quartet; qd; quartet of doublets; quin, quintet; m, multiplet; qs, quartet of singlets (<sup>11</sup>B). All coupling constants (*J*) are reported in Hertz (Hz). Mass spectra were obtained using TOF and LCQ Duo ion trap instruments operating in ESI<sup>+/-</sup> - or APCI-mode, as indicated. Melting points were

determined using a Fisher-Johns melting point apparatus. Use of 10  $\mu\text{L}$ , 25  $\mu\text{L}$ , 250  $\mu\text{L}$ , 500  $\mu\text{L}$ , 1000  $\mu\text{L}$ , and 5000  $\mu\text{L}$  Hamilton Company<sup>©</sup> syringes enabled greater accuracy when adding appropriately small volumes (<5000  $\mu\text{L}$ ). Error associated with each syringe was  $\pm 1\%$  of the nominal volume.<sup>277</sup>

Compounds available in the Thompson Lab that did not require synthesis: **9**,<sup>178</sup> **13**,<sup>179</sup> **19**,<sup>187</sup> **20**,<sup>188</sup> **46**,<sup>88</sup> **52**,<sup>206</sup> **91**,<sup>266</sup> 4-benzyl 2-*tert*-butyl ester 3,5-dimethyl-1*H*-pyrrole-2,4-dicarboxylic acid,<sup>278</sup> 2-benzyl 4-ethyl ester 3,5-dimethyl-1*H*-pyrrole-2,4-dicarboxylic acid.<sup>87</sup>

## 5.2 General Procedures

### 5.2.1 General Procedure for the Anhydrous Synthesis of *F*-BODIPYs (GP1)

These experiments used strictly anhydrous protocols, conditions and reagents. In an oven-dried round-bottom equipped with a stir bar, dipyrin HBr salt (0.16 mmol, 1 equiv) was dissolved in anhydrous  $\text{CH}_2\text{Cl}_2$  (13 mL) at room temperature (18-25  $^\circ\text{C}$ ), under  $\text{N}_2$ . Anhydrous  $\text{NEt}_3$  (6 equiv) was added, and the reaction mixture was stirred for 10 min. Anhydrous  $\text{BF}_3 \cdot \text{OEt}_2$  (9 equiv) was then added and the resulting solution was stirred, under  $\text{N}_2$ , for 2.5 h. The reaction mixture was concentrated *in vacuo* to yield the crude product, which was dissolved in ether (20 mL) and washed with 1 M HCl (3 x 20 mL). The organic fractions were dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated *in vacuo*. The resulting residue was purified via column chromatography on silica, eluting with  $\text{CH}_2\text{Cl}_2$ , to yield the desired *F*-BODIPY.

### 5.2.2 General Procedure for the Synthesis of *F*-BODIPYs with Added Water (GP2)

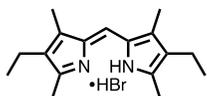
These experiments used strictly anhydrous protocols, conditions and reagents prior to addition of water. In an oven-dried round-bottom equipped with a stir bar, dipyrin HBr salt (0.16 mmol, 1 equiv) was dissolved in anhydrous CH<sub>2</sub>Cl<sub>2</sub> under N<sub>2</sub>, and distilled water (2 equiv) was added at room temperature. Once the water micelle was no longer visible (~45 min for 2 equiv), anhydrous NEt<sub>3</sub> (6 equiv) was added and the reaction mixture was stirred for 10 min. Anhydrous BF<sub>3</sub>•OEt<sub>2</sub> (9 equiv) was then added and the resulting solution was stirred, under nitrogen, for 2.5 h. The reaction mixture was concentrated *in vacuo* and the resulting residue was dissolved in CDCl<sub>3</sub> (4.00 mL) and benzene (4 μL) was added, with stirring. An aliquot (200 μL) of this solution was added to an NMR sample tube and diluted with CDCl<sub>3</sub> (400 μL). A <sup>1</sup>H NMR spectrum of the sample was collected, and the NMR-based yield was determined. To gain an isolated yield, the NMR sample was recombined with the remaining crude product, which was then dissolved in ether (20 mL) and washed with 1 M HCl (3 x 20 mL). The organic fraction was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The resulting residue was purified via column chromatography on silica, eluting with CH<sub>2</sub>Cl<sub>2</sub>, to yield the desired *F*-BODIPY.

### 5.2.3 General Procedure for the Optimized Open-air Bench-top Synthesis of *F*-BODIPYs (GP3)

Naturally air-dried glassware was used, without any provision to exclude air or moisture from the reaction vessel. In a round-bottom equipped with a stir bar, dipyrin HBr salt (0.16 mmol, 1 equiv) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (13 mL, lab-grade, non-anhydrous) at room temperature, under air. NEt<sub>3</sub> (6 equiv, lab-grade, non-anhydrous) was added and the reaction mixture was stirred for 10 min. Anhydrous BF<sub>3</sub>•OEt<sub>2</sub> (9 equiv) was then added and the resulting solution was sealed with a septum and stirred for 1.25 h. The septum was then removed, and NEt<sub>3</sub> (6 equiv, lab-grade, non-anhydrous) was added. The vessel was resealed and stirred for 5 min, after which the septum was again removed and anhydrous BF<sub>3</sub>•OEt<sub>2</sub> (9 equiv) was added. The resulting solution was sealed with a septum for a final time and then stirred for another 1.25 h. The reaction mixture was concentrated *in vacuo* and the resulting residue was dissolved in ether (20 mL) and washed with 1 M HCl (3 x 20 mL) and 5 M HCl (1 x 20 mL). The organic fraction was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The resulting residue was purified via column chromatography on silica, eluting with CH<sub>2</sub>Cl<sub>2</sub>, to yield the desired *F*-BODIPY.

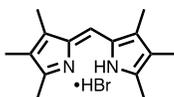
## 5.3 Synthesis of Compounds

### 3-Ethyl-5-[(4-ethyl-3,5-dimethyl-2*H*-pyrrol-2-ylidene)methyl]-2,4-dimethyl-1*H*-pyrrole Monohydrobromide (1)



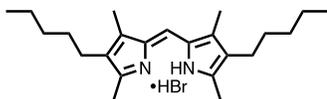
The title compound was synthesized according to a literature procedure<sup>104</sup> and isolated as a dark-red crystalline solid (6.8 g, 75%). <sup>1</sup>H NMR (300 MHz; CDCl<sub>3</sub>)  $\delta$  12.95 (br s, 2H), 7.02 (s, 1H), 2.66 (s, 6H), 2.42 (q,  $J = 7.6$  Hz, 4H), 2.26 (s, 6H), 1.07 (t,  $J = 7.6$  Hz, 6H), in accordance with previous literature.<sup>104</sup>

### 2,3,4-Trimethyl-5-[(3,4,5-trimethyl-2*H*-pyrrol-2-ylidene)methyl]-1*H*-pyrrole Monohydrobromide (2)



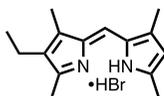
The title compound was synthesized according to a literature procedure<sup>104</sup> and isolated as a dark red crystalline solid (857 mg, 51%). <sup>1</sup>H NMR (300 MHz; CDCl<sub>3</sub>)  $\delta$  12.93 (br s, 2H), 7.02 (s, 1H), 2.64 (s, 6H), 2.24 (s, 6H), 1.97 (s, 6H), in accordance with previous literature.<sup>104</sup>

**2-[(3,5-Dimethyl-4-*n*-pentyl-2*H*-pyrrol-2-ylidene)methyl]-3,5-dimethyl-4-*n*-pentyl-1*H*-pyrrole Monohydrobromide (3)**



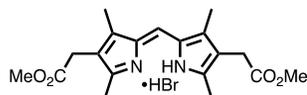
The title compound was synthesized according to a literature procedure<sup>104</sup> and isolated as a dark red solid (57 mg, 70%). <sup>1</sup>H NMR (300 MHz; CDCl<sub>3</sub>)  $\delta$  12.94 (br s, 2H), 7.02 (s, 1H), 2.65 (s, 6H), 2.39 (t,  $J = 7.5$  Hz, 4H), 2.25 (s, 6H), 1.46-1.28 (m, 12H), 0.89 (t,  $J = 6.9$  Hz, 6H), in accordance with previous literature.<sup>104</sup>

**2-[(3,5-Dimethyl-2*H*-pyrrol-2-ylidene)methyl]-4-ethyl-3,5-dimethyl-1*H*-pyrrole Monohydrobromide (4)**



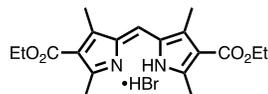
The title compound was synthesized according to a literature procedure<sup>186</sup> and isolated as a dark-red solid (720 mg, 71%). <sup>1</sup>H NMR (300 MHz; CDCl<sub>3</sub>)  $\delta$  13.10 (br s, 1H), 13.00 (br s, 1H), 7.05 (s, 1H), 6.13 (s, 1H), 2.69 (s, 3H), 2.67 (s, 3H), 2.43 (q,  $J = 7.6$  Hz, 2H), 2.34 (s, 3H), 2.27 (s, 3H), 1.08 (t,  $J = 7.6$  Hz, 3H), in accordance with previous literature.<sup>186</sup>

**Methyl Ester 5-[[4-(2-Methoxy-2-oxoethyl)-3,5-dimethyl-2*H*-pyrrol-2-ylidene]methyl]-2,4-dimethyl-1*H*-pyrrole-3-acetic Acid Monohydrobromide (5)**



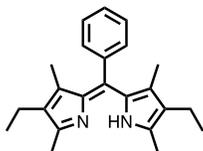
The title compound was synthesized according to a literature procedure<sup>105</sup> and isolated as a light orange solid (484 mg, 68%). <sup>1</sup>H NMR (300 MHz; CDCl<sub>3</sub>) δ 13.24 (br s, 2H), 7.12 (s, 1H), 3.69 (s, 6H), 3.44 (s, 4H), 2.70 (s, 6H), 2.31 (s, 6H), in accordance with previous literature.<sup>105</sup>

**Ethyl Ester 5-[[4-(Ethoxycarbonyl)-3,5-dimethyl-2*H*-pyrrol-2-ylidene]methyl]-2,4-dimethyl-1*H*-pyrrole-3-carboxylic Acid Monohydrobromide (6)**



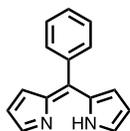
The title compound was synthesized according to a literature procedure<sup>105</sup> and isolated as a dark red solid (878 mg, 80%). <sup>1</sup>H NMR (300 MHz; CDCl<sub>3</sub>) δ 13.73 (br s, 2H), 7.47 (s, 1H), 4.35 (q, *J* = 7.1 Hz, 4H), 2.96 (s, 6H), 2.67 (s, 6H), 1.40 (t, *J* = 7.1 Hz, 6H). <sup>13</sup>C {<sup>1</sup>H} NMR (126 MHz; CDCl<sub>3</sub>): δ 163.2, 160.1, 150.7, 126.7, 123.2, 119.9, 76.9, 60.9, 15.6, 14.5, 12.5. <sup>1</sup>H and <sup>13</sup>C NMR data have not been previously reported for this compound.

**3-Ethyl-5-[(4-ethyl-3,5-dimethyl-2*H*-pyrrol-2-ylidene)phenylmethyl]-2,4-dimethyl-1*H*-pyrrole (7)**



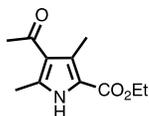
The title compound was synthesized according to a literature procedure<sup>191</sup> and isolated as a dark red solid (365 mg, 20% over two steps). <sup>1</sup>H NMR (300 MHz; CDCl<sub>3</sub>)  $\delta$  7.48-7.45 (m, 3H), 7.30-7.27 (m, 2H), 2.53 (s, 6H), 2.30 (q,  $J$  = 7.6 Hz, 4H), 1.28 (s, 6H), 0.98 (t,  $J$  = 7.6 Hz, 6H), in accordance with previous literature.<sup>191</sup>

**2-(Phenyl-2*H*-pyrrol-2-ylidenemethyl)-1*H*-pyrrole (8)**



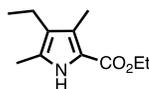
The title compound was synthesized according to a literature procedure<sup>191</sup> and isolated as an off-white solid (1.7 g, 26% over two steps). <sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>)  $\delta$  12.76 (br s, 1H), 7.66-7.66 (m, 2H), 7.53-7.44 (m, 6H), 6.63-6.62 (m, 2H), 6.42-6.41 (m, 2H), in accordance with previous literature.<sup>96</sup>

### Ethyl Ester 4-Acetyl-3,5-dimethyl-1*H*-pyrrole-2-carboxylic Acid (10)



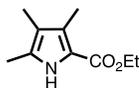
The title compound was synthesized according to a literature procedure<sup>81</sup> and isolated as an off-white solid (66.0 g, 54%). <sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>) δ 9.38 (br s, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 2.62 (s, 3H), 2.56 (s, 3H), 2.48 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H), in accordance with previous literature.<sup>81</sup>

### Ethyl Ester 4-Ethyl-3,5-dimethyl-1*H*-pyrrole-2-carboxylic Acid (11)



The title compound was synthesized according to a literature procedure<sup>180</sup> and isolated as a white solid (11.8 g, 84%). <sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>) δ 8.55 (br s, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 2.38 (q, *J* = 7.6 Hz, 2H), 2.28 (s, 3H), 2.20 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.05 (t, *J* = 7.6 Hz, 3H), in accordance with previous literature.<sup>180</sup>

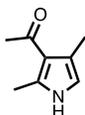
### Ethyl Ester 3,4,5-Trimethyl-1*H*-pyrrole-2-carboxylic Acid (12)



The title compound was synthesized according to a literature procedure<sup>181</sup> and isolated as an off-white solid (4.0 g, 25%). <sup>1</sup>H NMR (300 MHz; CDCl<sub>3</sub>) δ 8.46 (br s, 1H), 4.29 (q, *J*

= 7.1 Hz, 2H), 2.25 (s, 3H), 2.18 (s, 3H), 1.91 (s, 3H), 1.34 (t,  $J = 7.1$  Hz, 3H), in accordance with previous literature.<sup>81</sup>

### 1-(2,4-Dimethyl-1*H*-pyrrol-3-yl)ethanone (14)



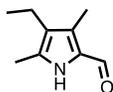
The title compound was synthesized according to a literature procedure<sup>81</sup> and isolated as an off-white solid (43.0 g, 66%). <sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>)  $\delta$  8.14 (br s, 1H), 6.36 (s, 1H), 2.50 (s, 3H), 2.43 (s, 3H), 2.27 (s, 3H), in accordance with previous literature.<sup>81</sup>

### 3-Ethyl-2,4-dimethyl-1*H*-pyrrole (15)



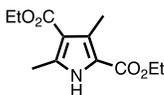
The title compound was synthesized according to a literature procedure<sup>81</sup> and isolated as a colourless liquid (6.8 g, 60%). <sup>1</sup>H NMR (300 MHz; CDCl<sub>3</sub>)  $\delta$  7.46 (br s, 1H), 6.40 (s, 1H), 2.42 (q,  $J = 7.5$  Hz, 2H), 2.19 (s, 3H), 2.06 (s, 3H), 1.11 (t,  $J = 7.5$  Hz, 3H), in accordance with previous literature.<sup>81</sup>

#### 4-Ethyl-3,5-dimethyl-1*H*-pyrrole-2-carboxaldehyde (16)



The title compound was synthesized according to a literature procedure<sup>182</sup> and isolated as an olive green solid (1.6 g, 80%). <sup>1</sup>H NMR (300 MHz; CDCl<sub>3</sub>) δ 9.47 (br s, 1H), 9.18 (s, 1H), 2.38 (q, *J* = 7.6 Hz, 2H), 2.27 (s, 3H), 2.24 (s, 3H), 1.06 (t, *J* = 7.6 Hz, 3H), in accordance with previous literature.<sup>182</sup>

#### 2,4-Diethyl Ester 3,5-Dimethyl-1*H*-pyrrole-2,4-dicarboxylic Acid (17)



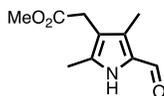
The title compound was synthesized according to a literature procedure<sup>183</sup> and isolated as an off-white solid (29.2 g, 41%). <sup>1</sup>H NMR (300 MHz; CDCl<sub>3</sub>) δ 8.99 (s, 1H), 4.36-4.26 (m, 4H), 2.56 (s, 3H), 2.51 (s, 3H), 1.39-1.33 (m, 6H), in accordance with previous literature.<sup>183</sup>

## 2,4-Dimethyl-1*H*-pyrrole (18)



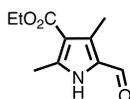
The title compound was synthesized according to a literature procedure<sup>184</sup> and isolated as a colourless liquid (3.9 g, 54%). <sup>1</sup>H NMR (300 MHz; CDCl<sub>3</sub>)  $\delta$  7.60 (br s, 1H), 6.47 (s, 1H), 5.84 (s, 1H), 2.32 (s, 1H), 2.20 (s, 1H), in accordance with previous literature.<sup>184</sup>

## Methyl Ester 5-Formyl-2,4-dimethyl-1*H*-pyrrole-3-acetic Acid (21)



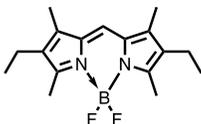
The title compound was synthesized according to a literature procedure<sup>189</sup> and isolated as an off-white solid (650 mg, 31%). <sup>1</sup>H NMR (300 MHz; CDCl<sub>3</sub>)  $\delta$  10.05 (br s, 1H), 9.49 (s, 1H), 3.70 (s, 3H), 3.39 (s, 2H), 2.34 (s, 6H), in accordance with previous literature.<sup>279</sup>

## Ethyl Ester 5-Formyl-2,4-dimethyl-1*H*-pyrrole-3-carboxylic Acid (22)



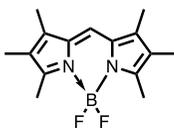
The title compound was synthesized according to a literature procedure<sup>190</sup> and isolated as a yellow green solid (1.87 g, 90%). <sup>1</sup>H NMR (300 MHz; CDCl<sub>3</sub>)  $\delta$  10.51 (s, 1H), 9.63 (br s, 1H), 4.33 (q,  $J = 7.1$  Hz, 2H), 2.59 (s, 3H), 2.55 (s, 3H), 1.37 (t,  $J = 7.1$  Hz, 3H), in accordance with previous literature.<sup>188</sup>

**(*T*-4)-Difluoro[3-ethyl-5-[(4-ethyl-3,5-dimethyl-2*H*-pyrrol-2-ylidene- $\kappa$ N)methyl]-2,4-dimethyl-1*H*-pyrrolato- $\kappa$ N]boron (26)**



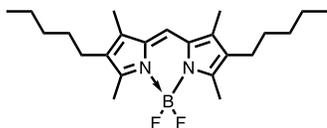
The title compound was synthesized from **1**<sup>104</sup> under non-anhydrous conditions according to GP3, and was isolated as a dark red solid (2.5 g, 98%). <sup>1</sup>H NMR (300 MHz; CDCl<sub>3</sub>)  $\delta$  6.95 (s, 1H), 2.49 (s, 6H), 2.38 (q, 4H,  $J = 7.7$  Hz), 2.16 (s, 6H), 1.06 (t, 6H,  $J = 7.7$  Hz), in accordance with previous literature.<sup>133</sup>

**(*T*-4)-Difluoro[5-[(3,4,5-trimethyl-2*H*-pyrrol-2-ylidene- $\kappa$ N)methyl]-2,3,4-trimethyl-1*H*-pyrrolato- $\kappa$ N]boron (27)**



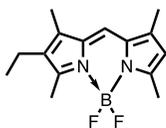
The title compound was synthesized from **2**<sup>104</sup> under non-anhydrous conditions according to GP3, and was isolated as a light orange solid (52 mg, 92%). <sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>)  $\delta$  6.94 (s, 1H), 2.48 (s, 6H), 2.15 (s, 6H), 1.93 (s, 6H), in accordance with previous literature.<sup>104</sup>

**(*T*-4)-Difluoro[5-[(3,5-dimethyl-4-*n*-pentyl-2*H*-pyrrol-2-ylidene- $\kappa$ N)methyl]-2,4-dimethyl-3-*n*-pentyl-1*H*-pyrrolato- $\kappa$ N]boron (28)**



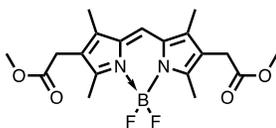
The title compound was synthesized from **3**<sup>104</sup> under non-anhydrous conditions according to GP3, and was isolated as a dark red solid (49 mg, 87%). <sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>)  $\delta$  6.94 (s, 1H), 2.48 (s, 6H), 2.34 (t, 7.5 Hz, 4H), 2.15 (s, 6H), 1.46-1.40 (m, 4H), 1.34-1.30 (m, 8H), 0.90 (t,  $J = 6.8$  Hz, 6H), in accordance with previous literature.<sup>133</sup>

**(*T*-4)-Difluoro[5-[(4-ethyl-3,5-dimethyl-2*H*-pyrrol-2-ylidene- $\kappa$ N)methyl]-2,4-dimethyl-1*H*-pyrrolato- $\kappa$ N]boron (29)**



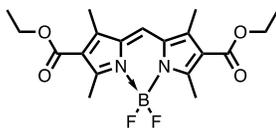
The title compound was synthesized from **4**<sup>186</sup> under non-anhydrous conditions according to GP3, and was isolated as a red solid (48 mg, 98%). <sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>)  $\delta$  6.99 (s, 1H), 6.00 (s, 1H), 2.51 (s, 3H), 2.49 (s, 3H), 2.39 (q, 2H,  $J = 7.7$  Hz), 2.23 (s, 3H), 2.17 (s, 3H), 1.07 (t, 3H,  $J = 7.7$  Hz), in accordance with previous literature.<sup>191</sup>

**(*T*-4)-Difluoro[4-(2-methoxy-2-oxoethyl)-2-[(4-(2-methoxy-2-oxoethyl)-3,5-dimethyl-2*H*-pyrrol-2-ylidene- $\kappa$ *N*)methyl]-3,5-dimethyl-1*H*-pyrrolato- $\kappa$ *N*]boron (30)**



The title compound was synthesized for the first time from **5**<sup>105</sup> under non-anhydrous conditions according to GP3, and was isolated as an orange solid (46 mg, 85%). M.p. 214-218 °C; <sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>)  $\delta$  7.05 (s, 1H), 3.69 (s, 6H), 3.40 (s, 4H), 2.51 (s, 6H), 2.21 (s, 6H); <sup>13</sup>C {<sup>1</sup>H} NMR (125 MHz; CDCl<sub>3</sub>)  $\delta$  171.2, 155.9, 139.1, 132.6, 122.5, 120.2, 52.3, 30.2, 12.9, 9.9; <sup>11</sup>B {<sup>1</sup>H} NMR (160 MHz; CDCl<sub>3</sub>)  $\delta$  0.85 (t, *J* = 33 Hz); <sup>19</sup>F {<sup>1</sup>H} NMR (470 MHz; CDCl<sub>3</sub>)  $\delta$  145.8 (qs, *J* = 55 Hz); HRMS-ESI (*m/z*): [M+Na]<sup>+</sup> calculated for C<sub>19</sub>H<sub>23</sub>N<sub>2</sub>O<sub>4</sub>BF<sub>2</sub>Na 415.1611; found 415.1626.

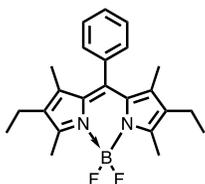
**(*T*-4)-Difluoro[4-ethoxycarbonyl-2-[(4-ethoxycarbonyl-3,5-dimethyl-2*H*-pyrrol-2-ylidene- $\kappa$ *N*)methyl]-3,5-dimethyl-1*H*-pyrrolato- $\kappa$ *N*]boron (31)**



The title compound was synthesized from **6**<sup>189</sup> under non-anhydrous conditions according to GP3, and was isolated as a pale yellow/orange solid (60 mg, 96%). <sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>)  $\delta$  7.40 (s, 1H), 4.33 (q, 4H, *J* = 7.2 Hz), 2.83 (s, 6H), 2.53 (s, 6H), 1.39 (t, 6H, *J* = 7.2 Hz); <sup>13</sup>C {<sup>1</sup>H} NMR (125 MHz; CDCl<sub>3</sub>)  $\delta$  164.2, 161.3, 146.0, 133.2, 123.5, 121.1, 60.4, 15.2, 14.5, 12.2; <sup>11</sup>B (160 MHz; CDCl<sub>3</sub>)  $\delta$  0.83 (t, *J* = 53 Hz); <sup>19</sup>F {<sup>1</sup>H} (470

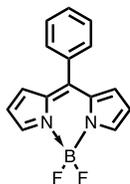
MHz; CDCl<sub>3</sub>)  $\delta$  143.2 (qs,  $J = 38$  Hz). HRMS-ESI ( $m/z$ ): [M+Na]<sup>+</sup> calculated for C<sub>19</sub>H<sub>23</sub>N<sub>2</sub>O<sub>4</sub>BF<sub>2</sub>Na 415.1611; found 415.1626. <sup>1</sup>H NMR data match that previously reported for this compound.<sup>159</sup> <sup>13</sup>C, <sup>11</sup>B, and <sup>19</sup>F NMR data have not been previously reported for this compound.

**(*T*-4)-Difluoro[4-ethyl-2-[(4-ethyl-3,5-dimethyl-2*H*-pyrrol-2-ylidene- $\kappa$ N)phenylmethyl]-3,5-dimethyl-1*H*-pyrrolato- $\kappa$ N]boron (32)**



The title compound was synthesized from dipyrin **7**<sup>280</sup> under non-anhydrous conditions according to GP3, and was isolated as a dark red solid (56 mg, 92%). <sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>)  $\delta$  7.49-7.46 (m, 3H), 7.29-7.27 (m, 2H), 2.53 (s, 6H), 2.30 (q,  $J = 4.5$  Hz, 4H), 1.27 (s, 6H), 0.98 (t,  $J = 7.5$  Hz, 6H), in accordance with previous literature.<sup>191</sup>

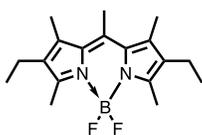
**(*T*-4)-Difluoro[2-[phenyl(2*H*-pyrrol-2-ylidene- $\kappa$ N)methyl]-1*H*-pyrrolato- $\kappa$ N]boron (33)**



The title compound was synthesized from dipyrin **8**<sup>280</sup> under non-anhydrous conditions according to GP3, and was isolated as a dark red solid (980 mg, 95%). <sup>1</sup>H NMR (300

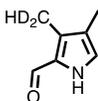
MHz; CDCl<sub>3</sub>)  $\delta$  7.95 (s, 2H), 7.62-7.50 (m, 5H), 6.95-6.93 (m, 2H), 6.56-6.54 (m, 2H), in accordance with previous literature.<sup>200</sup>

**(*T*-4)-Difluoro[3-ethyl-5-[1-(4-ethyl-3,5-dimethyl-2*H*-pyrrol-2-ylidene- $\kappa$ N)ethyl]-2,4-dimethyl-1*H*-pyrrolato- $\kappa$ N]boron (34)**



The title compound was synthesized from **9**<sup>178</sup> under non-anhydrous conditions according to GP3, and was isolated as a light orange solid (46 mg, 96%). <sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>)  $\delta$  2.60 (s, 3H), 2.50 (s, 6H), 2.40 (q,  $J$  = 7.5 Hz, 4H), 2.33 (s, 6H), 1.04 (t,  $J$  = 7.5 Hz, 6H), in accordance with previous literature.<sup>191</sup>

**3-(Methyl-*d*<sub>2</sub>)-4-methyl-1*H*-pyrrole-2-carboxaldehyde (40\*)**



The title compound was synthesized for the first time following a modified literature procedure.<sup>87</sup> To a suspension of **51\*** (63 mg, 0.29 mmol) in methanol (1.0 mL) at reflux temperature was added NaOH (4M, 1.0 mL) dropwise over several min, under N<sub>2</sub>. The resulting mixture was heated at reflux temperature for 30 min. Methanol was removed *in vacuo*, water was added (1.0 mL), and the reaction mixture was heated at reflux temperature for 1.5 h. After cooling, the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 5 mL)

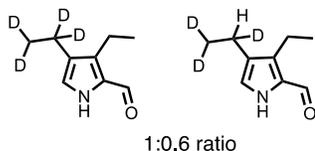
and the combined organic fractions were washed with water, brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and the solvent removed *in vacuo*. The resulting residue was purified via column chromatography on silica, eluting with a gradient of 20-30% EtOAc/hexanes, to yield the desired product as an off-white solid (19 mg, 52%). M.p. 131-132 °C; <sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>) δ 9.58 (s, 1H), 9.34 (s, 1H), 6.85-6.84 (m, 1H), 2.27-2.23 (m, 1H), 2.02 (s, 3H); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz; CDCl<sub>3</sub>) δ 177.3, 131.1, 129.7, 124.7, 121.1, 9.5, 8.1 (apparent quin, *J* = 19.5 Hz); HRMS-ESI (*m/z*): [M+Na]<sup>+</sup> calculated for C<sub>7</sub>H<sub>7</sub>D<sub>2</sub>N<sub>2</sub>O<sub>1</sub>Na<sub>1</sub> 148.0702; found 148.0700.

### 3,4-Dimethyl-1*H*-pyrrole-2-carboxaldehyde (**40**)



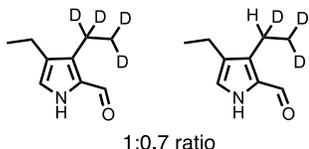
Following the same procedure used to prepare **40\***, aqueous NaOH (4 M, 9.5 mL) was added dropwise to a suspension of **51** (1.65 g, 7.56 mmol) in methanol (18 mL) at reflux temperature, under N<sub>2</sub>. Following the same work-up as for **40\***, the desired product was obtained as an off-white solid (534 mg, 57%). <sup>1</sup>H NMR (300 MHz; CDCl<sub>3</sub>) δ 9.63 (br s, 1H), 9.57 (s, 1H), 6.87-6.86 (m, 1H), 2.27 (s, 3H), 2.01 (s, 3H), in accordance with previous literature.<sup>281</sup>

**4-(Ethyl-1,1,2,2-*d*<sub>4</sub>)-3-ethyl-1*H*-pyrrole-2-carboxaldehyde and 4-(Ethyl-1,2,2-*d*<sub>3</sub>)-3-ethyl-1*H*-pyrrole-2-carboxaldehyde (41\*(**D**<sub>4</sub>) and 41\*(**D**<sub>3</sub>))**



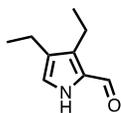
The title compounds were isolated for the first time by Thompson lab postdoctoral fellow Dr. Carlotta Figliola.<sup>282</sup> In an oven-dried round-bottom equipped with a stir bar, a mixture of pyrrole **64** (300 mg, 2.04 mmol) and Pd (10% on activated carbon, 30 mg, 10% w/w) in THF (25 mL) was stirred at room temperature under an atmosphere of deuterium for 19 h. The reaction mixture was filtered through Celite<sup>®</sup>, which was washed with MeOH (×3). The combined washings were concentrated *in vacuo*. The crude mixture was purified via column chromatography on silica, eluting with an EtOAc/hexanes to give a pale yellow solid (270 mg, 85%), containing both **41\*(D<sub>4</sub>)** and **41\*(D<sub>3</sub>)** in a 1:0.6 ratio. The following data corresponds to the deuterated compound **41\*(D<sub>4</sub>)**. <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>, 500 MHz) 10.58 (br s, 1H), 9.62 (s, 1H), 6.85 (d, 1H, *J* = 3.0 Hz), 2.77 (q, 2H, *J* = 7.6 Hz), 1.24 (t, 3H, *J* = 7.6 Hz), 1.17 (br s, 1H). Multiplet at 2.43-2.44 ppm arises from the CHD group of the deuterated compound **41\*(D<sub>3</sub>)**. <sup>13</sup>C NMR (CD<sub>2</sub>Cl<sub>2</sub>, 125 MHz) 177.9, 138.0, 129.4, 127.5, 125.2, 13.9-14.7 (m, CHD<sub>2</sub>), 17.8-16.9 (m, CD<sub>2</sub>), 17.3 (CH<sub>2</sub>), 17.2 (CH<sub>3</sub>). HRMS-ESI (*m/z*): [M+Na]<sup>+</sup> calcd for C<sub>9</sub>H<sub>9</sub>D<sub>4</sub>NNaO, 178.1140; found, 178.1139.

**3-(Ethyl-1,1,2,2-*d*<sub>4</sub>)-4-ethyl-1*H*-pyrrole-2-carboxaldehyde and 3-(Ethyl-1,2,2-*d*<sub>3</sub>)-4-ethyl-1*H*-pyrrole-2-carboxaldehyde (**41\*'(*D*<sub>4</sub>)** and **41\*'(*D*<sub>3</sub>)**)**



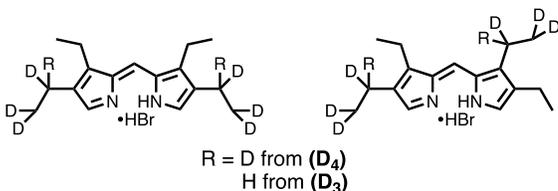
The title compounds were isolated for the first time by Thompson lab postdoctoral fellow Dr. Carlotta Figliola.<sup>282</sup> In an oven-dried round-bottom equipped with a stir bar, a mixture of pyrrole **64'** (190 mg, 1.28 mmol) and Pd (10% on activated carbon, 19 mg, 10% w/w) in THF (16 mL) was stirred at room temperature under an atmosphere of deuterium for 19 h. The reaction mixture was filtered through Celite<sup>®</sup>, which was washed with MeOH (×3). The combined washings were concentrated *in vacuo*. The crude mixture was purified via column chromatography on silica, eluting with an EtOAc/hexanes to give a pale yellow solid (175 mg, 88%), containing both **41\*'(*D*<sub>4</sub>)** and **41\*'(*D*<sub>3</sub>)** in a 1:0.7 ratio. The following data correspond to the deuterated compound **41\*'(*D*<sub>4</sub>)**. <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>, 500 MHz) 9.58 (s, 1H), 9.34 (br s, 1H), 6.87 (d, 1H, *J* = 3.0 Hz), 2.46 (q, 2H, *J* = 7.6 Hz), 1.19 (t, 3H, *J* = 7.6 Hz), 1.15 (br s, 1H). Multiplet at 2.69-2.74 ppm arises from the CHD group of the deuterated compound **41\*'(*D*<sub>3</sub>)**. <sup>13</sup>C NMR (CD<sub>2</sub>Cl<sub>2</sub>, 125 MHz) 177.7, 137.1, 129.4, 127.7, 124.0, 18.0 (CH<sub>2</sub>), 17.2-16.3 (m, CHD<sub>2</sub> and CD<sub>2</sub>), 14.9 (CH<sub>3</sub>). HRMS-ESI (*m/z*): [M+Na]<sup>+</sup> calcd for C<sub>9</sub>H<sub>9</sub>D<sub>4</sub>NNaO, 178.1140; found, 178.1138.

### 3,4-Diethyl-1*H*-pyrrole-2-carboxaldehyde (**41**)



The title compound was prepared according to a literature procedure<sup>182</sup> and isolated as an off-white solid (1.41 g, 75%). <sup>1</sup>H NMR (300 MHz; CDCl<sub>3</sub>)  $\delta$  9.60 (apparent d,  $J = 0.9$  Hz, 1H), 9.19 (br s, 1H), 6.86 (apparent d,  $J = 2.7$  Hz, 1H), 2.74 (q,  $J = 7.6$  Hz, 2H), 2.46 (apparent qd,  $J = 7.5, 0.6$  Hz, 2H), 1.25-1.18 (m, 6H), in accordance with previous literature.<sup>283</sup>

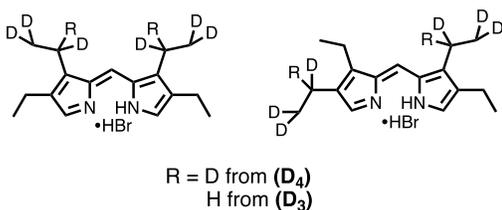
### 4-(Ethyl-1,1,2,2-*d*<sub>4</sub>)-3-ethyl-2-[(4-(ethyl-1,1,2,2-*d*<sub>4</sub>)-3-ethyl-2*H*-pyrrol-2-ylidene)methyl]-1*H*-pyrrole Monohydrobromide *and* 3-(Ethyl-1,1,2,2-*d*<sub>4</sub>)-4-ethyl-2-[(4-(ethyl-1,1,2,2-*d*<sub>4</sub>)-3-ethyl-2*H*-pyrrol-2-ylidene)methyl]-1*H*-pyrrole Monohydrobromide (sym-45\* *and* asym-45\*)



HBr (48% aqueous solution, 0.4 mL) was added drop-wise to a solution of the **41**\* pyrrole mixture (40 mg, 0.26 mmol) in MeOH (0.8 mL) and the solution was slowly heated to 65 °C and stirred for 5 min until complete consumption of the starting material according to TLC analysis. The reaction mixture was cooled to room temperature and stored in the freezer for 19 h. Filtration resulted in isolation of the precipitate as a crystalline dark green solid (22 mg, 50%) containing dipyrrens **sym-45\*** and **asym-45\***,

both in a 1:1 ratio. The following data correspond to **sym-45\*(D<sub>8</sub>)**: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) 13.28 (br s, 2H), 7.74 (d, 2H, *J* = 3.0 Hz), 7.28 (br s, 1H), 2.72 (q, 4H, *J* = 7.6 Hz), 1.21 (t, 6H, *J* = 7.6 Hz), 1.18-1.17 (m, 1H). The multiplet at 2.48 ppm arises from the CH<sub>2</sub> group of the **asym-45\*(D<sub>7</sub>)** from **41\*(D<sub>4</sub>)** and **41\*(D<sub>3</sub>)**. <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) 148.9, 141.7, 131.7, 127.4, 123.2, 18.38, 18.0, 17.9-17.5 (m, CD<sub>2</sub>), 16.8, 16.6-15.3 (m, CHD<sub>2</sub>), 14.3. The <sup>13</sup>C signals at 17.9 and 14.3 ppm arise from the CH<sub>3</sub> (x2) and CH<sub>2</sub> (x2), respectively, of the **asym-45\*(D<sub>6</sub>)** from **41\*(D<sub>3</sub>)** and **41\*(D<sub>3</sub>)**. HRMS-ESI (*m/z*): [M-Br]<sup>+</sup> calcd for C<sub>17</sub>H<sub>17</sub>D<sub>8</sub>N<sub>2</sub>, 265.2514; found, 265.2509.

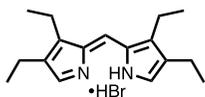
**3-(Ethyl-1,1,2,2-*d*<sub>4</sub>)-4-ethyl-2-[(3-(ethyl-1,1,2,2-*d*<sub>4</sub>)-4-ethyl-2*H*-pyrrol-2-ylidene)methyl]-1*H*-pyrrole Monohydrobromide and 3-(Ethyl-1,1,2,2-*d*<sub>4</sub>)-4-ethyl-2-[(4-(ethyl-1,1,2,2-*d*<sub>4</sub>)-3-ethyl-2*H*-pyrrol-2-ylidene)methyl]-1*H*-pyrrole Monohydrobromide (sym-45\*' and asym-45\*)**



The title compounds were isolated for the first time by Thompson lab postdoctoral fellow Dr. Carlotta Figliola;<sup>282</sup> analysis of spectra was performed by myself. HBr (48% aqueous solution, 400 μL) was added drop-wise to a solution of the **41\*' pyrrole mixture** (40 mg, 0.26 mmol) in MeOH (800 μL) and the solution was slowly heated to 65 °C and stirred for 5 min until complete consumption of the starting material according to TLC analysis. The reaction mixture was cooled to room temperature and stored in the freezer for 19 h. Filtration resulted in isolation of the precipitate as a crystalline dark green solid (22 mg,

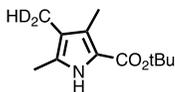
50%) containing dipyrrens **sym-45\*'** and **asym-45\***, both in a 1:1 ratio. The following data correspond to **sym-45\*' (D8)**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz) 13.28 (br s, 2H), 7.74 (d, 2H,  $J = 3.0$  Hz), 7.28 (br s, 1H), 2.48 (q, 4H,  $J = 7.6$  Hz), 1.21 (t, 6H,  $J = 7.6$  Hz), 1.18-1.17 (m, 1H). The multiplet at 2.70 ppm arises from the  $\text{CH}_2$  group of the **asym-45\* (D7)** from **41\*' (D4)** and **41\*' (D3)**.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz) 148.9, 141.7, 131.7, 127.4, 123.2, 18.1, 17.9, 17.3-18.1 (m,  $\text{CD}_2$ ), 16.6-15.7 (m,  $\text{CHD}_2$ ), 14.3. The  $^{13}\text{C}$  signals at 16.8 and 18.1 ppm arise from the  $\text{CH}_3$  ( $\times 2$ ) and  $\text{CH}_2$  ( $\times 2$ ), respectively, of the **asym-45\* (D6)** from **41\*' (D3)** and **41\*' (D3)**. HRMS-ESI ( $m/z$ ):  $[\text{M}-\text{Br}]^+$  calcd for  $\text{C}_{17}\text{H}_{17}\text{D}_8\text{N}_2$ , 265.2514; found, 265.2509.

## 2-[(3,4-Diethyl-2*H*-pyrrol-2-ylidene)methyl]-3,4-diethyl-1*H*-pyrrole Monohydrobromide (45)



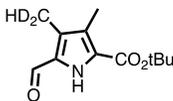
Following the same procedure used to prepare labelled dipyrrens **45\*** and **45\*'**, HBr (48% aqueous solution, 0.5 mL) was added drop-wise to a solution of **41** (50 mg, 0.33 mmol) in MeOH (1.0 mL). Following the same work-up as with labelled dipyrrens **45\*** and **45\*'**, the desired product was obtained as a black solid (27 mg, 49%).  $^1\text{H}$  NMR (500 MHz;  $\text{CDCl}_3$ )  $\delta$  13.29 (br s, 2H), 7.75 (m, 2H), 7.28 (s, 1H), 2.72 (q,  $J = 7.7$  Hz, 4H), 2.50 (q,  $J = 7.6$  Hz, 4H), 1.22 (m, 12H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz;  $\text{CDCl}_3$ )  $\delta$  149.0, 141.6, 131.6, 127.3, 123.2, 18.4, 18.0, 16.8, 14.3.  $^1\text{H}$  NMR data match that previously reported for this compound.<sup>216</sup>  $^{13}\text{C}$  NMR data have not been previously reported for this compound.

### ***tert*-Butyl Ester 4-(Methyl-*d*<sub>2</sub>)-3,5-dimethyl-1*H*-pyrrole-2-carboxylic Acid (46\*)**



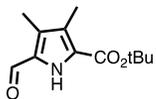
The title compound was synthesized for the first time following a modified literature procedure.<sup>210</sup> In an oven-dried round-bottom equipped with a stir bar, NaBD<sub>4</sub> (175 mg, 4.22 mmol) was added to a cooled solution (-10 °C, salt/ice) of **54** (500 mg, 2.27 mmol) in THF (4.5 mL), under N<sub>2</sub>. When almost all the NaBD<sub>4</sub> was dissolved, BF<sub>3</sub>•OEt<sub>2</sub> (750 μL, 6.07 mmol) was added slowly, dropwise, to avoid a dramatic increase in temperature (>0 °C). The resulting mixture was stirred for 1 h and monitored via TLC (20% EtOAc/hexanes) until starting material had been consumed. Once starting material was observed to be consumed, 0.5 M HCl was added until effervescence ceased, to destroy excess diborane. Water (equal volume to 0.5 M HCl added) was added and the mixture was extracted into ether (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The resulting residue was purified via column chromatography on silica, eluting with 20% EtOAc/hexanes, to yield the desired product as an off-white solid (60 mg, 13%). M.p. 136-138 °C; <sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>) δ 8.41 (br s, 1H), 2.22 (s, 3H), 2.17 (s, 3H), 1.91-1.86 (m, 1H), 1.56 (s, 9H); <sup>13</sup>C {<sup>1</sup>H} NMR (125 MHz; CDCl<sub>3</sub>) δ 161.3, 128.5, 126.6, 117.9, 116.8, 80.0, 28.6, 11.4, 10.6, 8.24 (apparent quin, *J* = 19.4 Hz); HRMS-ESI (*m/z*): [M+Na]<sup>+</sup> calculated for C<sub>12</sub>H<sub>17</sub>D<sub>2</sub>N<sub>1</sub>O<sub>2</sub>Na<sub>1</sub> 234.1434; found 234.1440.

***tert*-Butyl Ester 5-Formyl-4-(methyl-*d*<sub>2</sub>)-3-methyl-1*H*-pyrrole-2-Carboxylic Acid (47\*)**



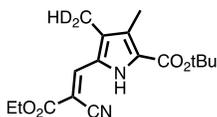
The title compound was synthesized for the first time following a modified literature procedure.<sup>284</sup> In an oven-dried round-bottom equipped with a stir bar, lead tetra-acetate (2.9 g, 6.6 mmol) was slowly added to a solution of **46\*** (610 mg, 2.9 mmol) in AcOH (3 mL) over 20 min. The mixture was heated at 80 °C for 30 min, and then allowed to cool to room temperature (23 °C). Ethylene glycol (200 µL) was then added to destroy excess oxidant. The reaction mixture was diluted with water (8 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 15 mL). The combined organic layers were washed with water (10 mL), and solvent was removed *in vacuo*. The resulting residue was dissolved in aqueous THF (50%, 10 mL) and heated at reflux temperature for 2 h. The mixture was diluted with ether (5 mL) and the organic layer separated. The organic layer was washed with sat. NaHCO<sub>3</sub> (20 mL), and brine (20 mL), and then dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> before the solvent was evaporated *in vacuo*. The resulting residue was purified via column chromatography on silica, eluting with a gradient of 20-30% EtOAc/hexanes, to yield the desired product as an off-white solid (350 mg, 54%). M.p. 100-102 °C; <sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>) δ 9.75 (s, 1H), 9.30 (br s, 1H), 2.28-2.24 (m, 1H), 2.24 (s, 3H), 1.57 (s, 9H); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz; CDCl<sub>3</sub>): δ 179.1, 160.4, 130.4, 129.7, 126.6, 126.0, 82.3, 28.5, 9.8, 8.2 (apparent quin, *J* = 19.7 Hz); HRMS-ESI (*m/z*): [M+Na]<sup>+</sup> calculated for C<sub>12</sub>H<sub>15</sub>D<sub>2</sub>N<sub>1</sub>O<sub>3</sub>Na<sub>1</sub> 248.1226; found 248.1221.

***tert*-Butyl Ester 5-Formyl-3,4-dimethyl-1*H*-pyrrole-2-carboxylic Acid (47)**



Following the same procedure used to prepare **47\***, lead tetra-acetate (26.2 g, 59 mmol) was added to a solution of *tert*-butyl 3,4,5-trimethylpyrrole-2-carboxylate<sup>88</sup> (5.4 g, 26 mmol) in AcOH (26 mL). Following the same work-up used with **47\***, the desired product was obtained as an off-white solid (5.5 g, 95%). <sup>1</sup>H NMR (300 MHz; CDCl<sub>3</sub>)  $\delta$  9.75 (s, 1H), 9.31 (br s, 1H), 2.28 (s, 3H), 2.24 (s, 3H), 1.58 (s, 9H); <sup>13</sup>C {<sup>1</sup>H} NMR (126 MHz; CDCl<sub>3</sub>)  $\delta$  179.1, 160.4, 130.4, 129.7, 126.6, 126.0, 82.3, 28.5, 9.9, 8.7. <sup>1</sup>H NMR data match that previously reported for this compound.<sup>88</sup> <sup>13</sup>C NMR data have not been previously reported for this compound.

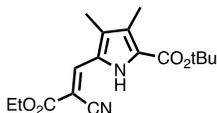
***tert*-Butyl Ester 5-(2-Cyano-3-ethoxy-3-oxo-1-propen-1-yl)-4-(methyl-*d*<sub>2</sub>)-3-methyl-1*H*-pyrrole-2-carboxylic Acid (48\*)**



The title compound was synthesized for the first time following a modified literature procedure.<sup>88</sup> A solution of methylamine (2 M in THF, 180  $\mu$ L) was added to a solution of **47\*** (350 mg, 1.61 mmol) and ethyl cyanoacetate (220  $\mu$ L, 2.12 mmol) in aqueous ethanol (95%, 800  $\mu$ L) at 80 °C. After several minutes of heating the product crystallized from solution and the mixture became thick with solid. The reaction mixture was cooled

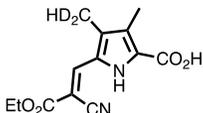
over ice and the product collected via Millipore™ suction filtration, rinsing with ice-cold ethanol, then hexanes, to yield the desired product as a brilliant yellow solid (386 mg, 78%). M.p. 181-183 °C; <sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>) δ 10.19 (br s, 1H), 8.03 (s, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 2.26 (s, 3H), 2.15-2.12 (m, 1H), 1.59 (s, 9H), 1.37 (t, *J* = 7.1 Hz, 3H); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz; CDCl<sub>3</sub>) δ 163.3, 159.6, 139.4, 133.5, 127.8, 126.5, 125.1, 118.3, 94.2, 82.6, 62.4, 28.4, 14.4, 10.0, 9.0 (apparent quin, *J* = 19.4 Hz); HRMS-ESI (*m/z*): [M+Na]<sup>+</sup> calculated for C<sub>17</sub>H<sub>20</sub>D<sub>2</sub>N<sub>2</sub>O<sub>4</sub>Na<sub>1</sub> 343.1597; found 343.1586.

***tert*-Butyl Ester 5-(2-Cyano-3-ethoxy-3-oxo-1-propen-1-yl)-3,4-dimethyl-1H-pyrrole-2-carboxylic Acid (48)**



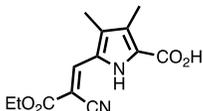
Following the same procedure used to prepare **48\***, a solution of methylamine (2 M in THF, 2.9 mL) was added to a solution of **47** (5.4 g, 25 mmol) and ethyl cyanoacetate (3.5 mL, 33 mmol) in aqueous ethanol (95%, 20 mL). Following the same work-up used with **48\***, the desired product was obtained as a brilliant yellow solid (6.2 g, 80%). <sup>1</sup>H NMR (300 MHz; CDCl<sub>3</sub>) δ 10.19 (br s, 1H), 8.04 (s, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 2.27 (s, 3H), 2.17 (s, 3H), 1.59 (s, 9H), 1.38 (t, *J* = 7.1 Hz, 3H); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz; CDCl<sub>3</sub>) δ 163.3, 159.6, 139.4, 133.5, 127.8, 126.5, 125.1, 118.3, 94.2, 82.6, 62.4, 28.4, 14.4, 10.0, 9.5. <sup>1</sup>H NMR data match that previously reported for this compound.<sup>88</sup> <sup>13</sup>C NMR data have not been previously reported for this compound.

## 5-(2-Cyano-3-ethoxy-3-oxo-1-propen-1-yl)-4-(methyl-*d*<sub>2</sub>)-3-methyl-1*H*-pyrrole-2-carboxylic Acid (49\*)



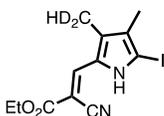
The title compound was synthesized for the first time following a modified literature procedure.<sup>88</sup> TFA (300  $\mu$ L) was added to a solution of **48\*** (387 mg, 1.21 mmol) in DCE (2.5 mL) at reflux temperature. The resulting solution was heated until the starting material was consumed, monitoring by TLC (25% EtOAc/hexanes). Product began to crystallize shortly after addition of TFA, and so more solvent was added as needed to the reaction mixture. The reaction mixture was cooled to 23  $^{\circ}$ C and placed in a freezer (-8  $^{\circ}$ C) to aid further precipitation. The mixture was filtered via Millipore<sup>TM</sup> suction filtration, washing with hexanes, to yield the desired product as a brilliant yellow solid (307 mg, 95%). M.p. 212-213  $^{\circ}$ C (decomp.); <sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>)  $\delta$  10.22 (br s, 1H), 8.08 (s, 1H), 4.37 (q,  $J$  = 7.1 Hz, 2H), 2.32 (s, 3H), 2.20-2.15 (m, 1H), 1.39 (t,  $J$  = 7.1 Hz, 3H); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz; CDCl<sub>3</sub>)  $\delta$  164.4, 163.0, 139.4, 133.3, 128.8, 126.5, 125.1, 117.9, 96.0, 62.7, 14.4, 10.2, 9.1 (apparent quin,  $J$  = 19.1 Hz); HRMS-ESI ( $m/z$ ): [M+Na]<sup>+</sup> calculated for C<sub>13</sub>H<sub>12</sub>D<sub>2</sub>N<sub>2</sub>O<sub>4</sub>Na<sub>1</sub> 287.0971; found 287.0981.

## 5-(2-Cyano-3-ethoxy-3-oxo-1-propen-1-yl)-3,4-dimethyl-1H-pyrrole-2-carboxylic Acid (**49**)



Following the same procedure used to prepare **49\***, TFA (6 mL) was added to a solution of **48** (6.00 g, 18.9 mmol) in DCE (40 mL) at reflux temperature. Following the same work-up used with **49\*** the desired product was obtained as a brilliant yellow solid (3.55 g, 72%).  $^1\text{H}$  NMR (500 MHz;  $\text{CDCl}_3$ )  $\delta$  10.22 (br s, 1H), 8.08 (s, 1H), 4.37 (q,  $J = 7.1$  Hz, 2H), 2.32 (s, 3H), 2.20 (s, 3H), 1.39 (t,  $J = 7.1$  Hz, 3H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz;  $\text{CDCl}_3$ )  $\delta$  164.0, 163.0, 139.4, 133.3, 128.7, 126.5, 125.0, 117.9, 96.0, 62.7, 14.4, 10.2, 9.5.  $^1\text{H}$  NMR data match that previously reported for this compound.<sup>88</sup>  $^{13}\text{C}$  NMR data have not been previously reported for this compound.

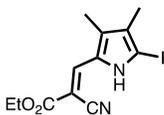
## Ethyl Ester 2-Cyano-3-(5-iodo-3-(methyl- $d_2$ )-4-methyl-1H-pyrrol-2-yl)-2-propenoic Acid (**50\***)



The title compound was synthesized for the first time following a modified literature procedure.<sup>88</sup> A mixture of **49\*** (253 mg, 0.959 mmol), anhydrous sodium acetate (337 mg, 3.33 mmol), acetic anhydride (195  $\mu\text{L}$ , 2.07 mmol), and acetic acid (2 mL) was heated, with stirring, until the solution became homogenous ( $\sim 105$   $^\circ\text{C}$ ). Immediately thereafter, a solution of iodine chloride (1 M in AcOH, 2.0 mL, 2 mmol) was quickly

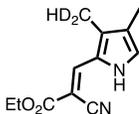
added. The reaction mixture was boiled for 5 min, until the purple vapours of free iodine had ceased. Water (15 mL) was slowly added, causing oiling and then crystallization of product. The solid was collected via Millipore™ suction filtration, washing extensively with water, and then dissolved in CH<sub>2</sub>Cl<sub>2</sub>. Saturated aqueous sodium sulfite (1 mL) was added, with stirring, followed by addition of water, and cooling to 0 °C. The organic layer was separated, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and evaporated *in vacuo* to yield the crude product, which was used immediately in the subsequent reaction without further purification (product not stable for periods longer than a few hours).

### **Ethyl Ester 2-Cyano-3-(5-iodo-3,4-dimethyl-1H-pyrrol-2-yl)-2-propenoic Acid (50)**



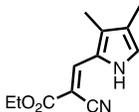
Following the same procedure used to prepare **50\***, a solution of iodine chloride (1 M in AcOH, 27 mL) was quickly added to a solution of **49** (3.55 g, 13.5 mmol), anhydrous sodium acetate (45.1 g, 44.2 mmol), and acetic anhydride (2.7 mL) in AcOH (27 mL) at reflux temperature. Following the same work-up for **50**, the desired crude product was obtained and used immediately in the subsequent reaction without further purification (product not stable for periods longer than a few hours).

## Ethyl Ester 2-Cyano-3-(3-(methyl-*d*<sub>2</sub>)-4-methyl-1*H*-pyrrol-2-yl)-2-propenoic Acid (51\*)



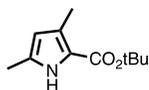
The title compound was synthesized for the first time following a modified literature procedure.<sup>87</sup> Zinc dust (315 mg, 4.8 mmol) was added to a solution of **50\*** (presumed 0.96 mmol) in AcOH (2.1 mL), swirling manually until a spontaneous reaction set in and the temperature rose to ~50 °C, after which the reaction mixture was stirred mechanically for 30 min. The reaction mixture was filtered through Celite® to remove zinc, washing with methanol until the washings were colourless. Solvent was removed *in vacuo*, and the resulting residue was crystallized from methanol/water and collected via Millipore™ suction filtration to yield the desired product as a brilliant yellow solid (68 mg, 32% over two steps). M.p. 155-157 °C; <sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>) δ 9.66 (br s, 1H), 8.00 (s, 1H), 6.99-6.98 (m, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 2.18-2.14 (m, 1H), 2.04 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 3H); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz; CDCl<sub>3</sub>) δ 164.3, 139.5, 134.4, 127.6, 125.0, 122.1, 119.8, 88.7, 61.9, 14.5, 10.0, 8.9 (apparent quin, *J* = 19.3 Hz); HRMS-ESI (*m/z*): [M+Na]<sup>+</sup> calculated for C<sub>12</sub>H<sub>12</sub>D<sub>2</sub>N<sub>2</sub>O<sub>2</sub>Na<sub>1</sub> 243.1073; found 243.1067.

## Ethyl Ester 2-Cyano-3-(3,4-dimethyl-1*H*-pyrrol-2-yl)-2-propenoic Acid (51)



Following the same procedure used to prepare **51\***, zinc dust (4.4 g, 67.5 mmol) was added to a solution of **50** (presumed 13.5 mmol) in AcOH (30 mL). Following the same work-up as with **51\***, the desired product was obtained as brilliant yellow solid (1.69 g, 57% over two steps).  $^1\text{H}$  NMR (300 MHz;  $\text{CDCl}_3$ )  $\delta$  9.66 (br s, 1H), 8.00 (s, 1H), 6.99-6.98 (m, 1H), 4.31 (t,  $J = 7.1$  Hz, 2H), 2.18 (s, 3H), 2.04 (s, 3H), 1.35 (d,  $J = 7.1$  Hz, 3H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz;  $\text{CDCl}_3$ )  $\delta$  164.3, 140.0, 139.5, 134.5, 127.6, 122.4, 122.1, 119.8, 61.9, 14.5, 10.0, 9.6; HRMS-ESI ( $m/z$ ):  $[\text{M}+\text{Na}]^+$  calculated for  $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_2\text{Na}_1$  241.0947; found 241.0952. HRMS,  $^1\text{H}$  and  $^{13}\text{C}$  NMR data have not been previously reported for this compound.

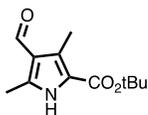
## *tert*-Butyl Ester 3,5-Dimethyl-1*H*-pyrrole-2-carboxylic Acid (53)



The title compound was synthesized following a modified literature procedure.<sup>203</sup> In an oven-dried round-bottom equipped with a stir-bar, *tert*-butyl 4-acetyl-3,5-dimethylpyrrole-2-carboxylate<sup>206</sup> (20 g, 84 mmol) was dissolved in benzene (1 L), under  $\text{N}_2$ . Ethylene glycol (184 mL) and pTSA (959 mg, 5.6 mmol) were added and the resulting mixture was stirred and heated at reflux temperature overnight (18 h), after

which it was cooled to room temperature and water was added (1 L). The resulting emulsion was extracted with  $\text{CHCl}_3$  ( $3 \times 1$  L). The organic fractions were washed with sat.  $\text{NaHCO}_3$  (2 L), water (2 L), dried over anhydrous  $\text{Na}_2\text{SO}_4$ , and concentrated *in vacuo*. The resulting residue was recrystallized from methanol/water and washed with hexanes to yield the desired product as a white solid (6.28 g, 38%).  $^1\text{H-NMR}$  (300 MHz;  $\text{CDCl}_3$ )  $\delta$  8.49 (br s, 1H), 5.77 (m, 1H), 2.27 (s, 3H), 2.23 (s, 3H), 1.56 (s, 9H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (125 MHz;  $\text{CDCl}_3$ )  $\delta$  161.4, 131.75, 131.68, 128.2, 119.2, 111.3, 80.3, 28.7, 13.20, 13.01.  $^1\text{H}$  NMR data match that previously reported for this compound.<sup>285</sup>  $^{13}\text{C}$  NMR data have not been previously reported for this compound.

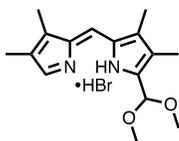
#### ***tert*-Butyl Ester 4-Formyl-3,5-dimethyl-1*H*-pyrrole-2-carboxylic Acid (54)**



The title compound was synthesized following a modified literature procedure.<sup>182</sup> In an oven-dried round-bottom equipped with a stir bar,  $\text{POCl}_3$  (4.0 mL) was added to DMF (8.5 mL), dropwise, at 0 °C under  $\text{N}_2$ . The resulting mixture was stirred for 15 min while warming to room temperature (23 °C). The DMF/ $\text{POCl}_3$  mixture was added to a stirred solution of **53** (6.8 g, 35 mmol) in DMF (25 mL) at 0 °C under  $\text{N}_2$ . The reaction mixture was stirred for 24 h at room temperature, quenched with water (40 mL), and extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 150$  mL). The combined organic layers were concentrated *in vacuo*. The resulting residue was recrystallized from methanol/water to yield the desired product as a white solid (3.6 g, 46%).  $^1\text{H}$  NMR (300 MHz;  $\text{CDCl}_3$ )  $\delta$  10.00 (s, 1H), 9.06 (br s, 1H),

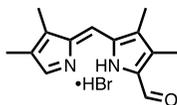
2.54 (s, 6H), 1.58 (s, 9H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz;  $\text{CDCl}_3$ )  $\delta$  186.3, 161.3, 139.9, 129.4, 121.7, 120.1, 81.8, 28.6, 12.7, 10.5.  $^1\text{H}$  NMR data match that previously reported for this compound.<sup>285</sup>  $^{13}\text{C}$  NMR data had not been previously reported for this compound.

## 2-(Dimethoxymethyl)-5-[(3,4-dimethyl-2*H*-pyrrol-2-ylidene)methyl]-3,4-dimethyl-1*H*-pyrrole Monohydrobromide (55)



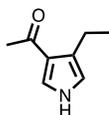
The title compound was synthesized for the first time following a modified literature procedure.<sup>105</sup> Chilled (0 °C) HBr (48% aqueous solution, 50  $\mu\text{L}$ ) was added to a solution of **40** (40.5 mg, 0.329 mmol) in methanol (3.3 mL) at 0 °C. Red precipitate began to form after 5 min of stirring. The reaction mixture was stirred for 1 h, and the solid was collected via suction filtration, yielding the title compound as a dark red solid (23 mg, 50%). M.p. 196-200 °C (decomp.);  $^1\text{H}$  NMR (500 MHz;  $\text{CDCl}_3$ )  $\delta$  13.56 (br s, 1H), 13.23 (br s, 1H), 7.66-7.64 (m, 1H), 7.27 (s, 1H), 6.05 (s, 1H), 3.55 (s, 6H), 2.30 (s, 3H), 2.28 (s, 3H), 2.14 (s, 3H), 2.07 (s, 3H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz;  $\text{CDCl}_3$ )  $\delta$  152.6, 144.5, 143.3, 142.1, 128.1, 126.8, 125.7, 124.7, 123.1, 99.9, 56.2, 10.4, 10.3, 10.1, 9.5; HRMS-ESI ( $m/z$ ):  $[\text{M}-\text{Br}]^+$  calculated for  $\text{C}_{16}\text{H}_{23}\text{N}_2\text{O}_2$  275.1754; found 275.1751.

### 3,4-Dimethyl-5-[(3,4-dimethyl-2*H*-pyrrol-2-ylidene)methyl]-1*H*-pyrrole-2-carboxaldehyde Monohydrobromide (56)



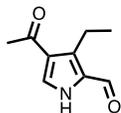
The title compound was synthesized for the first time following a modified literature procedure.<sup>105</sup> Aqueous HBr (48%, 50  $\mu$ L) was added to a solution of **40** (37 mg, 0.30 mmol) in methanol (3 mL) at reflux temperature. After 5-10 s the mixture turned a dark red, and the reaction vessel was immediately plunged into an ice bath ( $\leq 0$   $^{\circ}$ C), followed by addition of diethyl ether to dilute the mixture and assist in rapid cooling. The resulting ethereal solution was concentrated *in vacuo*, keeping the temperature below 25  $^{\circ}$ C, until a solid precipitate formed. The precipitate was collected via suction filtration and washed with ether to yield the title compound (14 mg, 20%). M.p. 185-189  $^{\circ}$ C (decomp);  $^1$ H NMR (300 MHz; CDCl<sub>3</sub>)  $\delta$  14.19 (br s, 1H), 13.64 (br s, 1H), 10.69 (s, 1H), 7.99-7.97 (m, 1H), 7.48 (s, 1H), 2.40 (s, 3H), 2.35 (s, 3H), 2.33 (s, 3H), 2.15 (s, 3H);  $^{13}$ C{ $^1$ H} NMR (126 MHz; CDCl<sub>3</sub>)  $\delta$  184.2, 149.8, 147.6, 142.4, 141.6, 131.9, 128.9, 127.8, 127.8, 125.2, 10.7, 10.3, 10.0, 9.7; HRMS-ESI ( $m/z$ ): [M-Br]<sup>+</sup> calculated for C<sub>14</sub>H<sub>17</sub>N<sub>2</sub>O<sub>1</sub> 229.1335; found 229.1340.

## 1-(4-Ethyl-1*H*-pyrrol-3-yl)ethanone (57)



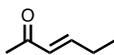
The title compound was synthesized following a modified literature procedure.<sup>59</sup> In an oven-dried round-bottom equipped with a stir bar, NaH (8.0 g, 200 mmol, 60% in oil) was suspended in anhydrous ether (180 mL), under N<sub>2</sub>. A solution of 3-hexen-2-one<sup>286</sup> (8.8 g, 90 mmol) and TosMIC (17.8 g, 91.2 mmol) in a mixture of anhydrous DMSO/Et<sub>2</sub>O (450 mL, 1:2) was slowly added to the well-stirred suspension of NaH via cannula transfer. After complete addition, the mixture was stirred at room temperature for 1 h. Excess NaH was quenched by slow the addition of water. The reaction mixture was thoroughly extracted with ethyl acetate (4 × 350 mL), and the combined organic extracts were washed with brine (12 × 300 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and the solvent removed *in vacuo* to furnish a dark brown oil. The oil was placed in a freezer overnight, producing a greasy solid which was continually extracted (Soxhlet) with pentane for 26 h to yield the desired product as a light brown solid after removal of the solvent in vacuo (7.9 g, 63%). <sup>1</sup>H NMR (300 MHz; CDCl<sub>3</sub>) δ 8.44 (br s, 1H), 7.37-7.36 (m, 1H), 6.59-6.57 (m, 1H), 2.80 (q, *J* = 7.4 Hz, 2H), 2.40 (s, 3H), 1.20 (t, *J* = 7.4 Hz, 3H), in accordance with previous literature.<sup>60</sup>

#### 4-Acetyl-3-ethyl-1*H*-pyrrole-2-carboxaldehyde (**58**)



The title compound and alkynyl by-products were synthesized for the first time following a modified literature procedure.<sup>182,213</sup> POCl<sub>3</sub> (2.0 mL, 22 mmol) was added, drop-wise, at 0 °C under N<sub>2</sub> to DMF (16 mL). The mixture was allowed to warm to room temperature, and then stirred for 15 min. This mixture was added drop-wise to a solution of **57** (2.2 g, 15 mmol) in DCE (49 mL), at 0 °C under N<sub>2</sub>. The resulting mixture was heated to 80 °C and stirred for an additional 80 min. Aqueous NaOH (2 M) was added to the reaction until pH > 8 and the resulting emulsion was heated at reflux temperature for 20 min. After cooling to room temperature, water (50 mL) was added, and the reaction mixture extracted with EtOAc (3 × 50 mL). The combined organic fractions were washed with brine (50 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. The crude mixture was purified via column chromatography on silica, eluting with an EtOAc/hexanes gradient from 20%-30% to afford the desired product, **58**, as a brown solid (330 mg, 14%). M.p. 119-123 °C; <sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>) δ 10.03 (br s, 1H), 9.74 (s, 1H), 7.61-7.60 (m, 1H), 3.11 (q, *J* = 7.5 Hz, 2H), 2.44 (s, 3H), 1.26 (t, *J* = 7.5 Hz, 4H); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz; CDCl<sub>3</sub>) δ 193.5, 179.1, 140.4, 130.7, 130.4, 125.0, 28.5, 17.9, 16.7; HRMS-ESI (*m/z*): [M+Na]<sup>+</sup> calculated for C<sub>9</sub>H<sub>11</sub>NO<sub>2</sub>Na 188.0682; found 188.0680.

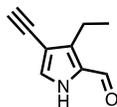
### 3-Hexen-2-one (63)



The title compound was synthesized following a modified literature procedure.<sup>212</sup>

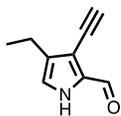
Propionaldehyde (102 g, 1.76 mol) was added to a solution of (acetylmethylene)triphenylphosphorane (93.5 g, 0.294 mol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (480 mL) at room temperature, under N<sub>2</sub>. The reaction was stirred until starting material was consumed, monitoring with TLC (30% ethyl acetate/hexanes). The solvent was removed *in vacuo*, using an unheated water bath to maintain temperature, i.e. not allow a significant decrease in vessel temperature with reducing pressure. A white precipitate formed, was collected, washed thoroughly with hexanes, and then the precipitate was discarded. The removal of solvent, precipitation, collection, and washing were repeated a second time. After the second wash, the hexanes filtrate was concentrated *in vacuo*, and fractionally distilled under vacuum, using a water-fed aspirator (~25-60 mmHg), collecting the desired product at 48 °C as a colourless liquid (18.1 g, 63 %). <sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>) δ 6.84 (dt, *J* = 16.0, 6.3 Hz, 1H), 6.06 (dt, *J* = 16.0, 1.5 Hz, 1H), 2.28-2.22 (m, 5H), 1.08 (t, *J* = 7.4 Hz, 3H), in accordance with previous literature.<sup>212</sup>

### 3-Ethyl-4-ethynyl-1*H*-pyrrole-2-carboxaldehyde (**64**)



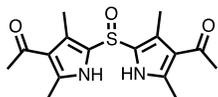
The title compound was isolated for the first time, along with **58** and **64'**, by Thompson lab postdoctoral fellow Dr. Carlotta Figliola.<sup>282</sup> POCl<sub>3</sub> (2.0 mL, 22 mmol) was added, drop-wise, at 0 °C under N<sub>2</sub> to DMF (16 mL). The mixture was allowed to warm to room temperature, and then stirred for 15 min. This mixture was added drop-wise to a solution of **57** (2.4 g, 15 mmol) in DCE (49 mL), at 0 °C under N<sub>2</sub>. The resulting mixture was heated to 80 °C and stirred for an additional 80 min. Aqueous NaOH (2 M) was added to the reaction until pH > 8 and the resulting emulsion was heated at reflux temperature for 20 min. After cooling to room temperature, water (50 mL) was added, and the reaction mixture extracted with EtOAc (3 × 50 mL). The combined organic fractions were washed with brine (50 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. The crude mixture was purified via column chromatography on silica, eluting with an EtOAc/hexanes gradient from 20%-30% to afford the desired product, **64**, as a brown solid (440 mg, 21%). M.p. 119-120 °C; <sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>) δ 9.64 (s, 1H), 9.46 (br s, 1H), 7.23-7.22 (m, 1H), 3.10 (s, 1H), 2.85 (q, *J* = 7.6 Hz, 2H), 1.30 (t, *J* = 7.6 Hz, 3H); <sup>13</sup>C {<sup>1</sup>H} NMR (125 MHz; CDCl<sub>3</sub>) δ 177.9, 141.6, 129.6, 128.6, 106.8, 79.6, 76.3, 18.0, 16; HRMS-ESI (*m/z*): [M+Na]<sup>+</sup> calculated for C<sub>9</sub>H<sub>9</sub>NONa 170.0576; found 170.0575.

#### 4-Ethyl-3-ethynyl-1*H*-pyrrole-2-carboxaldehyde (**64'**)



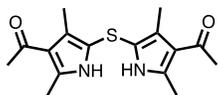
The title compound was isolated for the first time, along with **58** and **64**, by Thompson lab postdoctoral fellow Dr. Carlotta Figliola.<sup>282</sup> POCl<sub>3</sub> (2.0 mL, 22 mmol) was added, drop-wise, at 0 °C under N<sub>2</sub> to DMF (16 mL). The mixture was allowed to warm to room temperature, and then stirred for 15 min. This mixture was added drop-wise to a solution of **57** (2.4 g, 15 mmol) in DCE (49 mL), at 0 °C under N<sub>2</sub>. The resulting mixture was heated to 80 °C and stirred for an additional 80 min. Aqueous NaOH (2 M) was added to the reaction until pH > 8 and the resulting emulsion was heated at reflux temperature for 20 min. After cooling to room temperature, water (50 mL) was added, and the reaction mixture extracted with EtOAc (3 × 50 mL). The combined organic fractions were washed with brine (50 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. The crude mixture was purified via column chromatography on silica, eluting with an EtOAc/hexanes gradient from 20%-30% to afford the desired product, **64'**, as a brown solid (220 mg, 10%). M.p. 104-105 °C; <sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>) δ 9.68 (s, 1H), 9.28 (br s, 1H), 6.86 (br s, 1H), 3.35 (s, 1H), 2.58 (q, *J* = 7.6 Hz, 2H), 1.23 (t, *J* = 7.6 Hz, 3H); <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz; CDCl<sub>3</sub>) δ 178.5, 134.2, 132.5, 123.3, 114.7, 83.8, 75.2, 18.8, 14.5; HRMS-ESI (*m/z*): [M+Na]<sup>+</sup> calculated for C<sub>9</sub>H<sub>9</sub>NONa 170.0576; found 170.0578.

## 1,1'-[Sulfinylbis(2,4-dimethyl-1*H*-pyrrol-3,5-diyl)]bisethanone (88)



The title compound and **111** were prepared and isolated from the same reaction using a modified literature procedure.<sup>235</sup> A solution of *m*-CPBA ( $\leq 77\%$ , 430 mg, 1.59 mmol) in DMF (18 ml) was added, drop-wise under N<sub>2</sub>, to a solution of **89** (502 mg, 1.65 mmol) in DMF (36 mL). After complete addition of the *m*-CPBA solution (8 min), the resulting reaction mixture was stirred at 0 °C until all starting material had been consumed (1 h, monitoring via TLC). The reaction mixture was diluted with CHCl<sub>3</sub> (100 mL) and then washed with saturated NaHCO<sub>3</sub> (50 mL), followed by thorough washing with H<sub>2</sub>O (5 × 50 mL). The organic layer was dried with Na<sub>2</sub>SO<sub>4</sub> and then the solvent was removed *in vacuo*. The resulting residue was purified via column chromatography on silica, eluting with 50% ethyl acetate/hexanes up to 100% ethyl acetate, to yield the desired product as an off-white solid (248 mg, 48%), which began to noticeably degrade under ambient conditions (open-air, 20 °C) after 3 days. The title compound appeared to be stable at low temperatures (-20 °C, weeks). M.p. 132-134 °C, decomp 138 °C; <sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>)  $\delta$  11.41 (br s, 2H), 2.49 (s, 6H), 2.36 (s, 6H), 2.31 (s, 6H); <sup>13</sup>C {<sup>1</sup>H} NMR (126 MHz; CDCl<sub>3</sub>)  $\delta$  194.5, 141.3, 127.5, 122.6, 122.0, 31.2, 15.2, 12.2; HRMS-ESI (*m/z*): [M+Na]<sup>+</sup> calculated for C<sub>16</sub>H<sub>20</sub>N<sub>2</sub>O<sub>3</sub>SNa 343.1087; found 343.1076.

## 1,1'-[Thiobis(2,4-dimethyl-1*H*-pyrrol-3,5-diyl)]bisethanone (89)



The title compound was prepared using four unique methodologies.

### Method 1: Treatment of **14** with SOCl<sub>2</sub>

In an oven-dried round-bottom equipped with a stir bar, cold thionyl chloride (32  $\mu$ L, 0.44 mmol, -8  $^{\circ}$ C) was slowly added to a cooled solution (-10  $^{\circ}$ C, salt/ice) of **14** (81 mg, 0.59 mmol) and NEt<sub>3</sub> (90  $\mu$ L, 0.65 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (6 mL). The reaction mixture was stirred at -10  $^{\circ}$ C, under nitrogen, for 25 min. Methanol (2.0 mL) was added to quench excess thionyl chloride, and the reaction mixture was concentrated *in vacuo*.

The resulting residue was purified via column chromatography on silica, eluting with 50% ethyl acetate/hexanes, to yield the desired product as an off-white solid (62 mg, 70%). M.p. 250-252  $^{\circ}$ C (decomp); <sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>)  $\delta$  7.98 (br s, 2H), 2.46 (s, 6H), 2.44 (s, 6H), 2.40 (s, 6H); <sup>1</sup>H NMR (500 MHz; DMSO-*d*<sub>6</sub>)  $\delta$  11.13 (br s, 2H), 2.39 (s, 6H), 2.31 (s, 6H), 2.28 (s, 6H); <sup>13</sup>C {<sup>1</sup>H} NMR (126 MHz; DMSO-*d*<sub>6</sub>)  $\delta$  193.5, 136.4, 124.3, 120.9, 115.7, 30.7, 14.5, 12.7; HRMS-APCI (*m/z*): [M+H]<sup>+</sup> calculated for C<sub>16</sub>H<sub>21</sub>N<sub>2</sub>O<sub>2</sub>S 305.1318; found 305.1321; HRMS-ESI (*m/z*): [M+Na]<sup>+</sup> calculated for C<sub>16</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>SNa 327.1138; found 327.1128.

### Method 2: Treatment of **14** with SOBr<sub>2</sub>

In an oven-dried round-bottom equipped with a stir bar, cold thionyl bromide (48  $\mu$ L, 0.62 mmol, -8  $^{\circ}$ C) was slowly added to a cooled solution (-10  $^{\circ}$ C, salt/ice) of **14** (114 mg, 0.830 mmol) and NEt<sub>3</sub> (127  $\mu$ L, 0.913 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (8.3 mL). The reaction mixture was stirred at -10  $^{\circ}$ C, under nitrogen, for 15 min. Methanol (2.0 mL)

was added to quench excess thionyl chloride, and the reaction mixture was concentrated *in vacuo*. The resulting residue was purified via column chromatography on silica, eluting with 50% ethyl acetate/hexanes, to yield the desired product as an off-white solid (23 mg, 18%). M.p. 249-252 °C (decomp); <sup>1</sup>H NMR (300 MHz; DMSO-*d*<sub>6</sub>) δ 11.15 (br s, 2H), 2.39 (s, 6H), 2.31 (s, 6H), 2.28 (s, 6H); HRMS-ESI (*m/z*): [M+Na]<sup>+</sup> calculated for C<sub>16</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>SNa 327.1138; found 327.1145; in accordance with our previous data above.

### **Method 3: Treatment of 14 with S<sub>2</sub>Cl<sub>2</sub>**

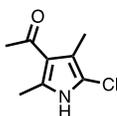
In an oven-dried round-bottom equipped with a stir bar, S<sub>2</sub>Cl<sub>2</sub> (50 μL, 0.64 mmol) was added to a cooled solution (0 °C) of **14** (169 mg, 1.23 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (12 mL). Immediately upon addition of S<sub>2</sub>Cl<sub>2</sub> the reaction mixture became thick with solid. The reaction mixture was stirred for 10 min, whereupon distilled water (1.0 mL) was added to quench the remaining S<sub>2</sub>Cl<sub>2</sub>. The solid was collected via suction filtration and dissolved in THF. The resulting solution was dried with MgSO<sub>4</sub> and concentrated *in vacuo*. The resulting residue was purified via column chromatography on silica, eluting with 50% ethyl acetate/hexanes, to yield the desired product as an off-white solid (30 mg, 16%); M.p. 250-252 °C (decomp); <sup>1</sup>H NMR (300 MHz; DMSO-*d*<sub>6</sub>) δ 11.23 (br s, 2H), 2.39 (s, 6H), 2.31 (s, 6H), 2.28 (s, 6H); HRMS-ESI (*m/z*): [M+Na]<sup>+</sup> calculated for C<sub>16</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>SNa 327.1138; found 327.1130; in accordance with our previous data.

### **Method 4: Treatment of 88 with SOCl<sub>2</sub>**

In an oven-dried round-bottom equipped with a stir bar, cold thionyl chloride (7.5 μL, 0.10 mmol, -8 °C) was slowly added to a cooled solution (-10 °C, salt/ice) of **88** (29 mg, 0.09 mmol) and NEt<sub>3</sub> (14 μL, 0.10 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (2 mL). The reaction mixture was stirred at -10 °C, under nitrogen, for 10 min. Methanol (1.0 mL) was added

to quench excess thionyl chloride, and the reaction mixture was concentrated *in vacuo*. The resulting residue was purified via column chromatography on silica, eluting with 50% ethyl acetate/hexanes, to yield the desired product as an off-white solid (10 mg, 37%). M.p. 250-252 °C (decomp); <sup>1</sup>H NMR (300 MHz; DMSO-*d*<sub>6</sub>) δ 11.16 (br s, 2H), 2.39 (s, 6H), 2.31 (s, 6H), 2.28 (s, 6H); HRMS-ESI (*m/z*): [M+Na]<sup>+</sup> calculated for C<sub>16</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>SNa 327.1138; found 327.1128; in accordance with our previous data.

### 1-(5-Chloro-2,4-dimethyl-1*H*-pyrrol-3-yl)ethanone (90)



The title compound was prepared using three unique methodologies.

#### **Method 1: Treatment of 14 with SOCl<sub>2</sub>**

In an oven-dried round-bottom equipped with a stir bar, cold thionyl chloride (32 μL, 0.44 mmol, -8 °C) was slowly added to a cooled solution (-10 °C, salt/ice) of **14** (81 mg, 0.59 mmol) and NEt<sub>3</sub> (90 μL, 0.65 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (6 mL). The reaction mixture was stirred at -10 °C, under nitrogen, for 25 min. Methanol (2.0 mL) was added to quench excess thionyl chloride, and the reaction mixture was concentrated *in vacuo*.

The resulting residue was purified via column chromatography on silica, eluting with 50% ethyl acetate/hexanes, to yield the desired product as an off-white solid (19 mg, 19%). M.p. 178-180 °C (decomp.); (500 MHz; DMSO-*d*<sub>6</sub>) δ 11.70 (br s, 1H), 2.37 (s, 3H), 2.30 (s, 3H), 2.10 (s, 3H); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz; DMSO-*d*<sub>6</sub>) δ 193.2, 133.7, 120.4, 114.5, 110.3, 30.6, 14.2, 11.2; HRMS-ESI (*m/z*): [M-H]<sup>-</sup> calculated for

C<sub>8</sub>H<sub>9</sub>ClNO 170.0378; found 170.0376; HRMS-ESI (*m/z*): [M+Na]<sup>+</sup> calculated for C<sub>8</sub>H<sub>10</sub>ClNONa 194.0343; found 194.0339. <sup>1</sup>H NMR reported in both CDCl<sub>3</sub> and DMSO-*d*<sub>6</sub> to correct a misreport of NMR solvent in previous literature.<sup>287</sup>

### **Method 2: Treatment of 14 with SO<sub>2</sub>Cl<sub>2</sub>**

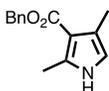
The title compound was prepared according to a modified literature procedure.<sup>288</sup> In an oven-dried round-bottom equipped with a stir bar, **14** (2.02 g, 14.7 mmol) was dissolved in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (150 mL) and cooled to -10 °C under N<sub>2</sub>. Freshly distilled, chilled, SO<sub>2</sub>Cl<sub>2</sub> (1.2 mL, 15 mmol, -8 °C) was slowly added to the reaction mixture. The reaction mixture was stirred for 30 min, whereupon methanol (10 mL) was added to quench remaining SO<sub>2</sub>Cl<sub>2</sub>. The reaction mixture was concentrated *in vacuo*. The resulting residue was purified via column chromatography on silica, eluting with 30%-50% ethyl acetate/hexanes, to yield the desired product as an off-white solid (1.64 g, 53%). <sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>) δ 8.02 (br s, 1H), 2.48 (s, 3H), 2.41 (s, 3H), 2.21 (s, 3H), in accordance with our previous data.

### **Method 3: Treatment of 88 with SOCl<sub>2</sub>**

In an oven-dried round-bottom equipped with a stir bar, cold thionyl chloride (14 μL, 0.19 mmol, -8 °C) was slowly added to a cooled solution (-10 °C, salt/ice) of **88** (55 mg, 0.17 mmol) and NEt<sub>3</sub> (26 μL, 0.19 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (4 mL). The reaction mixture was stirred at -10 °C, under nitrogen, for 10 min. Methanol (2.0 mL) was added to quench excess thionyl chloride, and the reaction mixture was removed *in vacuo*. The resulting residue was purified via column chromatography on silica, eluting with 50% ethyl acetate/hexanes, to yield the desired product as an off-white solid (10 mg, 20%). <sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>) δ 8.02 (br s, 1H), 2.48 (s, 3H), 2.41 (s, 3H), 2.21 (s, 3H);

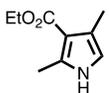
HRMS-ESI ( $m/z$ ):  $[M+Na]^+$  calculated for  $C_8H_{10}ClNONa$  194.0343; found 194.0345, in accordance with our previous data.

### **Benzyl Ester 2,4-Dimethyl-1*H*-pyrrole-3-carboxylic Acid (92)**



The title compound was prepared according to a literature procedure<sup>266</sup> from 4-benzyl 2-*tert*-butyl ester 3,5-dimethyl-1*H*-pyrrole-2,4-dicarboxylic acid and isolated as an off-white solid (600 mg, 82%). <sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>)  $\delta$  8.05 (br s, 1H), 7.40-7.32 (m, 5H), 6.33 (s, 1H), 5.28 (s, 2H), 2.51 (s, 2H), 2.24 (s, 3H), in accordance with previous literature.<sup>289</sup>

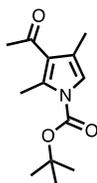
### **Ethyl Ester 2,4-Dimethyl-1*H*-pyrrole-3-carboxylic Acid (93)**



The title compound was prepared according to a modified literature procedure.<sup>266,290</sup> In an oven-dried round-bottom equipped with a stir bar, Pd/C (137 mg, ~10% w/w) and NEt<sub>3</sub> (10 drops) were added to a solution of 2-benzyl 4-ethyl ester 3,5-dimethyl-1*H*-pyrrole-2,4-dicarboxylic acid (1.0 g, 3.6 mmol) in THF (30 mL), under N<sub>2</sub>. The reaction vessel was subjected to three purge/fill cycles with H<sub>2</sub>. Once under an H<sub>2</sub> atmosphere, the reaction mixture was stirred at room temperature, monitoring with TLC, until starting material had been consumed (30 min). Once complete, the reaction mixture was filtered

through Celite® to remove Pd/C, washing with THF. The reaction mixture was concentrated, and the residue dried *in vacuo*. The resulting residue was dissolved in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (100 mL), under N<sub>2</sub>, after which TFA (9 mL, 120 mmol) was added, in a large excess to aid in dissolving the pyrrole. The reaction mixture was heated at 38 °C, monitoring with TLC, until the reaction was complete (30 min). The reaction mixture was poured into ice-cold 20% aqueous Na<sub>2</sub>CO<sub>3</sub> (200 mL) and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 100 mL). The organic layers were combined and washed with H<sub>2</sub>O (2 × 200 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The resulting residue was purified via column chromatography on silica, eluting with 15% ethyl acetate/hexanes, to yield the desired product as an off-white solid (290 mg, 48%). <sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>) δ 9.88 (br s, 1H), 6.30 (s, 1H), 4.15 (q, *J* = 7.0 Hz, 2H), 2.19 (s, 3H), 2.15 (s, 3H), 1.22 (t, *J* = 7.0 Hz, 3H), in accordance with previous literature.<sup>188</sup>

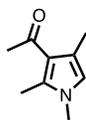
### ***tert*-Butyl Ester 3-Acetyl-2,4-dimethyl-1*H*-pyrrole-1-carboxylic Acid (94)**



The title compound was prepared for the first time according to a modified literature procedure.<sup>291</sup> In an oven-dried round-bottom equipped with a stir bar, di-*tert*-butyl dicarbonate (1.04 g, 4.68 mmol) was dissolved in anhydrous acetonitrile (9 mL) and bubbled with N<sub>2</sub> gas for 10 min, under N<sub>2</sub>, to prepare Solution One. In a second oven-dried round-bottom equipped with a stir bar, a solution of pyrrole **14** (212 mg, 1.55

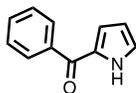
mmol) and DMAP (24 mg, 0.22 mmol) in anhydrous acetonitrile (15 ml) was bubbled with N<sub>2</sub> for 10 min under N<sub>2</sub>, to prepare Solution Two. Solution One was added to Solution Two slowly via cannula. The combined solution was stirred for 20 min, until all of **14** was observed to be consumed using TLC. Reaction solvent and excess di-*tert*-butyl dicarbonate were removed *in vacuo*, and the resulting residue was purified via column chromatography on silica, eluting with 15% ethyl acetate/hexanes, to yield the desired product as an off-white solid (320 mg, 87%). <sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>) δ 6.92-6.91 (m, 1H), 2.69 (s, 3H), 2.44 (s, 3H), 2.19-2.19 (m, 3H), 1.59 (s, 9H); <sup>13</sup>C {<sup>1</sup>H} NMR (126 MHz; CDCl<sub>3</sub>) δ 197.1, 149.3, 137.5, 126.3, 120.1, 119.0, 84.4, 84.4, 31.8, 28.1, 14.4, 13.4; HRMS-ESI (*m/z*): [M+Na]<sup>+</sup> calculated for C<sub>13</sub>H<sub>19</sub>NO<sub>3</sub>Na 260.1257; found 260.1264.

### 1-(1,2,4-Trimethyl-1*H*-pyrrol-3-yl)ethanone (**95**)



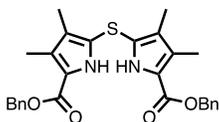
The title compound was prepared according to a literature procedure<sup>292</sup> and isolated as an off-white solid (1.3 g, 82%). <sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>) δ 6.27 (s, 1H), 3.46 (s, 3H), 2.47 (s, 3H), 2.41 (s, 3H), 2.25 (s, 3H), in accordance with previous literature.<sup>292</sup>

## Phenyl-1*H*-pyrrol-2-yl-methanone (**96**)



The title compound was prepared according to a literature procedure<sup>293</sup> and isolated as an off-white solid (37%, 1.8 g). <sup>1</sup>H NMR (300 MHz; CDCl<sub>3</sub>) δ 7.93-7.89 (m, 2H), 7.55-7.46 (m, 3H), 7.18-7.15 (m, 1H), 6.92-6.89 (m, 1H), 6.37-6.33 (m, 1H), in accordance with previous literature.<sup>294</sup>

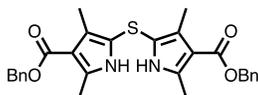
## Dibenzyl Ester 5,5'-Thiobis[3,4-dimethyl-1*H*-pyrrole-2-carboxylic acid] (**97**)



The title compound, and chlorinated pyrrole by-product (**121**) were prepared and isolated from the same reaction. In an oven-dried round-bottom equipped with a stir bar, cold thionyl chloride (15 μL, 0.21 mmol, -8 °C) was slowly added to a cooled solution (-10 °C, salt/ice) of **91**<sup>266</sup> (64 mg, 0.28 mmol) and NEt<sub>3</sub> (43 μL, 0.31 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (3.5 mL). The reaction mixture was stirred at -10 °C and allowed to warm to room temperature (20-25 °C), under N<sub>2</sub>. Once at room temperature, the reaction mixture was heated at reflux temperature for 20 h. Methanol (1.0 mL) was added to quench excess thionyl chloride, and the reaction mixture was concentrated *in vacuo*. The resulting residue was purified via column chromatography on silica, eluting with 15% ethyl acetate/hexanes, to yield the desired product, **97**, as an off-white solid (44 mg,

64%). M.p. 195-197 °C;  $^1\text{H}$  NMR (500 MHz; DMSO- $d_6$ )  $\delta$  11.68 (br s, 2H), 7.44-7.42 (m, 4H), 7.41-7.37 (m, 4H), 7.36-7.32 (m, 2H), 5.31 (s, 4H), 2.14 (s, 6H), 2.04 (s, 6H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz; DMSO- $d_6$ )  $\delta$  160.3, 136.5, 128.4, 127.9, 127.7, 125.7, 123.9, 121.5, 120.0, 65.1, 10.7, 9.4; HRMS-ESI ( $m/z$ ):  $[\text{M}+\text{Na}]^+$  calculated for  $\text{C}_{28}\text{H}_{28}\text{N}_2\text{O}_4\text{SNa}$  511.1662; found 511.1660.

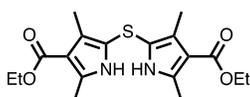
### Dibenzyl Ester 5,5'-Thiobis[2,4-dimethyl-1*H*-pyrrole-3-carboxylic acid] (**98**)



The title compound, and chlorinated pyrrole by-product (**122**), were prepared and isolated from the same reaction. In an oven-dried round-bottom equipped with a stir bar, cold thionyl chloride (16  $\mu\text{L}$ , 0.21 mmol, -8 °C) was slowly added to a cooled solution (-10 °C, salt/ice) of **92**<sup>266</sup> (70 mg, 0.31 mmol) and  $\text{NEt}_3$  (47  $\mu\text{L}$ , 0.34 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (3.0 mL). The reaction mixture was stirred at -10 °C and allowed to warm to room temperature (20-25 °C), under  $\text{N}_2$ . Once at room temperature, the reaction mixture was heated at reflux temperature for 2 h. Methanol (1.0 mL) was added to quench excess thionyl chloride, and the reaction mixture was concentrated *in vacuo*. The resulting residue was purified via column chromatography on silica, eluting with 15% ethyl acetate/hexanes, to yield the desired product, **98**, as an off-white solid (39 mg, 52%). M.p. 197-200 °C;  $^1\text{H}$  NMR (500 MHz;  $\text{CDCl}_3$ )  $\delta$  7.96 (br s, 2H), 7.41-7.39 (m, 4H), 7.37-7.36 (m, 4H), 7.32-7.29 (m, 2H), 5.26 (s, 4H), 2.42 (s, 6H), 2.38 (s, 6H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz;  $\text{CDCl}_3$ )  $\delta$  165.3, 137.8, 136.9, 128.6, 128.2, 128.1, 126.7, 115.6, 111.9, 65.5,

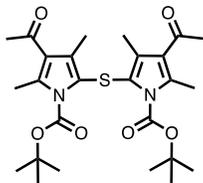
14.5, 12.5; HRMS-ESI ( $m/z$ ):  $[M+Na]^+$  calculated for  $C_{28}H_{28}N_2O_4SNa$  511.1662; found 511.1641.

**Diethyl Ester 5,5'-Thiobis[2,4-dimethyl-1*H*-pyrrole-3-carboxylic acid] (99)**



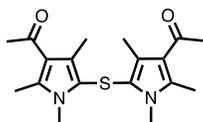
The title compound was prepared using new methodology. In an oven-dried round-bottom equipped with a stir bar, cold thionyl chloride (17  $\mu$ L, 0.23 mmol,  $-8$   $^{\circ}$ C) was slowly added to a cooled solution ( $-10$   $^{\circ}$ C, salt/ice) of **93**<sup>266</sup> (52 mg, 0.32 mmol) and  $NEt_3$  (50  $\mu$ L, 0.36 mmol) in anhydrous  $CH_2Cl_2$  (3.1 mL). The reaction mixture was stirred at  $-10$   $^{\circ}$ C and allowed to warm to room temperature (20-25  $^{\circ}$ C), under  $N_2$ . Once at room temperature, the reaction mixture was stirred for 1.5 h. Methanol (1.0 mL) was added to quench excess thionyl chloride, and the reaction mixture was concentrated *in vacuo*. The resulting residue was purified via column chromatography on silica, eluting with 15% ethyl acetate/hexanes, to yield the desired product as an off-white solid (19 mg, 32%). M.p. 189-192  $^{\circ}$ C;  $^1H$  NMR (500 MHz;  $CDCl_3$ )  $\delta$  7.90 (br s, 2H), 4.26 (q,  $J = 7.1$  Hz, 4H), 2.44 (s, 6H), 2.39 (s, 6H), 1.34 (t,  $J = 7.1$  Hz, 6H);  $^{13}C$   $\{^1H\}$  NMR (126 MHz;  $CDCl_3$ )  $\delta$  165.8, 137.5, 126.5, 115.6, 112.2, 59.5, 14.6, 14.3, 12.3; HRMS-ESI ( $m/z$ ):  $[M+Na]^+$  calculated for  $C_{18}H_{24}N_2O_4SNa$  387.1349; found 387.1344.

### Di-*tert*-butyl Ester 5,5'-Thiobis[3-acetyl-2,4-dimethyl-1*H*-pyrrole-1-carboxylic acid] (100)



In an oven-dried round-bottom equipped with a stir bar, cold thionyl chloride (33  $\mu\text{L}$ , 0.45 mmol,  $-8\text{ }^\circ\text{C}$ ) was slowly added to a cooled solution ( $-10\text{ }^\circ\text{C}$ , salt/ice) of **94** (142 mg, 0.586 mmol) and  $\text{NEt}_3$  (92  $\mu\text{L}$ , 0.66 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (6 mL). The reaction mixture was stirred at  $-10\text{ }^\circ\text{C}$ , under nitrogen, for 2 h 30 min. Methanol (2 mL) was added to quench excess thionyl chloride, and the reaction mixture was concentrated *in vacuo*. The resulting residue was purified via column chromatography on silica, eluting with 50% ethyl acetate/hexanes, to yield the desired product as an off-white solid (15.0 mg, 10%).  $^1\text{H}$  NMR (500 MHz;  $\text{CDCl}_3$ )  $\delta$  2.51 (s, 6H), 2.39 (s, 6H), 2.07 (s, 6H), 1.59 (s, 18H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz;  $\text{CDCl}_3$ )  $\delta$  196.6, 148.9, 137.1, 126.1, 124.9, 120.5, 85.8, 31.8, 28.0, 14.3, 12.6; HRMS-ESI ( $m/z$ ):  $[\text{M}+\text{Na}]^+$  calculated for  $\text{C}_{26}\text{H}_{36}\text{N}_2\text{O}_6\text{SNa}$  527.2186; found 527.2204.

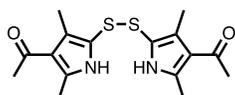
### 1,1'-[Thiobis(1,2,4-trimethyl-1*H*-pyrrol-3,5-diyl)]bisethanone (101)



In an oven-dried round-bottom equipped with a stir bar, cold thionyl chloride (30  $\mu\text{L}$ , 0.41 mmol,  $-8\text{ }^\circ\text{C}$ ) was slowly added to a cooled solution ( $-10\text{ }^\circ\text{C}$ , salt/ice) of **95** (84 mg,

0.56 mmol) and NEt<sub>3</sub> (85 μL, 0.61 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (6 mL). The reaction mixture was stirred at -10 °C, under N<sub>2</sub>, for 1 h. Methanol (2.0 mL) was added to quench excess thionyl chloride, and the reaction mixture was concentrated *in vacuo*. The resulting residue was purified via column chromatography on silica, eluting with 50% ethyl acetate/hexanes, to yield the desired product as an off-white solid (6 mg, 7%). <sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>) δ 3.44 (s, 6H), 2.50 (s, 6H), 2.45 (s, 6H), 2.42 (s, 6H); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz; CDCl<sub>3</sub>) δ 195.4, 138.2, 125.2, 122.0, 118.3, 31.5, 31.4, 14.1, 13.0; HRMS-ESI (*m/z*): [M+Na]<sup>+</sup> calculated for C<sub>18</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>SNa 355.1451; found 355.1436.

### 1,1'-[Dithiobis(2,4-dimethyl-1*H*-pyrrol-3,5-diyl)]bisethanone (102)



The title compound was prepared using two unique methodologies.

#### **Method 1: Treatment of 14 with S<sub>2</sub>Cl<sub>2</sub>**

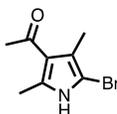
In an oven-dried round-bottom equipped with a stir bar, S<sub>2</sub>Cl<sub>2</sub> (50 μL, 0.64 mmol) was added to a cooled solution (0 °C) of compound **14** (169 mg, 1.23 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (12 mL). Immediately upon addition of S<sub>2</sub>Cl<sub>2</sub> the reaction mixture became thick with solid. The reaction mixture was stirred for 10 min, whereupon distilled water (1.0 mL) was added to quench the remaining S<sub>2</sub>Cl<sub>2</sub>. The solid was collected via suction filtration and dissolved in THF (insoluble in CH<sub>2</sub>Cl<sub>2</sub>, CHCl<sub>3</sub>, and ethyl acetate). The resulting solution was dried with MgSO<sub>4</sub> and the reaction mixture was concentrated *in vacuo*. The resulting residue was purified via column chromatography on silica, eluting with 50% ethyl

acetate/hexanes, to yield the desired product as an off-white solid (50 mg, 24%). M.p. 184-186 °C; <sup>1</sup>H NMR (500 MHz; DMSO-*d*<sub>6</sub>) δ 11.63 (br s, 2H), 2.43 (s, 6H), 2.29 (s, 6H), 1.80 (s, 6H); <sup>13</sup>C {<sup>1</sup>H} NMR (126 MHz; DMSO-*d*<sub>6</sub>) δ 193.5, 139.1, 129.8, 121.7, 115.8, 30.7, 14.5, 11.9; HRMS-ESI (*m/z*): [M+Na]<sup>+</sup> calculated for C<sub>16</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>S<sub>2</sub>Na 359.0858; found 359.0845.

### **Method 2: Treatment of **88** with SOCl<sub>2</sub>**

In an oven-dried round-bottom equipped with a stir bar, cold thionyl chloride (14 μL, 0.19 mmol, -8 °C) was slowly added to a cooled solution (-10 °C, salt/ice) of **88** (55 mg, 0.17 mmol) and NEt<sub>3</sub> (26 μL, 0.19 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (4 mL). The reaction mixture was stirred at -10 °C, under N<sub>2</sub>, for 10 min. Methanol (2 mL) was added to quench excess thionyl chloride, and the reaction mixture was concentrated *in vacuo*. The resulting residue was purified via column chromatography on silica, eluting with 50% ethyl acetate/hexanes, to yield the desired product as an off-white solid (8 mg, 14%). <sup>1</sup>H NMR (500 MHz; DMSO-*d*<sub>6</sub>) δ 11.63 (br s, 2H), 2.43 (s, 6H), 2.29 (s, 6H), 1.80 (s, 6H); HRMS-ESI (*m/z*): [M+Na]<sup>+</sup> calculated for C<sub>16</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>S<sub>2</sub>Na 359.0858; found 359.0862, in accordance with our previous data.

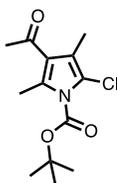
### **1-(5-Bromo-2,4-dimethyl-1H-pyrrol-3-yl)ethanone (103)**



In an oven-dried round-bottom equipped with a stir bar, cold thionyl bromide (48 μL, 0.62 mmol, -8 °C) was slowly added to a cooled solution (-10 °C, salt/ice) of **14** (114 mg,

0.830 mmol) and NEt<sub>3</sub> (127 μL, 0.913 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (8.3 mL). The reaction mixture was stirred at -10 °C, under N<sub>2</sub>, for 15 min. Methanol (1 mL) was added to quench excess thionyl chloride, and the reaction mixture was concentrated *in vacuo*. The resulting residue was purified via column chromatography on silica, eluting with 50% ethyl acetate/hexanes, to yield the desired product as an off-white solid (11 mg, 10 %). M.p. 50-53 °C (decomp); <sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>) δ 8.02 (br s, 1H), 2.49 (s, 3H), 2.42 (s, 3H), 2.22 (s, 3H); HRMS-ESI (*m/z*): [M+Na]<sup>+</sup> calculated for C<sub>8</sub>H<sub>10</sub>BrNONa 237.9838; found 237.9842. The <sup>1</sup>H NMR data has never been reported. The <sup>13</sup>C spectra was not collected due to instability of the title compound.

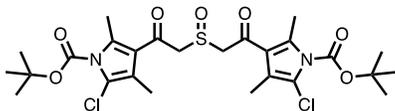
***tert*-Butyl Ester 3-Acetyl-5-chloro-2,4-dimethyl-1*H*-pyrrole-1-carboxylic Acid (107)**



The title compound was prepared for the first time according to a modified literature procedure.<sup>291</sup> In an oven-dried round-bottom equipped with a stir bar, di-*tert*-butyl dicarbonate (1.0 g, 4.7 mmol) was dissolved in anhydrous acetonitrile (9 mL) and bubbled with N<sub>2</sub> gas for 10 min, under N<sub>2</sub>, to prepare Solution One. In a second oven-dried round-bottom equipped with a stir bar, a solution of chlorinated pyrrole **90** (301 mg, 1.75 mmol) and DMAP (49 mg, 0.4 mmol) in anhydrous acetonitrile (15 mL) and anhydrous CH<sub>2</sub>Cl<sub>2</sub> (5 mL, required to solubilize pyrrole **90**) was bubbled with N<sub>2</sub> for 10 min under N<sub>2</sub>, to prepare Solution Two. Solution One was added to Solution Two slowly

via cannula. The combined solution was stirred for 20 min, until all of **90** was observed to be consumed via TLC. Reaction solvent and excess di-*tert*-butyl dicarbonate were removed *in vacuo*, and the resulting residue was purified via column chromatography on silica, eluting with 15% ethyl acetate/hexanes, to yield the desired product as an off-white solid (382 mg, 80%). <sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>) δ 2.59 (s, 3H), 2.46 (s, 3H), 2.21 (s, 3H), 1.65 (s, 9H); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz; CDCl<sub>3</sub>) δ 196.1, 148.3, 135.4, 124.3, 117.9, 114.1, 86.0, 31.7, 28.0, 14.2, 11.8; HRMS-ESI (*m/z*): [M+Na]<sup>+</sup> calculated for C<sub>13</sub>H<sub>19</sub>ClNO<sub>3</sub>Na 294.0867; found 294.0873.

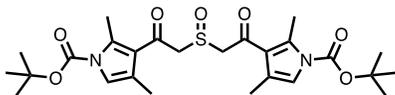
**Di-*tert*-butyl Ester 3,3'-[Sulfinylbis(1-oxo-2,1-ethanediyl)]bis(5-chloro-2,4-dimethyl-1*H*-pyrrole-1-carboxylic acid) (108)**



The title compound was prepared for the first time according to a modified literature procedure.<sup>235</sup> In an oven-dried round-bottom equipped with a stir bar, a solution of **107** (104 mg, 0.384 mmol) in anhydrous THF (1.5 mL) was bubbled with N<sub>2</sub> for 10 min, then cooled to -76 °C, all under N<sub>2</sub>. *n*-BuLi (1.6 M in hexanes, 265 μL, 0.424 mmol) was slowly added and the resulting mixture was stirred for 10 min at -76 °C. SOCl<sub>2</sub> (17 μL, 0.23 mmol) was slowly added, dropwise. The reaction mixture was stirred for an additional 15 min at -76 °C and then allowed to gradually warm to room temperature (20 °C) outside of the cold bath, after which water was added (10 mL). The resulting mixture was thoroughly extracted with diethyl ether (5 × 5 mL). The organic fractions were combined and washed with 0.25 M Na<sub>2</sub>CO<sub>3</sub> (20 ml) and water (2 × 20 mL), dried over

Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The resulting residue was purified via column chromatography on silica, eluting with 50% ethyl acetate/hexanes, to yield the desired product as an off-white amorphous solid (5 mg, 5%). <sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>) δ 4.58 (d, *J* = 14.7 Hz, 2H), 4.26 (d, *J* = 14.7 Hz, 2H), 2.59 (s, 6H), 2.22 (s, 6H), 1.62 (s, 18H); <sup>13</sup>C {<sup>1</sup>H} NMR (126 MHz; CDCl<sub>3</sub>) δ 189.4, 147.9, 137.5, 123.0, 117.6, 115.0, 86.7, 63.4, 28.0, 14.4, 11.9. HRMS-ESI (*m/z*): [M+Na]<sup>+</sup> calculated for C<sub>26</sub>H<sub>36</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>7</sub>SNa 611.1356; found 611.1369.

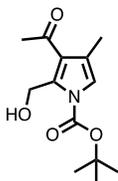
**Di-*tert*-butyl Ester 3,3'-[Sulfinylbis(1-oxo-2,1-ethanediyl)]bis(2,4-dimethyl-1*H*-pyrrole-1-carboxylic acid) (109)**



The title compound was prepared for the first time according to a modified literature procedure.<sup>235</sup> A solution of **94** (99 mg, 0.42 mmol) in anhydrous THF (2 mL) was bubbled with N<sub>2</sub> for 10 min, then cooled to -76 °C, all under N<sub>2</sub>. *n*-BuLi (1.6 M in hexanes, 290 μL, 0.464 mmol) was slowly added and the resulting mixture was stirred for 10 min at -76 °C. SOCl<sub>2</sub> (17 μL, 0.23 mmol) was added slowly dropwise. The reaction mixture was stirred for an additional 15 min at -76 °C and then allowed to gradually warm to room temperature (20 °C) outside of the cold bath, then water was added (10 mL). The resulting mixture was thoroughly extracted with diethyl ether (5 × 5 mL). The organic fractions were combined and washed with 0.25 M Na<sub>2</sub>CO<sub>3</sub> (20 mL) and water (2 × 20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The resulting residue was purified via column chromatography on silica, eluting with 50% ethyl acetate/hexanes, to

yield the desired product as an off-white amorphous solid (14 mg, 13%).  $^1\text{H}$  NMR (500 MHz;  $\text{CDCl}_3$ )  $\delta$  6.92 (br s, 2H), 4.57 (d,  $J = 14.7$  Hz, 2H), 4.28 (d,  $J = 14.7$  Hz, 2H), 2.72 (s, 6H), 2.23 (s, 6H), 1.59 (s, 19H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz;  $\text{CDCl}_3$ )  $\delta$  190.3, 148.9, 139.8, 125.1, 119.8, 119.6, 85.0, 63.9, 28.1, 14.6, 13.5; HRMS-ESI ( $m/z$ ):  $[\text{M}+\text{Na}]^+$  calculated for  $\text{C}_{26}\text{H}_{36}\text{N}_2\text{O}_7\text{SNa}$  543.2135; found 543.2148.

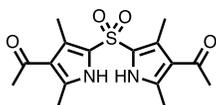
### ***tert*-Butyl Ester 3-Acetyl-2-methanol-4-methyl-1*H*-pyrrole-1-carboxylic Acid (110)**



In an oven-dried round-bottom equipped with a stir bar, **94** (415 mg, 2.5 mmol) was dissolved in anhydrous  $\text{CH}_2\text{Cl}_2$  (27 mL), under  $\text{N}_2$ , and cooled to  $-10$  °C. To this solution was added NBS (419 mg, 2.44 mmol) slowly, portion-wise, under a stream of  $\text{N}_2$ . After complete addition of NBS, the reaction mixture was allowed to warm to room temperature ( $25$  °C) over 1 h, after which it was heated at  $45$  °C for a further 2 h at which time NBS had been completely consumed (monitoring consumption of NBS via TLC, eluting with 10% EtOAc/Hex). The reaction mixture was diluted with  $\text{CH}_2\text{Cl}_2$  (10 mL) and aqueous NaOH (0.5 M, 25 mL) was added, with stirring. The organic phase was separated, and the aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 10$  mL). The combined organic extracts were washed with water (30 mL) and brine (30 mL), then dried over anhydrous  $\text{Na}_2\text{SO}_4$  and the solvent was removed *in vacuo*. The resulting residue was purified via column chromatography on silica, eluting with 10% ethyl acetate/hexanes, to

yield the title compound as an off-white solid (16 mg, 7%). M.p. 50 °C (decomp);  $^1\text{H}$  NMR (500 MHz;  $\text{CDCl}_3$ )  $\delta$  6.93-6.92 (m, 1H), 4.92 (d,  $J = 5.4$  Hz, 2H), 3.91-3.88 (m, 1H, -OH), 2.49 (s, 3H), 2.20 (d,  $J = 1.1$  Hz, 3H), 1.60 (s, 9H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz;  $\text{CDCl}_3$ )  $\delta$  197.8, 149.4, 139.3, 127.9, 120.1 (2 overlapping signals), 85.6, 55.0, 31.5, 28.1, 13.0. HRMS-ESI ( $m/z$ ):  $[\text{M}+\text{Na}]^+$  calculated for  $\text{C}_{13}\text{H}_{19}\text{NO}_4\text{Na}$  276.1206; found 276.1205.

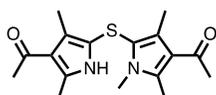
### 1,1'-[Sulfonylbis(2,4-dimethyl-1*H*-pyrrol-3,5-diyl)]bisethanone (111)



The title compound and **88** were prepared and isolated from the same reaction using a modified literature procedure.<sup>235</sup> A solution of *m*-CPBA ( $\leq 77\%$ , 430 mg, 1.59 mmol) in DMF (18 ml) was added, drop-wise under  $\text{N}_2$ , to a solution of **89** (502 mg, 1.65 mmol) in DMF (36 mL). After complete addition of the *m*-CPBA solution (8 min), the resulting reaction mixture was stirred at 0 °C until all starting material had been consumed (1 h, monitoring via TLC). The reaction mixture was diluted with  $\text{CHCl}_3$  (100 mL) and then washed with saturated  $\text{NaHCO}_3$  (50 mL), followed by thorough washing with  $\text{H}_2\text{O}$  ( $5 \times 50$  mL). The organic layer was dried with  $\text{Na}_2\text{SO}_4$  and then the solvent was removed *in vacuo*. The resulting residue was purified via column chromatography on silica, eluting with 50% ethyl acetate/hexanes up to 100% ethyl acetate, to yield the desired product, **88**, as an amorphous white solid (111 mg, 20%).  $^1\text{H}$  NMR (500 MHz;  $\text{DMSO}-d_6$ )  $\delta$  12.11 (br s, 2H), 2.45 (s, 6H), 2.33 (s, 6H), 2.31 (s, 6H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz;  $\text{DMSO}-d_6$ )  $\delta$

194.3, 138.4, 125.4, 124.5, 122.4, 31.1, 14.1, 11.3; HRMS-ESI ( $m/z$ ):  $[M+Na]^+$  calculated for  $C_{16}H_{20}N_2O_4SNa$  359.1036; found 359.1035.

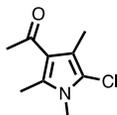
**1-[5-[(4-Acetyl-3,5-dimethylpyrrol-2-yl)thio]-1,2,4-trimethyl-1H-pyrrol-3-yl]ethanone (114)**



The title compound and **115** were prepared and isolated from the same reaction. Cold thionyl chloride (17  $\mu$ L, 0.24 mmol, -8 °C) was slowly added to a cooled solution (-10 °C, salt/ice) of **88** (76 mg, 0.24 mmol), **95** (361 mg, 2.41 mmol), and  $NEt_3$  (26  $\mu$ L, 0.26 mmol) in anhydrous  $CH_2Cl_2$  (5 mL), under nitrogen. Prior to cooling and thionyl chloride addition, the reaction mixture required 10 min of stirring at room temperature for all solid reagents to completely dissolve. Once thionyl chloride had been added, the reaction mixture was stirred at -10 °C and monitored via TLC (100% EtOAc) until **88** was consumed, 20 min. The reaction solvents were removed *in vacuo* and the resulting residue was crudely purified via column chromatography on silica, eluting with 25% EtOAc/hexanes up to 100% EtOAc. The still crude solid was fully purified using preparative TLC, with 100% ethyl acetate as the eluent. A single preparative TLC plate was cycled 3 times (run TLC plate in 100% EtOAc, air dry, run, air dry, run third and final time) to allow for ideal separation and furnish the desired product, **114**, as an off-white amorphous solid (6 mg, 8%).  $^1H$  NMR (500 MHz;  $CDCl_3$ )  $\delta$  7.82 (s, 1H), 3.55 (s, 3H), 2.55 (s, 3H), 2.47 (s, 3H), 2.44-2.42 (m, 9H), 2.39 (s, 3H);  $^{13}C$   $\{^1H\}$  NMR (126 MHz;  $CDCl_3$ )  $\delta$  195.4, 194.9, 138.3, 136.9, 126.5, 123.8, 122.2, 122.1, 118.7, 116.2, 31.4

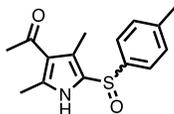
(two overlapping signals), 31.1, 15.5, 14.1, 13.1 (two overlapping signals); HRMS-ESI ( $m/z$ ):  $[M+Na]^+$  calculated for  $C_{17}H_{22}N_2O_2SNa$  341.1294; found 341.1304.

### 1-(5-Chloro-1,2,4-trimethyl-1H-pyrrol-3-yl)ethanone (115)



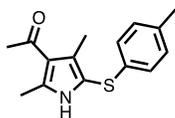
The title compound and **114** were prepared and isolated from the same reaction. Cold thionyl chloride (17  $\mu$ L, 0.24 mmol, -8  $^{\circ}$ C) was slowly added to a cooled solution (-10  $^{\circ}$ C, salt/ice) of **88** (76 mg, 0.24 mmol), **95** (361 mg, 2.40 mmol), and  $NEt_3$  (26  $\mu$ L, 0.26 mmol) in anhydrous  $CH_2Cl_2$  (5 mL), under nitrogen. Prior to cooling and thionyl chloride addition, the reaction mixture required 10 min of stirring at room temperature for all solid reagents to completely dissolve. Once thionyl chloride had been added, the reaction mixture was stirred at -10  $^{\circ}$ C and monitored via TLC (100% EtOAc) until **88** was consumed, 20 min. The reaction solvents were removed *in vacuo* and the resulting residue was purified via column chromatography on silica, eluting with 25% EtOAc/hexanes up to 100% EtOAc, to yield the desired product, **95**, as an off-white amorphous solid (15 mg, 4% from **95**).  $^1H$  NMR (500 MHz;  $CDCl_3$ )  $\delta$  3.48 (s, 3H), 2.49 (s, 3H), 2.41 (s, 3H), 2.24 (s, 3H);  $^{13}C\{^1H\}$  NMR (126 MHz;  $CDCl_3$ )  $\delta$  195.1, 134.7, 121.2, 115.2, 114.6, 77.2, 31.4, 30.8, 12.7, 12.4; HRMS-ESI ( $m/z$ ):  $[M+Na]^+$  calculated for  $C_9H_{12}ClN_2O$  208.0500; found 208.0496.  $^1H$  and  $^{13}C$  data have never been reported for this compound.

## 1-[2,4-Dimethyl-5-(4-methylphenyl)sulfinyl-1H-pyrrol-3-yl]ethanone (116)



The title compound was prepared for the first time according to a modified literature procedure.<sup>235</sup> To a solution of **118** (155 mg, 0.598 mmol) in DMF (12 mL) at -10 °C, was added, dropwise, a solution of *m*-CPBA (120 mg, 0.610 mmol) in DMF (6 mL), under N<sub>2</sub>. After 2 h, the reaction mixture was diluted with methanol (5 mL) and concentrated under reduced pressure. Water was added to the reaction mixture (60 mL), and the aqueous layer was thoroughly extracted with CH<sub>2</sub>Cl<sub>2</sub> (5 × 20 mL). The organic fractions were combined, washed with water (2 × 50 mL) and brine (50 mL) and then dried with Na<sub>2</sub>SO<sub>4</sub>. The reaction mixture was concentrated *in vacuo*, then purified via column chromatography on silica, eluting with 15% ethyl acetate/hexanes up to 25%, to yield the desired product as an off-white amorphous solid (103 mg, 63%). <sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>) δ 9.94 (s, 1H), 7.45 (d, *J* = 8.2 Hz, 2H), 7.27 (d, *J* = 8.1 Hz, 2H), 2.49 (s, 3H), 2.40-2.39 (m, 6H), 2.38 (s, 3H); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz; CDCl<sub>3</sub>) δ 194.8, 141.5, 140.8, 140.8, 140.4, 130.2, 127.4, 124.9, 122.3, 31.2, 21.5, 15.2, 12.4; HRMS-ESI (*m/z*): [M+Na]<sup>+</sup> calculated for C<sub>15</sub>H<sub>17</sub>NO<sub>2</sub>SNa 298.0872; found 298.0870; in accordance with previous literature<sup>295</sup>

## 1-[2,4-Dimethyl-5-(4-methylphenyl)thio-1H-pyrrol-3-yl]ethanone (118)



The title compound was prepared using two unique methodologies.

### Method 1: Treatment of **14** and *p*-Toluenesulfonyl Chloride with PPh<sub>3</sub>

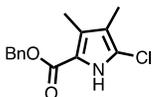
The title compound was prepared according to a modified literature procedure.<sup>243</sup> Pyrrole **14** (51 mg, 0.37 mmol), *p*-toluenesulfonyl chloride (137 mg, 0.719 mmol), and tricyclohexylphosphine (294 mg, 0.929 mmol) were dissolved in anhydrous dioxane (1.5 mL) under N<sub>2</sub> at room temperature (20 °C). Once completely in solution, the reaction mixture was heated at 50 °C for 20 h. The reaction solvent was removed *in vacuo*, and the resulting residue was purified via column chromatography on silica, eluting with 25% ethyl acetate/hexanes, to yield the desired product as an off-white amorphous solid (70 mg, 72%). <sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>): δ 8.10 (br s, 1H), 7.04 (d, *J* = 8.0 Hz, 2H), 6.91 (d, *J* = 8.2 Hz, 2H), 2.51 (s, 3H), 2.46 (s, 3H), 2.37 (s, 3H), 2.28 (s, 3H); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz; CDCl<sub>3</sub>) δ 195.2, 137.7, 135.7, 134.4, 130.0, 128.9, 126.3, 122.6, 113.6, 31.1, 21.0, 15.4, 13.2; HRMS-ESI (*m/z*): [M+Na]<sup>+</sup> calculated for C<sub>15</sub>H<sub>17</sub>NOSNa 282.0923; found 282.0911. <sup>1</sup>H and <sup>13</sup>C data have never been reported for this compound.

### Method 2: Treatment of **116** with SOCl<sub>2</sub>

Cold thionyl chloride (15 μL, 0.20 mmol, -8 °C) was slowly added to a cooled solution (-10 °C, salt/ice) of **116** (51 mg, 0.18 mmol) and NEt<sub>3</sub> (28 μL, 0.20 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (2 mL). The reaction mixture was stirred at -10 °C, under nitrogen, for 9 min. Methanol (1 mL) was added to quench excess thionyl chloride, and the solvents were

removed *in vacuo*. The resulting residue was purified via column chromatography on silica, eluting with 20% ethyl acetate/hexanes, to yield the desired product as an off-white solid (7.3 mg, 15%). <sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>): δ 8.10 (br s, 1H), 7.04 (d, *J* = 8.0 Hz, 2H), 6.91 (d, *J* = 8.2 Hz, 2H), 2.51 (s, 3H), 2.46 (s, 3H), 2.37 (s, 3H), 2.28 (s, 3H), in accordance with our previous data.

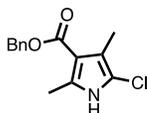
### Benzyl Ester 3,4-Dimethyl-5-chloro-1*H*-pyrrole-2-carboxylic Acid (**121**)



The title compound and **97** were prepared and isolated from the same reaction. In an oven-dried round-bottom equipped with a stir bar, cold thionyl chloride (15 μL, 0.21 mmol, -8 °C) was slowly added to a cooled solution (-10 °C, salt/ice) of **91**<sup>266</sup> (64 mg, 0.280 mmol) and NEt<sub>3</sub> (43 μL, 0.31 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (3.5 mL). The reaction mixture was stirred at -10 °C and allowed to warm to room temperature (20-25 °C), under N<sub>2</sub>. Once at room temperature, the reaction mixture was heated at reflux temperature for 20 h. Methanol (1 mL) was added to quench excess thionyl chloride, and the reaction mixture was concentrated *in vacuo*. The resulting residue was purified via column chromatography on silica, eluting with 15% ethyl acetate/hexanes, to yield the desired product, **121**, as an off-white solid (8 mg, 11 %). M.p. 153-155 °C; <sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>) δ 8.82 (br s, 1H), 7.42-7.32 (m, 5H), 5.31 (s, 2H), 2.28 (s, 3H), 1.95 (s, 3H). <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz; CDCl<sub>3</sub>) δ 160.7, 136.4, 128.7 (three overlapping

signals), 128.34, 128.31, 117.9, 117.4, 66.0, 11.1, 8.7; HRMS-ESI ( $m/z$ ):  $[M+Na]^+$  calculated for  $C_{14}H_{14}ClNO_2Na$  286.0605; found 286.0601.

### Benzyl Ester 2,4-Dimethyl-5-chloro-1H-pyrrole-3-carboxylic Acid (**122**)



The title compound and **98** were prepared and isolated from the same reaction. In an oven-dried round-bottom equipped with a stir bar, cold thionyl chloride (16  $\mu$ L, 0.21 mmol, -8  $^{\circ}$ C) was slowly added to a cooled solution (-10  $^{\circ}$ C, salt/ice) of **92**<sup>266</sup> (70 mg, 0.31 mmol) and  $NEt_3$  (47  $\mu$ L, 0.34 mmol) in anhydrous  $CH_2Cl_2$  (3.0 mL). The reaction mixture was stirred at -10  $^{\circ}$ C and allowed to warm to room temperature (20-25  $^{\circ}$ C), under  $N_2$ . Once at room temperature, the reaction mixture was heated at reflux temperature for 2 h. Methanol (1 mL) was added to quench excess thionyl chloride, and the reaction mixture was concentrated *in vacuo*. The resulting residue was purified via column chromatography on silica, eluting with 15% ethyl acetate/hexanes, to yield the desired product, **122**, as an off-white solid (12 mg, 14 %). M.p. 154-156  $^{\circ}$ C;  $^1H$  NMR (500 MHz;  $CDCl_3$ )  $\delta$  7.99 (br s, 1H), 7.46-7.44 (m, 2H), 7.41-7.38 (m, 2H), 7.36-7.33 (m, 1H), 5.32 (s, 2H), 2.49 (s, 3H), 2.21 (s, 3H);  $^{13}C\{^1H\}$  NMR (126 MHz;  $CDCl_3$ )  $\delta$  165.2, 136.9, 134.6, 128.6, 128.1, 128.0, 117.0, 111.4, 110.7, 65.5, 14.1, 11.1; HRMS-ESI ( $m/z$ ):  $[M+Na]^+$  calculated for  $C_{14}H_{14}ClNO_2Na$  286.0605; found 286.0606.

## Chapter 6 – Conclusions

### 6.1 Conclusions

The work described in this thesis has focused on the exploration and development of new methodologies towards the synthesis of pyrrolic frameworks and has built upon the foundations of fundamental pyrrole and dipyrin chemistry. Described in Chapter 2, a simple and robust open-air synthesis of *F*-BODIPYs from dipyrins, involving non-anhydrous reagents and requiring no precautions to exclude moisture, was developed. Simple in nature, this robust methodology requires the addition of two aliquots, separated by a period of waiting, of  $\text{NEt}_3$  and  $\text{BF}_3 \cdot \text{OEt}_2$  to afford *F*-BODIPYs in excellent yields. The ratio and amounts of  $\text{NEt}_3$  and  $\text{BF}_3 \cdot \text{OEt}_2$  used in each aliquot are critical to success (6 equivalents of  $\text{NEt}_3$  and 9 equivalents of  $\text{BF}_3 \cdot \text{OEt}_2$  per each aliquot). The greatest advantage to this methodology is the capability to furnish the desired *F*-BODIPYs in excellent yields while using an air-dried bench-top apparatus, without the need to either purchase anhydrous solvents or achieve and maintain anhydrous solvents and conditions.

Described in Chapter 3, the mechanism by which 2-formylpyrroles self-condense to afford dipyrins under acid-catalyzed conditions, and why a regioisomeric outcome could be observed, was investigated. Through a systematic study involving variously substituted and isotopically labelled 2-formyl-5-H-pyrroles, evidence was provided to suggest that not only does there exist two mechanistic pathways, but that the steric bulk of the substituent adjacent to the 5-unsubstituted position influences which pathway dominates. Thus, we determined that regioisomeric dipyrins may arise from the self-condensation of 2-formylpyrrole through the adoption of two mechanistic pathways.

Described in Chapter 4, the first preparation of dipyrrolyl sulfides via the electrophilic aromatic substitution of substituted pyrroles with thionyl chloride was developed. The new methodology featured an interesting auto-reduction of the sulfoxide centre of  $\text{SOCl}_2$  ( $[\text{S}]^{4+}$ ) to produce a sulfide-bridged ( $[\text{S}]^{2+}$ ) dipyrrole. The new synthesis was investigated and from a first-principles investigation a mechanism for the auto-reduction reaction was proposed.

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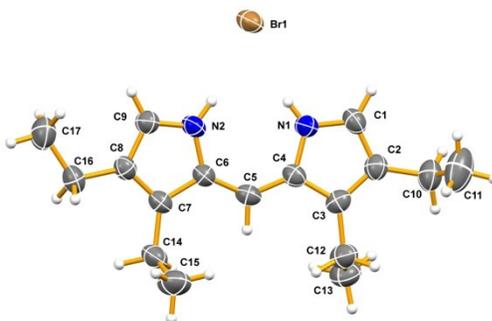
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## Appendix A: X-Ray Crystallographic Analysis Data

All data was collected and analyzed by Katherine Robertson at Saint Mary's University. The crystal chosen was attached to the tip of a 400  $\mu\text{m}$  MicroLoop with paratone-N oil. Measurements were made on a Bruker APEXII CCD equipped diffractometer (30 mA, 50 kV) using monochromated Mo K $\alpha$  radiation ( $\lambda = 0.71073 \text{ \AA}$ ) at 125 K.<sup>296</sup> The initial orientation and unit cell were indexed using a least-squares analysis of a random set of reflections collected from three series of  $0.5^\circ$   $\omega$ -scans, 15 s per frame and 12 frames per series, that were well distributed in reciprocal space. For data collection, four  $\omega$ -scan frame series were collected with  $0.5^\circ$  wide scans, 60 second frames and 366 frames per series at varying  $\phi$  angles ( $\phi = 0^\circ, 90^\circ, 180^\circ, 270^\circ$ ). The crystal to detector distance was set to 6 cm and a complete sphere of data was collected. Cell refinement and data reduction were performed with the Bruker SAINT<sup>296</sup> software, which corrects for beam inhomogeneity, possible crystal decay, Lorentz and polarization effects. A multi-scan absorption correction was applied (SADABS).<sup>297</sup> The structures were solved using SHELXT-2014<sup>298-300</sup> and was refined using a full-matrix least-squares method on  $F^2$  with SHELXL-2014.<sup>298-300</sup> The refinement was unremarkable. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms bonded to carbon were included at geometrically idealized positions and were not refined. The isotropic thermal parameters of the hydrogen atoms were fixed at  $1.2U_{\text{eq}}$  of the parent carbon atom or  $1.5U_{\text{eq}}$  for methyl hydrogens. The hydrogen atoms bonded to nitrogen were located in the next to final difference Fourier map. They were included in the final cycle of refinement and allowed to refine isotropically. The merging R-factor for this data set (0.138) is somewhat larger than desirable (level C checkcif alert). It is so high because the crystal used was very

small and very thin; it was difficult to center in the X-ray beam. All diagrams were prepared by using the program Mercury CSD 3.7.<sup>301</sup>

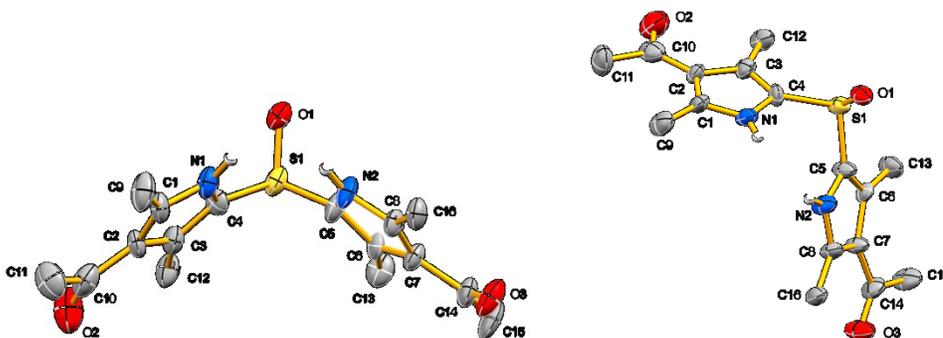
**3,7-(Diethyl-1,1,2,2-*d*<sub>4</sub>)-2,8-diethyl-5-H-4,6-dipyrrin hydrobromide (45\*)**



Empirical formula	C <sub>17</sub> H <sub>25</sub> BrN <sub>2</sub>	
Formula weight	337.30 g/mol	
Crystal description	clear red-orange thin rectangular plate	
Temperature	298(2) K	
Crystal system	Triclinic	
Space group	<i>P</i> -1	
Unit cell dimensions	<i>a</i> = 8.8132(4) Å	<i>α</i> = 111.160(3)°
	<i>b</i> = 9.1511(4) Å	<i>β</i> = 103.282(3)°
	<i>c</i> = 12.1393(6) Å	<i>γ</i> = 95.888(3)°
Volume	869.85(7) Å <sup>3</sup>	
<i>Z</i>	2	
<i>ρ</i> (calculated)	1.288 Mg/m <sup>3</sup>	
<i>μ</i> (Mo K $\alpha$ )	2.357 mm <sup>-1</sup>	
Crystal size	0.300 × 0.150 × 0.050 mm <sup>3</sup>	

Reflections collected	15590 (4216 unique, $R_{\text{int}} = 0.0325$ )
Goodness-of-fit	1.014
$R(F)$	0.0359
$R_w(F)$	0.0721

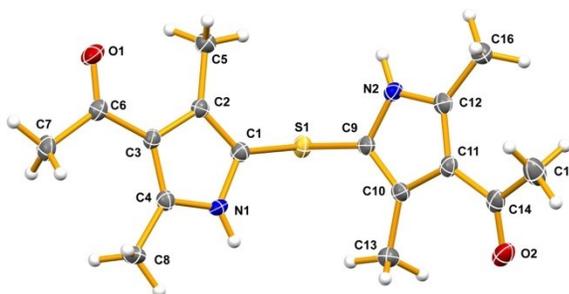
**1,1'-(sulfinyldi-1-(2,4-dimethyl-1*H*-pyrrol-3-yl)bis-ethanone (88)**



Empirical formula	$C_{16}H_{20}N_2O_3S$	
Formula weight	320.40 g/mol	
Crystal description	clear, colourless, flat, needle	
Temperature	124(2) K	
Crystal system	Monoclinic	
Space group	$C2/c$	
Unit cell dimensions	$a = 14.792(13) \text{ \AA}$	$\alpha = 90^\circ$
	$b = 16.881(15) \text{ \AA}$	$\beta = 100.898(10)^\circ$
	$c = 13.879(12) \text{ \AA}$	$\gamma = 90^\circ$
Volume	$3403(5) \text{ \AA}^3$	
$Z$	8	
$\rho$ (calculated)	$1.251 \text{ Mg/m}^3$	

$\mu$ (Mo K $\alpha$ )	0.203 mm <sup>-1</sup>
Crystal size	0.250 × 0.050 × 0.050 mm <sup>3</sup>
Reflections collected	15173 (2782 unique, $R_{\text{int}} = 0.3990$ )
Goodness-of-fit	0.956
$R(F)$	0.0997
$R_w(F)$	0.1680

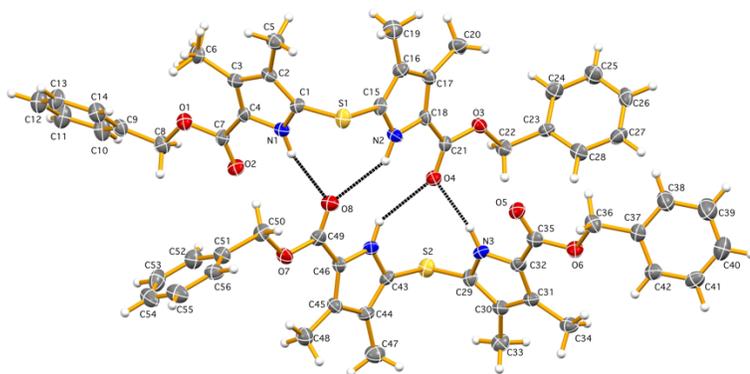
### Di(4-acetyl-3,5-dimethylpyrrole-2-yl) sulfide (89)



Empirical formula	C <sub>16</sub> H <sub>20</sub> N <sub>2</sub> O <sub>2</sub> S	
Formula weight	304.40 g/mol	
Crystal description	clear, light pink, rectangular prism	
Temperature	125(2) K	
Crystal system	Orthorhombic	
Space group	<i>Pbca</i>	
Unit cell dimensions	$a = 14.525(10)$ Å	$\alpha = 90^\circ$
	$b = 7.567(5)$ Å	$\beta = 90^\circ$
	$c = 27.347(19)$ Å	$\gamma = 90^\circ$
Volume	3006(4) Å <sup>3</sup>	
<i>Z</i>	8	

$\rho$ (calculated)	1.345 Mg/m <sup>3</sup>
$\mu$ (Mo K $\alpha$ )	0.222 mm <sup>-1</sup>
Crystal size	0.200 × 0.080 × 0.060 mm <sup>3</sup>
Reflections collected	33585 (3781 unique, $R_{\text{int}} = 0.1381$ )
Goodness-of-fit	1.004
$R(F)$	0.0535
$R_w(F)$	0.1128

### Di(5-benzyloxycarbonyl-3,4-dimethylpyrrole-2-yl) sulfide (97)

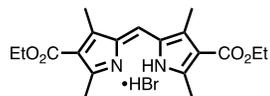


Empirical formula	C <sub>28</sub> H <sub>28</sub> N <sub>2</sub> O <sub>4</sub> S	
Formula weight	488.58 g/mol	
Crystal description	clear, colourless, long, thin needle	
Temperature	124(2) K	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	$a = 9.899(2)$ Å	$\alpha = 90^\circ$
	$b = 22.797(5)$ Å	$\beta = 96.826(2)^\circ$
	$c = 21.899(4)$ Å	$\gamma = 90^\circ$

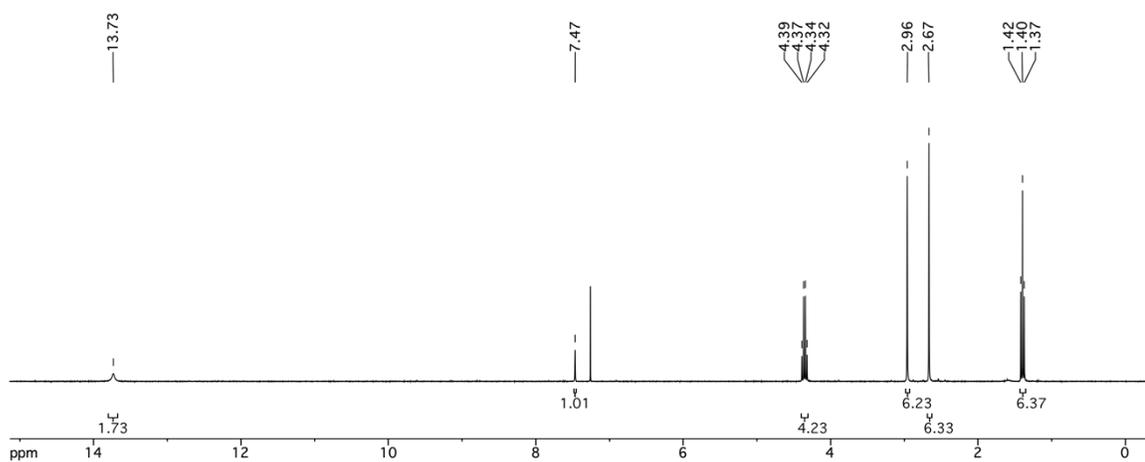
Volume	4907.9(17) Å <sup>3</sup>
<i>Z</i>	8
ρ (calculated)	1.323 Mg/m <sup>3</sup>
μ (Mo Kα)	0.170 mm <sup>-1</sup>
Crystal size	0.700 × 0.050 × 0.025 mm <sup>3</sup>
Reflections collected	40365 (6922 unique, R <sub>int</sub> = 0.1946)
Goodness-of-fit	1.000
<i>R</i> ( <i>F</i> )	0.0640
<i>R</i> <sub>w</sub> ( <i>F</i> )	0.104

## Appendix B: NMR Spectra for Synthesized Compounds

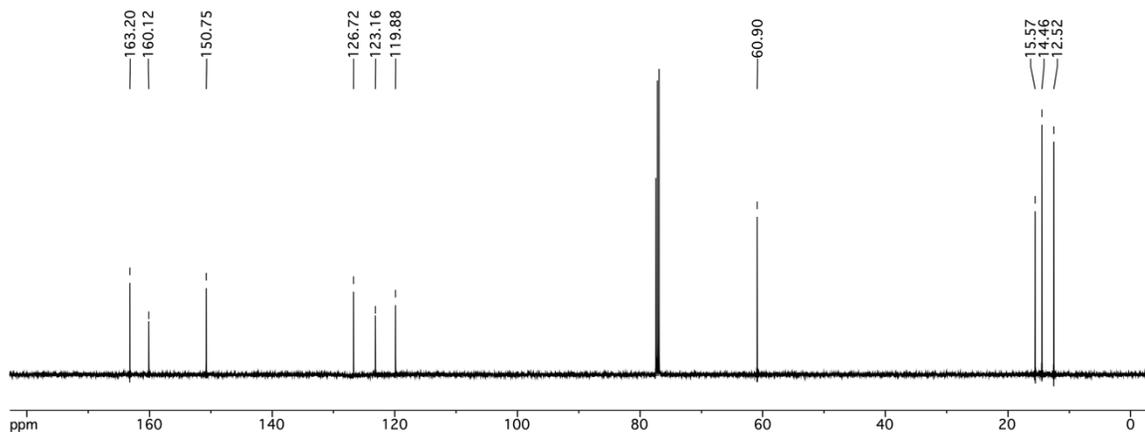
### Ethyl Ester 5-[[4-(Ethoxycarbonyl)-3,5-dimethyl-2*H*-pyrrol-2-ylidene]methyl]-2,4-dimethyl-1*H*-pyrrole-3-carboxylic Acid Monohydrobromide (6)



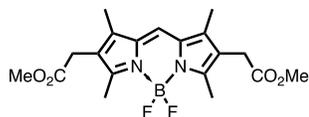
#### $^1\text{H}$ NMR ( $\text{CDCl}_3$ )



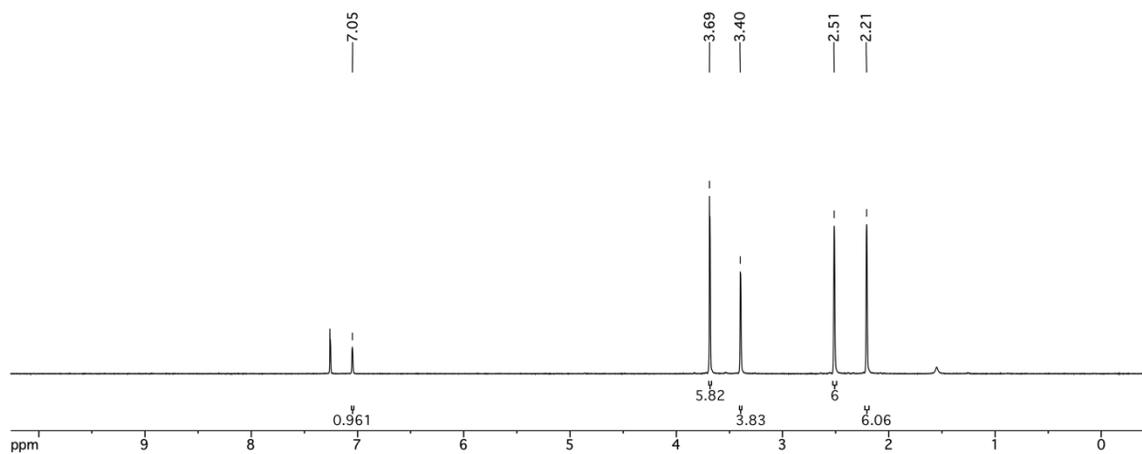
#### $^{13}\text{C}$ NMR ( $\text{CDCl}_3$ )



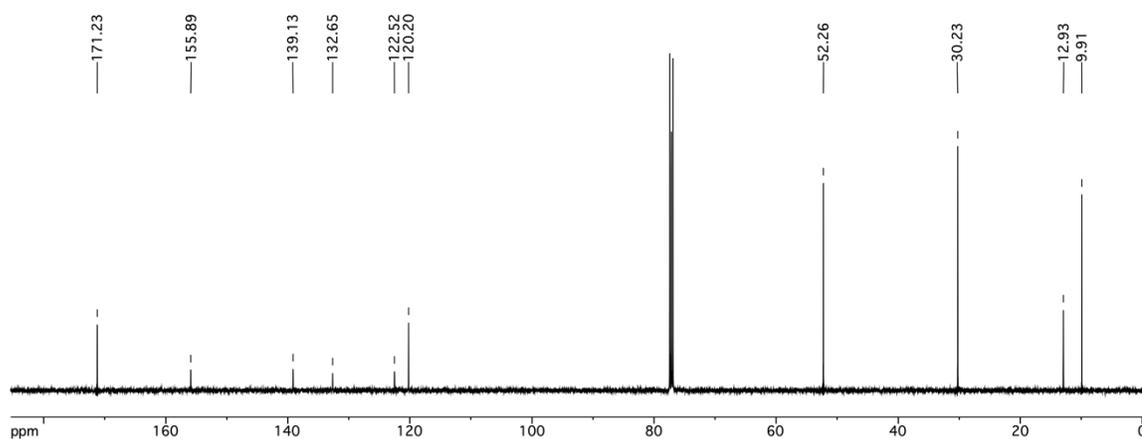
**(*T*-4)-Difluoro[4-(2-methoxy-2-oxoethyl)-2-[(4-(2-methoxy-2-oxoethyl)-3,5-dimethyl-2*H*-pyrrol-2-ylidene- $\kappa$ *N*)methyl]-3,5-dimethyl-1*H*-pyrrolato- $\kappa$ *N*]boron (30)**



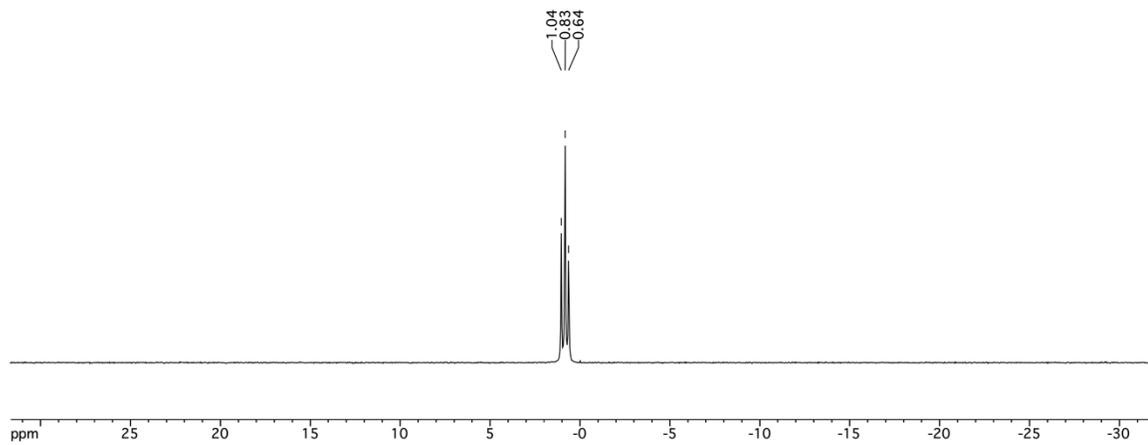
**<sup>1</sup>H NMR (CDCl<sub>3</sub>)**



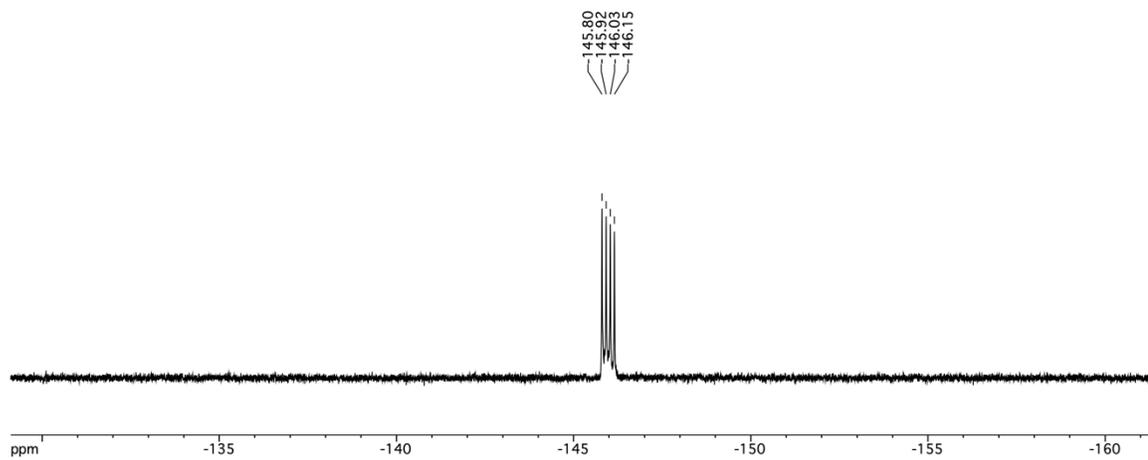
**<sup>13</sup>C NMR (CDCl<sub>3</sub>)**



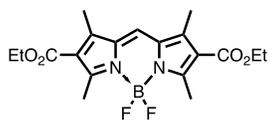
### $^{11}\text{B}$ NMR ( $\text{CDCl}_3$ )



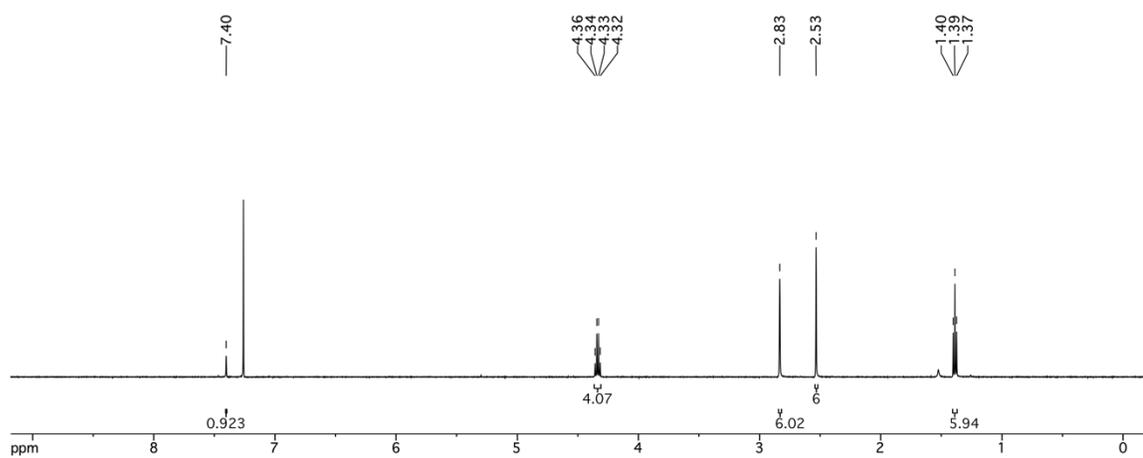
### $^{19}\text{F}$ NMR ( $\text{CDCl}_3$ )



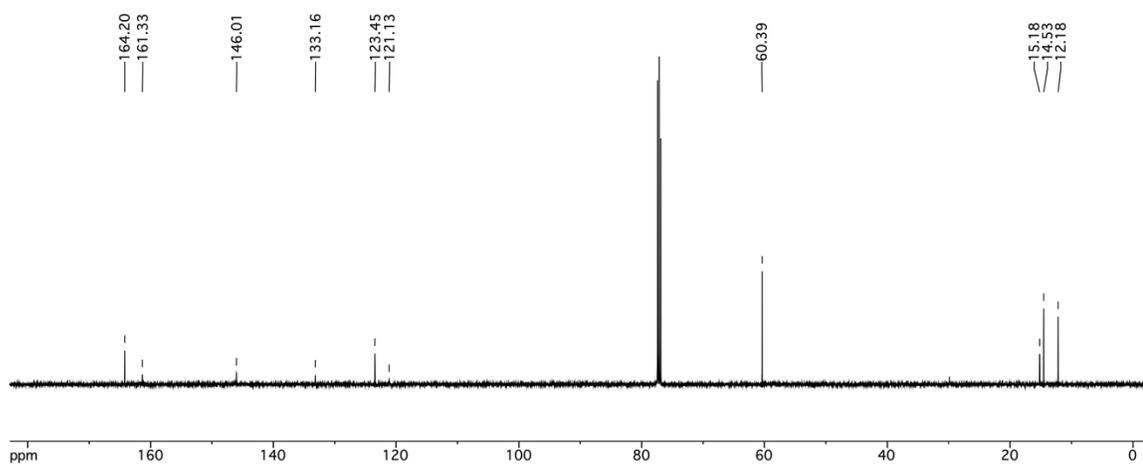
**(*T*-4)-Difluoro[4-ethoxycarbonyl-2-[(4-ethoxycarbonyl-3,5-dimethyl-2*H*-pyrrol-2-ylidene- $\kappa$ *N*)methyl]-3,5-dimethyl-1*H*-pyrrolato- $\kappa$ *N*]boron (31)**



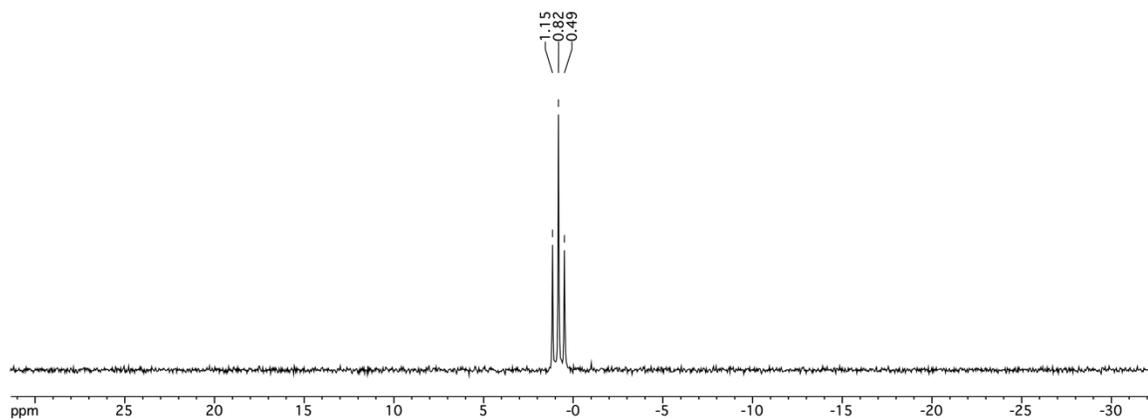
**$^1\text{H}$  NMR ( $\text{CDCl}_3$ )**



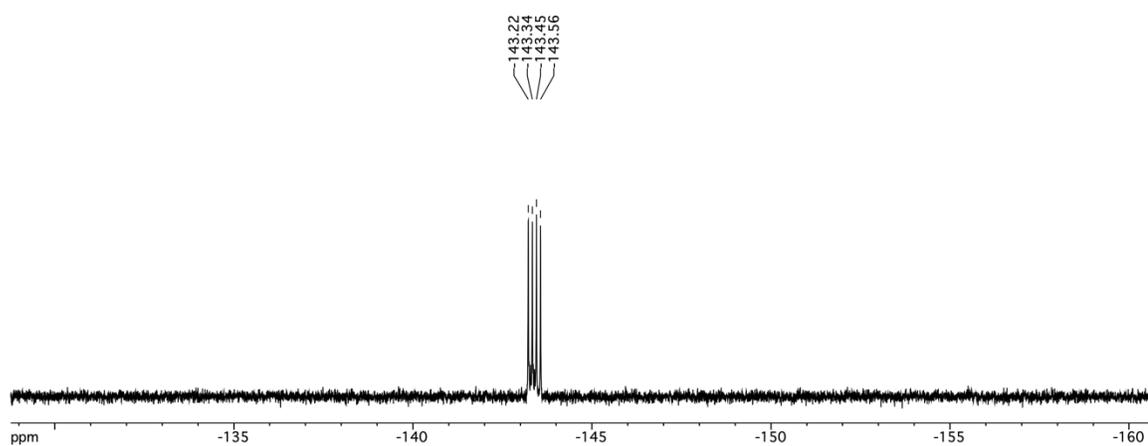
**$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )**



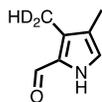
# $^{11}\text{B}$ NMR ( $\text{CDCl}_3$ )



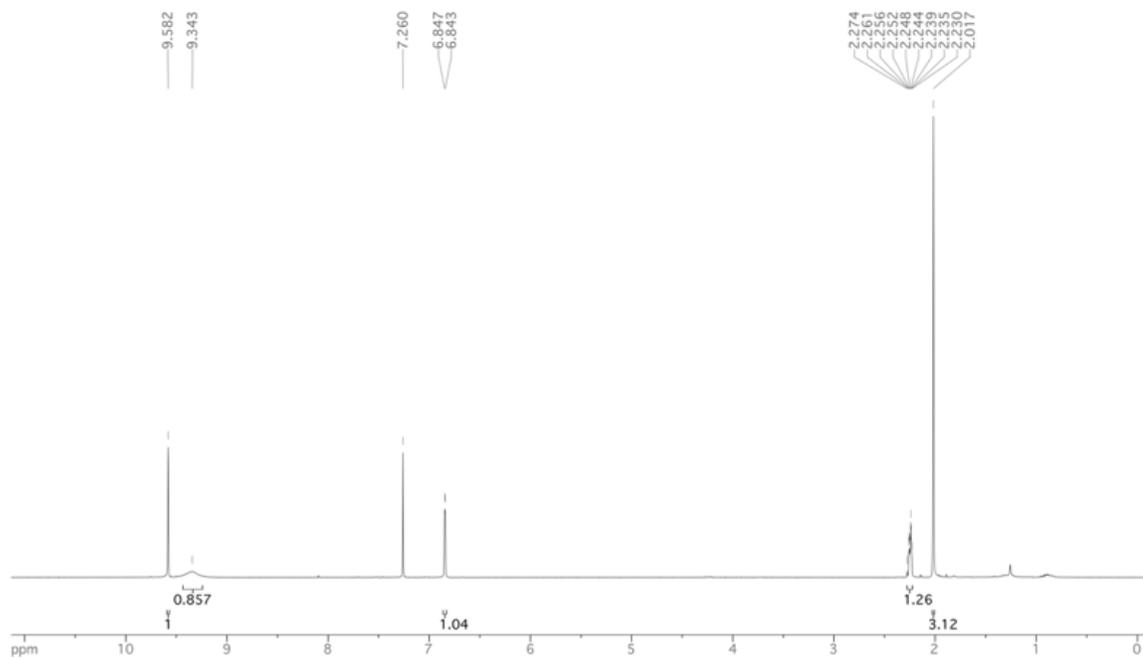
# $^{19}\text{F}$ NMR ( $\text{CDCl}_3$ )



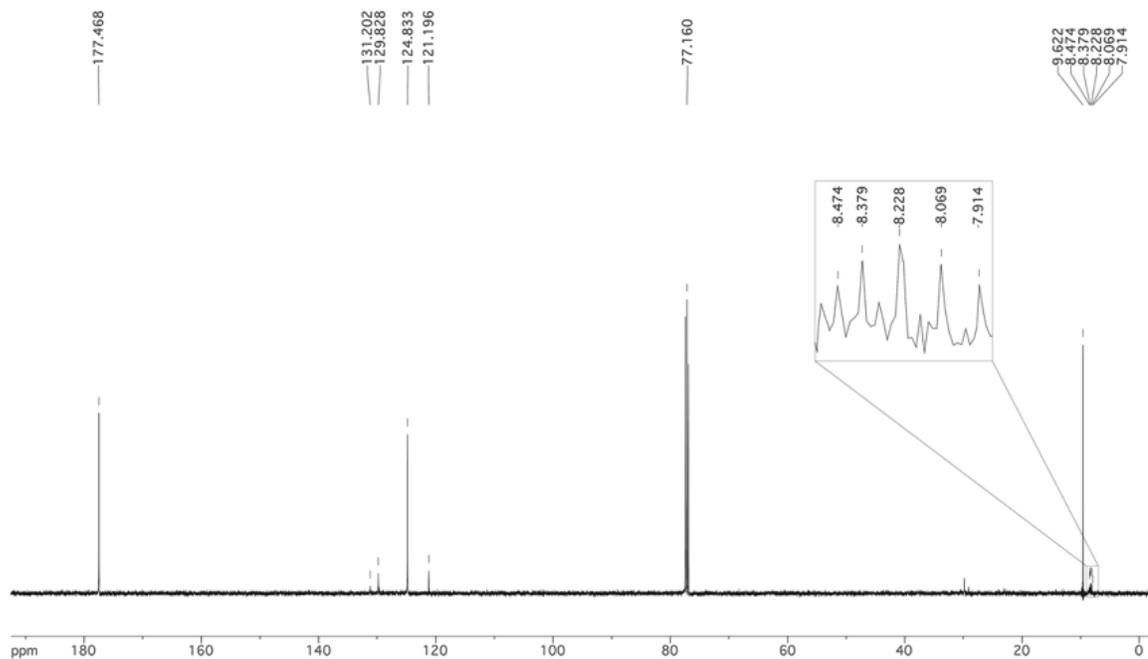
### 3-(Methyl-*d*<sub>2</sub>)-4-methyl-1*H*-pyrrole-2-carboxaldehyde (40\*)



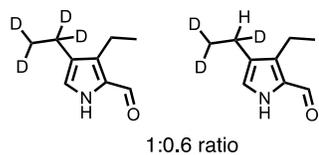
### <sup>1</sup>H NMR (CDCl<sub>3</sub>)



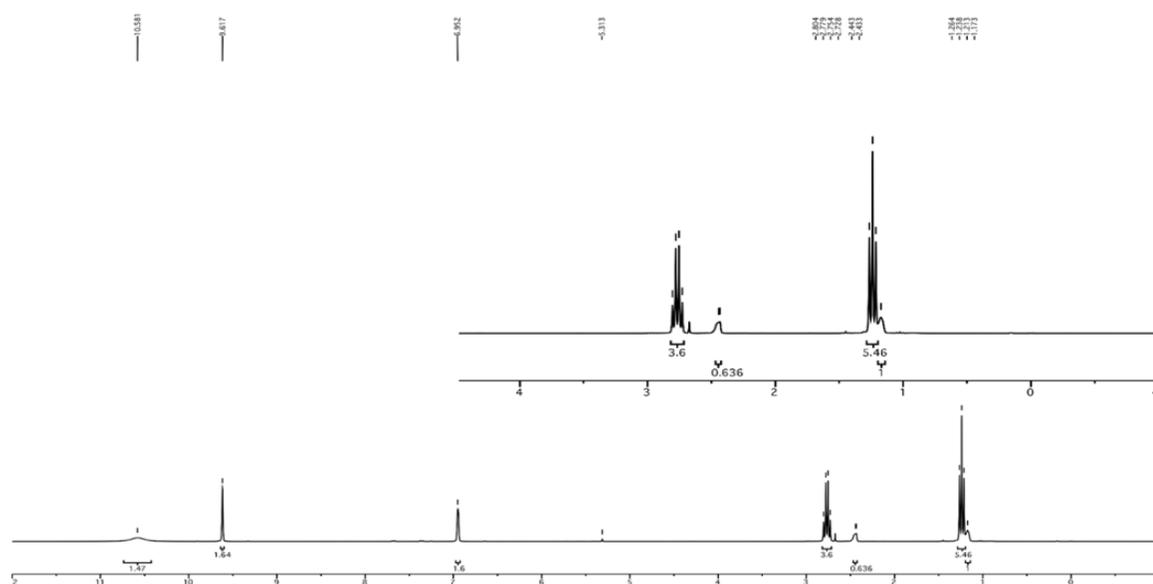
# <sup>13</sup>C NMR (CDCl<sub>3</sub>)



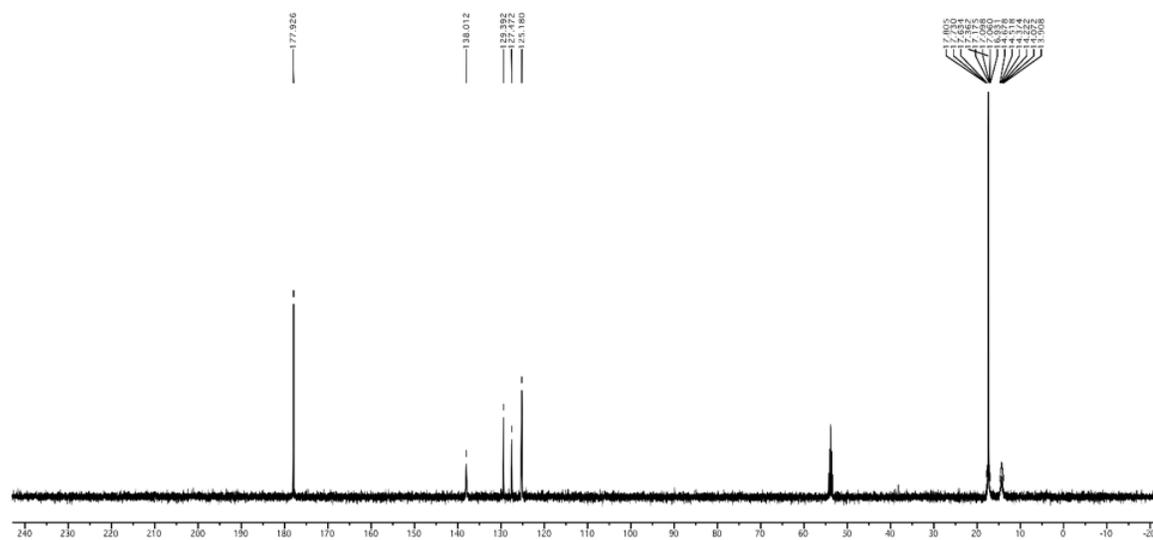
**4-(Ethyl-1,1,2,2-*d*<sub>4</sub>)-3-ethyl-1*H*-pyrrole-2-carboxaldehyde and 4-(Ethyl-1,2,2-*d*<sub>3</sub>)-3-ethyl-1*H*-pyrrole-2-carboxaldehyde (41\*(D<sub>4</sub>) and 41\*(D<sub>3</sub>))**



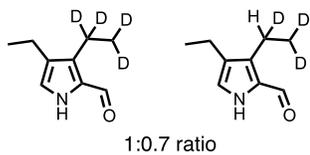
**<sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>)**



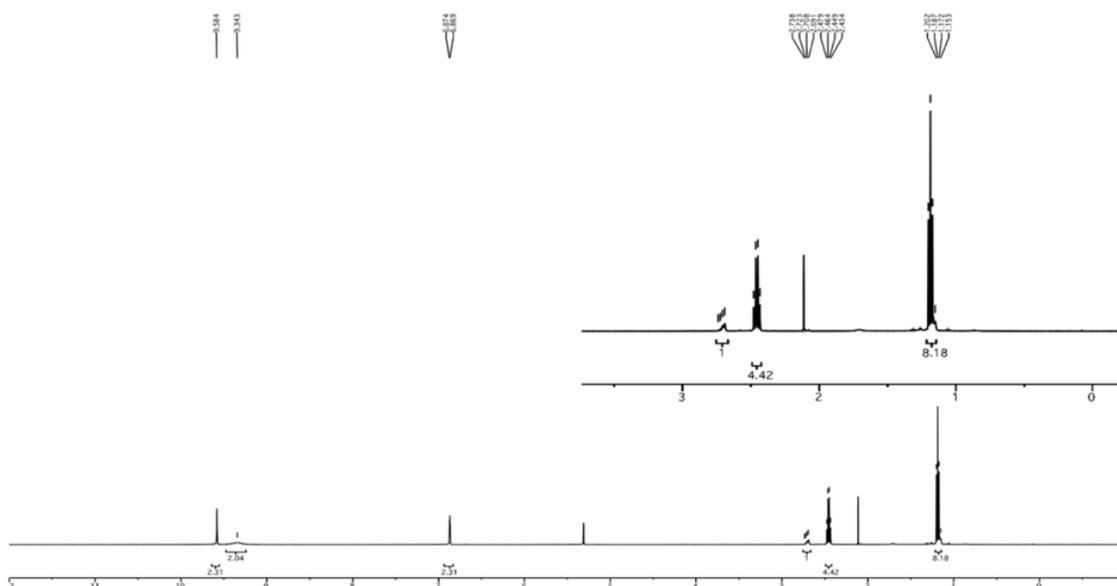
**<sup>13</sup>C NMR (CD<sub>2</sub>Cl<sub>2</sub>)**



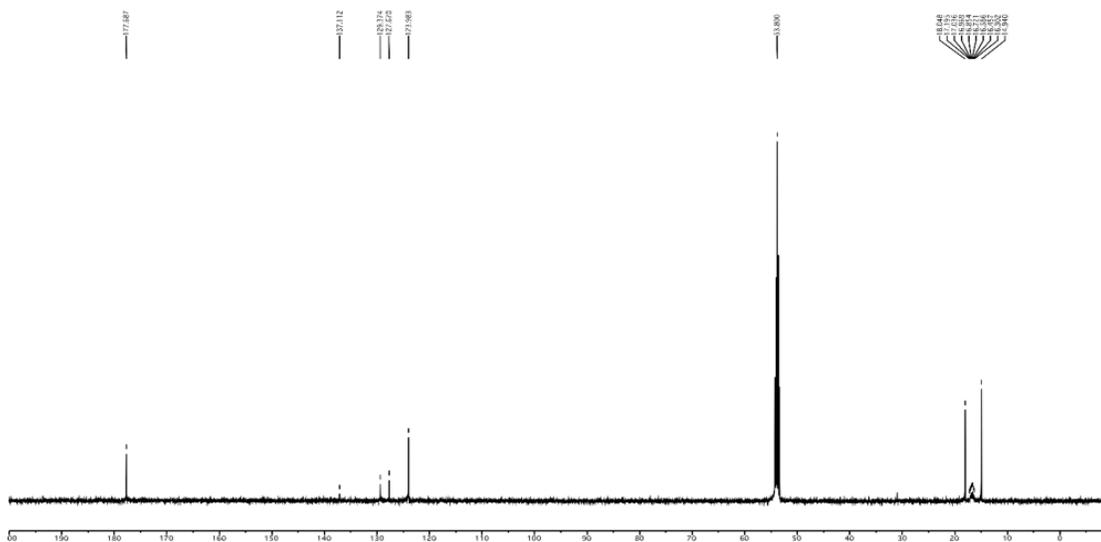
**3-(Ethyl-1,1,2,2-*d*<sub>4</sub>)-4-ethyl-1*H*-pyrrole-2-carboxaldehyde and 3-(Ethyl-1,2,2-*d*<sub>3</sub>)-4-ethyl-1*H*-pyrrole-2-carboxaldehyde (41\*'(D<sub>4</sub>) and 41\*'(D<sub>3</sub>))**



**<sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>)**

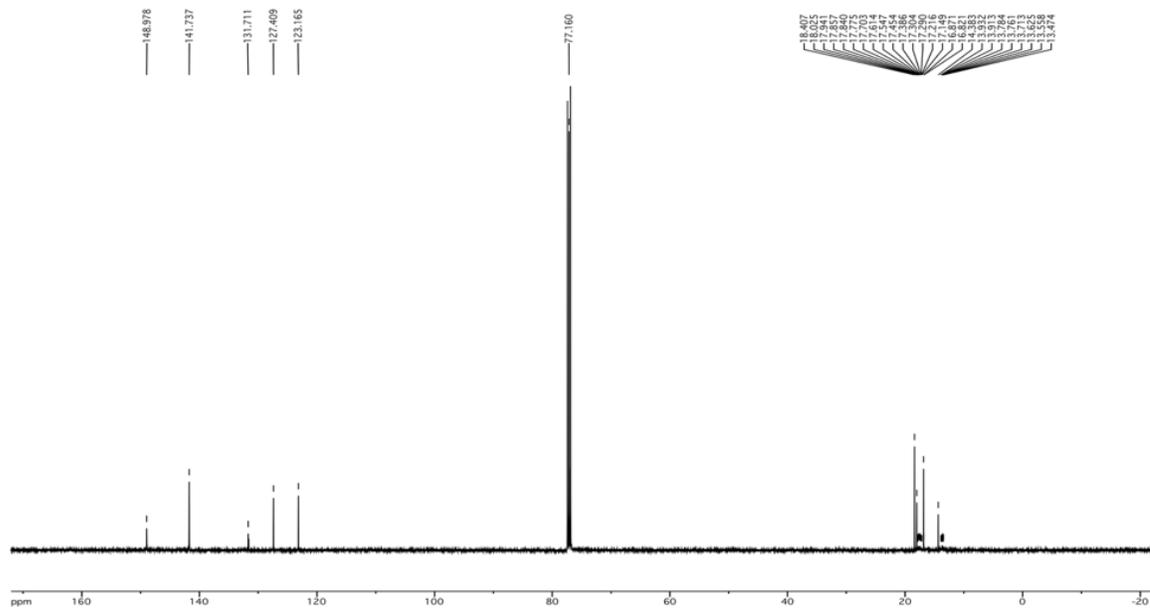


**<sup>13</sup>C NMR (CD<sub>2</sub>Cl<sub>2</sub>)**

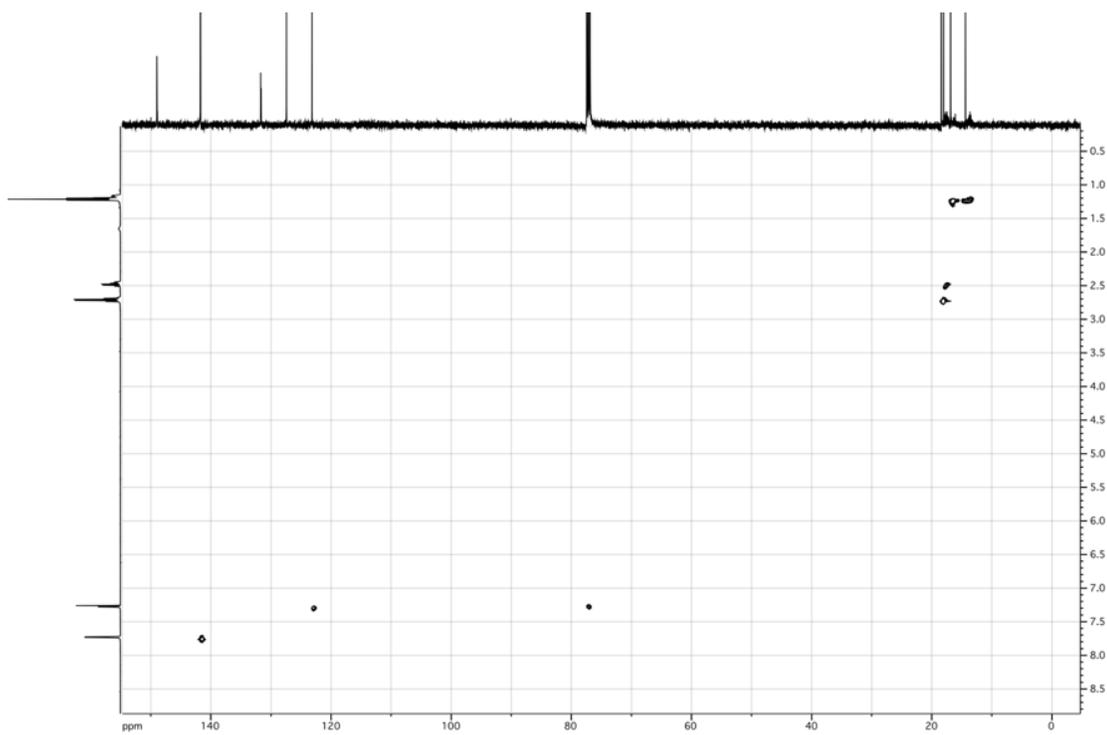




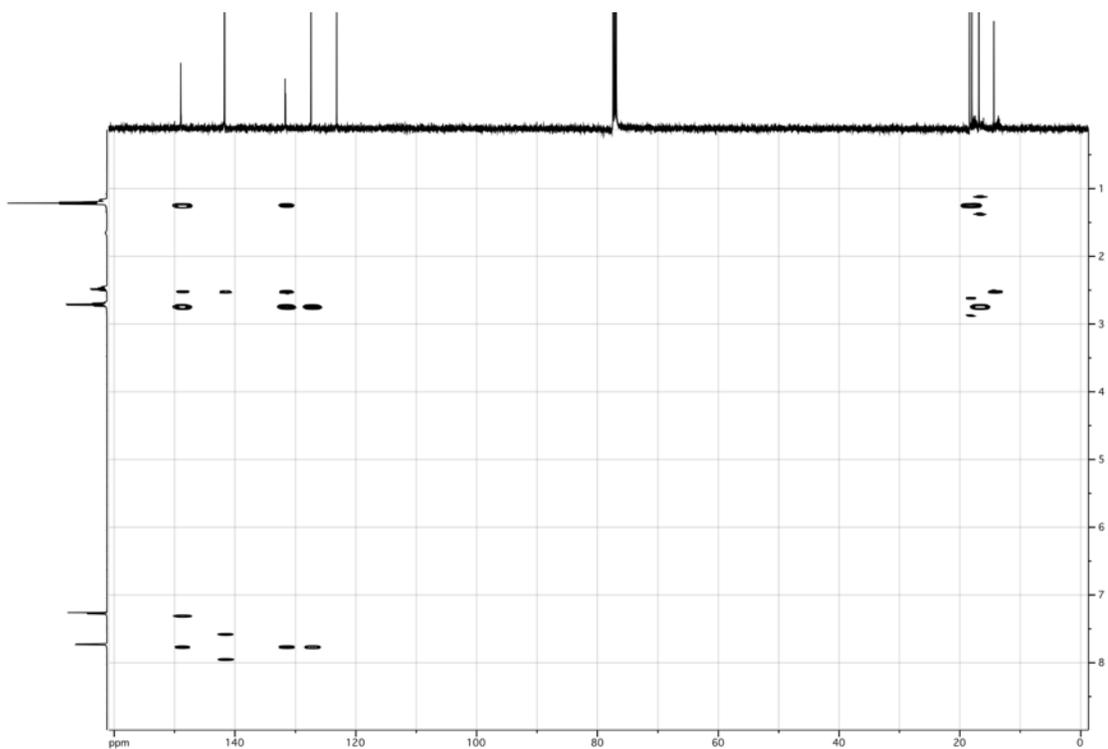
# $^{13}\text{C}$ NMR ( $\text{CDCl}_3$ )



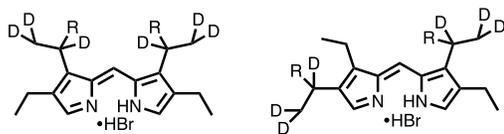
### HSQC NMR (CDCl<sub>3</sub>)



### HMBC NMR (CDCl<sub>3</sub>)

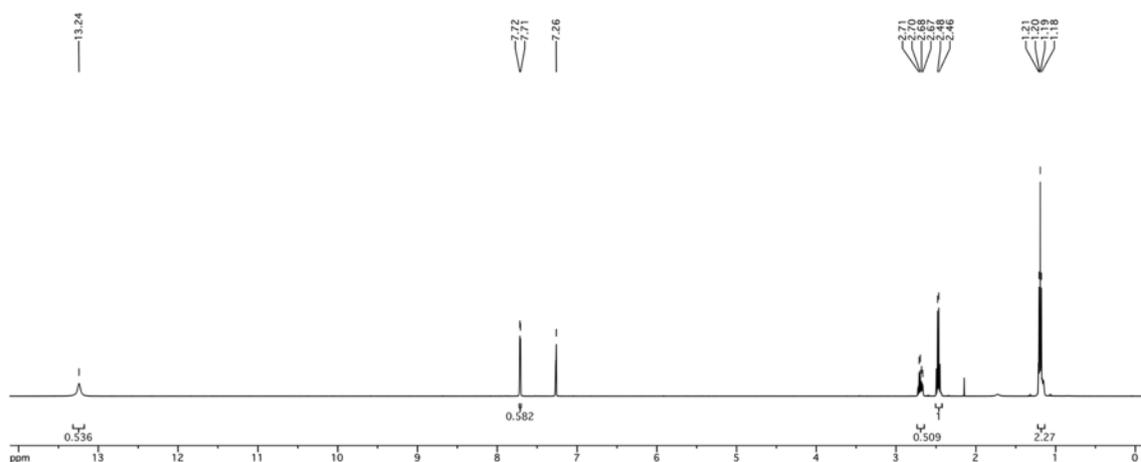


**3-(Ethyl-1,1,2,2-*d*<sub>4</sub>)-4-ethyl-2-[(3-(ethyl-1,1,2,2-*d*<sub>4</sub>)-4-ethyl-2*H*-pyrrol-2-ylidene)methyl]-1*H*-pyrrole Monohydrobromide and 3-(Ethyl-1,1,2,2-*d*<sub>4</sub>)-4-ethyl-2-[(4-(ethyl-1,1,2,2-*d*<sub>4</sub>)-3-ethyl-2*H*-pyrrol-2-ylidene)methyl]-1*H*-pyrrole Monohydrobromide (sym-45\*' and asym-45\*)**

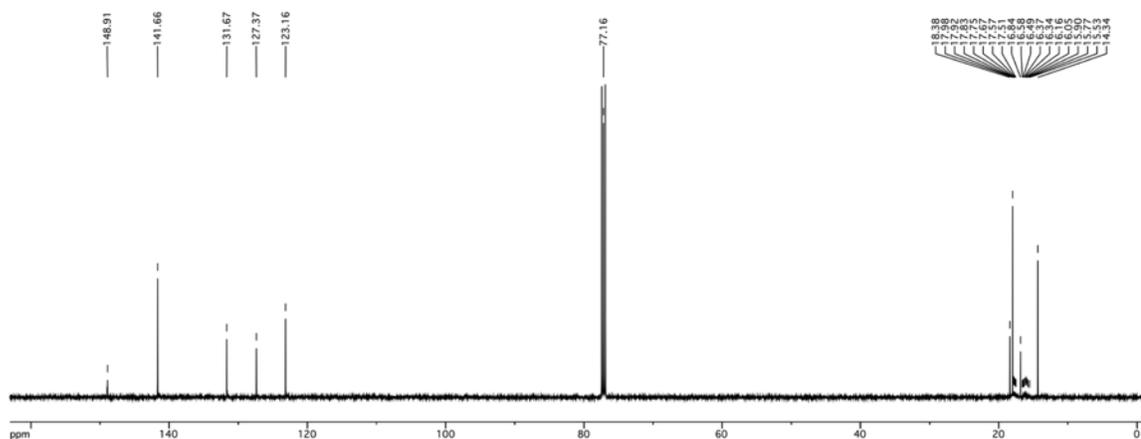


R = D from (**D**<sub>4</sub>)  
H from (**D**<sub>3</sub>)

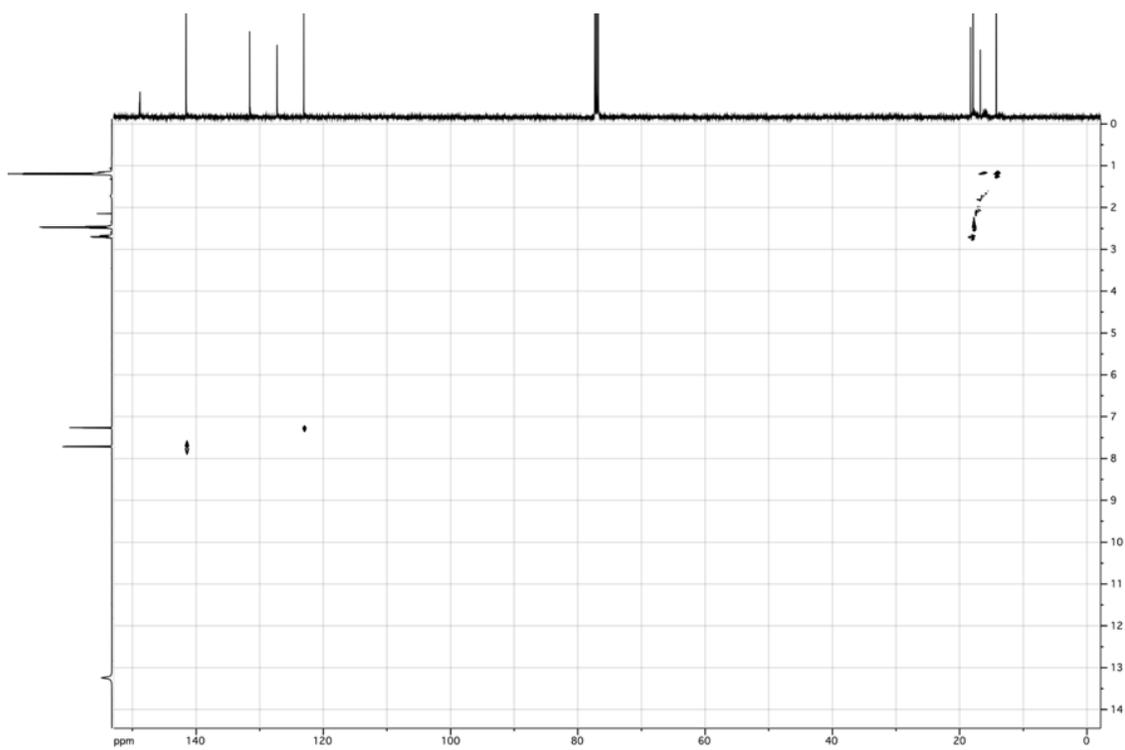
**<sup>1</sup>H NMR (CDCl<sub>3</sub>)**



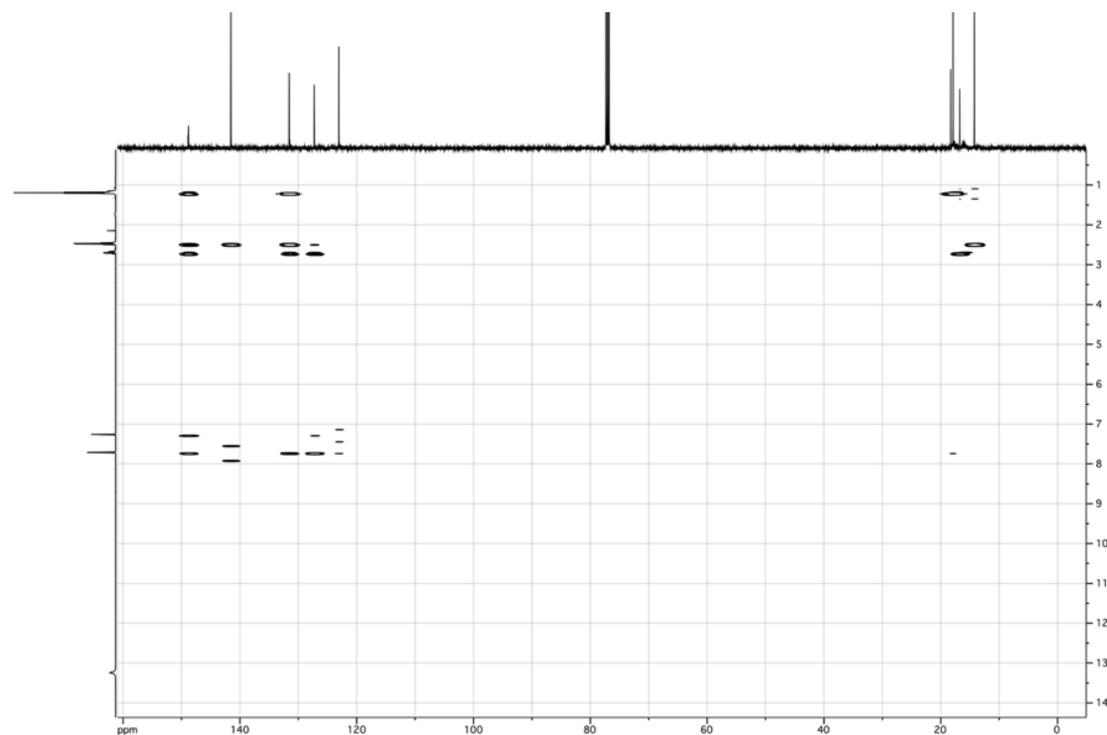
**<sup>13</sup>C NMR (CDCl<sub>3</sub>)**



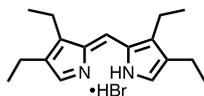
### HSQC NMR (CDCl<sub>3</sub>)



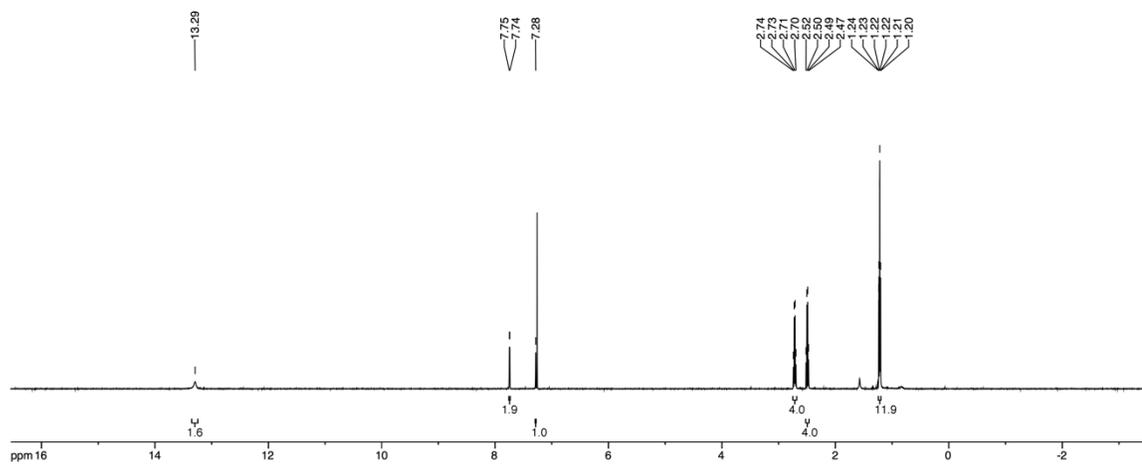
### HMBC NMR (CDCl<sub>3</sub>)



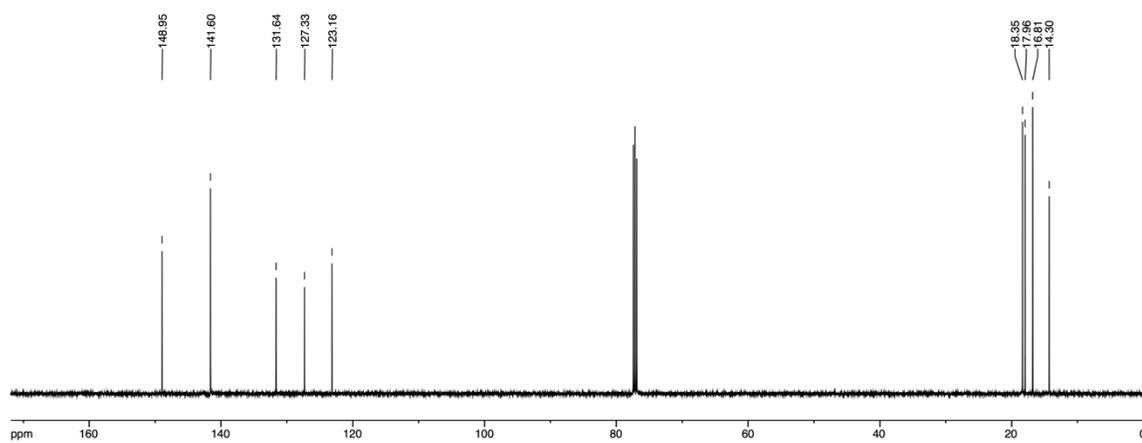
## 2-[(3,4-Diethyl-2*H*-pyrrol-2-ylidene)methyl]-3,4-diethyl-1*H*-pyrrole Monohydrobromide (45)



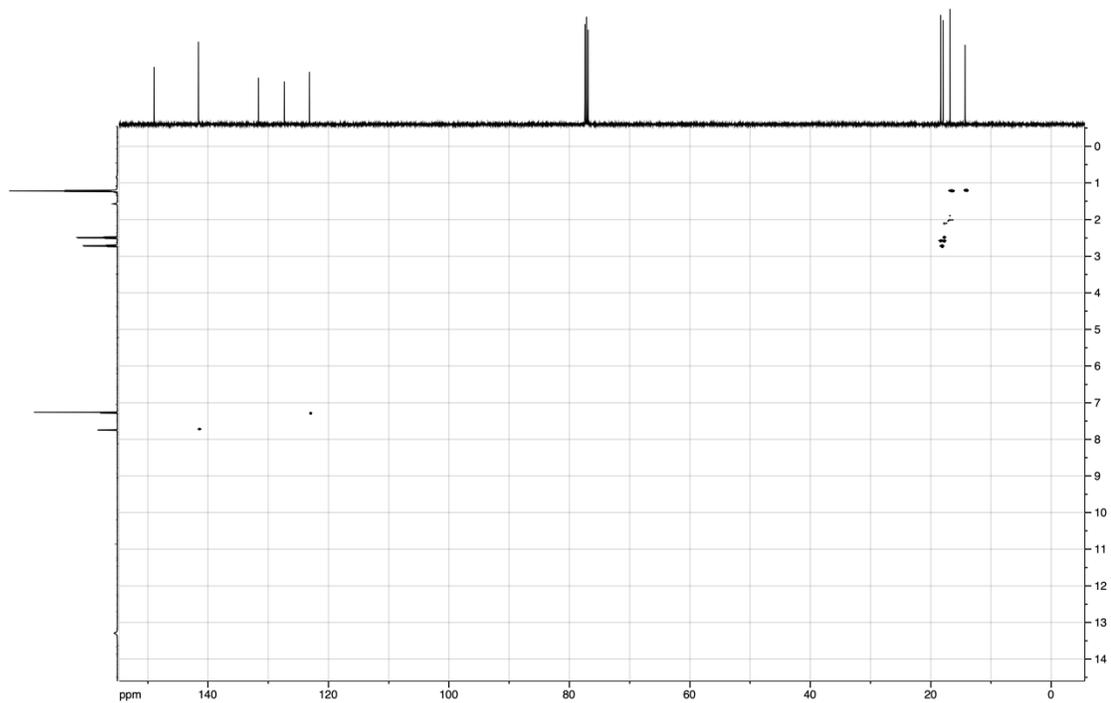
### <sup>1</sup>H NMR (CDCl<sub>3</sub>)



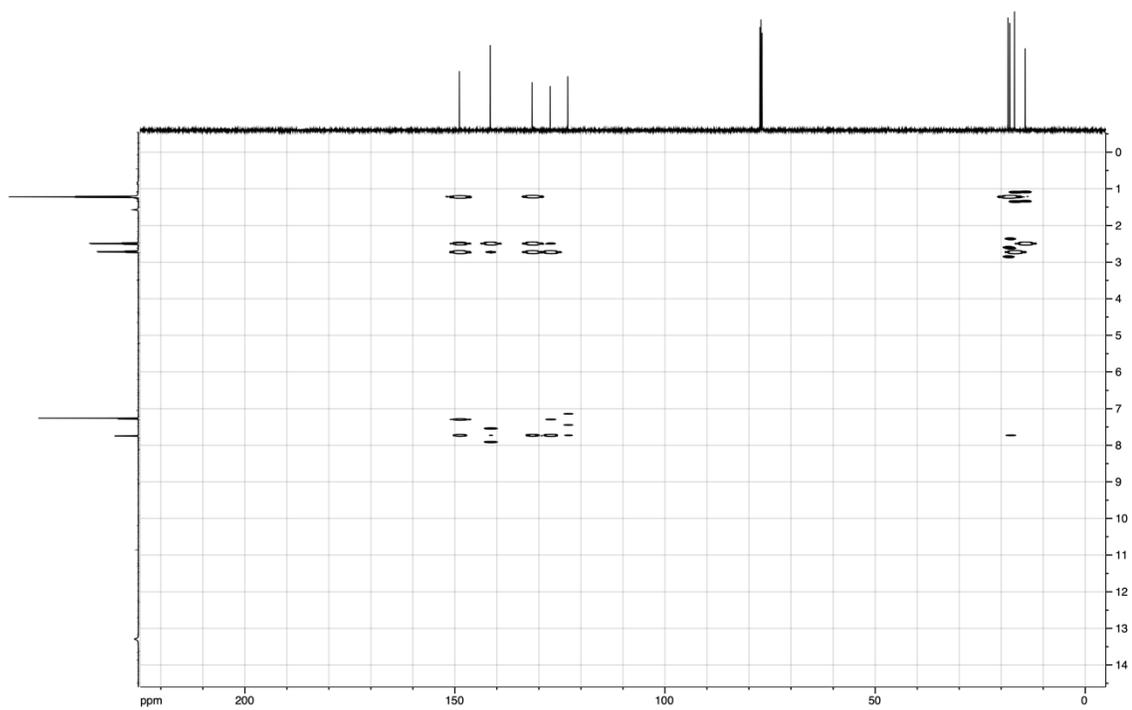
### <sup>13</sup>C NMR (CDCl<sub>3</sub>)



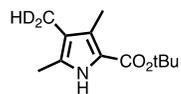
### HSQC NMR (CDCl<sub>3</sub>)



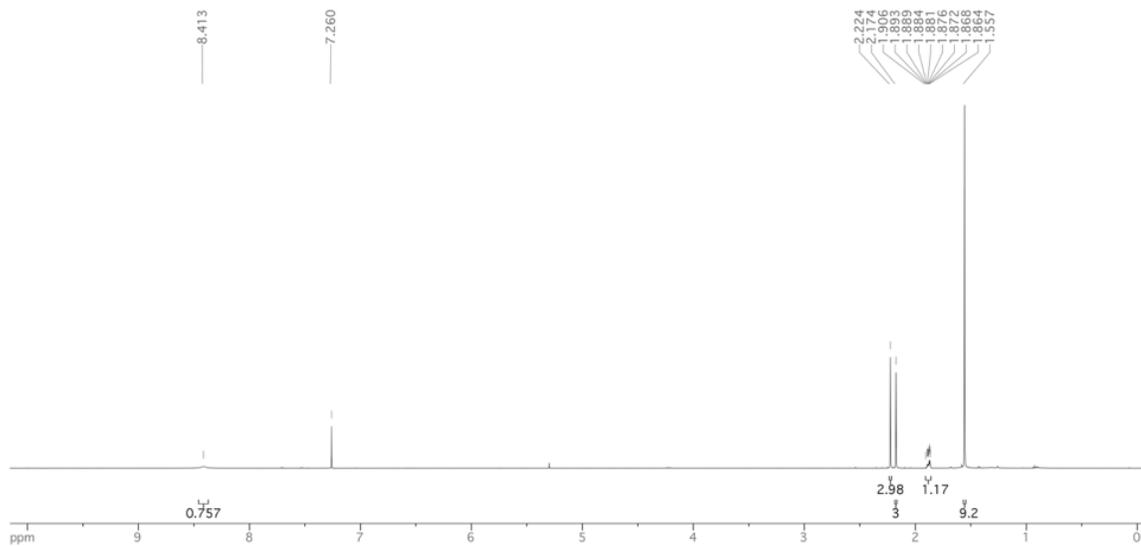
### HMBC NMR (CDCl<sub>3</sub>)



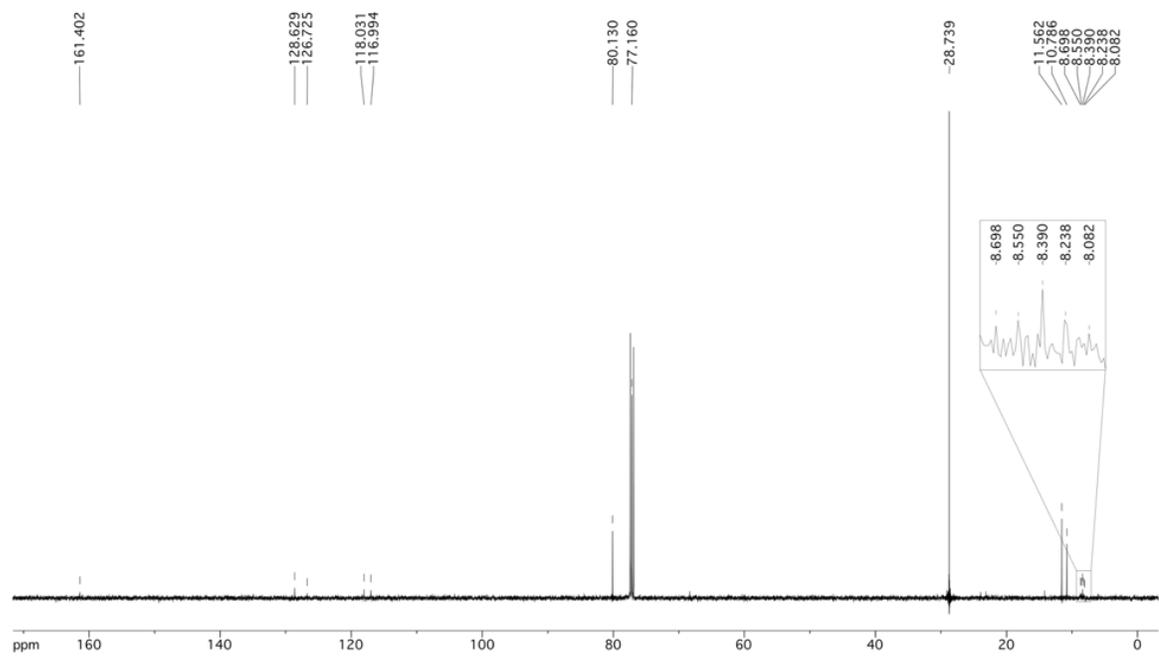
***tert*-Butyl Ester 4-(Methyl-*d*<sub>2</sub>)-3,5-dimethyl-1*H*-pyrrole-2-carboxylic Acid (46\*)**



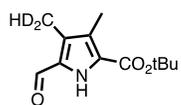
**<sup>1</sup>H NMR (CDCl<sub>3</sub>)**



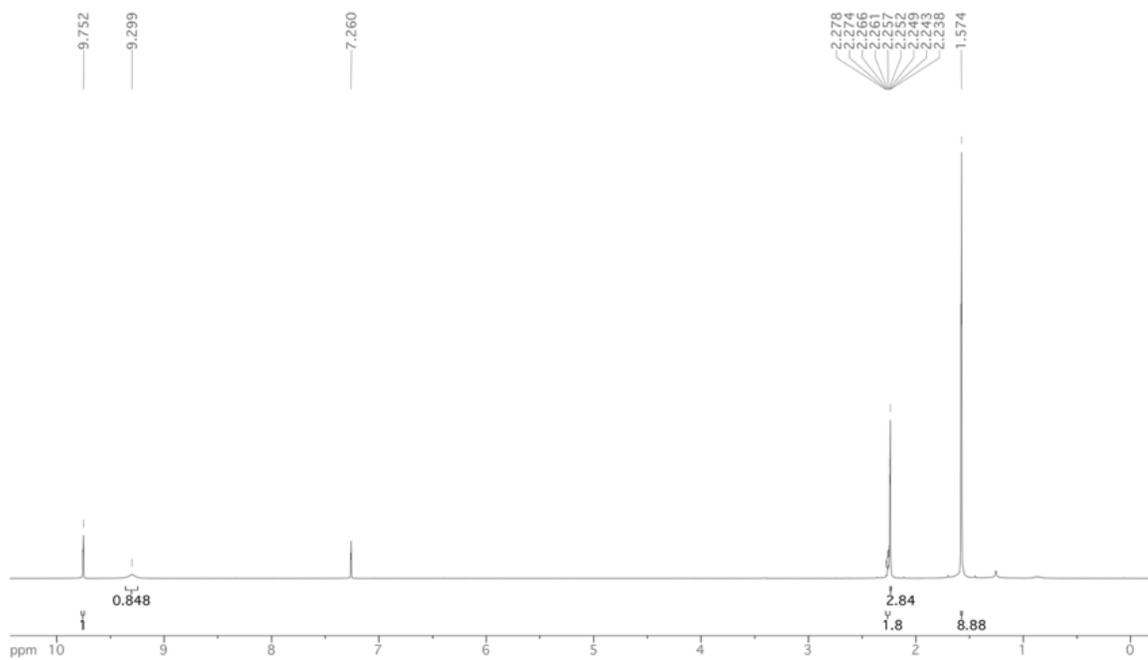
# $^{13}\text{C}$ NMR ( $\text{CDCl}_3$ )



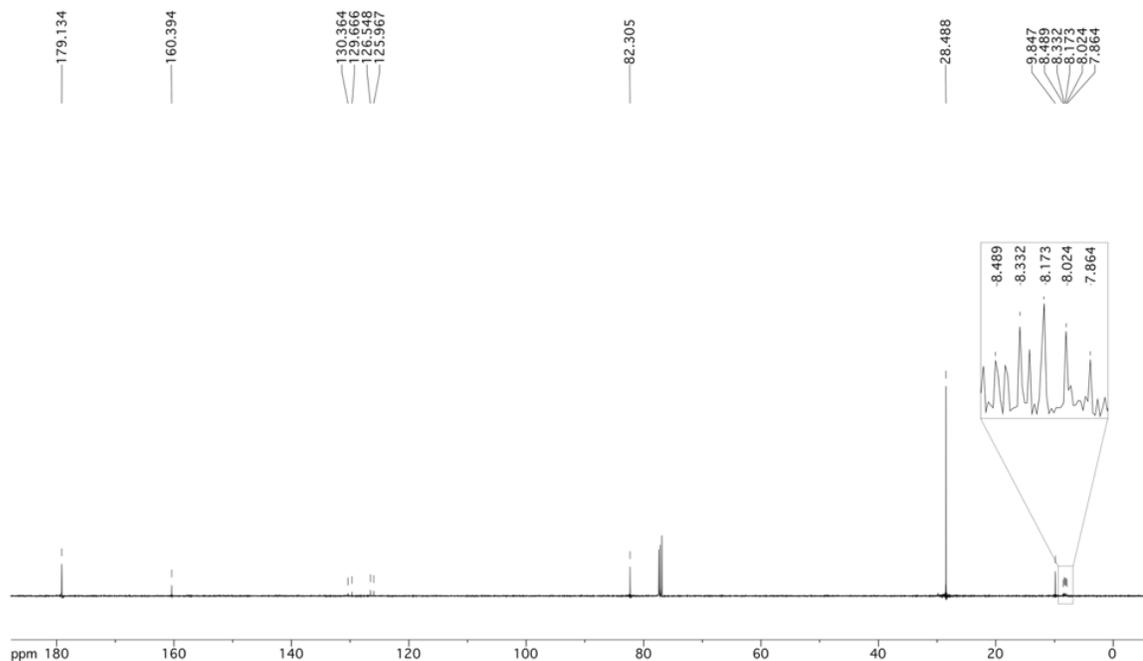
***tert*-Butyl Ester 5-formyl-4-(methyl-*d*<sub>2</sub>)-3-methyl-1*H*-pyrrole-2-Carboxylic Acid (47\*)**



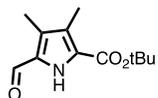
**<sup>1</sup>H NMR (CDCl<sub>3</sub>)**



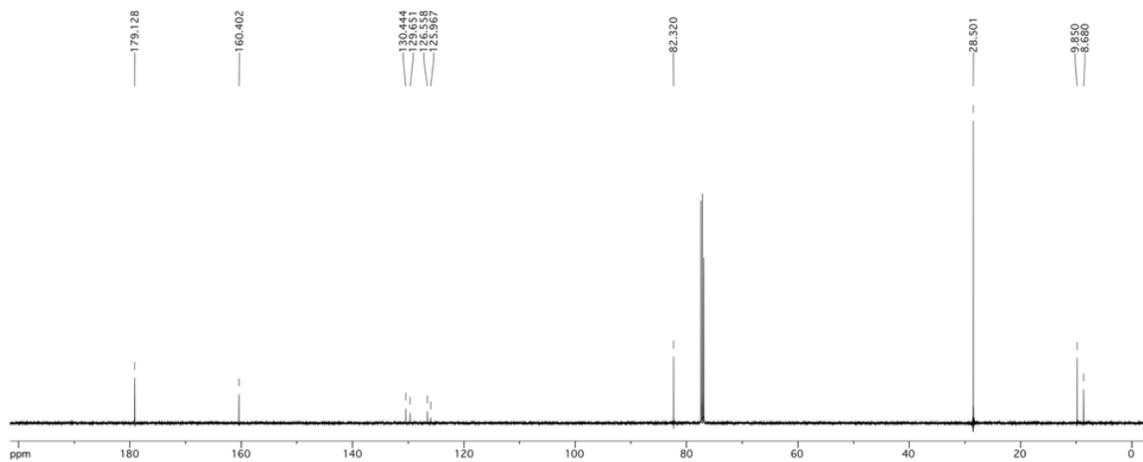
### $^{13}\text{C}$ NMR ( $\text{CDCl}_3$ )



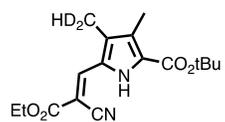
### *tert*-Butyl Ester 5-Formyl-3,4-dimethyl-1*H*-pyrrole-2-carboxylic Acid (47)



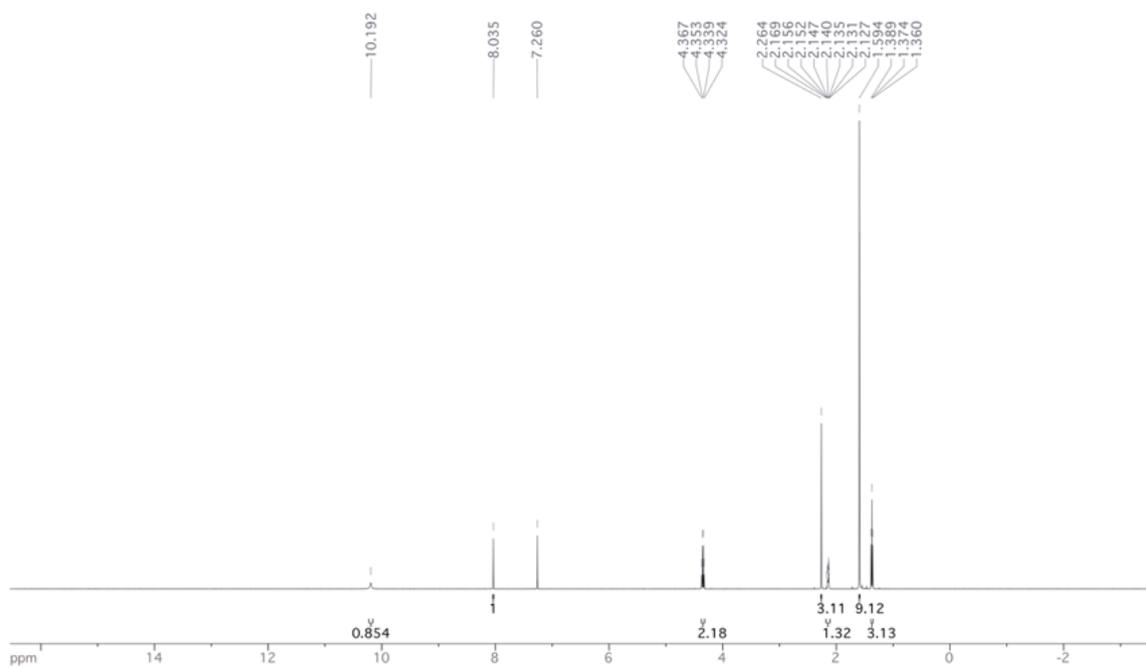
### $^{13}\text{C}$ NMR ( $\text{CDCl}_3$ )



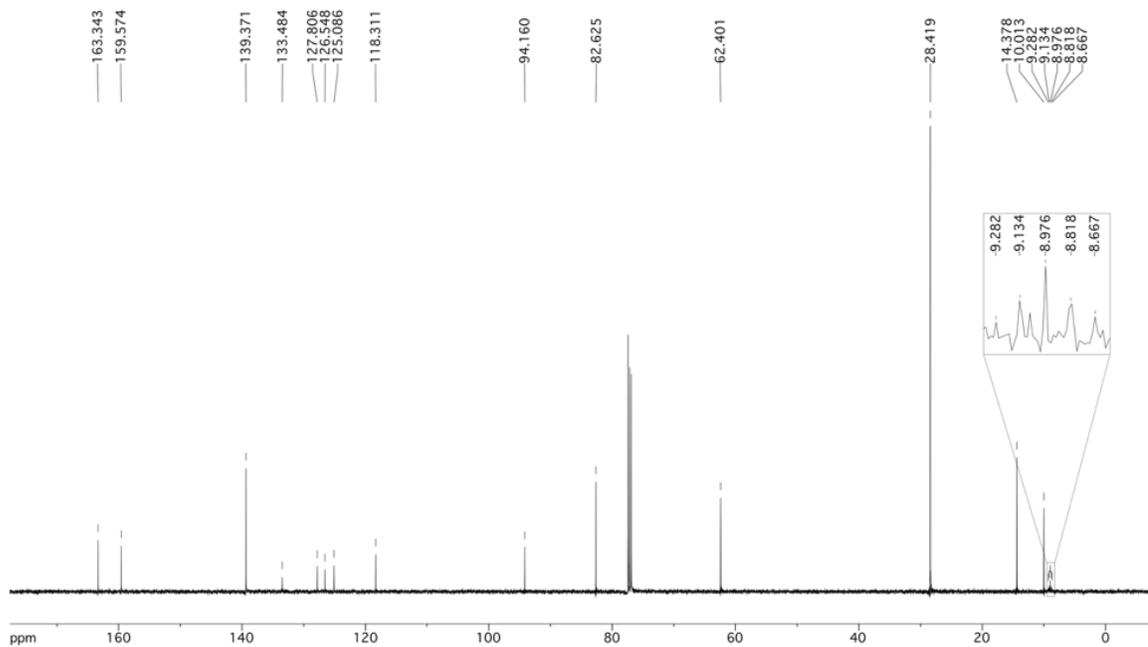
***tert*-Butyl Ester 5-(2-cyano-3-ethoxy-3-oxo-1-propen-1-yl)-4-(methyl-*d*<sub>2</sub>)-3-methyl-1*H*-pyrrole-2-carboxylic Acid (48\*)**



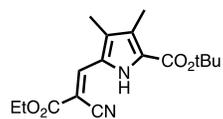
**<sup>1</sup>H NMR (CDCl<sub>3</sub>)**



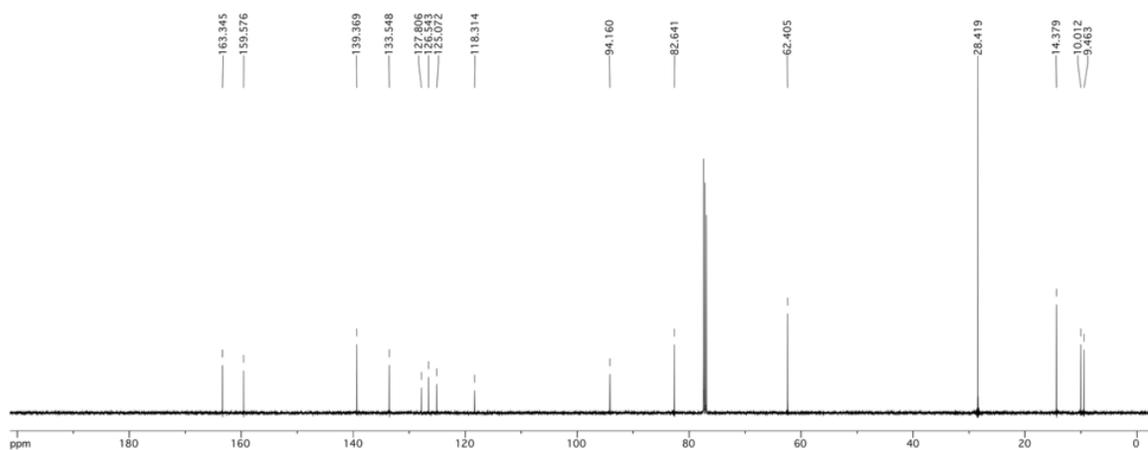
# $^{13}\text{C}$ NMR ( $\text{CDCl}_3$ )



***tert*-Butyl Ester 5-(2-Cyano-3-ethoxy-3-oxo-1-propen-1-yl)-3,4-dimethyl-1*H*-pyrrole-2-carboxylic Acid (48)**

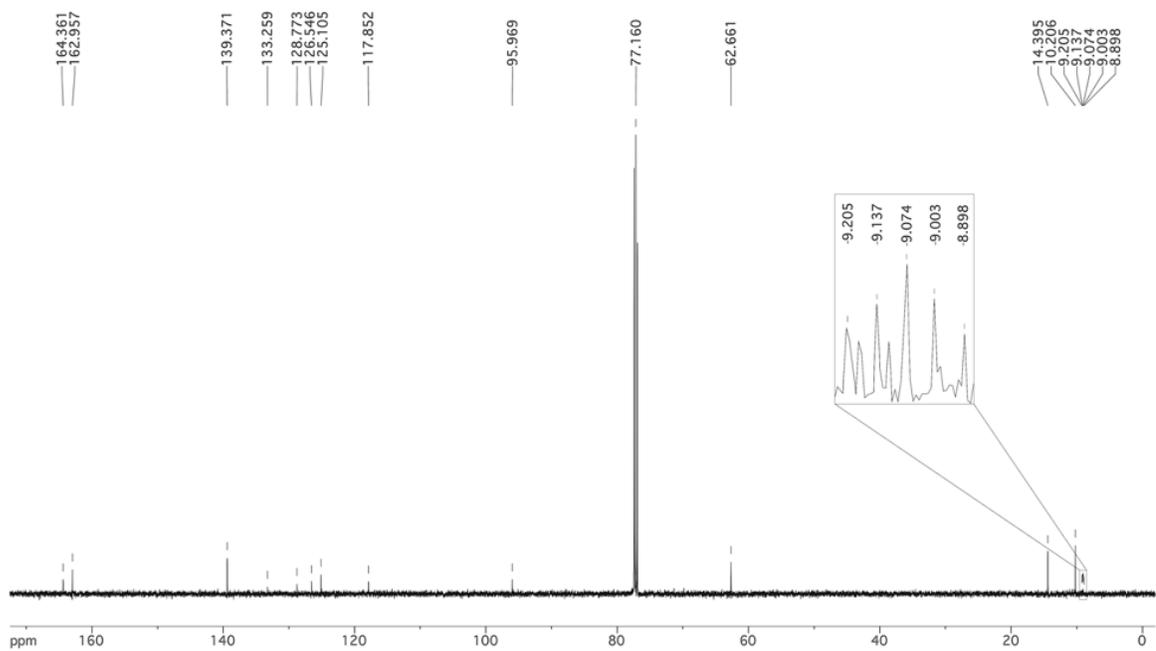


**<sup>13</sup>C NMR (CDCl<sub>3</sub>)**

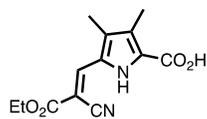




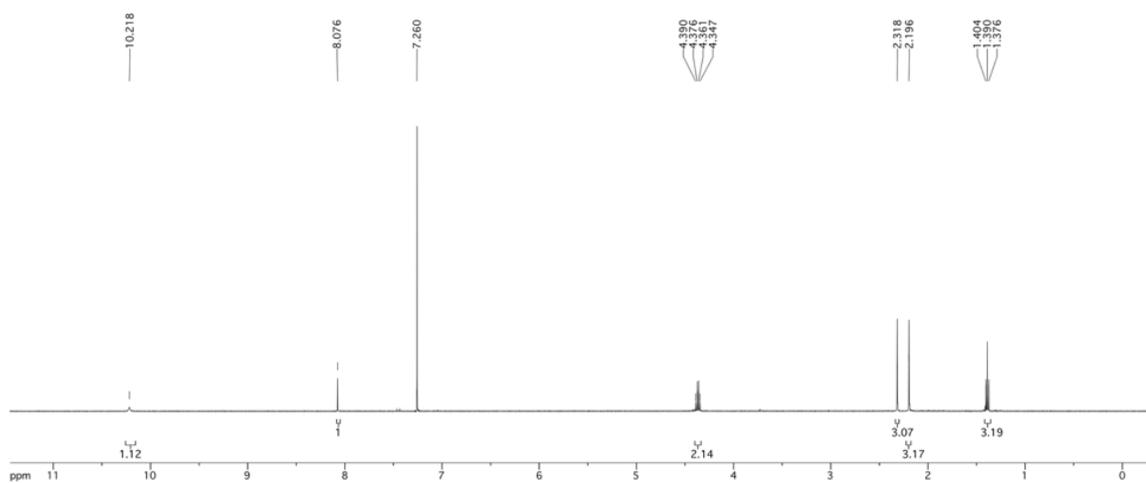
# $^{13}\text{C}$ NMR ( $\text{CDCl}_3$ )



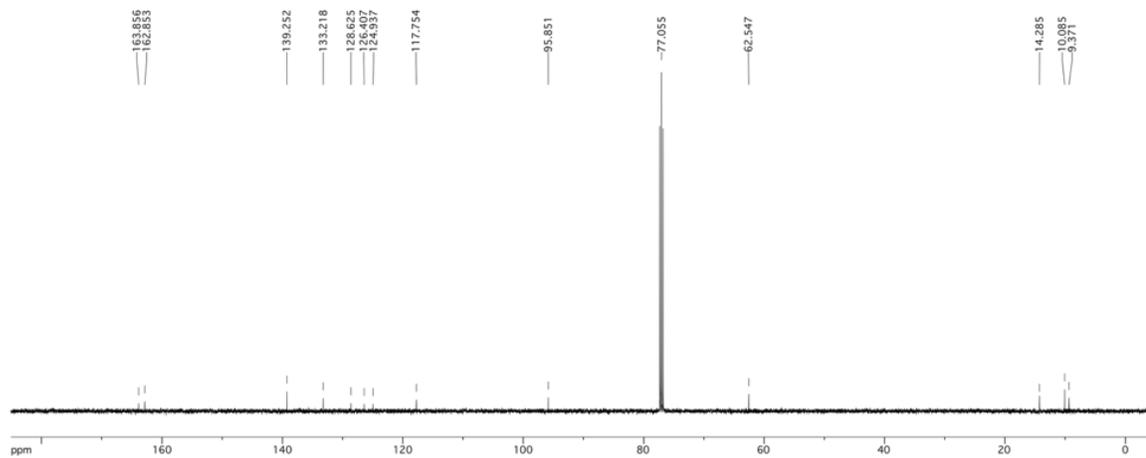
# 5-(2-Cyano-3-ethoxy-3-oxo-1-propen-1-yl)-3,4-dimethyl-1H-pyrrole-2-carboxylic Acid (49)



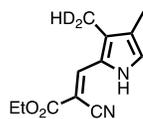
## <sup>1</sup>H NMR (CDCl<sub>3</sub>)



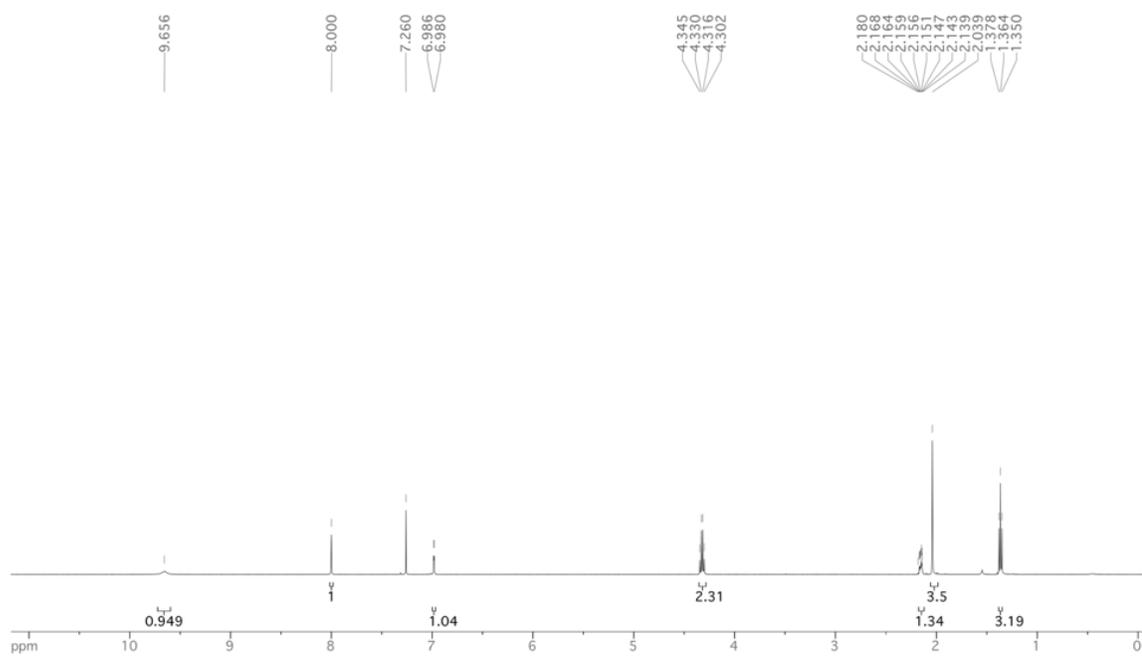
## <sup>13</sup>C NMR (CDCl<sub>3</sub>)



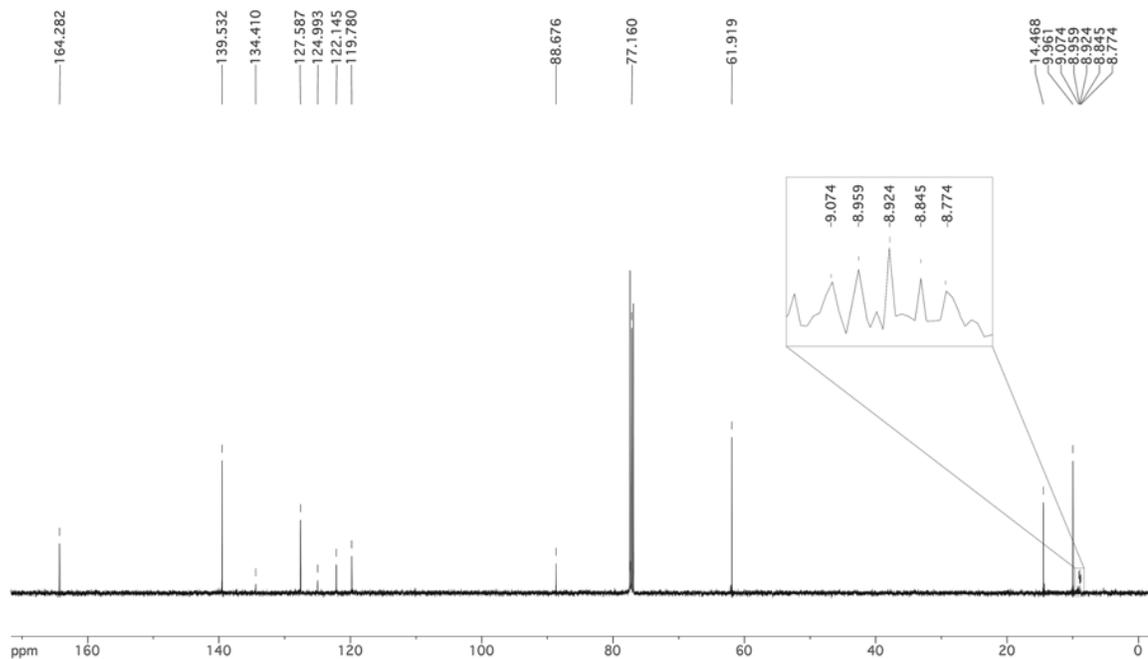
# Ethyl Ester 2-Cyano-3-(3-(methyl- $d_2$ )-4-methyl-1H-pyrrol-2-yl)-2-propenoic Acid (51\*)



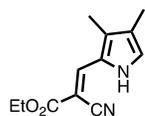
## $^1\text{H}$ NMR ( $\text{CDCl}_3$ )



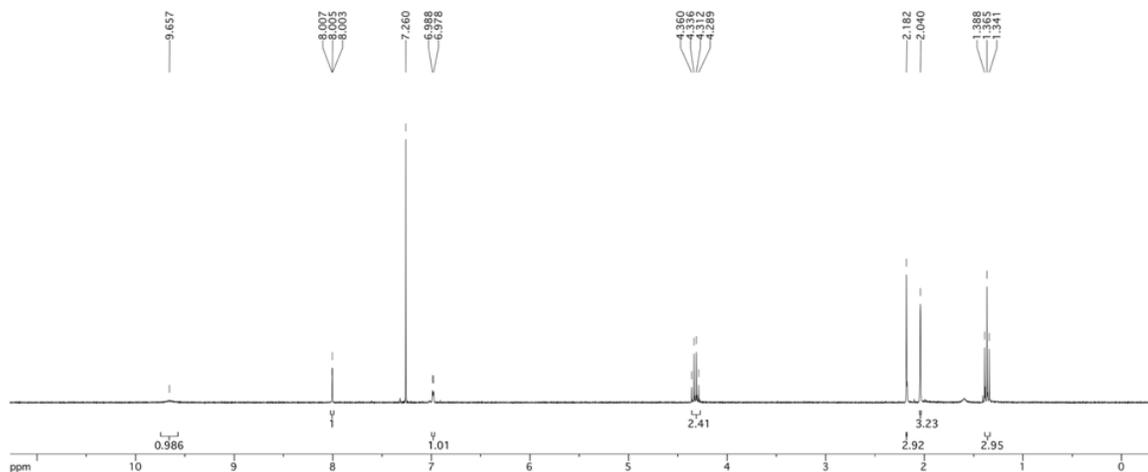
### $^{13}\text{C}$ NMR ( $\text{CDCl}_3$ )



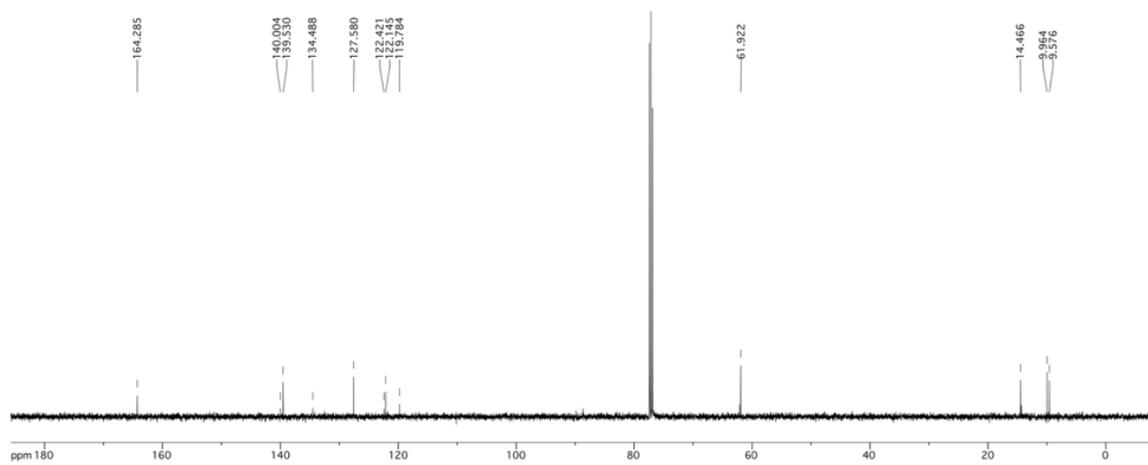
### Ethyl Ester 2-Cyano-3-(3,4-dimethyl-1H-pyrrol-2-yl)-2-propenoic Acid (51)



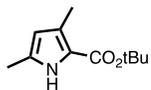
### $^1\text{H}$ NMR ( $\text{CDCl}_3$ )



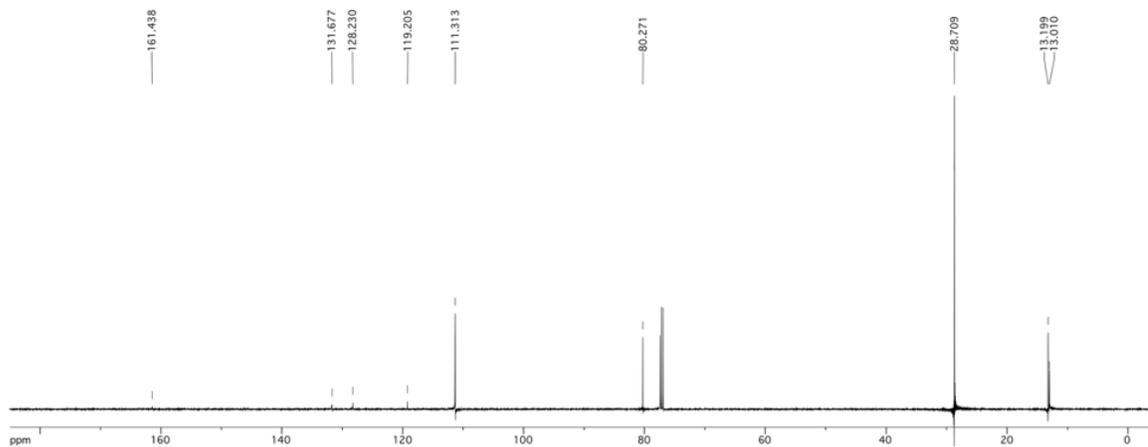
# $^{13}\text{C}$ NMR ( $\text{CDCl}_3$ )



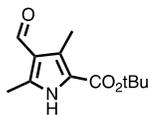
***tert*-Butyl Ester 3,5-Dimethyl-1*H*-pyrrole-2-carboxylic Acid (53)**



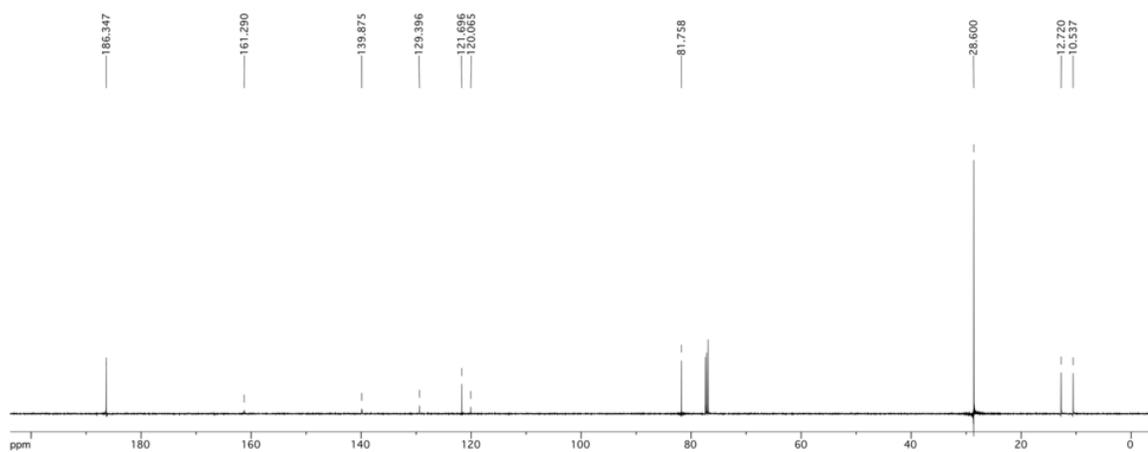
**$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )**



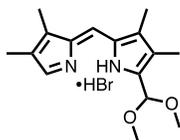
***tert*-Butyl Ester 4-Formyl-3,5-dimethyl-1*H*-pyrrole-2-carboxylic Acid  
(54)**



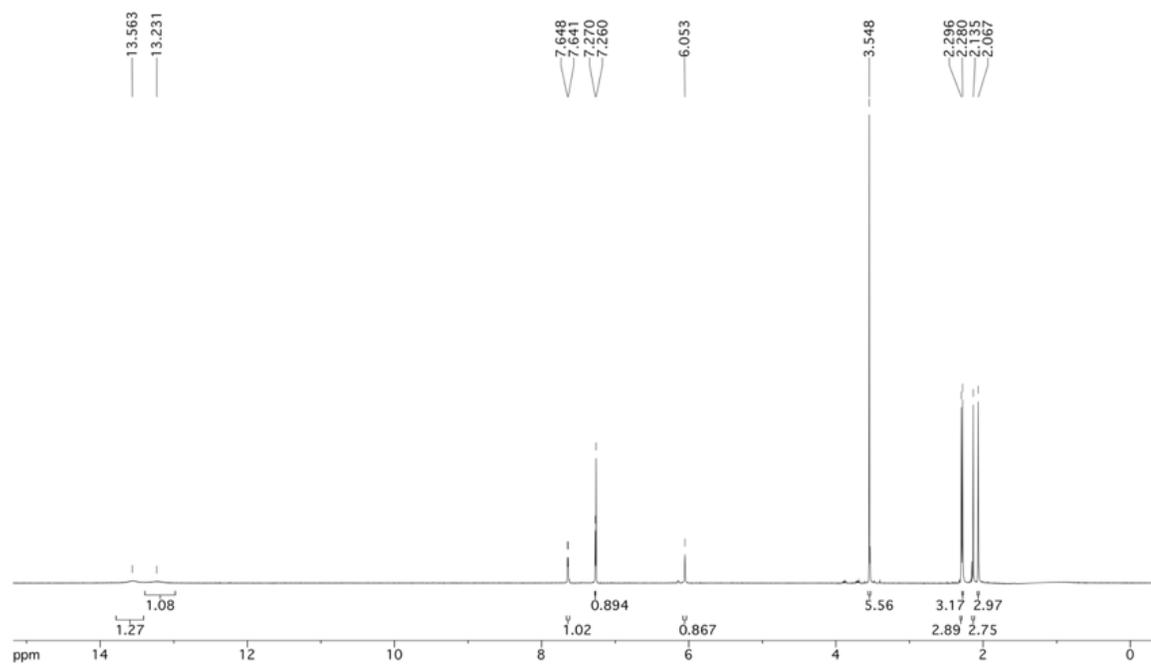
**<sup>13</sup>C NMR (CDCl<sub>3</sub>)**



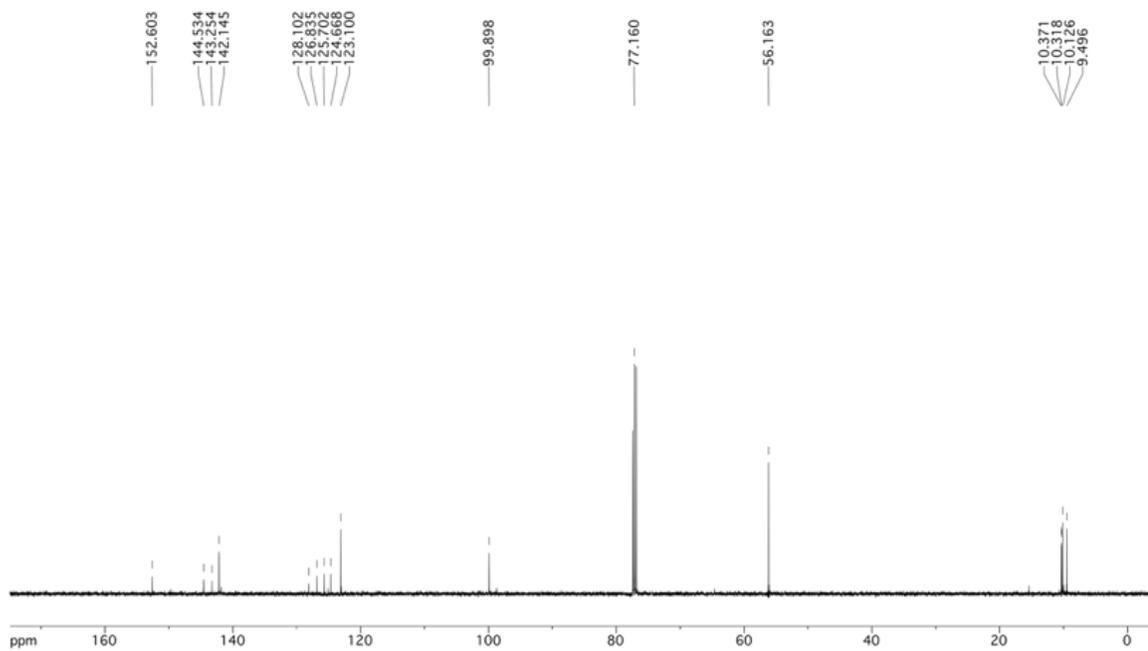
## 2-(Dimethoxymethyl)-5-[(3,4-dimethyl-2*H*-pyrrol-2-ylidene)methyl]-3,4-dimethyl-1*H*-pyrrole Monohydrobromide (55)



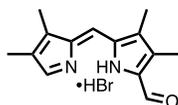
### <sup>1</sup>H NMR (CDCl<sub>3</sub>)



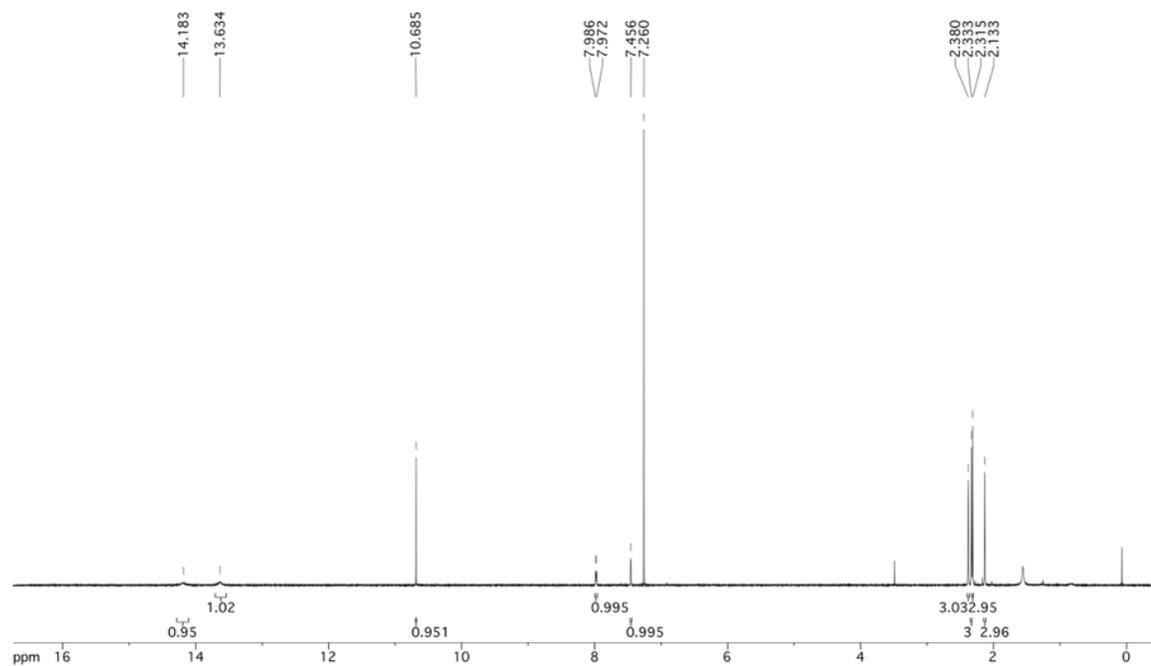
# $^{13}\text{C}$ NMR ( $\text{CDCl}_3$ )



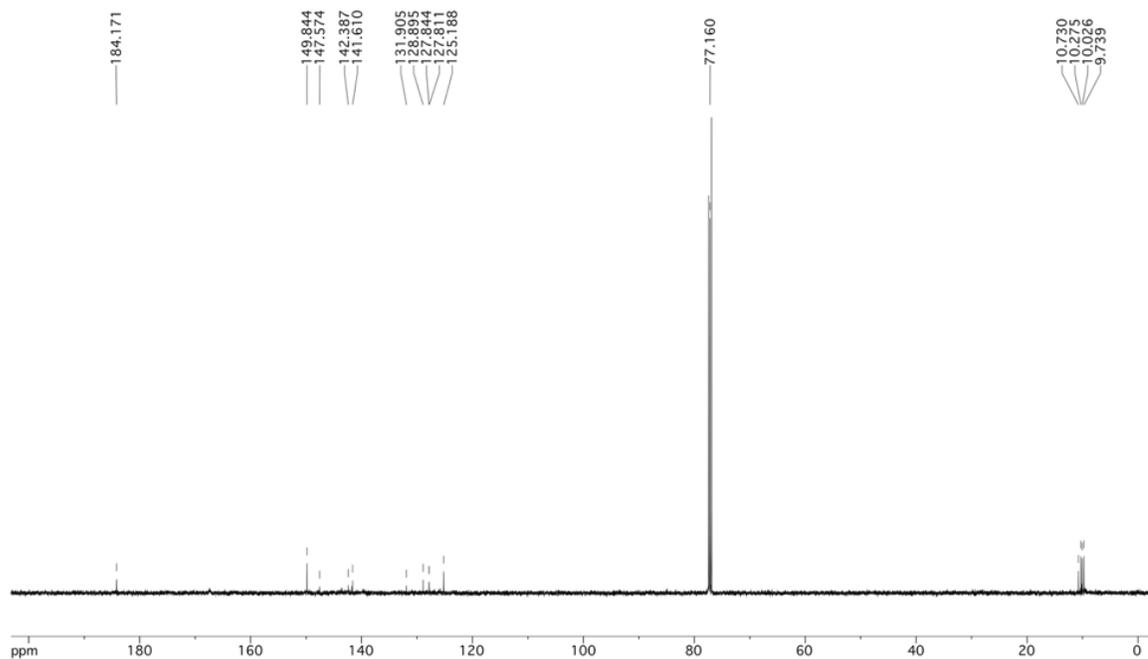
### 3,4-Dimethyl-5-[(3,4-dimethyl-2*H*-pyrrol-2-ylidene)methyl]-1*H*-pyrrole-2-carboxaldehyde Monohydrobromide (56)



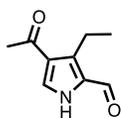
### <sup>1</sup>H NMR (CDCl<sub>3</sub>)



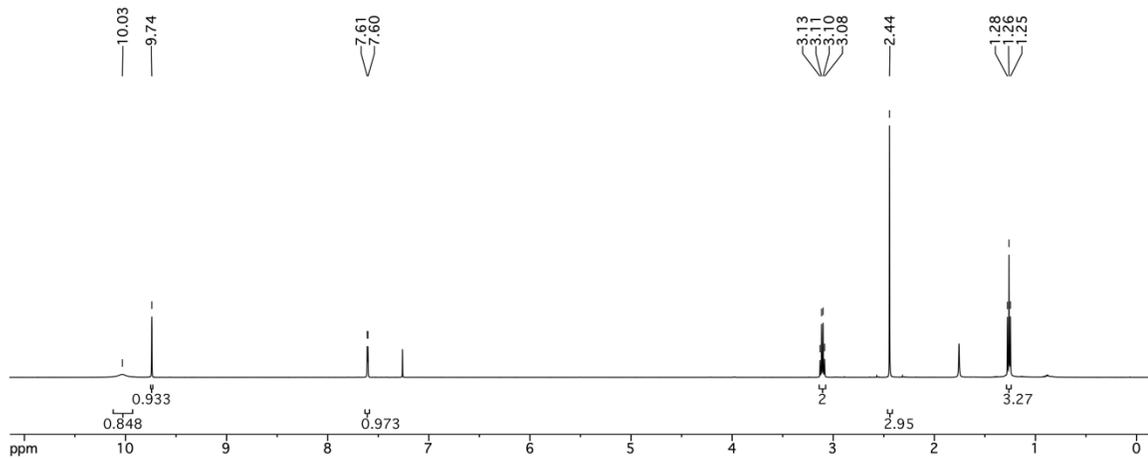
### $^{13}\text{C}$ NMR ( $\text{CDCl}_3$ )



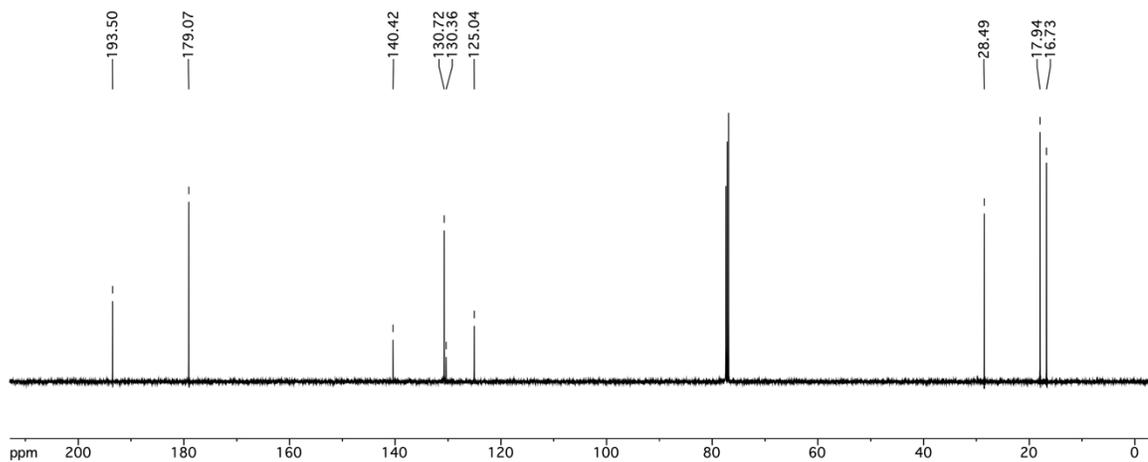
### 4-Acetyl-3-ethyl-1H-pyrrole-2-carboxaldehyde (58)



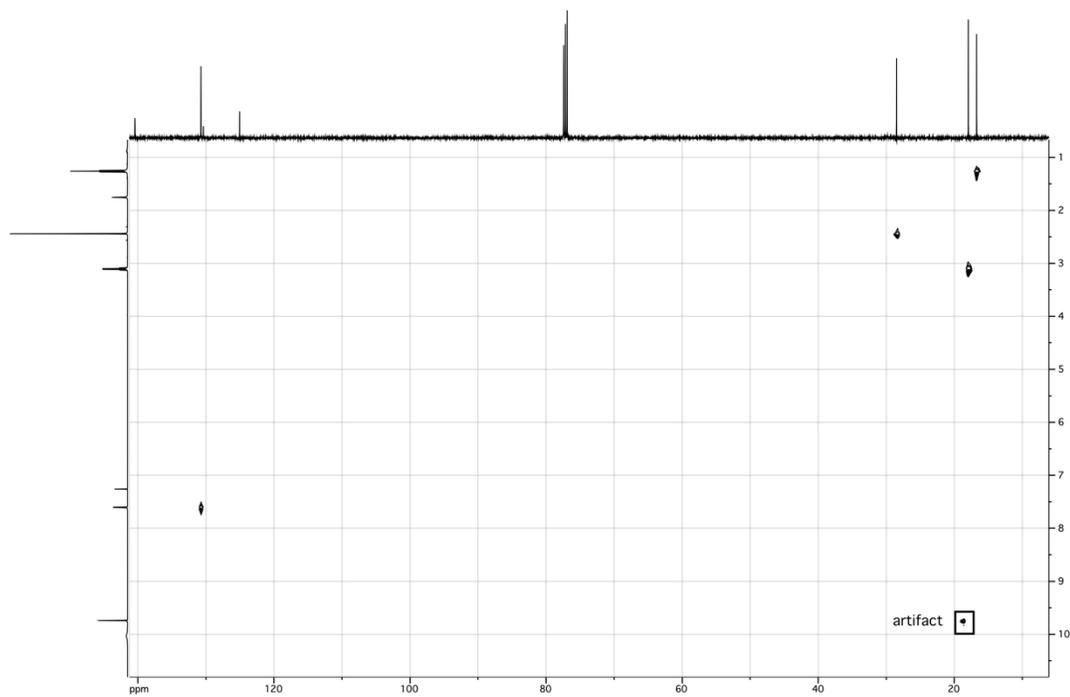
### $^1\text{H}$ NMR ( $\text{CDCl}_3$ )



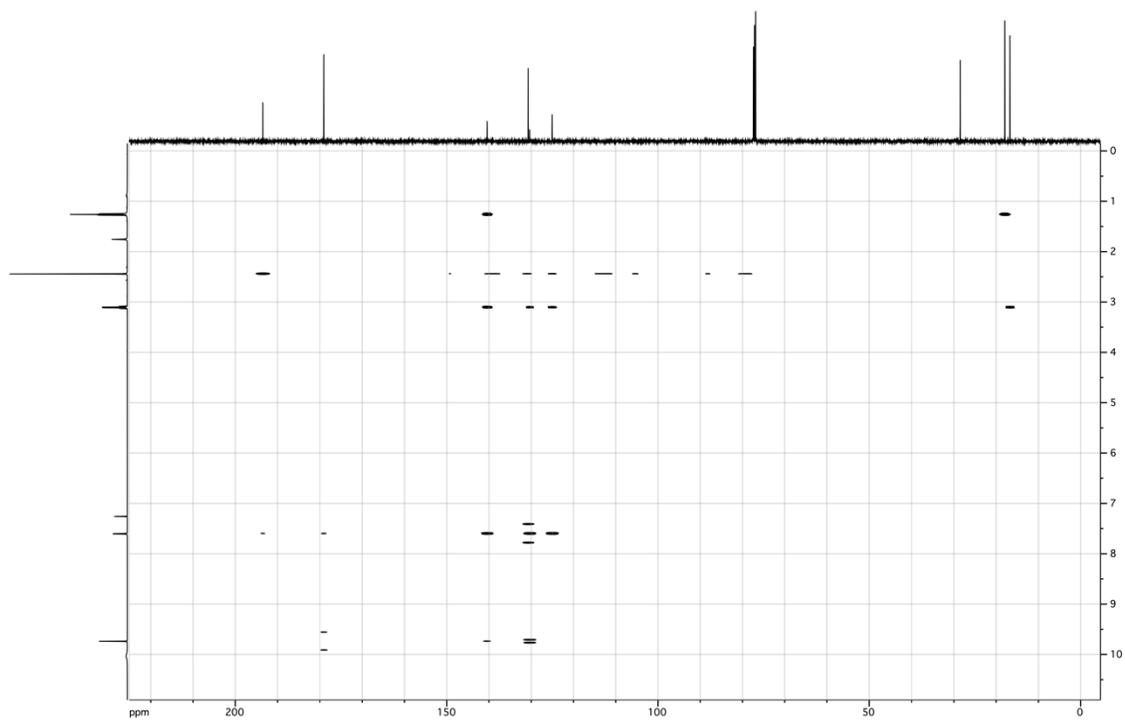
### $^{13}\text{C}$ NMR ( $\text{CDCl}_3$ )



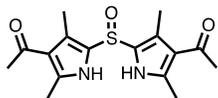
### HSQC NMR ( $\text{CDCl}_3$ )



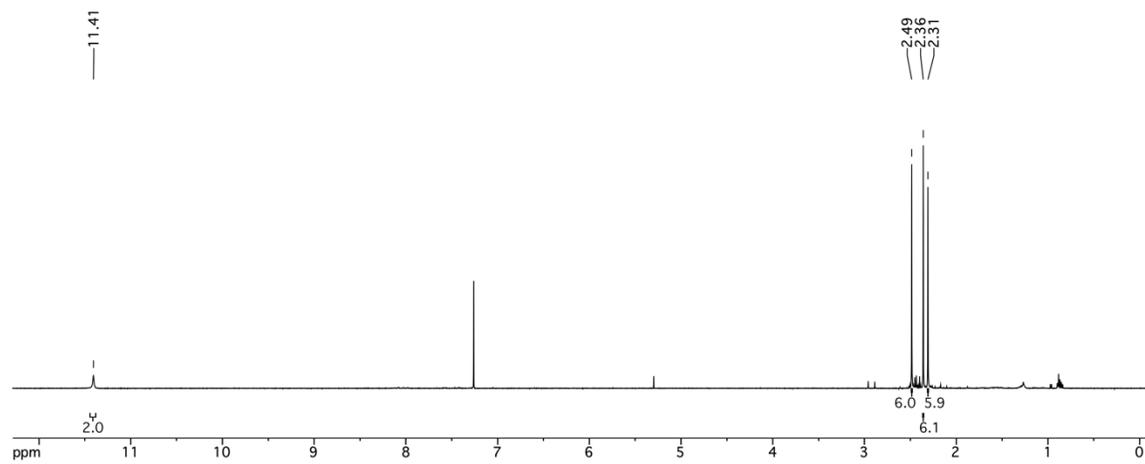
# HMBC NMR (CDCl<sub>3</sub>)



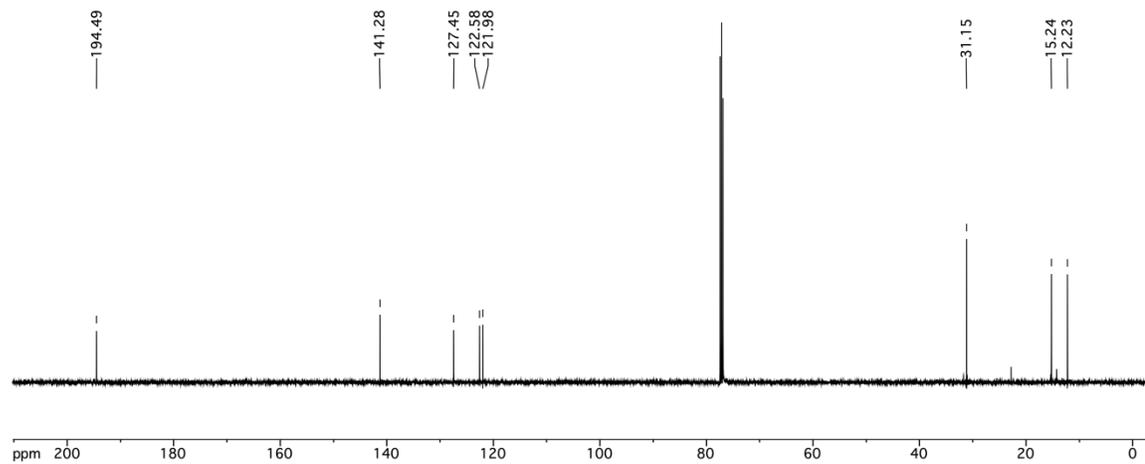
# 1,1'-[Sulfinylbis(2,4-dimethyl-1*H*-pyrrol-3,5-diyl)]bisethanone (88)



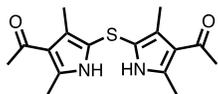
## <sup>1</sup>H NMR (CDCl<sub>3</sub>)



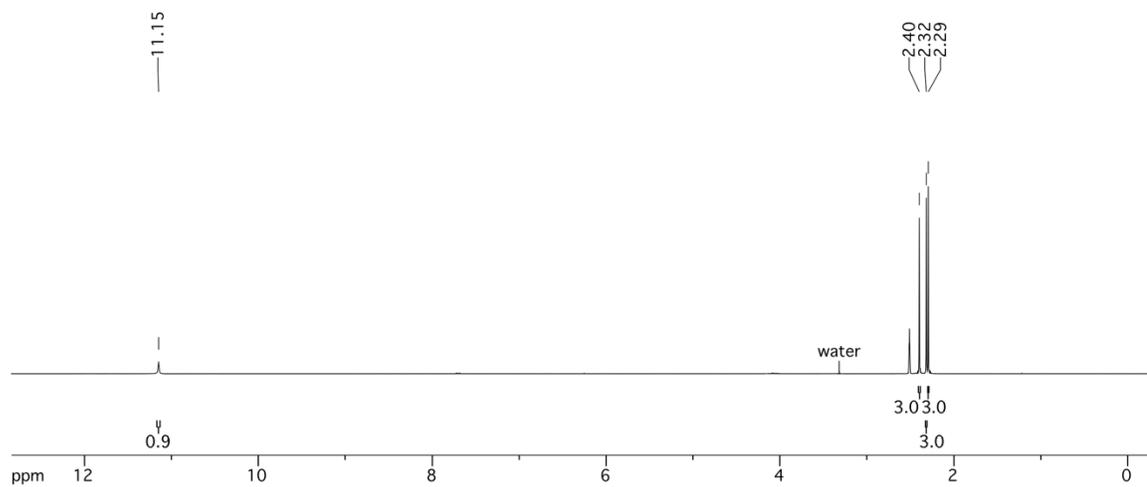
## <sup>13</sup>C NMR (CDCl<sub>3</sub>)



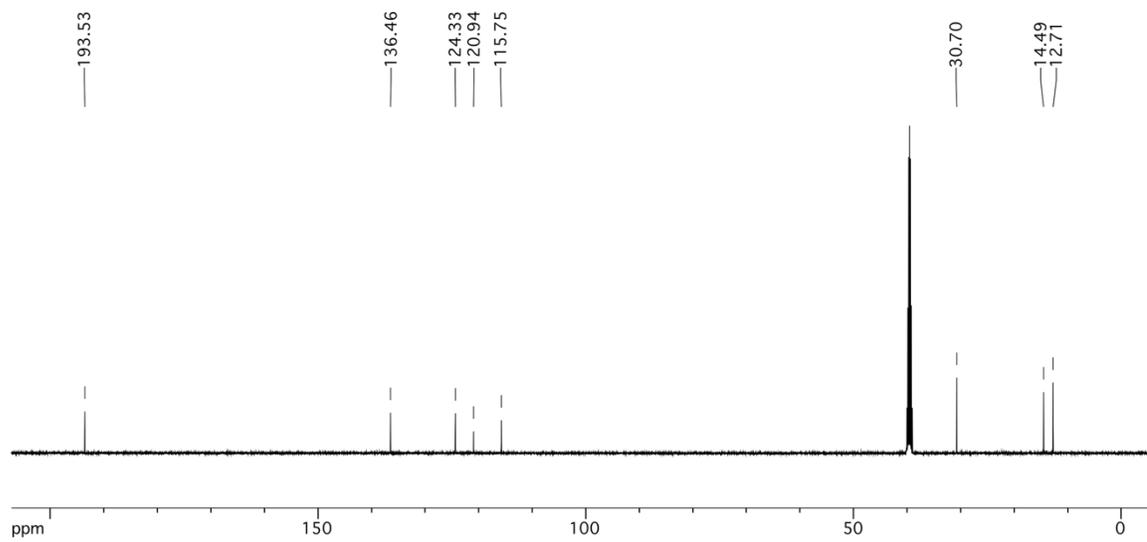
# 1,1'-[Thiobis(2,4-dimethyl-1*H*-pyrrol-3,5-diyl)]bisethanone (89)



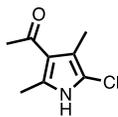
## <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)



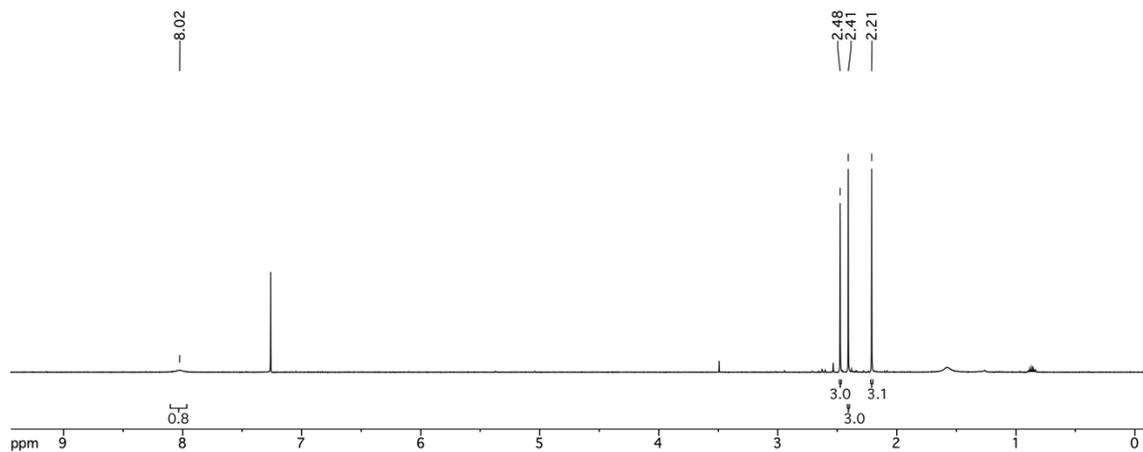
## <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>)



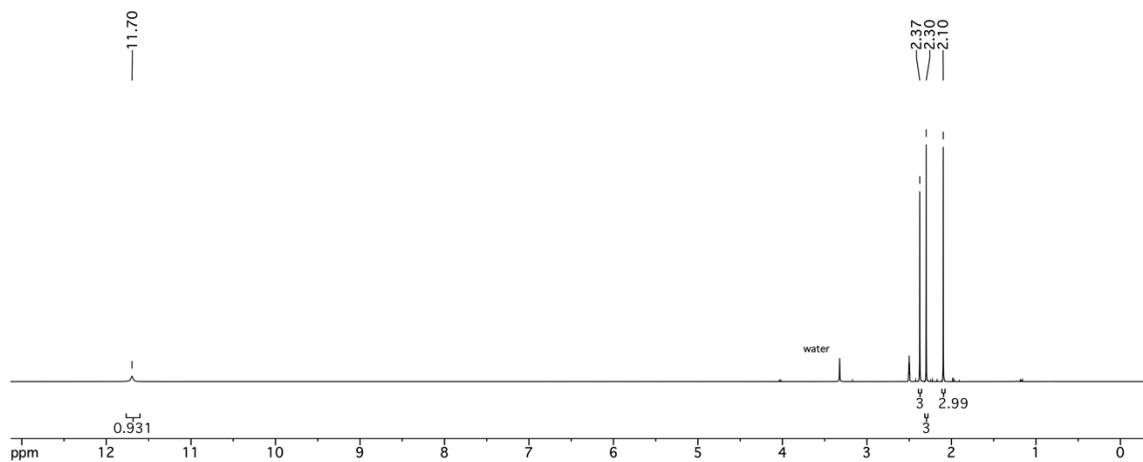
# 1-(5-Chloro-2,4-dimethyl-1H-pyrrol-3-yl)ethanone (90)



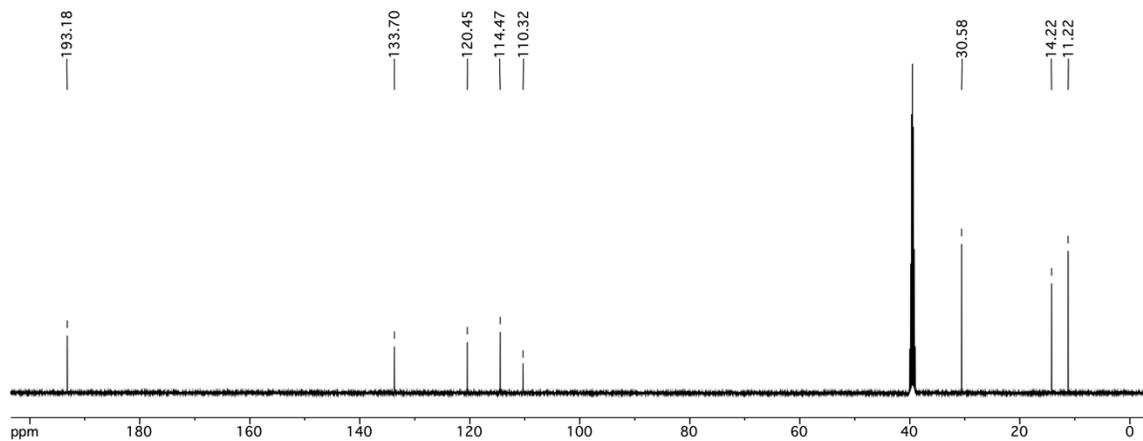
## <sup>1</sup>H NMR (CDCl<sub>3</sub>)



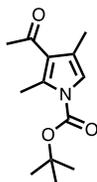
## <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)



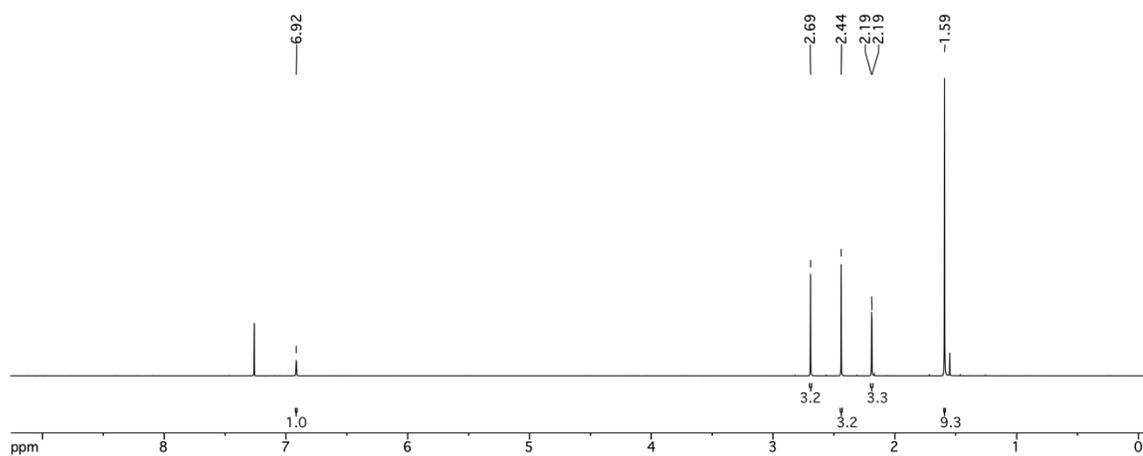
### $^{13}\text{C}$ NMR (DMSO- $d_6$ )



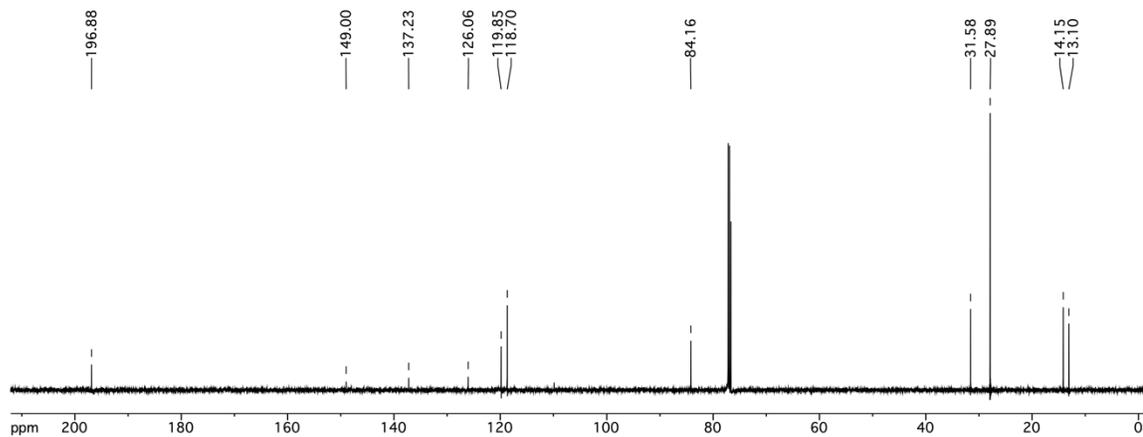
### *tert*-Butyl Ester 3-Acetyl-2,4-dimethyl-1*H*-pyrrole-1-carboxylic Acid (94)



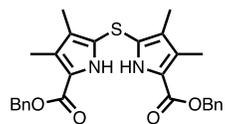
### $^1\text{H}$ NMR (CDCl $_3$ )



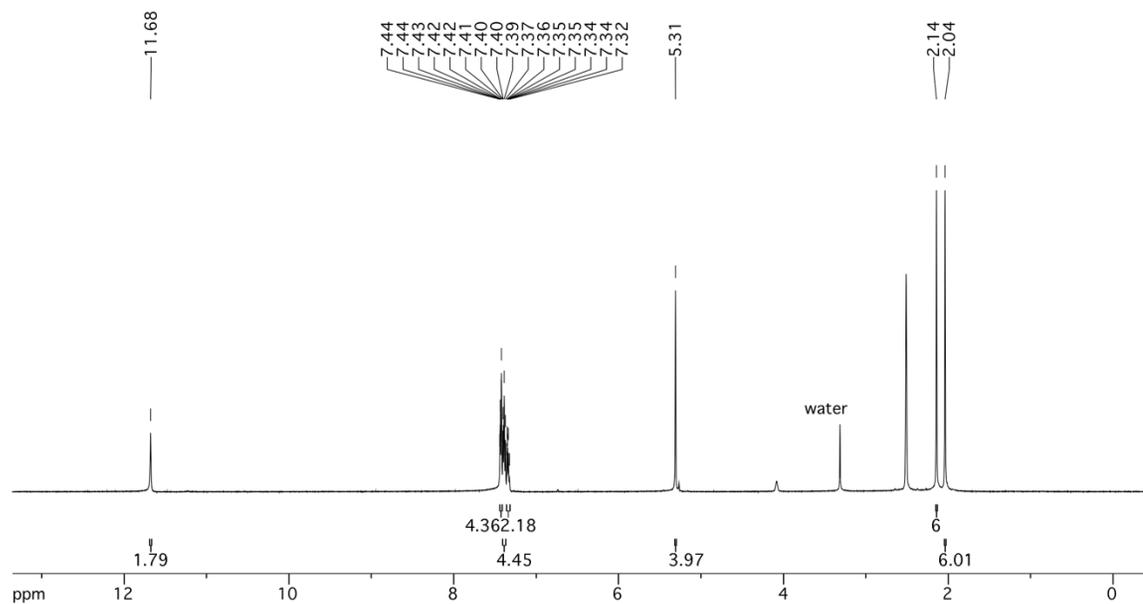
### $^{13}\text{C}$ NMR ( $\text{CDCl}_3$ )



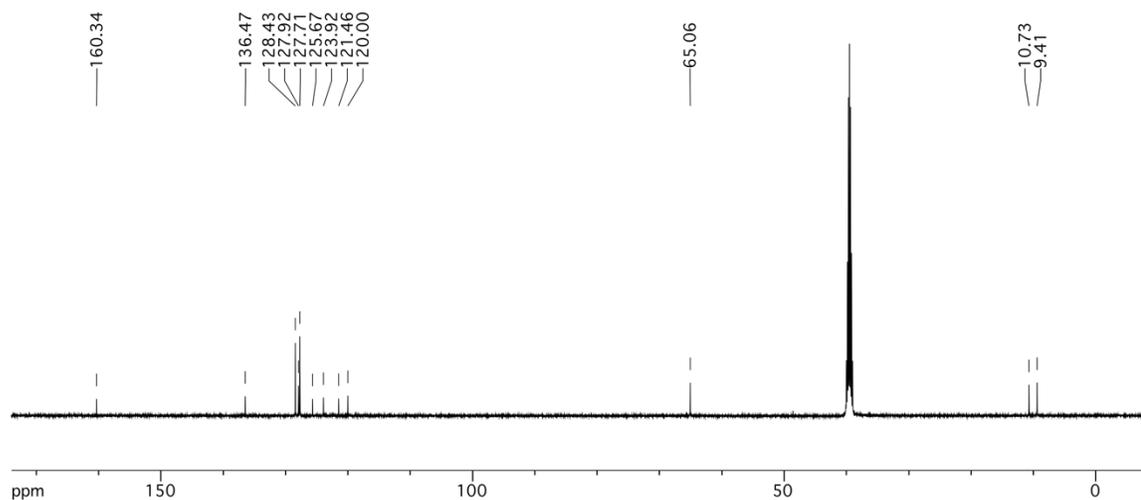
### Dibenzy Ester 5,5'-Thiobis[3,4-dimethyl-1*H*-pyrrole-2-carboxylic acid] (97)



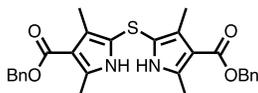
### $^1\text{H}$ NMR ( $\text{DMSO-}d_6$ )



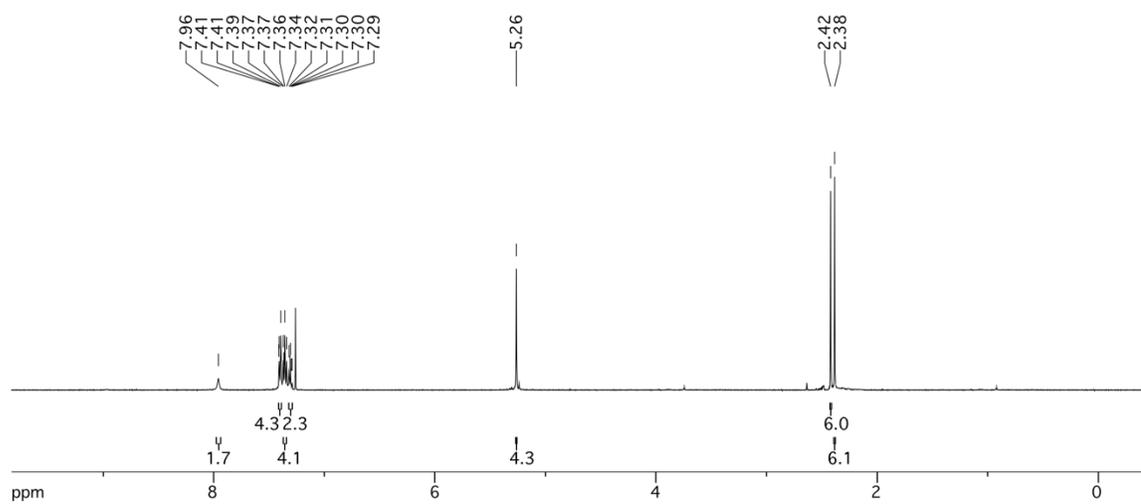
### $^{13}\text{C}$ NMR (DMSO- $d_6$ )



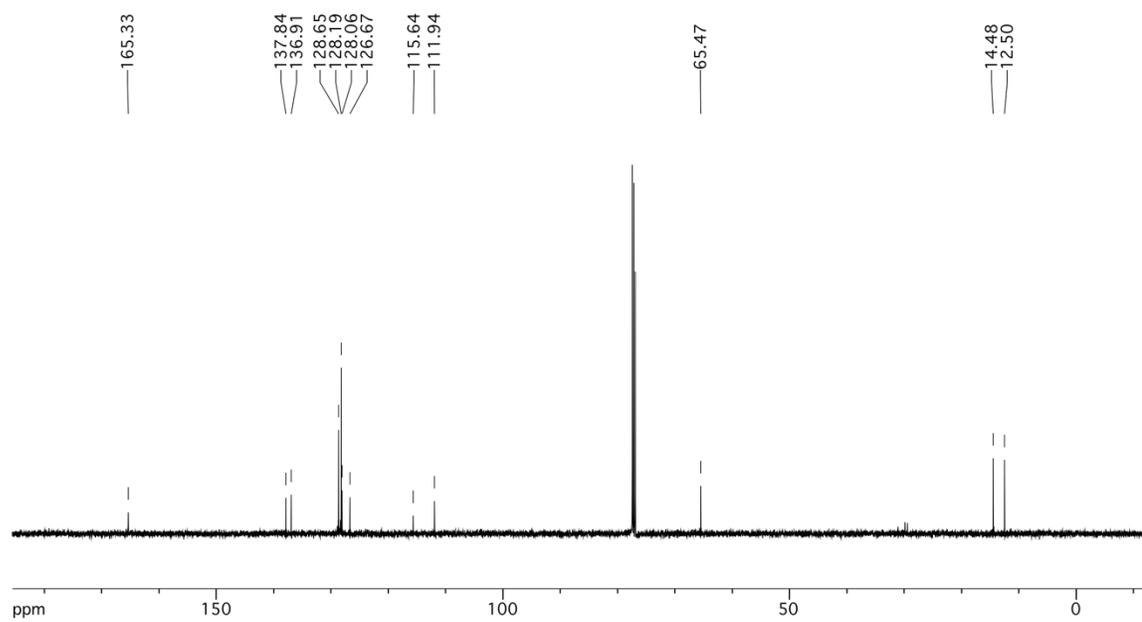
### Dibenzy Ester 5,5'-Tthiobis[2,4-dimethyl-1H-pyrrole-3-carboxylic acid] (98)



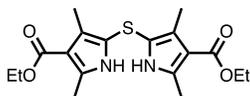
### $^1\text{H}$ NMR (CDCl $_3$ )



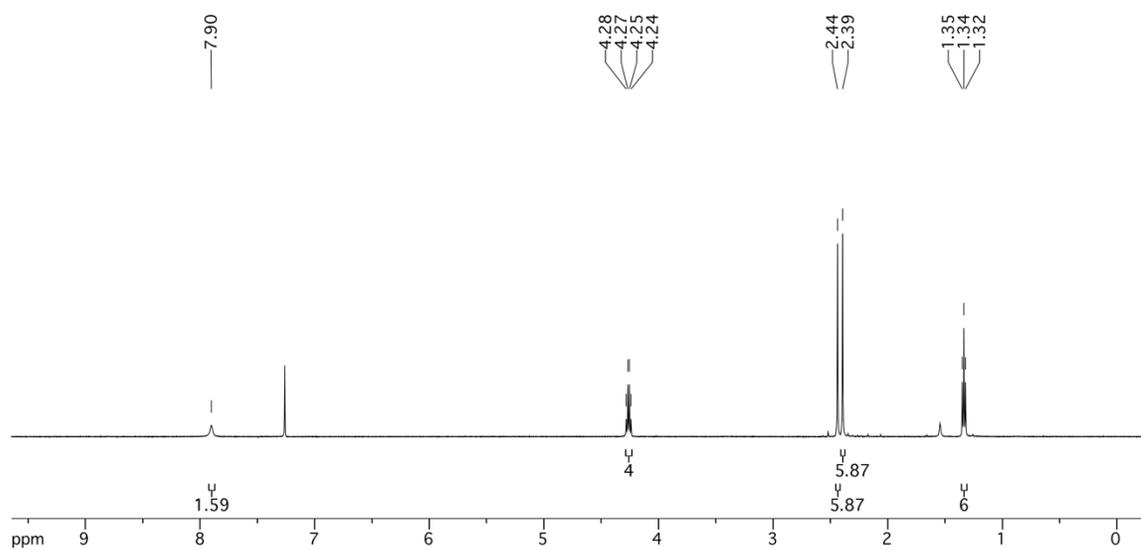
**$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )**



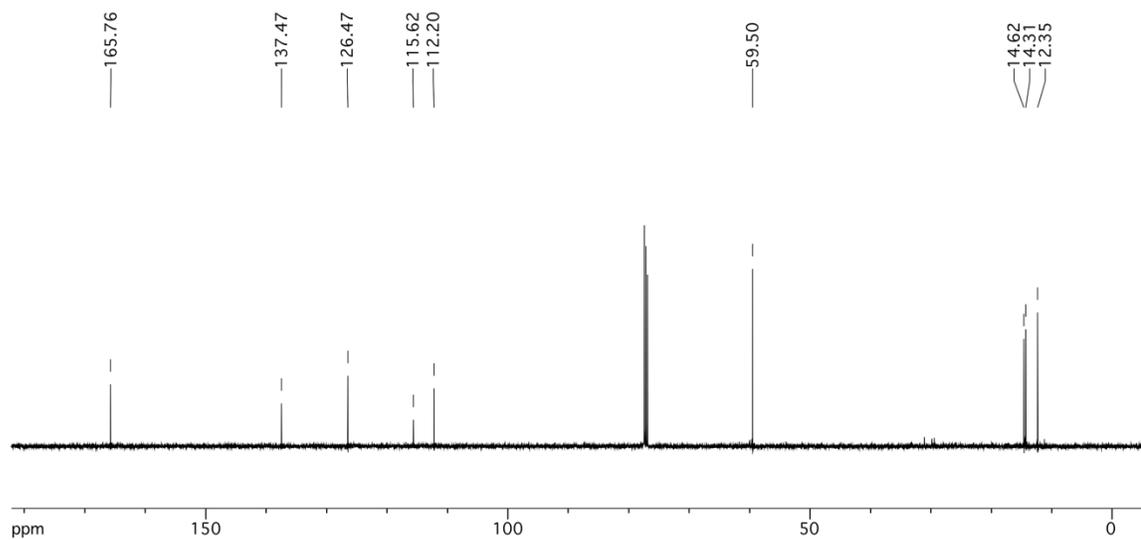
# Diethyl Ester 5,5'-Thiobis[2,4-dimethyl-1*H*-pyrrole-3-carboxylic acid] (99)



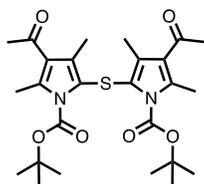
## <sup>1</sup>H NMR (CDCl<sub>3</sub>)



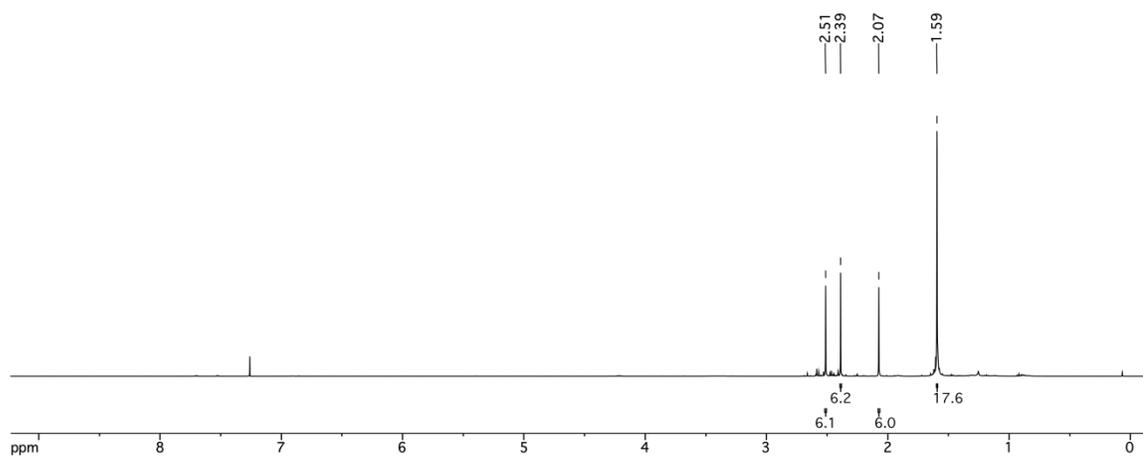
## <sup>13</sup>C NMR (CDCl<sub>3</sub>)



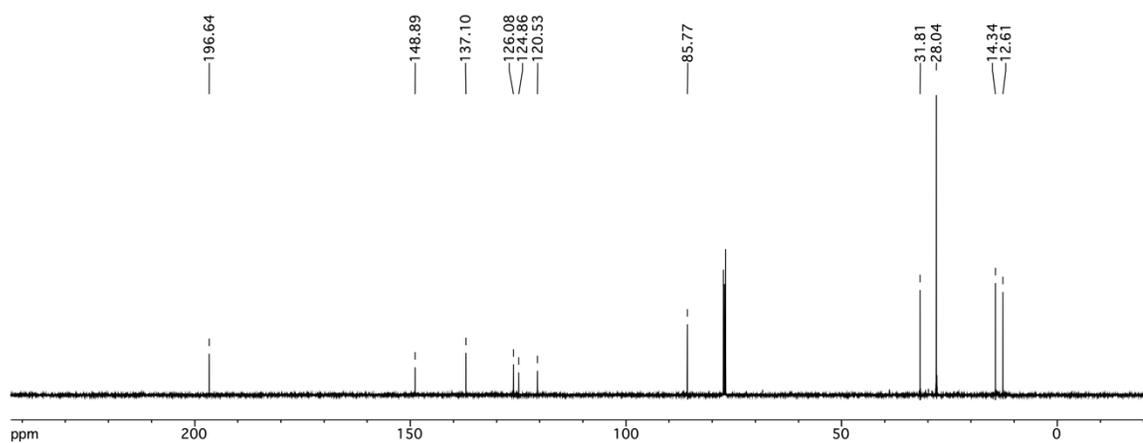
**Di-*tert*-butyl Ester 5,5'-Thiobis[3-acetyl-2,4-dimethyl-1*H*-pyrrole-1-carboxylic acid] (100)**



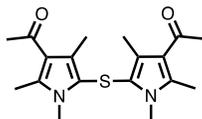
**$^1\text{H NMR}$  ( $\text{CDCl}_3$ )**



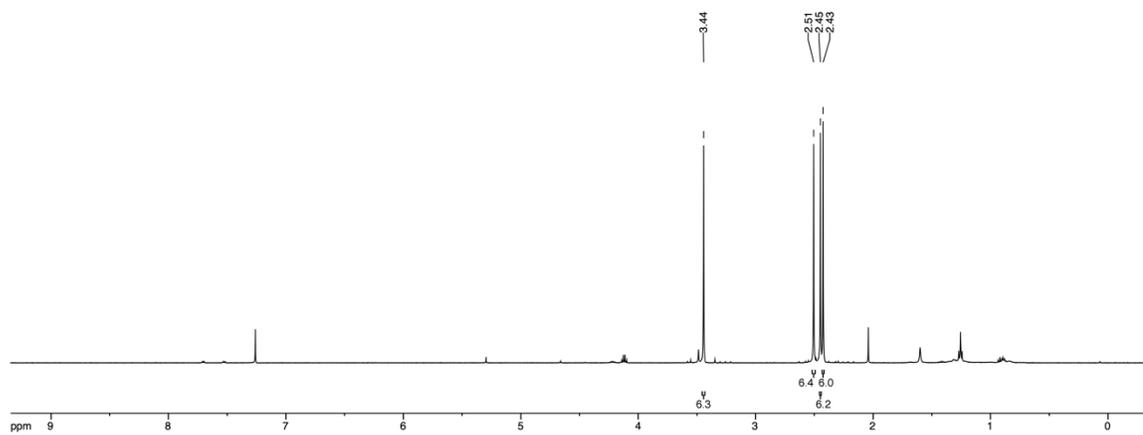
**$^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )**



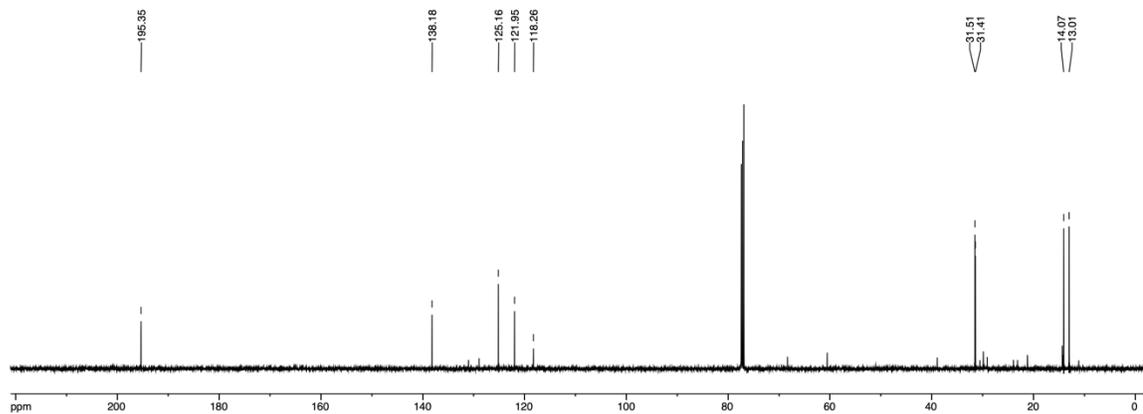
# 1,1'-[Thiobis(1,2,4-trimethyl-1*H*-pyrrol-3,5-diyl)]bisethanone (101)



## <sup>1</sup>H NMR (CDCl<sub>3</sub>)

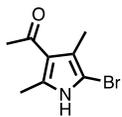


## <sup>13</sup>C NMR (CDCl<sub>3</sub>)

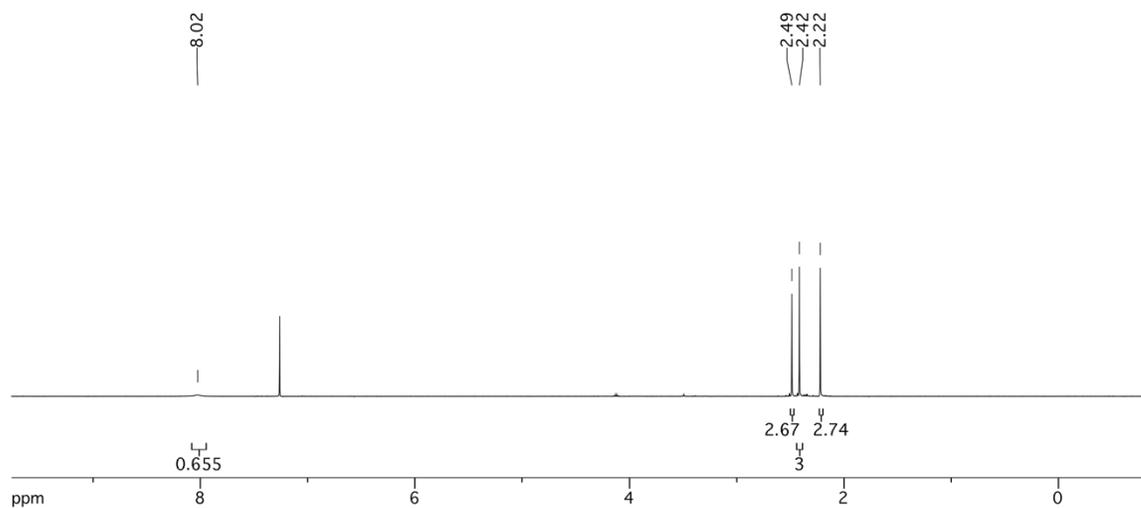




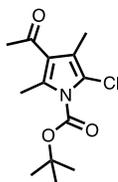
# 1-(5-Bromo-2,4-dimethyl-1H-pyrrol-3-yl)ethanone (103)



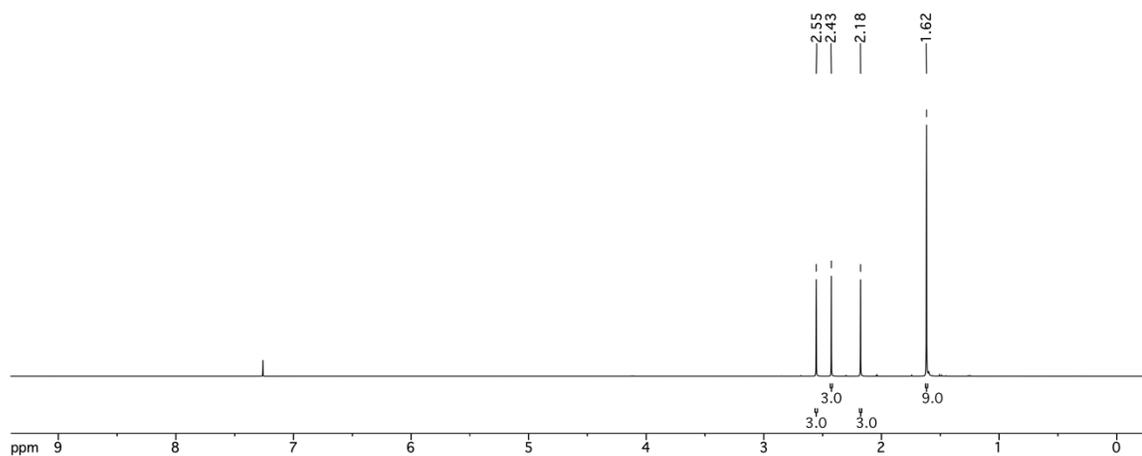
## $^1\text{H NMR}$ ( $\text{CDCl}_3$ )



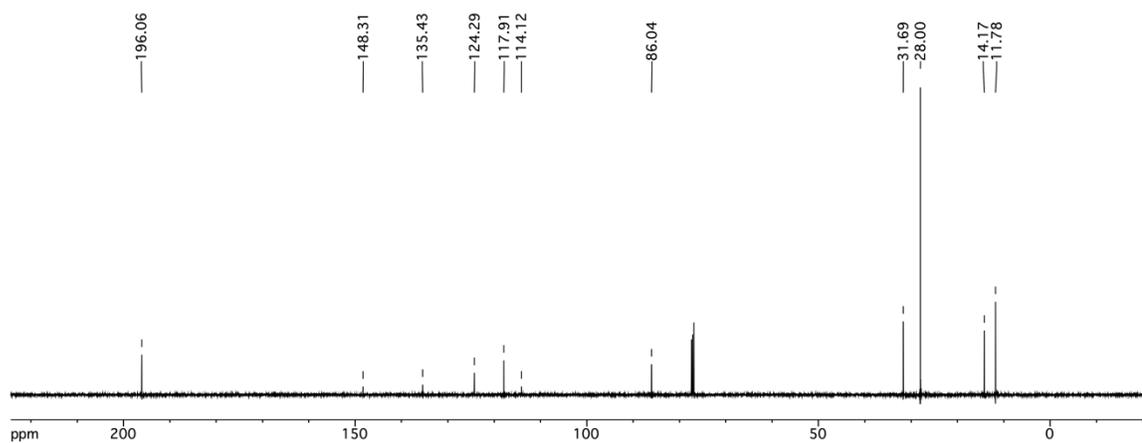
***tert*-Butyl Ester 3-Acetyl-5-chloro-2,4-dimethyl-1*H*-pyrrole-1-carboxylic Acid (107)**



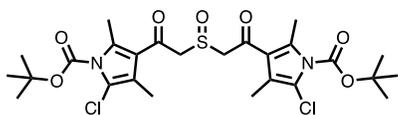
**<sup>1</sup>H NMR (CDCl<sub>3</sub>)**



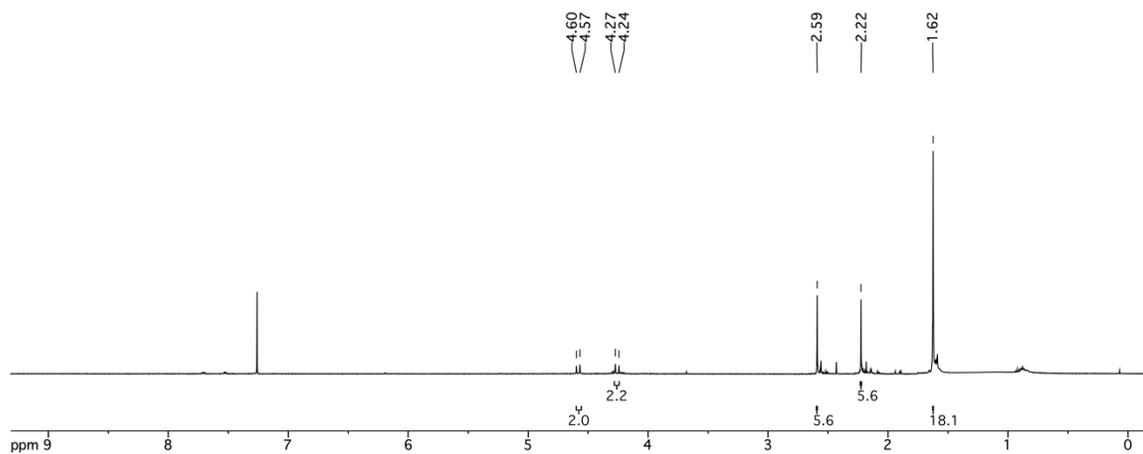
**<sup>13</sup>C NMR (CDCl<sub>3</sub>)**



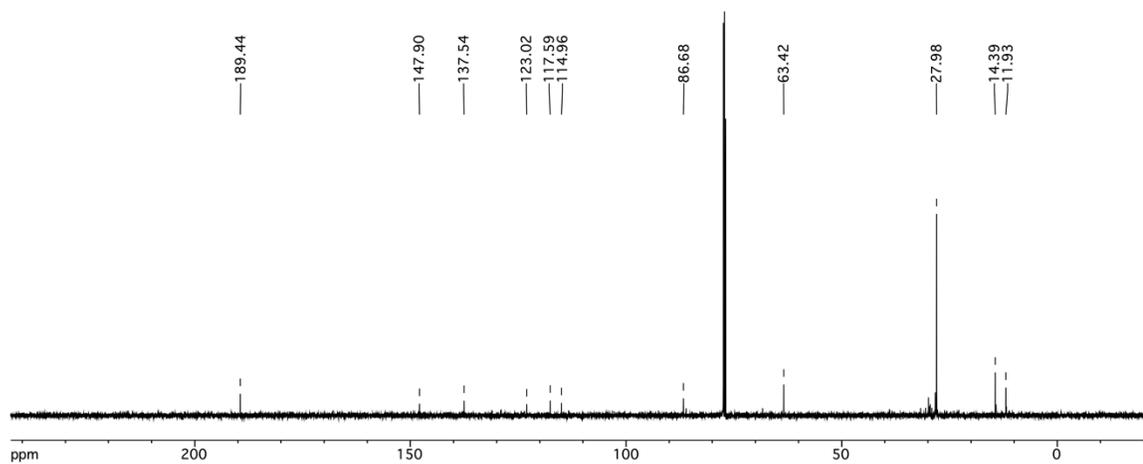
**Di-tert-butyl Ester 3,3'-[Sulfinylbis(1-oxo-2,1-ethanediyl)]bis(5-chloro-2,4-dimethyl-1H-pyrrole-1-carboxylic acid) (108)**



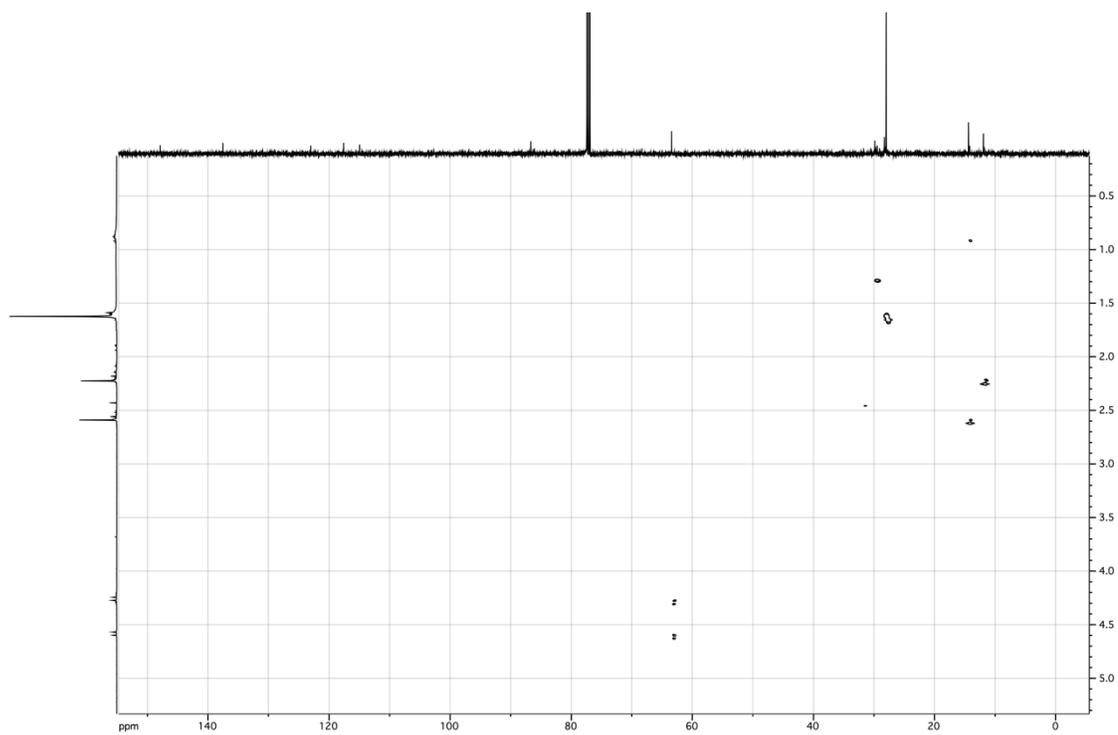
**<sup>1</sup>H NMR (CDCl<sub>3</sub>)**



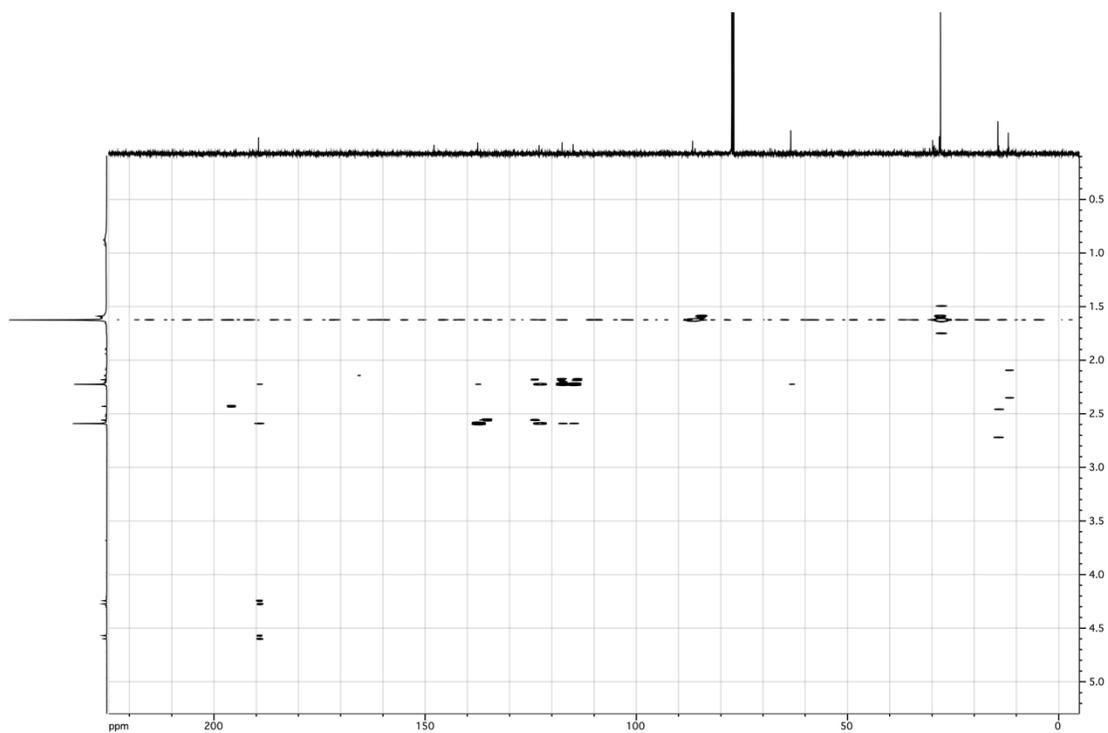
**<sup>13</sup>C NMR (CDCl<sub>3</sub>)**



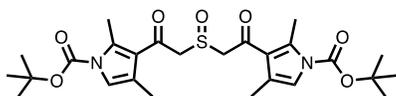
### HSQC NMR (CDCl<sub>3</sub>)



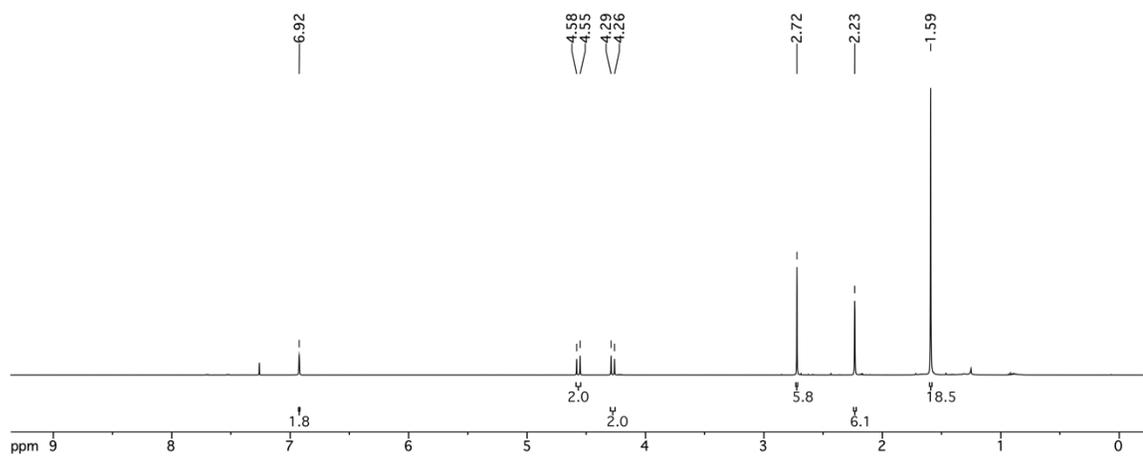
### HMBC NMR (CDCl<sub>3</sub>)



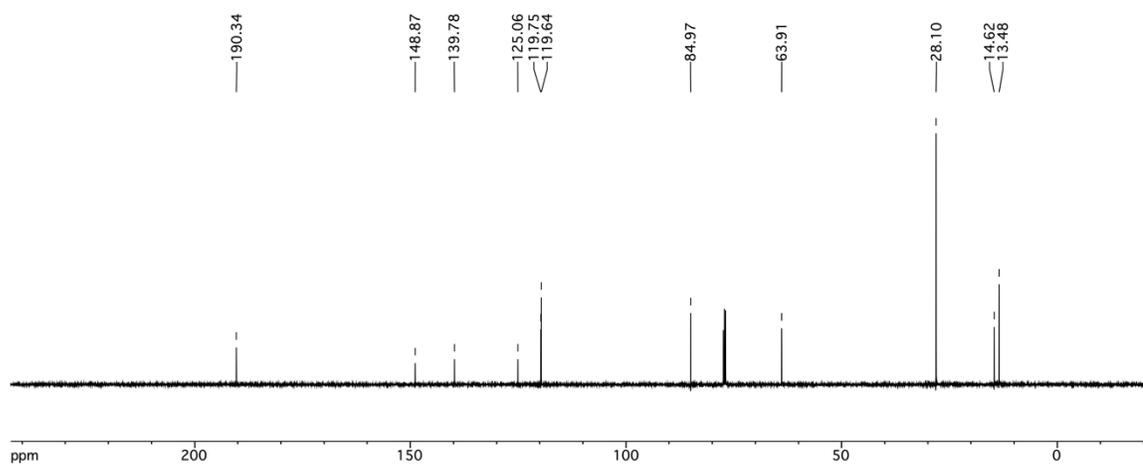
**Di-tert-butyl Ester 3,3'-[Sulfinylbis(1-oxo-2,1-ethanediyl)]bis(2,4-dimethyl-1H-pyrrole-1-carboxylic acid) (109)**



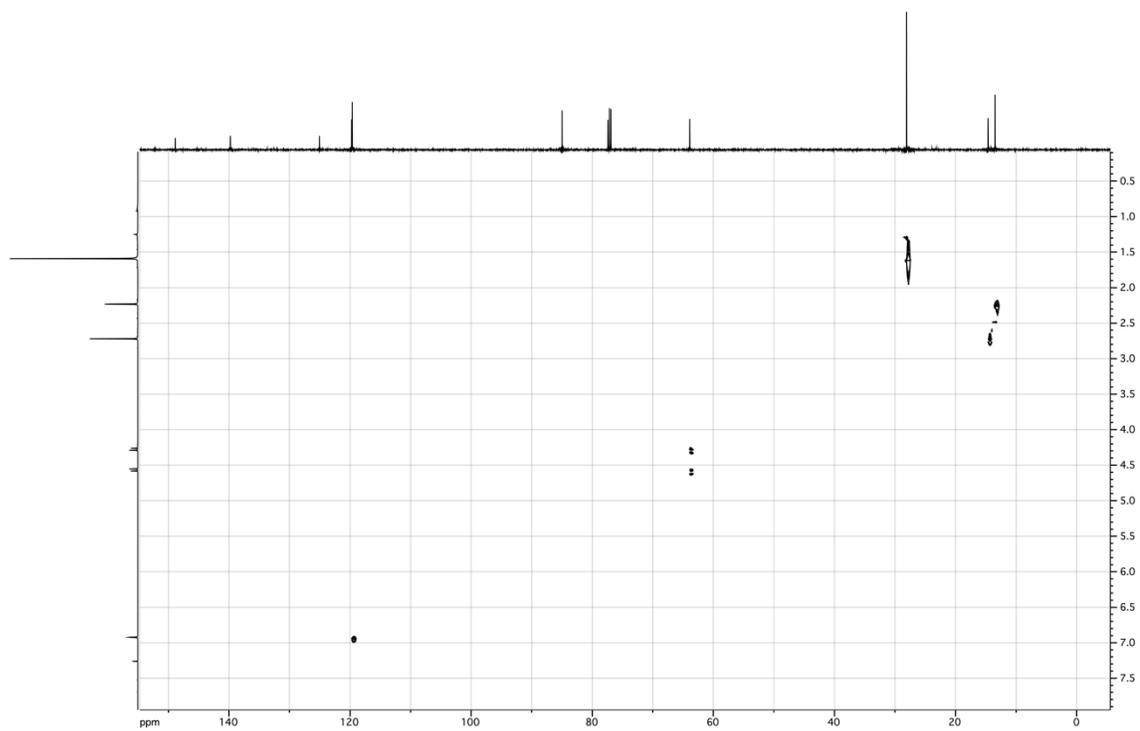
**<sup>1</sup>H NMR (CDCl<sub>3</sub>)**



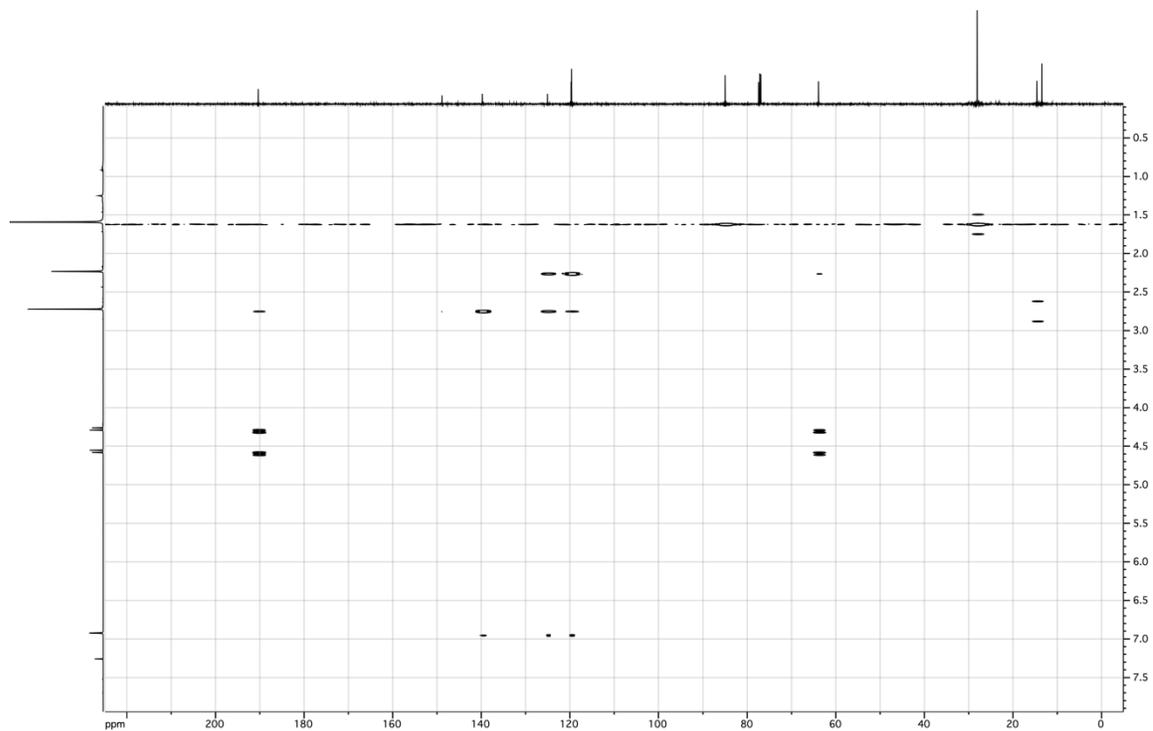
**<sup>13</sup>C NMR (CDCl<sub>3</sub>)**



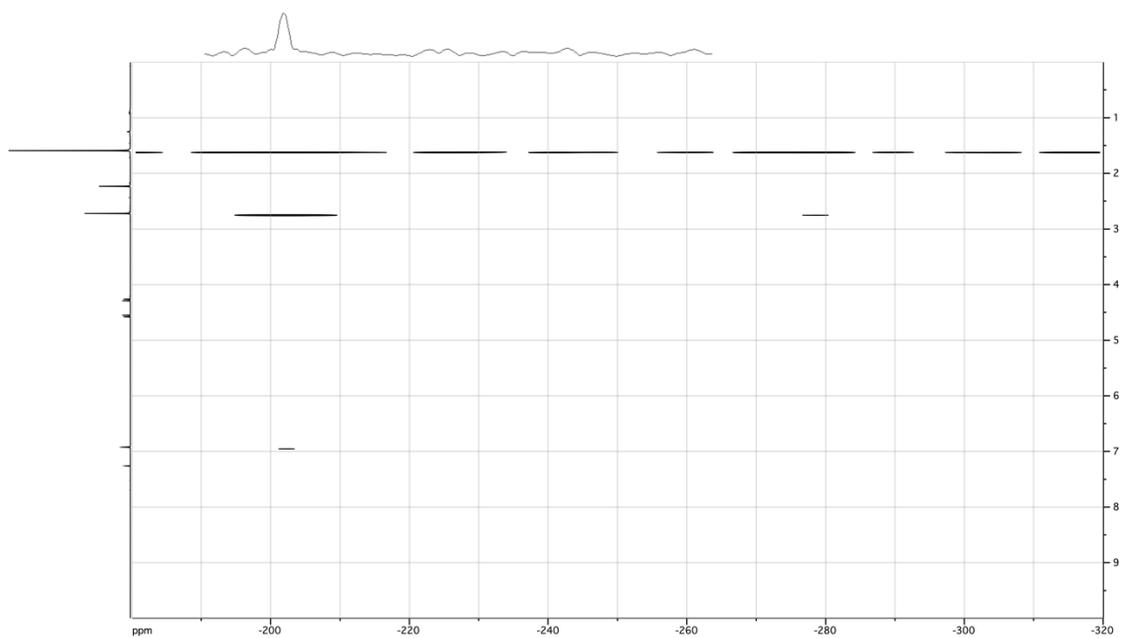
## HSQC NMR (CDCl<sub>3</sub>)



## HMBC NMR (CDCl<sub>3</sub>)

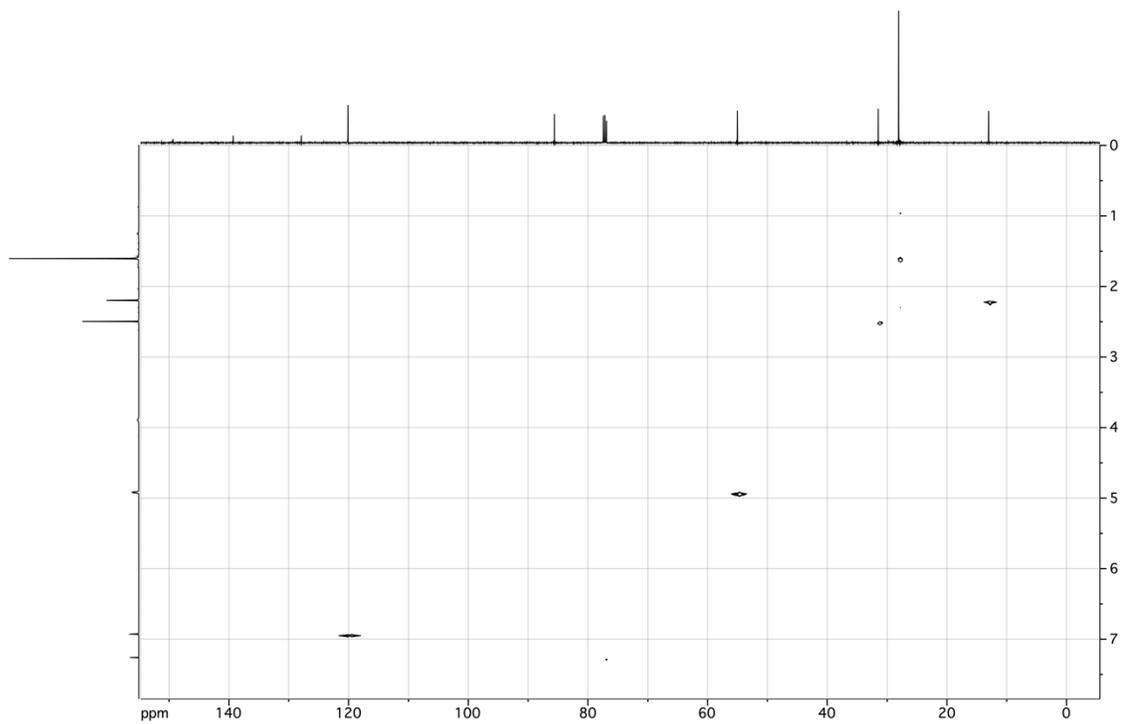


**$^{15}\text{N}$ - $^1\text{H}$  HMBC NMR ( $\text{CDCl}_3$ )**

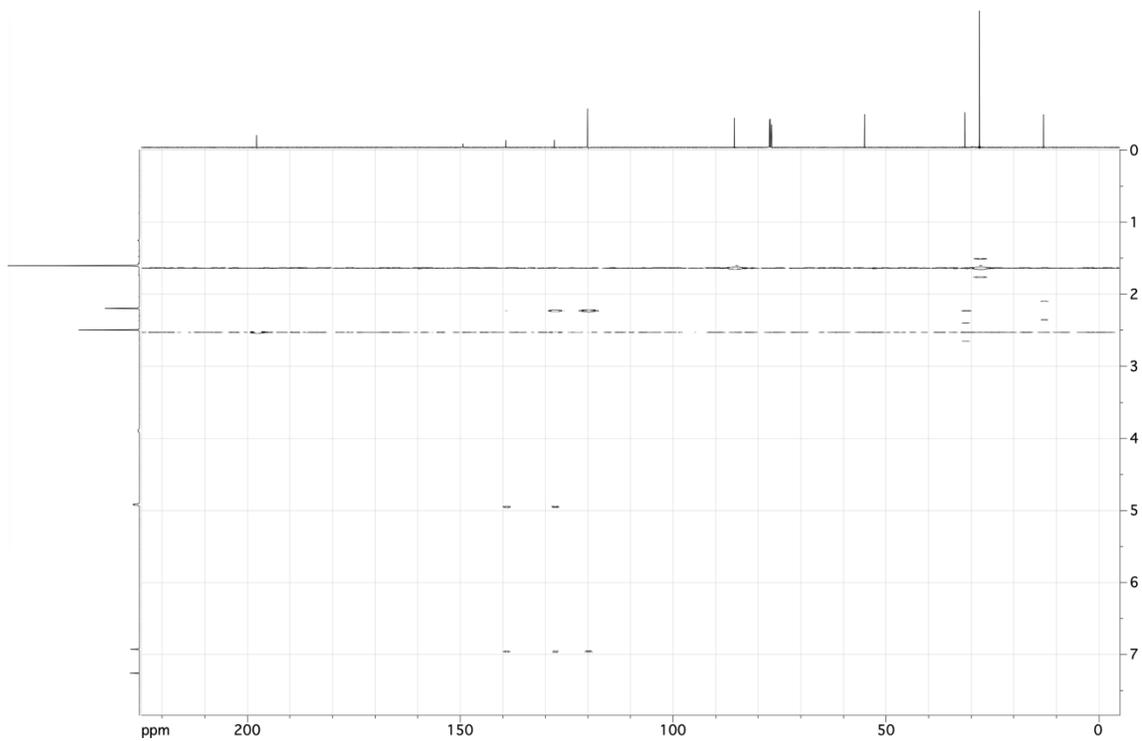




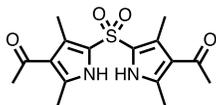
## HSQC NMR (CDCl<sub>3</sub>)



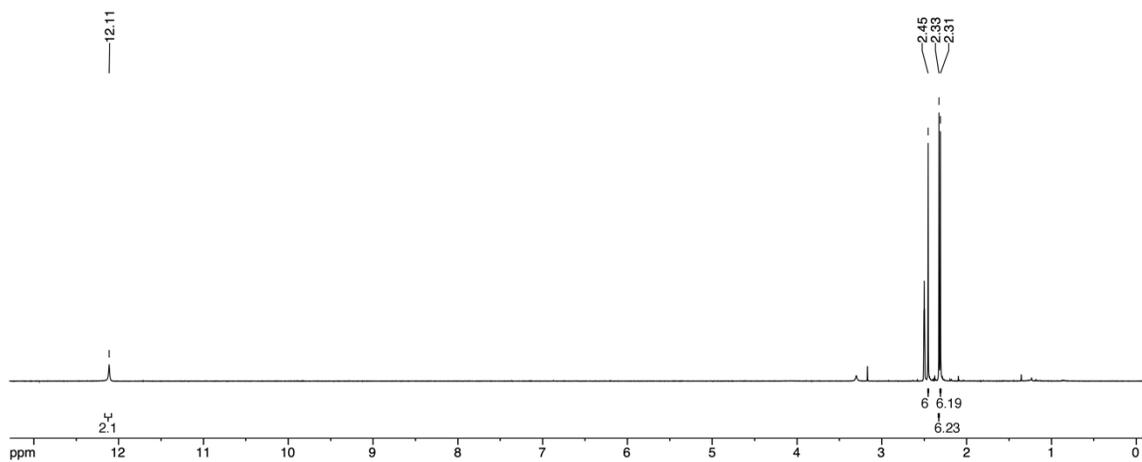
## HMBC NMR (CDCl<sub>3</sub>)



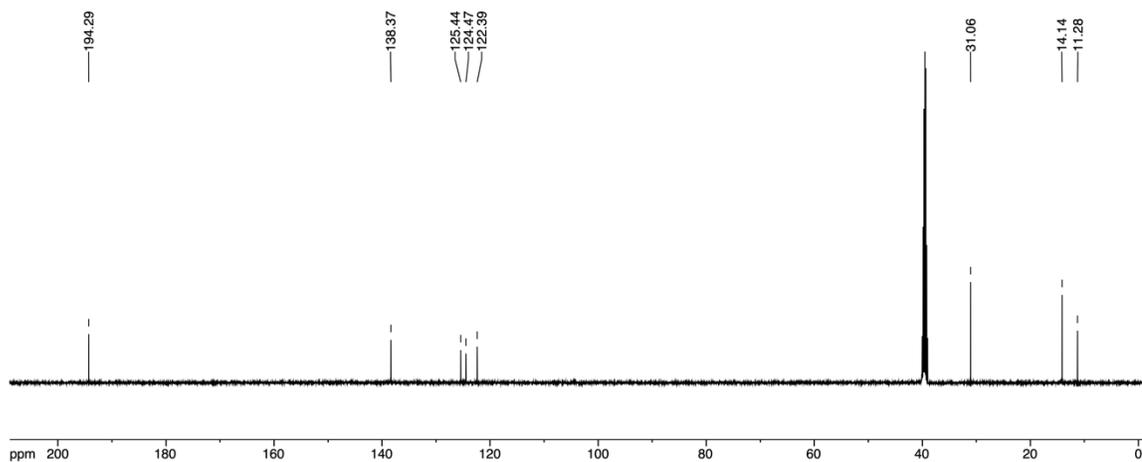
# 1,1'-[Sulfonylbis(2,4-dimethyl-1*H*-pyrrol-3,5-diyl)]bisethanone (111)



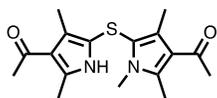
## <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)



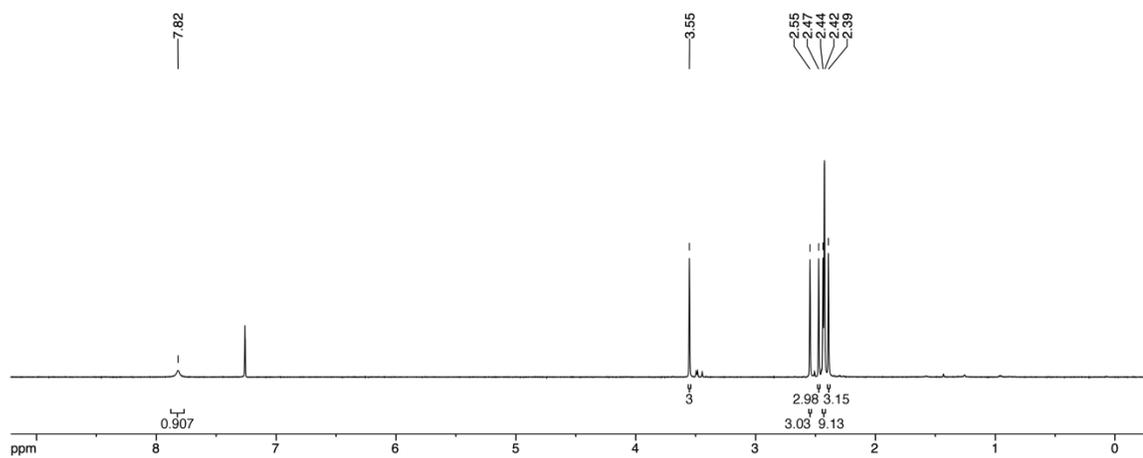
## <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>)



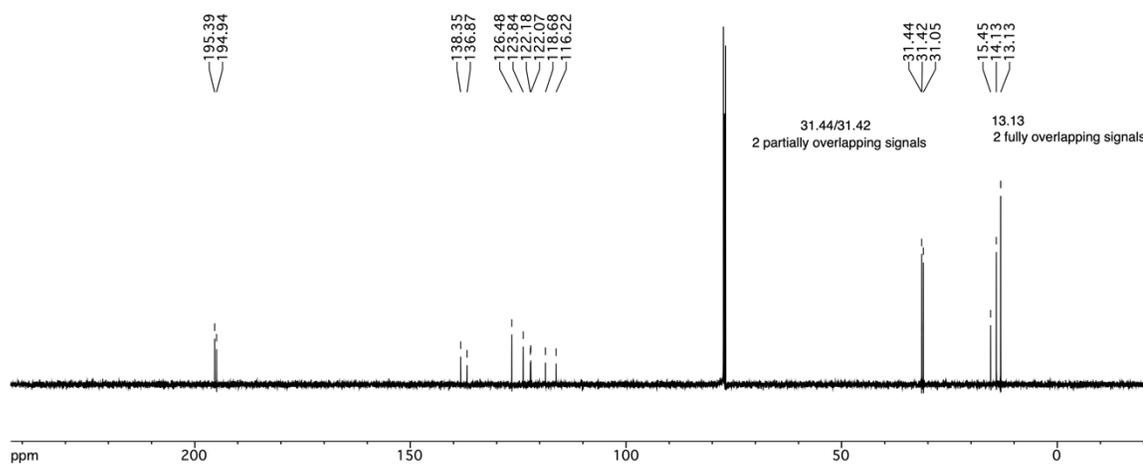
# 1-[5-[(4-Acetyl-3,5-dimethylpyrrol-2-yl)thio]-1,2,4-trimethyl-1H-pyrrol-3-yl]ethanone (114)



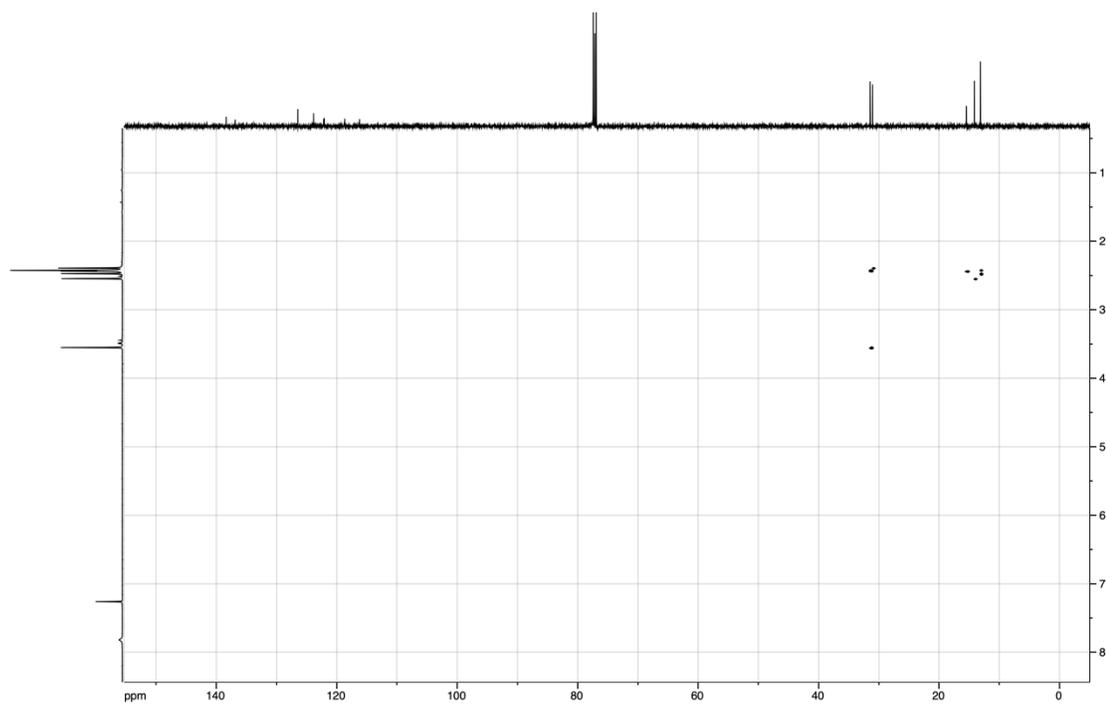
## <sup>1</sup>H NMR (CDCl<sub>3</sub>)



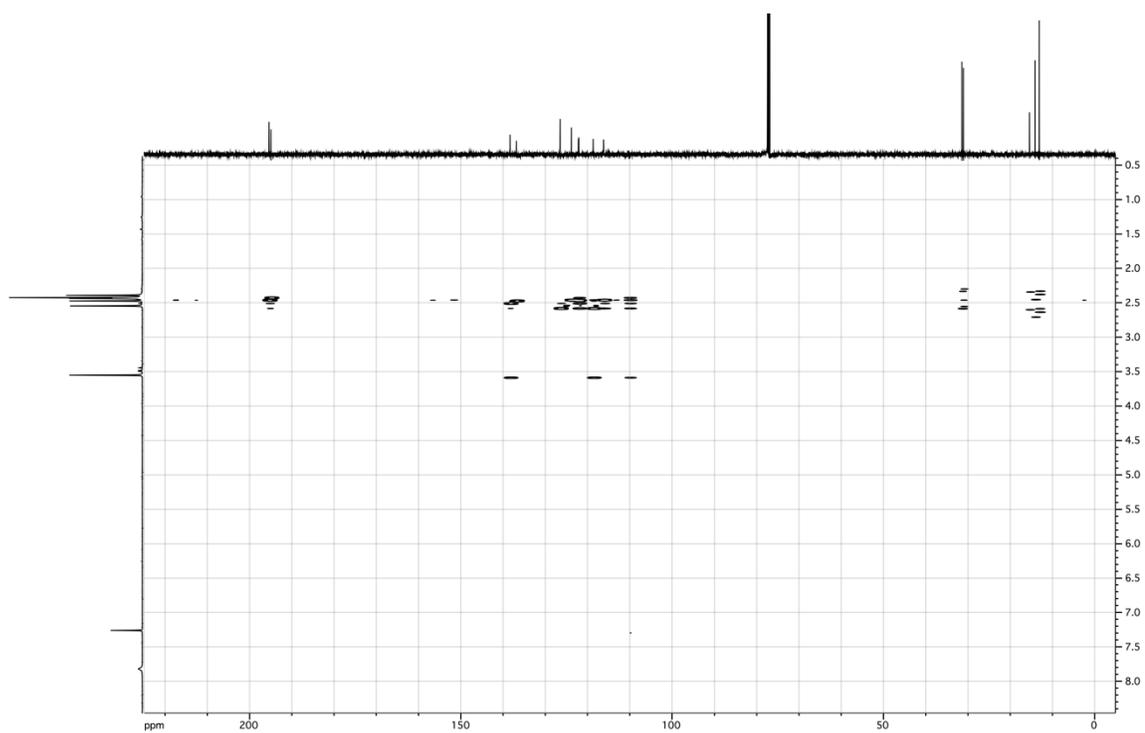
## <sup>13</sup>C NMR (CDCl<sub>3</sub>)



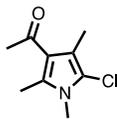
### HSQC NMR (CDCl<sub>3</sub>)



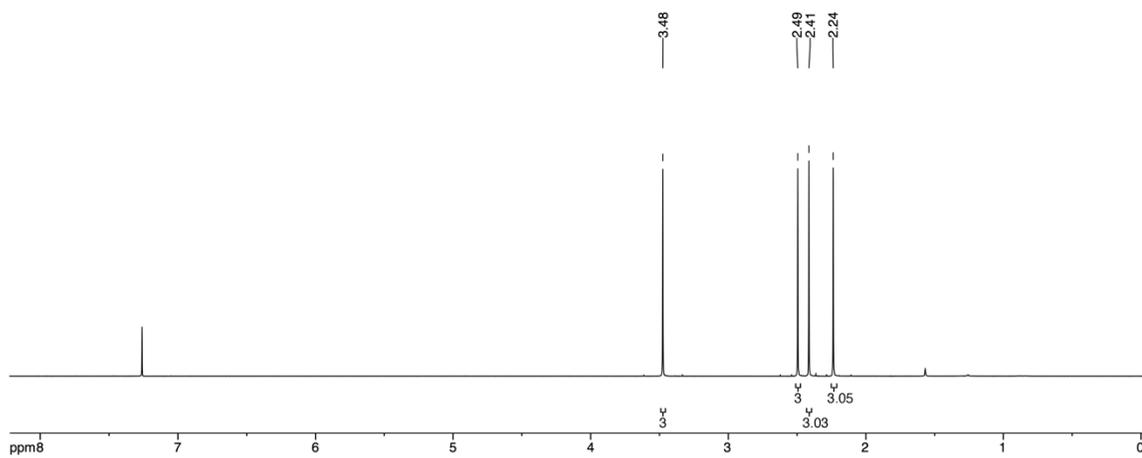
### HMBC NMR (CDCl<sub>3</sub>)



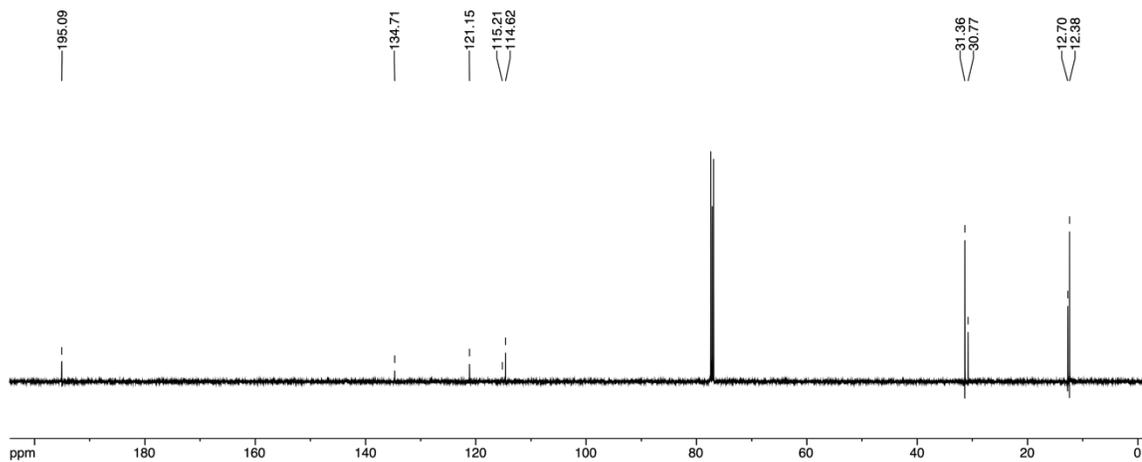
# 1-(5-Chloro-1,2,4-trimethyl-1*H*-pyrrol-3-yl)ethanone (115)



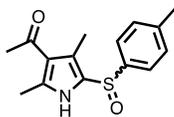
## <sup>1</sup>H NMR (CDCl<sub>3</sub>)



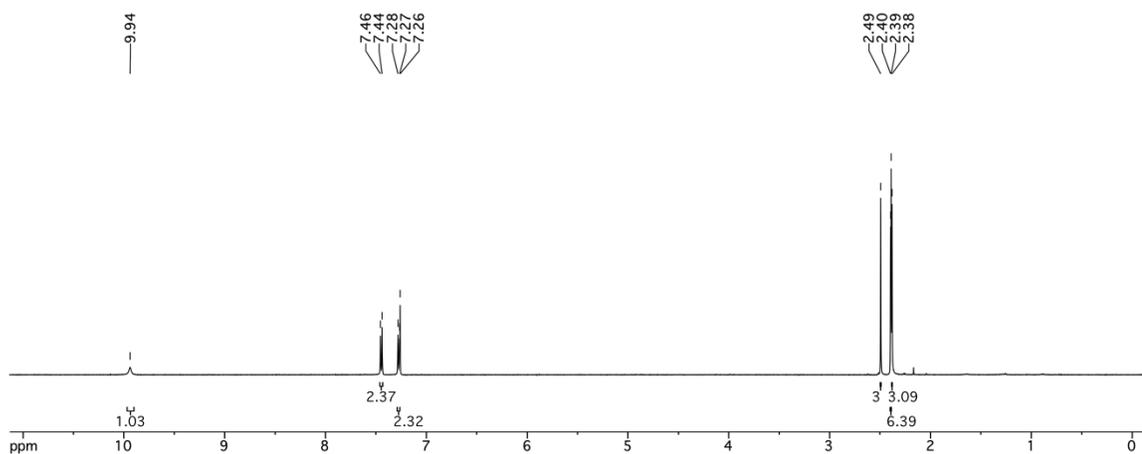
## <sup>13</sup>C NMR (CDCl<sub>3</sub>)



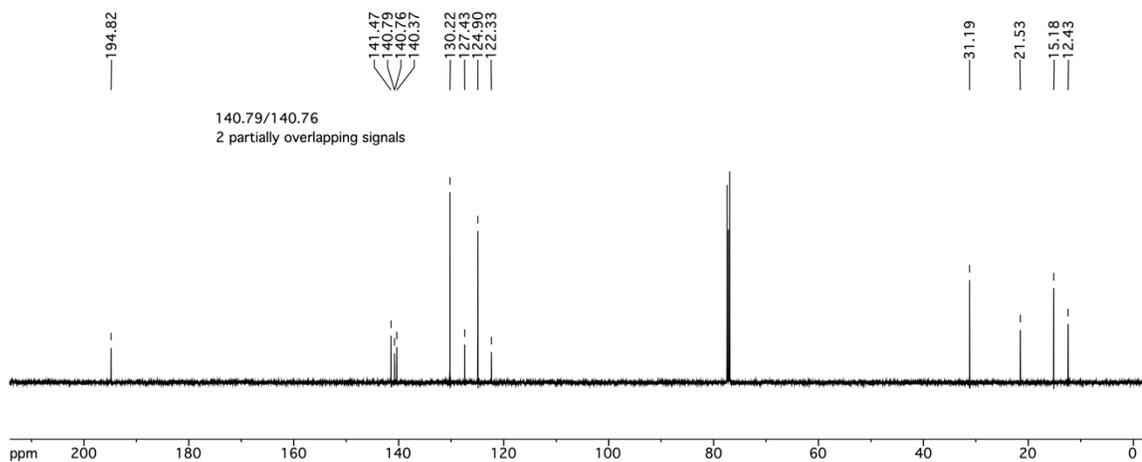
# 1-[2,4-Dimethyl-5-(4-methylphenyl)sulfinyl-1H-pyrrol-3-yl]ethanone (116)



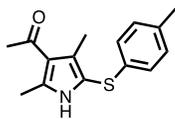
## <sup>1</sup>H NMR (CDCl<sub>3</sub>)



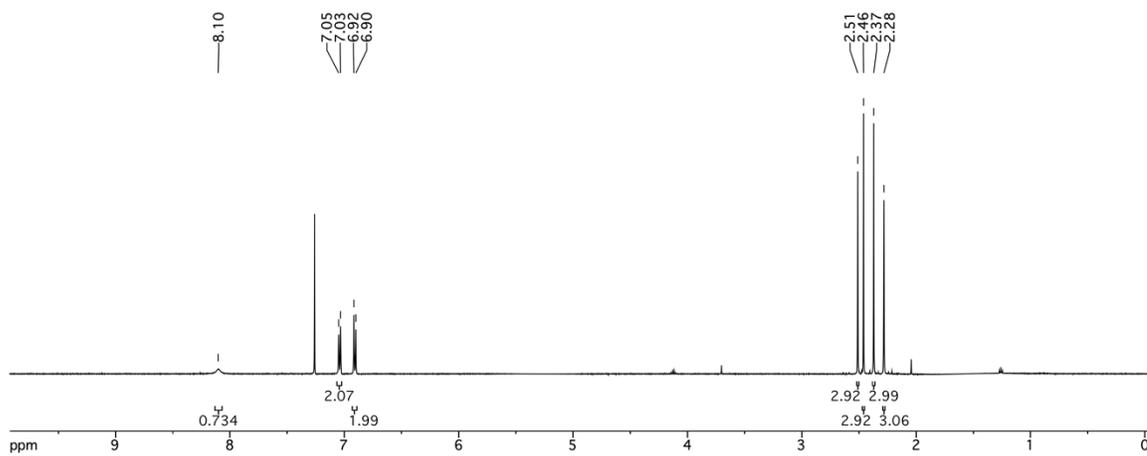
## <sup>13</sup>C NMR (CDCl<sub>3</sub>)



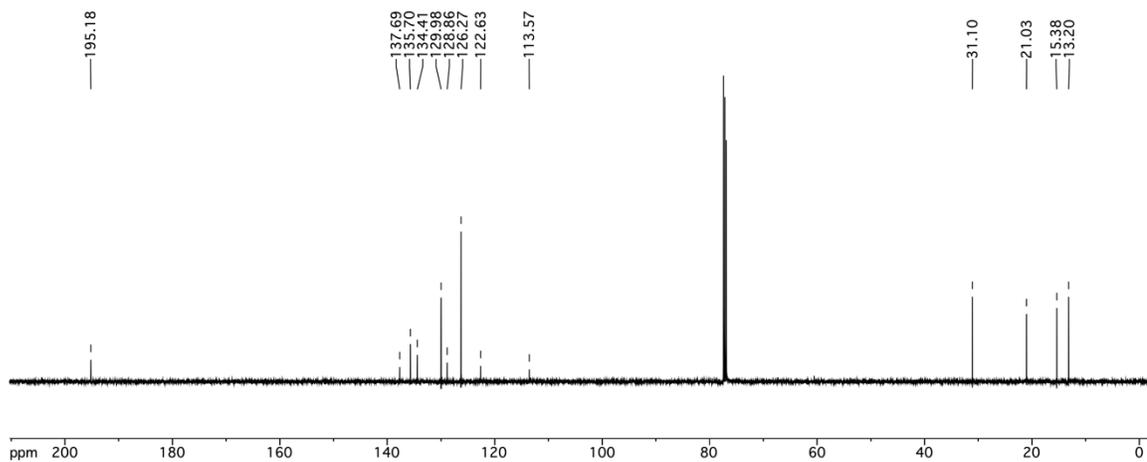
# 1-[2,4-Dimethyl-5-(4-methylphenyl)thio-1H-pyrrol-3-yl]ethanone (118)



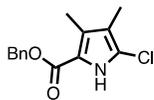
## <sup>1</sup>H NMR (CDCl<sub>3</sub>)



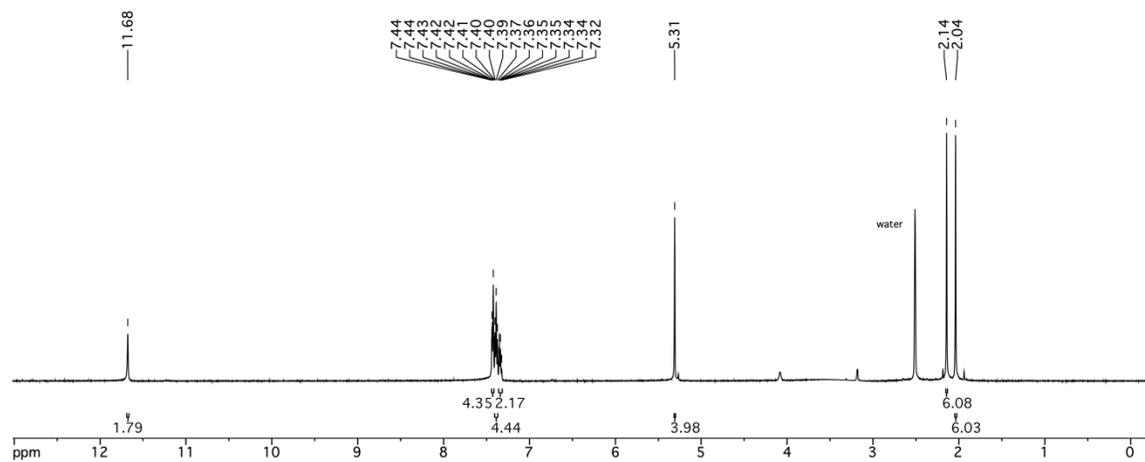
## <sup>13</sup>C NMR (CDCl<sub>3</sub>)



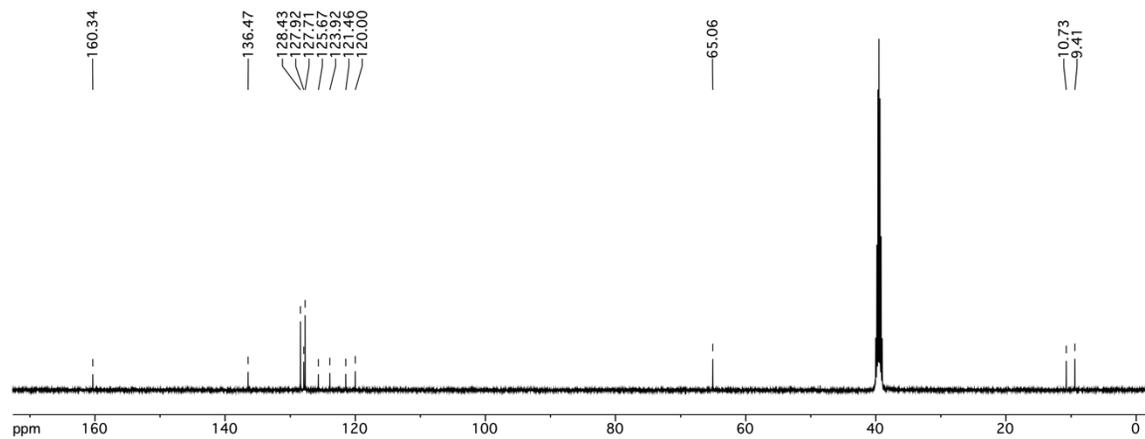
# Benzyl Ester 3,4-Dimethyl-5-chloro-1H-pyrrole-2-carboxylic Acid (121)



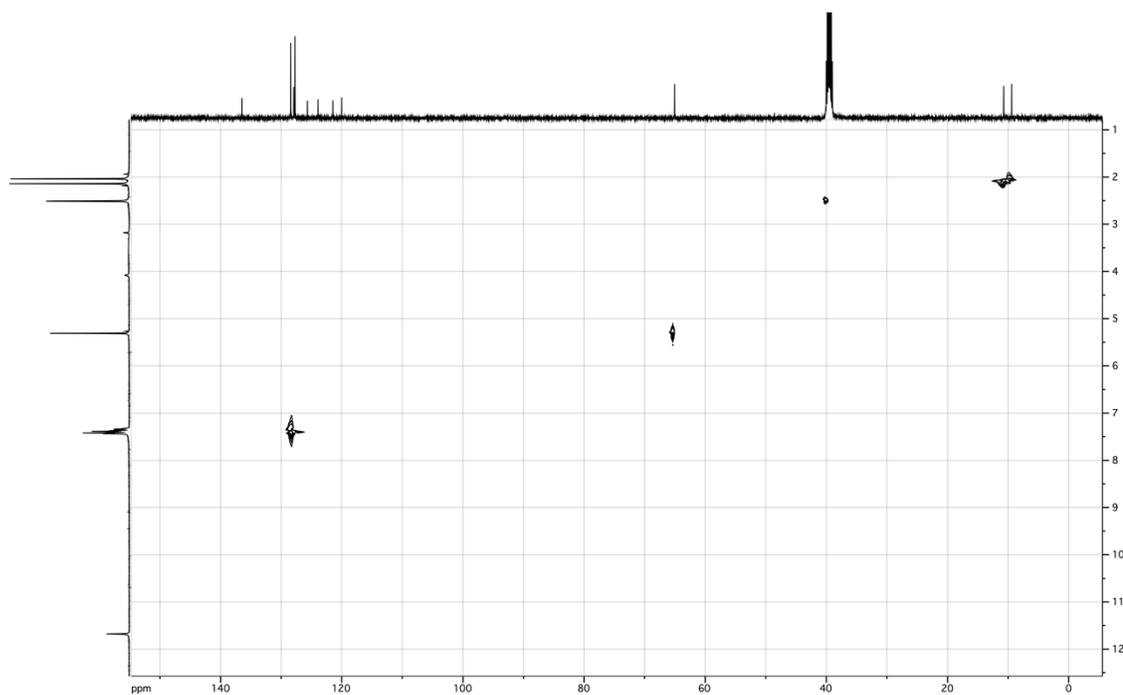
## <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)



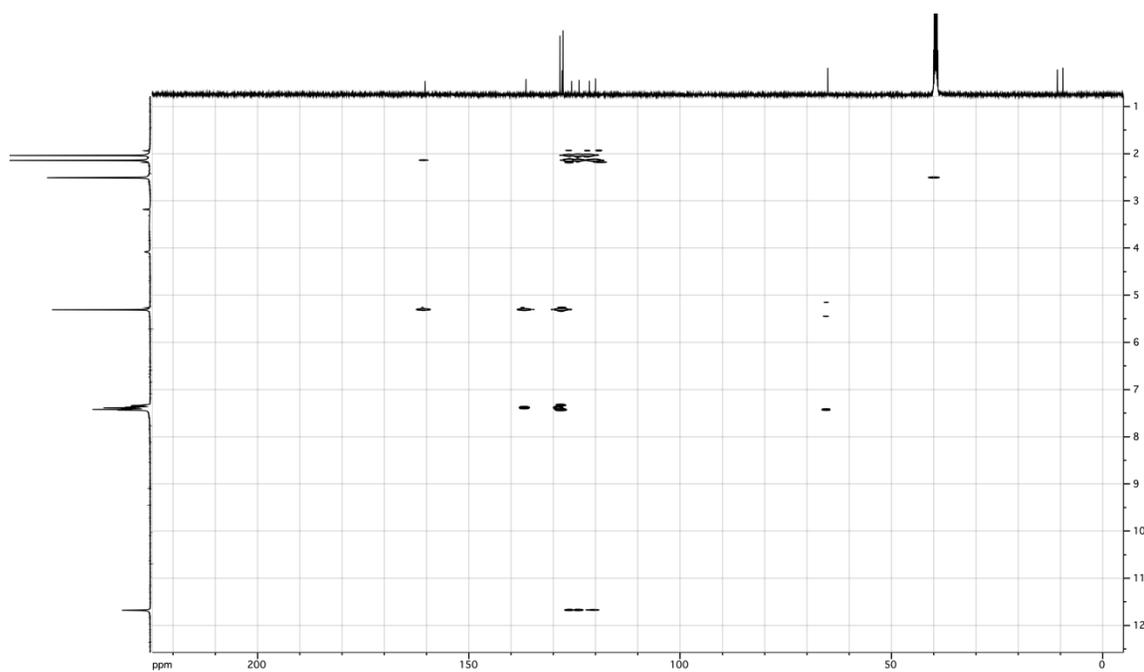
## <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>)



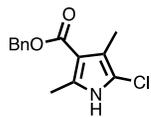
### HSQC NMR (DMSO-*d*<sub>6</sub>)



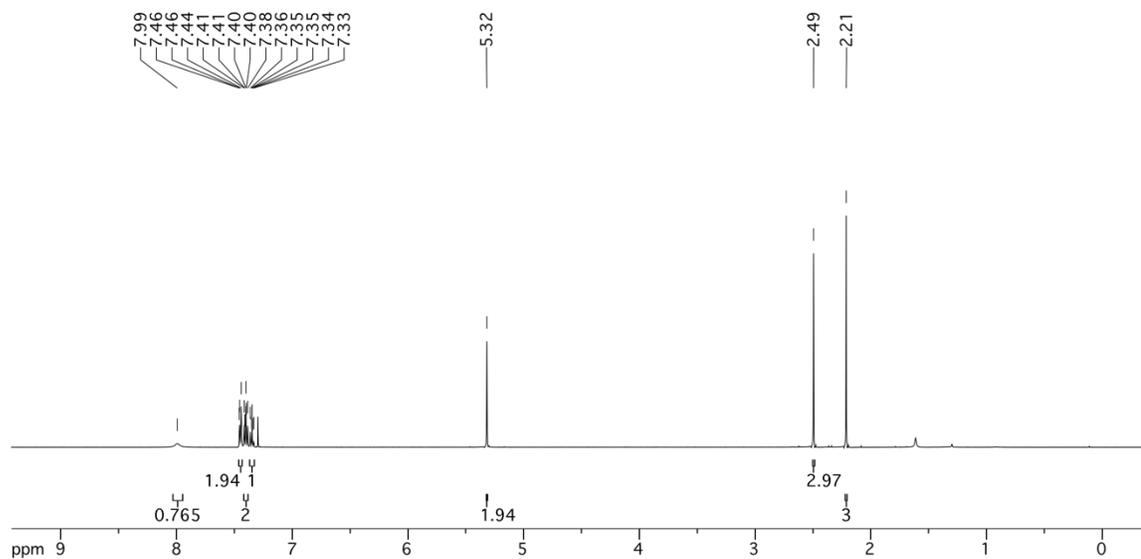
### HMBC NMR (DMSO-*d*<sub>6</sub>)



## Benzyl Ester 2,4-Dimethyl-5-chloro-1*H*-pyrrole-3-carboxylic acid (122)



### <sup>1</sup>H NMR (CDCl<sub>3</sub>)



### <sup>13</sup>C NMR (CDCl<sub>3</sub>)

