The Synthesis of Prodigiosene-Based Anticancer Reagents and Development of Reactions for Dipyrrin-Based Molecules

by

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Abstract

Prodigiosenes, dipyrrins and *F*-BODIPYs are related pyrrolic compounds that share a common, conjugated backbone structure composed of an adhered pyrrole and azafulvene unit. Prodigiosenes are tripyrrolic compounds isolated from the *Serrantia* and *Streptomyces* genus of bacteria. In addition to possessing an array of immunosuppressive activities, they also exhibit the capacity for the induction of apoptosis in malignant cells. Dipyrrins are a main component of a variety of porphyrin-based, biologically relevant molecules, including many precursors along the pathway to molecules such as heme and vitamin- B_{12}. They are themselves very strong chromophores, and have historically been utilized as dyes. *F*-BODIPYs are boron complexes of dipyrrins, and possess highly fluorescent character. These molecules are significantly more stable than their dipyrrin precursors, enabling their use in a vast quantity of important active fields of research.

The first project investigated involves the synthesis of several prodigiosenes containing short-chain, ester-substituted moieties. The anticancer properties of these molecules were determined utilizing the NCI 60-cell line screen. One molecule containing a pentyl-ester chain showed promise as an anticancer agent, and was further tested in a toxicity assay as well as using a hollow-fibre assay. The cross-membrane ion transport properties of this compound were also examined using an egg-yolk 1-phosphatidylcholine model, and these results validated via competitive protonation of a native prodigiosin analogue. In addition to the synthesis of these prodigiosenes, preliminary work examining the use of decarboxylative coupling as a replacement for the low-yielding Suzuki-coupling step is also reported.

The second project investigated focuses on the synthesis and characterization of compounds arising from 1-methylated dipyrrins. Microwave heating under pressurized conditions facilitates deuterium labelling of the 1-methyl group using protic, deuterated solvents. This reactivity is deactivated by the presence of acyl-substitution at the adjacent 2-position. Conjugate addition with *N*-phenylmaleimide has generated a new class of dipyrrins bearing 2,5-dioxo-1-phenylpyrrolidin-3-yl pendant groups at the 1-methyl position. Moreover, the first isolation of a 1-(methylenedipyrromethane)-dipyrrin, an unstable intermediate in the formation of 1-(vinylpyrrolyl)-dipyrrins, is also described.

The final project investigated describes syntheses pertaining to of *F*-BODIPYs. The first portion of the report focuses on substitution reactions at the boron atom of the simplest, unsubstituted *F*-BODIPY. Attempted alkylation, alkoxylation and arylation reactions of this framework are reported. Chlorination to form the *Cl*-BODIPY is described, as is decomplexation from this form to generate the stable salt of the otherwise unstable unsubstituted dipyrrin core. The second portion of this project focuses on sulfination reactions of Knorr-type 1-ester pyrroles. Crystal structures of thiono-ester pyrroles are discussed, as is the first reported 1,3,2-thiazaphosphole derived from pyrrole. The generation of *F*-BODIPY products from alkyl-substituted, Knorr-type 1-ester pyrroles under microwave heating conditions is also reported. This reaction represents a four-step, one-pot process (averaging approximately 65% yield per step) to form high-value *F*-BODIPY products from simple starting materials.

List of Abbreviations Used

δ: Chemical shift

Boc: *tert*-Butylcarbonyl

bs: Broad singlet

CCDC: Cambridge Crystallographic Data Centre

$CDCl_3$: Deuterated chloroform

d: Doublet

DABCO: 1,4-Diazabicyclo[2.2.2]octane

DDQ: 2,2-Dichloro-5,6-dicyano-1,4-benzoquinone

DIPEA: Diisopropylethylamine

DMAP: Dimethylaminopyridine

DMSO: Dimethylsulfoxide

DME: Dimethoxyethane

EDC: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide

Eq.: Equivalents (figures and tables only)

ESI^+: Positive ion detected electron spray ionization

EYPC: Egg-yolk 1-phosphatidylcholine

F-BODIPY: 4,4-Difluoro-4-bora-3a,4a-diaza-*s*-indacene

GI_{50}: Growth inhibition, 50%

HMBC: Heteronuclear multiple bond correlation

HSQC: Heteronuclear single quantum coherence

IP: Intraperitonial

IUPAC: International Union of Pure and Applied Chemistry

J: Coupling constant

LC_{50}: Lethal concentration, 50%

LCQ: Liquid Chromatography Quadrupole

LiHMDS: Lithium bis(trimethylsilyl)amide

m: Multiplet

MeOD: Deuterated methanol

MS: Mass spectrometry

MSA: Methanesulfonic acid

m/z: Mass to charge ratio

NCI: National Cancer Institute

q: Quartet

s: Singlet

SC: Subcutaneous

SEM: [2-(Trymethylsilyl)ethoxy]methyl acetal

t: Triplet

TEAB : Triethylammonium bromide

TF_2O : Trifluoromethanesulfonic anhydride

TGI : Total growth inhibition

TLC : Thin-layer chromatography

TMSOTf: Trimethylsilyl trifluoromethanesulfonate

TOF: Time of flight

UDEFT: Uniform driven equilibrium Fourier transform

Acknowledgements

I would like to begin by expressing my sincerest gratitude for my supervisor, Dr. Alison Thompson. Her guidance has enabled my development both academically and professionally; the importance of her unwavering support throughout the duration of this degree cannot be overstated, and I am truly grateful. I also wish to extend my thanks to Dr. Jean Burnell, Dr. Laura Turculet and Dr. Alex Speed for acting as my committee, and for their aid throughout my degree, as well as in the process of writing this thesis. I wish to acknowledge the National Science and Engineering Research Council of Canada, The Killam Trusts, and The Beatrice Hunter Cancer Research Institute for financial support.

I would like to thank several researchers both at Dalhousie and abroad for their contributions: Dr. Stanley Cameron (Dalhousie) and Katherine Robertson (Saint Mary's University) for their work relating to X-ray crystallography; Dr. Mike Lumsden (Dalhousie) for assisting with NMR experiments; Mr. Xiao Feng (Dalhousie) for recording and processing the mass spectra of my compounds; Dr. Jeff Davis (Maryland) for performing the prodigiosene anion transport experiments reported herein; and all of the support staff within the Department of Chemistry who made this research possible.

I also wish to acknowledge past and current colleagues; much of the work presented in this thesis is the product of the discussions they have shared with me over the years: Dr. Sarah Crawford, Dr. Estelle Marchal, Dr. Deborah Smithen, Dr. Carlotta Figliola, Dr. Md. Imam Uddin, Dr. Jennifer Melanson, Travis Lundrigan, Cassandra Hawco, Michael Beh, Sarah Greening, as well as the dozens of undergraduate students I have had the pleasure of working with.

Finally, I wish to thank my family. My wife, Claudia, and my step-daughter, Joëlle: your patience, encouragement and support are an integral part of this document. To my parents, Steve and Juanita Groves: you have always encouraged me to pursue my dreams and aspirations. I can't thank you enough for this. I also wish to thank my brother, Colin Groves, as well as my parent-in-laws, Robert Tremblay and Carole L'Ecuyer, whose continued support has been invaluable during this degree.

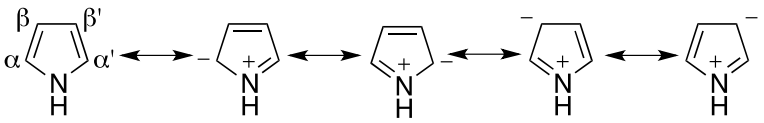
Chapter 1: Introduction

Section 1.1: An Overview of Pyrrole

Pyrroles are a well-studied class of chemicals that are found in a variety of diverse and synthetically distinct constructs. The earliest report of pyrrole describes isolation of a red-oil from coal tar, and is dated to 1834;[1] the structural formula of the compound would later be determined in 1870.[2] The discovery of pyrrole as a fundamental component of many important biologically relevant compounds such as heme,[3] chlorophyll,[4] and vitamin B_{12},[5] propagated research in pyrrolic syntheses during the first half of the 20th century. The role of pyrrole as the major building block for porphyrins has resulted in pyrrole being one of the best-studied heterocyclic frameworks of the past hundred years. As a result, pyrrole and its extended frameworks continue to be used in a variety of fields of research that span beyond the scope of this introduction.

IUPAC naming of pyrroles dictates assignment of the nitrogen atom as position 1, with subsequent numbering continuing around the ring, with accordance to functionality. In the case of symmetric systems, a 2:2' and 3:3' nomenclature is commonly used to differentiate identical or related carbon positions. Use of α- and β-designations to describe the 2 and 3 positions are ubiquitous in the literature, and stem from historical syntheses of porphyrin species.

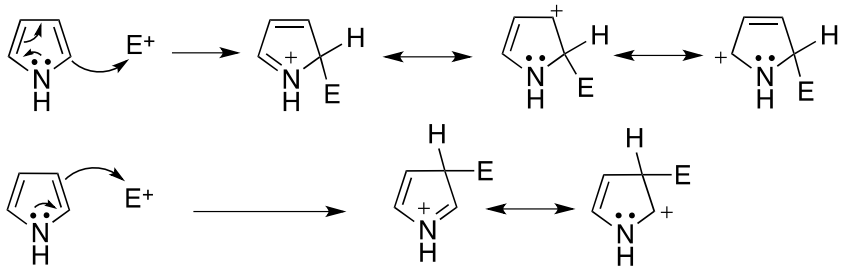
Figure 1-1: **Pyrrole and its resonance forms**



1-1

The chemistry of the pyrrole ring arises as a function of the resonance forms present within the ring due to delocalization of the lone-pair electrons present on the nitrogen atom (Figure 1-1). Delocalization of the electrons facilitates an aromatic, 6 π-electron structure, increasing stability of the pentacyclic ring relative to the isoelectronic cyclopentadiene. Although pyrrole is best described as a neutral, non-zwitterionic molecule, contribution from the resonance forms bearing formal charge results in significant electron density at both the α- and β- positions. As a result, electrophilic addition at both the α- and β-positions is enabled, with reaction of the α-position occurring preferentially. This phenomenon can be explained through calculation of electron densities by theoretical means,[6] however, electrophile-pyrrole cation complexes can also be used to rationalize this preference (Figure 1-2).

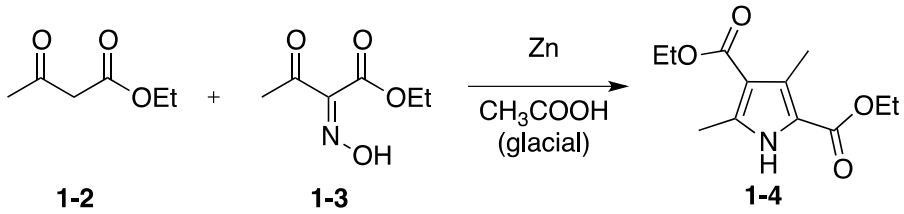
Figure 1-2: **Resonance forms of α- and β-electrophile-pyrrole complexes**



Three contributing resonance forms stabilize the α-electrophile intermediate, while attack at the β-position results in only two. In general, a mixture of both α-(major) and β-(minor)substituted products is obtained when pyrrole is reacted with an electrophile. Exclusive formation of the β-substituted product can be achieved, but requires either substitution of the α-positions with non-hydrogen functionalities, or the use of a specific, sterically-hindering *N*-protecting group such as TIPS.[7] Like most aromatic rings, the reactivity of pyrrole is heavily modified by the presence of electron-withdrawing and

electron-donating functionalities appended to the ring. Furthermore, many synthetic methodologies for making pyrroles introduce electron-withdrawing groups in the process. This is due, in part, to these syntheses being derived from the first synthesis of pyrrole reported by Knorr in 1884 (Scheme 1-1).[8]

Scheme 1-1: **Knorr pyrrole synthesis**

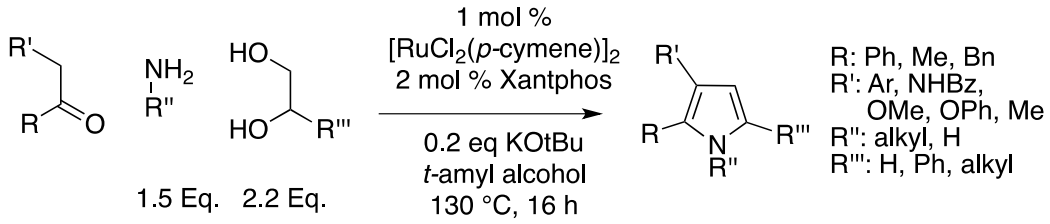


1-2 **1-3** **1-4**

Due to the convenience with which this reaction can be modified and scaled, the 2,4-dicarboxylate and 3,5-dimethyl substitution pattern is pervasive in syntheses utilizing pyrroles. Indeed, nearly every pyrrole reported in this thesis is derived from a modified Knorr reaction.

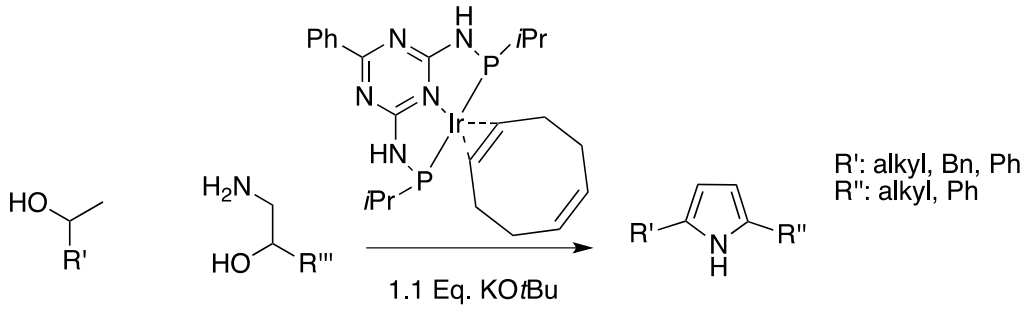
Modern syntheses of pyrrole are an active field of research. A brief literature search will return numerous methodologies developed within the past several years. [9-18] Many of these procedures use specialized molecules as starting materials, and complex reagents to facilitate the transformation. As pyrroles are often the central building blocks for more complicated molecules, especially in drug design, the capacity to introduce complicated substitution patterns has become increasingly vital in pyrrole syntheses.

Scheme 1-2: **Ruthenium-catalyzed pyrrole synthesis developed by Beller *et al.***



Multi-component reactions, such as the one developed by Beller *et al.* (Scheme 1-2),[19] are now commonly employed when a small amount of a specially-substituted compound is required. Furthermore, the rise of metal-catalyzed reactions has had a significant influence on pyrrole syntheses. Although base-promoted reactions have historically been preferred for making pyrroles, much of the new, high-impact, literature has utilized metal-mediated transformations. As an example, the iridium-catalyzed synthesis developed by Kempe and Michlik (Scheme 1-3) makes use of simple molecules derived from renewable feedstocks.[20]

Scheme 1-3: **Iridium-catalyzed synthesis developed by Michlik and Kempe**

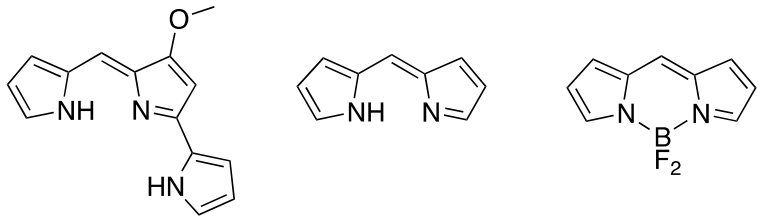


A full description of the scope of pyrrole syntheses would be gratuitous provided the intended use of this document. However, it is important to recognize the significance of pyrrole synthesis as an active field of research.

Section 1.2: Prodigiosene, Dipyrrin and *F*-BODIPY Pyrrolic Scaffolds

The work reported in this thesis focuses on molecular scaffolds composed of two and three pyrrole units. The specific frameworks studied are called prodigiosenes, dipyrrins and *F*-BODIPYs (Figure 1-3).

Figure 1-3: **Prodigiosene, dipyrrin and *F*-BODIPY**



PRODIGIOSENE **DIPYRRIN** ***F*-BODIPY**

All three of these molecules possess a central, fully conjugated, planar 2-azafulvene pyrrole, or dipyrrin, unit. This central core is responsible for strong absorbance bands in the visible region of the electromagnetic spectrum; consequently, these compounds are intensely coloured, ranging between yellow to deep purple coloration.

Although all three motifs share underlying physical similarities, the subtle structural changes in prodigiosenes and *F*-BODIPYs result in significant modifications to their chemistry and practical use, relative to dipyrrins. Prodigiosenes, possessing an appended tertiary pyrrole ring and alkoxy substituent, act as efficient ion-transporters in cellular environments. This activity garners significant anticancer properties. For this reason, modern chemical research on prodigiosene frameworks is based on improving the methodologies for synthesizing the tripyrrolic framework with various functionalities appended around the ring.[21] Research improving the synthesis of dipyrrins has not significantly progressed in over fifty years, as direct modification of the core is hindered by reactivity for both nucleophiles and electrophiles in the decomplexed, or free-base, state. Regardless, dipyrrins and their metal complexes continue to be a topic of modern research.[22] They are frequently synthesized as intermediates for porphyrins,[23] corroles[24] and chlorins,[25] and are synthesized for a variety of modern purposes. For example, dipyrrin-metal complexes have recently been utilized to develop nanosheet materials,[26]

and have found use in catalytic *N*-group transfer chemistry.[27] Although many dipyrrin-metal complexes exhibit fluorescence,[22] boron-dipyrrin complexes, or *F*-BODIPYs, have exceptional fluorescence qualities and rugged chemical stability relative to many other regularly-used fluorescence scaffolds.[28] For this reason, synthesis of these frameworks is a remarkably active field of research; dozens of articles using *F*-BODIPYs are published each month, as of June 2017.

Research focusing on all three of these frameworks is presented in this thesis. Due to the relative chemical diversity of these scaffolds, each subsequent chapter has been individually dedicated to research focusing specifically on one of the three frameworks. Each chapter contains an introduction to the substrate being studied, as well sections for results and discussion, conclusion and experimental. Chapter 2 focuses on the synthesis of several prodigiosenes containing ester functionalities bearing linear chains of three to six carbons. These compounds were synthesized and characterized, and their anticancer properties were then determined via submission to the National Cancer Institute for analysis using the NCI 60-cell line screen. One of these molecules exhibited sufficiently potent properties as to be selected for testing in a toxicity assay, and was also subjected to testing in a hollow-fibre assay. As an excess of this compound was synthesized, the cross-membrane ion transport properties of this compound were also examined using an egg-yolk 1-phosphatidylcholine model, and these results validated via competitive protonation of a native prodigiosin analogue. In addition to the synthesis of these short-alkyl chain prodigiosenes, preliminary work was performed examining the potential for use of decarboxylative coupling as a replacement for the low-yielding Suzuki-coupling step is also reported with the chapter. This involved testing the process on an assortment

of electron-poor pyrroles, as well as attempting the procedure on a dipyrrin and dipyrromethane.

Chapter 3 focuses on dipyrrins, or more specifically, the reactivity of 1-methylated free-base dipyrrins; the synthesis and characterization of new compounds arising from this reactivity is explored. The isolation of a 1-(methylenedipyrromethane)-dipyrrin, an unstable intermediate in the formation of 1-(vinylpyrrolyl)-dipyrrins that arises through reactivity of the 1-methyl functionality, is explored. Furthermore, microwave heating under pressurized conditions was used to facilitate deuterium labelling of the 1-methyl group in the presence of protic, deuterated solvents. Regioselectivity in this reaction was induced by the inclusion of acyl-substitution at the adjacent 2-position of the dipyrrin; this inhibition is not global, and does not affect distal 1'-methyl functionalities. Furthermore, conjugate addition reactions to the 1-methyl position with *N*-phenylmaleimide were explored, and a set of dipyrrins bearing 2,5-dioxo-1-phenylpyrrolidin-3-yl pendant groups was generated.

Chapter 4 focuses on synthetic work pertaining to *F*-BODIPYs. The first section discusses reactions of the fully unsubstituted *F*-BODIPY. This molecule was only recently characterized, and represented the only stable form of the unsubstituted dipyrrin core. Attempted alkylation, alkoxylation and arylation reactions of this framework are reported in this thesis. Chlorination of the *F*-BODIPY was performed to generate the *Cl*-BODIPY, as was decomplexation from this form to generate the HCl salt of the parent unsubstituted dipyrrin core. This salt was stable to ambient conditions, and facilitated the first characterization of the dipyrrin core. The second section of this chapter focuses on sulfination reactions of Knorr-type 1-ester pyrroles, and their utility in the generation of

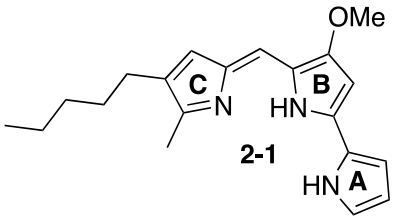
F-BODIPYs. Crystal structures of the starting material thiono-ester pyrroles are discussed, as is the side product of their generation: a 1,3,2-thiazaphosphole derived from pyrrole. The synthesis of *F*-BODIPY products from alkyl-substituted, Knorr-type 1-ester pyrroles under microwave heating conditions is then discussed. This reaction represents a four-step, one-pot process (averaging approximately 65% yield per step), and generates high-value *F*-BODIPY products from simple starting materials. The thesis is then concluded with a conclusion chapter, reiterating the conclusions of Chapters 2 through 4.

Chapter 2: Prodigiosene-Based Anticancer Reagents

Section 2.1: Background Information Regarding Prodigiosin

Prodigiosin is a red pigment belonging to a family of tripyrrolic alkaloids first isolated from Serratia and Streptomyces bacterial strains in 1929.[29] In the early sixties, a complete structure was conclusively derived via total synthesis by Rapoport and Holden (Figure 2-1).[30]

Figure 2-1: **Prodigiosin**

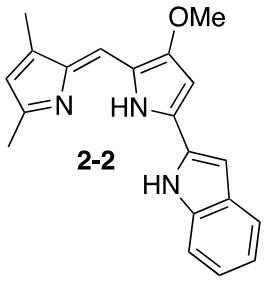


The term prodigiosene was coined first by Hearn *et al.* as a means to differentiate between the parent pyrrolyldipyrromethene skeleton, prodigisosin, and its natural and synthetic analogues.[31] Prodigiosenes exhibit a variety of biological activities in metabolic processes, and have been shown to influence human immune response, antibiotic activity and cell-proliferation.[32-34] The use of prodigiosin and its analogues as therapeutic agents for the treatment of various cancers is storied: as early as 1893, William Coley was treating patients with a vaccine composed of killed bacteria, including *Serratia marcescens.*[35] Vaccination with these toxic mixtures continued throughout the 19th century, ending upon assignment of Coley Toxin as a "new drug" in the wake of the thalidomide crisis during the sixties. Interest in prodigiosenes as therapeutics was renewed with development of novel synthetic methodologies in the latter half of the

twentieth century: variation of the prodigiosin core, and subsequent evaluation of these molecules as potential anticancer agents, has flourished in recent years.

The anti-proliferative activity of prodigiosenes has been studied extensively. It has been determined that cell death arises from both apoptotic (induction of programmed cell death via activated cell-controlled pathways) and necrotic (destructive cell death) mechanisms, and is certainly non-singular.[36-40] Copper-assisted cleavage of double-stranded DNA has been shown to occur,[41-45] whereby intercalation of a prodigiosin-Cu(II) complex is observed within DNA base pairs, resulting in destruction of the DNA. Furthermore, cross-membrane H/Cl ion transport has been repeatedly cited as an important component of prodigiosene cytotoxicity.[43,46-49] Toxicity of prodigiosenes has also been attributed to inhibition of the Bcl-2 family of anti-apoptotic proteins.[50] Obatoclax (**2-2**,Figure 2-2), an indole-prodigiosene currently undergoing Stage II clinical trials for treatment of leukemia and lymphoma,[51] has been shown to activate apoptosis via induction of the Bcl-2 family of proteins. Prodigiosenes exhibit other reactivity within the cell, such as phosphate inhibition[52] and intercalation of G-quadruplex DNA.[53] In summary, the reactivity of prodigiosenes within the cell is complex, and continues to be an active area of research.

Figure 2-2: **Chemical structure of Obatoclax**

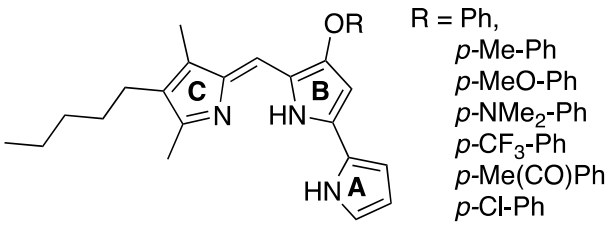


2-2

The inherent toxicity of prodigiosenes limits their use in clinical trials; indeed, the therapeutic window between an effective dose and a toxic dose of a prodigiosene is too narrow for innocuous treatment.[54] Several different strategies are used by chemists to increase the efficacy of small molecule drugs in anticancer treatment. To increase uptake of the toxic drug (in our case, prodigiosenes), molecular moieties that target tumour cells are often attached to the drug. By attaching moieties that target the cancer cells, uptake in healthy cells is relatively reduced, thereby reducing the effective toxicity of the drug. Prodigiosin-bioconjugate synthesis is an active area of research within the Thompson group,[55] and continues to be a popular approach for exploring prodigiosin as a cancer-treatment reagent.

Alternatively, selective uptake of small molecules in tumours can be promoted through modification of the structural features of the anticancer compound. These changes to the core may facilitate a preference for uptake in malignant cells, as opposed to healthy tissues. The correlation between the cytotoxic activity of the derivatives, and changes to the structure are known as structure-activity relationships, or S.A.R.s. Structure-activity studies of prodigiosin have established that the tri-pyrrolic core is essential for induction of the anticancer effects.[43,45,56,57] It has been shown that the nature of the β-alkoxy substituent of the pyrrolic B ring is critical to the observation of cyto-toxic effects in prodigiosene.[58,59] Recent studies within the Thompson group have shown that anticancer activity is preserved when the methyl functionality is replaced with a variety of *p*-substituted phenyl derivatives (Figure 2-3).[60]

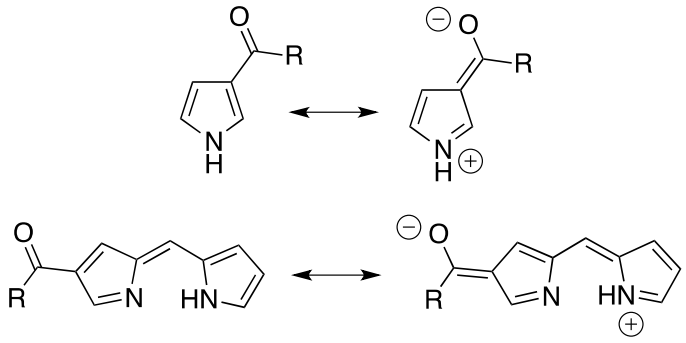
Figure 2-3: **Prodigiosin B-ring analogues**



Due to the long-believed importance of the B-ring alkoxy substituent, most S.A.R.s for prodigiosenes have been determined via analysis of compounds that have been functionalized at the A- and C-rings of prodigiosene.

Within the Thompson research group, a facile method for the development of C-ring functionalized prodigiosenes has been developed and used to produce a wide assortment of variants.[60-64] The inclusion of acyl-functionality at the 3-position of the C-ring has eased the handling of otherwise unstable mono and bis-pyrrolic intermediates. Withdrawal of electron density from the pyrrolic nitrogen atom reduces the inherent nucleophilicity of the pyrrole moiety (Figure 2-2).

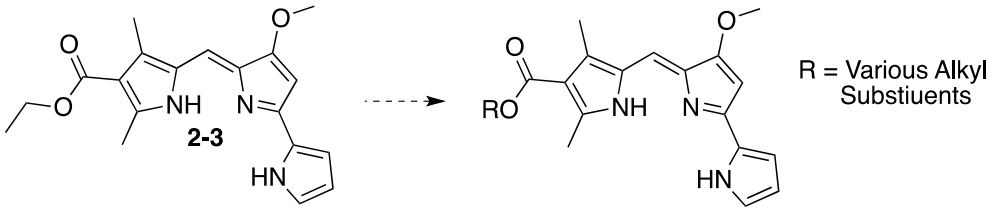
Figure 2-2: **β-Carbonyl resonance in pyrrole and dipyrrin**



Testing of Thompson-group derivatized prodigiosenes as potential substrates for medical use is performed by collaborators at the National Cancer Institute (NCI). The NCI possesses the capacity for high-throughput screening against 60 different human cancer cell lines, including variants representing leukemia, melanoma and cancers of the

lung, colon, brain, ovary, breast, prostate, and kidney cancers. An initial screen performed by Regourd *et al.* revealed an ethyl ester derivative, **2-3** (Figure 2-4), that retained much of the anticancer activity of prodigiosin, **2-1** (Figure 2-1).[64]

Figure 2-4: **C-Ring modified prodigiosene 2-3 and potential targets**



In addition to an impressive cytotoxic profile, **2-3** retained significant capacity for H^+/Cl^- transmembrane ion transport, relative to other 3-carbonyl prodigiosenes.[51] The presence of the carbonyl group does significantly reduce the basicity of the dipyrrin moiety, and can be used to rationalize this change. The propensity of **2-3** for copper(II) mediated DNA cleavage was also determined, and found to be slightly less that the parent compound. The ease of synthesis of **2-3**, and the maintenance of the key biological characteristics of the prodigiosene core made the synthesis of various alkyl ester derivatives an attractive goal.

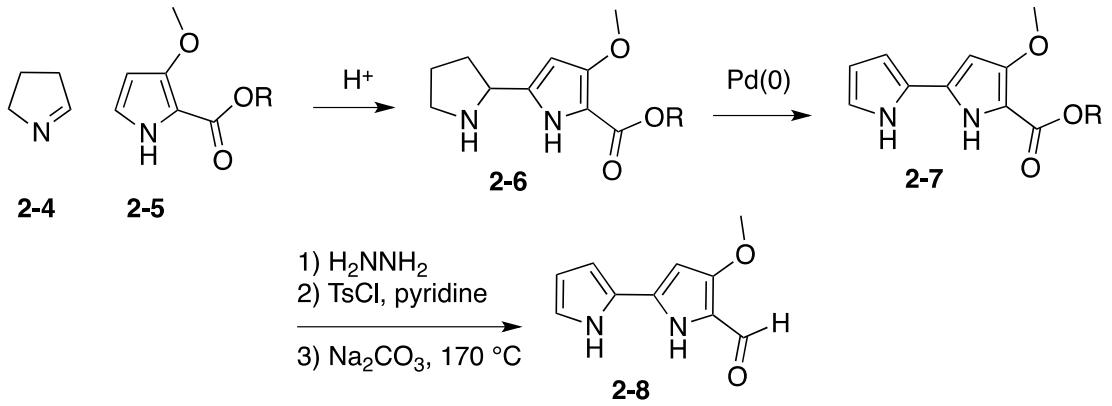
Section 2.2: Reported Synthesis of Prodigiosenes

As mentioned previously, the first total synthesis of prodigiosin was performed by Rapoport and Holden,[65] whose methodology hinged upon development of chemistry for the synthesis of 2,2'-bispyrrole **2-8** (

Scheme 2-1). Condensation of the methoxy-containing B-ring **2-5** with 1-pyrroline **2-4** was performed, to generate a saturated A-ring intermediate, **2-6**. Subsequent Pd(0)-catalyzed dehydrogenation produced the unsaturated variant **2-7**.

Finally, a McFayden-Stevens reduction of the ester to an aldehyde was performed to produce intermediate **2-8**.

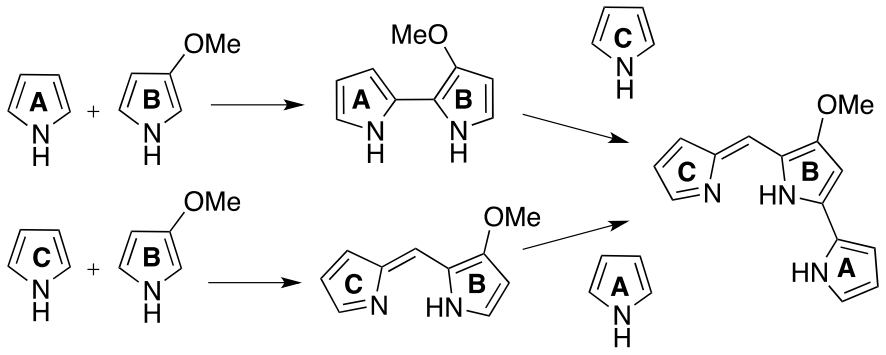
Scheme 2-1: **Rapoport and Holden's synthesis of on route to prodigiosin 2-1**



The final reduction step was low yielding (formation of **2-8**), usually between 20 and 40%. Despite the low yields, this methodology for installation of the formyl group remained popular for the synthesis of **2-1**, as well as other prodigiosenes, well into the nineties.[46,66] However, the need for the dehydrogenative step has been essentially eliminated by the popularization of aryl-aryl cross-coupling chemistry.

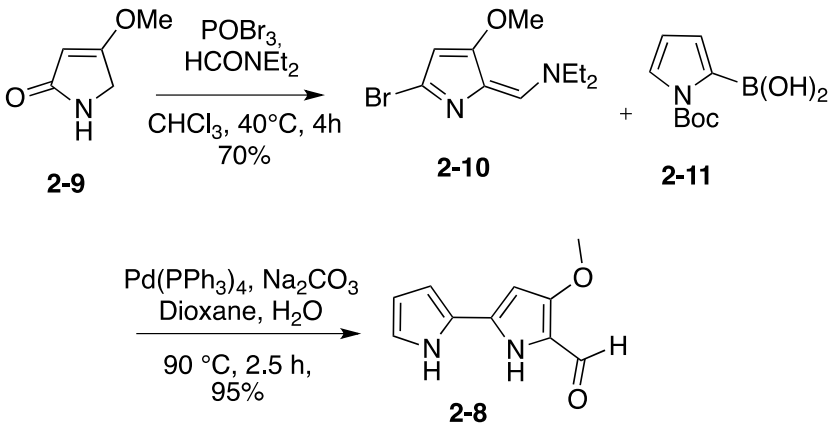
No route to prodigiosenes has risen as the single, optimal synthetic approach. This is due largely to the two disconnection strategies that can be straightforwardly proposed: synthesis of the A-B ring bond, followed by attachment of the C ring (Figure 2-5, top) is certainly possible, as described above. Alternatively, formation of the C-B connection, followed by cross coupling to attach the A ring (Figure 2-5, bottom), can be proposed.

Figure 2-5: **Prodigiosene disconnection strategies**



The top, [A+B]+C, approach used by Rapopoprt and Holden fell out of favour in the late nineties, but enjoyed a revival in use, due to the work of Lavallée *et al.* in 2006 (Scheme 2-2).[67] From the readily available pyrrolinone **2-9**, generation of the bromo-eneamine pyrrole **2-10** was achieved in high yields. A Suzuki coupling with *N*-Boc pyrrole-2-boronic acid (**2-11**) afforded the bi-aryl aldehyde, **2-8**. Subsequent condensation of **2-8** with an appropriate 2-H pyrrole would afford the desired prodigiosene.

Scheme 2-2: **Lavallée's method for prodigiosene synthesis**

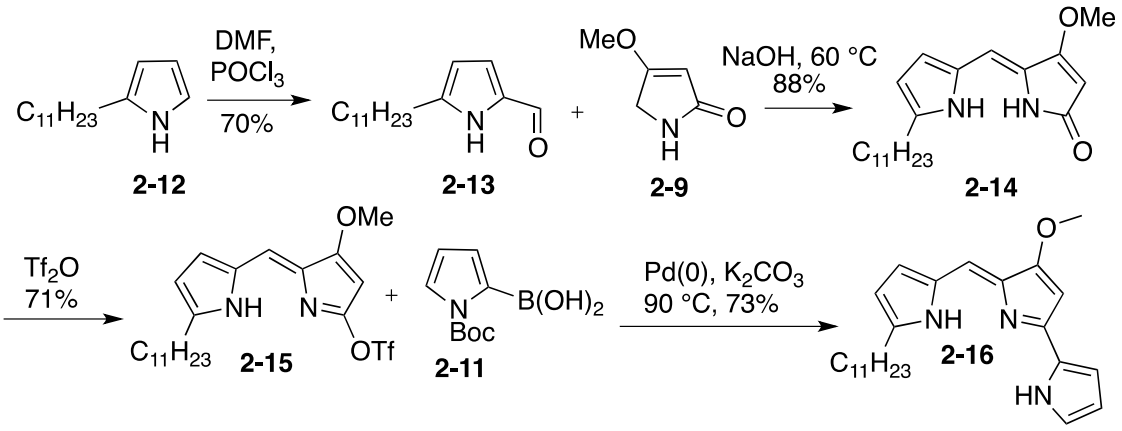


Supplanting the need for the typically low yielding McFayden-Stevens reduction was a significant development. This methodology is versatile, as a variety of synthetic prodigiosenes have been prepared using this methodology. Indeed, the aforementioned

Obatoclax (Figure 2-2) is produced according to this method.[68] The process has also been shown to be scalable to the kilogram scale. Unfortunately, inconsistencies regarding the reproducibility of the described bromo-formylation have been noted. Indeed, this process has been met with little success within our research group, and beyond.[69]

The method utilized within the Thompson research group is a modified procedure first described by D'Alessio and Rossi in their synthesis of undecylprodigiosin **2-16** in 1996 (Scheme 2-3).[70] This method has since been used in a variety of syntheses by D'Alsessio and coworkers.[37,39,57,71]

Scheme 2-3: **D'Alessio's method for prodigiosene synthesis**



Using a [C+B]+A approach, D'Alessio and coworkers showed that condensation of a 2-formyl pyrrole, **2-13**, generated using classic Vilsmeier-Haack conditions, with pyrrolinone **2-9** can be readily achieved under basic conditions. This methodology for introduction of the *meso*-carbon atom provided significant advantages compared to use of the McFayden-Stevens reduction. The dipyrrinone produced, **2-14**, was then readily converted to the triflated dipyrrin **2-15** via treatment with triflic anhydride. Subsequently, Suzuki coupling conditions were employed in the presence of Boc-protected pyrrole-α-boronic acid **2-11** to generate the undecylprodigiosin **2-16** in excellent yield. This method

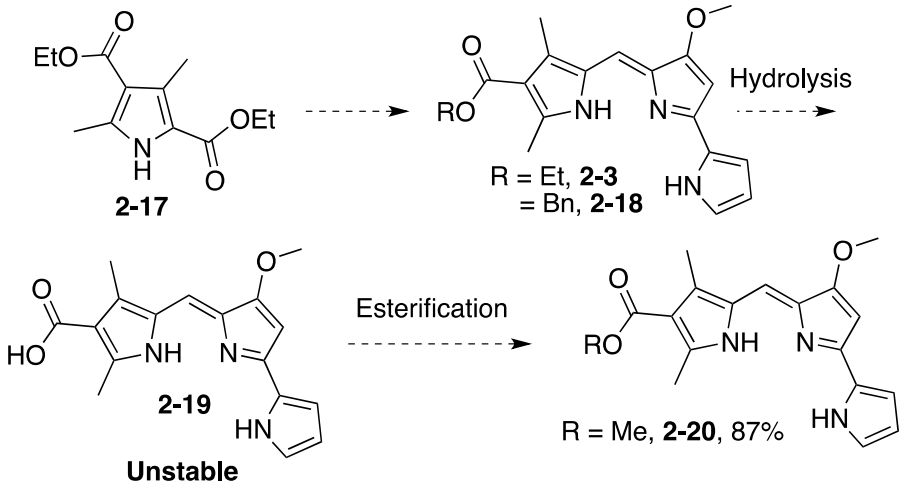
was novel in its synthetic pliability; in theory, synthesis of C-ring modified prodigiosenes was available in three synthetic steps from 2-formyl pyrrole. This methodology has been adapted by the Thompson lab, and modified to generate a large number of prodigiosenes.

Section 2.3: Results and Discussions

2.3.1 Alkyl Ester Prodigiosene Synthesis

The goal of the research project was the production of a number of prodigiosenes bearing short alkyl esters. Due to ease of synthesis of pyrrole **2-17** via Knorr condensation of ethyl acetoacetate, significant quantities of prodigiosene **2-3** were available for experimentation.[63] Ideally, hydrolysis of **2-3** followed by esterification of the resulting acid would yield the target prodigiosenes in a concise manner.

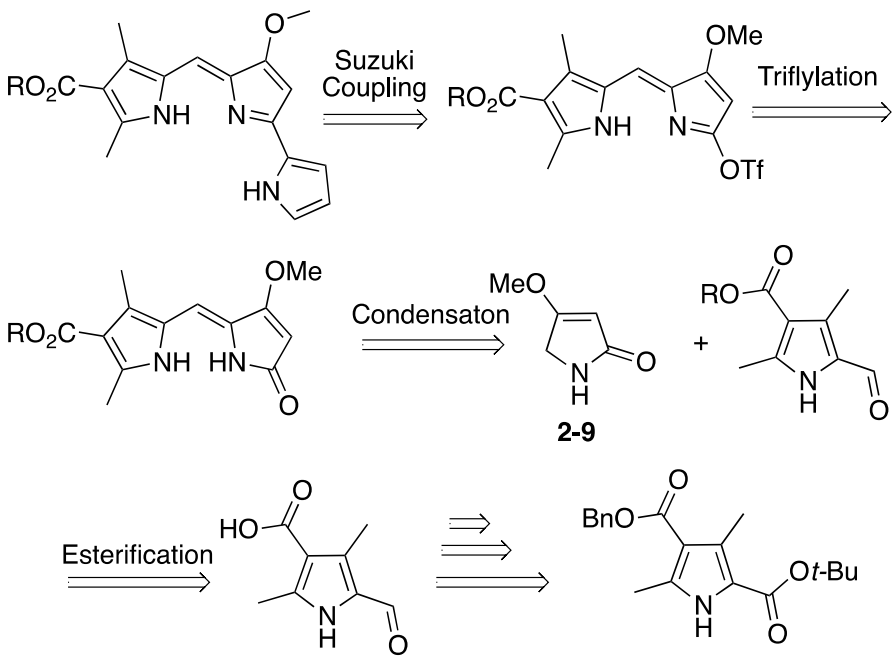
Figure 2-6: **Planned transesterification of 2-3**



A number of attempts were undertaken to realize this reactivity; unfortunately, the prodigiosene acid, **2-19** was determined to be unstable under conditions required for hydrolysis of the ester. Attempts to produce **2-19** also involved the benzyl ester **2-18**, using hydrogenolysis, to no avail. Although mass spectrometry hinted at the presence of

the corresponding decarboxylated product from the crude reaction mixture, no presence of the acid was detectable. Many other attempts to perform this transformation were undertaken by previous members of the Thompson group. Unfortunately, they were equally unsuccessful, save a single example of a methyl-ester product: a high-pressure, microwave-promoted trans-esterification of **2-3** using sodium methoxide in methanol could be used to obtain prodigiosene **2-20** in an 87% yield.[63] Unfortunately, this methodology was not applicable to other esters. Similar attempts to trans-esterify were performed at earlier stages in the synthetic process, but were also unsuccessful. As a result, it was decided that the ester component of the C-ring would be installed earlier in the synthesis. Figure 2-7 shows the retro-synthetic route for this procedure.

Figure 2-7: **Retro-synthetic analysis for ester-substituted prodigiosenes**

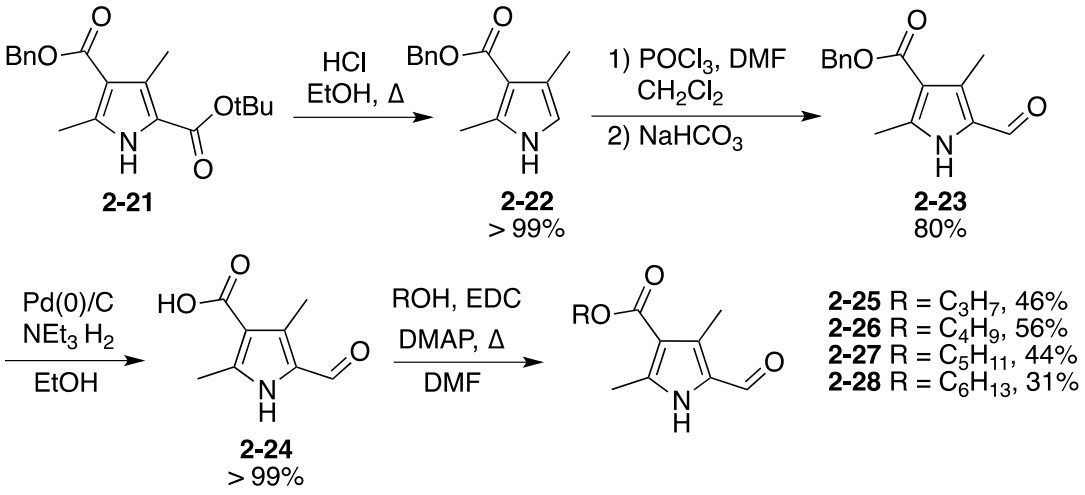


Based on the synthetic approach developed by D'Alessio, the prodigiosene would be generated by Suzuki coupling between *N*-Boc-2-pyrrole boronic acid, **2-11**, and a triflated dipyrrin. The dipyrrin would be accessed through triflylation of a dipyrrinone,

which in turn would be produced through condensation of 4-methoxy-3-pyrrolin-2-one, **2-9**, and the requisite 2-formyl pyrrole. The pyrrole will already possess the desired ester, having had it previously installed from a carboxylic acid. The acid itself would be prepared over several steps from a Knorr pyrrole.

The first portion of the synthesis thus involved preparation of 2-formyl pyrrole esters for conjugation with pyrrolinone **2-9** (Scheme 2-4).

Scheme 2-4: **Synthesis of aldehydes 2-25 to 2-28**



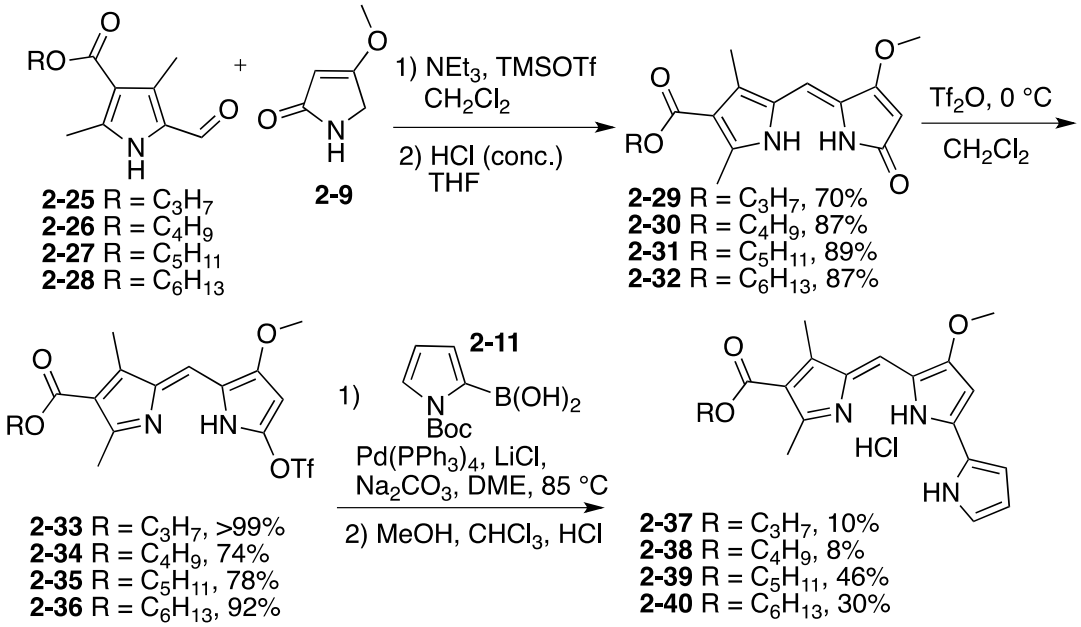
Due to the requirement to differentiate the 2- and 4- esters of the chosen pyrrole for this synthesis, pyrrole **2-21** was selected as the starting material for the synthetic route.[72] Elimination of the *t*-butyl moiety was achieved using acidic ethanol, followed by decarboxylation *in situ* with heating at reflux temperature to quantitatively provide the α-free pyrrole, **2-22**. This compound was carried forward without further purification, and subjected to Vilsmeier-Haack formylation conditions to produce the 2-formyl pyrrole, **2-23** which was purified via crystallization from a solution of 1:1 ethyl acetate/hexanes. Hydrogenolysis of the benzyl ester of **2-23** was achieved in quantitative yield using palladium on activated carbon as catalyst, providing the acid **2-24**. All of the steps to this

point occurred in very good yields, affording sufficient material for production of the ester-containing pyrroles, **2-25** to **2-28**, on gram scale.

Condensation of acid **2-24** with alkyl alcohols was then performed. As the ethyl ester containing prodigiosene **2-3** showed the most promise as an anticancer reagent during the NCI screening process,[64] and as only longer chains had been tested at the time, short-carbon chain alcohols were used as coupling partners. Specifically, propanol, butanol, pentanol and hexanol were used for reaction. Following the Steglich protocol for esterification,[73] the acid **2-24** was treated with EDC and DMAP, and subsequently with the requisite alcohol to promote formation of esterified products. Despite observation of complete consumption of the acid starting material using TLC analysis, isolation of the products **2-25** to **2-28** using aqueous work-up procedures did not result in high yields, instead furnishing between 31% and 56%. Separation of the required esters from residual alcohol remaining in the organic phase was non-trivial, and multiple subjections to flash chromatography were required to obtain purified product. Presumably, some pyrrole-containing material was lost either as the anhydride, as an amide salt of DMAP or EDC, or during the purification process. Regardless, sufficient amounts of pure products were produced to carry forward with the syntheses.

With the esters **2-25** to **2-28** in hand, the literature approach[63] for C-ring derivatized prodigiosenes was continued (Scheme 2-5).

Scheme 2-5: **Synthesis of prodigiosenes bearing short alkyl chain esters**

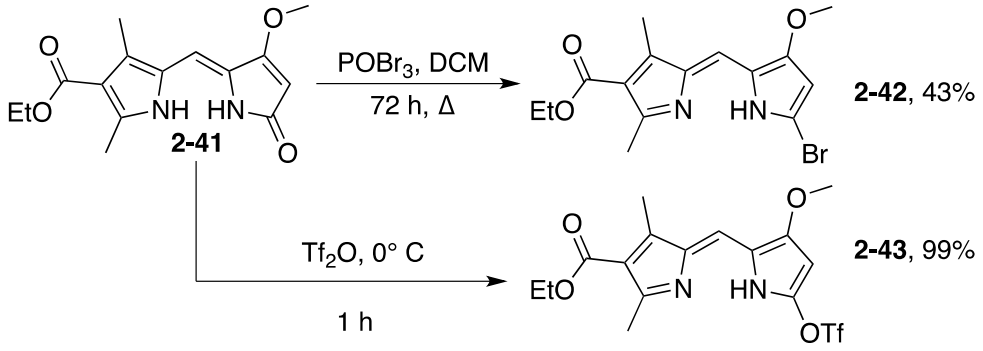


Originally, D'Alessio *et al.* had used strongly basic conditions to achieve the condensation of 2-foryml pyrrole with 4-methoxy-3-pyrrolin-2-one.[70] The yields for this reaction when applied to the synthesis of the first generation of prodigiosin analogues prepared in the Thompson group was between 65 and 69%.[64] Unfortunately, basic conditions are not highly compatible with the presence of the moderately fragile ester moiety, and an alternative set of conditions was developed. A Mukaiyama-type aldol condensation utilizing TMSOTf and triethylamine was used to condense pyrrolinone **2-9** and conjugated-formyl pyrroles.[63] Furthermore, these reactions produced dipyrrinones in higher yields than those reported for the first generation products. Pyrroline **2-9** is synthesized on gram scales in a three-step process, following a literature procedure.[74] After activation of a solution of pyrrolinone **2-9** in dichloromethane with TMSOTf, aldehydes **2-25** to **2-28** were added to the reaction mixture. The reaction was neutralized with phosphate buffer, and the products extracted into dichloromethane. After removal of

the organic solvents, the intermediate aldol products were taken up in THF, and the resulting solution acidified with HCl to induce elimination of the hydroxyl functionality. After concentration, precipitation of the bright yellow solids, **2-39** to **2-42**, was induced via addition of water. The products were produced in very good yield, ranging between 70 and 89%.

Attachment of the final, A-ring of the pyrrole was performed using Suzuki coupling methodology. The boronic acid component, *N*-Boc-2-pyrrole boronic acid **2-11**, is commercially available. Thus, methodology for formation of a suitable activated dipyrrin is required. Two techniques are commonly employed to generate this functionality on dipyrrinones; D'Alessio and coworkers originally employed a triflylation reaction with Tf_2O, introducing a pseudo-halide coupling partner in their synthesis of undecylprodigiosin (Scheme 2-3).[70] Although this methodology has proven versatile, the synthesis of prodigiosene derivatives, especially Obatoclax, performed by Lavallée *et al.* popularized bromination as an alternative for this synthesis.[68] These methodologies, as employed on the ester-containing dipyrrinone **2-41**, are shown in Scheme 2-6.

Scheme 2-6: **Derivatization of dipyrrinone**



Utilization of the bromo-dipyrrins is attractive; these compounds have been reported to be considerably more stable to atmospheric conditions, relative to the triflylated

products.[63] Unfortunately, the rate of bromination is reported to be sluggish, and reaction times are typically on the order of days. The fastest reported time for this process is 17 hours.[61,62] Although some high yields have been reported via this methodology, typically a moderate yield between 50 and 70% is reported. When tested on the readily available ethyl ester-containing dipyrrinone **2-41**, a similar result was indeed observed. The electronic effects of substitution on the distal pyrrole appear to play a significant role in rate of success of the bromination; introduction of acyl functionality, either via an ester or ketone, has been shown repeatedly within the Thompson lab to reduce the effectiveness of the bromination. Conversely, triflylation has been used effectively where acylated dipyrrinones have been reacted.[55,61,63,64] When repeated, a very high yield of dipyrrin triflate **2-43** (99%) was achieved using the same dipyrrinone **2-41**. The procedure is rapid, typically reacting to completion within an hour. Although dipyrrins bearing triflyl-protected alcohols have been shown to occasionally suffer from instability, and sometimes require special care and storage, the electron withdrawing nature of the ester moiety on **2-29** to **2-32** counteracts this. These compounds can be handled without precaution to exclude moisture, and are not susceptible to degradation when stored in a refrigerated environment at -5 °C

Bearing these considerations in mind, conversion of the dipyrrinones to their triflylated derivatives was performed. Dipyrrinones **2-29** to **2-32** were dissolved in dichloromethane and the solutions cooled to 0 °C; subsequently, Tf_2O was added. These reactions were typically complete within an hour, although an additional equivalent of Tf_2O was required in some cases. Upon completion, the reaction was quenched, worked-

up, and the product mixture purified via flash chromatography to produce the bright yellow solids, **2-33** to **2-36** in high yields (Scheme 2-5).

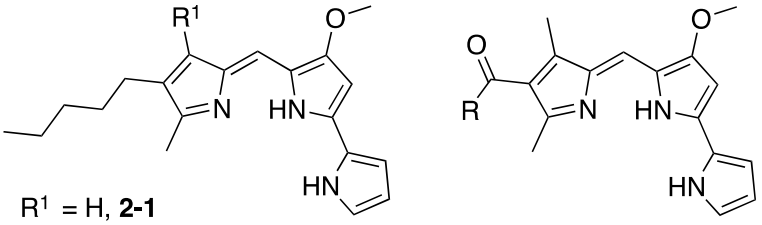
The final step in the synthesis of the prodigiosenes involved Suzuki coupling of the newly generated triflates with *N*-Boc-2-pyrrole boronic acid (**2-11**). The Suzuki coupling procedure for attachment of the A-ring in prodigiosenes has been used in a variety of syntheses, from both bromo- and triflylated- dipyrrins, although the yields vary significantly. The triflates, **2-33** to **2-36**, were dissolved in degassed dimethoxyethane (DME) with lithium chloride, *N*-Boc-2-pyrrole boronic acid **2-11**, sodium bicarbonate and palladium catalyst. The mixture was heated at reflux temperature (85°C), upon which formation of the dark-red prodigiosene products was readily observed via the darkening of the mixture. The reaction mixture was then heated at reflux temperature overnight to enable complete consumption of the starting materials. The prodigiosenes were isolated as free-bases following purification over Brockman (III) basic alumina, and were subsequently treated with HCl to generate the salts, **2-37** to **3-40** in low-to-moderate yields. Although these yields are quite low, the Suzuki coupling of prodigiosenes is reported to be inconsistent at best.[55,61] Indeed, much optimization was required to obtain the conditions utilized for the coupling of these products, and an alternative approach to the use of these conditions would be desirable.

2.3.2 Biological Analysis

Following synthesis, analysis of the biological properties of prodigiosenes **2-37** to **2-40** was performed. As discussed previously (Section 1.4), prodigiosenes possess significant anti-proliferative and cytotoxic effects on a variety of cell lines. In order to efficiently screen our derivatives, they were submitted to the National Cancer Institute

(NCI). As part of the Developmental Therapeutics Program (http://dtp.cancer.gov), the NCI offer a tiered *in vitro* and *in vivo* screening analysis of novel therapeutics, with preference for rationally designed small-molecule drugs. The benefit of this approach, designated the NCI-60 assay, lies in the fact that efficacy against specific strains of cancer becomes evident, as do fingerprint patterns across the entire screen. Following stringent purity verification via high pressure liquid chromatography, compounds **2-38** and **2-39** (the butyl and pentyl ester derivatives) were submitted for analysis.

Table 2-1: **NCI-60 cell line average responses to C-ring esters**



Prodigiosene	**GI_{50}** (nM mean)	**TGI** (μM mean)	**LC_{50}** (μM mean)
Prodigiosin **2-1**	14	2.1	0.3
Methyl analogue, **2-1Me**	15	0.1	1.0
R = O-butyl **2-38**	117	2.0	14.5
R = O-pentyl **2-39**	36	0.6	4.6

Table 2-1 contains a summary of the results obtained from the NCI-60 assay for compounds **2-38** and **2-39**. The data corresponding to the natural product prodigiosin **2-1**, and an analogue (**2-1Me**) of the natural product bearing a methyl substituent at the unsubstituted β-position of the C-ring, are also included. Several parameters regarding the toxicity of the compounds is presented. The first, GI_{50}, represents the concentration of

drug that is required to inhibit growth of the cancer cells by fifty percent. The concentration of dose required to induce total growth inhibition (TGI) is also shown, as is the dose required for elimination of fifty percent of the cells (LC_{50}). The numbers presented are averages across all sixty cell lines that the prodigiosenes were exposed to. The derivatized pentyl ester, **2-38**, demonstrated notable reactivity in comparison to the natural product, **2-1**. While maintaining growth inhibition capacity (GI_{50}: 36 nM vs. 14 nM), a decrease in toxicity by a factor of ten was observed (LC_{50}: 4.6 μm vs. 0.3 μm). With respect to improving the usefulness of prodigiosenes as therapeutic reagents, these characteristics are desirable. Compound **2-39** is less toxic than natural prodigiosin, thus, tumour growth can be otherwise equally inhibited using a 10-fold decrease in dosage of the pentyl ester **2-39**, compared to prodigiosin.

These results were sufficiently successful so as to initiate testing of **2-39** at the next stage of investigation by the NCI. This is notable, as less than 8% percent of the compounds submitted to the NCI by the Thompson research group move beyond this phase. Following the *in vitro* analysis performed on the 60-cell line, a hollow fibre assay is performed *in vivo* using mice as test subjects. To determine the effective dose to be administered for the hollow fibre assay, a non-tumoured animal toxicity assay is first performed (Table 2-2).

Table 2-2: **Toxicity assay for prodigiosene 2-39**

Entry	**Dose Conc.** (mg/mL)	**Injection Vol.** (μL/g body wt)	**Dose/Units** (μL/g body wt)	**Death Days**
1	100[a]	1	100	1
2	100[a]	2	200	-[c]
3	25[b]	0.5	12.5	-
4	25[b]	1	25	-
5	25[b]	2	50	-

[a] Barely acceptable suspension in DMSO; settles rapidly. [b] Smooth suspension: homogenous. [c] Prepared dose was very thick; solution stuck in syringe. Full required dose was not administered.

Injection of prodigiosene **2-39** was administered to five different test subjects in DMSO at varying doses, and the animals observed for two weeks to determine a non-lethal dosage of the compound. The mixture of **2-39** was prepared at a concentration of 100 or 25 mg/mL. At 100 mg/mL, a described "barely-acceptable" suspension was formed. Although injection of 100 dose/units of compound was tolerated with this suspension, injection of 200 dose/units was inhibited by the sticky nature of the mixture, and a full dose was not administered. Regardless, administration of the full 100 dose/units resulted in death of the subject after a single day. Using the 25 mg/mL solution, doses of 12.5, 25 and 50 dose/units were dispensed to three different test subjects. All three of these mice survived the two-week observation period, and as such, 50 μL/g body weight was selected as the optimal treatment dose for the pending hollow fibre assay. It should be noted that, until this point, only a very small amount of **2-39** was required for testing: less than ten milligrams. To perform the hollow fibre assay, the NCI required at least 65 mg of additional material. Synthesis of **2-39** was thus repeated using larger, gram scale reactions at the early stages to produce more than 400 mg of the final product.

Although a full description of the hollow fibre assay is beyond the scope of this thesis,[75] a brief discussion describing the methodology is required to be able to comprehend the results of the assay. The purpose of the assay is to act as a screening method for compounds to be tested using a traditional xenograft model. As xenograft modeling, the process of grafting cancerous tissue on to healthy mouse subjects, is both time and resource intensive, the hollow fibre assay acts to remove insufficiently effective treatments from the pool of drug candidates at an earlier stage. The assay itself utilizes polyvinylidine fluoride "hollow fibres," with an internal diameter of 1 mm. The walls of the fibre are permeable to compounds with molecular weights less than 500,000 g/mol. The fibres are individually cultured with twelve different strains of cancer, subsequently cut into 2 cm portions, and then heat sealed. Six fibres are then implanted into each mouse, three in the intraperitonial (IP) compartment and three in the subcutaneous (SC) compartment. Treatment with a potential drug candidate is then administered four times per day for 5-6 days, and the fibres are then collected. The mass of the viable cells remaining in each fiber is then determined using the colourimetric MTT dye conversion assay.[76] If greater than 50% of the viable cells have been killed in a fibre, the anticancer agent is determined to have had a positive effect. For each assay, a maximum score of 96 is possible. This number is derived from the usage of 12 cell lines, 2 implant sites, 2 different dose levels, and 2 points/positive fibre. In this way, an individual score out of 96 can be rapidly assigned to a drug candidate, and this score can then be used to identify drug candidates to be used in xenograft modeling.

The results of the hollow fibre assay for prodigiosene **2-39** can be seen in Figure 2-8. The information provided by the NCI report is not itself descriptive of the

methodology, except to describe the basic details of the experiment. The designations of the various cell-types are provided, as are the maximum dosage levels and the dosage scheduling. The most relevant values in the report pertain to the IP and SC scores; of the 96 possible points, prodigiosene **2-39** received a score of 12. In order for a drug to be considered for xenograft modeling, either a total score of 20 must be achieved, or an SC score of 8 or higher. As neither target was achieved, it was decided that NCI interest in **2-39** as an anticancer reagent would end at this stage of screening.

Figure 2-8: **Results of NCI hollow fibre assay for prodigiosene 2-39**

DTP Hollow Fiber Screening Data for NSC: 763729

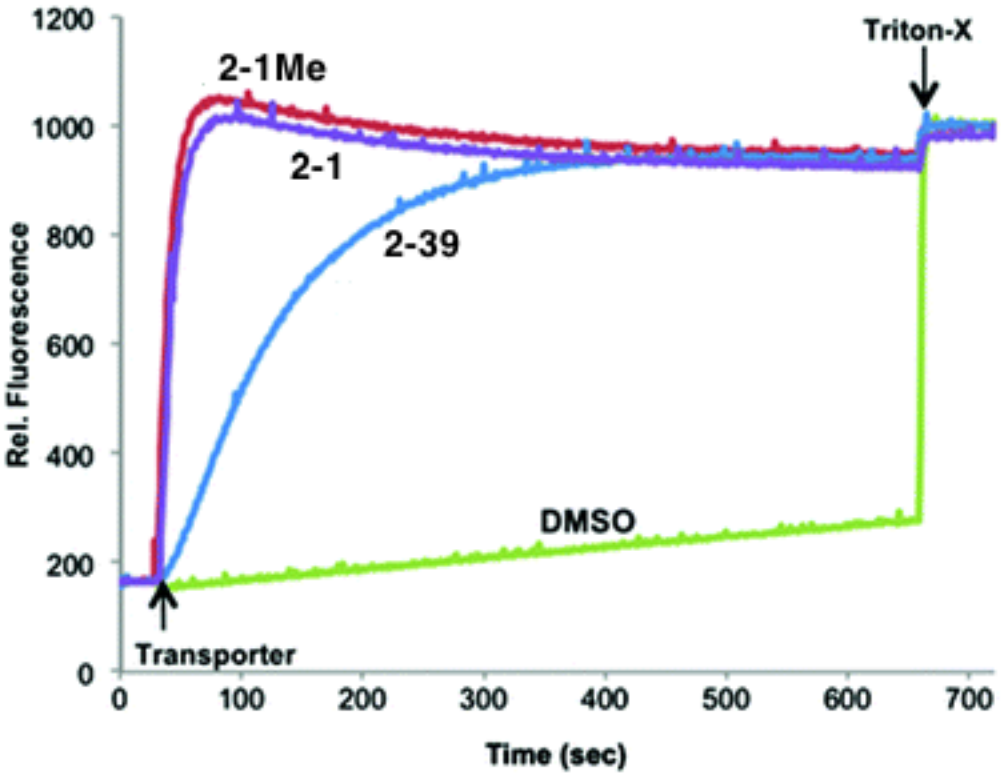
763729 was tested against the following disease types and cell lines.

Experiment ID	Panel Name	Cell name	Schedule	Route	High Dose
HF1954	Breast Cancer	MDA-MB-231	QD X 4	IP	20 mg/kg/dose
	Non-Small Cell Lung Cancer	NCI-H23	QD X 4	IP	20 mg/kg/dose
	Colon Cancer	SW-620	QD X 4	IP	20 mg/kg/dose
HF1955	Colon Cancer	COLO 205	QD X 4	IP	20 mg/kg/dose
	Melanoma	LOX IMVI	QD X 4	IP	20 mg/kg/dose
	Ovarian Cancer	OVCAR-3	QD X 4	IP	20 mg/kg/dose
HF1956	Non-Small Cell Lung Cancer	NCI-H522	QD X 4	IP	10 mg/kg/dose
	CNS Cancer	U251	QD X 4	IP	10 mg/kg/dose
	Melanoma	UACC-62	QD X 4	IP	10 mg/kg/dose
HF1957	Melanoma	MDA-MB-435	QD X 4	IP	10 mg/kg/dose
	Ovarian Cancer	OVCAR-5	QD X 4	IP	10 mg/kg/dose
	CNS Cancer	SF-295	QD X 4	IP	10 mg/kg/dose

IP Score 8 out of 48
SC Score 4 out of 48
Total 12 out of 96
Cell kill: N

As excess compound **2-39** had been synthesized for the hollow fibre assay, and as no further testing was required by the NCI, the excess material was sent to collaborators to measure its other properties. As mentioned previously, H^+/Cl^- ion transport across lipophilic cell membranes is reported as a mechanism for the induction of apoptosis by prodigiosenes in cells. To measure the ability of synthetic prodigiosenes to engage in cross-membrane transport, an EYPC (egg-yolk 1-phosphatidylcholine) liposome model is used by the research group headed by Dr. Jeff Davis (Maryland) (Figure 2-9). The Davis and Thompson group have a long-standing collaboration.[47,60,61]

Figure 2-9: **H^+/Cl^- cross membrane transport of prodigiosenes**



A liposome model, containing both a chloride-specific dye lucigenin, as well as excess NaCl, was loaded in a buffered solution (pH 7.43) containing $NaNO_3$. Lucigenin fluorescence is quenched in the presence of chloride; as such, cross-membrane anionic

transport (Cl^- passes out of membrane, NO_3^- passes in) can be measured using fluorimetry.[77] Figure 2-9 depicts fluorescence, plotted as a function of time, following addition of three prodigiosenes. In the absence of a transporter (DMSO curve, coloured green), anion diffusion across the membrane is observed as an increase in fluorescence (Cl^- out, NO_3^- in) over several minutes. Both the natural product **2-1** and methylated analogue **2-1Me** proficiently engage in transport, eliciting an immediate response, as seen in analysis of the red and purple curves. Although **2-39** also facilitates Cl^- transport, a decrease in efficiency is observed compared to the natural product. However, this level of transport is still very high compared to many compounds that are considered efficient transporters.[78] To better quantify the anion transport of **2-39**, the Davis group performed concentration-dependent Hill analyses of **2-1**, **2-1Me** and **2-39** to determine the EC_{50} values of the compounds. EC_{50} is defined as the concentration of transporter required for influx of 50% of the chloride anions at 150 seconds under ambient conditions (Table 2-3).

Table 2-3: **EC_{50} values for prodigiosenes 2-1, 2-1Me and 2-39**

Prodigiosene	**EC_{50}** (nM)[a]
2-1	3.2
2-1Me	1.3
2-39	18.7

[a]EC50 values indicate the concentration of transporter needed to achieve 50% of maximal chloride efflux at t = 150 s and 25 °C in 20 mM HEPES buffer(pH 7.43).

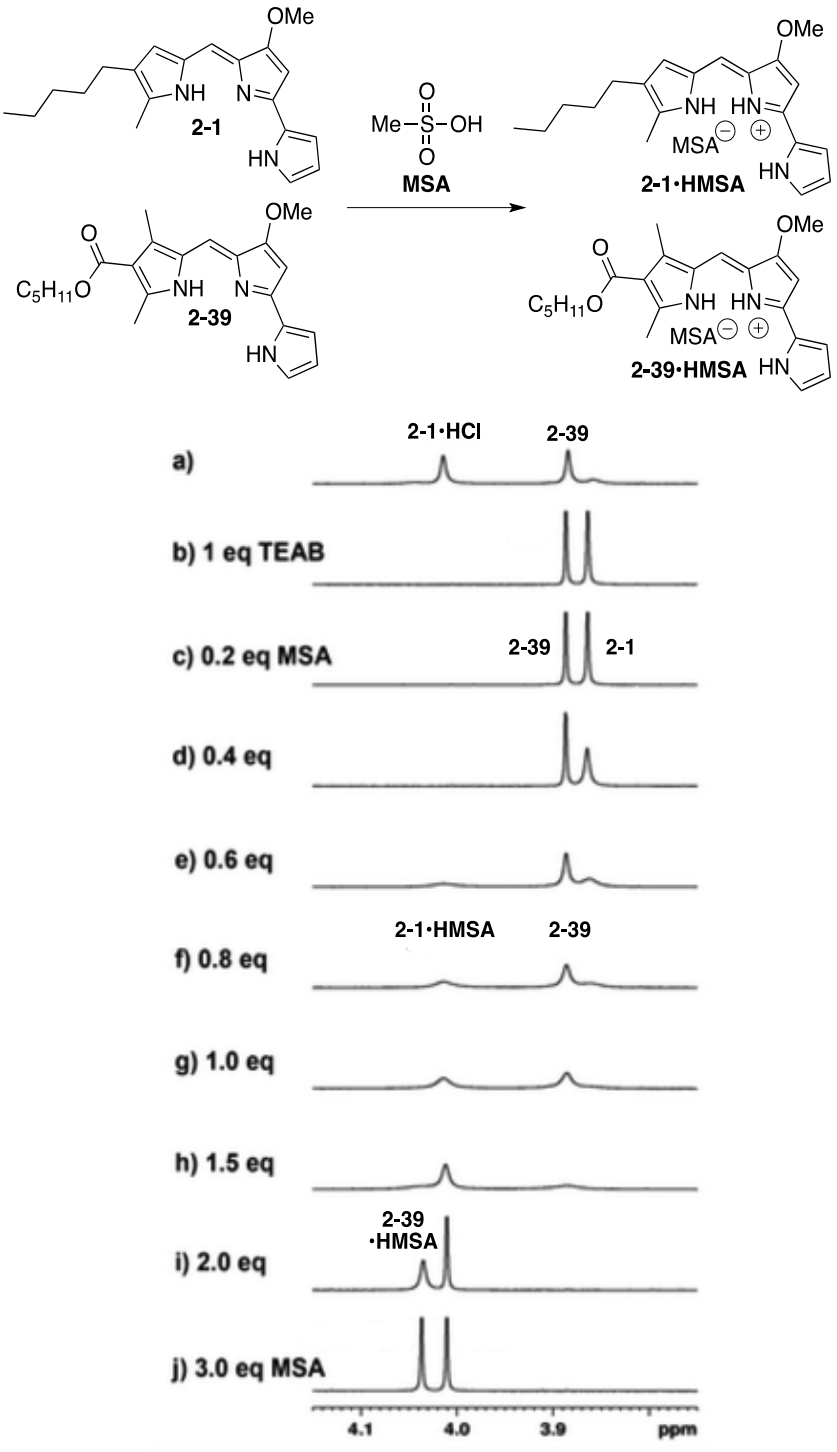
For compounds **2-1** and **2-1Me**, relatively similar values of 3.2 and 1.3 nM were obtained respectively. The value obtained for **2-39**, 18.7 nM, indicates that presence of an ester

appended to the C-ring of the prodigiosene decreases the effective anion transport by approximately a factor of ten. Indeed, this trend was determined to also be true for a variety of prodigiosenes not related to this work.

Based on these results, the Davis group rationalized that the reduced ion-transfer capacity observed for **2-39** was likely related to basicity of the dipyrrin moiety, as the protonated form of the prodigiosene is required for ion transfer. As such, a less basic dipyrrin moiety would be less able to effect ion transfer. To investigate the relative basicities of **2-1** and **2-39**, the Davis group performed a competitive ^{1}H NMR experiment using CD_3CN as a solvent (Figure 2-10). For clarity, the region of the spectra depicting the methoxy moiety of the prodigiosenes is shown in the figure (2.8-4.1 ppm). The first trace (a), depicts an equimolar mixture of free-base prodigiosin **2-1** mixed with the HCl salt of **2-39**. Immediately, the relative basicity of the compounds is displayed as formation of **2-1•HCl** is observed in favour of the ester-salt in a greater than 9:1 ratio. Addition of a single equivalent of triethylammonium bicarbonate (TEAB) was then performed, and conversion of both **2-1** and **2-39** to their free-base forms was observed with signals at 3.86 and 3.88 ppm, respectively (trace b). Addition of 1 equivalent of methanesulfonic acid (MSA) was then achieved in 0.2 equivalent increments (traces c-g). As shown in Figure 2-10, the methoxy signal for prodigiosin **2-1** free-base at 3.86 ppm broadens significantly with each subsequent addition of MSA, leaving the signal for **2-39** unaffected. The broadening of the signal at 3.86 ppm is accompanied by the formation of a signal representing **2-1•HMSA** at 4.01 ppm. Addition of excess MSA (traces h, i and j) induces a decrease of the signal at 3.88 ppm for free-base **2-39**, and the arrival of a signal at 4.04 ppm corresponding to the HMSA salt of **2-39**. From this study, it was definitively

concluded that the ester moiety appended to the C-ring of **2-39** plays a significant role in reducing the basicity of the dipyrrin moiety of prodigiosenes.

Figure 2-10: **^{1}H NMR spectra representing competitive protonation of 2-1 and 2-39**

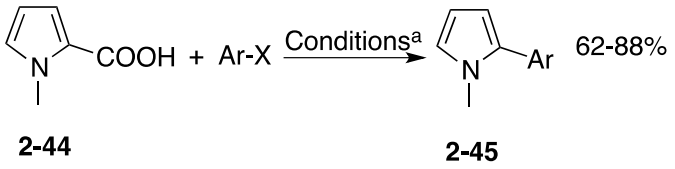


2.3.3 Decarboxylative Coupling as an Alternative to Suzuki Coupling for the Synthesis of Prodigiosenes

Carbon-carbon bond formation between aromatic systems via metal-mediated processes is a well-studied reaction, with the use of catalytic amounts of palladium(0) proving to be exceptionally useful in this regard. Researchers such as Heck, Stille, Sonogoshira and Suzuki have enjoyed widespread use of their respective techniques in a variety of industrial and academic syntheses. Recently, one of the lesser known bi-aryl coupling techniques involving the decarboxylation of aryl carboxylic acids, has enjoyed a rise in use. Although a copper-mediated decarboxylative reaction has been developed for some time now,[79] recent advances have facilitated the use of a Heck-type reaction involving activated aliphatic carboxylic acids.[80] The catalytic cycle proposed by Forgione *et al.* for this process is complicated, and coupling has been shown to occur through a variety of competitive pathways.[80]

Forgione *et al.* has used this coupling technique to couple a variety of five-membered, heteroatomic ring systems (furans, thiophenes and thiozoles, indoles and pyrrole) with an assortment of halogenated or pseudo-halogenated aromatic systems.[80] Most pertinent to this work was the regioselective coupling of *N*-methyl-2-pyrrole carboxylic acid (**2-44**) with various aryl halides at the 2-position of the pyrrole in moderate-to-high yields (Scheme 2-7).

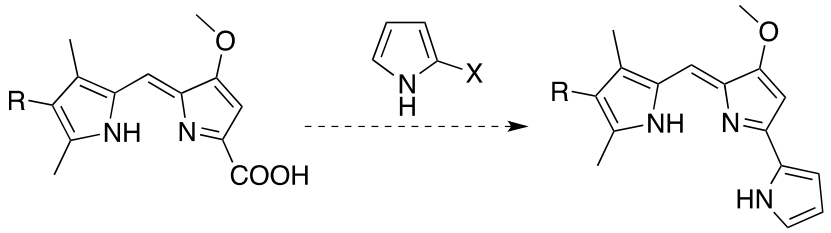
Scheme 2-7: **Decarboxylative coupling with *N*-methyl-2-pyrrole carboxylic acid 2-44**



[a] 1-methyl-2-pyrrolecarboxylic acid (0.80 mmol, 2.0 eq.), aryl halide (0.40 mmol, 1 eq.), Pd[P(*t*-Bu)$_3$]$_2$ (5 mol %), *n*-Bu$_4$NCl·H$_2$O (0.40 mmol, 1 eq.), Cs$_2$CO$_3$ (0.60 mmol, 1.5 eq.), DMF (4 mL), microwave, 170 °C, 8 min.

This method has demonstrated considerable versatility, and can be facilitated using a variety of halogenated or pseudo-halogenated aryl groups, solvents, bases and catalysts. For the current work, we first explored the potential of coupling 2-pyrrole carboxylic acids with a 2-aryl halides for eventual inclusion as a step in the synthesis of prodigiosenes (Scheme 2-8).

Scheme 2-8: **Decarboxylative coupling for prodigiosene synthesis**



As mentioned previously, the Suzuki coupling used as the last step to link the A and B rings in prodigiosenes is typically the lowest yielding step in the synthesis. [64] As such, a high-yielding replacement for this procedure is desirable, and was the goal of this work.

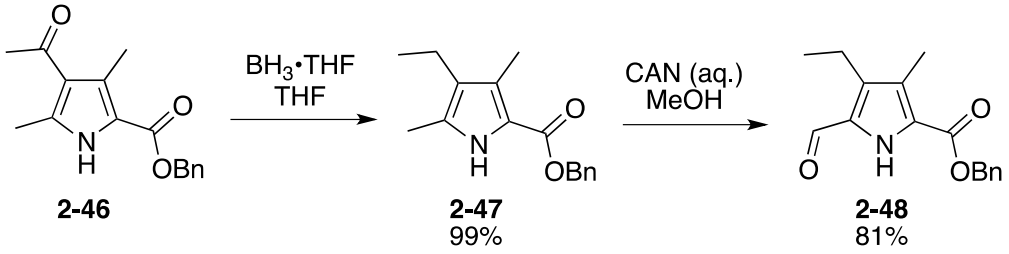
As an assessment of the reproducibility of literature procedures for this reaction, pyrrole **2-44** was purchased from Maybridge chemical supplier, and the reported coupling conditions[80] were repeated using benzylbromide as the aryl-halogen (Scheme 2-7). Pyrrole **2-44**, tetrabutylammonium bromide, cesium chloride, bis(tri-tert-butylphosphate)palladium(0) and benzylbromide were added to a 2-5 mL microwave vial

and dissolved through the addition of anhydrous DMF. The vial was then sealed, and the contents subjected to microwave heating at 170 °C for 8 minutes, after which the product was extracted into ethyl acetate, and the resulting solution washed repeatedly with water to remove residual DMF. The product mixture was then purified via flash chromatography on silica. The desired bi-aryl was isolated in a 84% yield, comparable to the reported literature value of 88%.[80]

Although Forgione and co-workers discussed the use of a variety of aryl-halogens for coupling, only one pyrrole (**2-44**) was tested. If this reaction is to be used for coupling in other pyrrolic systems, substrate tolerance in the pyrrole needs to first be explored. Furthermore, *N*-alkyl protective groups, such as the methyl substituent used in **2-44**, represent a significant synthetic roadblock. The removal of *N*-alkyl groups is not facile with pyrroles, except in very specific cases such as use of a benzyl or SEM groups.[7] For our purposes, it is also necessary to determine whether decarboxylative coupling can be performed on a highly substituted, free-base dipyrrin.

As strongly electron-withdrawing groups are commonly featured in prodigiosene intermediates, attempts were made to couple phenyl bromide with pyrroles bearing acyl and formyl functionalities. The preparation of several pyrroles for this purpose is shown in Scheme 2-9.

Scheme 2-9: **Synthesis of benzyl 2-pyrrole carboxylates**

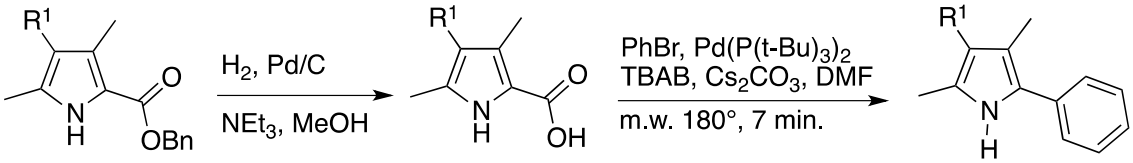


2-46 **2-47** 99% **2-48** 81%

Pyrrole **2-46** is readily produced on decagram scales following literature procedures,[81] and was available in large quantities within the lab. Adapting the reduction procedure developed for prodigiosene syntheses commonly used within the lab,[61] pyrrole **2-47** was generated in a 99% yield via slow addition of BH_3•THF to a solution of **2-46** in THF. After stirring for 18 hours, the reaction was carefully quenched with HCl (aq.), and the product was obtained as a pure, white solid. Pyrrole **2-48** was obtained via oxidization of **2-47** in methanol using ceric ammonium nitrate (2.1 M, 4 equivalents). With cooling at 0 °C, **2-48** precipitated from solution as a fluffy, white solid and obtained in an 81% yield, without the requirement of further purification upon isolation via filtration.

2-44, used by Forgione *et al.,* is *N*-protected with a methyl functionality. Although the authors do not discuss whether attempts at coupling *N*-H-2-pyrrole carboxylic acid with benzylbromide were performed, it is likely that methyl protection was required so as to inhibit the reactivity inherent to nitrogenous pyrrolic hydrogen atoms. To quickly test whether this was indeed true, pyrroles **2-46** and **2-49** were utilized (Scheme 2-10).

Scheme 2-10: **Attempted coupling of *N*-H-2-pyrrole carboxylic acids**



2-46 R^1 = Ac
2-49 R^1 = H

Isolated as Intermediate

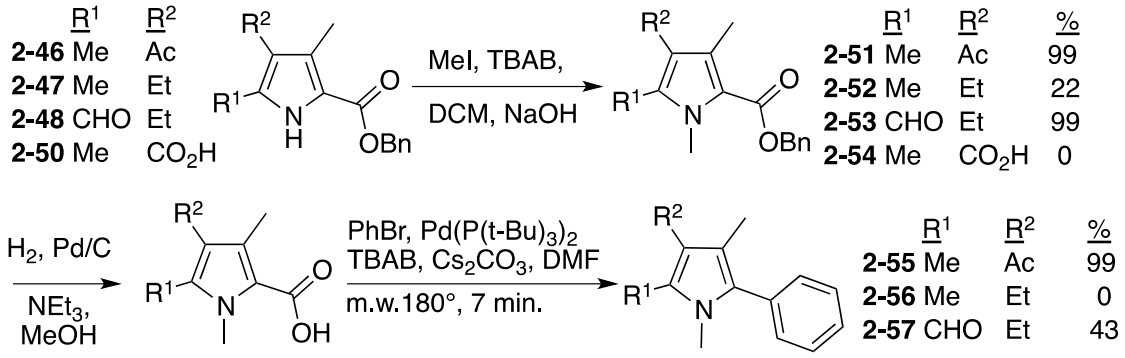
Not Isolated

Bearing no electron withdrawing functionality, pyrrole **2-49** served as a rapidly-accessible analogue to an unprotected (*N*-H) version of **2-44**. Prepared following literature procedures,[82] **2-49** and **2-46** were treated to standard hydrogenolysis conditions.[61] The starting materials were dissolved in methanol with triethylamine and

activated palladium on carbon, under nitrogen. A hydrogen atmosphere was then introduced via a balloon. After stirring for several hours, TLC analysis was used to determine that the starting material had been consumed, and the reaction mixture was then worked up via filtration over Celite®. Due to the relative instability of 2-pyrrole carboxylic acids, these products were treated as intermediates and taken on to the coupling step of the reaction immediately. Following the same procedure outlined for the synthesis of **2-45** from **2-44** (Scheme 2-7), coupling of the acids of **2-46** and **2-49** with phenyl bromide was attempted. In both cases, the resulting mixtures included residual starting materials, as well as a significant portion of decarboxylated pyrrole. These results were not encouraging, and confirmed the suspicion that the *N*-alkyl protection of **2-44** is indeed a prerequisite to effective reaction.

With this in mind, the methylation of pyrroles **2-46** to **2-47** was then attempted adapting a literature procedure using phase-transfer catalysis.[83] In addition, the readily available pyrrole **2-50** bearing an acid functionality at the 4-position was also reacted (Scheme 2-11).

Scheme 2-11: ***N*-Methylation, hydrogenolysis and decarboxylative coupling of benzyl 2-pyrrole carboxylate derivatives**



Pyrroles **2-46** to **2-48**, and **2-50**, were dissolved in dichloromethane with tetrabutylammonium bromide (10 mol %) and methyl iodide at 0° C. A solution of sodium hydroxide (5 M) was added drop-wise to solution, with stirring, and the mixture was allowed to react and warm to room temperature overnight. During this time, pyrroles **2-46** and **2-48** were reacted to completion. Following typical organic workup and purification over a short pad of silica, the compounds were isolated in exceptional yields as pure white solids. However, the reaction of pyrrole **2-47**, bearing no electron withdrawing group at either the 4- or 5-positions, had not reached completion within this time. Additional equivalents of methyl iodide were added to the reaction mixture to induce reactivity, and the vessel was heated at reflux temperature for several days. Unfortunately, this did not induce further reaction of the starting material. The mixture of **2-47** and **2-52** was thus worked up, and the product purified via flash chromatography on silica (20% ethyl acetate/hexanes) to produce an emerald green solid in 22% yield. The emerald green colour of the product is associated with an as-of-now unknown impurity related to the preceding boron reduction step involving BH_3. It should be noted that no trace of ^{11}B nuclei was observable by NMR analysis, and analysis of the products using ^{1}H NMR spectroscopy revealed no impurities in any reasonable quantity. Despite the success of methylation in the case of formyl and acyl pyrroles **2-46** and **2-48**, methylation of the 4-pyrrole acid **2-50** was wholly unsuccessful. Upon analysis of the reaction using TLC, it appeared that some portion of the starting material was present in the aqueous phase of the reaction mixture as the carboxylate anion. As such, it is suspected that the starting material was not available, in solution, for reaction with the iodomethane. After neutralization of the reaction mixture, the starting material was reclaimed, but as a

mixture of **2-49** and the decarboxylated pyrrole. Several other procedures for attempted methylation were attempted, including treatment of **2-50** with NaH for deprotonation, as well a procedure utilizing DABCO as a base and dimethylcarbonate as a methylating reagent. Unfortunately, these trials were equally unsuccessful, and attempts to methylate this compound were abandoned.

With *N*-methyl pyrroles **2-51** to **2-53** in hand, hydrogenolysis of the benzyl 2-ester functionality was implemented (Scheme 2-11) following the same procedure used for hydrogenolysis of **2-46** and **2-49 (**Scheme 2-10**)**.[61] As mentioned previously, the relative instability of 2-pyrrole carboxylic acids requires the immediate use of these products for the coupling step. The carboxylic acids of **2-51** and **2-53** were relatively stable to workup. However, the acid of **2-52** rapidly displayed the red colouration characteristic of polymerized pyrrole upon removal of the reaction solvent *in vacuo*. As **2-52** contains no secondary electron withdrawing moiety appended to the frame of the pyrrole, this is not surprising. Despite this observation, the crude material was carried forward to the final coupling step.

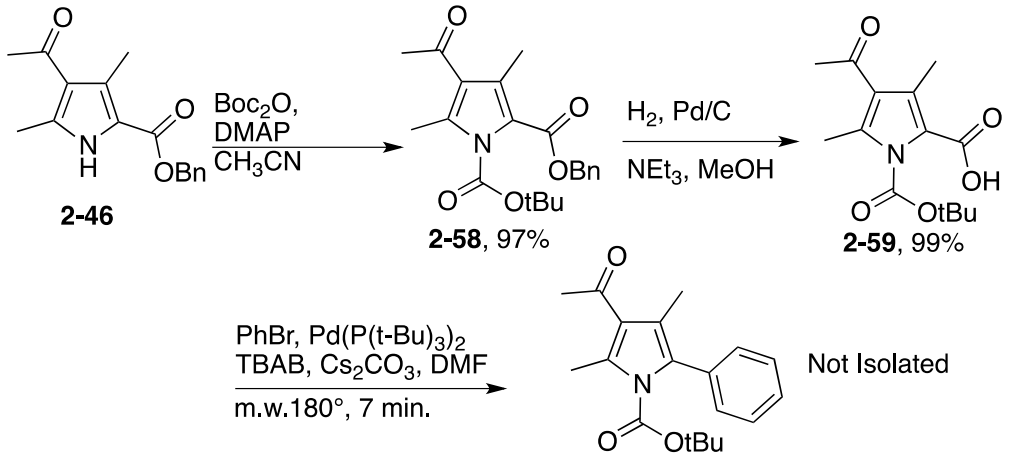
The 2-carboxylic acids were subjected to the decarboxylative coupling conditions reported by Fogrione *et al*.[80] As with reference compound **2-44**, the pyrroles were combined with tetrabutylammonium bromide, cesium chloride, bis(tri-tert-butylphosphate)palladium(0) and phenylbromide (0.5 equivalents) in an open 2-5 mL microwave vial, placed under nitrogen, and dissolved in anhydrous DMF. The vials were stirred, and microwave heated to 170 °C for 8 minutes. The product mixtures were extracted, washed repeatedly with water to remove residual DMF, and dried using anhydrous sodium sulfate.

Unsurprisingly, reaction of the acid of **2-52** was not successful. Both the acid and benzylbromide could be identified using TLC, as well as a third, non-isolable product that decomposed to a pink, presumably poly-pyrrolic, compound upon workup. As decarboxylation of 2-carboxylpyrroles can occur at temperatures greater than 150 °C,[84] this product mixture presumably arises from the decarboxylated α-free derivative. Conversely, the reaction of the carboxylic acids of **2-51** and **2-53** with benzylbromide under identical conditions was successful. Following purification on silica, pyrroles **2-55** and **2-57** were isolated as mixtures of the desired bi-aryls and the corresponding (stable) α-free derivatives. The ratios of aryl:α-free pyrroles were approximately 3:1 and 10:1, respectively. Despite the difficulty in separating the products from the minor side products, yields of 99% for **2-55** and 43% for **2-57** were promising. As the literature conditions called for two equivalents of 2-pyrrole acid and a single equivalent of phenyl bromide, the presence of α-free pyrrole is expected. Indeed, in the case of compound **2-55**, the reaction was repeated using a single equivalent of pyrrole and 1.1 equivalents of benzylbromide to yield the 2-phenyl pyrrole in a 99% yield without the presence of excess decarboxylated pyrrole. In addition to these described reactions, it is worth noting that attempts to couple benzylbromide with 4-pyrrole carboxylic acid **2-50** (an *N*-H pyrrole, like **2-46** and **2-49**) were also made, but were not successful.

With these outcomes, we moved on to address the second synthetic roadblock hindering these products from use in synthesis of prodigiosin derivatives. While methyl and benzyl protection of pyrrolic nitrogen is easily facilitated using a variety of conditions, deprotection requires severe conditions, and is low yielding. As such, an alternative protecting group suitable for use in decarboxylative coupling is required. One

of the most commonly used *N*-protection strategies is treatment with di-tert-butyl dicarbonate, to afford a Boc-protected pyrrole.[7] As pyrrole **2-46** underwent successful *N*-methyl protection, a Boc-protected version of this compound was synthesized, and used to evaluate the utility of *N*-Boc protection for the aryl coupling (Scheme 2-12).

Scheme 2-12: **Decarboxylative coupling with Boc protected pyrrole**



2-46

2-58, 97%

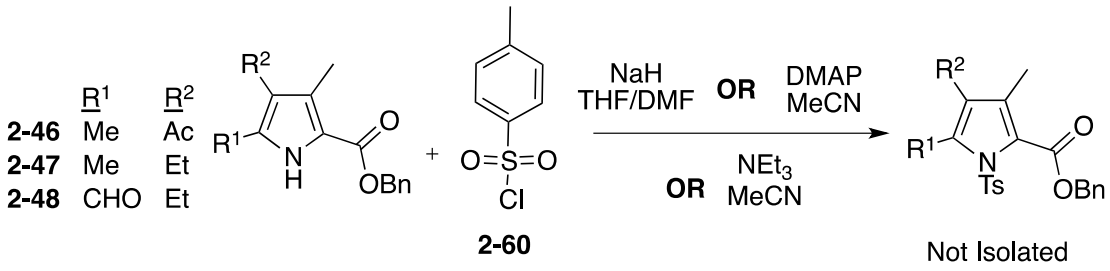
2-59, 99%

Pyrrole **2-46** was stirred in acetonitrile with DMAP (0.12 equivalents) under nitrogen, and a solution of Boc_2O (2.7 equivalents) in acetonitrile was added drop-wise to the solution. After stirring for 30 minutes, the solvent was removed *in vacuo*, and the mixture was purified on basic alumina (EtOAc/Hex, 2/8). The protected pyrrole **2-58** was isolated as a light yellow oil in 97% yield. Hydrogenolysis was then performed following the typical procedure (Scheme 2-10) to produce the stable acid **2-59** in a seemingly quantitative yield. Unfortunately, subjecting **2-59** to decarboxylative coupling conditions did not yield the desired phenyl pyrrole; instead, the majority of the material was recollected as the *N*-deprotected, decarboxylated pyrrole.

Shifting focus, *N*-protection via tosylation was explored. Although tosyl groups are widely employed in pyrrole protection, and despite their use for protection of a variety of 2-pyrrole carboxylates,[7] literature examples for *N*-tosyl protection on benzyl-2-

pyrrole carboxylates are not reported. Bearing this in mind, a variety of attempts were made to produce these compounds using pyrroles **2-46** to **2-48** (Scheme 2-13**)**.

Scheme 2-13: **Attempted tosylation of benzyl-2-pyrrole carboxylates**

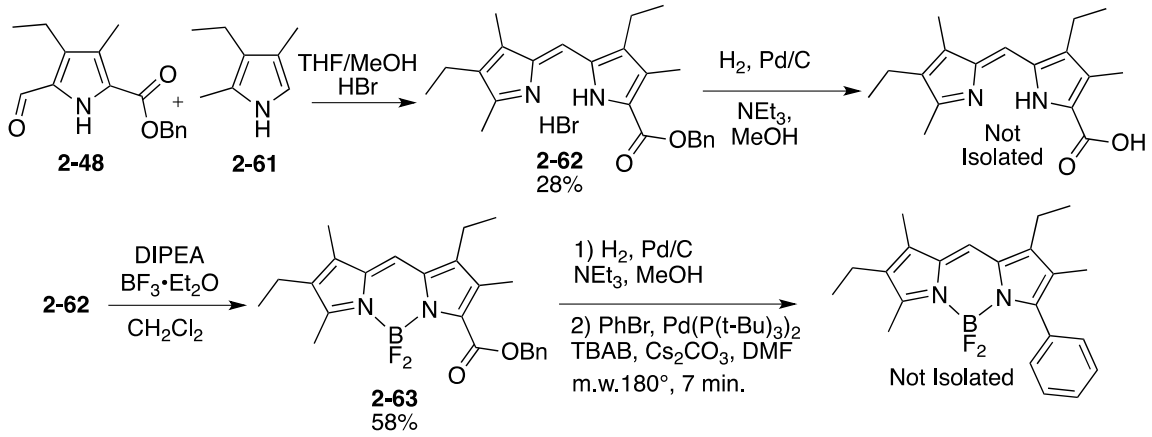


Using several different methodologies, the pyrroles were subjected to various conditions for tosylation. NaH is commonly employed for generation of pyrrole-sodium salts; following a literature procedure, [85] a suspension of NaH in solvent was added to pyrroles **2-46** to **2-48** in either anhydrous THF or DMF (each employed in separate reactions). The reactions were stirred for an hour, during which evolution of H_2 gas was observed. Tosyl chloride was then added, and the mixture stirred overnight. Unfortunately, none of the desired product was generated. Additional equivalents of base were added in an effort to forward the reaction, to no avail. Additionally, the temperatures of the reactions were also increased. However, in each case, only tosic acid and starting materials were isolable as products. A second methodology, using DMAP as the base, has been demonstrated to work with pyrroles bearing non-benzyl esters by the Thompson Group. Using a single equivalent of DMAP, small amounts of 2-formyl pyrroles were protected. Unfortunately, as with the reactions utilizing NaH, this method was not successful. As a final attempt, a methodology utilizing triethylamine, as well as a catalytic amount of DMAP was attempted.[86] To a solution of pyrrole in acetonitrile, a single equivalent of triethylamine was added with DMAP (0.1 equivalents). The reactions were stirred at room temperature,

with no success. Again, despite attempts to push the reaction forward via addition of extraneous base and via heating at reflux temperature, no formation of *N*-tosylated pyrroles was observed.

Although model testing on pyrroles is important, the goal of this project is to explore the potential for decarboxylative coupling involving a pyrrolyldipyrrin. Several different dipyrrins bearing carboxylic acid functionality at the 1-position were synthesized. As a starting point, the synthesis of benzyl 1-dipyrrin carboxylate **2-62** was performed.

Scheme 2-14: **Decarboxylative coupling from 1-dipyrrin and 1-*F*-BODIPY carboxylates**

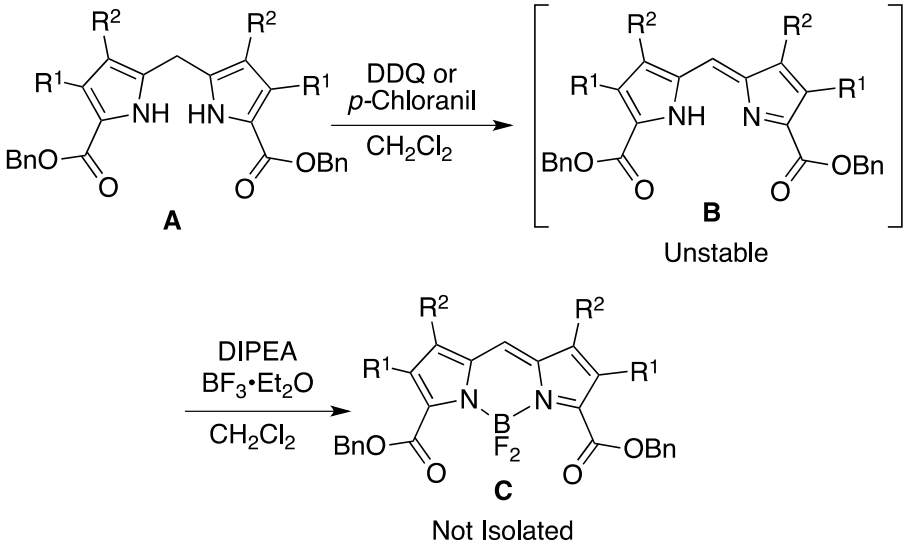


The pyrroles **2-48** and **2-61** (prepared according to a literature procedure)[87] were dissolved in a mixture of methanol and tetrahydrofuran (1:1), the solution was bubbled with nitrogen, and two equivalents of concentrated hydrobromic acid were then added. Consumption of starting materials was rapid (observed using analysis via TLC); however, the dipyrrin did not precipitate from solution as expected. After several hours, the mixture was diluted with Et_2O to precipitate the product, and the dipyrrin was collected as a red solid in modest yield. Hydrogenolysis was then attempted following the

procedure outlined previously (Scheme 2-10). Unfortunately, where the hydrogenolysis of the benzyl 1-pyrrole carboxylates was straightforward, the hydrogenolysis of **2-62** was unsuccessful. A complex mixture of reaction products was produced, and no formation of the product carboxylic acid was detectable using either ^{1}H NMR or low resolution mass spectrometry. As the decarboxylation of the acid is presumably complicating this transformation, formation of the protected *F*-BODIPY product was attempted. *F*-BODIPYs are often stable to transformations that otherwise fail on the parent dipyrrin.[28] Dipyrrin **2-62** was dissolved in anhydrous dichloromethane and treated with diisopropylethylamine (DIPEA, 6 equivalents) and BF_3•Et_2O (9 equivalents). After stirring overnight for 16 hours, the fluorescent product was detectable using TLC analysis. Following workup and purification over silica (10% EtOAc/Hex), the red solid **2-63** was isolated in a moderate yield (58%). The *F*-BODIPY was subjected to the same hydrogenolysis procedure used for the parent dipyrrin; upon isolation, the orange-solid was pure according to TLC analysis. Rather than risk decarboxylation, the acid was immediately subjected to the coupling conditions described by Forgione *et al.* (Scheme 2-7). Unfortunately, no formation of the desired phenyl-coupled product was observed. Rather, unreacted benzylbromide was detected by TLC analysis, along with a number of baseline, decomposition material.

A second approach, utilizing oxidation of benzyl 1,9-dipyrrin dicarboxylates was then attempted (Scheme 2-15).

Scheme 2-15: **Attempted oxidation of benzyl 1,9-dipyrrin carboxylates and *in situ* formation of *F*-BODIPYs**



Meso-H dipyrrins bearing benzyl esters at the 1- and 9- positions are unknown in the synthetic literature; indeed, the only mention of these compounds occurs in the context of measuring the oxidation potential of the starting material dipyrromethanes.[88] Several precursors bearing alkyl and unsubstituted positions on the backbone were synthesized according to literature procedures (**A**, R^1 = H, Me, R^1 = H, Et, COR, CO_2R),[89] and oxidation was attempted using standard dipyrrin oxidizing reagents (DDQ or *p*-chloranil). The consumption of the dipyrromethane starting materials (**A)** could be monitored using TLC analysis, and was congruent with the observation of dipyrrin products (**B**). However, upon workup and attempted isolation of these products by flash chromatography, only the starting materials could be isolated. Auto-reduction of these products under atmospheric conditions occurred in all attempted reactions. As with dipyrrin **2-62**, formation of *F*-BODIPYs was attempted as a means to stabilize the dipyrrin carboxylate products. Adapting a procedure for the *in situ* generation of *F*-

BODIPYs from dipyrromethanes, DIPEA and BF_3•Et_2O were added to a solution containing the oxidized intermediates (**B**). Unfortunately, no complexation with boron was observed, and no *F*-BODIPY products were produced.

Despite significant literature precedence for formation of *F*-BODIPYs bearing dicarboxyl functionality at the 1- and 9- positions, only a single example exists of such a compound bearing an unsubstituted *meso*-position.[90] As the importance of substitution of the *meso*-position relating to the formation of *F*-BODIPYs has been discussed elsewhere, [91,92] it is perhaps worth revisiting this dipyrrin decarboxylative coupling using *meso*-phenyl substituted dipyrrins. Regardless of these results, the stability of 2-dipyrrin acids is indeed a concern moving forward with this project. Although decarboxylation is required for reactivity, it may be occurring at temperatures lower than those required for palladium coupling. As transesterification has been performed on prodigiosenes at temperatures as high as 140 °C, it is hoped that decarboxylative coupling will still be viable using these substrates.

Section 2.4: Conclusions

In summary, a novel set of prodigiosene analogues have been synthesized, adding to the library of compounds produced by members of the Thompson lab. The NCI, using their 60-cancer cell line panel, has subjected these derivatives to anti-proliferative analysis. The pentyl ester in particular, **2-39**, demonstrated considerable anti-proliferative properties and was synthesized on a larger scale for analysis using hollow fibre assays. Ultimately, the toxicological profile of the compound was deemed insufficient for testing using a traditional xenograft model. Collaborators working with Dr. Jeff Davis

(Maryland) used **2-39** as a model against which to measure the basicity and ion-transport capabilities of ester-appended prodigiosenes. This work has been published.[61]

Decarboxylative coupling of 2-pyrrole carboxylic acids with aryl halides has been shown to be viable on *N*-methyl pyrroles bearing various acyl functionalities pendant at the 4- and 5- positions of the pyrrole ring. Although *N*-unprotected pyrroles did not undergo decarboxylative arylation, it is hoped that the use of reversible *N*-protection might be successful. Experimentation with a larger variety of dipyrrin carboxylic acids required, in order to ascertain if decarboxylative aryl-aryl coupling is viable.

Section 2.5: Experimental

2.5.1 General Experimental

All chemicals were purchased and used as received unless otherwise indicated. Hexanes and dichloromethane used for chromatography were obtained crude and purified by distillation under atmospheric conditions before use. Anhydrous solvents were used as received. Flash chromatography was performed using Silicycle ultra pure silica (230-400 mesh) or Brockmann III (150 mesh) activated basic or neutral alumina oxide, as indicated. TLC was performed using glass-backed silica gel plates or plastic-backed neutral alumina plates. Visualization of TLC plates was performed using UV light (254 nm) and/or vanillin stain. Moisture-sensitive reactions were performed in oven, or flame-dried glassware under a positive pressure of nitrogen. Air and moisture-sensitive compounds were introduced by syringe. NMR spectra were recorded at the NMR-3 facility (Dalhousie University) using a Bruker 500 MHz or a Bruker 300 MHz spectrometer. Some crude spectra were also obtained on a, now decommissioned, Bruker

250 MHz spectrometer. ^{1}H and ^{13}C chemical shifts are expressed in parts per million (ppm) using use the solvent signal as reference, according to literature values.[93] ^{11}B, ^{19}F and ^{31}P chemical shifts were referenced using the absolute referencing procedure standard for Bruker digital spectrometers, with $BF_3 \bullet Et_2O$ (15% in $CDCl_3$), CCl_3F and H_3PO_4 (aq.) defining the 0 ppm position respectively. All coupling constants (*J*) are reported in Hertz (Hz). Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Splitting patterns preceded by an "a" are defined as apparent signals. All mass spectra were recorded by Mr. Xiao Feng using TOF and LCQ Duo ion trap instruments operating in ESI^+ mode. All microwave-promoted reactions were performed using a Biotage Initiator 8 laboratory microwave apparatus, 0–400 W power, 2.45 GHz. Pyrrolinone **2-9** was prepared according to a literature procedure. [82]

2.5.2 General Procedure I for the Synthesis of Esters 2-25 to 2-28

To a stirred solution of 5-formyl-2,4-dimethyl-1H-pyrrole-3-carboxylic acid **2-24** in dry CH_2Cl_2 (50 mL) was added DMAP (1.1 equivalents) and EDC (1.1 equivalents) followed by the alcohol (desired amount, as indicated for each compound) and the resulting solution was heated at reflux temperature for 1-2 days. The reaction mixture was then cooled to room temperature, and washed twice in a separatory funnel with water (2 x 50 mL) and then with brine (50 mL). The organic fraction was then dried over sodium sulfate, and concentrated *in vacuo*. Purification using chromatography over silica (ethyl acetate/hexanes, 20/80) gave the desired products.

2.5.3 General Procedure II for the Synthesis of Dipyrrinones 2-29 to 2-32

To a solution of 4-methoxy-3-pyrrolin-2-one, **2-9**, (2.2 equivalents) in dry CH_2Cl_2 (45 mL) was added triethylamine (6.0 equivalents) at 0 °C. Then TMSOTf (3.0 equivalents) was added drop-wise via syringe. After 20 minutes, a solution of the requisite aldehyde (1 equivalents) in dry CH_2Cl_2 (45 mL) was added. The reaction mixture was stirred at this temperature for three hours, then TMSOTf (0.6 equivalents) was added. After one hour stirring at 0 °C the reaction was quenched by the addition of phosphate buffer (pH = 7, 100 mL). The solution was extracted with CH_2Cl_2 (3 x 100 mL), and the combined organic fractions were then washed with brine and dried (Na_2SO_4). After evaporation of the solvent the resulting brown oil was dissolved in THF (90 mL) and concentrated aqueous HCl (300 μL) was added. After a few minutes the reaction was quenched via addition of saturated aqueous $NaHCO_3$ (200 mL), then extracted with CH_2Cl_2 (3 x 100 mL). The combined organic fractions were then washed with water (2 x 100 mL). After concentration *in vacuo*, the resulting suspension was filtered to isolate the solid, and then washed with water and hexane to give the product as a yellow solid.

2.5.4 General Procedure III for the Synthesis of Triflyl Dipyrrins 2-33 to 2-36

To a suspension of the dipyrrinone (1 equivalents), in dry CH_2Cl_2 (60 mL) at 0 °C was slowly added Tf_2O (2.8 equivalents). After 4 h stirring at this temperature, the reaction was quenched by the addition of sat. aqueous $NaHCO_3$ (70 mL), then extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine, and then dried over sodium sulfate. After evaporation of the solvents under reduced pressure, the

crude material was purified using flash column chromatography (SiO_2, EtOAc/hexane 1/9) to give the desired products.

2.5.5 General Procedure IV for the Synthesis of Prodigiosenes 2-37 to 2-40

The triflylated dipyrrin (1 equivalents) was dissolved in DME (9 mL), then LiCl (3 equivalents) and boronic acid (1.2 equivalents) were added. The solution was degassed by bubbling with N_2, and then tetrakis(triphenylphosphine)palladium(0) (10 mol/%) was added. Then a degassed 2 M solution of Na_2CO_3 was added (4 equivalents) and the suspension was stirred at 85 °C for 18 h. After cooling, the solution was poured into water (100 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine (100 mL), and then dried over sodium sulfate. Purification using chromatography (Al_2O_3 neutral type III, EtOAc/hexane 1/9 then 2/8) gave a red film. The product was dissolved in a mixture of MeOH/$CHCl_3$ (20:1) and treated with a 0.1 M solution of HCl in MeOH (1.5 equivalents). After 15 minutes stirring the solvents were reduced under reduced pressure, inducing precipitation. The obtained solid was isolated via filtration, and washed with water and hexane or methanol, to give a dark brown-red solid.

2.5.6 General Procedure V for Hydrogenolysis of Benzyl 2-Pyrrole Carboxylates

Adapting a literature procedure,[61] benzyl 2-pyrrole carboxylate (1-10 mmol,1 equivalent) and 10 mol% palladium on activated carbon were dissolved in ethanol (100 mL), and triethylamine (0.5 mL) was added. The mixture was purged three times with N_2 before introduction of an H_2 atmosphere. After stirring for 5 hours the reaction was complete, and a N_2 atmosphere was introduced. The reaction was then filtered through a plug of

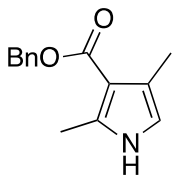
Celite® to remove the catalyst, and the plug was rinsed with methanol (3 x 50 mL). Removal of the solvent *in vacuo* gave a bright white solid.

2.5.7 General Procedure VI for the Decarboxylative Coupling of 2-Pyrrole Carboxylic Acids

Adapting the general procedure outline by Forgione *et al*.,[80] 2-pyrrole carboxylic acids (1 equivalent), phenyl bromide (1.1 equivalents), tetra-n-butylammonium chloride hydrate (1 equivalents), cesium carbonate (0.60 mmol, 1.5 equivalents), and $Pd(P(t\text{-}Bu)_3)_2$ (0.05 equivalents) were combined in an open microwave vial. The vessel was sealed, a nitrogen atmosphere was introduced via the septum cap, and anhydrous DMF was added (4 mL). The mixture was stirred for 30 s, and then submitted to microwave conditions (170 °C, 8 min, high absorption). The mixture was diluted with ethyl acetate (50 mL). The organic layer was washed with brine (3 x 50 mL) to remove residual DMF, and then washed again with $NaHCO_3$ (50 mL, 1M (aq)). The organic layer was dried over Na_2SO_4. After evaporation of the solvents under reduced pressure, the crude material was purified using flash column chromatography (SiO_2, EtOAc/hexane, 10% → 30%) to give the desired products.

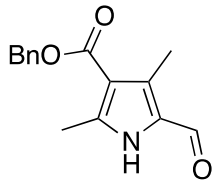
Section 2.6: Synthesis

Benzyl 2,4-dimethyl-1*H*-pyrrole-3-carboxylate (2-22)



Following a literature procedure,[61] a stirred solution of 4-benzyl 2-tert-butyl 3,5-dimethyl-1*H*-pyrrole-2,4-dicarboxylate (**2-21**) (15 g, 45 mmol) in ethanol (100 mL) at 0 °C was prepared, and concentrated hydrochloric acid (20.4 mL, 20.2 mol) was then added slowly. The resulting mixture was stirred at 65 °C for 4 hours. After cooling to room temperature, the mixture was poured into water (200 mL) and the product extracted into CH_2Cl_2 (3 x 50 mL). The combined organic fractions were washed with brine and water, dried over sodium sulfate, and concentrated *in vacuo* to give an off-white solid (10.3 g, 99%) which was used for the next step without further purification.

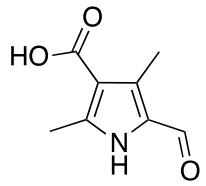
Benzyl 5-formyl-2,4-dimethyl-1H-pyrrole-3-carboxylate (2-23)



Following a literature procedure,[61] to a stirred solution of DMF (3.70 mL, 48.0 mol) in CH_2Cl_2 (50 mL) at 0 °C was added drop-wise $POCl_3$ (4.40 mL, 48.0 mmol) under N_2. The solution was stirred at room temperature for 15 minutes, and the mixture was then added drop-wise to a stirred solution of **2-22** (10.0 g, 43.5 mmol) in CH_2Cl_2 (100 mL) at 0 °C over a period of 15 minutes. The reaction mixture was then heated at reflux for 2 hours. After cooling to room temperature, 1 M $NaHCO_3$ (0.2 L, 0.2 mol) was added: the mixture was then heated at reflux temperature for 1 hour. After cooling to room temperature, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic fractions were washed with brine and water, dried over sodium sulfate, and concentrated *in vacuo* to give a light brown solid which was crystallized from hexane/EtOAc (70:30) to give an off-white fluffy crystalline solid

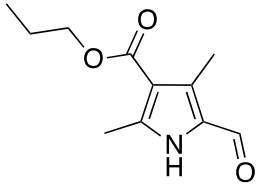
(8.93 g, 80 %). δ_H ($CDCl_3$, 250 MHz) 2.29 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 5.33 (s, 2H, CH_2Ph), 7.26-7.47 (m, 5H, Ar-H), 9.59 (s, 1H, HCO) 10.67 (bs, 1H, NH). These data matches reported literature values.[63]

5-Formyl-2,4-dimethyl-1*H*-pyrrole-3-carboxylic acid (2-24)



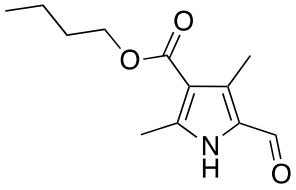
Following a literature procedure,[61] benzyl 5-formyl-2,4-dimethyl-1*H*-pyrrole-3-carboxylate **2-23** (8.0 g, 31.0 mmol) and 10 mol% palladium on activated carbon (1.64 g, 1.55 mmol) were dissolved in ethanol (100 mL), and triethylamine (0.5 mL) was added. The reaction vessel was purged three times with N_2 before introduction of a H_2 atmosphere. After stirring for 5 hours the reaction was complete, and a N_2 atmosphere was introduced. The mixture was then filtered through a plug of Celite® to remove the catalyst, and the plug was rinsed with methanol (3 x 50 mL). Removal of the solvent *in vacuo* gave a bright white solid (5.18 g, 99%). δ_H ($CDCl_3$, 250 MHz): 2.29 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 9.57 (s, 1H, HCO). Signals corresponding to the acidic and nitrogenous protons were not visible in the spectrum. This data matches reported literature values.[63]

Propyl 5-formyl-2,4-dimethyl-1*H*-pyrrole-3-carboxylate (2-25)



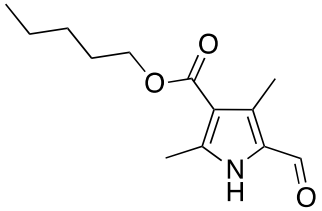
According to general procedure **I** and using *n*-propanol (15 equivalents), this compound was obtained as an off-white solid (372 mg, 46%). Mp = 164° C. δ_H ($CDCl_3$, 500 MHz) 1.02 (t, 3H, *J* = 7.4 Hz, CH_2CH_3), 1.76 (asextet, 2H *J* = 7.0 Hz, CH_2CH_3), 2.55 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 4.21 (t, 2H, *J* = 6.6 Hz, OCH_2), 9.60 (s, 1H, HCO), 10.16 (bs, 1H, NH); δ_C ($CDCl_3$, 125 MHz) 10.8, 10.9, 14.6, 22.3, 65.6, 114.3, 128.4, 136.3, 143.8, 165.2, 177.5; ESI: $[M+Na]^+$ ($C_{11}H_{15}NO_3$): 232.0590 (calculated); 232.0944 (experimental).

Butyl 5-formyl-2,4-dimethyl-1*H*-pyrrole-3-carboxylate (2-26)



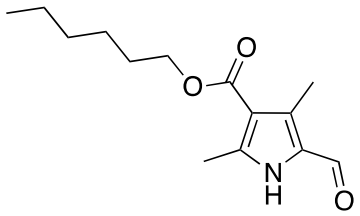
According to general procedure **I** and using *n*-butanol (15 equivalents), this compound was obtained as an off-white solid (530 mg, 56%). Mp = 164 °C. δ_H ($CDCl_3$, 500 MHz) 0.97 (t, 3H, *J* = 7.5 Hz, CH_2CH_3), 1.42-1.50 (m, 2H, CH_2CH_3), 1.69-1.85 (m, 2H, OCH_2CH_2), 2.55 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 4.25 (t, 2H, *J* = 6.5 Hz, OCH_2), 9.60 (s, 1H, HCO), 10.43 (bs, 1H, NH); δ_C ($CDCl_3$, 125 MHz) 10.9, 13.9, 14.5, 19.6, 31.0, 63.8, 114.3, 128.4, 136.5, 144.0, 165.2, 177.5; ESI: $[M+Na]^+$ ($C_{12}H_{17}NO_3Na$) 246.1101 (calculated); 246.1088 (experimental).

Pentyl 5-formyl-2,4-dimethyl-1*H*-pyrrole-3-carboxylate (2-27)



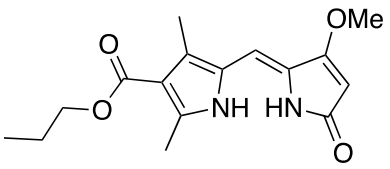
According to an amended general procedure **I** using 1-pentanol (5.0 equivalents) in DMF (10 mL), this compound was obtained as an off-white solid (348 mg, 38%). Mp = 166 °C. δ_H ($CDCl_3$, 500 MHz) 0.92 (t, 3H, J = 6.8 Hz, CH_2CH_3), 1.34-1.45 (m, 4H, $CH_2CH_2CH_3$), 1.74 (aquintet, 2H, J = 6.8 Hz, OCH_2CH_2), 2.55 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 4.24 (t, 2H, J = 6.8 Hz, OCH_2), 9.60 (s, 1H, HCO), 9.99 (bs, 1H, NH); δ_C ($CDCl_3$, 125 MHz) 10.8, 10.9, 14.6, 22.5, 28.5, 28.6, 64.1, 114.4, 128.4, 136.2, 143.6, 165.2, 177.5; ESI: $[M+Na]^+$ ($C_{13}H_{19}NO_3$) 260.1263 (calculated); 260.1257 (experimental).

Hexyl 5-formyl-2,4-dimethyl-1*H*-pyrrole-3-carboxylate (2-28)



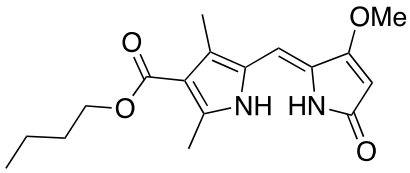
According to an amended general procedure **I** using hexanol (5.0 equivalents) in DMF (10 mL), this compound was obtained as an off-white solid (192 mg, 31%). Mp = 167 °C. δ_H ($CDCl_3$, 500 MHz) 0.90 (t, 3H, J = 7.0 Hz, CH_2CH_3), 1.30-1.33 (m, 4H, $CH_2CH_2CH_3$), 1.39-1.45 (m, 2H, $OCH_2CH_2CH_2$), 1.73 (aquintet, 2H, J = 7.0 Hz, OCH_2CH_2), 2.55 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 4.24 (t, 2H, J = 7.0 Hz, OCH_2), 9.58 (s, 1H, HCO), 10.79 (bs, 1H, NH); δ_C ($CDCl_3$, 125 MHz) 10.8, 14.1, 14.4, 22.7, 26.0, 28.9, 31.6, 64.0, 114.3, 128.4, 136.8, 144.3, 165.2, 177.5; ESI: $[M+Na]^+$ ($C_{14}H_{21}NO_3$): 274.1419 (calculated); 274.1414 (experimental).

(*Z*)-Propyl 5-((3-methoxy-5-oxo-1*H*-pyrrol-2(5H)-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrole-3-carboxylate (2-29)



This compound was obtained according to general procedure **II**, from **2-25**, as a bright yellow solid (290 mg, 70%). Mp = 158 °C. δ_H ($CDCl_3$, 500 MHz) 1.03 (t, 3H, J = 7.4 Hz, CH_2CH_3), 1.76 (asextet, 2H, J = 7.4, CH_2CH_3), 2.38 (s, 3H, CH_3), 2.65 (s, 3H, CH_3), 3.89 (s, 3H, OCH_3), 4.20 (t, 2H, J = 6.5 Hz, OCH_2), 5.09 (s, 1H, Pyr-H), 6.38 (s, 1H, *meso*-H), 10.57 (bs, 1H, NH), 10.98 (bs, 1H, NH); δ_C ($CDCl_3$, 125 MHz) 11.0, 11.5, 14.3, 22.4, 58.4, 65.3, 90.3, 99.8, 112.7, 122.5, 123.6, 128.3, 141.8, 166.0, 168.2, 173.6; ESI: $[M+Na]^+$ ($C_{16}H_{20}N_2O_4$): 327.1321 (calculated); 327.1315 (experimental).

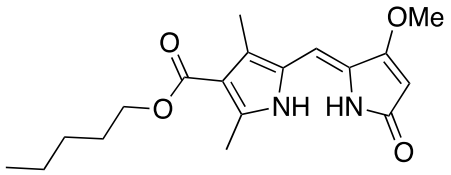
(*Z*)-Butyl 5-((3-methoxy-5-oxo-1*H*-pyrrol-2(5H)-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrole-3-carboxylate (2-30)



This compound was obtained according to general procedure **II**, from **2-26**, as a bright yellow solid (548 mg, 87%). Mp = 158 °C. δ_H (DMSO-d_6, 500 MHz) 0.91 (t, 3H, J = 7.5 Hz, CH_2CH_3), 1.35-1.43 (m, 2 H, CH_2CH_3), 1.60-1.65 (m, 2H, OCH_2CH_2), 2.20 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 4.12 (t, 2H, J = 6.5 Hz, OCH_2), 5.25 (s, 1H, Pyr-H), 6.02 (s, 1H, *meso*-H), 9.64 (s, 1H, NH), 10.90 (s, 1H, NH); δ_C (DMSO-d_6, 125 MHz) 11.1, 13.8, 19.2, 30.6, 58.7, 62.9, 91.5, 95.0, 111.7, 122.2, 124.4, 125.4, 139.5,

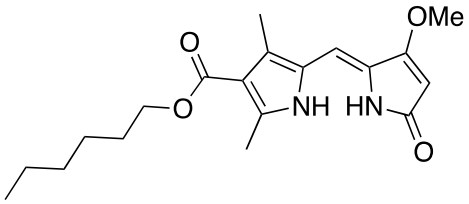
165.1, 167.2, 171.3;* ESI: $[M+Na]^+$ ($C_{17}H_{22}N_2O_4$): 341.1477 (calculated); 341.1472 (experimental).*Note: one signal missing, likely buried under DMSO solvent signal.

(*Z*)-Pentyl 5-((3-methoxy-5-oxo-1*H*-pyrrol-2(5H)-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrole-3-carboxylate (2-31)



This compound was obtained according to general procedure **II**, from **2-27**, as a bright yellow solid (948 mg, 93%). Mp = 160 °C. δ_H (DMSO-d_6, 500 MHz): 0.88 (t, 3H, J = 7.0 Hz, CH_2CH_3), 1.31-1.36 (m, 4H, $CH_2CH_2CH_3$), 1.65 (aquintet, 2H, J = 6.9 Hz, OCH_2CH_2), 2.21 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 4.12 (t, 2H, J = 6.5 Hz, OCH_2), 5.26 (s, 1H, Pyr-H), 6.02 (s, 1H, *meso*-H), 9.64 (bs, 1H, NH), 10.90 (bs, 1H, NH); δ_C (DMSO-d_6, 125 MHz) 10.9, 13.6, 13.9, 21.8, 27.9, 28.0, 58.4, 62.9, 91.4, 94.5, 111.5, 122.0, 124.0, 125.3, 139.1, 164.8, 166.9, 170.8; ESI: $[M+Na]^+$ ($C_{18}H_{24}N_2O_4$): 355.1634 (calculated); 355.1628 (experimental).

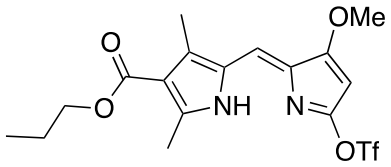
(*Z*)-Hexyl 5-((3-methoxy-5-oxo-1*H*-pyrrol-2(5H)-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrole-3-carboxylate (2-32)



This compound was obtained according to general procedure **II** from **2-28** as a bright yellow solid (213 mg, 87%). Separate crystallizations produced batches containing pure

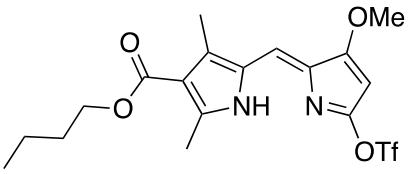
product, as well as *E/Z* isomeric mixtures. Mp = 162 °C. δ_H (DMSO-d_6, 250 MHz) 0.87 (t, 3H, *J* = 6.6 Hz, CH_3CH_3), 1.18-1.45 (m, 6H, $(CH_2)_3CH_3$), 1.63 (q, 2H, *J* = 6.8 Hz, OCH_2CH_2), 2.22 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 4.13 (t, 2H, *J* = 6.4 Hz, OCH_2), 5.26 (s, 1H, Pyr-H), 6.02 (s, 1H, *meso*-H), 9.66 (bs, 1H, NH), 10.93 (s, 1H, NH); δ_C (DMSO-d_6, 125 MHz) 11.0, 13.7, 13.9, 22.1, 25.4, 28.4, 30.9, 58.5, 62.9, 91.4, 94.6, 95.4, 100.8, 111.2, 111.5, 122.1, 123.6, 124.0, 125.3, 127.7, 137.3, 139.2, 163.8, 164.8, 166.9, 168.5, 170.9; ESI: $[M+Na]^+$ ($C_{19}H_{26}N_2O_4$): 369.1790 (calculated); 369.1785 (experimental) *Note: ^{13}C NMR data obtained from mixture of E and Z isomers, resulting in two sets of dipyrrinone core ^{13}C signals.

(*Z*)-Propyl 2-((3-methoxy-5-(((trifluoromethyl)sulfonyl)oxy)-*1H*-pyrrol-2-yl)methylene)-3,5-dimethyl-2*H*-pyrrole-4-carboxylate (2-33)



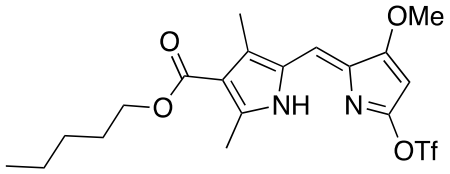
This compound was obtained according to general procedure **III**, from **2-29**, as a bright yellow solid (186 mg, 99%). δ_H ($CDCl_3$, 500 MHz) 1.02 (t, 3H, *J* = 7.4 Hz, CH_2CH_3), 1.76 (asextet, 2H, *J* = 7.1 Hz, CH_2CH_3), 2.43 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3), 4.21 (t, 2H, *J* = 6.6 Hz, OCH_2), 5.43 (s, 1H, Pyr-H), 7.13 (s, 1H, *meso*-H), 10.99 (bs, 1H); δ_C ($CDCl_3$, 125 MHz) 11.0, 11.7, 15.2, 22.3, 59.0, 65.6, 87.6, 114.4*, 119.2, 126.1, 133.4*, 135.4*, 144.8*, 161.9*, 165.3*, 168.2*; ESI: $[M+Na]^+$ ($C_{17}H_{19}F_3N_2O_6S$): 459.0814 (calculated); 459.0808 (experimental). *Note: signals barely distinguishable from baseline signal. Assignments made through comparison to related structures. Signal for CF_3 carbon indistinguishable from baseline.

(*Z*)-Butyl 2-((3-methoxy-5-(((trifluoromethyl)sulfonyl)oxy)-*1H*-pyrrol-2-yl)methylene)-3,5-dimethyl-2*H*-pyrrole-4-carboxylate (2-34)



This compound was obtained according to general procedure **III**, from **2-30**, as a bright yellow solid (418 mg, 74%). δ_H ($CDCl_3$, 500 MHz) 0.97 (t, 3H, J = 7.4 Hz, CH_2CH_3), 1.46 (asextet, 2H, J = 7.5 Hz, CH_2CH_3), 1.72 (aquintet, 2H, J = 7.3 Hz, OCH_2CH_2), 2.42 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3), 4.25 (t, 2H, J = 6.6 Hz, OCH_2), 5.43 (s, 1H, Pyr-H), 7.12 (s, 1H, *meso*-H), 10.99 (bs, 1H); δ_C ($CDCl_3$, 125 MHz) 11.7, 13.9, 15.1, 19.6, 31.0, 59.0, 63.7, 87.6, 114.4, 119.2, 126.1, 133.3, 135.4, 144.8, 161.8, 165.4, 168.2;* ESI: $[M+Na]^+$ ($C_{18}H_{21}F_3N_2O_6S$): 473.0970 (calculated); 473.0965 (experimental). *Signal for CF_3 carbon indistinguishable from baseline.

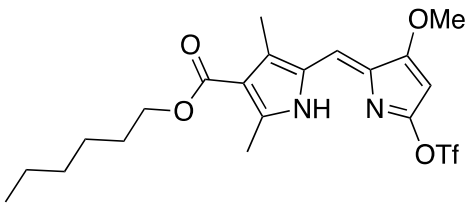
(*Z*)-Pentyl 2-((3-methoxy-5-(((trifluoromethyl)sulfonyl)oxy)-*1H*-pyrrol-2-yl)methylene)-3,5-dimethyl-2*H*-pyrrole-4-carboxylate (2-35)



This compound was obtained according to general procedure **III**, from **2-31**, as a bright yellow solid (914 mg, 99%). δ_H ($CDCl_3$, 500 MHz) 0.92 (t, 3H, J = 7.0 Hz, CH_2CH_3), 1.35-1.44 (m, 4H, $CH_2CH_2CH_3$), 1.74 (aquintet, 2H, J = 7.1 Hz, OCH_2CH_2), 2.42 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3), 4.24 (t, 2H, J = 6.7 Hz, OCH_2), 5.43 (s, 1H, Pyr-H), 7.12 (s, 1H, *meso*-H), 10.99 (bs, 1H, NH); δ_C ($CDCl_3$, 75 MHz) 11.6, 14.1, 15.1,

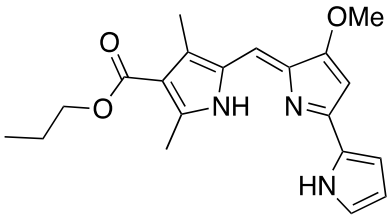
22.5, 28.5, 28.7, 59.0, 64.0, 87.6, 114.4, 118.8 (q, J = 320 Hz), 119.1, 126.1, 133.4, 135.4, 144.8, 161.9, 165.3, 168.2; ESI: $[M+Na]^+$ ($C_{19}H_{19}F_3N_2O_6S$): 487.1127 (calculated); 487.1132 (experimental).

(*Z*)-Hexyl 2-((3-methoxy-5-(((trifluoromethyl)sulfonyl)oxy)-*1H*-pyrrol-2-yl)methylene)-3,5-dimethyl-2*H*-pyrrole-4-carboxylate (2-36)



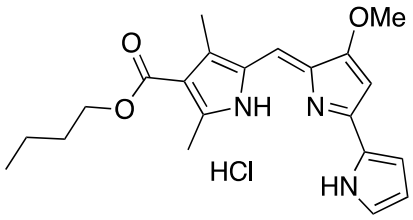
This compound was obtained according to general procedure **III**, from **2-32**, as a bright yellow solid (100 mg, 92%). δ_H ($CDCl_3$, 500 MHz) 0.90 (t, 3H, J = 7.0 Hz, CH_2CH_3), 1.31-1.34 (m, 4H, $CH_2CH_2CH_3$), 1.40-1.46 (m, 2H, $OCH_2CH_2CH_2$), 1.73 (aquintet, 2H, J = 7.1 Hz, OCH_3CH_3), 2.43 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3), 4.24 (t, 2H, J = 6.6 Hz, OCH_2), 5.45 (s, 1H, Pyr-H), 7.14 (s, 1H, *meso*-H), 11.02 (bs, 1H, NH); δ_C ($CDCl_3$, 125 MHz) 11.7, 14.2, 15.1, 22.7, 26.0, 28.9, 31.6, 59.0, 64.1, 87.6, 114.4, 118.7 (q, J = 319 Hz), 119.1, 126.1, 133.3, 135.4, 144.8, 161.8, 165.3, 168.2; ESI: $[M+H]^+$ ($C_{20}H_{26}F_3N_2O_6S$): 479.1419 (calculated); 479.1458 (experimental).

(*Z*)-Propyl 5-((4'-methoxy-1*H*,5'*H*-[2,2'-bipyrrol]-5'-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrole-3-carboxylate hydrochloride (2-37)



This compound was synthesized according to general procedure **IV**, from **2-33**, omitting the final step and collected in the free-base form as a purple-red film (12 mg, 10%). Mp = 163 °C. δ_H ($CDCl_3$, 500 MHz) 0.98 (t, 3H, J = 7.4 Hz, CH_2CH_3), 1.70 (asextet, 2H, J = 7.0 Hz, CH_2CH_3), 2.16 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 3.99 (s, 3H, OCH_3), 4.13 (t, 2H, J = 6.5 Hz, OCH_2), 6.06 (s, 1H, Ar-H), 6.19 (bs, 1H, Pyr-H), 6.71 (d, 1H, J = 3.0 Hz, Pyr-H), 6.73 (bs, 1H, Pyr-H), 6.94 (s, 1H, *meso*-H);* δ_C (125 MHz; $CDCl_3$): 11.0, 11.7, 13.1, 22.3, 58.7, 65.3, 89.9, 96.1, 110.7, 112.5, 113.6, 123.2, 126.1, 128.3, 131.8, 140.1, 143.4, 160.8, 165.7, 169.1; $[M+H]^+$ ($C_{20}H_{24}N_3O_3$): 354.1773 (calculated); 354.1812 (experimental). UV (CH_2Cl_2) λ_{max} (ε): 525 (19000).*Note that *N*-H signals of prodigiosenes are exchangeable in the free-base form, and are not visible in ^1H spectra.

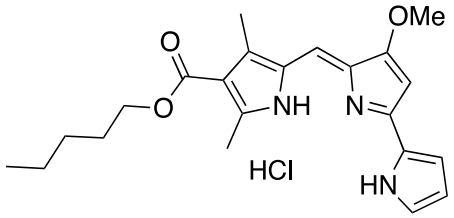
(*Z*)-Butyl 5-((4'-methoxy-1*H*,5'*H*-[2,2'-bipyrrol]-5'-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrole-3-carboxylate hydrochloride (2-38)



This compound was synthesized according to general procedure **IV**, from **2-34**, as a purple film (10 mg, 8%). δ_H ($CDCl_3$, 500 MHz) 0.97 (t, 3H, J = 7.5 Hz, CH_2CH_3), 1.43-1.50 (m, 2H, CH_2CH_3), 1.70-1.76 (m, 2H, OCH_2CH_2), 2.51 (s, 3H, CH_3), 2.81 (s, 3H, CH_3), 4.04 (s, 3H, OCH_3), 4.26 (t, 2H, J = 6.5 Hz, OCH_2), 6.10 (bs, 1H, Pyr-H), 6.37-6.39 (m, 1H, Pyr-H), 7.00 (bs, 1H, Pyr-H), 7.10 (s, 1H, *meso*-H), 7.29 (bs, 1H, Pyr-H), 12.66 (bs, 1H, NH), 12.72 (bs, 1H, NH), 12.93 (bs, 1H, NH); δ_C ($CDCl_3$, 125 MHz) 12.0, 13.9, 15.0, 19.6, 31.0, 59.1, 64.0, 93.4, 112.5, 113.0, 116.0, 119.1, 122.2, 122.6, 123.5,

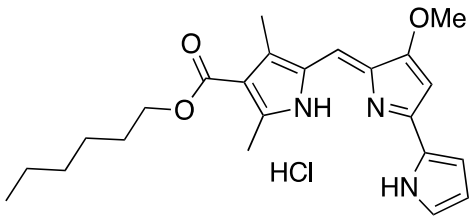
128.6, 140.6, 150.1, 150.5, 164.8, 166.8; ESI: $[M+H]^+$ ($C_{21}H_{26}N_3O_3$): 368.1929 (calculated); 368.1969 (experimental). UV (CH_2Cl_2) λ_{max} (ε): 525 (19000).

(*Z*)-Pentyl 5-((4'-methoxy-1*H*,5'*H*-[2,2'-bipyrrol]-5'-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrole-3-carboxylate hydrochloride (2-39)



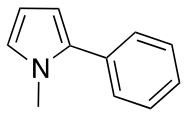
This compound was synthesized according to general procedure **IV**, from **2-35**, as a purple solid (341 mg, 42%). Mp = 164 °C. δ_H ($CDCl_3$, 500 MHz) 0.93 (t, 3H, J = 7.0 Hz, CH_2CH_3), 1.35-1.45 (m, 4H, $CH_2CH_2CH_3$), 1.75 (aquintet, 2H, J =7.01 Hz, OCH_2CH_2), 2.52 (s, 3H, CH_3), 2.82 (s, 3H CH_3), 4.05 (s, 3H, OCH_3), 4.25 (t, 2H, J = 6.64, OCH_2), 6.10 (s, 1H, Ar-H), 6.39 (bs, 1H, Pyr-H), 7.00 (bs, 1H, Pyr-H), 7.11 (s, 1H, *meso*-H), 7.29 (s, 1H, Pyr-H), 12.66 (bs, 1H, NH), 12.72 (bs, 1H, NH), 12.95 (bs, 1H, NH); δ_C ($CDCl_3$, 125 MHz) 12.0, 14.1, 14.9, 22.4, 28.4, 28.5, 59.1, 64.2, 93.4, 112.5, 112.8, 115.8, 119.0, 122.0, 122.4, 123.4, 128.3, 140.4, 150.0, 150.2, 164.6, 166.7; ESI: $[M+H]^+$ ($C_{22}H_{28}N_3O_3$): 354.2131 (calculated); 382.2125 (experimental). UV (CH_2Cl_2) λ_{max} (ε): 525 (19000).

(*Z*)-Hexyl 5-((4'-methoxy-1*H*,5'*H*-[2,2'-bipyrrol]-5'-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrole-3-carboxylate hydrochloride (2-40)



This compound was synthesized according to general procedure **IV**, from **2-36**, as a purple-red solid (22 mg, 30%). Mp = 165 °C. δ_H ($CDCl_3$, 500 MHz) 0.90 (t, 3H, *J* = 7.0 Hz, CH_2CH_3), 1.28-1.38 (m, 4H, $CH_2CH_2CH_3$), 1.40-1.47 (m, 2H, $OCH_2CH_2CH_2$), 1.73 (aquintet, 2H, *J* = 7.1 Hz, OCH_2CH_2), 2.49 (s, 3H, CH_3), 2.79 (s, 3H, CH_3), 4.02 (s, 3H, OCH_3), 4.23 (t, 2H, *J* = 6.6 Hz, OCH_2), 6.06 (s, 1H, Ar-H), 6.36 (d, 1H, *J* = 2.5 Hz, Pyr-H), 6.96 (bs, 1H, Pyr-H), 7.07 (bs, 1H, Pyr-H), 7.26 (s, 1H, *meso*-H),* 12.68 (bs, 2H, 2 x NH), 12.87 (bs, 1H, NH); δ_C ($CDCl_3$, 125 MHz) 12.0, 14.1, 15.0, 22.7, 26.0, 28.9, 31.6, 59.1, 64.3, 93.4, 112.5, 113.0, 115.9, 119.0, 122.1, 122.5, 123.5, 128.5, 140.6, 150.1, 150.4, 164.8, 166.7; ESI: $[M+H]^+$ ($C_{23}H_{30}N_3O_3$): 396.2287 (calculated); 396.2282 (experimental). UV (CH_2Cl_2) λ_{max} (ε): 525 (19000).*Note: signal overlap with $CDCl_3$.

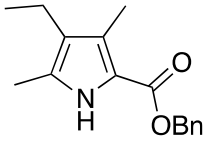
1-Methyl-2-phenyl-1*H*-pyrrole (2-45)



Following a literature procedure,[80] pyrrole **2-44** (100 mg, 0.80 mmol, provided from Maybridge chemical supplier) was reacted with phenylbromide to provide **2-45** as a colourless solid (63 mg, 85%). δ_H ($CDCl_3$, 250 MHz) 3.70 (s, 3H, CH_3), 6.26 (bs, 1H,

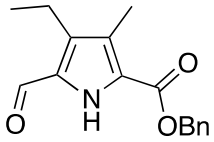
Pyr-H), 6.75 (bs, 1H, Pry-H), 7.36 (bs, 1H, Pyr-H), 7.40-7.46 (m, 5H, Ar-H). These data match reported literature values.

Benzyl 4-ethyl-3,5-dimethyl-1*H*-pyrrole-2-carboxylate (2-47)



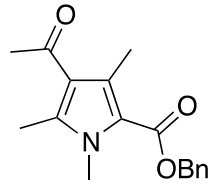
Pyrrole **2-46**[81] (5g, 18.4 mmol) was dissolved in anhydrous THF (50 mL) under an N_2 environment, and cooled to 0 °C using an external ice bath. A solution of borane•THF (36.8 mL, 36.8 mmol, 1.0 M in THF) was added drop-wise, via addition funnel, over 20 minutes with rapid stirring. The reaction was allowed to reach room temperature, and was then stirred overnight (18 h). Upon completion, the reaction was quenched with careful addition of water (5 mL), and HCl (10 mL, 1.0 M, aq) was then added to the solution. The mixture was then poured into sat. $NaHCO_3$ (100 mL), and the organic layer separated and washed with brine (3 x 30 mL) and dried over anhydrous sodium sulfate. Upon removal of the solvent *in vacuo*, the product was obtained as a turquoise solid (4.62 g, 99%).* δ_H ($CDCl_3$, 250 MHz) 1.05 (t, 3H, J = 7.5 Hz, $CH_2\mathit{CH_3}$), 2.20 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.38 (q, 2H, J = 7.5 Hz, $\mathit{CH_2}CH_3$), 5.31 (s, 2H, CH_2Ph), 7.44-7.32 (m, 5H, Ar-H), 8.61 (bs, 1H, NH). This data matches reported literature values.[94] *Despite recrystallization of the product in methanol, the turquoise colour of the product persisted, although no impurities were observable in the ^1H NMR spectrum.

Benzyl 4-ethyl-5-formyl-3-methyl-1*H*-pyrrole-2-carboxylate (2-48)



Adapting a literature procedure,[95] pyrrole **2-47** (2 g, 7.78 mmol) was dissolved in methanol under atmospheric conditions. Cerium ammonium nitrate (17.6 g, 31.9 mmol) was added as a solution in water (15 mL) with stirring. Formation of a white precipitate was readily observed. After stirring for 45 min, no trace of starting material was detected using TLC analysis. The reaction vessel was cooled to 0 °C, and the precipitate was collected via suction filtration. The solid was washed with hexanes, and then collected via dissolution in CH_2Cl_2.The organic layer was dried over Na_2SO_4, and following removal of the solvent *in vacuo*, the product was obtained without further purification as a white solid (1.7 g, 81%). δ_H ($CDCl_3$, 250 MHz) 1.19 (t, 3H, J = 7.6 Hz, CH_2CH_3), 2.30 (s, 3H, CH_3), 2.74 (q, 2H, J = 7.6 Hz, CH_2CH_3), 5.33 (s, 2H, CH_2Ph), 7.35-7.43 (m, 5H, Ar-H), 9.49 (bs, 1H, NH), 9.75 (s, 1H, HCO). These data matche reported literature values.[96]

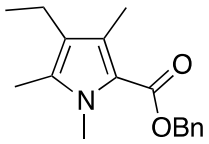
Benzyl 4-acetyl-1,3,5-trimethyl-pyrrole-2-carboxylate (2-51)



Adapting a literature procedure,[83] pyrrole **2-46** (500 mg, 1.84 mmol) was dissolved in CH_2Cl_2 (20 mL) and tetrabutylammonium bromide (59 mg, 0.184 mmol) and methyl iodide (126 µl, 2.02 mmol) were added. The mixture was stirred vigorously at 0 °C as

aqueous sodium hydroxide (10 mL, 5 M) was added drop-wise. The mixture darkened, and was allowed to warm to room temperature as the reaction stirred overnight (18 h). The organic fraction was separated and washed with brine (100 mL), dried over sodium sulfate, and filtered over a pad of neutral silica using methanol:CH_2Cl_2 (5:95). After removal of the solvent *in vacuo,* pyrrole **2-51** was isolated as an off-white solid (611 mg, 99%). δ_H (500 MHz; $CDCl_3$) 2.45 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 3.77 (s, 3H, NCH_3), 5.32 (s, 2H, CH_2Ph), 7.43-7.33 (m, 5H, Ar-H); δ_C ($CDCl_3$, 125 MHz) 12.4, 13.7, 32.0, 33.2, 66.1, 123.5, 128.3, 128.8, 129.5, 136.2, 140.5, 162.1, 196.6;* ESI: $[M+Na]^+$ ($C_{17}H_{19}NO_3$): 308.1263 (calculated); 308.1257 (experimental).*Two aromatic signals unaccounted for in ^{13}C NMR spectrum.

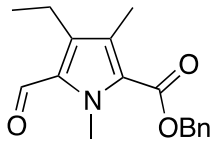
Benzyl 4-ethyl-1,3,5-trimethyl-pyrrole-2-carboxylate (2-52)



Adapting a literature procedure,[83] pyrrole **2-47** (2.12 g, 8.2 mmol) was dissolved in CH_2Cl_2 (20 mL) and tetrabutylammonium bromide (264 mg, 0.82 mmol) and methyl iodide (564 µl, 9.06 mmol) were added. The mixture was stirred vigorously at 0 °C as aqueous sodium hydroxide (20 mL, 5 M) was added drop-wise. The reaction vessel and condenser tube were sealed, and the mixture was heated at 50 °C for 3 days. Although a considerable amount of starting material was still present, the organic fraction was separated and washed with brine (100 mL), and dried over sodium sulfate. Purification using chromatography (SiO_2, EtOAc/hexane 1/9 then 2/8) furnished pyrrole **2-52** as a colourless oil (482 mg, 22%). δ_H (500 MHz; $CDCl_3$) 1.02 (t, 3H, J = 7.5 Hz, CH_2CH_3),

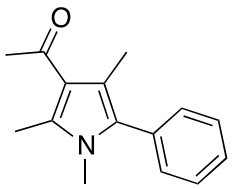
2.16 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 2.39 (q, 2H, J = 7.5 Hz, CH_2CH_3), 3.77 (s, 3H, NCH_3), 5.29 (s, 2H, CH_2Ph), 7.30 (t, 1H, J = 7.2 Hz, Ar-H), 7.36 (t, 2H, J = 7.4 Hz, Ar-H), 7.42 (d, 2H, J = 7.3 Hz, Ar-H); δ_C ($CDCl_3$, 125 MHz) 10.4, 11.8, 15.8, 17.6, 33.1, 53.6, 65.26, 122.8, 127.6, 128.0, 128.1, 128.6, 137.1, 162.1;* ESI: $[M+Na]^+$ ($C_{17}H_{21}NO_2$): 294.1470 (calculated); 294.1465. *One aromatic signal unaccounted for in ^{13}C-NMR spectrum.

Benzyl 4-ethyl-5-formyl-1,3-dimethyl-pyrrole-2-carboxylate (2-53)



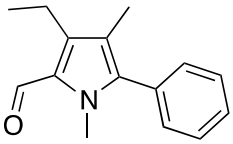
Adapting a literature procedure,[83] pyrrole **2-48** (1.7 g, 6.27 mmol) was dissolved in CH_2Cl_2 (20 mL) and tetrabutylammonium bromide (202 mg, 0.627 mmol) and methyl iodide (429 µl, 6.89 mmol) were added. The mixture was stirred vigorously at 0 °C as aqueous sodium hydroxide (15 mL, 5M) was added drop-wise. The mixture darkened, and was allowed warm to room temperature as the reaction stirred overnight (18 h). The organic fraction was separated and washed with brine (100 mL), dried over sodium sulfate, and filtered over a pad of neutral silica using methanol:CH_2Cl_2 (5:95). After removal of the solvent *in vacuo,* pyrrole **2-53** was isolated as an impure brown solid (1.78g, ~99% mmol). δ_H (500 MHz; $CDCl_3$) 1.13 (t, 3H, J = 7.5 Hz, CH_2CH_3), 2.20 (s, 3H, CH_3), 4.16 (s, 3H, NCH_3), 5.35 (s, 2H, CH_2Ph), 7.45-7.34 (m, 5H, Ar-H), 9.89 (s, 1H, HCO); ESI: $[M+Na]^+$ ($C_{17}H_{19}NO_3$): 308.1263 (calculated); 308.1257.

1-(1,2,4-Trimethyl-5-phenyl-1*H*-pyrrol-3-yl)ethanone (2-55)



To generate the 2-carboxylic acid required for coupling, pyrrole **2-51** was subjected to general procedure **V** for hydrogenolysis to produce the acid as a white solid (356 mg, 99%). δ_H (500 MHz; $CDCl_3$) 2.44 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 2.56 (s, 3H, CH_3), 3.78 (s, 3H, NCH_3). The material was used crude, and subjected to general procedure **VI**, to isolate **2-55** as a beige solid (123 mg, 99%). δ_H (500 MHz; $CDCl_3$) 2.17 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 2.56 (s, 3H, CH_3), 3.34 (s, 3H, NCH_3), 7.25 (d, 2H, J = 6.9 Hz, Ar-H), 7.38 (t, 1H, J = 7.4 Hz, Ar-H), 7.44 (t, 2H, J = 7.4 Hz, Ar-H); δ_C ($CDCl_3$, 125 MHz) 12.7, 13.0, 31.6, 31.7, 116.4, 121.6, 127.8, 128.5, 131.2, 131.6, 132.1, 135.7, 196.1; ESI: $[M+Na]^+$ ($C_{15}H_{17}NO$): 250.1208 (calculated); 250.1202 (experimental).

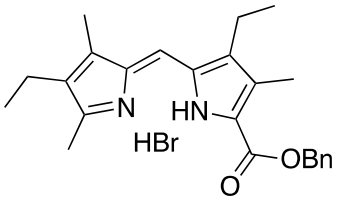
3-Ethyl-1,4-dimethyl-5-phenyl-1*H*-pyrrole-2-carbaldehyde (2-57)



To generate the 2-carboxylic acid required for coupling, pyrrole **2-53** (459 mg, 1.61 mmol) was subjected to general procedure **V** for hydrogenolysis. Some impurities persisted, and so an acid-base wash was performed: the carboxylic acid was dissolved in CH_2Cl_2 (30 mL), and washed with NaOH (1M, 30 mL). The organic layer was removed, and the basic layer acidified with citric acid. The carboxylic acid of **2-53** was extracted into CH_2Cl_2. Removal of the organic layer *in vacuo* yielded the carboxylic acid as a white

solid (169 mg, 54%). δ_H (500 MHz; $CDCl_3$) 1.16 (t, 3H, J = 7.6 Hz, $CH_2\mathit{CH_3}$), 2.29 (s, 3H, CH_3), 2.74 (d, 2H, J = 7.6 Hz, $\mathit{CH_2}CH_3$), 4.20 (s, 3H, NCH_3), 9.94 (s, 1H, HCO). The material was used crude, and subjected to general procedure **VI**, to isolate **2-57** as a beige solid (78 mg, 43%). δ_H (500 MHz; $CDCl_3$) 1.22 (t, 3H, J = 7.6 Hz, $CH_2\mathit{CH_3}$), 1.93 (s, 3H, CH_3), 2.76 (q, 2H, J = 7.6 Hz, $\mathit{CH_2}CH_3$), 3.75 (s, 3H, NCH_3), 7.29 (d, 2H, J = 6.9 Hz, Ar-H), 7.41 (t, 1H, J = 7.4 Hz, Ar-H), 7.47 (t, 2H, J = 7.3 Hz, Ar-H), 9.75 (s, 1H, HCO); δ_C ($CDCl_3$, 125 MHz) 9.2, 16.7, 17.3, 34.2, 117.3, 127.2, 128.5, 128.6, 130.3, 130.8, 139.7, 141.3, 177.7; ESI: $[M+Na]^+$ ($C_{15}H_{17}NO$): 250.1208 (calculated); 250.1202 (experimental). A small amount of decarboxylated pyrrole product was also produced, and was not easily separated using chromatography (SiO_2, 1→5% EtOAc/Hexanes).

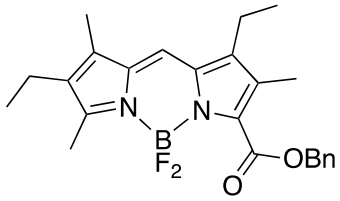
(Z)-Benzyl 4-ethyl-5-((4-ethyl-3,5-dimethyl-2H-pyrrol-2-ylidene)methyl)-3-methyl-1H-pyrrole-2-carboxylate hydrobromide (2-62)



Pyrrole **2-48** (1.075 g, 3.96 mmol) and **2-61** (535 μL, 3.96 mmol, prepared according to a literature procedure)[87] were dissolved in tetrahydrofuran/methanol (10 mL, 1/1), at room temperature with stirring under a nitrogen atmosphere. Concentrated hydrobromic acid (689 μL, 7.92 mmol) was added drop-wise to the solution. The mixture was stirred for four hours, after which the starting materials were consumed, as monitored using TLC analysis. The solution and the precipitate were poured into chilled Et_2O (100 mL) with stirring, and the precipitate was collected through suction filtration. The product was washed with Et_2O and dried under vacuum to render the brick-red dipyrrin salt (1.36 g,

75%). δ_H (500 MHz; $CDCl_3$) 1.10 (t, 3H, J = 7.6 Hz, CH_2CH_3), 1.14 (t, 3H, J = 7.6 Hz, CH_2CH_3), 2.26 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.45 (q, 2H, J = 7.6 Hz, CH_2CH_3), 2.67 (q, 2H, J = 7.6 Hz, CH_2CH_3), 2.80 (s, 3H, CH_3), 5.47 (s, 2H, CH_2Ph), 7.17 (s, 1H, *meso*-H), 7.29 (d, 1H, J = 7.3 Hz, Ar-H), 7.34 (t, 2H, J = 7.3 Hz, Ar-H); 7.62 (d, 1H, J = 7.4 Hz, Ar-H); 12.53 (bs, 1H, NH), 14.86 (bs, 1H, NH); δ_C ($CDCl_3$, 125 MHz) ESI: $[M+H]^+$ undetermined.

7-((Benzyloxy)carbonyl)-2,9-diethyl-5,5-difluoro-1,3,8-trimethyl-5*H*-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diazaborinin-4-ium-5-uide (2-63)

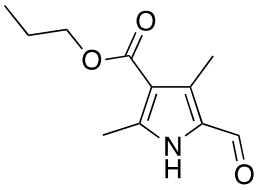


To a solution of **2-62** (1.145 g, 2.51 mmol) in CH_2Cl_2 (100 mL) under nitrogen, DIPEA (2.62 mL, 15.1 mmol) was added, and the solution was stirred for 30 minutes. BF_3•OEt_2 (2.79 mL, 22.6 mmol) was then added slowly over several minutes, and the mixture was stirred for 18 hours, after which no starting material remained as indicated via analysis using TLC. The organic layer was washed with saturated $NaHCO_3$ (aq., 100 mL), separated, and then dried over $MgSO_4$. The solvent was removed *in vacuo*. Purification using silica (ethyl acetate/hexanes, 1:9 V/V) gave the title compound as a dark red solid (541 mg, 51 %). δ_H (500 MHz; $CDCl_3$) 1.08 (t, 3H, J = 7.7 Hz, CH_2CH_3), 1.11 (t, 3H, J = 7.7 Hz, CH_2CH_3), 2.16 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 2.40 (q, 2H, J = 7.6 Hz, CH_2CH_3), 2.57 (q, 2H, J = 7.6 Hz, CH_2CH_3), 2.61 (s, 3H, CH_3), 5.39 (s, 2H, CH_2Ph), 7.05 (s, 1H, *meso*-H), 7.31 (d, 1H, J = 7.3 Hz, Ar-H), 7.36 (t, 2H, J = 7.4 Hz, Ar-H); 7.50 (d, 1H, J = 7.4 Hz, Ar-H); δ_C ($CDCl_3$, 125 MHz) 9.6, 10.9, 13.8, 14.2, 16.4, 17.4, 17.74,

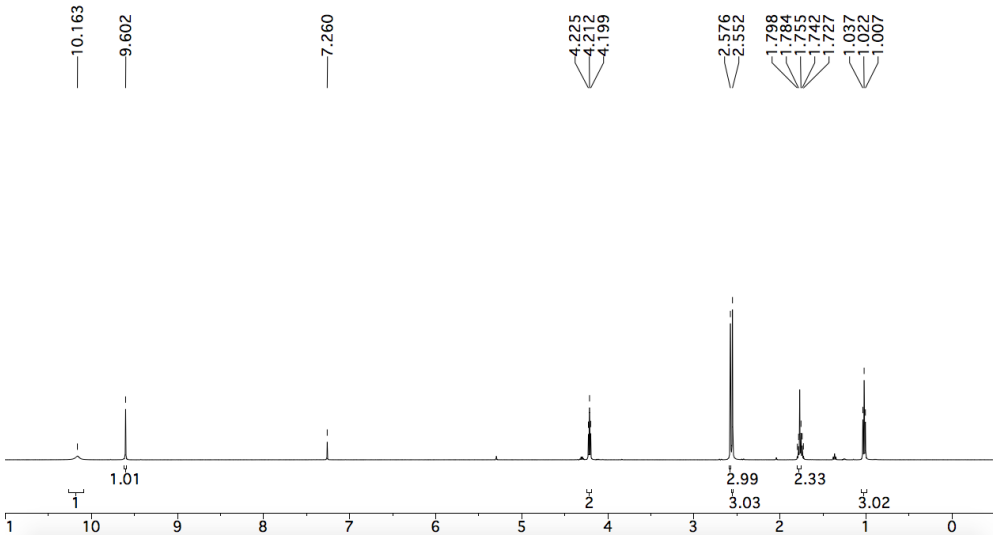
66.7, 120.26, 128.10, 128.50, 128.63, 131.97, 135.80, 136.25, 136.57, 137.62, 140.08, 141.00, 161.66, 166.91, 171.29; ESI: $[M+H]^+$ undetermined.

Section 2.7: NMR Spectra

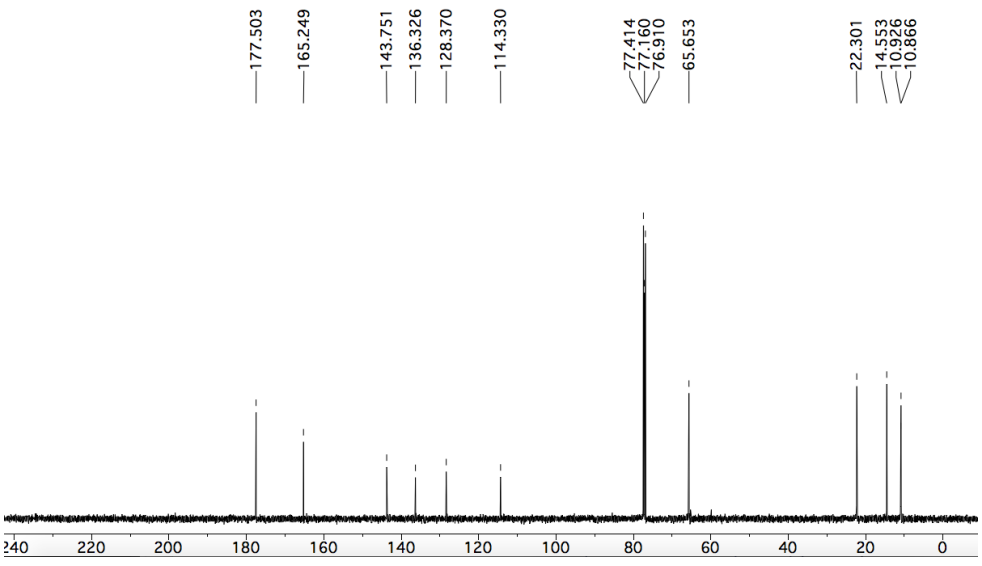
Propyl 5-formyl-2,4-dimethyl-1*H*-pyrrole-3-carboxylate (2-25)



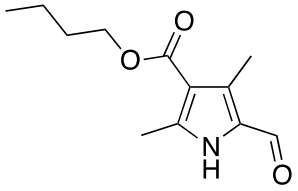
^{1}H NMR ($CDCl_3$, 500 MHz):



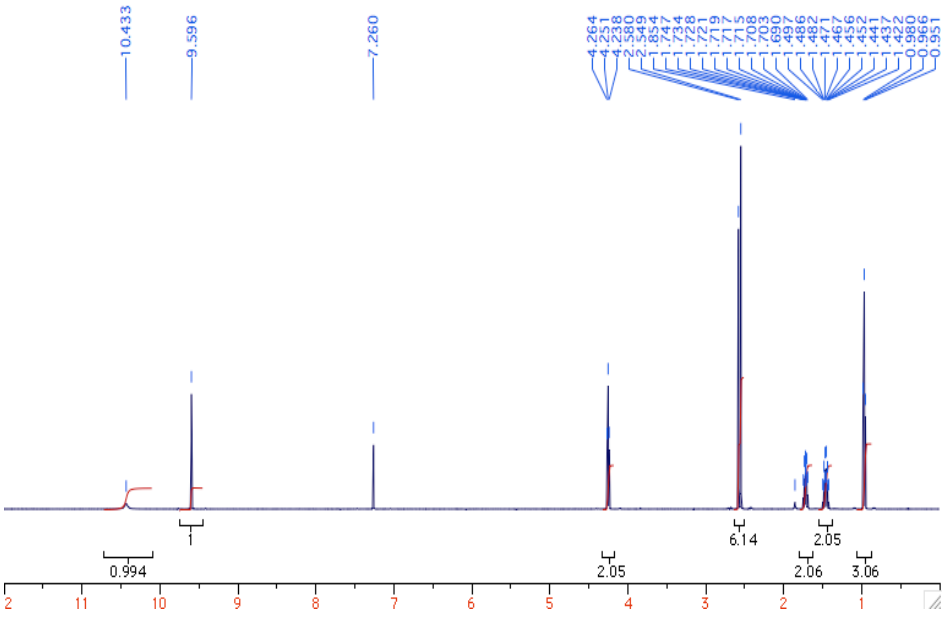
^{13}C UDEFT NMR ($CDCl_3$, 125 MHz):



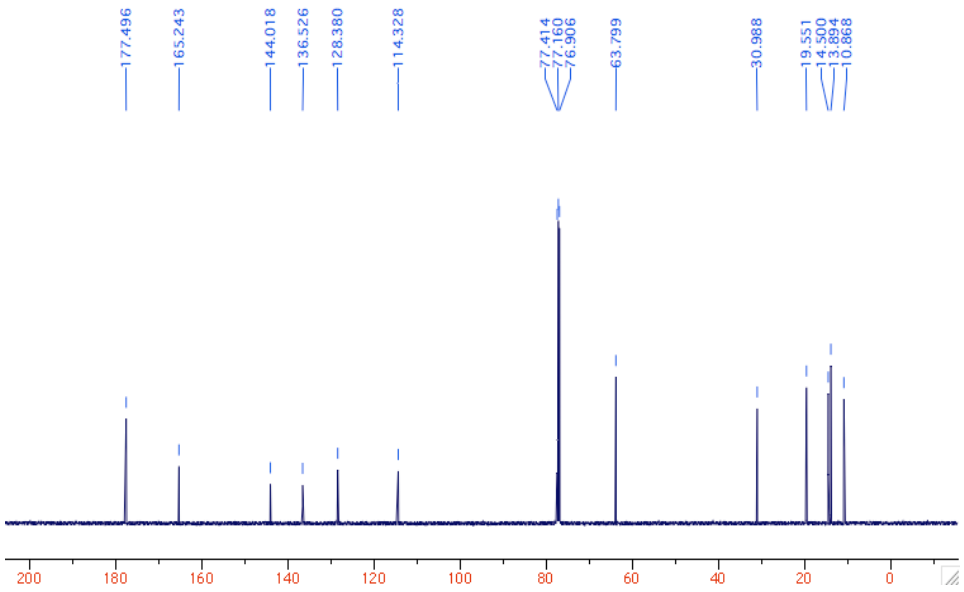
Butyl 5-formyl-2,4-dimethyl-1*H*-pyrrole-3-carboxylate (2-26)



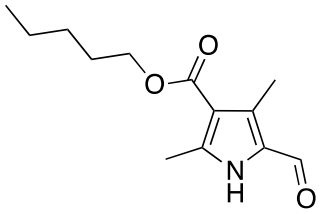
^{1}H NMR ($CDCl_3$, 500 MHz):



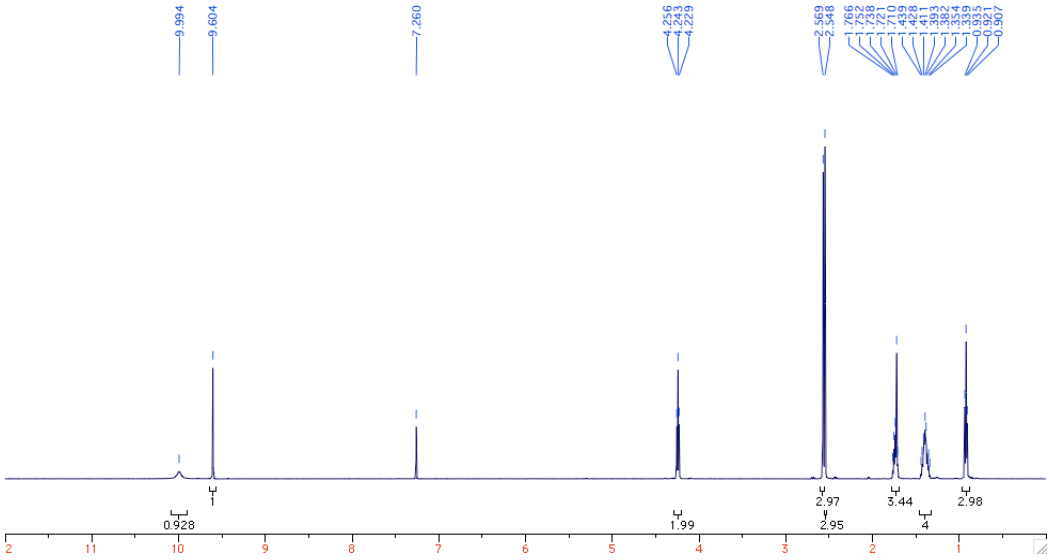
^{13}C UDEFT NMR ($CDCl_3$, 125 MHz):



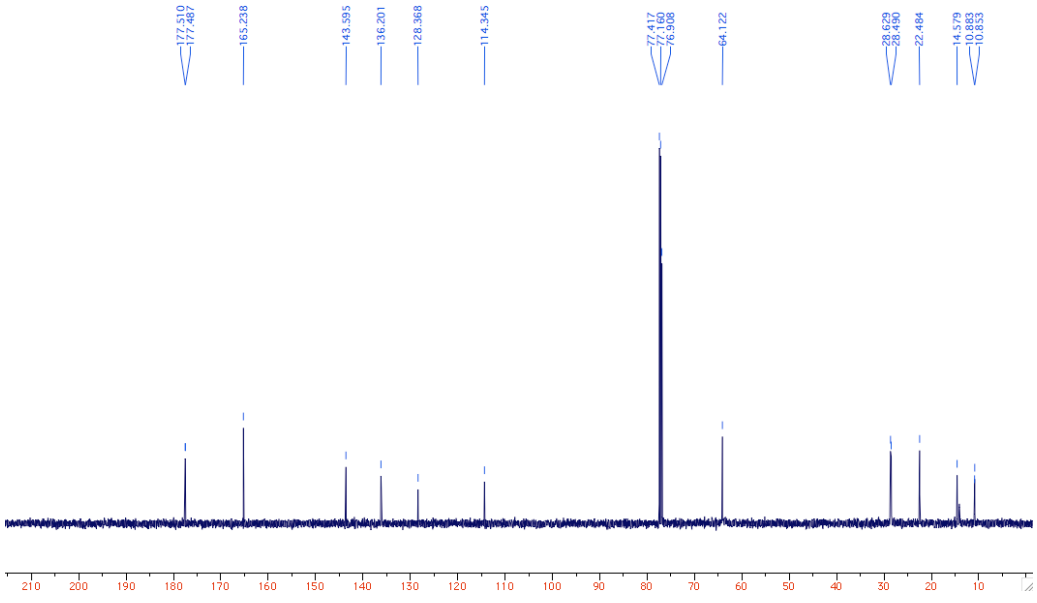
Pentyl 5-formyl-2,4-dimethyl-1*H*-pyrrole-3-carboxylate (2-27)



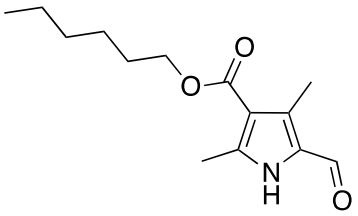
^{1}H NMR ($CDCl_3$, 500 MHz):



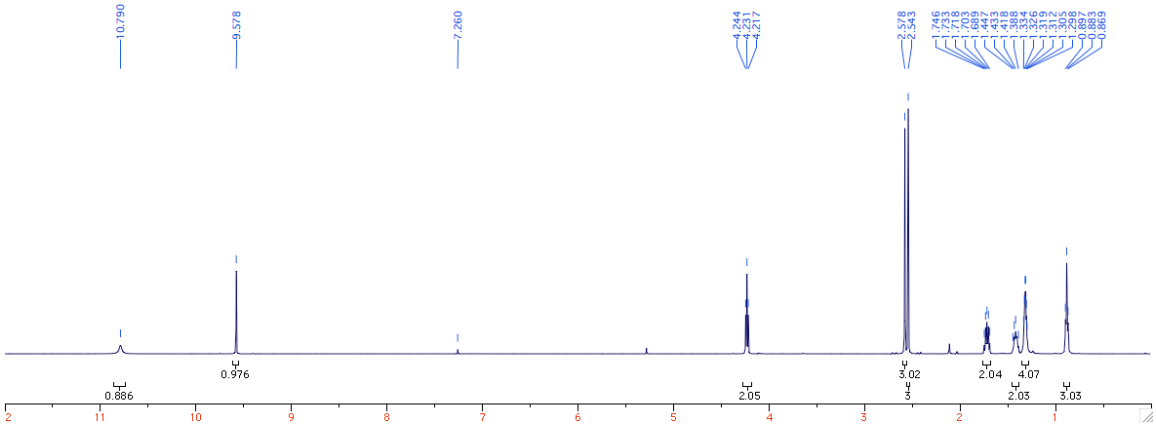
^{13}C UDEFT NMR ($CDCl_3$, 125 MHz):



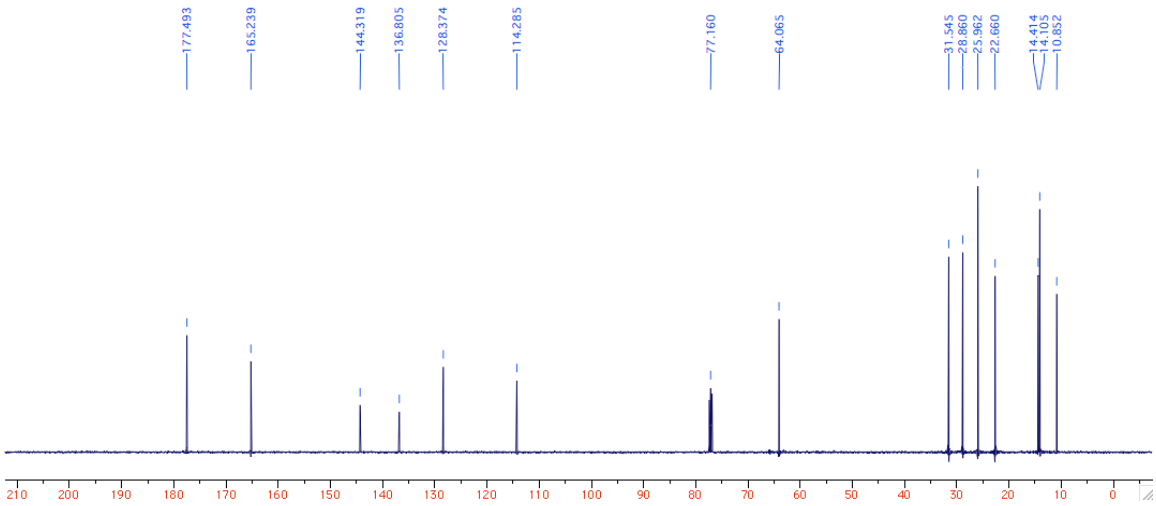
Hexyl 5-formyl-2,4-dimethyl-1*H*-pyrrole-3-carboxylate (2-28)



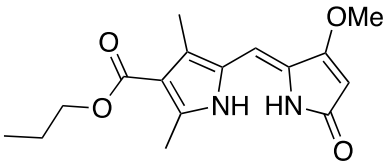
^{1}H NMR ($CDCl_3$, 500 MHz):



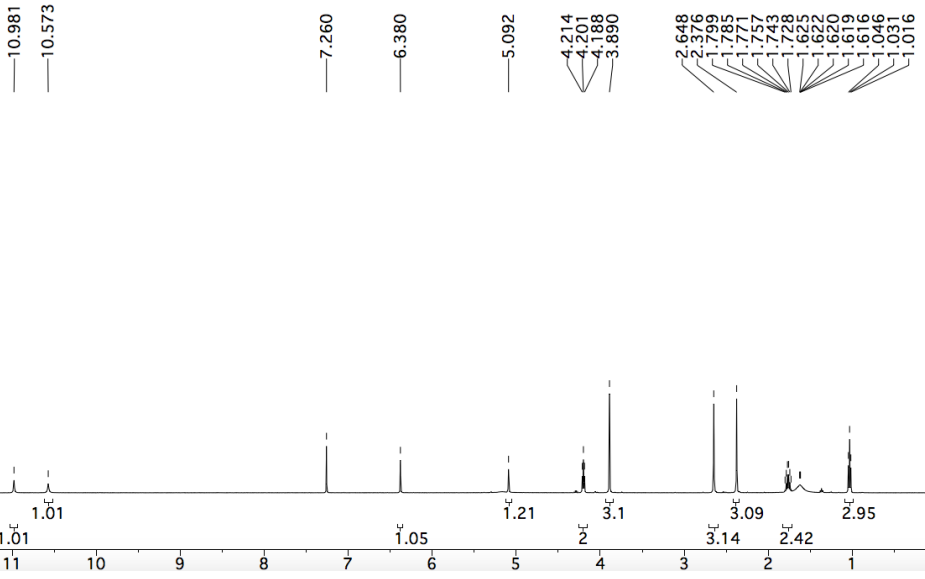
^{13}C UDEFT NMR ($CDCl_3$, 125 MHz):



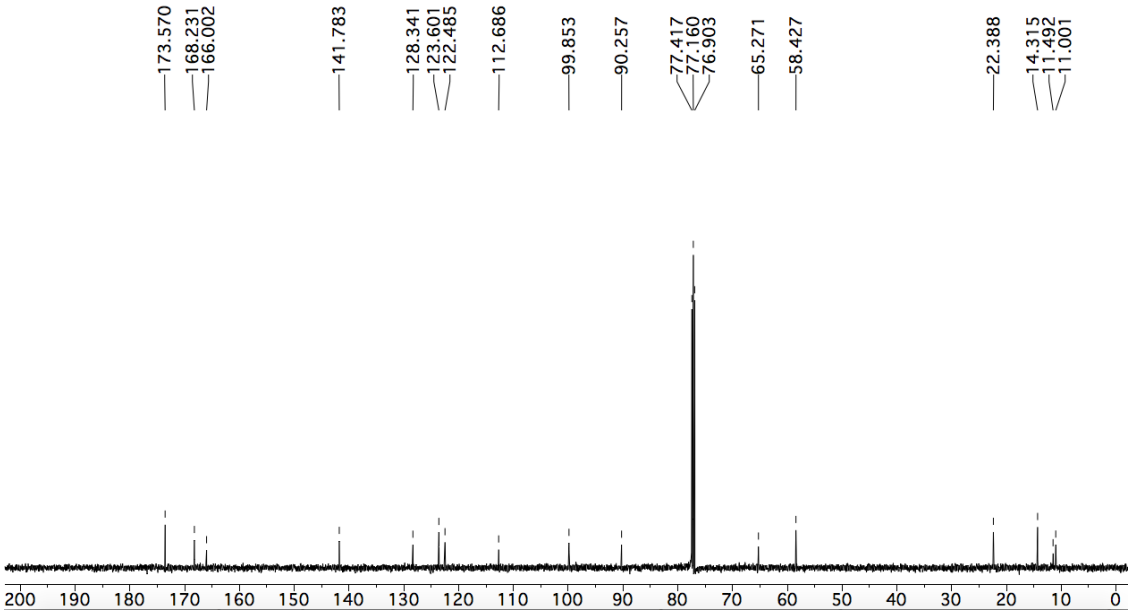
(*Z*)-Propyl 5-((3-methoxy-5-oxo-1*H*-pyrrol-2(5H)-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrole-3-carboxylate (2-29)



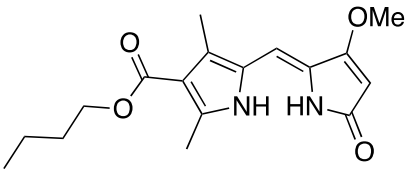
^{1}H NMR ($CDCl_3$, 500 MHz):



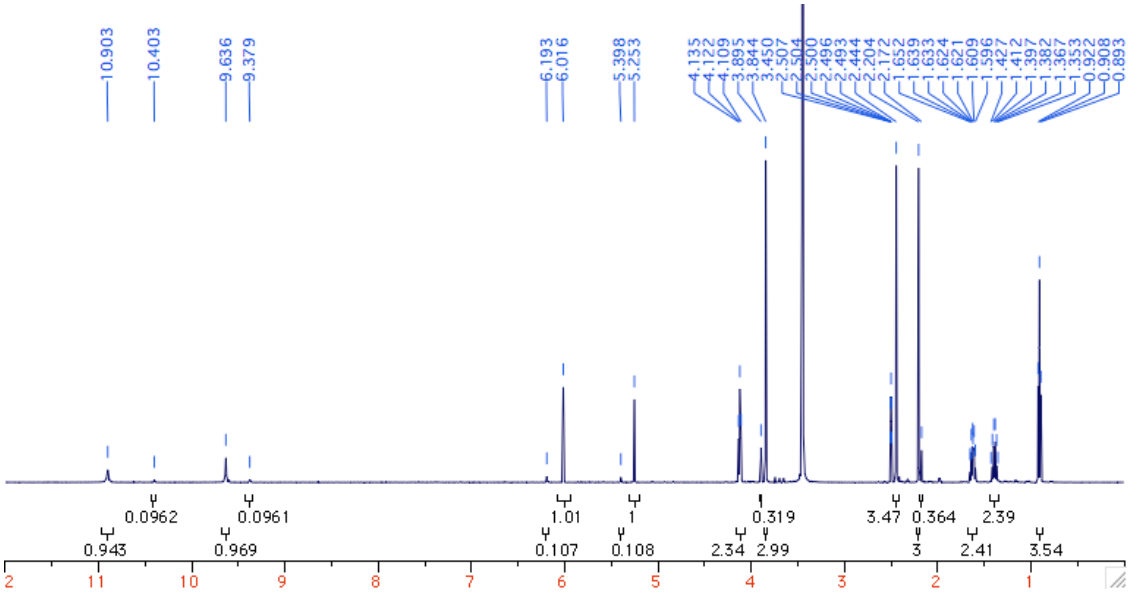
^{13}C UDEFT NMR ($CDCl_3$, 125 MHz):



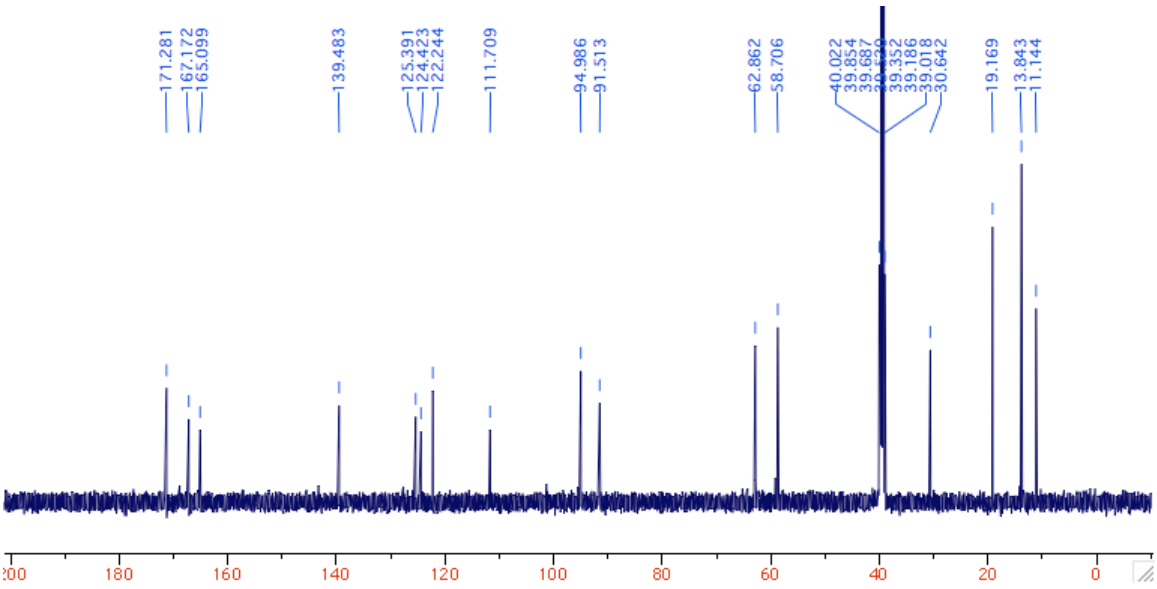
(*Z*)-Butyl 5-((3-methoxy-5-oxo-1*H*-pyrrol-2(5H)-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrole-3-carboxylate (2-30)



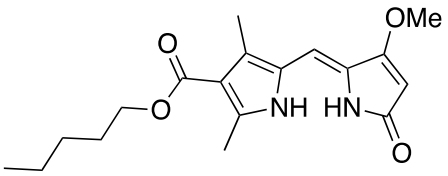
^{1}H NMR (DMSO-d$_6$, 500 MHz):



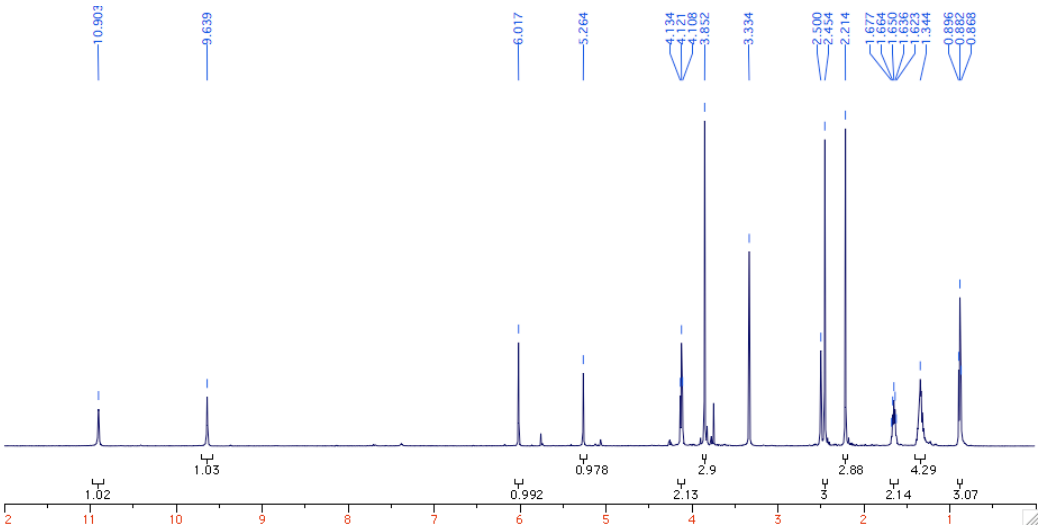
^{13}C UDEFT NMR (DMSO-d$_6$, 125 MHz):



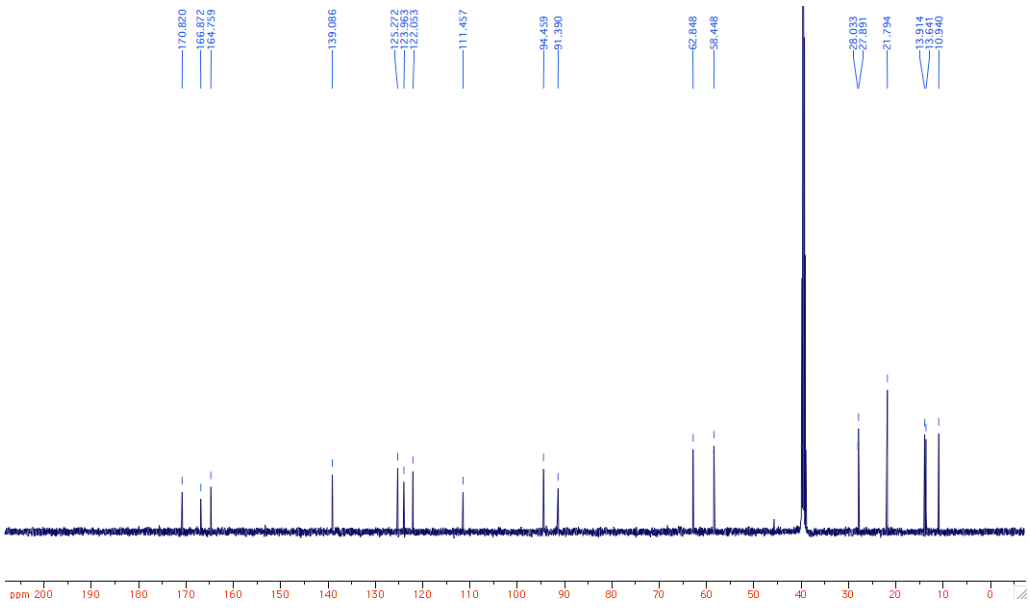
(*Z*)-Pentyl 5-((3-methoxy-5-oxo-1*H*-pyrrol-2(5H)-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrole-3-carboxylate (2-31)



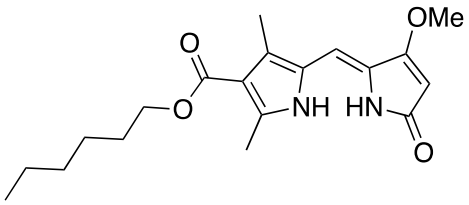
^{1}H NMR ($CDCl_3$, 500 MHz):



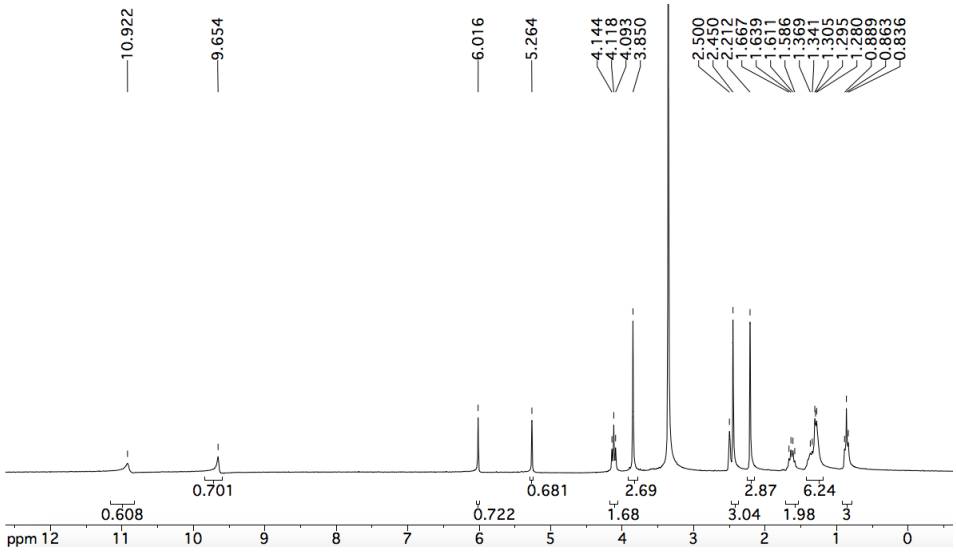
^{13}C UDEFT NMR ($CDCl_3$, 125 MHz):



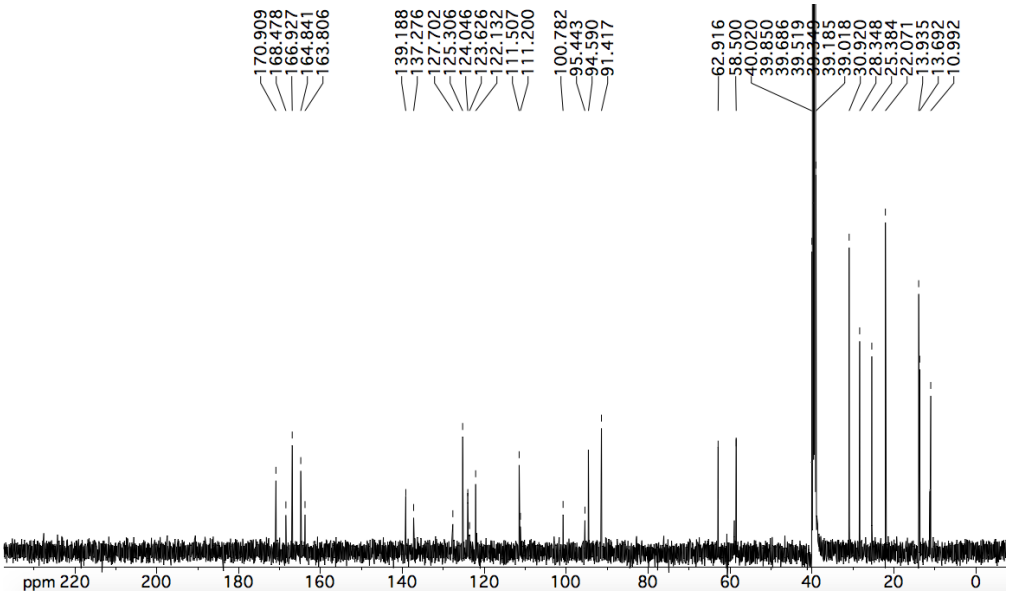
(*Z*)-Hexyl 5-((3-methoxy-5-oxo-1*H*-pyrrol-2(5H)-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrole-3-carboxylate (2-32)



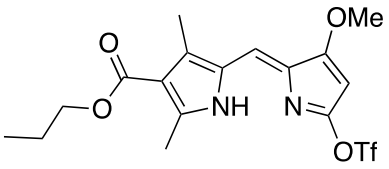
^{1}H NMR (DMSO-d$_6$, 250 MHz):



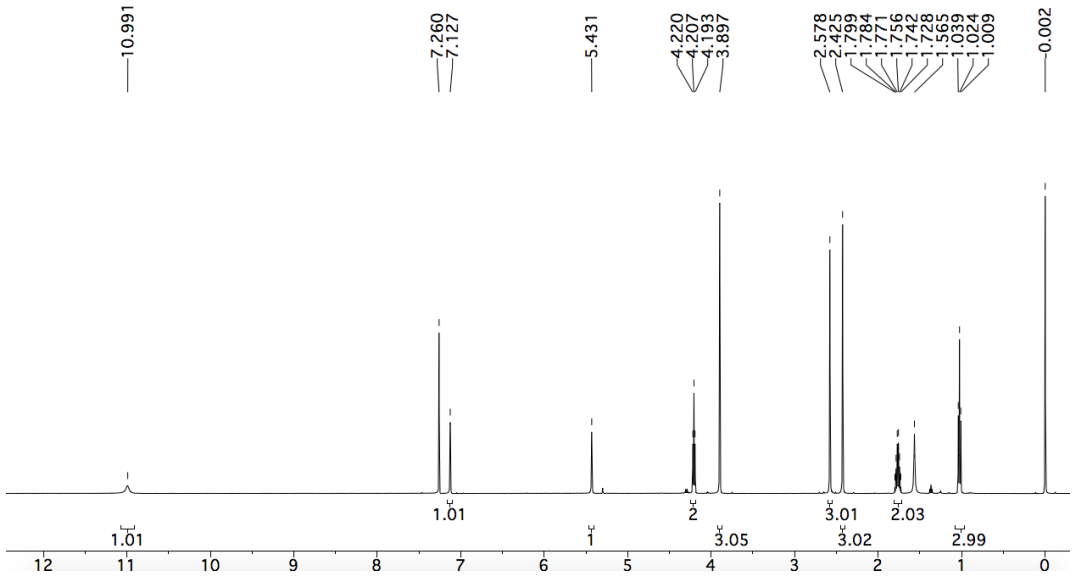
^{13}C UDEFT NMR (DMSO-d$_6$, 125 MHz):



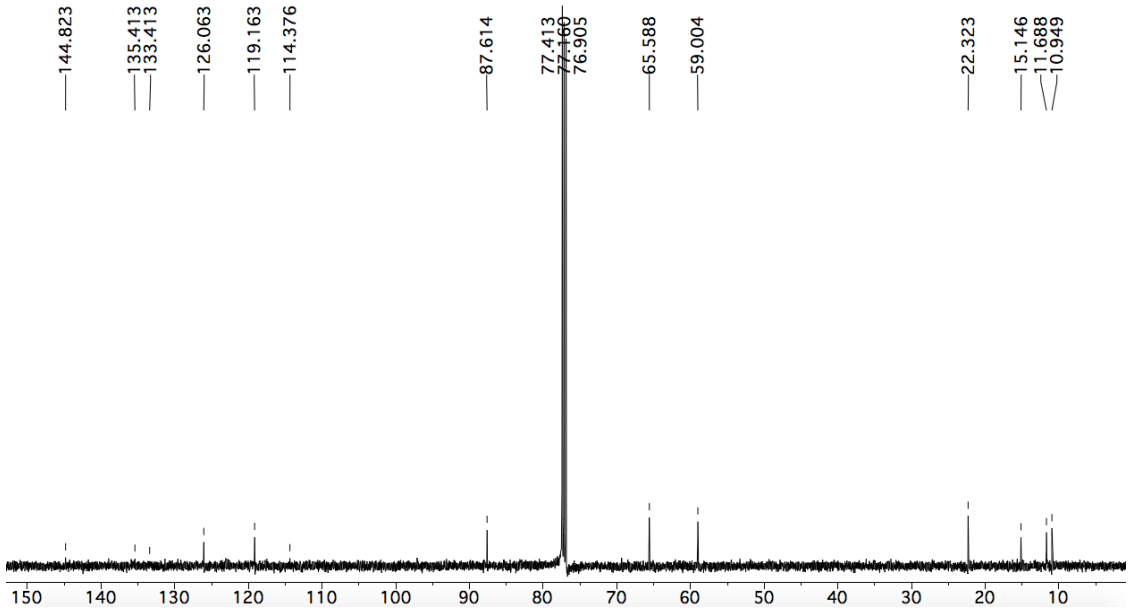
(*Z*)-Propyl 2-((3-methoxy-5-(((trifluoromethyl)sulfonyl)oxy)-*1H*-pyrrol-2-yl)methylene)-3,5-dimethyl-2*H*-pyrrole-4-carboxylate (2-33)



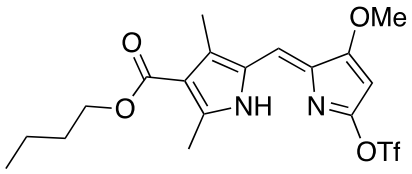
^{1}H NMR ($CDCl_3$, 500 MHz):



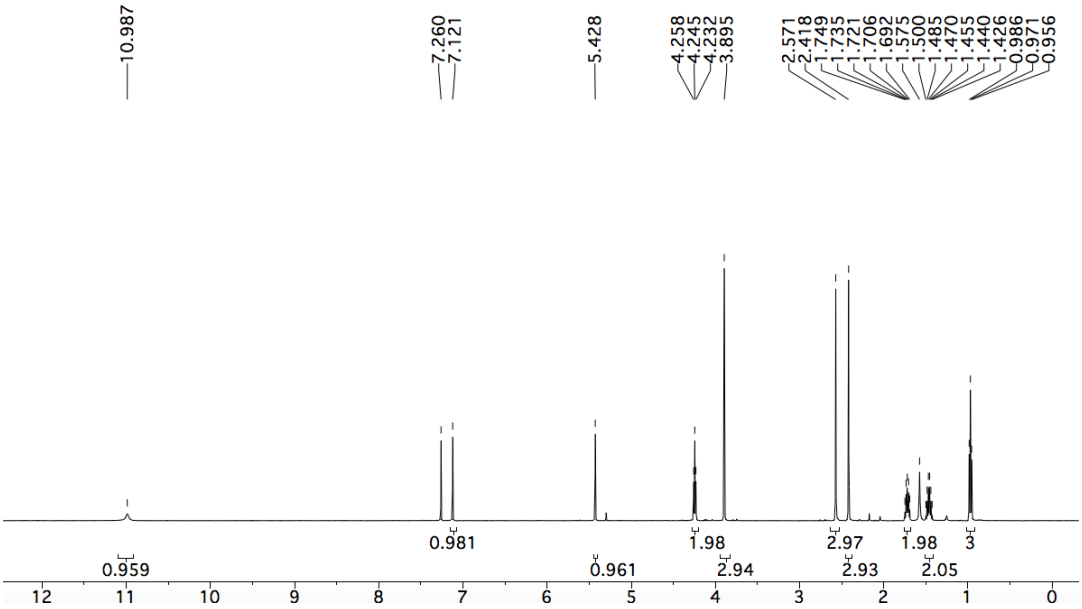
^{13}C UDEFT NMR ($CDCl_3$, 125 MHz):



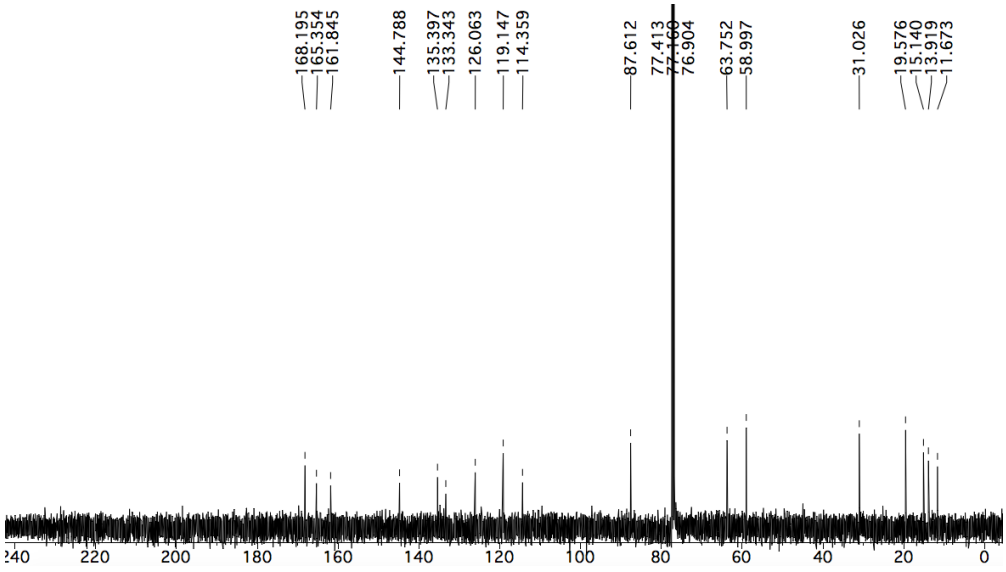
(*Z*)-Butyl 2-((3-methoxy-5-(((trifluoromethyl)sulfonyl)oxy)-*1H*-pyrrol-2-yl)methylene)-3,5-dimethyl-2*H*-pyrrole-4-carboxylate (2-34)



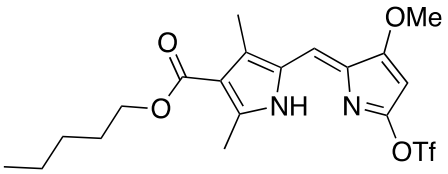
^{1}H NMR ($CDCl_3$, 500 MHz):



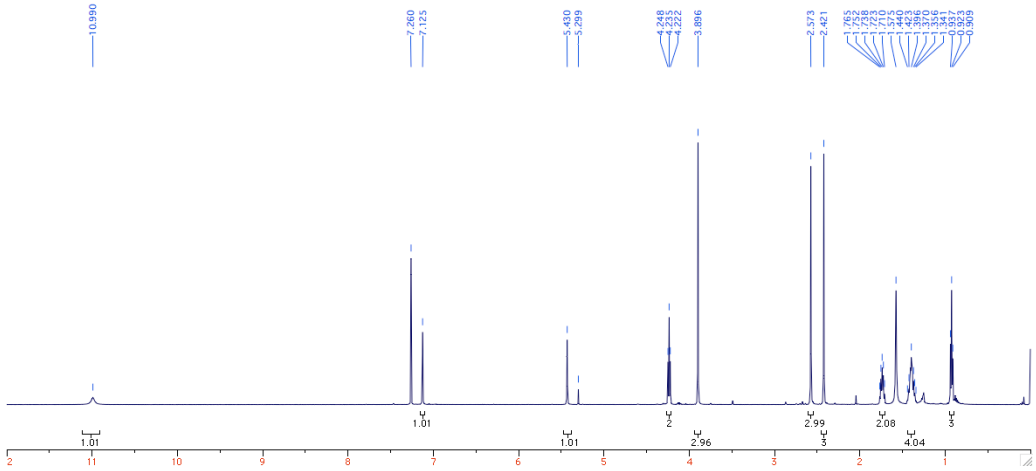
^{13}C UDEFT NMR ($CDCl_3$, 125 MHz):



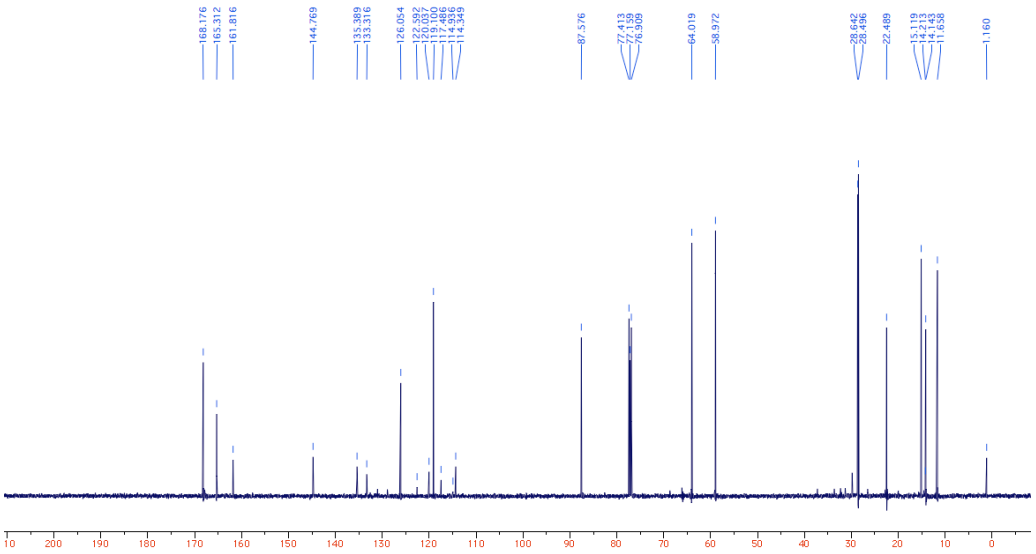
(*Z*)-Pentyl 2-((3-methoxy-5-(((trifluoromethyl)sulfonyl)oxy)-*1H*-pyrrol-2-yl)methylene)-3,5-dimethyl-2*H*-pyrrole-4-carboxylate (2-35)



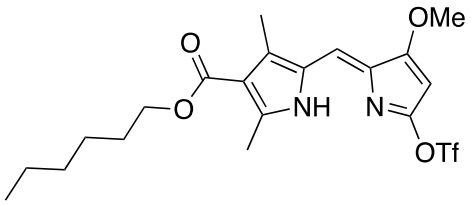
^{1}H NMR ($CDCl_3$, 500 MHz):



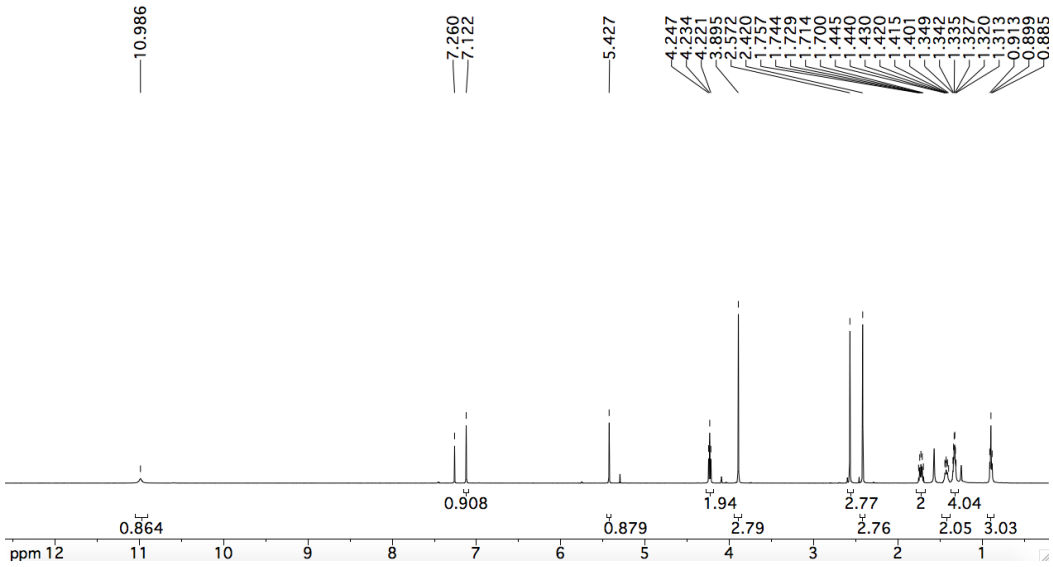
^{13}C UDEFT NMR ($CDCl_3$, 125 MHz):



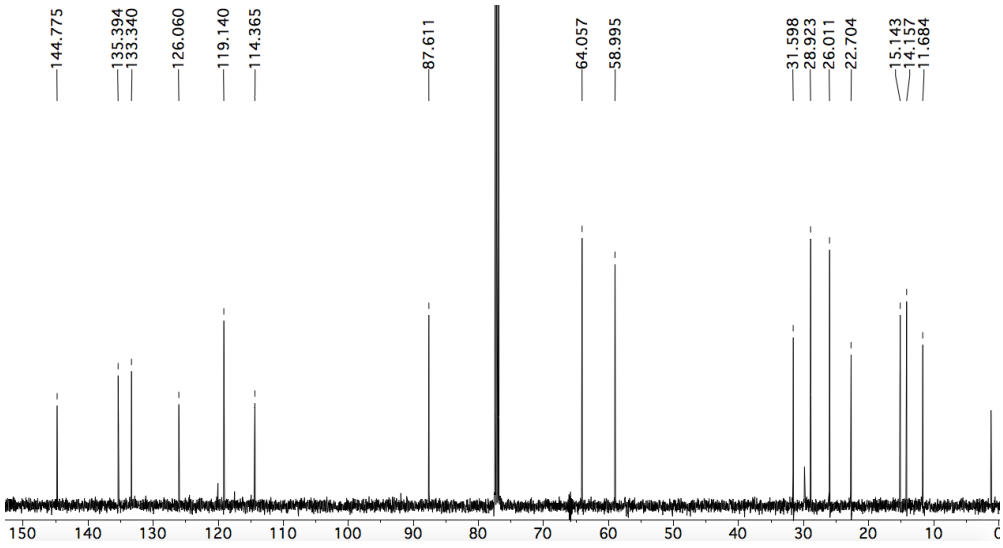
(*Z*)-Hexyl 2-((3-methoxy-5-(((trifluoromethyl)sulfonyl)oxy)-*1H*-pyrrol-2-yl)methylene)-3,5-dimethyl-2*H*-pyrrole-4-carboxylate (2-36)



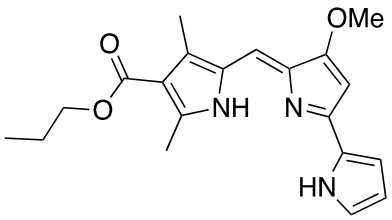
^{1}H NMR ($CDCl_3$, 500 MHz):



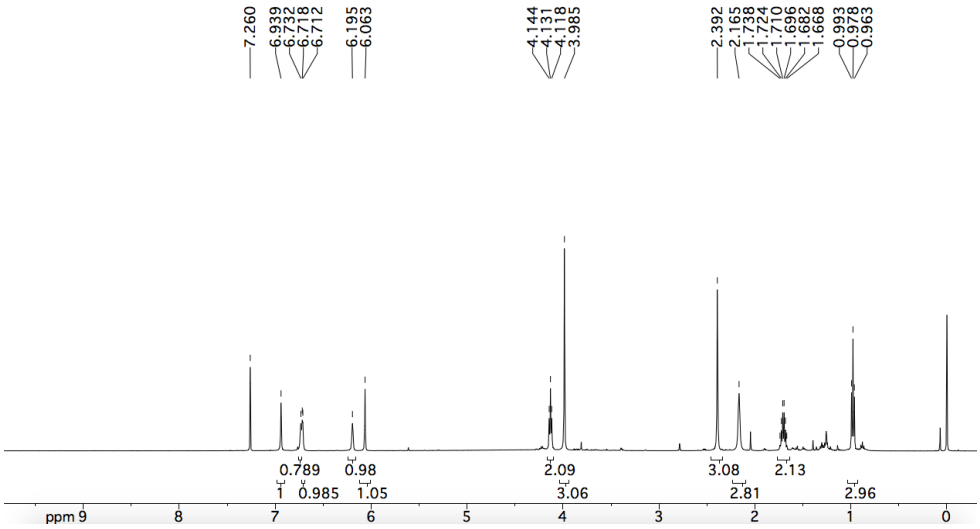
^{13}C UDEFT NMR ($CDCl_3$, 125 MHz):



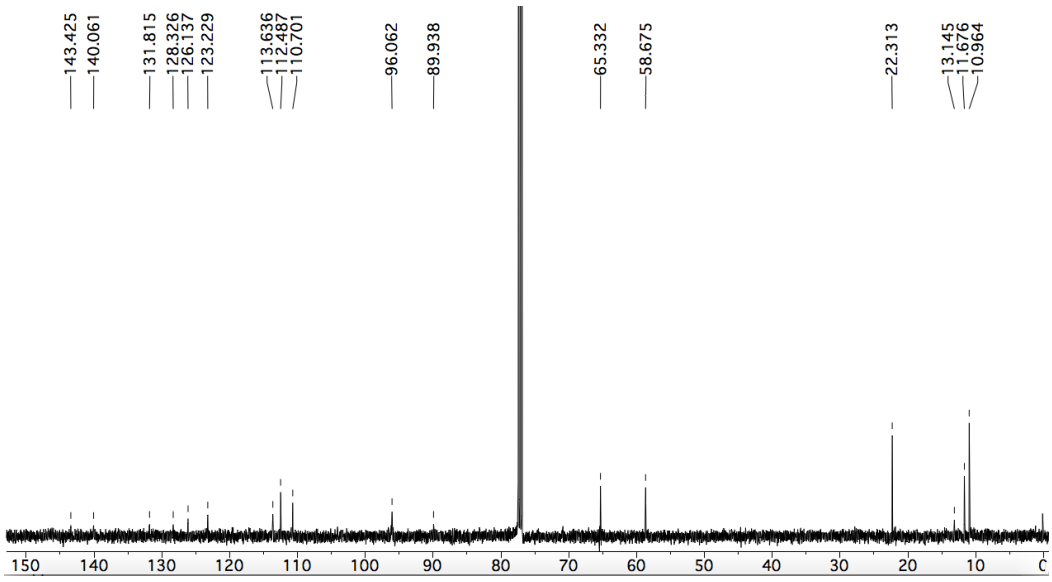
(*Z*)-Propyl 5-((4'-methoxy-1*H*,5'*H*-[2,2'-bipyrrol]-5'-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrole-3-carboxylate hydrochloride (2-37)



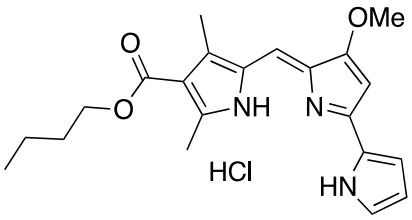
^{1}H NMR ($CDCl_3$, 500 MHz):



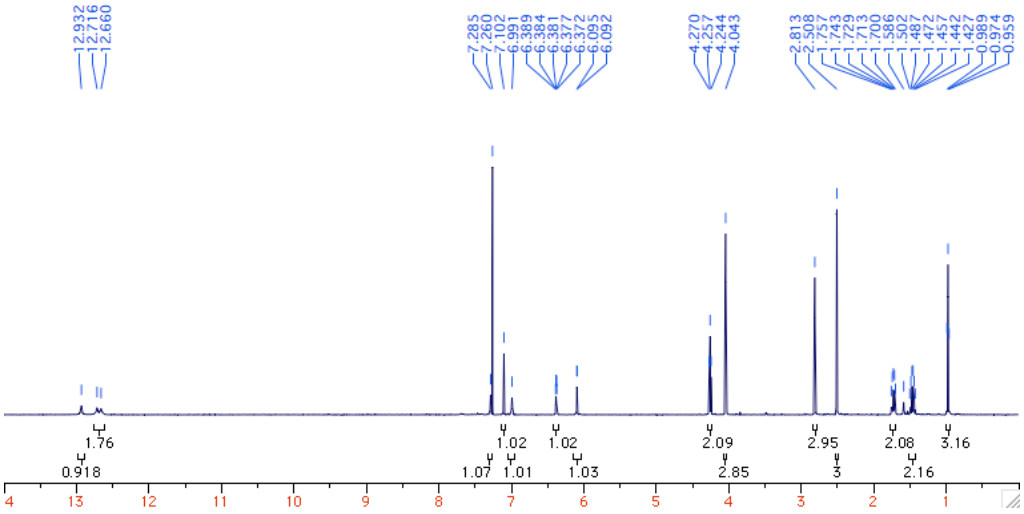
^{13}C UDEFT NMR ($CDCl_3$, 125 MHz):



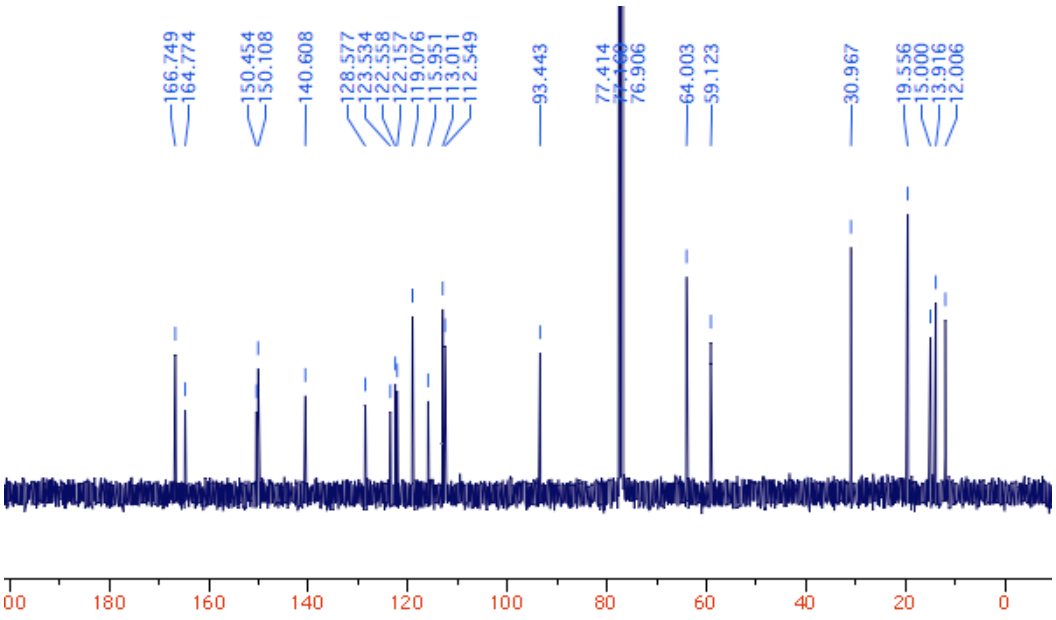
(*Z*)-Butyl 5-((4'-methoxy-1*H*,5'*H*-[2,2'-bipyrrol]-5'-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrole-3-carboxylate hydrochloride (2-38)



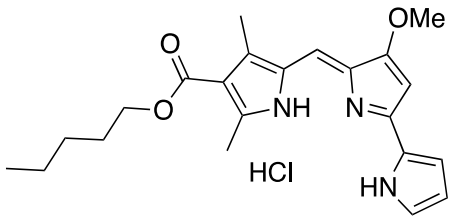
^{1}H NMR ($CDCl_3$, 500 MHz):



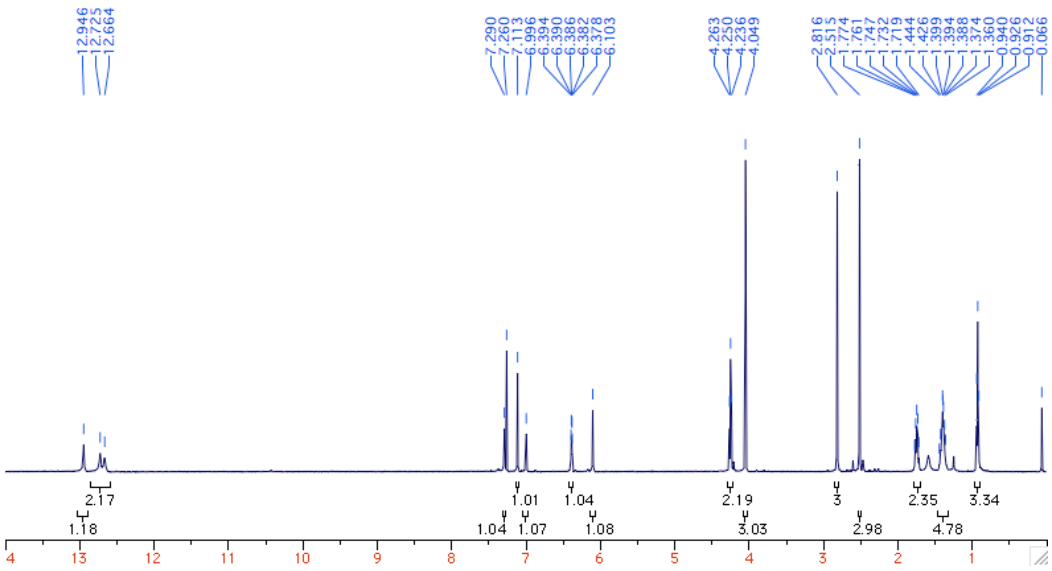
^{13}C UDEFT NMR ($CDCl_3$, 125 MHz):



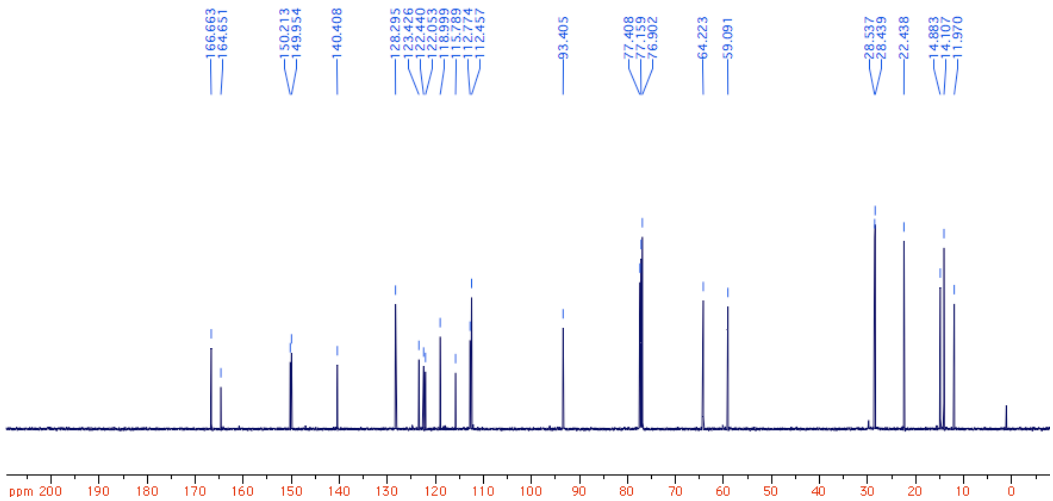
(*Z*)-Pentyl 5-((4'-methoxy-1*H*,5'*H*-[2,2'-bipyrrol]-5'-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrole-3-carboxylate hydrochloride (2-39)



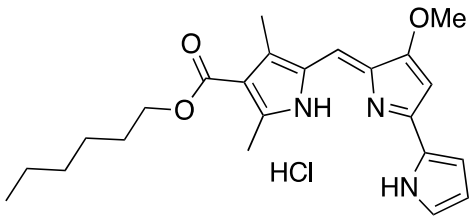
^{1}H NMR ($CDCl_3$, 500 MHz):



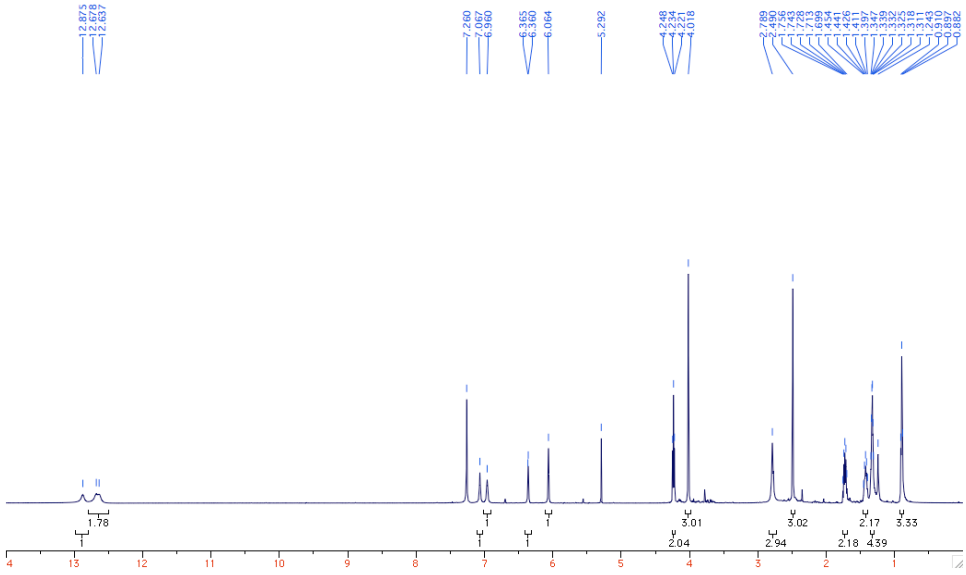
^{13}C UDEFT NMR ($CDCl_3$, 125 MHz):



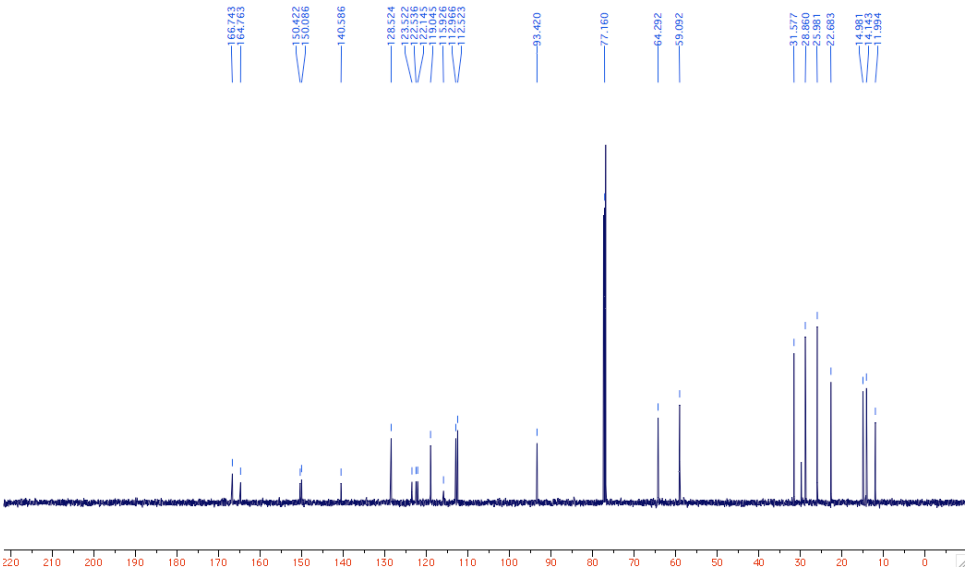
(*Z*)-Hexyl 5-((4'-methoxy-1*H*,5'*H*-[2,2'-bipyrrol]-5'-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrole-3-carboxylate hydrochloride (2-40)



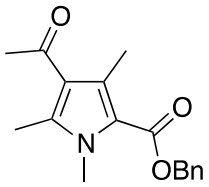
^{1}H NMR ($CDCl_3$, 500 MHz):



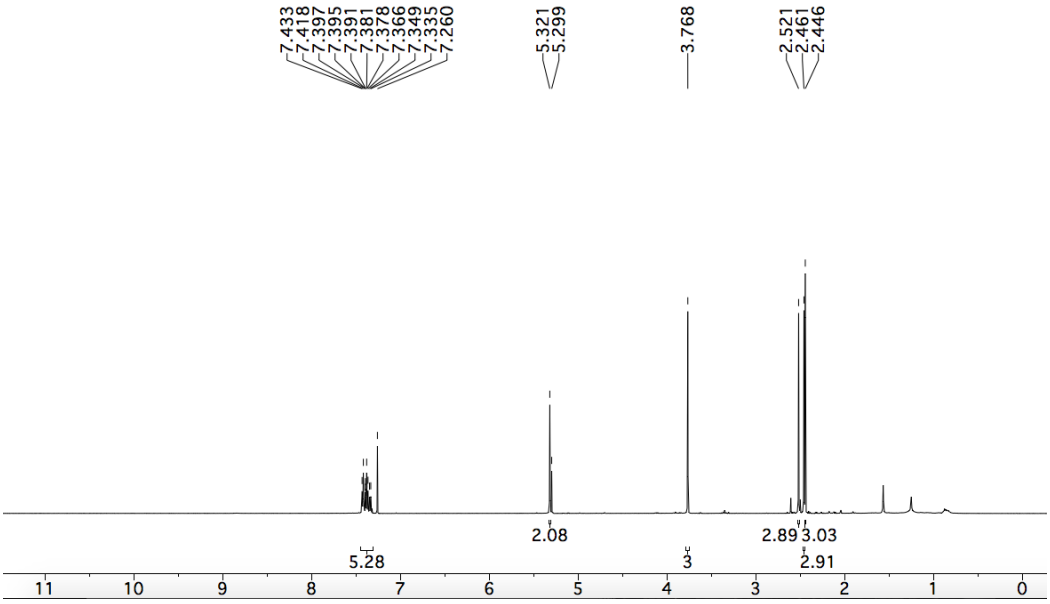
^{13}C UDEFT NMR ($CDCl_3$, 125 MHz):



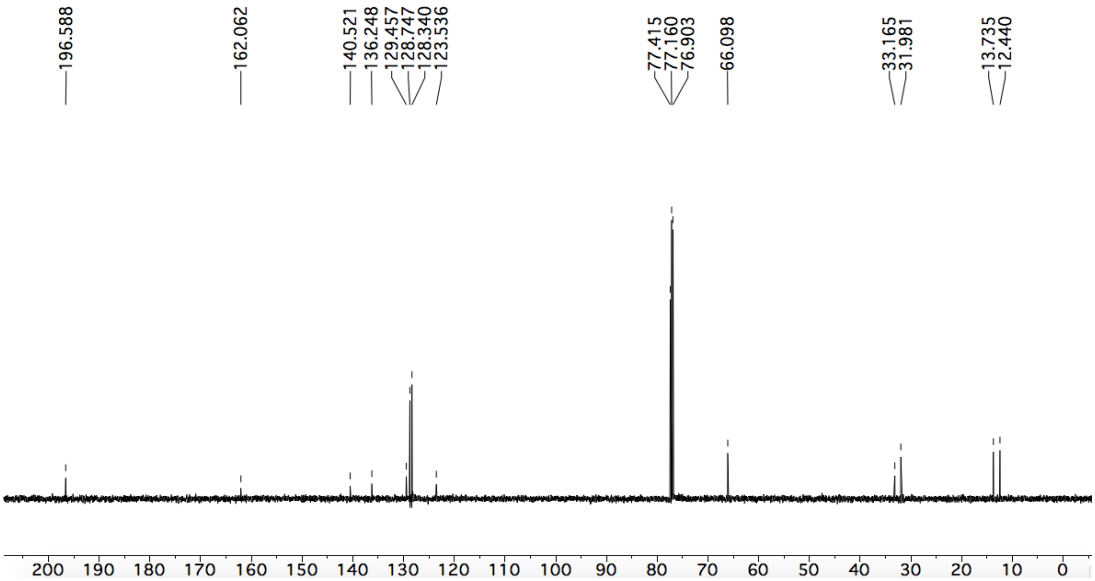
Benzyl 4-acetyl-1,3,5-trimethyl-pyrrole-2-carboxylate (2-51)



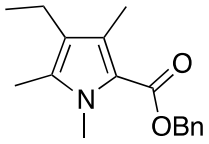
^{1}H NMR ($CDCl_3$, 500 MHz):



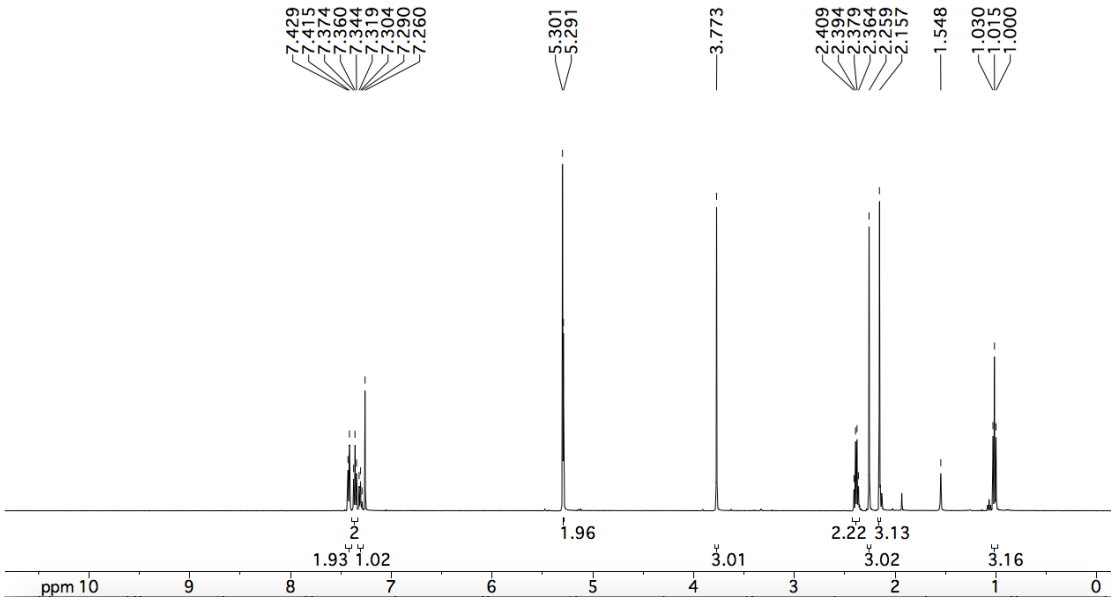
^{13}C UDEFT NMR ($CDCl_3$, 125 MHz):



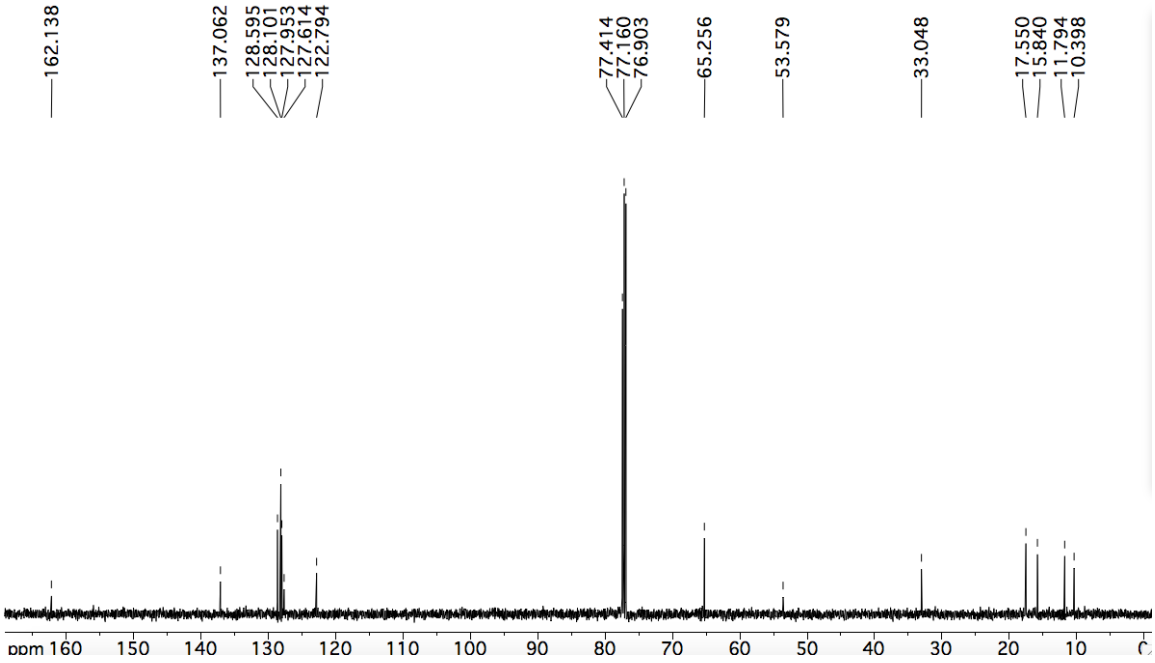
Benzyl 4-ethyl-1,3,5-trimethyl-pyrrole-2-carboxylate (2-52)



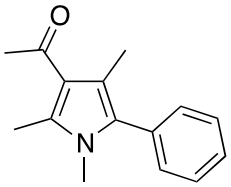
^{1}H NMR ($CDCl_3$, 500 MHz):



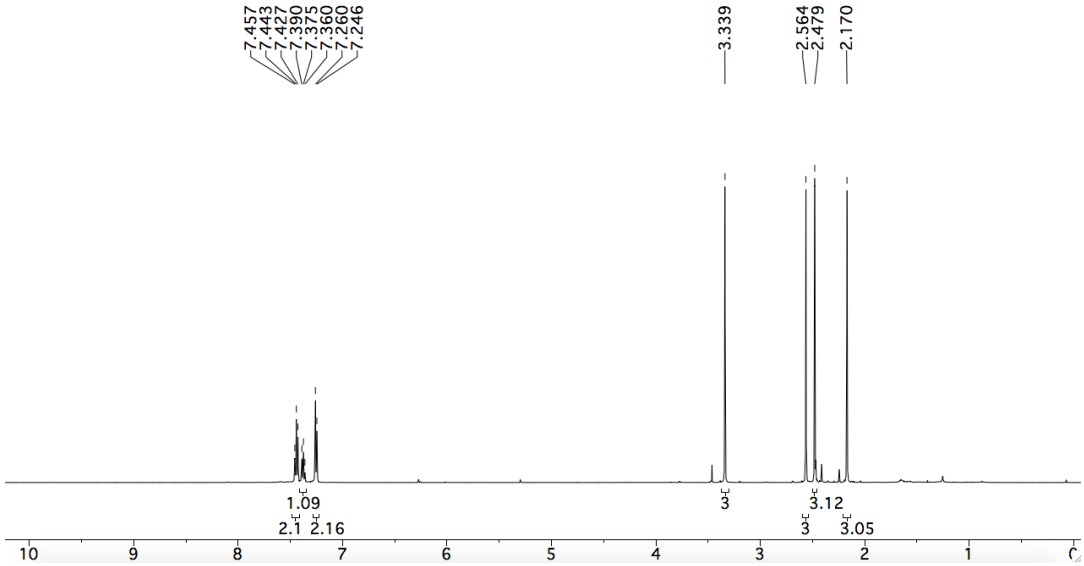
^{13}C UDEFT NMR ($CDCl_3$, 125 MHz):



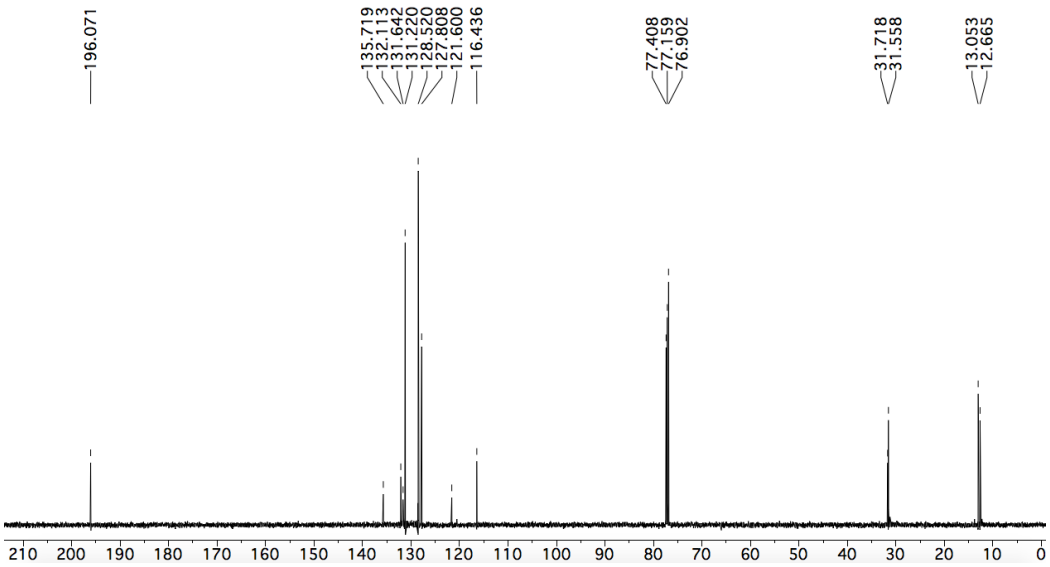
1-(1,2,4-Trimethyl-5-phenyl-1*H*-pyrrol-3-yl)ethanone (2-55)



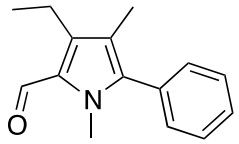
^{1}H NMR ($CDCl_3$, 500 MHz):



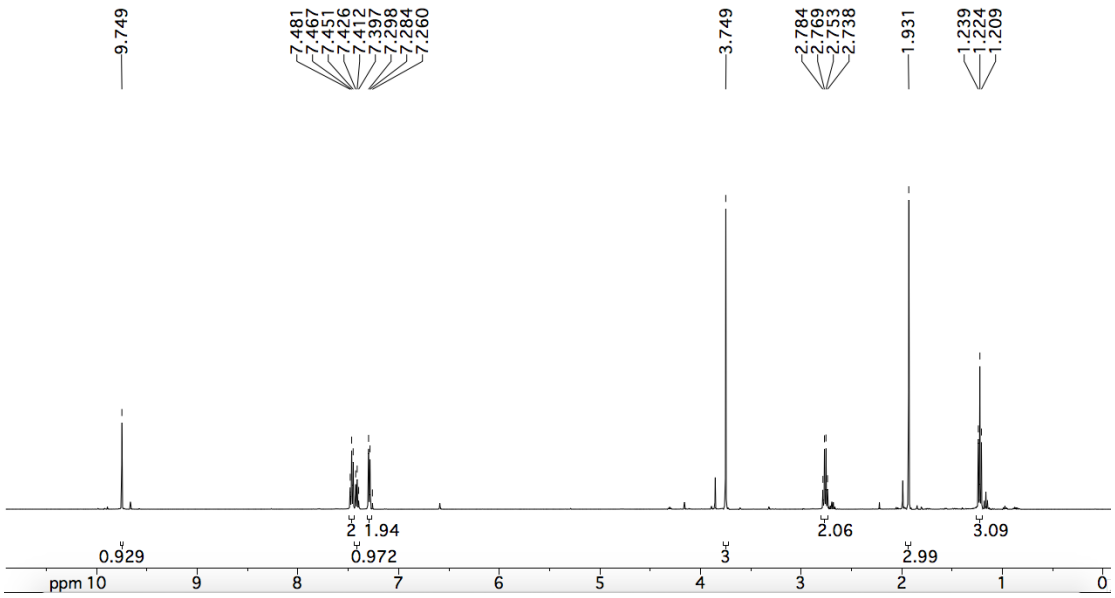
^{13}C UDEFT NMR ($CDCl_3$, 125 MHz):



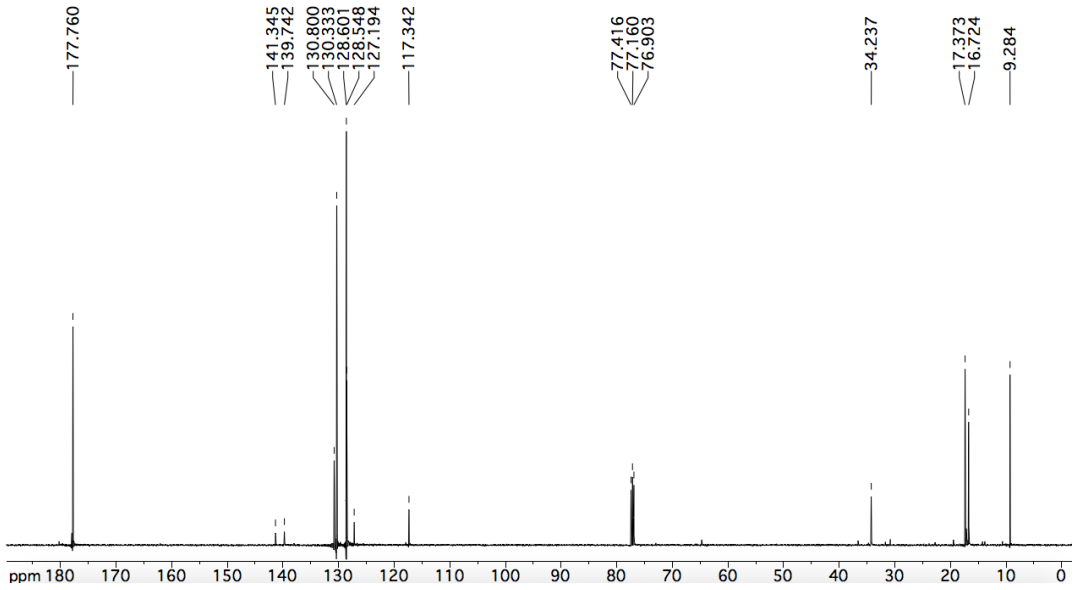
3-Ethyl-1,4-dimethyl-5-phenyl-1*H*-pyrrole-2-carbaldehyde (2-57)



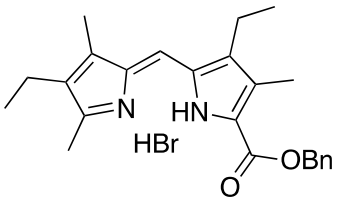
^{1}H NMR ($CDCl_3$, 500 MHz):



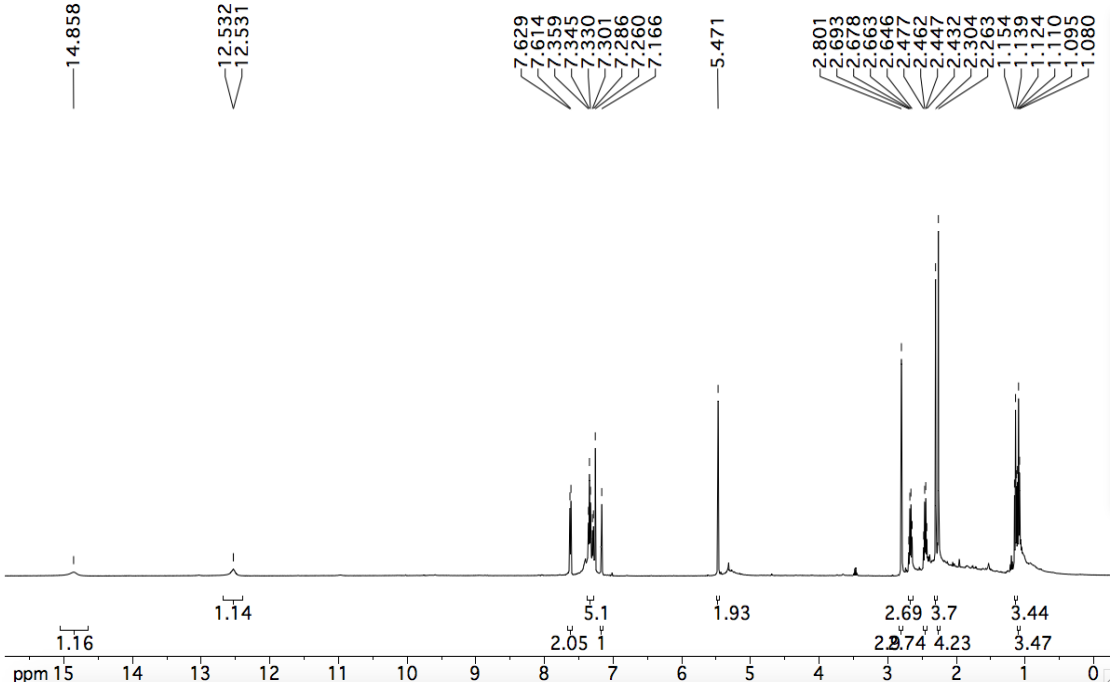
^{13}C UDEFT NMR ($CDCl_3$, 125 MHz):



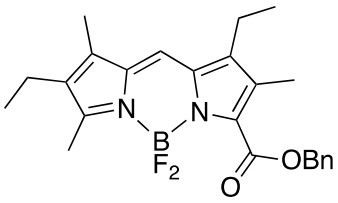
(Z)-Benzyl 4-ethyl-5-((4-ethyl-3,5-dimethyl-2H-pyrrol-2-ylidene)methyl)-3-methyl-1H-pyrrole-2-carboxylate hydrobromide (2-62)



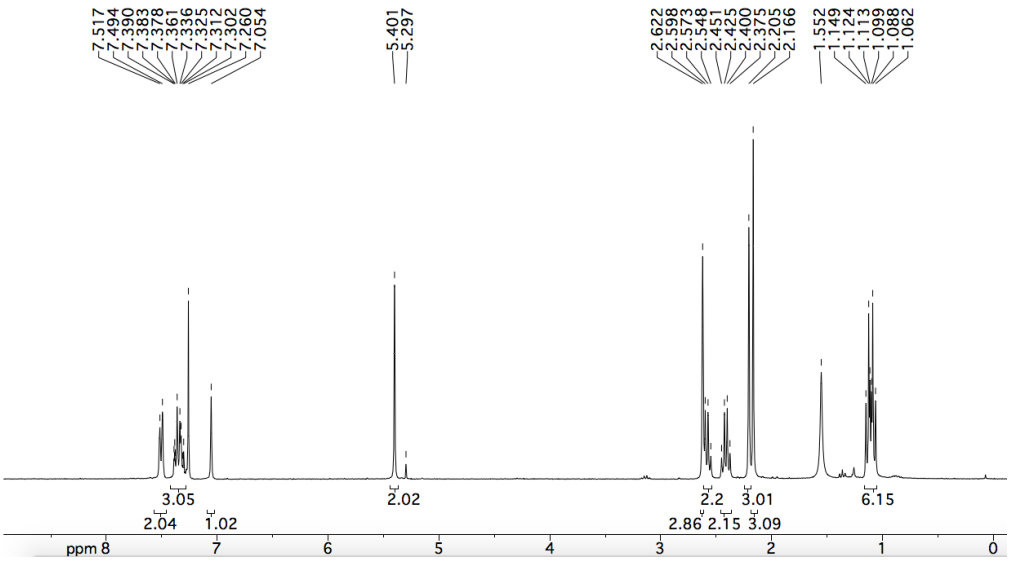
^{1}H NMR ($CDCl_3$, 500 MHz):



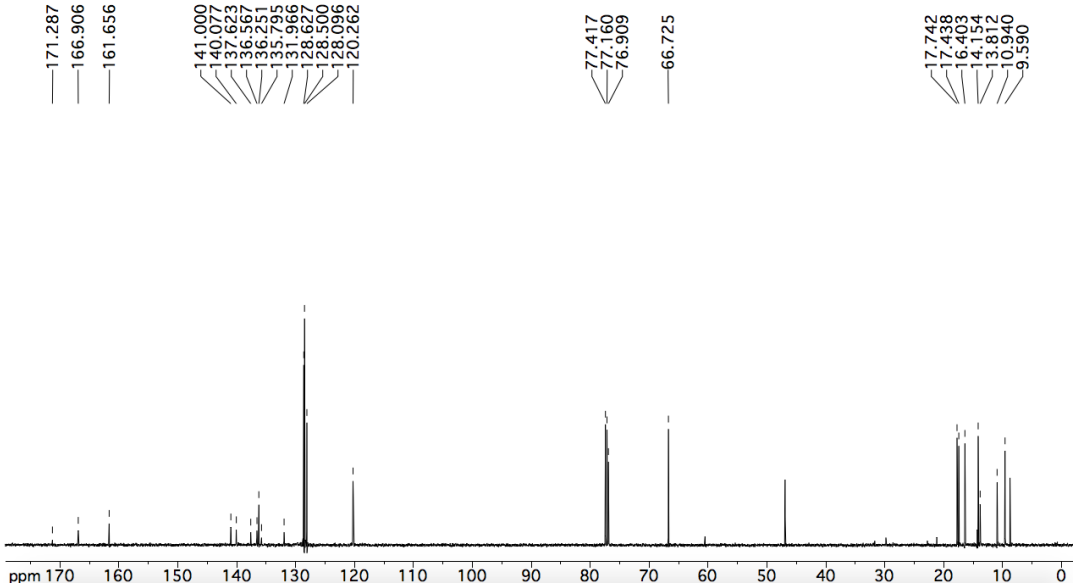
7-((Benzyloxy)carbonyl)-2,9-diethyl-5,5-difluoro-1,3,8-trimethyl-5*H*-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diazaborinin-4-ium-5-uide (2-63)



^{1}H NMR ($CDCl_3$, 300 MHz):



^{13}C UDEFT NMR ($CDCl_3$, 125 MHz):

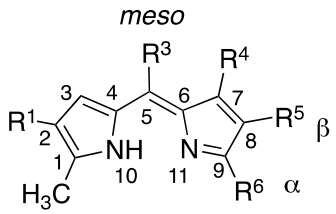


Chapter 3: Reactivity of the 1-Methyl Functionality on Free-Base Dipyrrins

Section 3.1: Background Information Regarding 1-Methyl Dipyrrins

Dipyrrins have classically been studied for use in the synthesis of porphyrin frameworks. Although the synthesis of porphyrins is still very much a contemporary topic of research, interest in dipyrrins is now also influenced by the stunning optical properties exhibited by dipyrrin metal and metalloid complexes.[97] Boron dipyrrinato complexes, *F*-BODIPYs, have been the subject of an outpouring of recent study related to their optical properties, and are used for a variety of purposes,[98] which will be better discussed in Chapter 4. Most new synthetic methodologies for manipulating dipyrrins involve their metal complexes,[97] presumably because dipyrrins in the free-base state are inherently less stable relative to both their salt and complexed forms.[97] This makes free-base dipyrrins generally undesirable as synthetic intermediates, especially for researchers who are unfamiliar or uncomfortable handling pyrrolic materials. There is significant opportunity for improvement of synthetic techniques involving free-base dipyrrins, as very few such modern synthetic reactions are reported.

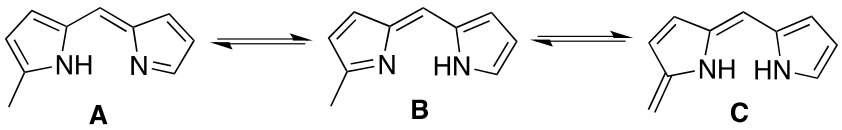
Figure 3-1: **IUPAC numbering for the dipyrrin backbone**



The compounds discussed herein contain a methyl group at the 1-position of the dipyrrin backbone (Figure 3-1). This naming convention was established by IUPAC in 1987;[99] dipyrrins are formally composed of a pyrrole and an azafulvene unit attached via the 2-position of the original pyrrole, and the external alkene functionality of the fulvene. Common substituents decorating the pyrrolic backbone of the dipyrrin include alkyl, aryl, carbonyl and halo substituents.[22,91,92,100-106] Dipyrrins borrow idiomatic naming conventions from pyrroles, in that the 1- and 9- positions are designated as the α-positions, while the 2-, 3-, 7- and 8- positions are designated as β-positions (Figure 3-1). Due to the often asymmetric nature of dipyrrins, these labels can be insufficient when discussing these compounds; nonetheless, the α and β designations are frequently used in the literature.

In cases where substitution is symmetric about the 5-, or *meso*-, position, electron density is shared evenly among the eleven core atoms of the dipyrrin frame, allowing for chemical equivalency of the pyrrolic nitrogen atoms (Figure 3-2, structures **A** and **B**).

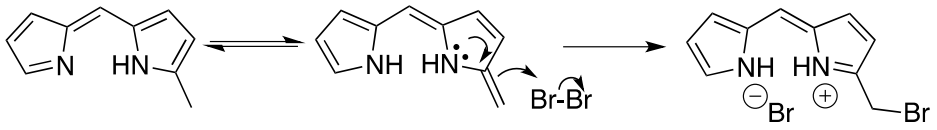
Figure 3-2: **Tautomerization of 1-methyl dipyrrins**



In addition to the expected tautomerism involving the two nitrogen atoms, 1-methyl dipyrrins have also been suggested to possess an additional tautomeric form (Figure 3-2, structure **C**).[107] These suggestions have arisen in the context of reactivity at the 1-methyl position of dipyrrins: reactions, such as the addition of molecular bromine to the methyl functionality, are typically thought to occur via an oxidative or radical mechanism.[107] This belief is founded in the comparatively better-studied reactivity of 2-methyl pyrroles

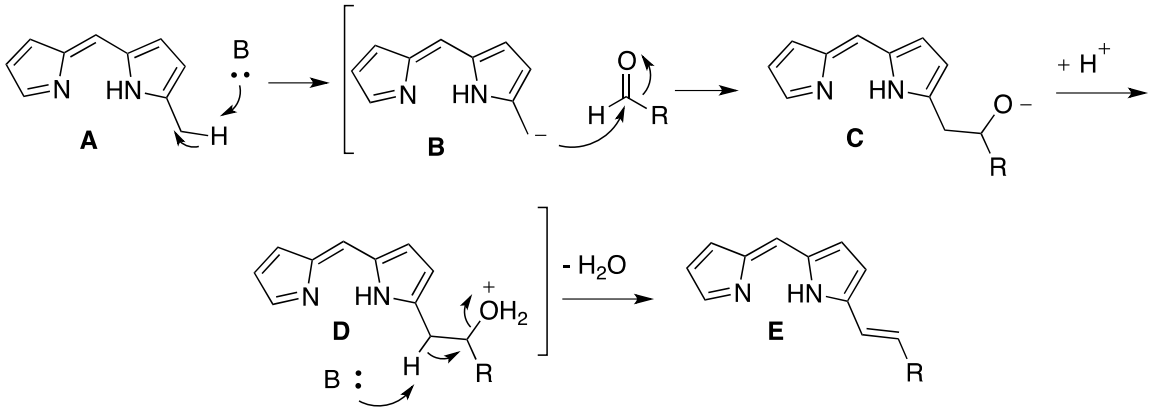
that react via these mechanisms. Provided the tautomeric form shown above (**C**), it is conceivable that reactions such as the addition of molecular bromine involve an electrophilic addition (Figure 3-3).[108]

Figure 3-3: **Proposed electrophilic addition of Br_2 to 1-methyl dipyrrins**



Beyond the scope of reactions involving oxidative conditions (treatment with Br_2, $Pb(OAc)_2$ or $(NH_4)_2Ce(NO_3)_6$ for example),[95,109] the tautomeric form of 1-methyl dipyrrins for carbon-carbon bond formation has only been invoked to describe base-catalyzed Knoevenagel-like condensations yielding conjugated, vinylagous products (Figure 3-4).

Figure 3-4: **Mechanism of base-catalyzed Knoevenagel-like condensation of 1-methyl dipyrrins**



The goal of the present work was to explore reactions utilizing thermal heating to promote similar reactivity in 1-methyl dipyrrins, in the absence of a weak base. The first isolation of non-vinylagous dipyrrins reacted at the 1-methyl position is reported herein,

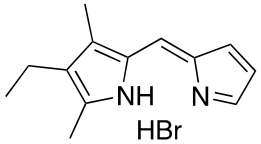
alongside deuterium labeling studies that support the culpability of the exo-cyclic tautomeric state in these transformations.

Section 3.2: Results and Discussions

3.2.1 Reactivity of 1-Methyl Dipyrrins as a Pathway for Decomposition

Initial interest in the reactivity of 1-methyl dipyrrins was instigated after observation of decomposition of dipyrrin HBr salt **3-1•HBr** over several months on the benchtop (Figure 3-5).

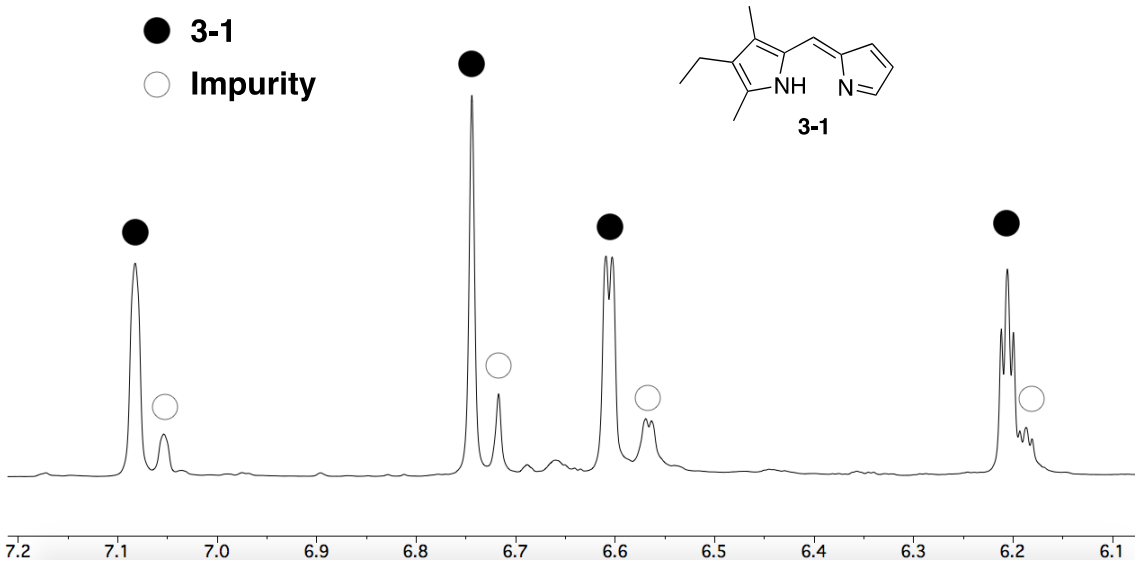
Figure 3-5: **Chemical structure of dipyrrin 3-1•HBr**



3-1•HBr

A fresh sample of **3-1•HBr** was prepared, and stored for six months in a sample vial sealed with Parafilm. Over the duration of this time, the colour of the sample darkened significantly from red to brown-red; as dipyrrin•HBr salts are known to possess exceptional stability under ambient conditions, often surviving storage for decades without decomposition, this observation was unexpected. Although the sample had been initially pure, analysis using ^{1}H NMR revealed the presence of a secondary dipyrrin-like impurity. To provide clarity in the spectrum, the solid was converted to its free-base form and dissolved in MeOD (Figure 3-6).

Figure 3-6: **Partial ^{1}H NMR spectrum revealing decomposition product of free-base 3-1**



*Spectrum obtained using MeOD.

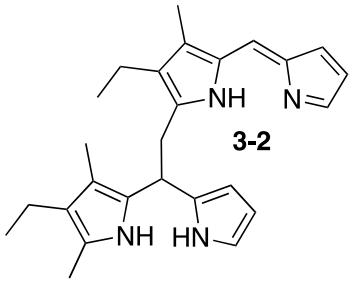
Flash chromatography using Brockman III basic alumina was used to isolate the impurity, **3-2**. The impurity exhibited a higher polarity than **3-1**, when analyzed using TLC; as such, **3-1** was eluted using an ethyl acetate:hexanes (1:19) solvent system. Increasing the polarity of the eluent (1:19 to 1:9) allowed for visualization of **3-2** on the column, as the compound leached away from the dark brown mass adhered to the top of the alumina pad. The solid **3-2** was isolated, but as an impure sample. It was surmised that the stability of the compound was low, and that degradation was occurring during purification or upon removal of the solvent *in vacuo*. Attempts to purify the compound via recrystallization were not successful. Dipyrrins are often purified via conversion to their HBr salts followed by precipitation from ether. Unfortunately, washing the impure sample of the isolated impurity with hydrobromic acid (30 mL, 1M), to hopefully generate the corresponding HBr salt, resulted in formation of an insoluble tar-like

product. Purification via column chromatography was reattempted, with efforts made to limit the amount of time the solid spent on the column; fortunately, several milligrams of pure material were thus obtained (3% yield from original material).

Confirming the structure of the impurity, **3-2**, was not trivial. Within the ^{1}H NMR spectrum, a second set of aromatic pyrrolic hydrogen signals was present, in addition to the signals expected for the starting material **3-1**. The signal representing the 1-methyl group of the parent compound **3-1** (2.32 ppm) was no longer present, while the second methyl signal (2.08 ppm) had doubled in intensity in the isolated impurity, and now represented six hydrogen atoms. The formation of a second methylene ethyl signal was also observed in **3-2**. The appearance of a new methyl signal further up-field, relative to compound **3-1**, was also observed (1.90 ppm), along with two new signals at 3.25 and 4.70 ppm representing two and one hydrogen atoms, respectively. Chemical shifts in the 3-5 ppm range are not typically observed for simple alkyl dipyrrins. Attempts to use 2D NMR techniques to conclusively elucidate the structure were hindered by overlap in the aromatic region of the ^{13}C NMR spectrum. Analysis of the impurity **3-2** using low-resolution ESI mass spectrometry revealed a strong signal at 201.1 *m/z*. This signal corresponds to the mass of the ionized, protonated parent compound **3-1**. This result contradicted the observations made based on the ^{1}H NMR spectrum. A second signal at 401.3 *m/z* was also observed in the ESI mass spectrum, corresponding to the mass value $[2(\mathbf{3\text{-}1})+H]^{+}$. Dimeric signals in ESI mass spectrometry are not uncommon, and signals representing $[2M+H]^{+}$ are often observed in spectra for dipyrrins prepared within the Thompson research group.[92] Although the observation of a signal at 401.3 *m/z* could be explained by the formation of dimeric ions in the mass spectrometer, an alternative

hypothesis was formed such that the impurity **3-2** is constitutionally isomeric to two monomers of the starting material, **3-1**. Based on this hypothesis, and taking into consideration the observations made based on the ^{1}H NMR spectrum, a structure for **3-2** was proposed (Figure 3-7).

Figure 3-7: **Structure of dimeric decomposition product 3-2**

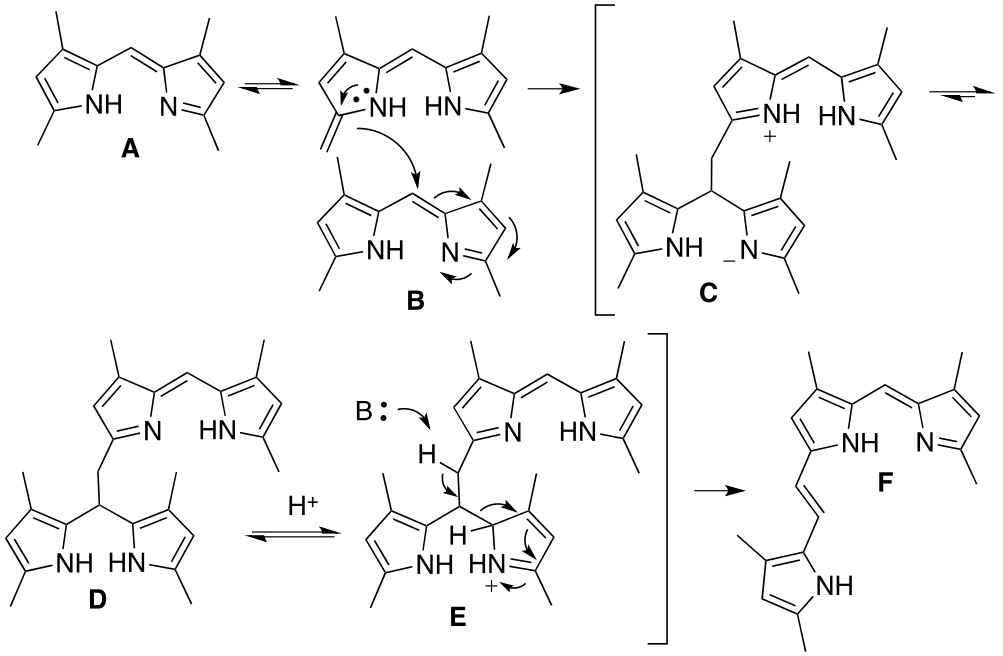


This 1-(methylenedipyrromethane)-dipyrrin framework has not been characterized in the literature. An in-depth search, using the structural tools provided by CAS (Scifinder) did not provide any matches for compounds bearing this 1-(methylenedipyrromethane)-dipyrrin framework. However, further research into the original literature regarding the reactivity of 1-methyl functional dipyrrins did produce a single example of this framework being proposed as a result of nucleophilic attack by the electrophilic 1-methyl functionality at the *meso*-position of dipyrrins.[110]

Indeed, in 1978 Treibs and coworkers reported heating a solution of free-base dipyrrin (**A**, Figure 3-8) in methanol at reflux temperature under an ammonia atmosphere to generate what was described as a dark yellow intermediate dipyrrin, **D**. However, this material was not characterized, and it was described as highly unstable. Instead, the mixture was acidified with hydrochloric acid to initiate formation of the green/blue 1-(vinylpyrrolyl)-dipyrrin **F** in low yields (1.6%, 500 mg of product from 20 g of starting

material). The authors also report significant formation of "black amorphous byproducts," as well as reclamation of "significant quantities of starting material."

Figure 3-8: **Proposed mechanism of formation of 1-(vinylpyrrolyl)-dipyrrins**



With this information in hand, improving the formation of **3-2** was attempted. As formation of **3-2** on the bench occurred via presumed thermal degradation with time, it stood to reason that production of this compound could be accelerated via heating, and inhibited through cooling. Indeed, samples of **3-1•HBr** and free-base **3-1** were stored at 0 °C in the freezer for a period of 30 days, with no observed formation of **3-2**. A series of reactions to determine the effects of heating were then performed.

As a first reaction, 100 mg of hydrobromide salt, **3-1•HBr** was dissolved in 4 mL of methanol:chloroform (1:1, to improve solubility) and heated at 100 °C in the microwave for 15 minutes (Table 3-1, entry 1) The red colour of the solution persisted though the course of the reaction, with no formation of the described green/blue colour expected for 1-(vinylpyrrolyl)-dipyrrins, and no decomposition products. This experiment

was repeated at 150 °C (the upper temperature threshold possible given microwave conditions in this solvent system) for an hour with similar results. Treibs and co-workers described performing their reaction on the free-base dipyrrins and not the HBr salt; and so, **3-1•HBr** was dissolved in dichloromethane, and washed with sodium hydroxide to produce the free-base. After extraction and drying over sodium sulfate, the solvent was removed and the brown film was dried under vacuum. As Treibs used a solution of his free-base dipyrrin in methanol (Figure 3-8),[110] similar conditions were adopted for dipyrrin **3-1**. Following introduction of a nitrogen atmosphere and dissolution of the free-base in anhydrous methanol, **3-1** was stirred at reflux temperature for four hours using conventional heating. No formation of the expected product was observed via TLC analysis (Table 3-1, entry 2). However, a significant portion of the starting material was recovered, and formation of black, amorphous material began to occur.

Table 3-1: **Formation of 3-2 from free-base 3-1**

Entry	Heating	T (°C)	Time	Solvent	3-1 (% recov.)	3-2 (%)
1[a]	MW	100→150	15 min	MeOH/$CHCl_3$	99	0
2	Δ	65	4 h	methanol	82	0
3	Δ	80	12 h	toluene	15	trace
4	Δ	100	12 h	toluene	0	trace
5	MW	80	15 min	methanol	52	0
6	MW	100	15 min	methanol	20	4
7	MW	100	1 h	methanol	0	0
8	MW	120	15 min	methanol	0	0

[a] **3-1•HBr** used for reaction.

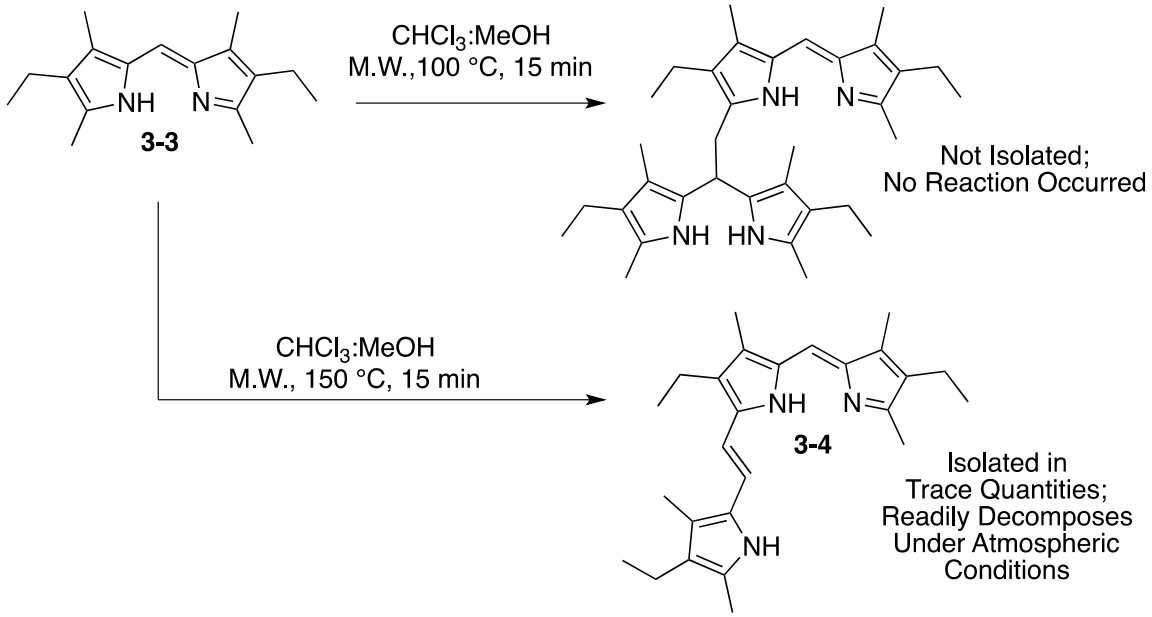
To allow for an increase in the temperature of reaction, experiments were thus run in anhydrous toluene at 80 and 100 °C for 12 hours (Table 3-1, entries 3 and 4). Gratifyingly, both reaction mixtures contained sufficient quantities of **3-2** as to be visible via analysis using TLC. Unfortunately, as before, purification of **3-2** was not facile, and a pure sample of the material was not isolated.

As free-base dipyrrins are prone to decomposition at high reaction temperatures,[111] microwave heating was utilized as a means to more precisely control the temperature ramping and exposure times. Indeed, it has been shown that microwave-enhanced heating can significantly increase rates of reaction, although the mechanism for this increase is hotly contested.[112] The first microwave promoted-reaction of **3-1** involved heating a methanolic solution at 80 °C for 15 minutes (Table 3-1, entry 5). Increased reactivity was evident via observation of the colour of the reaction mixture after heating: what had previously been a clear, bright yellow solution had darkened to brown. Although trace amounts of **3-2** were observable using TLC analysis, no product was isolable via chromatography. A second trial involved heating at 100 °C for 15 minutes was thus performed, with improved results. Purification over basic alumina, eluting with ethyl acetate:hexanes (1:19 to 1:4) provided a 4% yield of **3-2** (Table 3-1, entry 6). Attempts to improve the yield were made by increasing both the length and temperature of the reaction (Table 3-1, entries 7 and 8). However, neither method was forthcoming. Indeed, decomposition of all dipyrrin-like materials was instead observed under these latter two sets of conditions. These reactions demonstrate the relative instability of the free-base dipyrrin: by simply increasing the temperature by 20 °C, or by slightly

extending the total length of reaction, both the starting material and products transform into amorphous black material.

As a general rule, the stability of dipyrrins increases with increasing alkyl substitution of the dipyrrolic backbone. With this in mind, we hoped to determine whether the symmetric dipyrrin, **3-3**, could be reacted in a similar fashion to **3-1** (Scheme 3-1). As **3-3** is substituted at both the 1- and 9- positions, it is conceivable that isolation of both a di- and trimeric product would be feasible.

Scheme 3-1: **Attempted dimerization of dipyrrin 3-3**



To test this, a solution of **3-3** in chloroform:methanol (1:1, to improve solubility) was heated at 100 °C for 15 minutes in the microwave. No reactivity was observed, and the starting material was recollected without any indication of decomposition. The temperature was increased to 150 °C, and the reaction repeated. After heating, the dark brown colouration of the starting material was replaced by a vivid green. A portion of starting material was unreacted (20%, crude yield), and the presence of a polar, blue compound was detected via TLC analysis. In addition, significant formation of other

polar compounds, at the baseline of the plate, was also observed. Upon elution over basic alumina and using a low polarity eluent, the blue compound maintained its colouration. As the polarity of the eluent was increased (1:99 → 1:4 ethyl acetate:hexanes), a bathochromic shift in the light absorption of the solution was observed for the unknown product. Although the compound appeared blue in less-polar eluent, elution under the 1:4 mixture of ethylacetate:hexanes yielded a red-purple solution as the compound exited the column. The compound either ran concomitant with the less polar dipyrrin **3-3**, exiting as a mixture, or adhered to the alumina at low solvent polarities. A solvent gradient was used to remove the remainder of the product. However, only a complex mixture was isolated, and analysis of the mixed products using ^{1}H NMR spectroscopy revealed the appearance of several methyl and ethyl signals, as well as the formation of two COSY-coupled vinylic peaks at 6.06 and 6.67 ppm. Examination of the mixture using ESI mass spectrometry revealed (in addition to starting material), an ion of mass 389.3 *m/z*. This mass correlates to the addition of a krypto-pyrrolic unit to the starting material, as well as a single carbon and hydrogen atom. These observations led us to conclude that the formation of 1-(vinylpyrrolyl)-dipyrrin **3-4** occurred upon heating (26% crude yield). Unfortunately, further purification was hindered by the instability of the product.

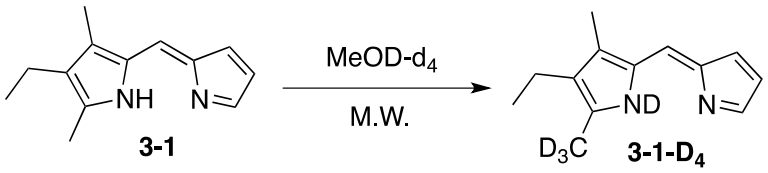
Outside of the report by Treibs *et al*., 1-(vinylpyrrolyl)-dipyrrins are sparingly reported in the literature. [110,113,114] Compounds that are analogous to **3-4** have been reported to exhibit similar solvatochromic properties, and possess similar stabilities under an ambient setting. The most recently reported literature conditions for the formation of these tripyrrolic species report oxidation of a 2-methyl, *meso*-H dipyrrin using manganese and molecular oxygen in refluxing DMF (18%).[113] Indeed, authors suggest the formation

of a 1-formyl substituted dipyrrin and Knoevenagel-type condensation at reflux temperature in DMF. In contrast, the reaction described in Scheme 3-1 was performed in the absence of a catalytic metal, and in the absence of oxygen (the microwave vial had been purged with nitrogen). These results suggest that formation of 1-(vinylpyrrolyl)-dipyrrins, such as **3-4**, may be initiated by exposure to high temperature, and does not necessarily require the addition of manganese and oxygen for reaction.

3.2.2 Deuterium Exchange on 1-Methyl Dipyrrins

To support the conclusion that the increase in temperature induces formation of the tautomer depicted in Figure 3-2, experiments were performed to determine whether the hydrogens at the 1-methyl position could be exchanged with deuterium under thermal conditions similar to those required for generation of dimer **3-2** (Table 3-1). Microwave-promoted heating of solutions of dipyrrins in deuterated, protic sFaolvent was thus performed (Table 3-4). Some dimer was also formed.

Table 3-2: **Deuterium exchange on dipyrrin 3-1**



3-1 **3-1-D$_4$**

Entry	t (min)	T (°C)	% Yield
1	30	60	0
2	30	70	0
3	30	80	0
4	30	90	0[a]
5	15	100	17

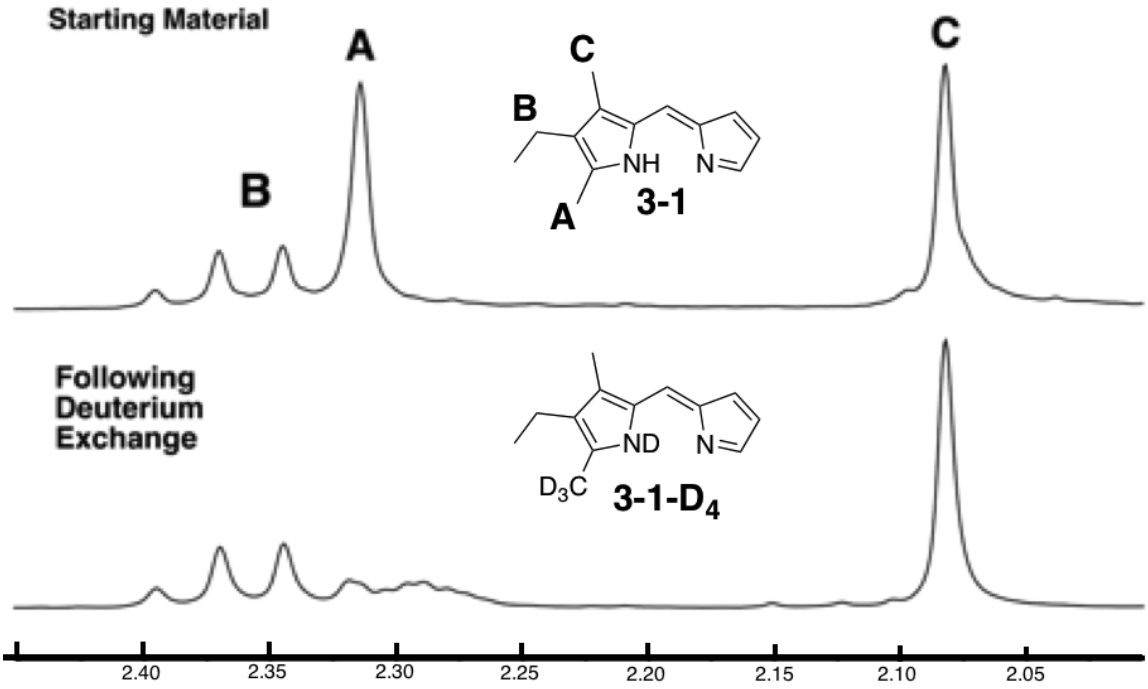
[a] Partial exchange observed.

As a first investigation, the free-base dipyrrin **3-1** was chosen due to inactivity of the HBr salt when attempting to form dimer **3-2**. The dipyrrin was dissolved in deuterated methanol, the solution was purged with nitrogen and then exposed to microwave-promoted heating at 60, 70, 80 and 90 °C for 30 minutes (Table 3-2, entries 1-4). With each increase in temperature, the reaction mixture became increasingly dark. ^{1}H NMR spectra of the crude mixtures corresponding to entries 1-3 did not reveal proton exchange. However, increasing the temperature to 90 °C resulted in considerable broadening of the 1-methyl signal at 2.31 ppm. This broadening was accompanied by the formation of up-field satellite signals in the ^{1}H NMR spectrum between 2.34 and 2.30 ppm, and a small but quantifiable drop in total integrated area of the signal representing the 1-methyl relative to the starting material. The amount of product isolable following chromatography was not sufficient for full characterization, and thus another reaction was performed at 100 °C for 15 minutes (Table 3-2, entry 5). Analysis of the crude reaction

products using ^{1}H NMR spectroscopy revealed that the methyl signal at 2.31 ppm had been significantly repressed. Furthermore, sufficient material survived the reaction conditions for isolation of clean product via chromatography. It is notable that the thermal barrier to deuterium exchange on dipyrrin **3-1** occurred at the lowest temperature previously required for formation of the dimeric decomposition product, **3-2** (100 °C, Table 3-1). This is a significant result, as the deuteration experiments confirm the proposed threshold for induction of the tautomeric dipyrrin state for dipyrrin **3-1**. Testing was performed to determine whether deuterium exchange on the hydrobromide salt of dipyrrin **3-1** could be facilitated. **3-1•HBr** was dissolved in a 1:1 mixture of MeOD:$CDCl_3$, at 150 °C for 30 minutes in a mixture of deuterated chloroform and methanol. As was expected, due to the previous inactivity of the dipyrrin HBr salts in the dimerization reaction, no proton exchange (or decomposition) was observed upon inspection of the crude material using ^{1}H NMR.

As deuterium exchange occurs for each proton on the 1-methyl substituents, as well as the *N*-H moiety, the products obtained from the successful deuteration experiments on free-base **3-1** contained a mixture of deuterated products (D_x, where X = 0→4). A ^{1}H NMR spectrum of a deuterium-containing free-base dipyrrin, **3-1-D$_4$**, is shown in Figure 3-9.

Figure 3-9: **^{1}H NMR spectra depicting loss of 1-methyl signal in free-base dipyrrin 3-1**



As the exchange for deuterium occurs at the 1-methyl position of **3-1**, nearly complete loss of the low-field methyl signal was observed, corresponding to methyl **A** (2.31 ppm, Figure 3-9). The D_1, D_2, D_3, and D_4 dipyrrins are all observable in the acquired mass spectrum. Furthermore, suppression of the 1-methyl carbon (**A**) is observed in the ^{13}C NMR spectrum, as ^{1}J coupling with the deuterium splits the signal corresponding to the carbon atom to below the detectable baseline.

Although the reactive methyl substituent has been assumed to be consistent with literature reports, i.e. located at the 1-position of the dipyrrin,[110] use of 2D NMR techniques would enable conclusive elimination of the possibility that deuteration had occurred at the 3-methyl position. Unfortunately, long-range ^{4}J coupling hindered conclusive characterization of free-base dipyrrin **3-1**, and so instead the symmetric dipyrrin **3-3** was fully characterized using HSQC and HMBC experiments. Subsequently,

deuteration enabled the conclusive elucidation of the reactive methyl functionality at the 1-position (Table 3-3). Symmetric dipyrrin **3-3** underwent hydrogen exchange at 150 °C, and thus **3-3-D$_7$** was isolated in a 15% yield following column chromatography on basic alumina. Notably, under these conditions, all six of the 1- and 9-methyl protons underwent exchange, resulting in characterization of the D_7 species via mass spectrometry. The proton signals correlating to H_D, H_E and H_I of **3-3•HBr** were assigned using a 1D ^{1}H NMR spectrum, due to their recognizable nature (ethyl and *meso*-hydrogen). Thus, carbon atoms D, E and I were also assigned through observation of C-H correlation in the HSQC spectrum. Analysis of the HMBC spectrum revealed the signal at 130.0 ppm in the ^{13}C NMR spectrum to be C_C, through correlation to H_E (Figure 3-10).

Figure 3-10: **HMBC spectra cross-sections depicting ^{1}H-^{13}C hetero-correlations in deuterated free-base 3-3-D$_7$**

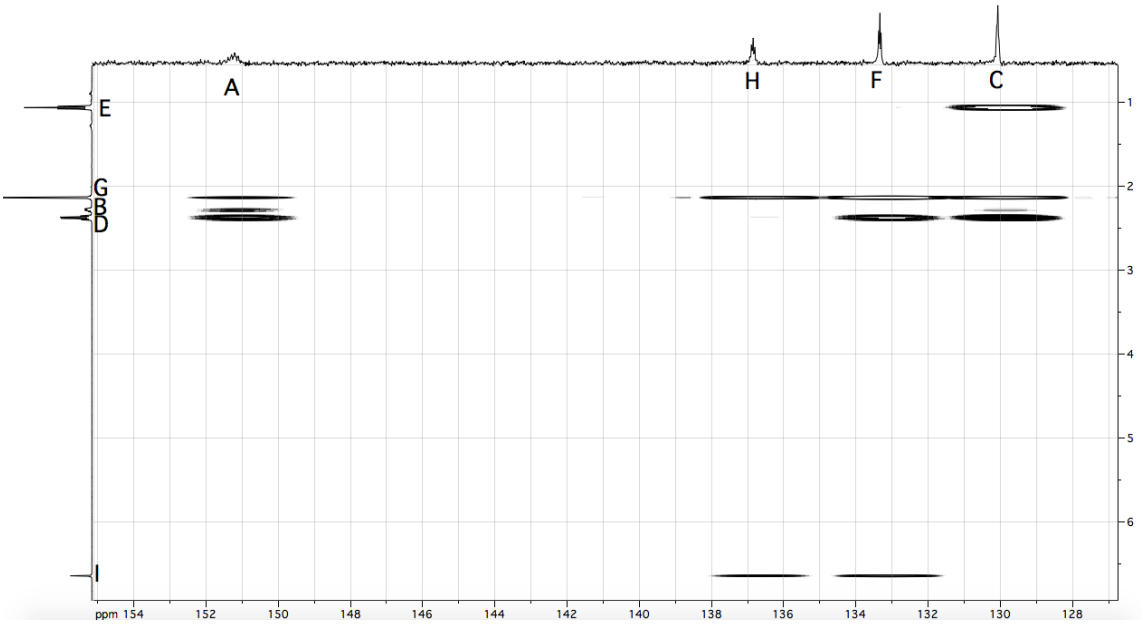
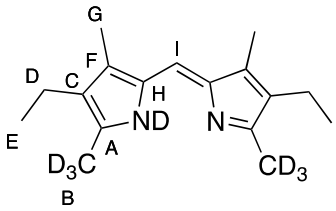


Table 3-3: **Structural assignment of deuterated free-base dipyrrin 3-3**



Proton Label	Shift (ppm)	Carbon Label	Shift (ppm)
---	---	A	151.2
B	2.31[a]	B	14.3[a]
---	---	C	130.0
D	2.37	D	17.9
E	1.06	E	15.0
---	---	F	133.3
G	2.13	G	9.6
---	---	H	136.8
I	6.40	I	115.39

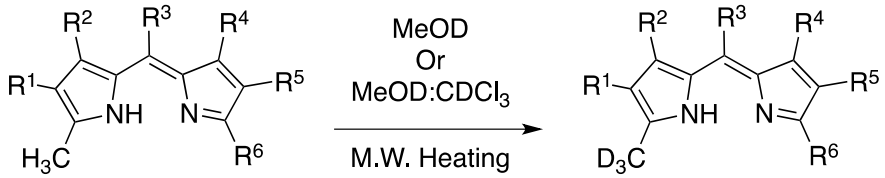
[a] Signal significantly suppressed in spectrum of deuterated compound

The methyl signal at 2.13 ppm in the ^{1}H NMR spectrum showed HMBC correlation to all pyrrolic C atoms, (C_A, C_C, C_F and C_H), but correlated weakly with the signal at 151.2 ppm. The methyl signal at 2.31 ppm correlated to two of the pyrrolic carbon signals (130.0 and 151.2 ppm) but not to the signals at 133.3 and 136.8 ppm. As the *meso*-H correlated to only these two carbon signals in the HMBC spectrum (133.3 and 136.8 ppm), these signals must be C_F and C_H. Of these two, only C_F should correlate to the ethyl signal, and indeed, only the signal at 133.3 ppm showed this correlation. Thus, C_F was assigned as 133.3 ppm, and C_H as 136.8 ppm. Only the 3-methyl of **3-3** is

expected to correlate to C_H via HMBC. Thus, it was concluded that H_B and H_G were represented by the signals at 2.31 and 2.13 ppm, respectively, and that the reactive, deuterium exchanging methyl is, indeed, the 1-methyl.

With the reactive group of **3-3** confirmed as the 1-methyl, a variety of other dipyrrins were thus reacted to determine the scope of this deuteration technique (Table 3-4). Several free-base dipyrrins sharing similar alkyl substitution patterns, and thus similar stabilities, as **3-1** were then evaluated. Free-base dipyrrins **3-5**, **3-6** and **3-7** were prepared from their respective HBr salt via a basic wash with NaOH (1.0 M); after subsequent drying, the dipyrrins were dissolved in MeOD (4 mL) and heated in the microwave at 100 °C for fifteen minutes.

Table 3-4: **Deuterium exchange on various 1-methyl dipyrrins**



Entry	Dipyrrin	R^1:R^2:R^3:R^4:R^5:R^6	Solvent	t (min)	T (°C)	Yield (%)
1	**3-1**	Et:Me:H:H:H:H	MeOD	15	100	17
2	**3-5**	Et:Et:H:H:H:H	MeOD	15	100	5
3	**3-6**	Et:Et:H:Me:H:H	MeOD	15	100	18[d]
4	**3-7**[a]	Et:Me:H:H:H:H	MeOD	15	100	0
5	**3-3**	Et:Me:H:Me:Et:Me	MeOD: $CDCl_3$	15	150	15
6	**3-8**	Et:Me:Ph:Me:Et:Me	MeOD: $CDCl_3$	30	150	40
7	**3-13**	CO_2Bn:Me:H:Me:Et:Me	MeOD: $CDCl_3$	15	100	0[b]
8	**3-13**	CO_2Bn:Me:H:Me:Et:Me	MeOD: $CDCl_3$	15	150	81[c,d]
9	**3-14**	CO_2Et:Me:H:Me:Et:Me	MeOD: $CDCl_3$	15	150	89[c,d]
10	**3-15**	COMe:Me:H:Me:Et:Me	MeOD: $CDCl_3$	15	125	76[c,d]

[a] *N*-methyl protected on R^{4-6} pyrrolic unit; starting materials did not survive reaction conditions. [b] Starting materials reclaimed. [c] Exchange only occurred on electron-rich pyrrolic unit. [d] Free-base product was sufficiently stable for conversion to HBr salt following isolation as free-base.

The products were purified using column chromatography over basic alumina using a 1:9 ethyl acetate:hexanes eluent to remove black amorphous decomposition product, and to yield the deuterated solids. Although alkyl dipyrrins **3-5** and **3-6** did undergo hydrogen exchange, deuteration did not occur as fully as for compound **3-1**. As with compound **3-1**, the less substituted **3-5** was not amenable to conversion to the more-stable HBr salt following reaction, and was isolated in a low yield of only 5% (Table 3-4,

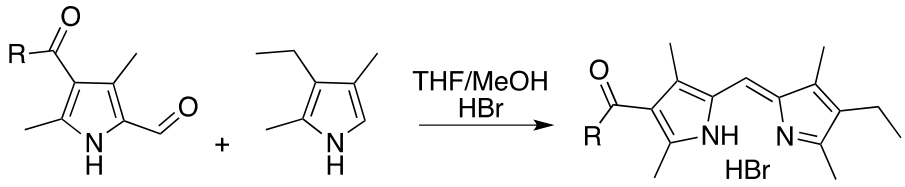
entry 2). Although the yield of converted dipyrrin **3-6** was still rather low, 18% (Table 3-4, entry 3), the product did survive conversion to the HBr salt. Curiously, **3-7**, the *N*-methyl protected version of **3-1** (Table 3-4, entry 4) completely decomposed under the same conditions required for the deuterium exchange on **3-1**. As described above, the more-substituted dipyrrin **3-3** underwent near-total exchange at the 1-methyl position, but reaction required a higher temperature (150 °C) and still suffered from significant decomposition resulting in a 15% isolated yield following column chromatography (Table 3-4, entry 5).

All examples of deuterium exchange were thus far performed on *meso*-H dipyrrins. To determine whether *meso*-substitution affects this reactivity, *meso*-phenyl, krypto-dipyrrin **3-8** was subjected to microwave-promoted heating in MeOD:$CDCl_3$ (4 mL) for 30 minutes (Table 3-4, entry 6). A considerable amount of decomposition occurred. However, a 40% yield of deuterated **3-8** was obtained following purification on basic alumina. The *m/z* base-peak in the low-resolution mass spectrum correlated to the D_7 dipyrrin. Interestingly, a mass spectrometric signal correlating to the D_9 species was differentiable from baseline noise, indicating minor deuterium exchange with hydrogen at positions other than the 1,9-dimethyl and *N*-H positions. This change was not detectable in either the ^1H or ^{13}C NMR spectra, supporting the notion that deuteration at the 1- and 9- position is dominant, alongside exchange at the pyrrolic nitrogen.

Moving away from the simple alkyl substituted dipyrrins, the role of electron withdrawing groups upon deuterium exchange of 1-methyl protons was explored. The reactivity of pyrroles in general is significantly modified by the presence of ester or acyl substituents at any of the ring positions.[107] Where extended π-conjugation is present at the

2-position, the compound is generally less sensitive to a variety of reactions, but will tolerate harsher conditions.[115] Dipyrrins containing more than one carbonyl group adjacent to the ring are typically prepared via formation of the dipyrromethane precursor, followed by oxidation to the dipyrrin.[108] However, these dipyrrins are not stable, and readily collapse back to the dipyrromethane upon exposure to aqueous conditions.[108] Thus, asymmetric dipyrrins containing only one deactivated (carbonyl-containing) pyrrolic unit were synthesized for deuterium exchange. MacDonald-type coupling of a 2-H pyrrole with a 2-formyl pyrrole using hydrobromic acid is a common method for the synthesis of asymmetric dipyrrins. Unfortunately, the success of this method is dependent on the substitution pattern of each of the pyrroles.[107] If the α-free, 2-H pyrrole is insufficiently nucleophilic due to the presence of electron withdrawing groups, the dipyrrin•HBr salt will not be isolated. As a result of these limitations, and despite attempts to synthesize various other substrates, only three dipyrrins were produced to this end (Scheme 3-2).

Scheme 3-2: **Synthesis of asymmetric mono-acylated dipyrrins**



3-9 R = OBn
3-10 R = OEt
3-11 R = Me

3-12

3-13•HBr R = OBn, 90%
3-14•HBr R = OEt, 98%
3-15•HBr R = Me, 70%

The requisite 1-formyl pyrroles, **3-9**, **3-10** and **3-11**, as well as so-called "krypto" pyrrole **3-12** were synthesized according to literatures methods.[61,87,116] The pyrroles were dissolved in a mixture of methanol and tetrahydrofuran (1:1), the solution bubbled with nitrogen, and a single equivalent of concentrated hydrobromic acid then added. Brick-red

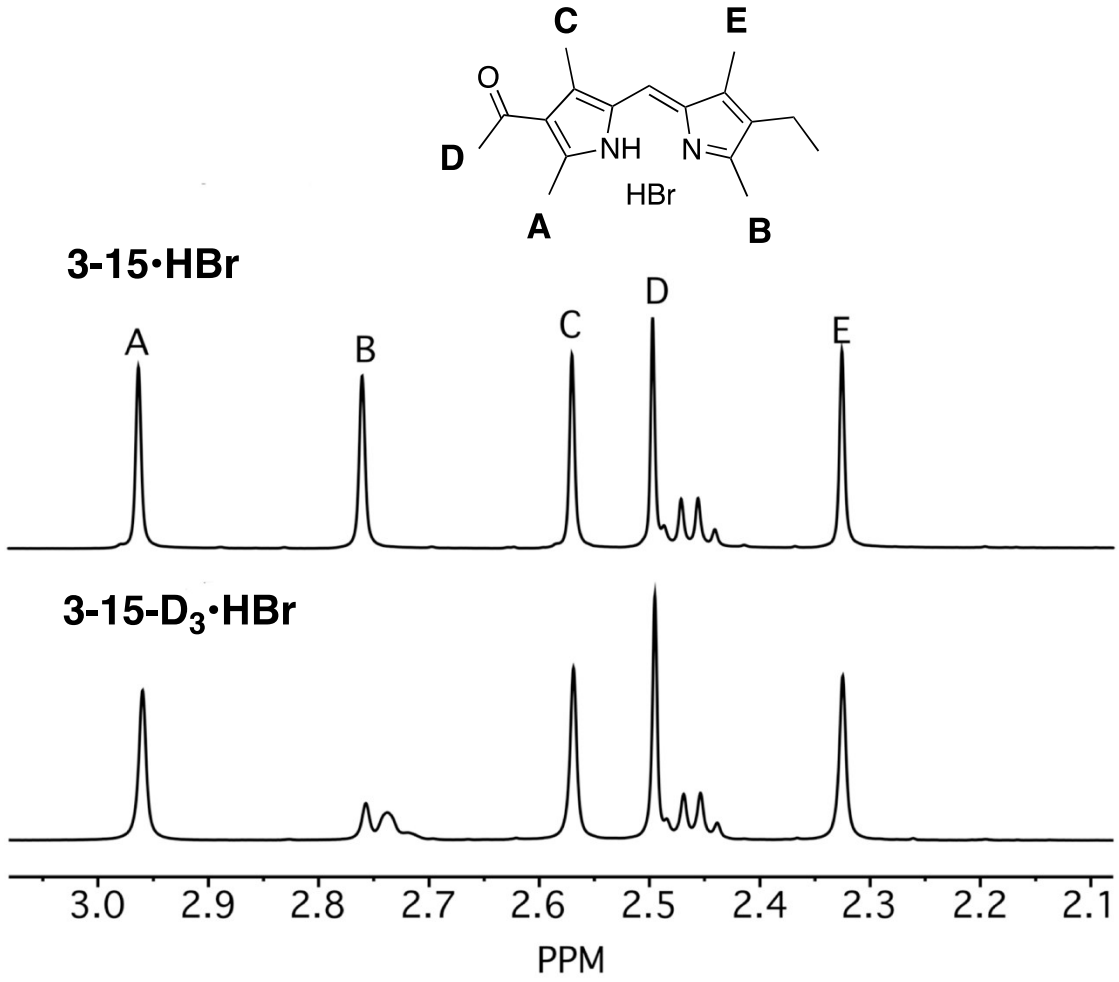
precipitates **3-13•HBr**, **3-14•HBr**, and **3-15•HBr** were formed immediately. The products were further precipitated upon the addition of ether. After washing with ether, and drying over sodium sulfate, the products were isolated in excellent yields. None of these dipyrrins have been reported in the recent literature, although single reports of **3-14•HBr** and **3-15•HBr** can be accessed via Scifinder, but lack NMR spectral data.[117,118]

The deuteration of these dipyrrins was then explored. The benzyl ester dipyrrin, **3-13•HBr** was converted to its free-base via NaOH wash (1.0 M). After drying, the resulting solid was dissolved in a mixture of $CDCl_3$ and MeOD, and the resulting solution was heated at 100 °C for 15 minutes in the microwave reactor. Similar to symmetrical dipyrrin **3-3**, minimal exchange was observed in the ^{1}H NMR spectrum of the crude product. At this temperature, no decomposition of the dipyrrin was evident, and the starting material was recovered; thus, a second reaction was run at 150 °C for 15 minutes. Analysis of the crude ^{1}H NMR spectrum revealed that one of the four singlet methyl signals had been significantly, but not totally, suppressed, and several smaller shoulder signals had arisen slightly up-field of the methyl corresponding to the partially deuterated products (D_1, D_2, D_3 and D_4). The presence of the acyl functional group granted significant thermal stability, and a drastic increase in the yield of the reaction was observed. The free-base dipyrrin was purified over activated basic alumina, and converted back to the hydrobromide salt via a wash using 1M HBr (aqueous) to produce an orange solid in an 81% yield (Table 3-4, entry 8). Although a wash with HBr induced decomposition of the partially alkyl-substituted dipyrrins (**3-1** and **3-5**), the presence of the acyl functionality on the dipyrrin backbone is sufficient so as to stabilize the molecule, and increase the storage life-time of the product molecule. The procedure was

repeated with the ethyl ester dipyrrin (**3-14**) at 150 °C, and the acetyl dipyrrin (**3-15**) at 125 °C, with isolated yields of the deuterated compounds of 89 and 71% following conversion to salt, respectively (Table 3-4, entries 9 and 10).

^{1}H NMR spectra of compound **3-15•HBr**, taken before and after reaction, are shown in Figure 3-11.

Figure 3-11: **Deuteration of dipyrrin 3-15•HBr**



The identities of the methyl signals were conclusively elucidated using 2D NMR techniques. Deuterium exchange occurred exclusively at the 9-methyl functionality in all three reactions (Figure 3-11, methyl **B**). Notably, signals due to each of the D_1, D_2, and

D_3 species appear in the mass spectra for the isolated material, unsurprisingly given the presence of the small ^{1}H NMR signals upfield of the original methyl signal. Attempts were made to also deuterate the 1-methyl position of **3-15** (Figure 3-11, methyl **A**) via the use of increased temperature and the addition of various bases. However, no deuteration of this position could be achieved. To rationalize the regioselectivity observed in the deuteration of dipyrrins **3-13**, **3-14** and **3-15**, consideration of the intermediary conjugate bases that presumably develop during tautomerization may be useful (Figure 3-12).

Figure 3-12: **Resonance forms of deprotonated 1 and 9-methyl, 2-acyl dipyrrins**

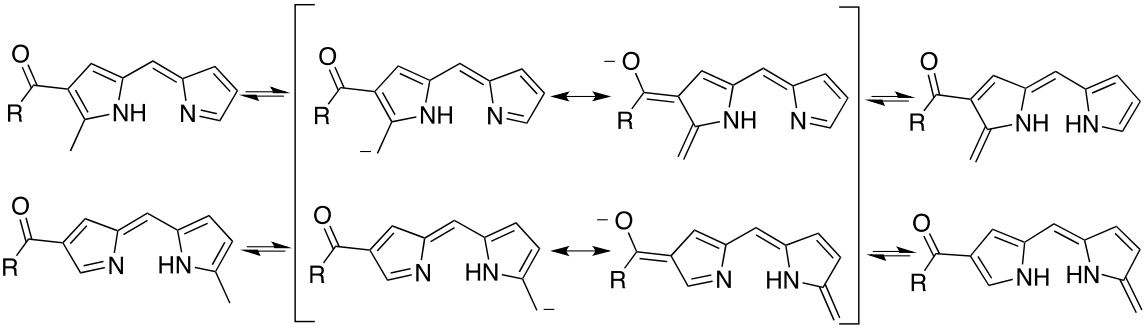


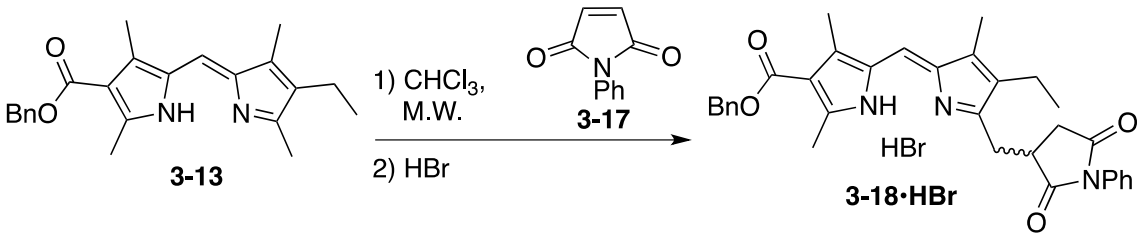
Figure 3-12, top, depicts deprotonation of the 1-methyl group adjacent to the carbonyl functionality. Resonance stabilization of the conjugate base, afforded by the carbonyl group, results in a charge distribution that stretches over five atoms. However, deprotonation of the distal 9-methyl group (Figure 3-12, bottom) produces a more conjugated anion spanning eleven atoms. Subsequently, the pK_a of the CH_3 protons on the distal 9-methyl group is anticipated to be lower than those corresponding to the 1-methyl group adjacent to the β-carbonyl. As such, deuterium exchange at the 9-methyl group is favoured over that of the 1-methyl position, as demonstrated experimentally. Use of theoretical modeling to predict pK_a values of α-methyl groups adjacent and distal to deactivating groups would be desirable in the future.

3.2.3 Addition of Electrophiles to 1-Methyl Dipyrrins

As mentioned previously, other than Knoevenagel-type reactions (as well as a class of reactions utilizing similar reactivity in dipyrrinones for the synthesis of bilirubin derivatives),[119] carbon-carbon bond formation from the 1-methyl substituent is otherwise unreported. Furthermore, with the exception of the report of Treibs *et al*. that details the formation of an intermediate analogous to **3-2**,[110] no reactions are known whereby the 1-methyl moiety of dipyrrins maintains its sp^3 hybridized nature. As condensation of the 1-methyl substituent with electrophiles in Knoevenagel fashion requires the use of an auxiliary base, elimination of the intermediate hydroxy functional group is readily promoted, and the vinyl-substituted dipyrrins thus obtained (Figure 3-4). Due to the success of our deuterium exchange at elevated temperature, we hypothesized that electrophilic attack could occur at 1-methyl positions of dipyrrins to generate a sp^3 centre bearing $–CH_2R$ functionality.

As **3-13** proved to be a durable substrate for deuteration, this compound was chosen as a model with which to work. α,β-Unsaturated carbonyl compounds serve as excellent acceptors of nucleophiles, and thus the conjugate addition of **3-13** to the stable, highly activated compound *N*-phenylmaleimide **3-17** was explored (Table 3-5).
As the HBr salts have been shown to be inactive thus far, the dipyrrin free-bases were prepared as before, by NaOH (aq.) wash. After drying, the starting material was dissolved in chloroform, and the solution then bubbled with nitrogen before addition of the maleimide as a solid. The first reaction was performed in the microwave reactor at 100 °C (Table 3-5, entry 1).

Table 3-5: **Conjugate addition of *N*-phenyl maleimide 3-17 to dipyrrin 3-13**



Entry	Eq. 3-17	t (min)	T (°C)	3-13 (% recov.)	Yield (%)
1	1	15	100	100	0
2	1	15	125	95	0[a]
3	1	15	150	54	42
4	1.5	45	150	22	73
5	2	90	150	10	85

[a] Trace product detectable by TLC analysis.

No reactivity was observed after 15 minutes, and so the experiment was thus repeated at 125 °C (entry 2). Darkening of the solution from yellow to brown occurred; although a significant amount of starting material was present in the reaction mixture, a second compound was evident by TLC analysis on alumina. A trace amount of the expected conjugate addition product was isolable using column chromatography, contained in a mixture of impurities. Although ^{1}H NMR spectroscopy was not useful in confirming the identity of the material, analysis by mass spectrometry confirmed the presence of the desired adduct, **3-18**. It should be noted that in addition to these products, the formation of blue-coloured products, presumably analogous to the 1-(vinylpyrrolyl)-dipyrrins discussed earlier (**F**, Figure 3-8), could also be observed by TLC analysis. Although attempts were made to isolate these compounds via chromatographic methods,

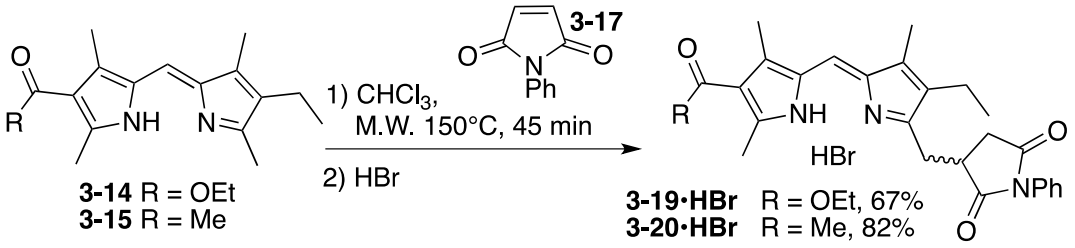
they were present in only trace quantities and proved unstable either to atmospheric conditions, or to the conditions required for their purification.

With this result, the temperature of the experiment was increased to 150 °C. After 15 minutes, formation of the (2,5-dioxo-1-phenylpyrrolidin-3-yl)methyl)-dipyrrin **3-18** was evident by TLC analysis. Separation of the product from unreacted dipyrrin starting material by chromatography was performed; unfortunately, unreacted *N*-phenylmaleimide **3-17** co-eluted with the product under these elution conditions. The mixture of **3-17** and **3-18** was dissolved in chloroform, washed with 1.0 M hydrobromic acid, concentrated, and poured into diethyl ether to precipitate a brown solid (42% yield, Table 3-5, entry 3). As both starting materials were present in the final reaction mixture, another trial was performed for 45 minutes at 150 °C. As polymerization of maleimide occurs at high temperatures,[120] 1.5 equivalents were utilized to account for lost electrophile. After 45 minutes at 150 °C, a small amount of pyrrolic starting material still remained, as did unreacted maleimide. However, the isolated yield of **3-18•HBr** was much-improved (73%, entry 4). It was determined that the conditions could be further optimized through the addition of two equivalents of *N*-phenylmaleimide, with microwave heating at 150 °C for 1.5 hours. The product, **18•HBr**, was thus obtained in a yield of 85% (Table 3-5, entry 5). Excess unreacted maleimide was identified in the product mixture, and the colour of the solution had darkened considerably, indicating some decomposition of starting materials.

The reaction was repeated using ethyl ester dipyrrin **3-14** and acyl dipyrrin **3-15**. Adapting the procedures used for Table 3-5, (entries 3 and 4, 1.5 equivalents of **3-7** and 45 minute reaction time) the maleimide addition products **3-19•HBr** and **3-20•HBr** were

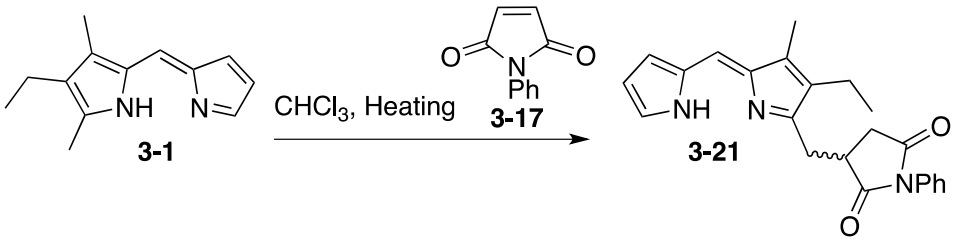
isolated in yields of 67 and 82%, respectively (Scheme 3-3). The work up and general appearance of the reactions involving **3-14** and **3-15** were comparable to those described for **3-13**.

Scheme 3-3: **Conjugate addition of *N*-phenylmaleimide 3-17 to dipyrrins 3-14 and 3-15**



Contrarily, addition of *N*-phenyl maleimide to the less stable, alkyl-substituted dipyrrin **3-1** was less fruitful than reactions involving dipyrrins **3-13** to **3-15** bearing electron-withdrawing substituents. Free-base dipyrrin **3-1** was dissolved in anhydrous chloroform, and the solution was bubbled with nitrogen before the addition of **3-17**. After heating the solution at 100 °C for 15 minutes in the microwave reactor, a noticeable darkening of the solution had occurred. A considerable amount of starting material was observed by TLC analysis. Fortunately, as with dipyrrins **3-13** to **3-15**, a second dark-yellow, dipyrrin-like compound was observable using TLC analysis, with a higher polarity relative to the starting material. Chromatography over activated basic alumina using a ethyl acetate:hexanes gradient (1:9 to 2:8) was used to purify the product **3-21** (Table 3-6).

Table 3-6: **Conjugate addition of *N*-phenylmaleimide to dipyrrin 3-1**



Entry	Eq. 3-17	t	T (°C)	Heating	Yield[a] (%)
1	1.5	15 min	100	MW	21
2	1.5	15 min	150	MW	15
3	1.5	24 h	61	Δ	15

[a] Product isolated as a mixture of **3-16** and **3-20**. Yield calculated from % molar ratio of products, as observed by ^{1}H NMR spectra.

Unfortunately, as in the formation of **3-18**, **3-19** and **3-20**, co-elution of **3-21** with **3-17** occurred. Analysis of an ESI$^+$ mass spectrum of the mixture revealed that a compound with a mass matching the target conjugate addition product, **3-21**, had indeed been synthesized. Unfortunately, purification via conversion to the hydrobromide salt was not successful, resulting in decomposition of the products. Neither a wash with hydrobromic acid (1.0 M, 30 mL) nor the controlled reaction of a single equivalent of concentrated hydrobromic acid at 0 °C provided **3-21•HBr**. This result is reminiscent of the previously mentioned attempts to form the HBr salt of the alkyl substituted, deuterated dipyrrin **3-1** directly from the free-base. As such, the product **3-21** was not successfully purified. Several attempts at purification by column chromatography were performed using various solvent systems were unsuccessful, as were attempts to recrystallize the product.

A brief attempt was made to optimize the conditions of this reaction; a second trial was performed at 150 °C. However, a decrease in the crude yield of product was

observed. Conversely, mild heating under thermal conditions for a longer amount of time was explored (Table 3-6, entry 3). Heating of a solution of the starting materials in chloroform at reflux temperature for a period of 24 hours did, gratifyingly, result in the formation of some of the expected adduct (15%). However, the starting material had decomposed in this time. This result indicates that temperatures lower than those used for deuterium conversion (100 °C, microwave heating for 15 minutes) are capable of activating the 1-methyl position of compound **3-1**.

Although reaction of **3-1** with **3-17** was successful, several challenges regarding the addition of electrophiles to the 1-methyl group of dipyrrins endure. A balance exists between the high temperatures required to access the dipyrrin-tautomer, and the moderate temperatures required to maintain the integrity of the starting materials. Decomposition of the dipyrrin and polymerization of maleimide are hindering factors at high temperatures. Furthermore, despite many attempts to add various other α,β-unsaturated carbonyl compounds to substrates **3-13** to **3-15**, *N*-phenylmaleimide has thus far been the only compound to cleanly react with 1-methyl dipyrrins. Maleic anhydride typically reacts under the conditions required for addition of maleimide. However, when reacting maleic anhydride with benzyl-ester dipyrrin **3-13** under the conditions required for addition of maleimide, the reaction was messy. Multiple products were generated, consisting of maleic acid ring-opened products, as well as decarboxylated versions of these products. Although the formation of these molecules can be monitored by analysis of a mass spectrum of the crude products, purification of these substrates was hindered by the complexity of the reaction mixture. Attempted reaction with alkyl and benzyl halides,

methyliodide or benzylbromide, for example, were unsuccessful as the substrates either remained unreacted, or the reactions led to a complex reaction mixture.

With access to a limited series of maleimide-appended dipyrrins, a brief survey of their reactivity for boron complexation was performed. Conversion of dipyrrins **3-18** to **3-21** to *F*-BODIPYs was attempted using standard conditions (6 equivalents of NEt_3 and 9 equivalents of BF_3•Et_2O). In each case, either no complexation was observed, or only a small amount of *F*-BODIPY was isolable (less than 10%). In the case of isolation, decomplexation was observed upon dissolution in solvents for NMR analysis. This behaviour is unusual, as the parent dipyrrins are typically readily converted to *F*-BODIPYs and are stable to characterization. Further study is required to determine the origin of this reactivity.

Section 3.3: Conclusions

The activation of the 1-methyl moiety of free-base dipyrrins has been utilized to several ends. Firstly, the thermal decomposition products, 1-(pyrrolyl)-dipyrrin dimers, have been isolated and characterized for the first time since their proposal in 1978.[110] The stability of these compounds is certainly in question, and understanding the routes through which decomposition of dipyrrin frameworks occurs is important for a variety of reasons; for example, the increasing prevalence of dipyrrins for use as fluorescent tags in medical imaging, coupled with the realization that *F*-BODIPYs are not as stable as has been previously suggested,[100] means that frameworks such as compound **3-2** would need to be studied for biological effects before *F*-BODIPYs can be approved for use in human

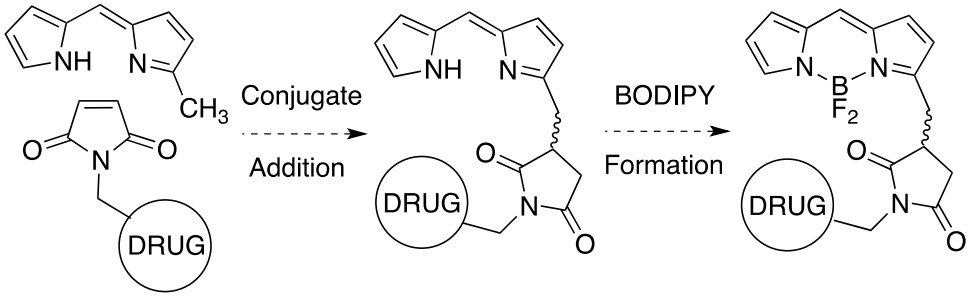
subjects. Further study regarding the biological interaction of **3-2**, with collaborators, would be of interest, provided an improved method of synthesis.

Deuteration of the 1-methyl position on dipyrrins has been shown to be accessible following a simple procedure. As the 1-methyl substituent often serves as a synthetic handle for the synthesis of porphyrins,[121] this methodology allows for facile incorporation of a deuterium label at the *meso*-position of a porphyrin. Similarly, this deuteration phenomenon could have potential for the deuteration of a number of dipyrrin-containing constructs, including prodigiosenes, *F*-BODIPYs, and other dipyrrinato metal complexes that are desired for their optical properties. Furthermore, selective deuteration has been shown to occur where appropriate acyl functionalities are present. This allows for additional synthetic control of the labeling process. Further research on this topic will aim to expand on the effect of acyl functionalization at other positions of the dipyrrin on the deuteration process.

Finally, a methodology for the conjugate addition of *N*-phenylmaleimide to the 1-methyl position of free-base dipyrrins has been developed. This is the first literature report of direct C-C bond formation between the α-methyl group of a free-base dipyrrin and any other carbon source. The technique is applicable to both alkyl and mono-acyl substituted dipyrrins. However, reasonable yields have so far only been attainable with dipyrrins containing a stabilizing acyl functionality. Although the practical application of this chemistry is limited by the scope of reactive electrophiles, maleimides represent a class of compounds that are frequently studied for use in medicinal labeling chemistry.[122] Typically, a drug is attached to the *N*-terminal position of a maleimide. Sulfhydryl groups are then added across the maleimide double bond to form physiologically stable linkages.

Conjugate addition of a 1-methyl dipyrrin to a maleimide-drug conjugate would allow for generation of drug-appended *F*-BODIPYs in as few as two synthetic steps (Figure 3-13).

Figure 3-13: **BODIPY tagging of pendant-maleimide drug molecules**



Although the barriers to this chemistry are present in the reluctance of maleimide-appended dipyrrins to complex with BF_3.Et_2O, the potential for fast access to *F*-BODIPY labeled drug molecules via the procedures described here is alluring.

Section 3.4: Experimental

3.4.1 General Experimental

All chemicals were purchased and used as received unless otherwise indicated. Hexanes and dichloromethane used for chromatography were obtained crude and purified via distillation under atmospheric conditions before use. Anhydrous solvents were used as received. Flash chromatography was performed using Silicycle ultra pure silica (230-400 mesh) or Brockmann III (150 mesh) activated basic or neutral alumina oxide, as indicated. TLC was performed using glass-backed silica gel plates or on plastic-backed neutral alumina plates. Visualization of TLC plates was performed using UV light (254 nm) and/or vanillin stain. Moisture-sensitive reactions were performed using flame-dried glassware under a positive pressure of nitrogen. Air and moisture-sensitive compounds were introduced via syringe. NMR spectra were recorded at the NMR-3 facility

(Dalhousie University) using a Bruker 500 MHz or a Bruker 300 MHz spectrometer. ^{1}H and ^{13}C chemical shifts are expressed in parts per million (ppm) using the solvent signal as reference.[93] ^{11}B and ^{19}F chemical shifts were referenced using the absolute referencing procedure standard for Bruker digital spectrometers, with BF_3•Et_2O (15% in $CDCl_3$) and CCl_3F defining the 0 ppm position, respectively. All coupling constants (*J*) are reported in Hertz (Hz). Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Splitting patterns preceded by an "a" are defined as apparent signals. Methyl assignments are numbered according to Figure 3-1. All mass spectra were recorded by Mr. Xiao Feng using TOF and LCQ Duo ion trap instruments operating in ESI+ mode. The reported masses of deuterated compounds correspond to the base-peak of the low-resolution spectrum. All microwave-promoted reactions were performed using a Biotage Initiator 8 laboratory microwave apparatus, 0–400 W power, 2.45 GHz. Starting material pyrroles were prepared according to literature procedures.[87,116,61]

3.4.2 General Procedure I for the Synthesis of Asymmetric Dipyrrin•HBr Salts via MacDonald Coupling

Appropriate 1-formyl pyrrole and 1-H pyrrole were dissolved in tetrahydrofuran/methanol (10 mL, 1/1), at room temperature with stirring under a nitrogen atmosphere. Concentrated hydrobromic acid (1.5 equivalents) was added drop-wise to the solution. The mixture was stirred until the starting materials were consumed, as monitored using TLC analysis. The solution and the precipitate were poured into chilled Et_2O (50 mL) with stirring, and the precipitate was collected through suction filtration (colours ranged between bright orange and red, with varying levels of

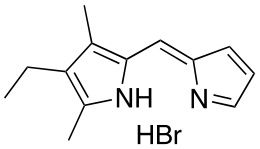
crystallinity). The product was washed with Et_2O and dried under vacuum to render the dipyrrin salt.

3.4.3 General Procedure II for the Preparation and use of Free-Base Dipyrrins in Deuterium Exchange Experiments

A sample of dipyrrin•HBr salt (50 or 100 mg) was dissolved in CH_2Cl_2 (30 mL) and then washed with NaOH (1 M, aq., 30 mL). The organic layer was dried over Na_2SO_4, the solvent removed under vacuum and the solid then dried using a vacuum oven. The resulting free-base was sealed in a microwave vessel under a nitrogen atmosphere, and then dissolved in anhydrous, deuterated methanol (4 mL), or in a 1:1 mixture of deuterated methanol and chloroform (to improve solubility), The reaction mixture was heated for 15 minutes (between 100 and 150 °C, as stated and necessary for the specific experiment). Purification of the reaction products over Brockman III basic alumina eluting with ethyl acetate:hexanes (1:19 → 1:4, as necessary), followed by removal of the solvent *in vacuo* gave the deuterated dipyrrins as bright yellow films. The dipyrrins were dissolved in dichloromethane (30 mL) and washed with hydrobromic acid (1 M, 30 mL). Separation of the organic layer and removal of the solvent *in vacuo* produced the dipyrrin•HBr salts as brightly coloured solids.

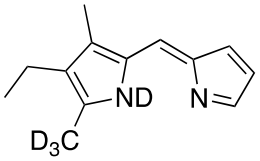
Section 3.5: Synthesis

(*Z*)-2-((2*H*-Pyrrol-2-ylidene)methyl)-4-ethyl-3,5-dimethyl-1*H*-pyrrole hydrobromide (3-1•HBr)



This compound was synthesized according to general procedure **I** from 3,5-dimethyl-4-ethyl-2-formylpyrrole (400 mg, 4.21 mmol)[87] and freshly distilled pyrrole (567 µL, 4.21 mmol), as a bright orange solid (953 mg, 80%). δ_H (500 MHz, $CDCl_3$) 1.09 (t, 3H, J = 7.6 Hz, CH_2CH_3), 2.29 (s, 3H, 3-CH_3), 2.44 (q, 2H, J = 7.6 Hz, CH_2CH_3), 2.74 (s, 3H, 1-CH_3), 6.48 (s, 1H, Pyr-H), 7.09 (s, 1H, Pyr-H), 7.20 (s, 1H, *meso*-H), 7.67 (s, 1H, Pyr-H), 13.34 (bs, 1H, NH), 13.54 (bs, 1H, NH); δ_C (125 MHz, $CDCl_3$) 10.2. 13.5, 14.2, 17.3, 114.7, 124.7, 127.3, 129.3, 132.0, 133.6, 137.7, 145.3, 162.0; ESI: $[M+H]^+$ ($C_{13}H_{17}N_2$): 201.1392 (calculated); 201.1385 (experimental). These data match literature values.[123]

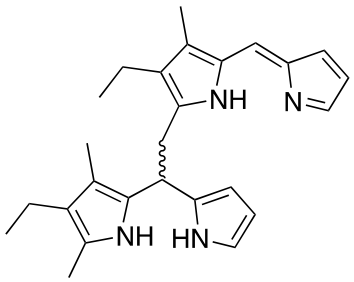
(*Z*)-2-((2*H*-Pyrrol-2-ylidene)methyl)-4-ethyl-3,5($^2H_3$)-dimethyl-1^2*H*-pyrrole (3-1-D_4)



Deuteration was performed according to general procedure **II**, using dipyrrin **3-1** (100 mg, 0.357 mmol) and heating at 100 °C for 15 min. Conversion to the hydrobromide salt via wash with hydrobromic acid (1M, 30 mL) induced decomposition; instead, the compound was characterized as the free-base dipyrrin, and isolated as a yellow film (12 mg, 17%). δ_H (300 MHz, $CDCl_3$) 1.07 (t, 3H, J = 7.6 Hz, CH_2CH_3), 2.08 (s, 3H, 3-CH_3),

2.31 (s, 3H, 1-CH_3, signal depressed), 2.36 (q, 2H, J = 7.6 Hz, CH_2CH_3), 6.23 (s, 1H, Pyr-H), 6.55 (s, 1H, Pyr-H), 6.66 (s, 1H, *meso*-H), 7.07 (s, 1H, Pyr-H); δ_C (125 MHz, $CDCl_3$) 9.6, 14.4, 16.6 (m, splitting observed due to deuterium coupling in $D_{1\rightarrow3}$ compounds) 18.2, 110.5, 117.6, 117.7, 125.4, 131.4, 137.8, 139.7, 149.4, 171.4; ESI: $[M+H]^+$ ($C_{13}H_{14}D_3N_2$): 204.1580 (calculated); 204.1575 (experimental). *ND signal not observed in ^1H NMR spectrum.

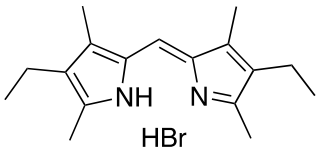
(*Z*)-2-((2*H*-Pyrrol-2-ylidene)methyl)-4-ethyl-5-(2-(4-ethyl-3,5-dimethyl-1*H*-pyrrol-2-yl)-2-(1*H*-pyrrol-2-yl)ethyl)-3-methyl-1*H*-pyrrole (3-2)



A sample of **3-1•HBr** was left on the bench in a sealed sample vial for the duration of six months, during which decomposition to **3-2** occurred under ambient conditions. Purification over Brockman III basic alumina eluting with a gradient of EtOAc:hexanes (1:19 to 1:9) provided **3-2** as a brown film. Alternatively, a sample of **3-1•HBr** (100 mg, 0.357 mmol) was dissolved in CH_2Cl_2 (30 mL), and washed with NaOH (1 M, 30 mL). After separation, the organic layer was dried over Na_2SO_4, and the solvent removed under vacuum. Following drying *in vacuo*, the compound was dissolved in dry methanol (4 mL) and the solution sealed in a microwave vessel under a nitrogen atmosphere. The compound was heated for 15 minutes in the microwave at 100 °C. Following removal of the solvent *in vacuo,* purification (as above) and removal of the solvent *in vacuo* gave **3-2** as a brown film (6 mg, 4 %). δ_H (300 MHz, $CDCl_3$) 0.98 (t, 3H, J = 7.3 Hz, CH_2CH_3),

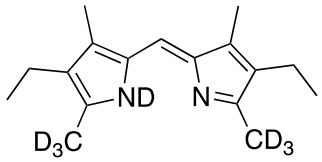
1.04 (t, 3H, J = 7.4 Hz, CH_2CH_3), 1.90 (s, 3H, Pyr-CH_3), 2.08 (s, 6H, overlapping Pyr-CH_3 and Dipyr-CH_3), 2.25 (adt, 2H, J = 14.5, 7.2 Hz, Dipyr-CH_2CH_3), 2.36 (adt, 2H, J = 15.1, 7.6 Hz, Pyr-CH_2CH_3), 3.26 (dd, 2H, J = 16.1, 6.6 Hz, Dipyr-CH_2CH), 4.70 (t, 1H, J = 6.6 Hz, CH_2CH(Pyr)$_2$), 6.03 (d, 1H, J = 2.5 Hz, Pyr-H), 6.16 (t, 1H, J = 3.0 Hz, Pyr-H), 6.24 (t, 1H, J = 3.1 Hz, Dipyr-H), 6.58 (dd, 1H, J = 3.7, 1.0 Hz, Dipyr-H), 6.66 (bs, 1H, Pyr-H), 6.70 (s, 1H, *meso*-H), 7.01 (bs, 1H, Dipyr-H), 7.67 (bs, 1H, Pyr-NH), 8.55 (bs, 1H, Pyr-NH); δ_C (125 MHz, $CDCl_3$) 9.2, 9.6, 11.2, 14.4, 15.8, 17.7, 17.9, 34.2, 36.1, 105.4, 108.2, 110.7, 113.7, 116.6, 117.7, 118.2, 118.6, 120.6, 121.2, 125.9, 126.1, 131.2, 134.5, 138.1, 140.0, 173.1;* ESI: $[M+H]^+$ ($C_{26}H_{33}N_4$): 401.2705 (calculated); 401.2709 (experimental). Partial reversion to starting material (**3-1**) occurred over the time-frame of NMR analysis for ^{13}C-UDEFT, COSY, HSQC and HMBC experiments; one reported signal in ^{13}C NMR spectrum is missing for **3-2**, due possibly to overlap with **3-1** signals.

(*Z*)-3-Ethyl-5-((4-ethyl-3,5-dimethyl-2*H*-pyrrol-2-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrole hydrobromide (3-3•HBr)



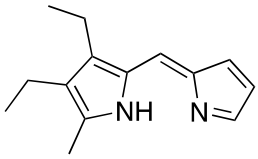
Compound **3-3** was prepared according to a literature procedure,[124] and isolated as a brick red solid (93 mg, 84%). δ_H (300 MHz, $CDCl_3$) 1.06 (t, 6H, J = 7.6 Hz, CH_2CH_3) 2.25 (s, 6H, 3-CH_3), 2.41 (q, 4H, J = 7.6 Hz, CH_2CH_3), 2.65 (s, 6H, 1-CH_3), 7.01 (s, 1H, *meso*-H), 12.90 (bs, 2H, N-H); δ_C (125 MHz, $CDCl_3$) 10.2, 13.0, 14.6, 17.4, 118.8, 126.3, 130.7, 141.4, 153.9; ESI: $[M+H]^+$ ($C_{17}H_{25}N_2$): 257.2012 (calculated); 257.2018 (experimental). This data matches reported literature values.[124]

(*Z*)-3-Ethyl-5-((4-ethyl-3,5($^2H_3$)-dimethyl-2*H*-pyrrol-2-ylidene)methyl)-2,4($^2H_3$)-dimethyl-1^2*H*-pyrrole (3-3-D$_7$)



Deuteration was performed according to general procedure **II**, using 100 mg of **3-3** and heating at 150 °C for 15 min. Following purification on alumina, the product was sufficiently stable as the free-base dipyrrin without concern of deterioration, and was isolated as a yellow film (12 mg, 15%). δ_H (500 MHz, $CDCl_3$) 1.06 (t, 6H, J = 7.6 Hz, CH_2CH_3) 2.13 (s, 6H, 3-CH_3), 2.31 (s, 6H, 1-CH_3, signal depressed), 2.38 (q, 4H, J = 7.6 Hz, CH_2CH_3), 6.64 (s, 1H, *meso*-H), 9.46 (s, 1H, NH, signal depressed); δ_C (125 MHz, $CDCl_3$) 9.6, 14.3 (m, splitting observed due to deuterium coupling in $D_{1\rightarrow6}$ compounds), 15.0, 17.9, 115.4, 130.0, 133.3, 136.8, 151.1; ESI: $[M+H]^+$ ($C_{17}H_{18}D_6N_2$): 262.2316 (calculated); 262.2311 (experimental).

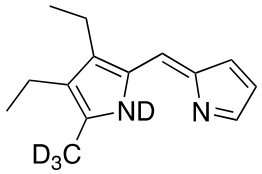
(*Z*)-2-((2*H*-Pyrrol-2-ylidene)methyl)-3,4-diethyl-5-methyl-1*H*-pyrrole (3-5)



The material, **3-5•HBr**, synthesized by John Paine III during his thesis work using described literature methods,[107] was recrystallized in cold methanol. The salt was then dissolved in CH_2Cl_2 (30 mL) and washed with NaOH (1M, 30 mL) to yield the free-base material as a brown solid. δ_H (500 MHz, $CDCl_3$) 1.11 (t, 3H, J = 7.6 Hz, CH_2CH_3), 1.17 (t, 3H, J = 7.6 Hz, CH_2CH_3), 2.34 (s, 3H, Pyr-CH_3), 2.38 (q, 2H, J = 7.6 Hz, CH_2CH_3),

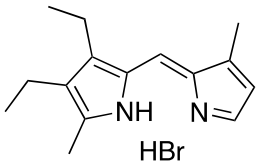
2.52 (q, 2H, J = 7.6 Hz, CH_2CH_3), 6.25 (at, 1H, J = 2.9 Hz, Pyr-H), 6.58 (d, 1H, J = 3.2 Hz, Pyr-H), 6.68 (s, 1H, *meso*-H), 7.08 (bs, 1H, Pyr-H), 10.30, 1H, N-H); δ_C (125 MHz, $CDCl_3$) 14.9, 16.9, 17.1, 18.0, 18.1, 110.5, 117.6, 117.8, 125.5, 131.4, 137.1, 146.2, 148.2, 171.2. *Free-base dipyrrin NMR values reported rather than HBr salt, as deuterated sample (**3-5-D$_4$**) was not stable to reconversion to salt.

(*Z*)-2-((2*H*-Pyrrol-2-ylidene)methyl)-3,4-diethyl-5($^2H_3$)-methyl-1^2*H*-pyrrole (3-5-D$_4$)



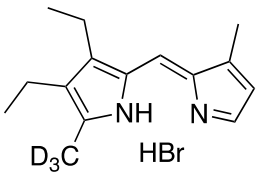
Deuteration was performed according to general procedure **II**, using 100 mg (0.32 mmol) of **3-5•HBr** and heating at 150 °C for 15 min. Only minimal deuteration of the compound was observed. Conversion to the hydrobromide salt induced decomposition, and thus the free-base dipyrrin was isolated as a yellow film following purification on alumina (3 mg, 5%). δ_H (300 MHz, $CDCl_3$) 1.08 (t, 3H, J = 7.6 Hz, CH_2CH_3), 1.15 (t, 3H, J = 7.6 Hz, CH_2CH_3), 2.32 (s, 3H, Pyr-H, signal depressed), 2.37 (q, 2H, J = 7.6 Hz, CH_2CH_3), 2.50 (q, 2H, J = 7.6 Hz, CH_2CH_3), 6.23 (dd, 1H, J = 3.5, 2.7 Hz, Pyr-H), 6.55 (dd, 1H, J = 3.5, 0.9 Hz, Pyr-H), 6.65 (s, 1H, *meso*-H), 7.07 (bs, 1H, Pyr-H); ESI: $[M+H]^+$ ($C_{14}H_{17}D_2N_2$): 217.1674 (calculated); 217.1671 (experimental). *ND signal not observed in ^{1}H NMR spectrum.

(*Z*)-3,4-Diethyl-2-methyl-5-((3-methyl-2*H*-pyrrol-2-ylidene)methyl)-1*H*-pyrrole hydrobromide (3-6•HBr)



The material, **3-6•HBr**, synthesized by John Paine III during his thesis work using described literature methods,[107] was recrystallized in cold methanol and obtained as a dark-red solid. δ_H (500 MHz, $CDCl_3$) 1.11 (t, 3H, J = 7.6 Hz, CH_2CH_3), 1.22 (t, 3H, J = 7.6 Hz, CH_2CH_3), 2.38 (s, 3H, 7-CH_3), 2.44 (q, 2H, J = 7.6 Hz, CH_2CH_3), 2.69 (q, 2H, J = 7.6 Hz, CH_2CH_3), 2.72 (s, 3H, 1-CH_3), 6.32 (s, 1H, Pyr-H), 7.17 (s, 1H, *meso*-H), 7.61(s, 1H, Pyr-H), 13.13 (bs, 1H, NH), 13.31 (bs, 1H, NH). δ_C (125 MHz, $CDCl_3$) 12.3, 13.4, 14.8, 17.19, 17.24, 18.3, 115.5, 120.9, 126.2, 127.1, 132.0, 137.9, 143.1, 150.5, 159.8;

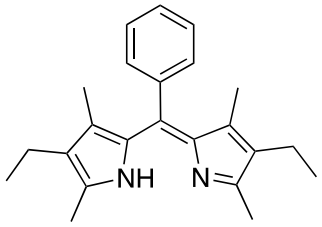
(*Z*)-3,4-Diethyl-2($^2H_3$)-methyl-5-((3-methyl-2*H*-pyrrol-2-ylidene)methyl)-1*H*-pyrrole hydrobromide (3-6-D_3•HBr)



Deuteration was performed according to general procedure **II**, using 100 mg of **3-6•HBr** (0.34 mmol) of sample and heating at 150 °C for 15 min. The product was sufficiently stable for conversion to the hydrobromide salt, and was isolated as an orange, crystalline solid (18 mg, 18%). δ_H (300 MHz, $CDCl_3$) 1.10 (t, 3H, J = 7.6 Hz, CH_2CH_3), 1.22 (t, 3H, J = 7.6 Hz, CH_2CH_3), 2.38 (s, 3H, 7-CH_3), 2.44 (q, 2H, J = 7.6 Hz, CH_2CH_3), 2.70 (q,

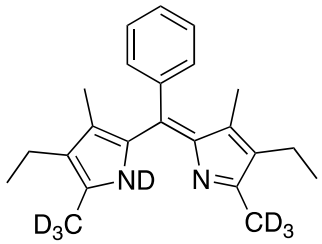
2H, J = 7.6 Hz, CH_2CH_3), 2.72 (s, 3H, 1-CH_3, signal depressed), 6.31 (d, 1H, J = 1.4 Hz, Pyr-H), 7.16 (s, 1H, *meso*-H), 7.60 (bs, 1H, Pyr-H), 13.12 (bs, 1H, NH), 13.29 (bs, 1H, NH).* ESI: $[M+H]^+$ ($C_{15}H_{18}D_2N_2$): 230.1752 (calculated); 230.1747 (experimental).

(*Z*)-3-Ethyl-5-((4-ethyl-3,5-dimethyl-2*H*-pyrrol-2-ylidene)(phenyl)methyl)-2,4-dimethyl-1*H*-pyrrole (3-7)



Compound **3-7** was synthesized according to a literature procedure,[100] from 3,5-dimethyl-4-ethyl-2-formylpyrrole (163 µL, 1.21 mmol)[87] and freshly distilled benzaldehyde. The product was isolated as a red, crystalline solid (782 mg, 82%). δ_H (300 MHz, $CDCl_3$) 0.98 (t, 6H, J = 7.5 Hz, CH_2CH_3), 1.21 (s, 6H, 3-CH_3), 2.29 (q, 4H, J = 7.5 Hz, CH_2CH_3), 2.33 (s, 6H, 1-CH_3), 7.27-7.35 (m, 2H, Ar-H), 7.36-7.45 (m, 3H, Ar-H). These data match reported literature values.[100]

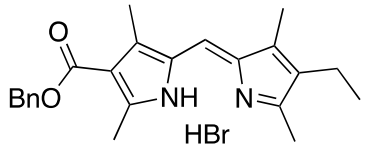
(*Z*)-3-Ethyl-5-((4-ethyl-3,5($^2H_3$)-dimethyl-2*H*-pyrrol-2-ylidene)(phenyl)methyl)-2($^2H_3$),4-dimethyl-1^2*H*-pyrrole (3-7-D_7)



Deuteration was performed according to general procedure **II**, with **3-7** (50 mg) and heating at 150 °C for 30 min. Significant decomposition was observed. The product was

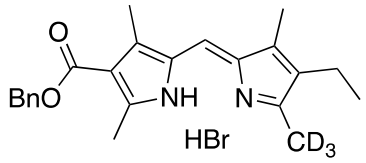
sufficiently stable for purification on basic alumina and was isolated as a brown solid (20 mg, 40%). δ_H (300 MHz, $CDCl_3$) 0.98 (t, 6H, J = 7.5 Hz, CH_2CH_3), 1.20 (s, 6H, 3-CH_3), 2.28 (q, 4H, J = 7.5 Hz, CH_2CH_3), 2.32 (s, 6H, 1-CH_3, signal depressed), 7.28-7.35 (m, 2H, Ar-H), 7.38-7.45 (m, 3H, Ar-H); ESI: $[M+H]^+$ ($C_{23}H_{22}D_7N_2$): 340.2770 (calculated); 340.2765 (experimental). ND signal missing from ^{1}H NMR spectrum.

(*Z*)-Benzyl 5-((4-ethyl-3,5-dimethyl-2*H*-pyrrol-2-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrole-3-carboxylate hydrobromide (3-13•HBr)



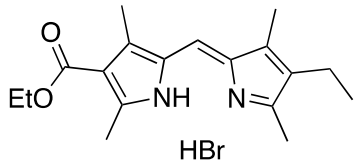
This compound was synthesized according to general procedure **I** from benzyl 5-formyl-2,4-dimethyl-1*H*-pyrrole-3-carboxylate (400 mg, 1.55 mmol)[61] and 3,5-dimethyl-4-ethyl-2-formylpyrrole (210 µL, 1.55 mmol)[87] to yield **3-13•HBr** as an orange, crystalline solid (617 mg, 90%). δ_H (500 MHz, $CDCl_3$) 1.02 (t, 3H, J = 7.6 Hz, CH_2CH_3), 2.31 (s, 3H, 7-CH_3), 2.35 (q, 2H, J = 7.6 Hz, CH_2CH_3), 2.56 (s, 3H, 3-CH_3), 2.62 (s, 3H, 9-CH_3), 2.82 (s, 3H, 1-CH_3), 5.28 (s, 2H, OCH_2Ph), 7.20 (s, 1H, *meso-H*), 7.28-7.42 (m, 5H, Ar-H), 13.01 (bs, 1H, NH), 13.42 (bs, 1H, NH); δ_C (125 MHz, $CDCl_3$); 10.3, 12.3, 13.2, 14.1, 15.0, 17.2, 66.2, 117.1, 120.4, 124.6, 128.4, 128.4, 128.7, 132.9, 135.9, 144.7, 145.7, 154.8, 160.5, 163.5. ESI: $[M+H]^+$ ($C_{23}H_{27}N_2O_2$): 363.2073 (calculated); 363.2069 (experimental).

(*Z*)-Benzyl 5-((4-ethyl-3,5($^2H_3$)-dimethyl-2*H*-pyrrol-2-ylidene)methyl)-2($^2H_3$),4-dimethyl-1*H*-pyrrole-3-carboxylate hydrobromide (3-13-D_3•HBr)



Deuteration was performed according to general procedure **II**, using **3-13** (100 mg) and heating at 150 °C for 15 min. The product was sufficiently stable for conversion to the hydrobromide salt, which was isolated as an orange, crystalline solid (81 mg, 81%). δ_H (300 MHz, $CDCl_3$) 1.06 (t, 3H, J = 7.6 Hz, CH_2CH_3), 2.30 (s, 3H, 7-CH_3), 2.39 (q, 2H, J = 7.6 Hz, CH_2CH_3), 2.57 (s, 3H, 3-CH_3), 2.62 (s, 3H, 9-CH_3, signal depressed), 2.87 (s, 3H, 1-CH_3), 5.30 (s, 2H, OCH_2Ph), 7.19 (s, 1H, *meso-H*), 7.32-7.42 (m, 5H, Ar-H), 13.10 (bs, 1H, NH), 13.53 (bs, 1H, NH); δ_C (125 MHz, $CDCl_3$) Not obtained for deuterated sample; $[M+H]^+$ ($C_{23}H_{24}D_3N_2O_2$): 366.2261 (calculated); 366.2218 (experimental).

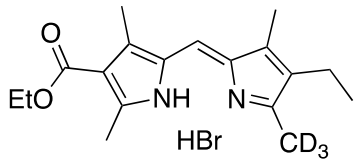
(*Z*)-Ethyl 5-((4-ethyl-3,5-dimethyl-2*H*-pyrrol-2-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrole-3-carboxylate hydrobromide (3-14•HBr)



This compound was synthesized according to general procedure **I** from ethyl 5-formyl-2,4-dimethyl-1*H*-pyrrole-3-carboxylate (400mg, 1.55 mmol)[61] and 3,5-dimethyl-4-ethyl-2-formylpyrrole (210 µL, 1.55 mmol)[87] to yield **3-14•HBr** as an orange, crystalline solid (956 mg, 90%). δ_H (500 MHz, $CDCl_3$) 1.07 (t, 3H, J = 7.6 Hz, Pyr-CH_2CH_3), 1.37 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 2.32 (s, 3H, 7-CH_3), 2.43 (q, 2H, J = 7.6 Hz, Pyr-CH_2CH_3), 2.57

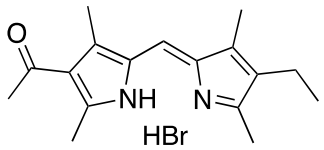
(s, 3H, 3-CH_3), 2.71 (s, 3H, 9-CH_3), 2.88 (s, 3H, 1-CH_3), 4.31 (q, 2H, J = 7.1 Hz, O$CH_2$$CH_3$), 7.21 (s, 1H, *meso*-H), 13.09 (bs, 1H, NH), 13.52 (s, 1H, NH); δ_C (125 MHz, $CDCl_3$) 10.3, 12.2, 13.3, 14.3, 14.5, 15.1, 17.3, 60.4, 117.7, 120.3, 124.8, 128.4, 133.0, 144.5, 145.9, 155.1, 160.4, 163.9; ESI: $[M+H]^+$ ($C_{18}H_{25}N_2O_2$): 301.1916 (calculated); 301.1911 (experimental).

(*Z*)-Ethyl 5-((4-ethyl-3,5($^2H_3$) -dimethyl-2*H*-pyrrol-2-ylidene)methyl)-2($^2H_3$),4-dimethyl-1*H*-pyrrole-3-carboxylate hydrobromide (3-14-D_3•HBr)



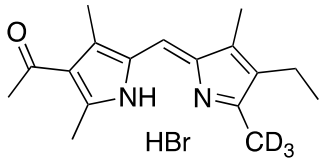
Deuteration was performed according to general procedure **II**, using **3-14** (100 mg) and heating at 150 °C for 15 min. The product was sufficiently stable for conversion to the hydrobromide salt, and was isolated as an orange, crystalline solid (89 mg, 89%). δ_H (500 MHz, $CDCl_3$) 1.07 (t, 3H, J = 7.6 Hz, Pyr-CH_2*CH_3)*, 1.37 (t, 3H, J = 7.1 Hz, OCH_2*CH_3*), 2.31 (s, 3H, 7-CH_3), 2.43 (q, 2H, J = 7.6 Hz, Pyr-*CH_2*CH_3), 2.57 (s, 3H, 3-CH_3), 2.69 (s, 3H, 9-CH_3, signal depressed), 2.89 (s, 3H, 1-CH_3), 4.32 (q, 2H, J = 7.1 Hz, O$CH_2$$CH_3$), 7.21 (s, 1H, *meso*-H), 13.11 (bs, 1H, NH), 13.54 (s, 1H, NH); δ_C (125 MHz, $CDCl_3$) 10.3, 12.2, 13.3 (m, splitting observed due to deuterium coupling in $D_{1\rightarrow3}$ compounds) 14.3, 14.5, 15.1, 17.3, 60.4, 117.7, 120.3, 124.8, 128.5, 133.0, 144.5, 145.9, 155.1, 160.4, 163.9; ESI: $[M+H]^+$ ($C_{18}H_{22}D_3N_2O_2$): 304.2104 (calculated); 304.2099 (experimental).

(*Z*)-1-(5-((4-Ethyl-3,5-dimethyl-2*H*-pyrrol-2-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrol-3-yl)ethanone hydrobromide (3-15•HBr)



This compound was synthesized according to general procedure **I** from 4-acetyl-2-formyl-3,5-dimethyl-1*H*-pyrrole (200 mg, 1.21 mmol)[116] and 3,5-dimethyl-4-ethyl-2-formylpyrrole (163 μL, 1.21 mmol)[87] to yield **3-15•HBr** as an orange, crystalline solid (296 mg, 70%). δ_H (500 MHz, $CDCl_3$) 1.10 (t, 3H, J = 7.6 Hz, CH_2CH_3), 2.33 (s, 3H, 7-CH_3), 2.46 (q, 2H, J = 7.6 Hz, CH_2CH_3), 2.50 (s, 3H, $COCH_3$), 2.57 (s, 3H, 3-CH_3), 2.76 (s, 3H, 9-CH_3), 2.96 (s, 3H, 1-CH_3), 7.22 (s, 1H, *meso*-H), 13.15 (bs, 1H, NH), 13.66 (bs, 1H, NH); δ_C (125 MHz, $CDCl_3$) 10.3, 12.8, 13.5, 14.3, 15.8, 17.4, 31.7, 120.3, 124.7, 126.7, 129.0, 133.4, 144.2, 144.7, 153.5, 161.4, 194.3; ESI: $[M+H]^+$ ($C_{17}H_{23}N_2O$): 278.1810 (calculated); 278.1805 (experimental).

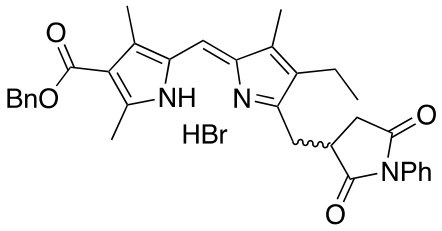
(*Z*)-1-(5-((4-Ethyl-3,5($^2H_3$)-dimethyl-2*H*-pyrrol-2-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrol-3-yl)ethanone hydrobromide (3-15-D_3•HBr)



Deuteration was performed according to general procedure **II**, using **3-15** (50 mg) and heating at 125 °C for 15 min. The product was sufficiently stable for conversion to the hydrobromide salt, and was isolated as an orange, crystalline solid (38 mg, 81%). δ_H (500 MHz, $CDCl_3$) 1.10 (t, 3H, J = 7.6 Hz, CH_2CH_3), 2.32 (s, 3H, 7-CH_3), 2.45 (q, 2H, J = 7.6

Hz, CH_2CH_3), 2.49 (s, 3H, $COCH_3$), 2.57 (s, 3H, 3-CH_3), 2.76 (s, 3H, 9-CH_3, signal depressed), 2.96 (s, 3H, 1-CH_3), 7.22 (s, 1H, *meso*-H), 13.15 (bs, 1H, NH), 13.65 (bs, 1H, NH); δ_C (125 MHz, $CDCl_3$) 10.3, 12.9, 13.5 (m, splitting observed due to deuterium coupling in $D_{1\rightarrow3}$ compounds), 14.3, 15.8, 17.4, 31.7, 120.3, 124.7, 126.7, 129.0, 133.4, 144.2, 144.7, 153.5, 161.4, 194.3; ESI: $[M+H]^+$ ($C_{17}H_{21}D_2N_2O$): 273.1936 (calculated); 273.1928 (experimental).

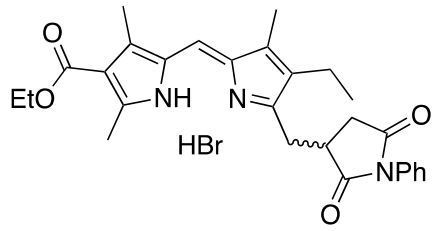
(*Z*)-Benzyl 5-((5-((2,5-dioxo-1-phenylpyrrolidin-3-yl)methyl)-4-ethyl-3-methyl-2*H*-pyrrol-2-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrole-3-carboxylate hydrobromide (3-18•HBr)



A sample of **3-13•HBr** (50 mg, 0.11 mmol) was dissolved in CH_2Cl_2 (30 mL) and the solution washed with NaOH (1M, aq., 30 mL). The organic layer was dried over Na_2SO_4, and the solvent then removed under vacuum. Following drying *in vacuo,* **3-13** and *N*-phenyl maleimide (**3-17**, 39 mg, 0.23 mmol) were dissolved in anhydrous chloroform (4 mL) in a microwave vessel under a nitrogen atmosphere, and the vessel then sealed. The reaction mixture was heated for 1.5 hours at 150 °C in the microwave reactor. Removal of the solvent *in vacuo*, purification of the resulting crude material over Brockman III basic alumina eluting with a solvent gradient of EtOAc:hexanes (1:9 → 2:8) and removal of the solvent *in vacuo* gave a mixture of **3-18** and residual *N*-phenylmaleimide. The material was dissolved in CH_2Cl_2 (30 mL) and the solution was then washed with HBr

(1M, aq., 30 mL) to form the dipyrrin hydrobromide salt. The organic layer was concentrated, and the product precipitated with diethyl ether. After suction filtration and washing with diethyl ether, **3-18•HBr** was obtained as a brown solid (70 mg, 85%). δ_H (500 MHz, $CDCl_3$) 1.11 (t, 3H, *J* = 7.5 Hz, CH_2CH_3), 2.34 (s, 3H, 7-CH_3), 2.49 (dd, 1H, *J* = 14.1, 6.8 Hz, 8-C*H*HCH_3), 2.53 (dd, 1H, *J* = 14.2, 7.0 Hz, 8-CH*H*CH_3), 2.60 (s, 3H, 3-CH_3), 2.93 (s, 3H, 1-CH_3), 3.02 (dd, 1H, *J* = 18.3, 5.9 Hz, COC*H*HCH), 3.20 (dd, 1H, *J* = 18.3, 9.3 Hz, COCH*H*CH), 3.43 (dd, 1H, *J* = 14.4, 8.0 Hz, 9-C*H*H), 3.60 (dd, 1H, *J* = 14.1, 7.2 Hz, 9-CH*H*), 3.96 (adt, 1H, *J* = 14.9, 7.6 Hz, CH_2CHCH_2), 5.33 (s, 2H, OCH_2Ph), 7.46-7.27 (m, 11H, ArH and *meso*-H), 13.25 (bs, 1H, NH), 13.63 (bs, 1H, NH); δ_C (125 MHz, $CDCl_3$) 10.5, 12.4, 14.7, 15.5, 17.4, 27.8, 34.9, 40.7, 66.5, 118.3, 121.4, 125.7, 126.6, 128.4, 128.6, 128.6, 128.7, 128.8, 129.3, 131.9, 133.0, 135.9, 145.0, 148.0, 157.1, 158.2, 163.4, 174.4, 177.1; ESI: $[M+H]^+$ ($C_{33}H_{34}N_3O_4$): 536.2549 (calculated); 536.2544 (experimental).

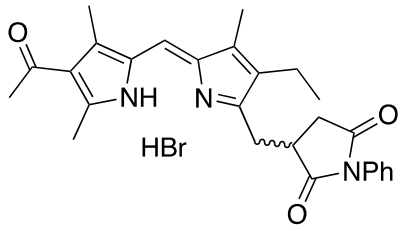
(*Z*)-Ethyl 5-((5-((2,5-dioxo-1-phenylpyrrolidin-3-yl)methyl)-4-ethyl-3-methyl-2*H*-pyrrol-2-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrole-3-carboxylate hydrobromide (3-19•HBr)



A sample of **3-14•HBr** (50 mg, 0.13 mmol) was dissolved in CH_2Cl_2 (30 mL) and the solution washed with NaOH (1M, aq. 30 mL). The organic layer was dried over Na_2SO_4, and the solvent then removed under vacuum. Following drying *in vacuo,* **3-14** was

combined and *N*-phenyl maleimide (**3-17**, 34 mg, 0.20 mmol) were dissolved in anhydrous chloroform (4 mL) in a microwave vessel under a nitrogen atmosphere, and the vessel then sealed. The reaction mixture was heated for 45 minutes at 150 °C in the microwave reactor. Removal of the solvent *in vacuo*, purification of the resulting crude material over Brockman III basic alumina eluting with a solvent gradient of EtOAc:hexanes (1:9 → 3:7) and removal of the solvent *in vacuo* gave **3-19** as a brown film. The material was dissolved in CH_2Cl_2 (30 mL) and the solution was then washed with HBr (1M, aq.30 mL) to form the dipyrrin hydrobromide salt. The organic layer was concentrated, and the product precipitated using diethyl ether. After suction filtration and washing with diethyl ether, **3-19•HBr** was obtained as a fluffy, brown-green solid (49 mg, 67%). δ_H (500 MHz, $CDCl_3$) 1.12 (t, 3H, *J* = 7.6 Hz, CH_2CH_3), 1.40 (t, 3H, *J* = 7.1 Hz, OCH_2CH_3) 2.36 (s, 3H, 7-CH_3), 2.49 (adt, 1H, *J* = 14.1, 6.8 Hz, 8-CH_2CH_3), 2.62 (s, 3H, 3-CH_3), 2.95 (s, 3H, 1-CH_3), 3.03 (dd, 1H, *J* = 18.4, 6.0 Hz, COC*H*HCH), 3.21 (dd, 1H, *J* = 18.3, 9.3 Hz, COCH*H*CH), 3.44 (dd, 1H, *J* = 14.1, 8.3 Hz, 9-C*H*H), 3.60 (dd, 1H, *J* = 14.1, 7.3 Hz, 9-CH*H*), 3.96 (adt, 1H, *J* = 14.9, 7.6 Hz, CH_2CHCH_2), 4.35 (q, 2H, *J* = 7.1 Hz, OCH_2CH_3), 7.28-7.29 (m, 3H, *o*-Ar-H and *meso*-H), 7.37 (t, 1H, *J* = 7.4 Hz, *p*-Ar-H), 7.45 (t, 2H, *J* = 7.7 Hz, *m*-Ar-H), 13.26 (bs, 1H, NH), 13.63 (bs, 1H, NH); δ_C (125 MHz, $CDCl_3$) 10.5, 12.3, 14.5, 14.8, 15.4, 17.5, 27.7, 35.0, 40.8, 60.7, 118.7, 121.4, 125.7, 126.6, 128.5, 128.8, 129.3, 131.9, 132.9, 144.8, 148.0, 157.2, 157.8, 163.7, 174.5, 177.1; ESI: $[M+H]^+$ ($C_{28}H_{32}N_3O_4$): 474.2393 (calculated); 474.2387 (experimental).

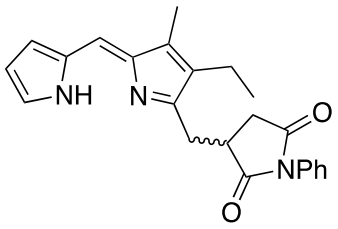
(*Z*)-3-((2-((4-Acetyl-3,5-dimethyl-1*H*-pyrrol-2-yl)methylene)-4-ethyl-3-methyl-2*H*-pyrrol-5-yl)methyl)-1-phenylpyrrolidine-2,5-dione hydrobromide (3-20•HBr)



A sample of **3-15•HBr** (50 mg, 0.14 mmol) was dissolved in CH_2Cl_2 (30 mL) and the solution washed with aqueous sodium hydroxide (1 M, 30 mL). The organic layer was dried over Na_2SO_4, and the solvent then removed under vacuum. Following drying *in vacuo,* **3-15** and *N*-phenyl maleimide (**3-17**, 37 mg, 0.21 mmol) were dissolved in anhydrous chloroform (4 mL) in a microwave vessel under a nitrogen atmosphere, and the vessel then sealed. The reaction mixture was heated for 45 minutes at 150 °C in the microwave reactor. Removal of the solvent *in vacuo*, purification of the resulting crude material over Brockman III basic alumina eluting with a solvent gradient of EtOAc:hexanes (1:9 → 3:7) and removal of the solvent *in vacuo* gave **3-20** as a brown film. The material was dissolved in CH_2Cl_2 (30 mL) and the solution was then washed with HBr (1M, aq.30 mL) to form the dipyrrin hydrobromide salt. The organic layer was concentrated, and the product precipitated with diethyl ether. After suction filtration and washing with diethyl ether, **3-20•HBr** was obtained as a fluffy, brown-green solid (60 mg, 82%). δ_H (500 MHz, $CDCl_3$) 1.12 (t, 3H, J = 7.6 Hz, CH_2CH_3), 2.36 (s, 3H, 7-CH_3), 2.54-2.47 (m, 5H, $COCH_3$ and 8-CH_2CH_3), 2.59 (s, 3H, 3-CH_3), 2.96 (s, 3H, 1-CH_3), 3.02 (dd, 1H, J = 18.4, 5.9 Hz, COC*H*HCH), 3.20 (dd, 1H, J = 18.5, 9.3 Hz, COCH*H*CH), 3.44 (dd, 1H, J = 14.1, 8.3 Hz, 9-C*H*H), 3.59 (dd, 1H, J = 14.1, 7.3 Hz, 9-CH*H*), 3.95 (aquintet, 1H, J = 7.8, CH_2CHCH_2), 7.28 (d, 2H, J = 7.7 Hz, *o*-Ar-H), 7.32 (s, 1H, *meso*-

H), 7.36 (t, 1H, J = 7.4 Hz, *p*-Ar-H), 7.44 (t, 2H, J = 7.7 Hz, *m*-Ar-H), 13.22 (bs, 1H, NH), 13.65 (bs, 1H, NH); δ_C (125 MHz, $CDCl_3$) 10.5, 12.9, 14. 7, 16.0, 17.4, 27.8, 31.7, 34.9, 40.9, 121.5, 125.5, 126.6, 127.4, 128.8, 128.9, 129.3, 131.9, 133.2, 145.2, 145.9, 155.5, 158.6, 174.5, 177.1, 194.1; ESI: $[M+H]^+$ ($C_{27}H_{30}N_3O_4$): 444.2287 (calculated); 444.2282 (experimental).

(*Z*)-3-((2-((1*H*-Pyrrol-2-yl)methylene)-4-ethyl-3-methyl-2*H*-pyrrol-5-yl)methyl)-1-phenylpyrrolidine-2,5-dione (3-21)

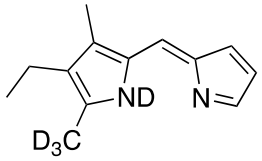


A sample of **3-1•HBr** (100 mg, 0.36 mmol) was dissolved in CH_2Cl_2 (30 mL) and the solution washed with NaOH (1M, aq. 30 mL). The organic layer was dried over Na_2SO_4, and the solvent then removed under vacuum. Following drying *in vacuo,* **3-1** and *N*-phenyl maleimide (**3-17**, 39 mg, 0.54 mmol) were dissolved in anhydrous chloroform (4 mL) in a microwave vessel under a nitrogen atmosphere, and the vessel then sealed. The mixture was heated for 15 minutes at 100 °C in the microwave reactor. Removal of the solvent *in vacuo*, purification of the resulting crude mixture over Brockman III basic alumina eluting with a solvent gradient of EtOAc:hexanes (1:9 t→ 2:8) and removal of the solvent *in vacuo* gave a mixture of **3-21** and residual *N*-phenylmaleimide. The product was unstable to salt conversion, hindering removal of *N*-phenylmaleimide using an ether wash, and thus a mixture of **3-17** and **3-21** was isolated as a brown solid (41 mg total, 28 mg of **3-21**, 21%, as determined from the ^{1}H NMR spectrum). δ_H (500 MHz,

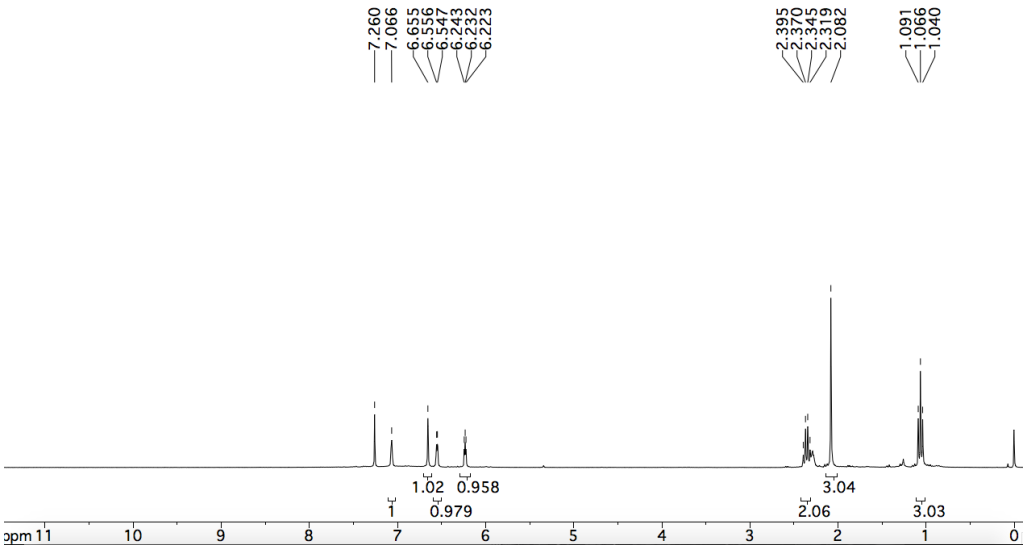
$CDCl_3$) 1.10 (t, 3H, J = 7.6 Hz, CH_2CH_3), 2.10 (s, 3H, 3-CH_3), 2.38 (q, 2H, J = 7.6 Hz, CH_2CH_3), 3.05 (dd, 1H, J = 18.4, 5.4 Hz, COC*H*H), 3.15 (dd, 1H, J = 18.4, 9.4 Hz, COCH*H*), 3.21 (dd, 1H, J = 17.8, 4.2 Hz, 1-C*H*H), 3.27 (dd, 1H, J = 17.7, 6.6 Hz, 1-CH*H*), 3.51 (td, 1H, J = 10.1, 5.9 Hz, CH_2CHCH_2), 6.13 (t, 1H, J = 3.1 Hz, Pyr-H), 6.56 (d, 1H, J = 2.8 Hz, Pyr-H), 6.64 (bs, 1H, Pyr-H), 6.71 (s, 1H, *meso*-H), 6.85 (s, **3-17** alkene signal), 7.25-7.29 (m, 2H, Ar-H, with some **3-17** aromatic signal), 7.34-7.49 (m, 3H, Ar-H, with some **3-17** aromatic signal); δ_C (125 MHz, $CDCl_3$) 9.6, 14.6, 17.9, 30.3, 34.7, 38.1, 110.7, 118.6, 119.3, 126.2, 126.6, 128.6, 129.2, 130.5, 132.2, 137.2, 140.8, 148.8, 170.0, 176.5, 179.0; ESI: $[M+H]^+$ ($C_{23}H_{24}N_3O_2$): 374.1863 (calculated); 374.1853 (experimental). ^{13}C NMR spectrum reported is from a lower-yielding reaction using a deficit of **3-17**; although no maleimide is present in this product mixture, significant impurities are present in the form of silicone grease and CH_2Cl_2. Thus, the ^1H, COSY, HSQC and HMBC spectra reported are from a more concentrated sample containing residual **3-17** and EtOAc. NH signal missing from ^1H NMR spectrum.

Section 3.6: NMR Spectra

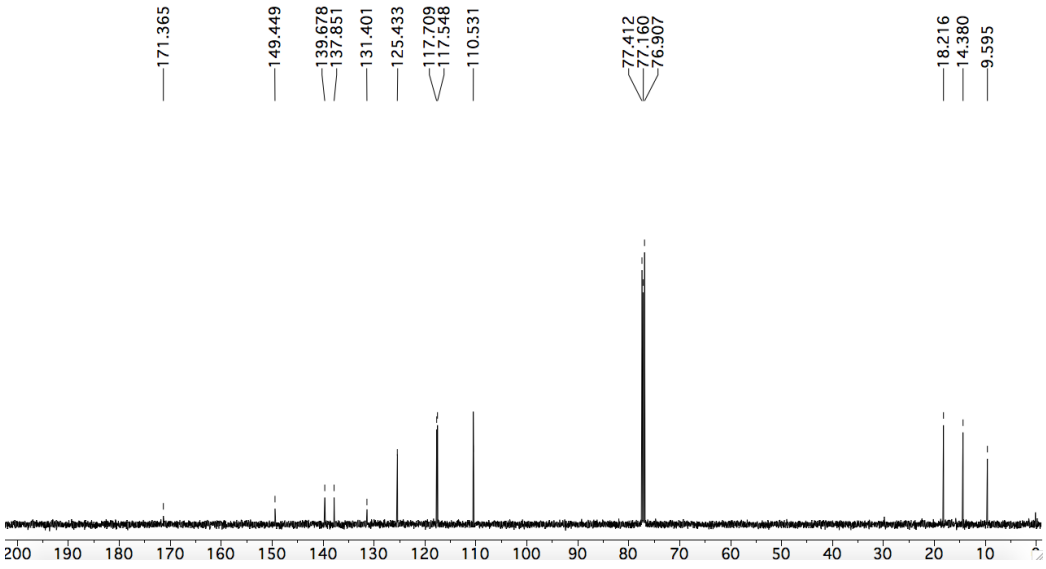
(*Z*)-2-((2*H*-Pyrrol-2-ylidene)methyl)-4-ethyl-3,5($^2H_3$)-dimethyl-1^2*H*-pyrrole (3-1-D$_4$)



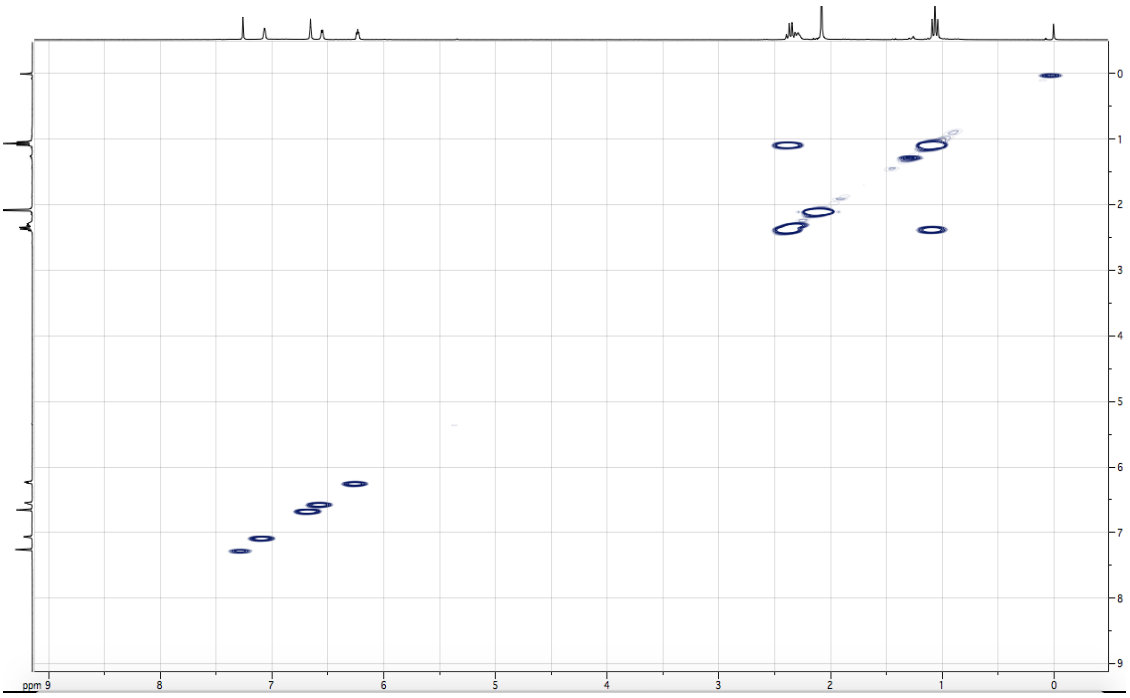
^{1}H NMR ($CDCl_3$, 300 MHz):



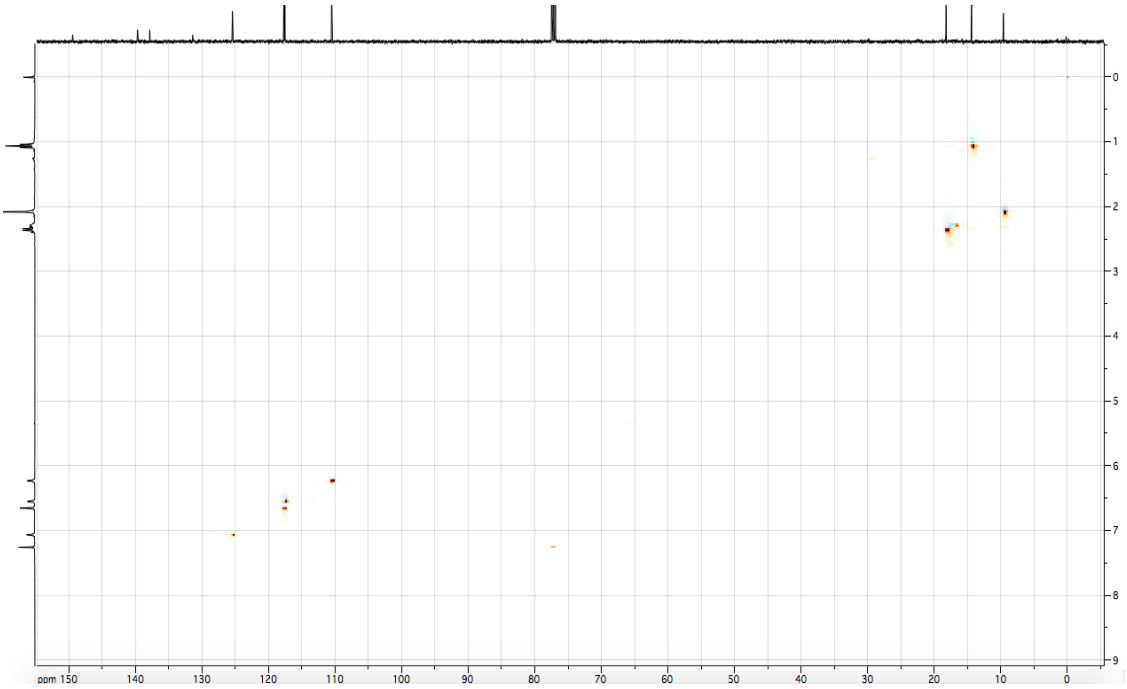
^{13}C UDEFT NMR ($CDCl_3$, 125 MHz):



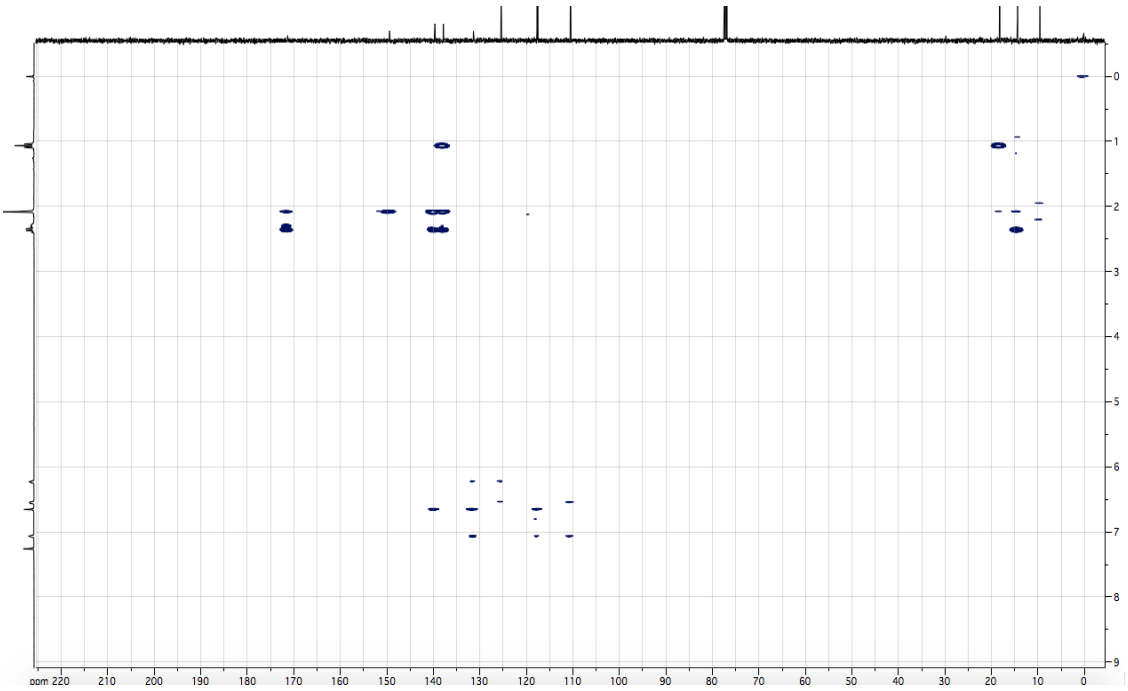
2D COSY ($CDCl_3$):



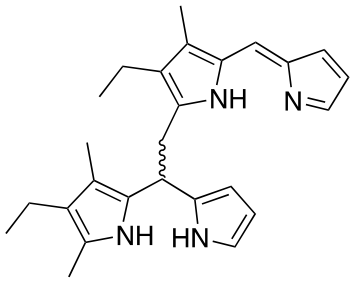
2D HSQC ($CDCl_3$):



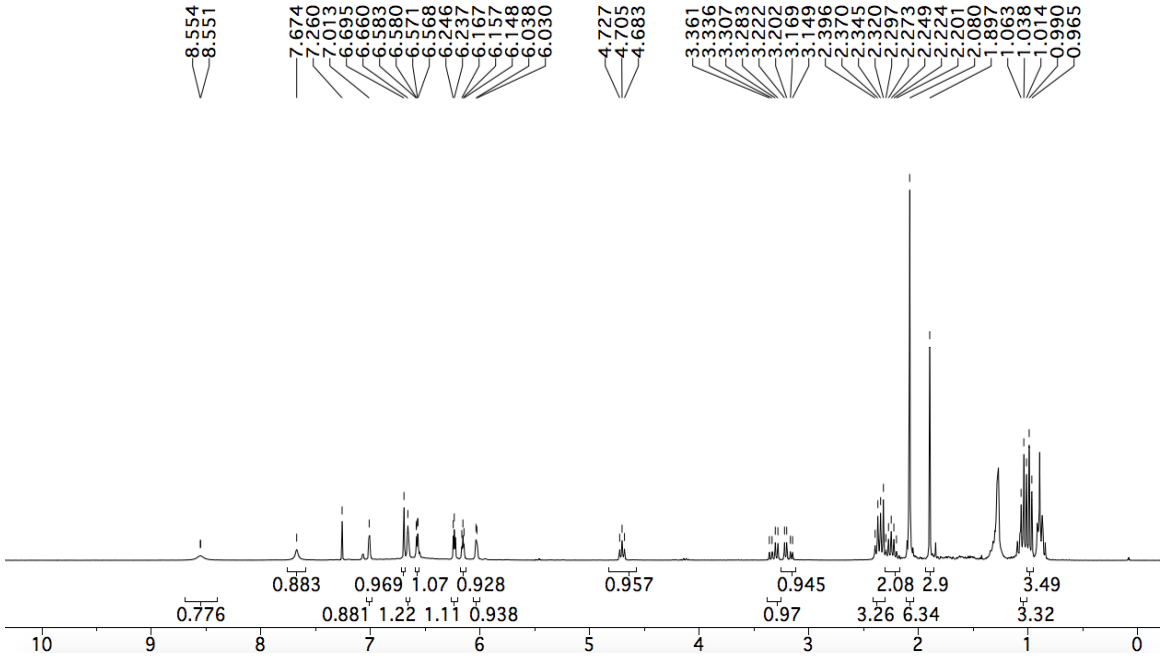
2D HMBC ($CDCl_3$):



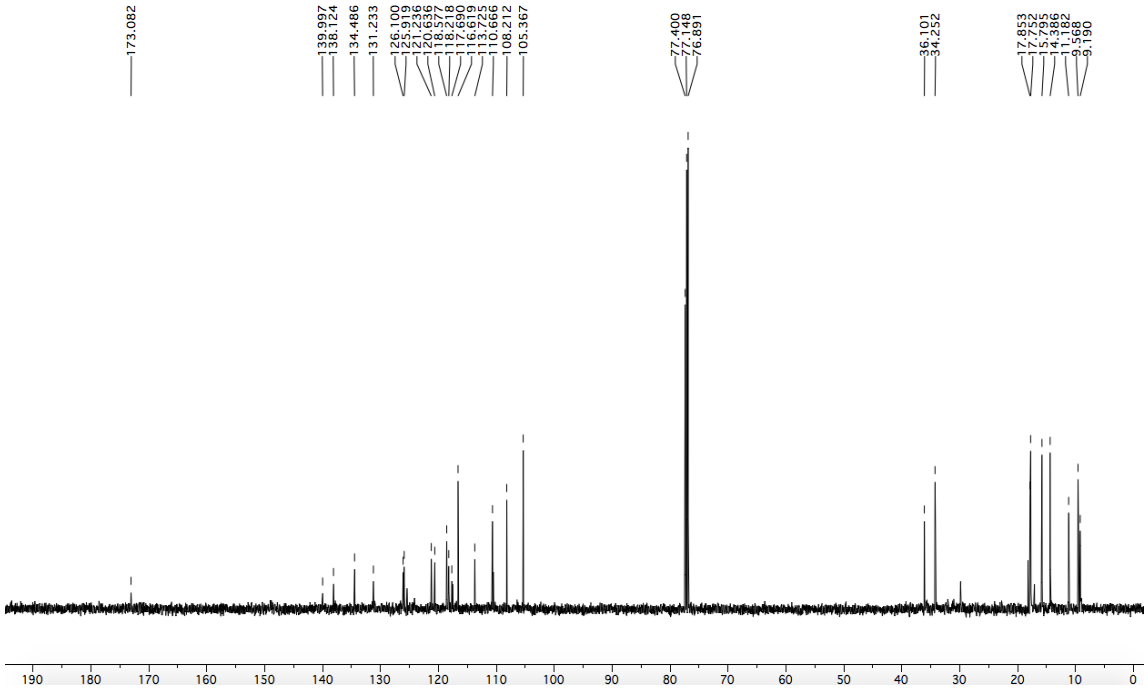
(*Z*)-2-((2*H*-Pyrrol-2-ylidene)methyl)-4-ethyl-5-(2-(4-ethyl-3,5-dimethyl-1*H*-pyrrol-2-yl)-2-(1*H*-pyrrol-2-yl)ethyl)-3-methyl-1*H*-pyrrole (3-2)



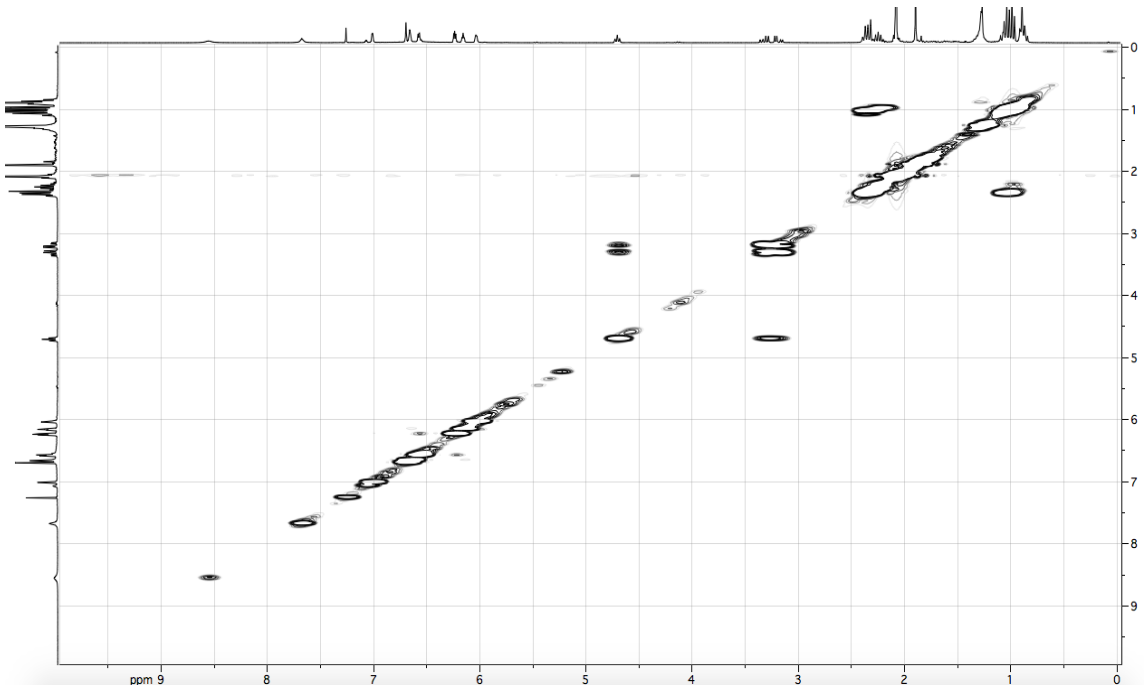
^{1}H NMR ($CDCl_3$, 300 MHz):



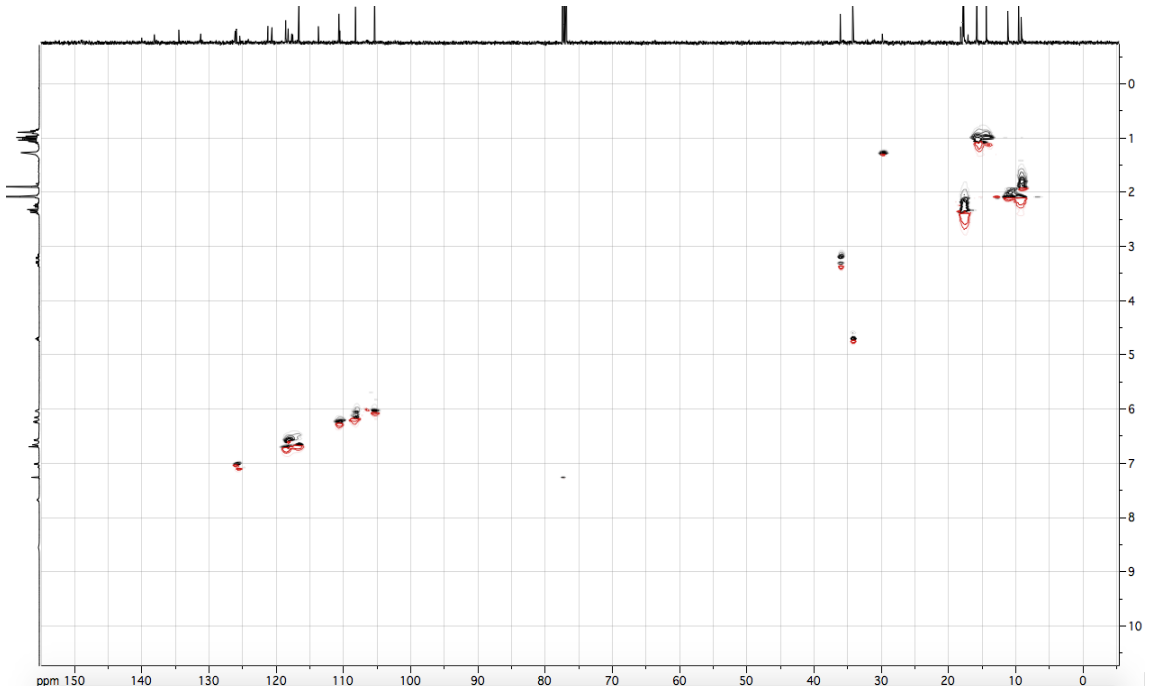
^{13}C UDEFT NMR ($CDCl_3$, 125 MHz):



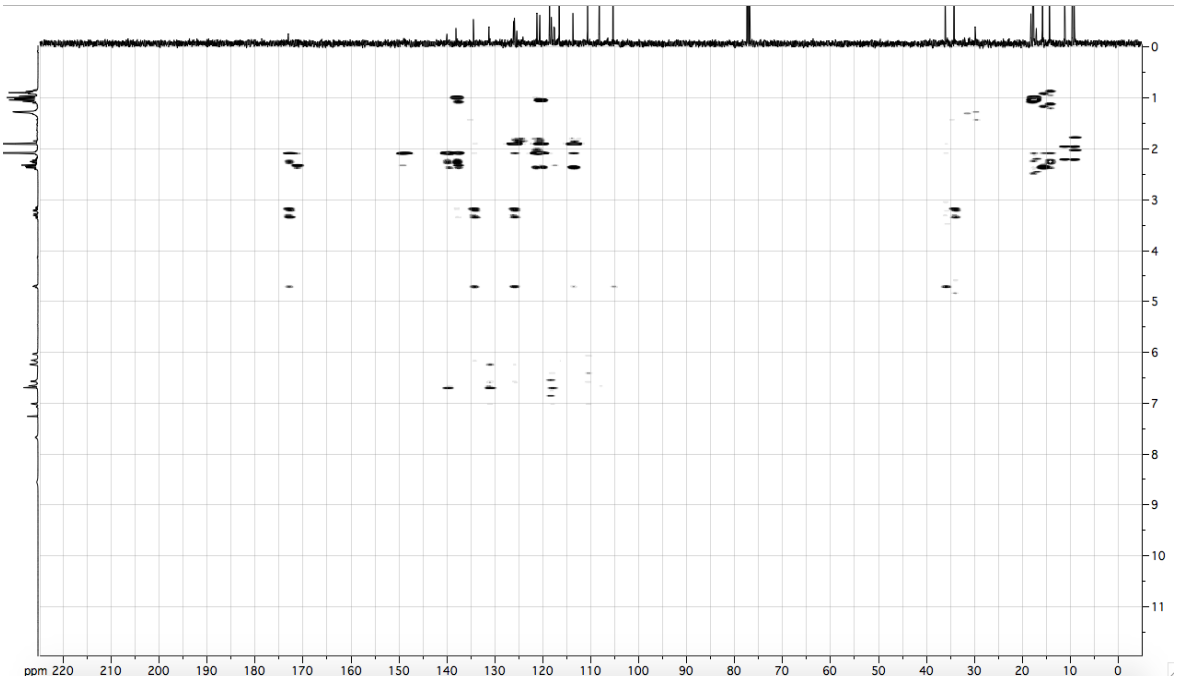
2D COSY ($CDCl_3$):



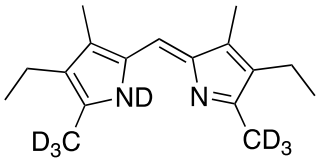
2D HSQC ($CDCl_3$):



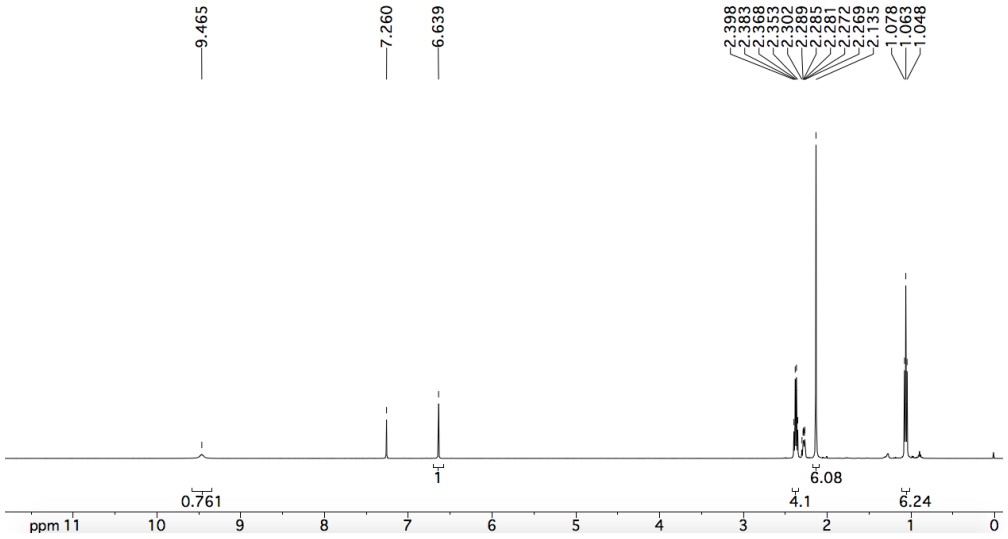
2D HMBC ($CDCl_3$):



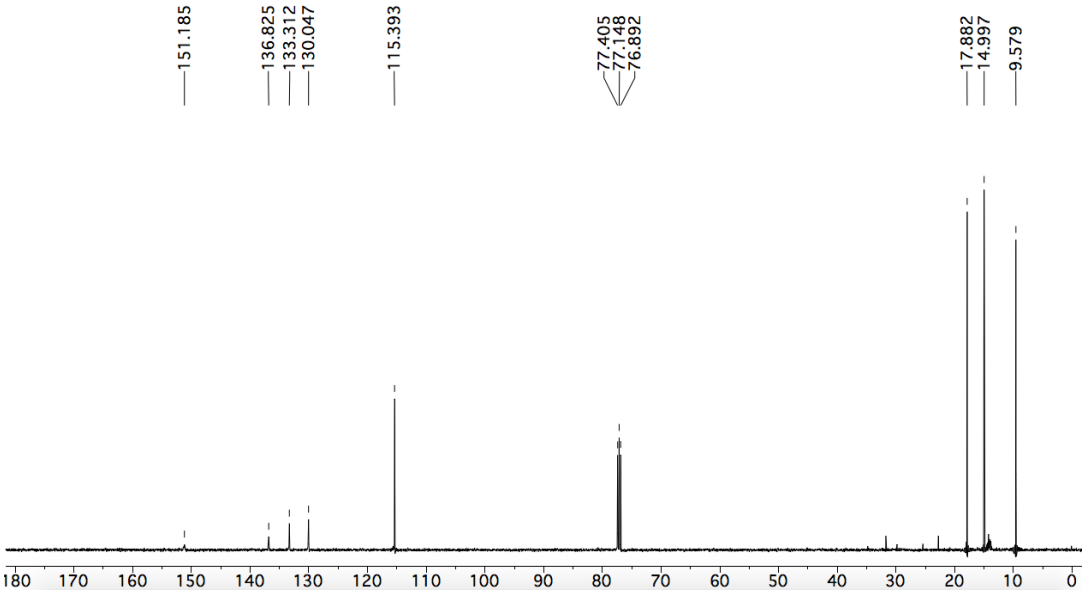
(*Z*)-3-Ethyl-5-((4-ethyl-3,5($^2H_3$)-dimethyl-2*H*-pyrrol-2-ylidene)methyl)-2,4($^2H_3$)-dimethyl-1^2*H*-pyrrole (3-3-D$_7$)



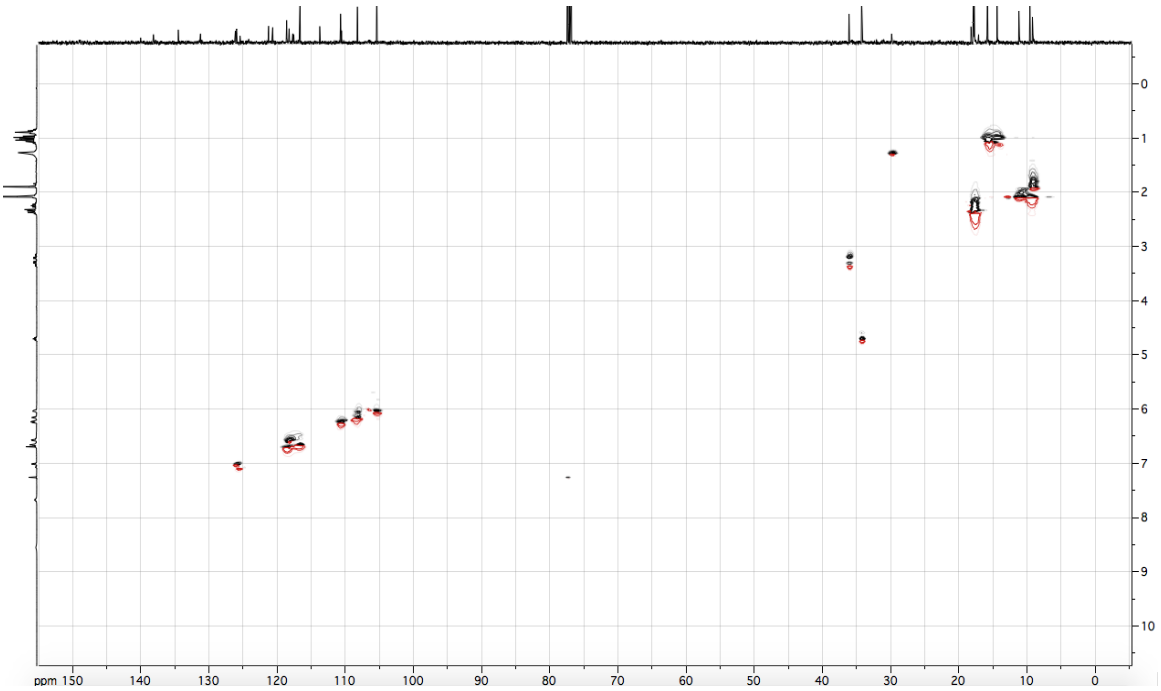
^{1}H NMR ($CDCl_3$, 500 MHz):



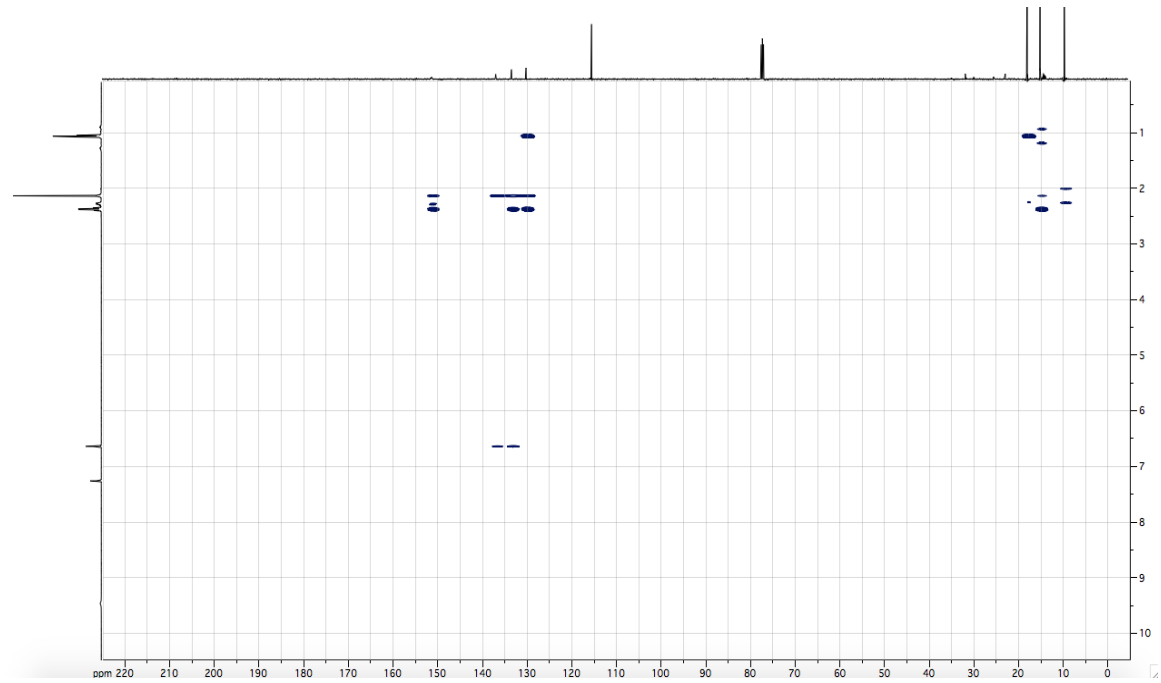
^{13}C UDEFT NMR ($CDCl_3$, 125 MHz):



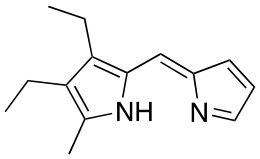
2D HSQC ($CDCl_3$):



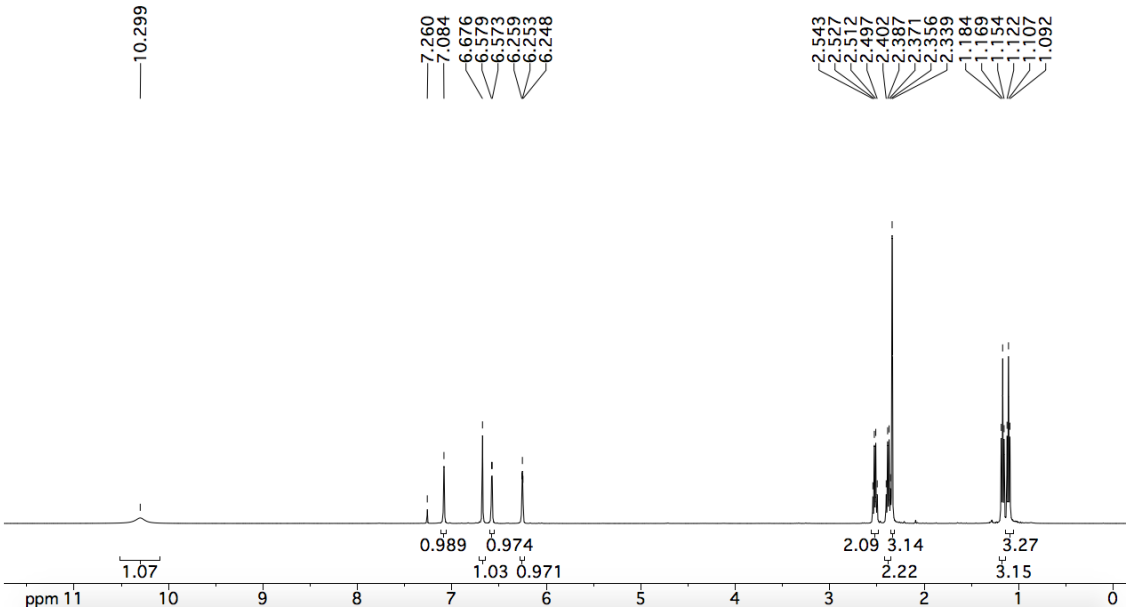
2D HMBC ($CDCl_3$):



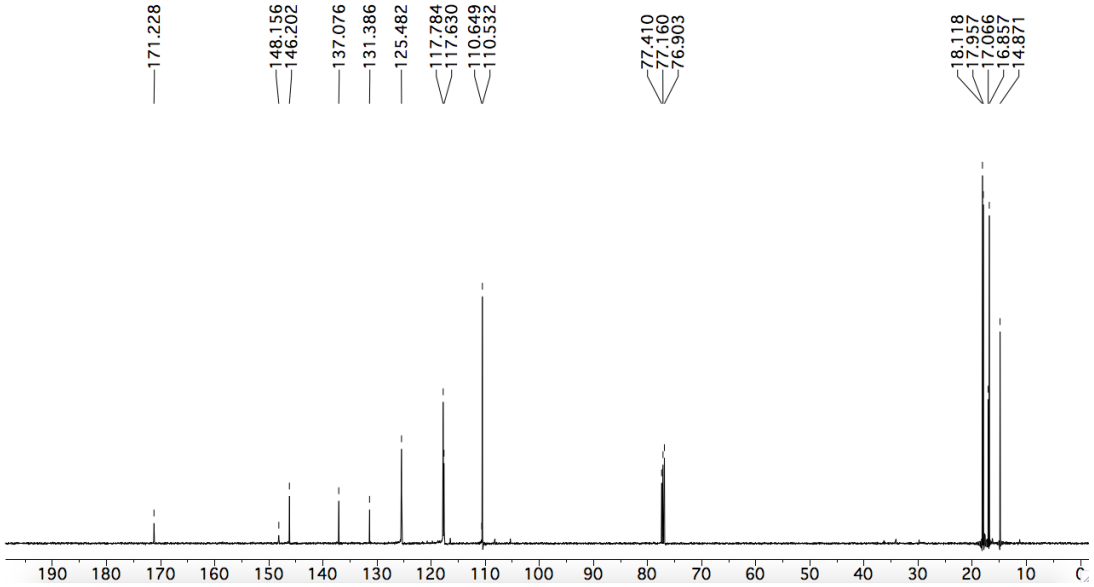
(*Z*)-2-((2*H*-Pyrrol-2-ylidene)methyl)-3,4-diethyl-5-methyl-1*H*-pyrrole (3-5)



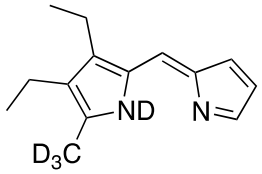
^{1}H NMR ($CDCl_3$, 500 MHz):



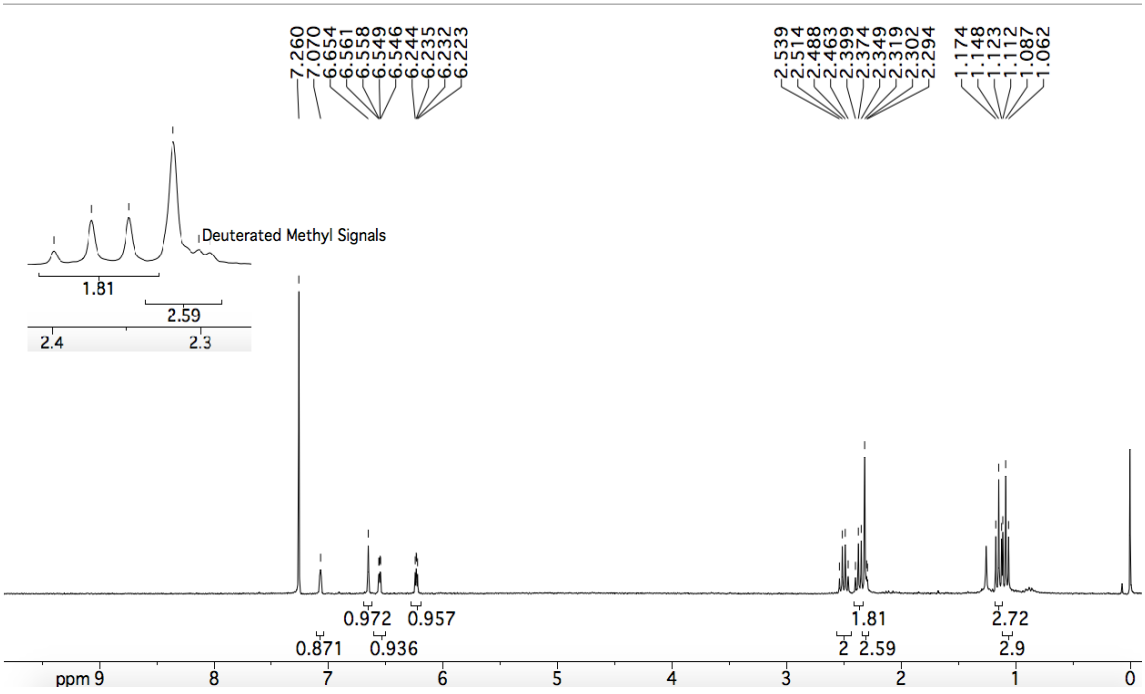
^{13}C UDEFT NMR ($CDCl_3$, 125 MHz)



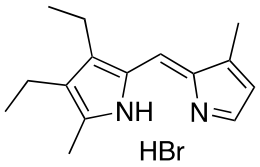
(*Z*)-2-((2*H*-Pyrrol-2-ylidene)methyl)-3,4-diethyl-5($^2H_3$)-methyl-1^2*H*-pyrrole (3-5-D_4)



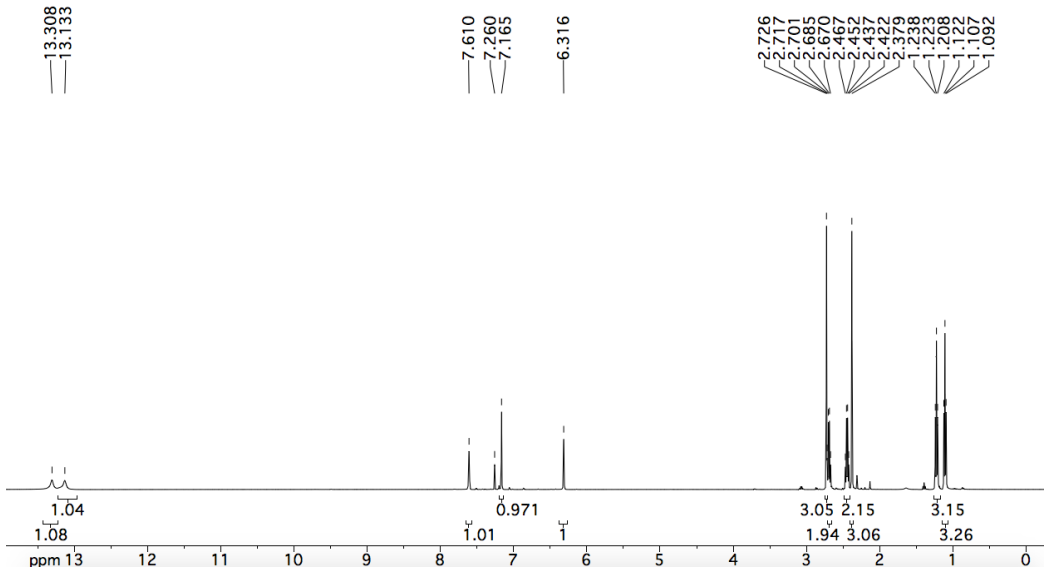
^{1}H NMR ($CDCl_3$, 300 MHz):



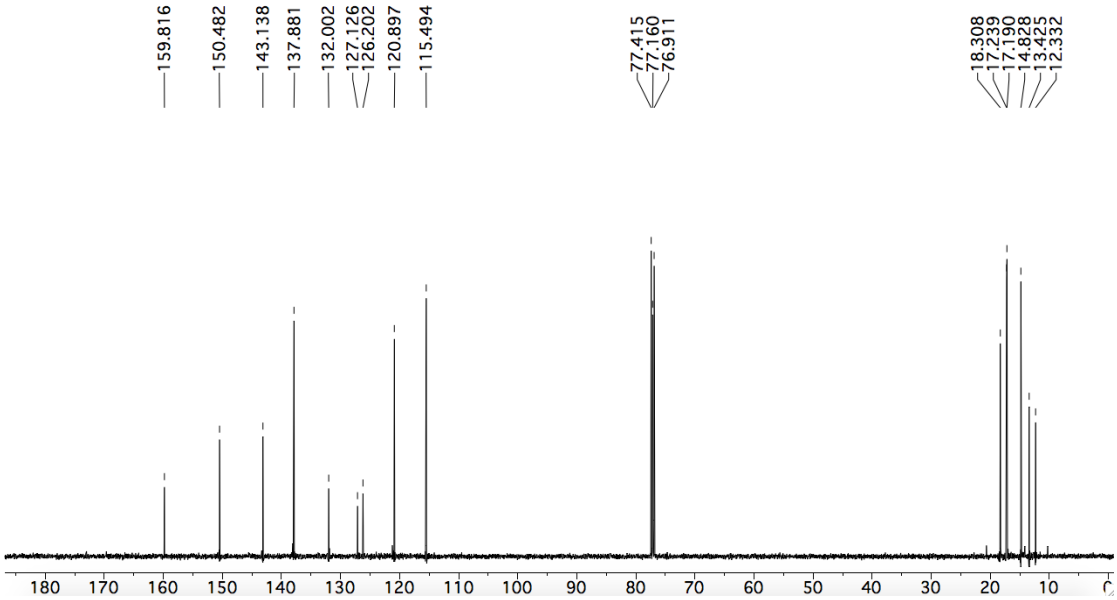
(*Z*)-3,4-Diethyl-2-methyl-5-((3-methyl-2*H*-pyrrol-2-ylidene)methyl)-1*H*-pyrrole hydrobromide (3-6•HBr)



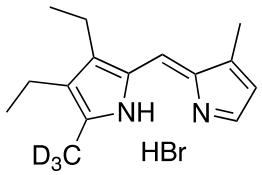
^{1}H NMR ($CDCl_3$, 500 MHz):



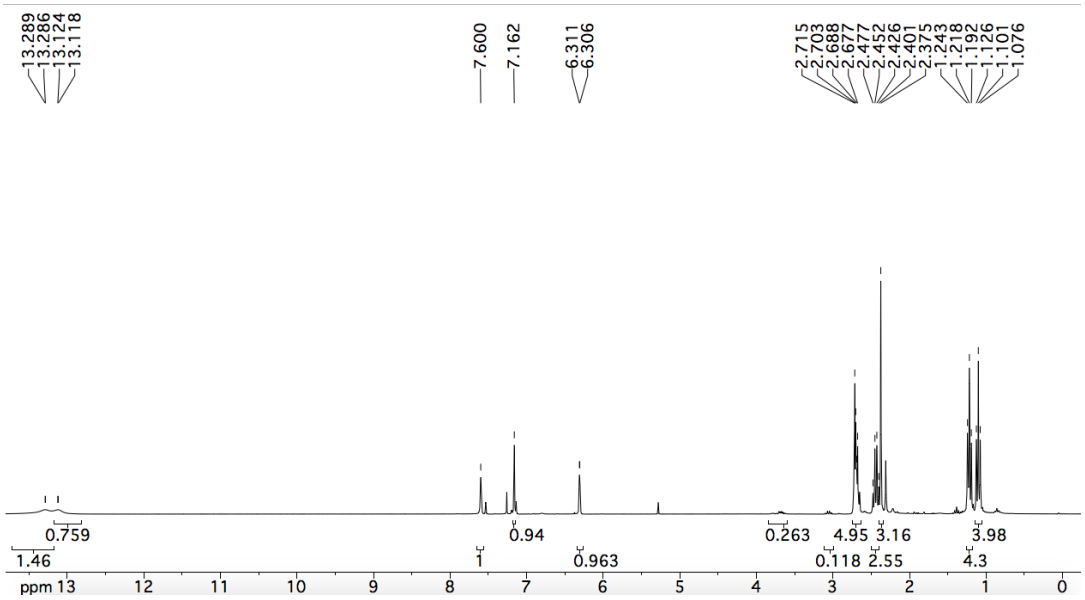
^{13}C UDEFT NMR ($CDCl_3$, 125 MHz)



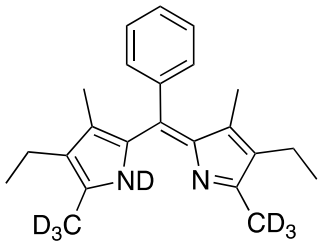
(*Z*)-3,4-Diethyl-2($^2H_3$)-methyl-5-((3-methyl-2*H*-pyrrol-2-ylidene)methyl)-1*H*-pyrrole hydrobromide (3-6-D_3•HBr)



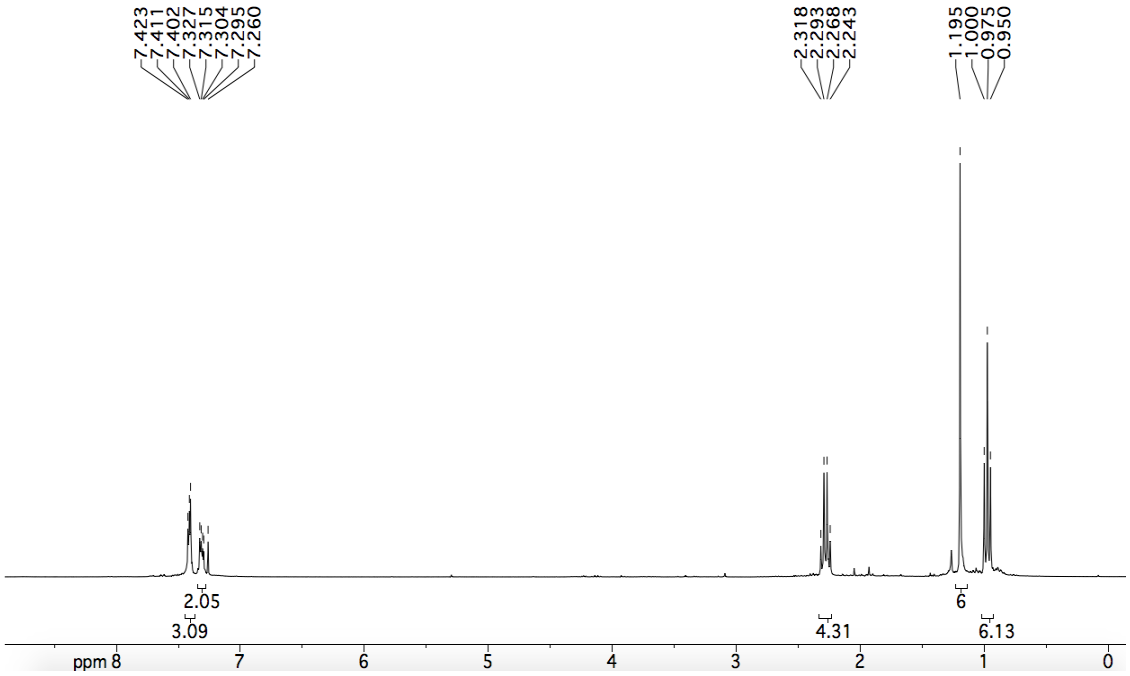
^{1}H NMR ($CDCl_3$, 300 MHz):



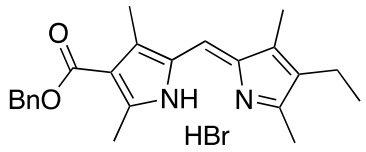
(*Z*)-3-Ethyl-5-((4-ethyl-3($^2H_3$),5-dimethyl-2*H*-pyrrol-2-ylidene)(phenyl)methyl)-2($^2H_3$),4-dimethyl-1^2*H*-pyrrole (3-7-D_7)



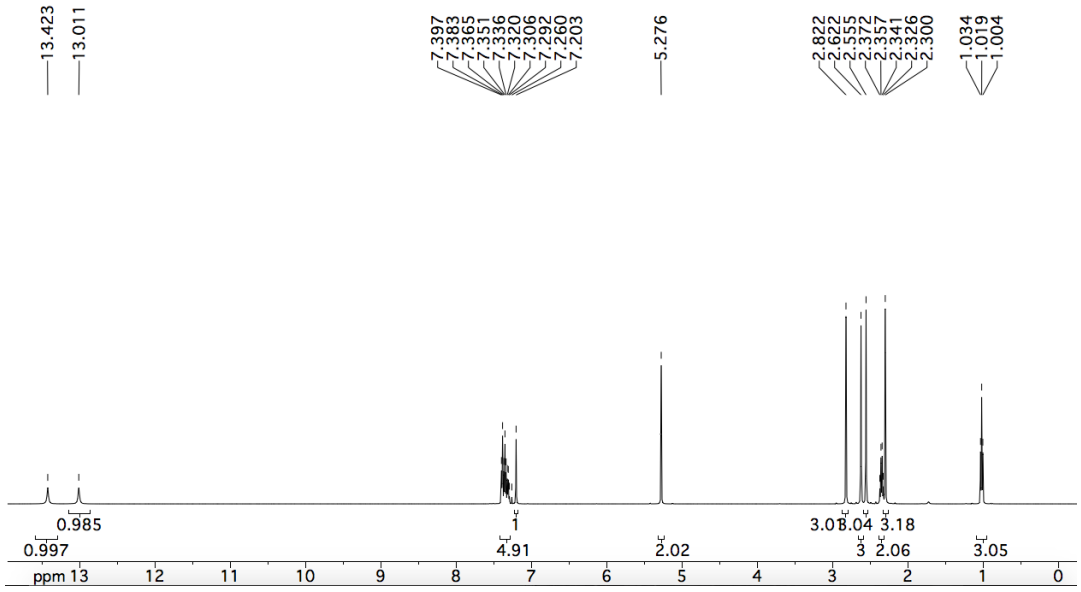
^{1}H NMR ($CDCl_3$, 300 MHz):



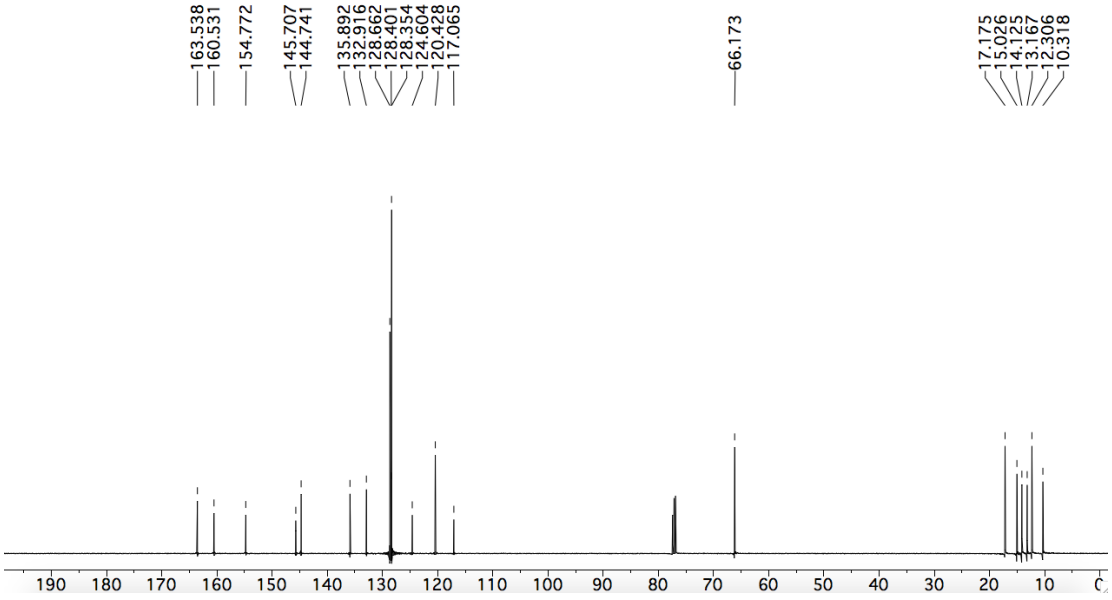
(*Z*)-Benzyl 5-((4-ethyl-3,5-dimethyl-2*H*-pyrrol-2-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrole-3-carboxylate hydrobromide (3-13•HBr)



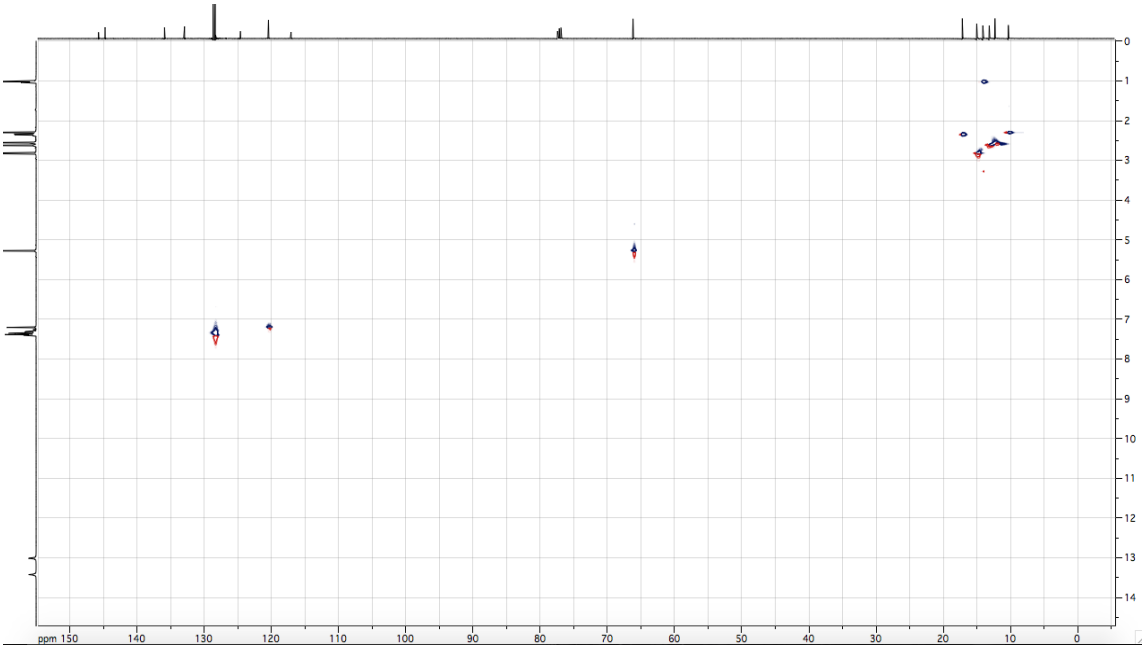
^{1}H NMR ($CDCl_3$, 500 MHz):



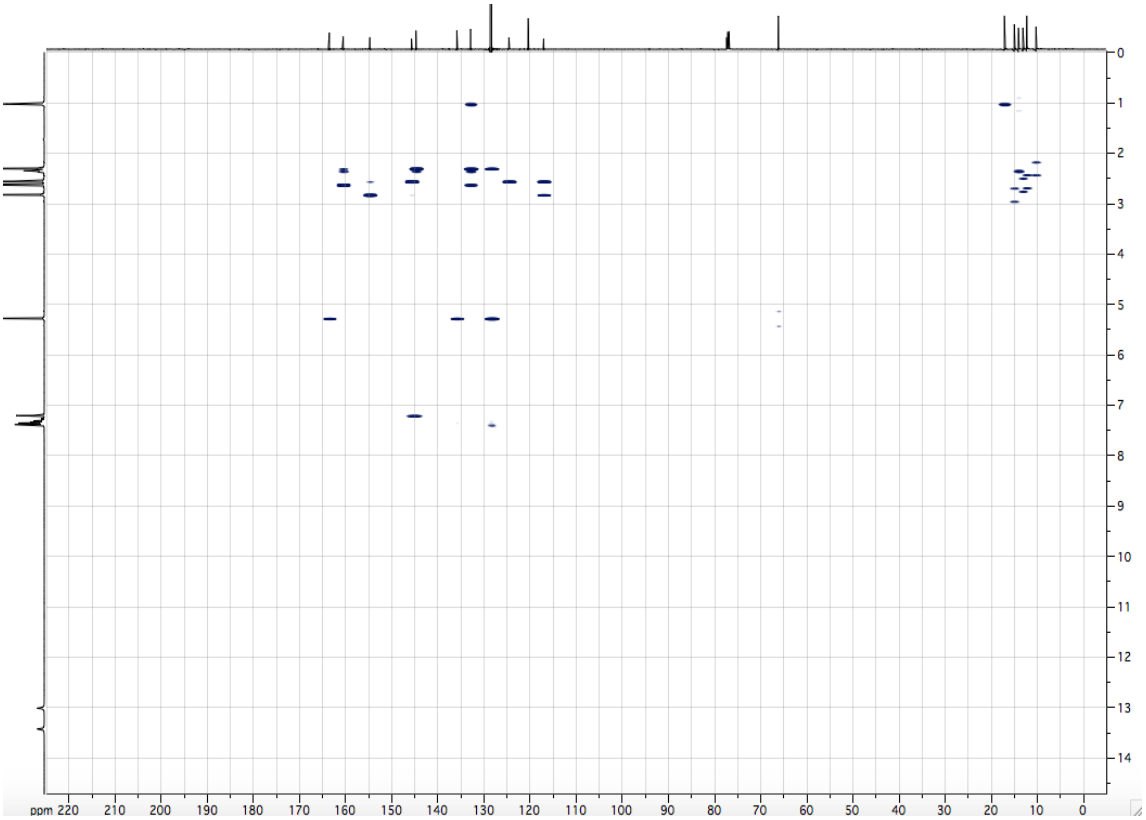
^{13}C UDEFT NMR ($CDCl_3$, 125 MHz):



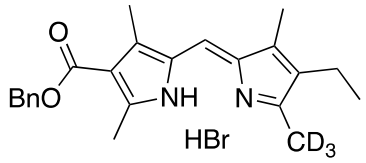
2D HSQC ($CDCl_3$):



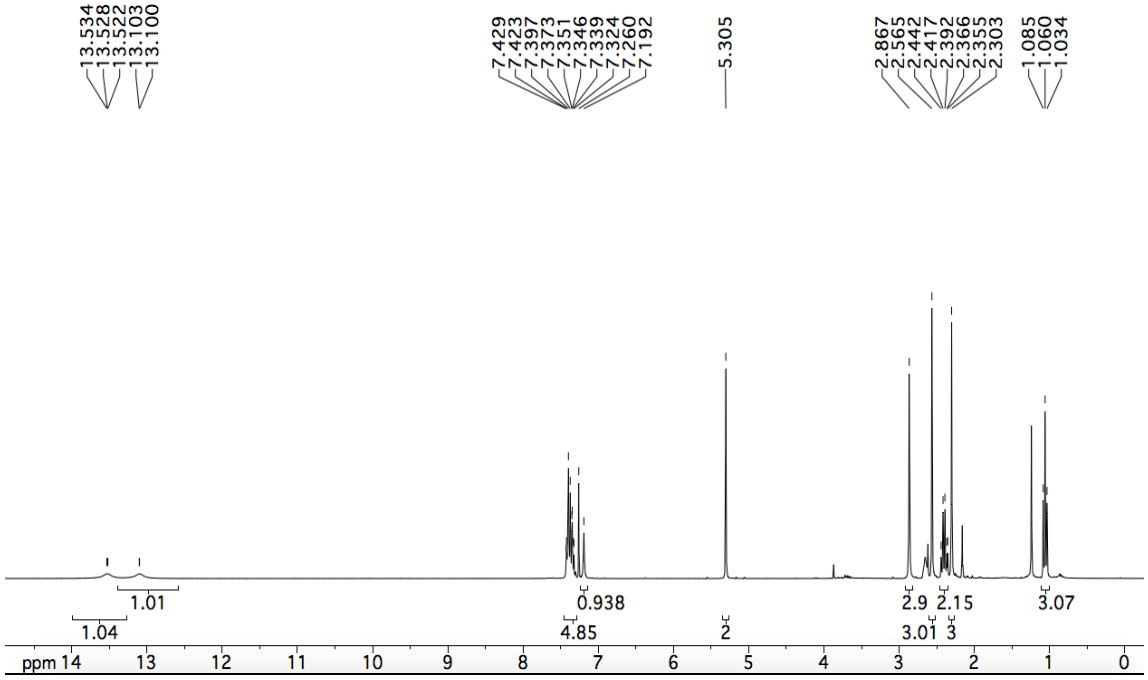
2D HMBC ($CDCl_3$):



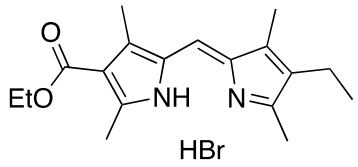
(*Z*)-Benzyl 5-((4-ethyl-3,5 -dimethyl-2*H*-pyrrol-2-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrole-3-carboxylate hydrobromide (3-13-D_3•HBr)



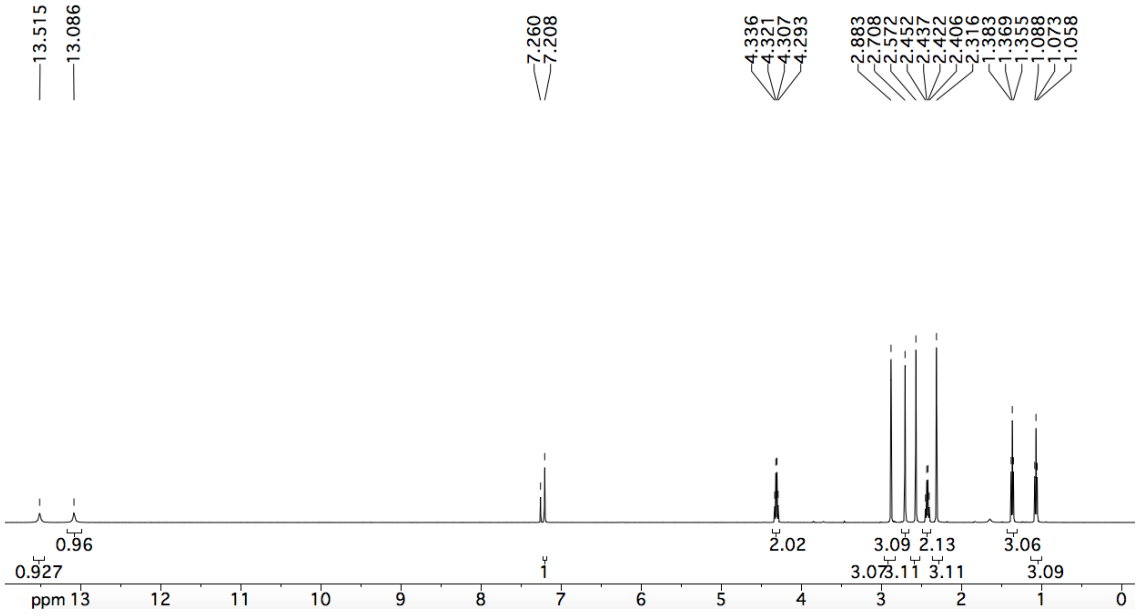
^{1}H NMR ($CDCl_3$, 300 MHz):



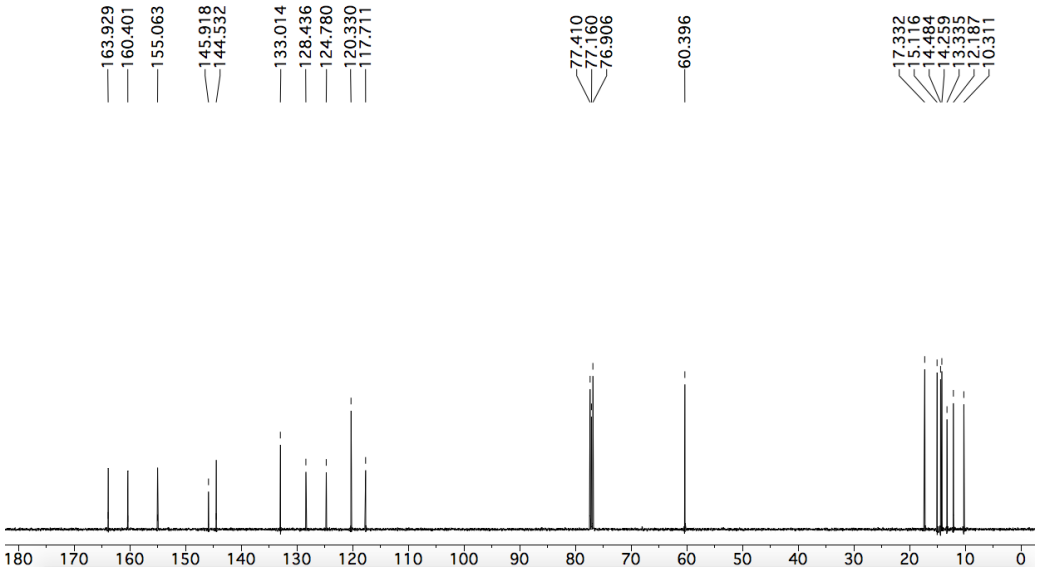
(*Z*)-Ethyl 5-((4-ethyl-3,5-dimethyl-2*H*-pyrrol-2-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrole-3-carboxylate hydrobromide (3-14•HBr)



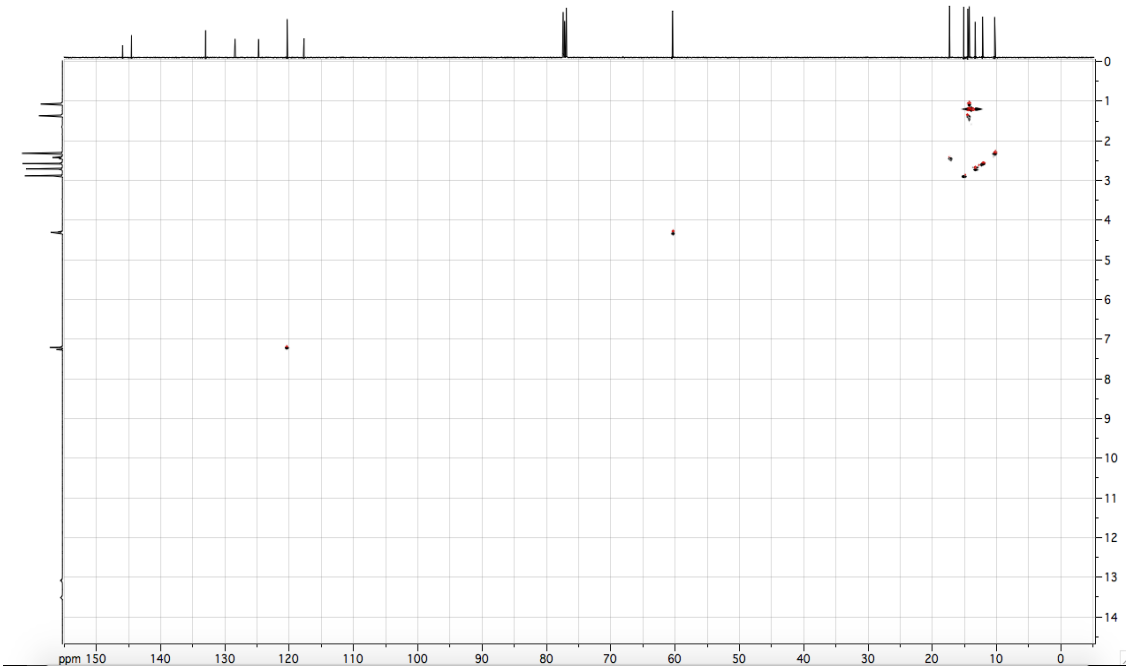
^{1}H NMR ($CDCl_3$, 500 MHz):



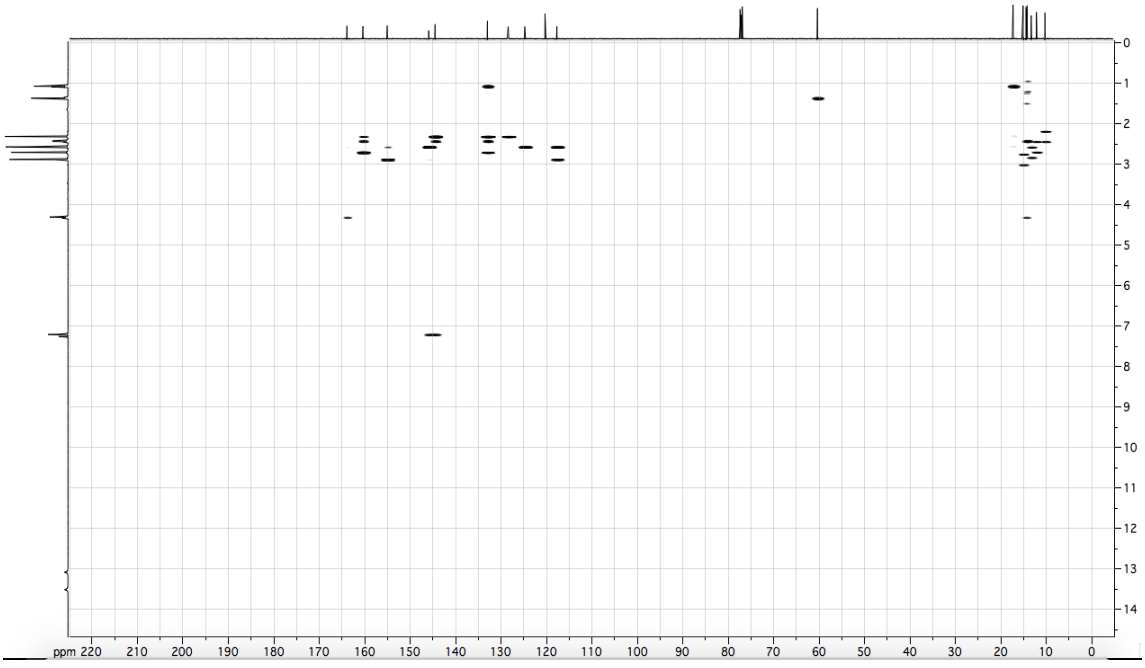
^{13}C UDEFT NMR ($CDCl_3$, 125 MHz):



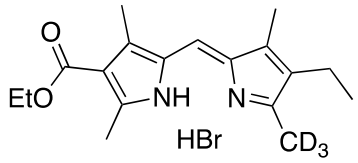
2D HSQC ($CDCl_3$):



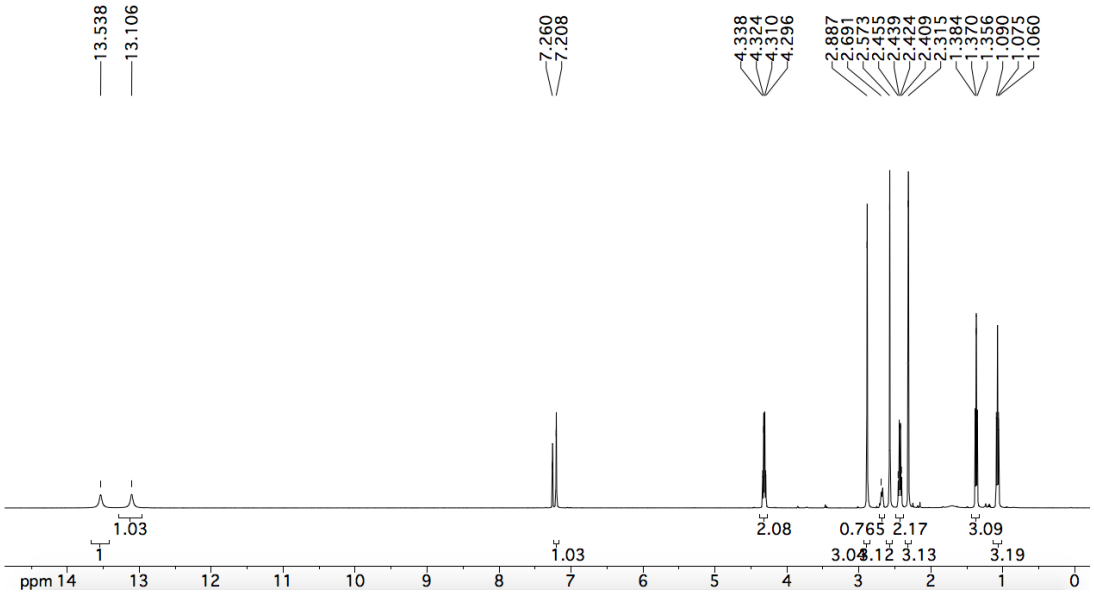
2D HMBC ($CDCl_3$):



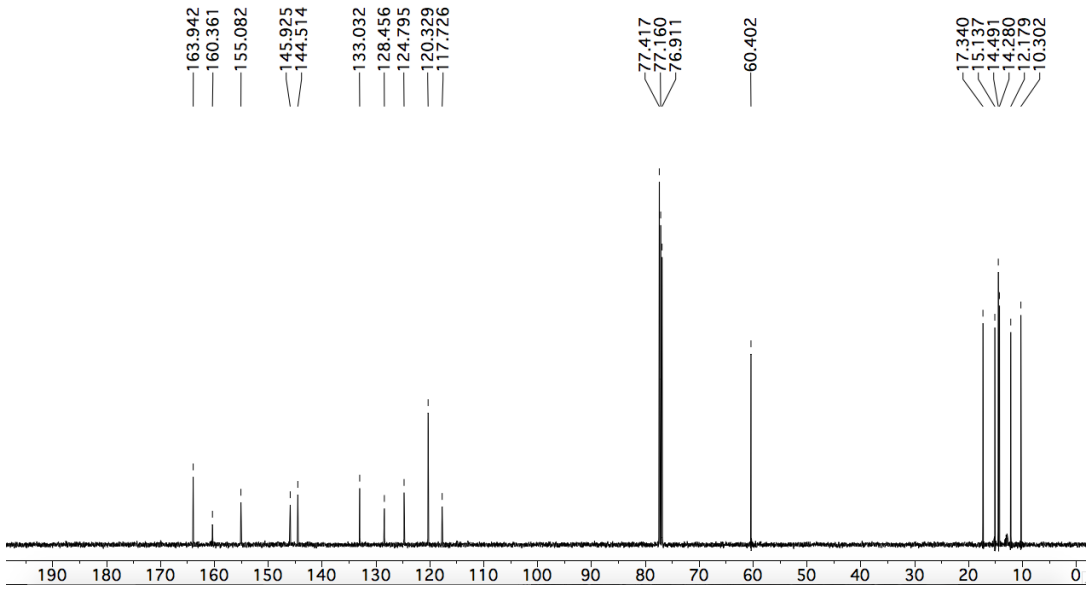
(*Z*)-Ethyl 5-((4-ethyl-3,5($^2H_3$)-dimethyl-2*H*-pyrrol-2-ylidene)methyl)-2($^2H_3$),4-dimethyl-1*H*-pyrrole-3-carboxylate hydrobromide (3-14-D$_3$•HBr)



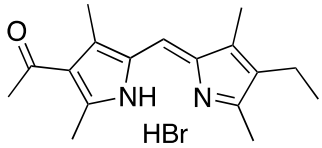
. ^{1}H NMR ($CDCl_3$, 500 MHz):



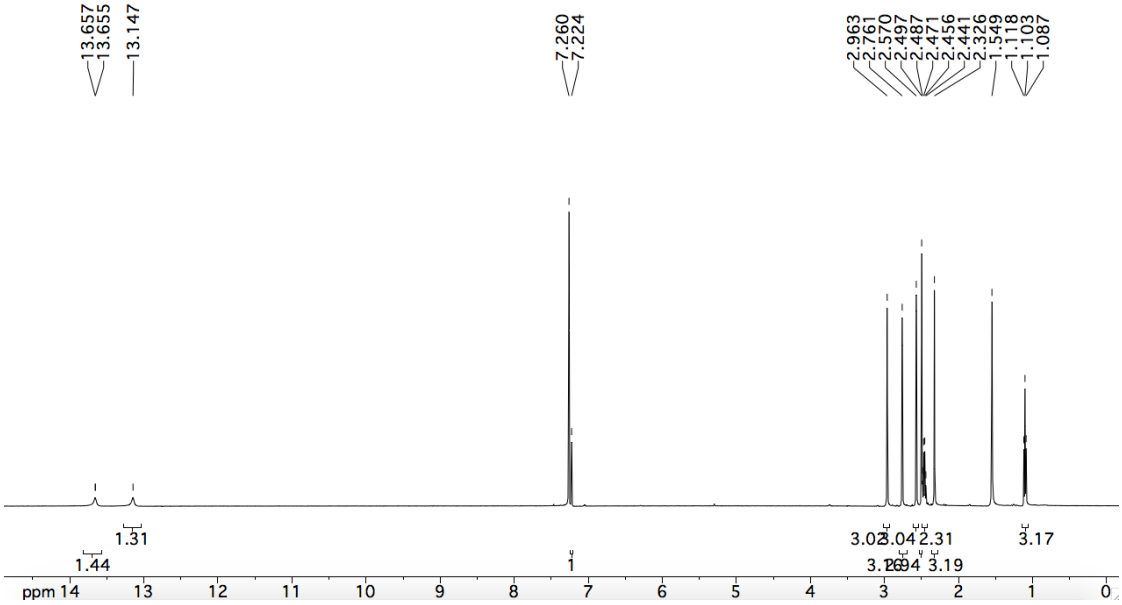
^{13}C UDEFT NMR ($CDCl_3$, 125 MHz):



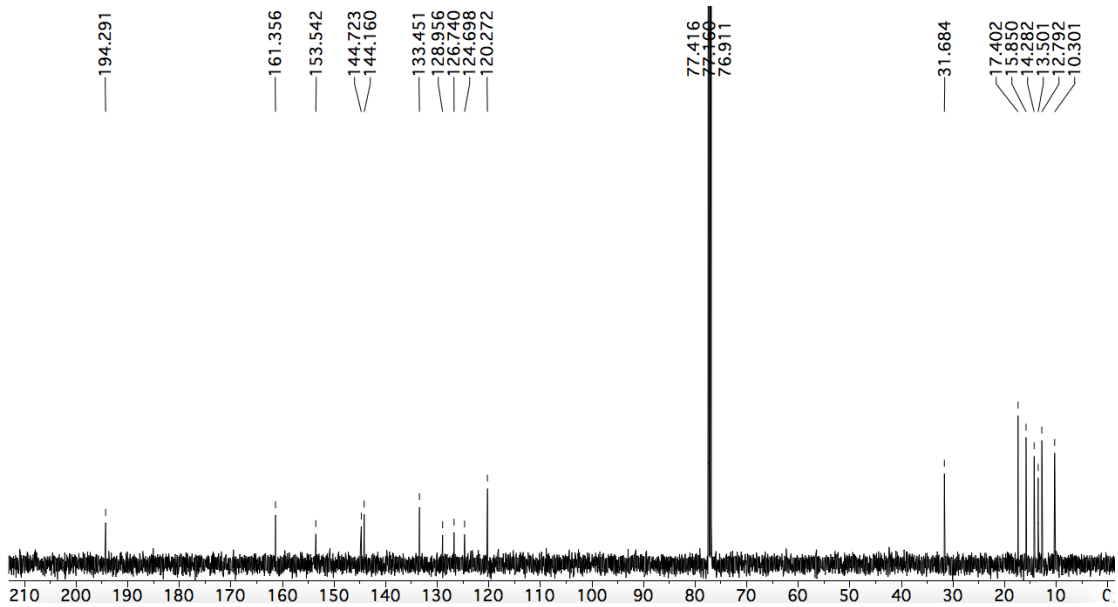
(*Z*)-1-(5-((4-Ethyl-3,5-dimethyl-2*H*-pyrrol-2-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrol-3-yl)ethanone hydrobromide (3-15•HBr)



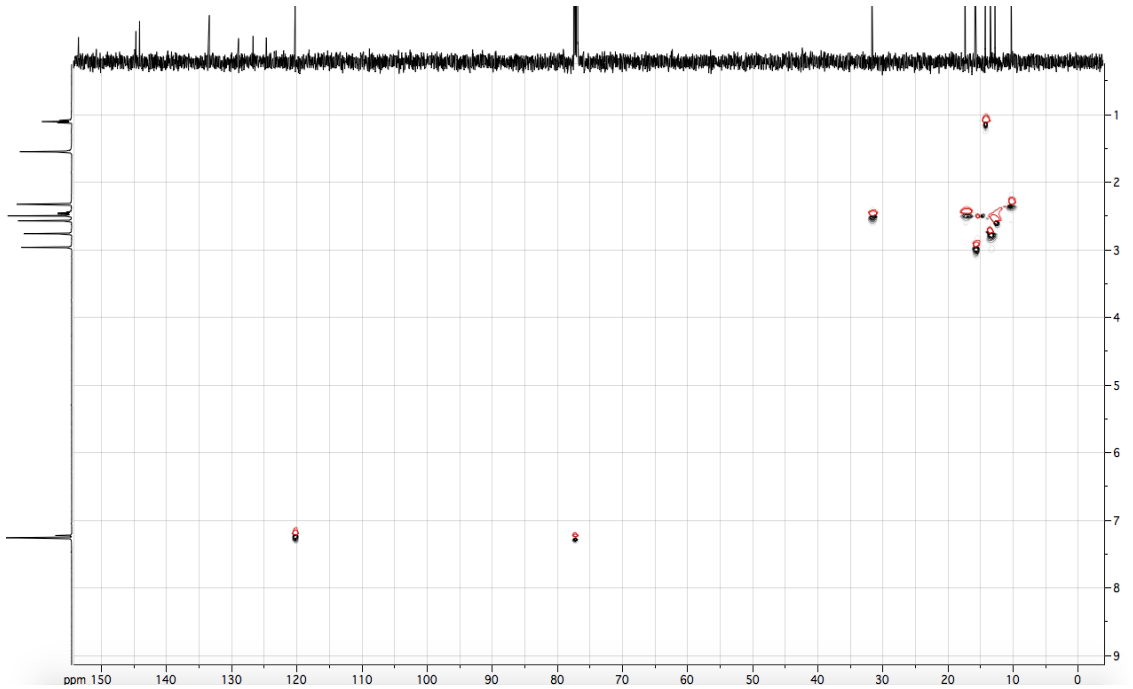
^{1}H NMR ($CDCl_3$, 500 MHz):



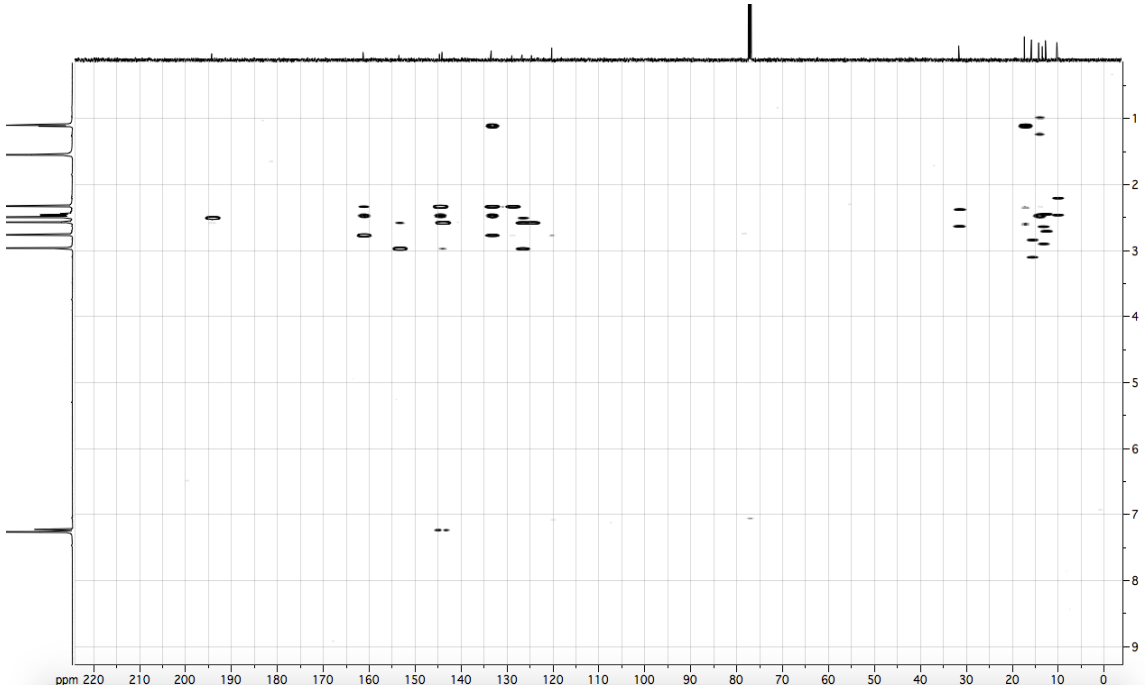
^{13}C UDEFT NMR ($CDCl_3$, 125 MHz):



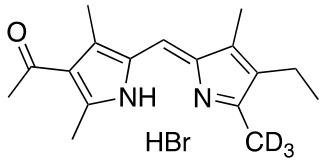
2D HSQC ($CDCl_3$):



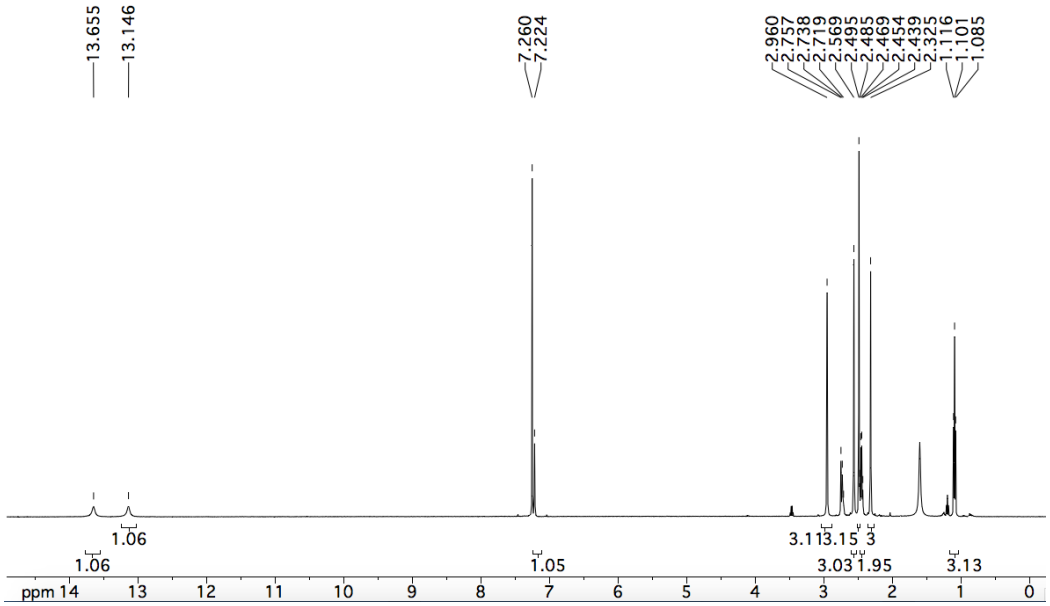
2D HMBC ($CDCl_3$):



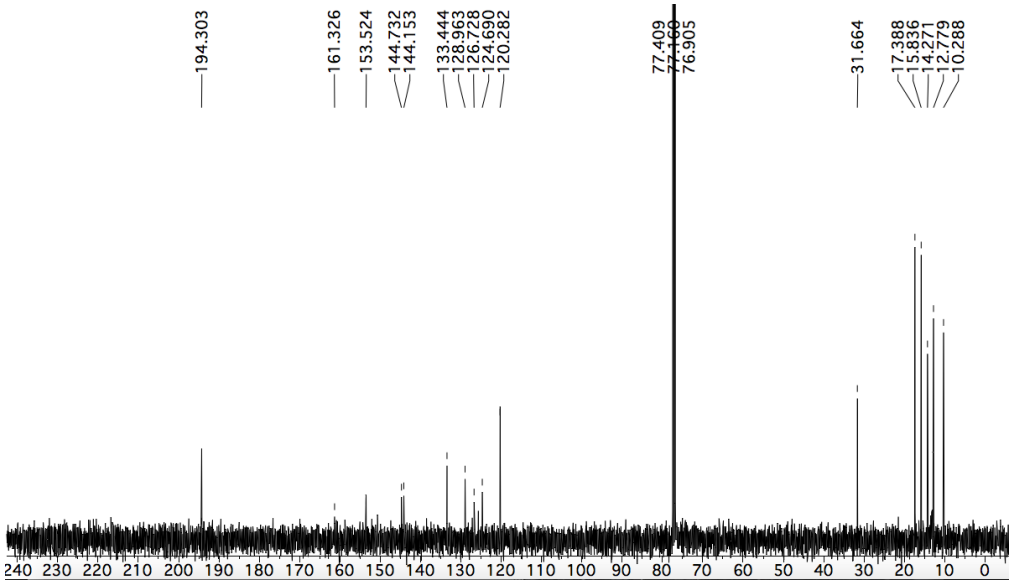
(*Z*)-1-(5-((4-Ethyl-3,5($^2H_3$)-dimethyl-2*H*-pyrrol-2-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrol-3-yl)ethanone hydrobromide (3-15-D_3•HBr)



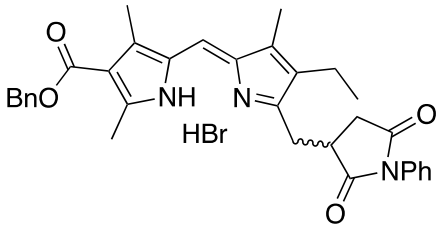
^{1}H NMR ($CDCl_3$, 500 MHz):



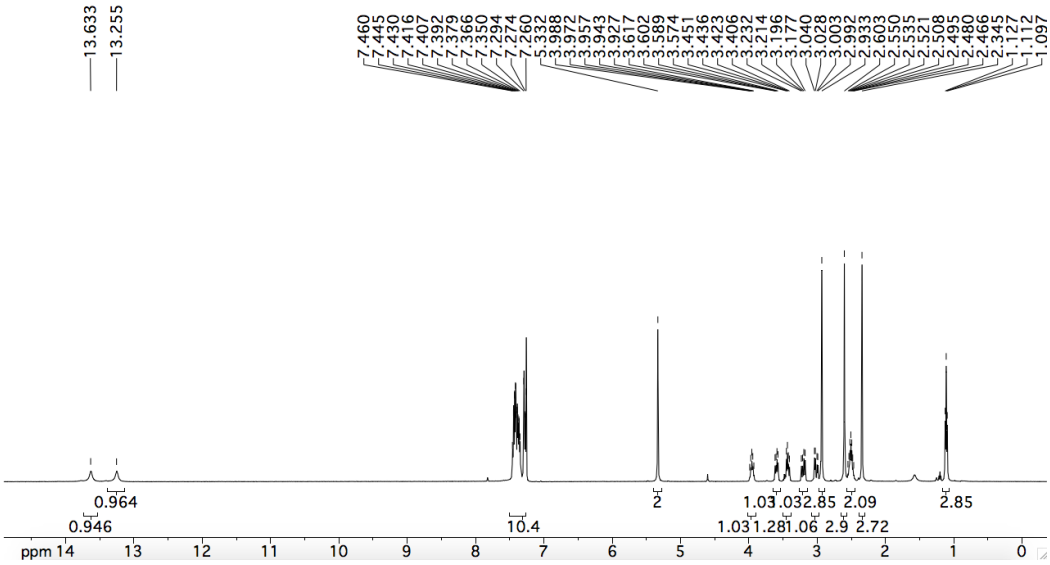
^{13}C UDEFT NMR ($CDCl_3$, 125 MHz):



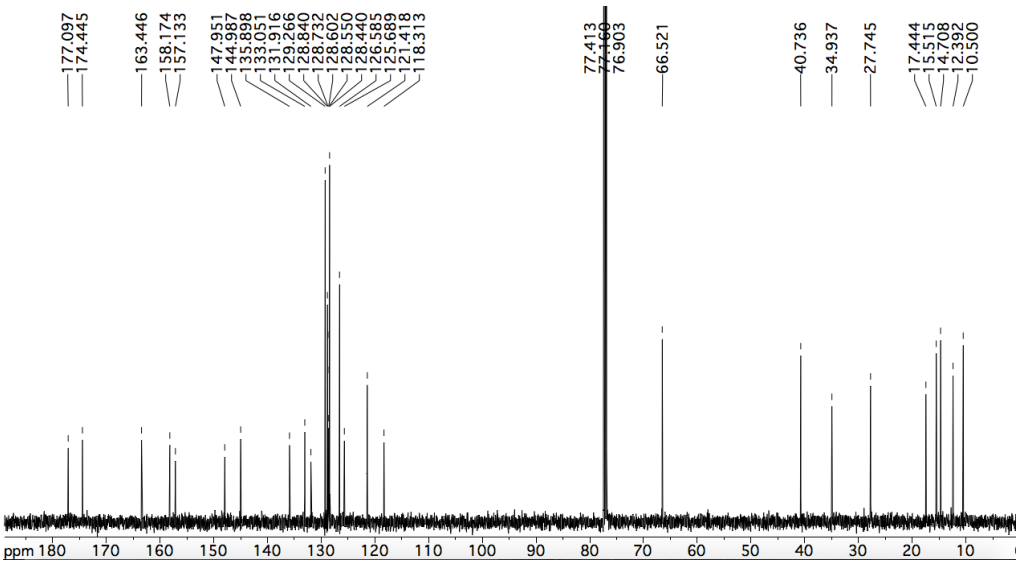
(*Z*)-Benzyl 5-((5-((2,5-dioxo-1-phenylpyrrolidin-3-yl)methyl)-4-ethyl-3-methyl-2*H*-pyrrol-2-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrole-3-carboxylate hydrobromide (3-18•HBr)



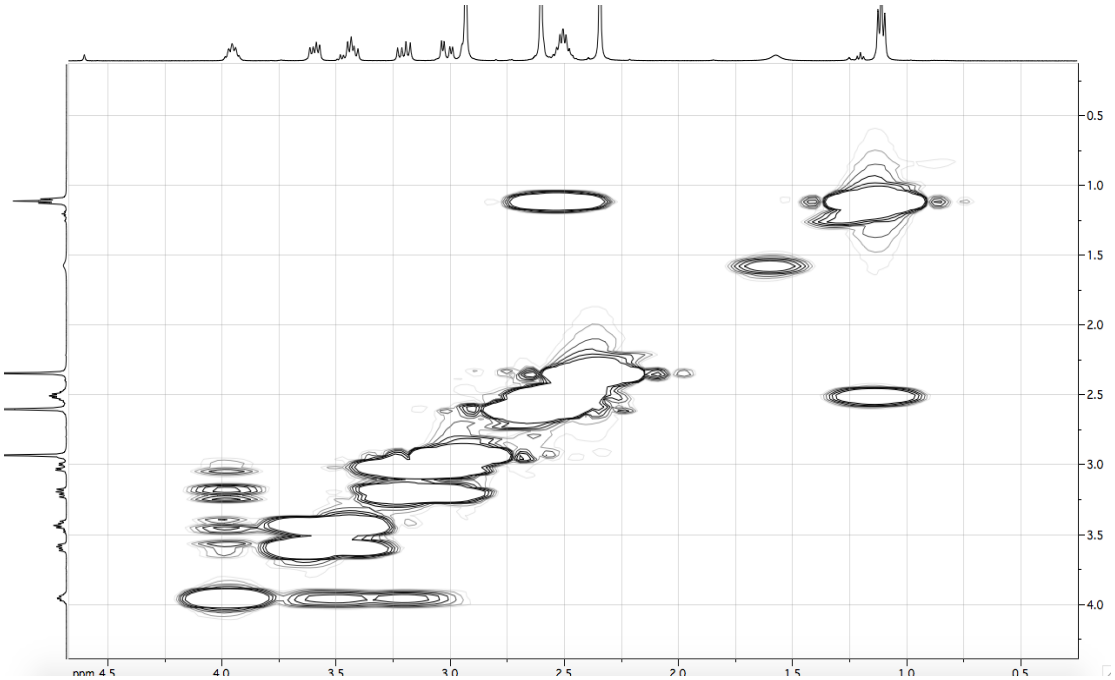
^{1}H NMR ($CDCl_3$, 500 MHz):



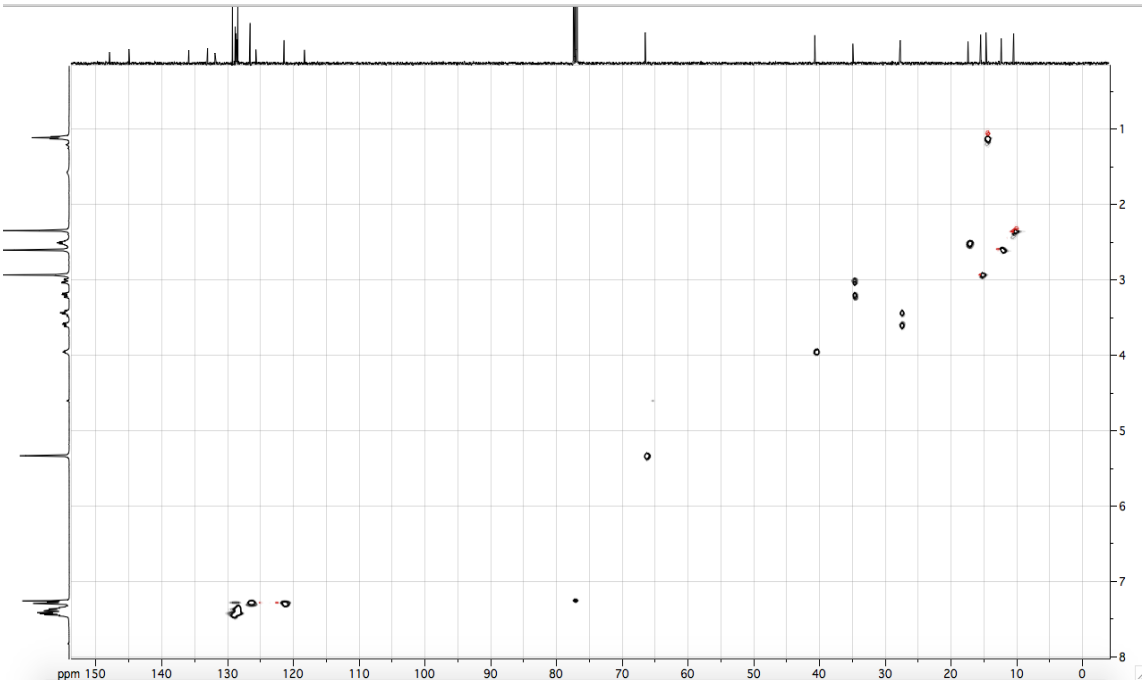
^{13}C UDEFT NMR ($CDCl_3$, 125 MHz):



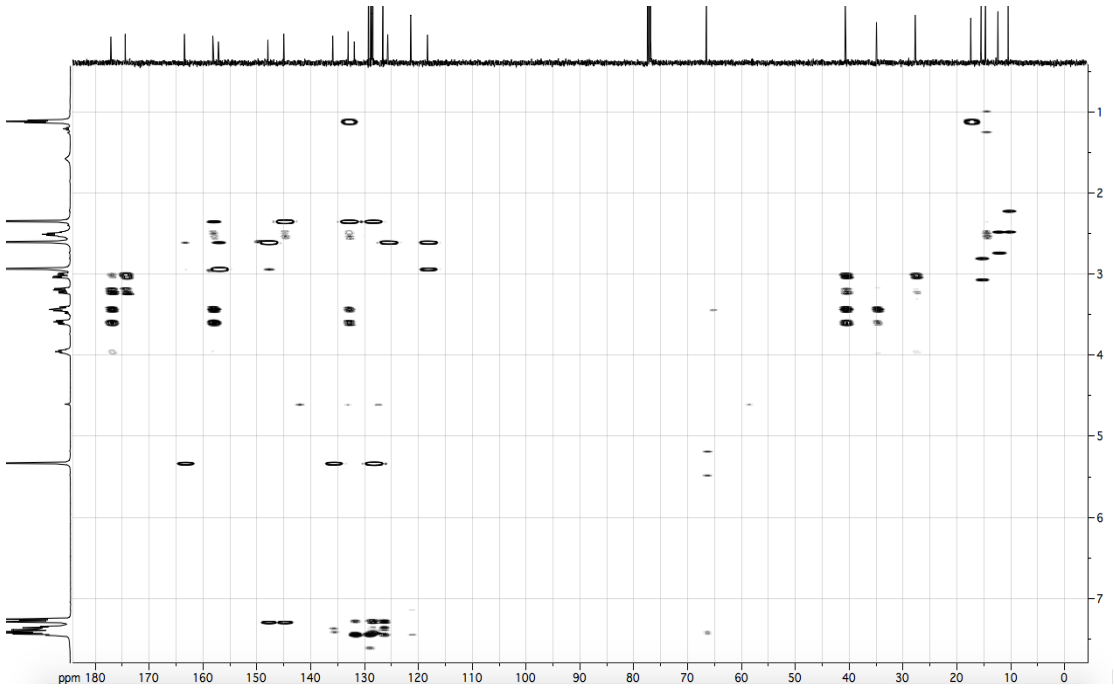
2D COSY ($CDCl_3$):



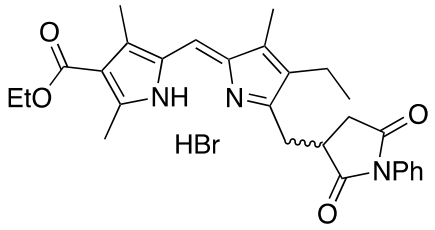
2D HSQC ($CDCl_3$):



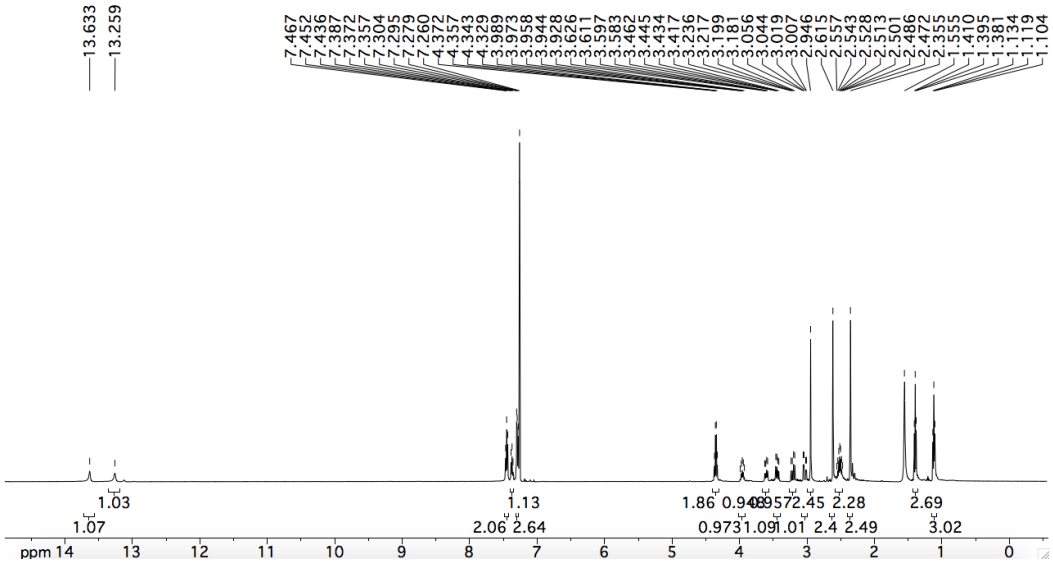
2D HMBC ($CDCl_3$):



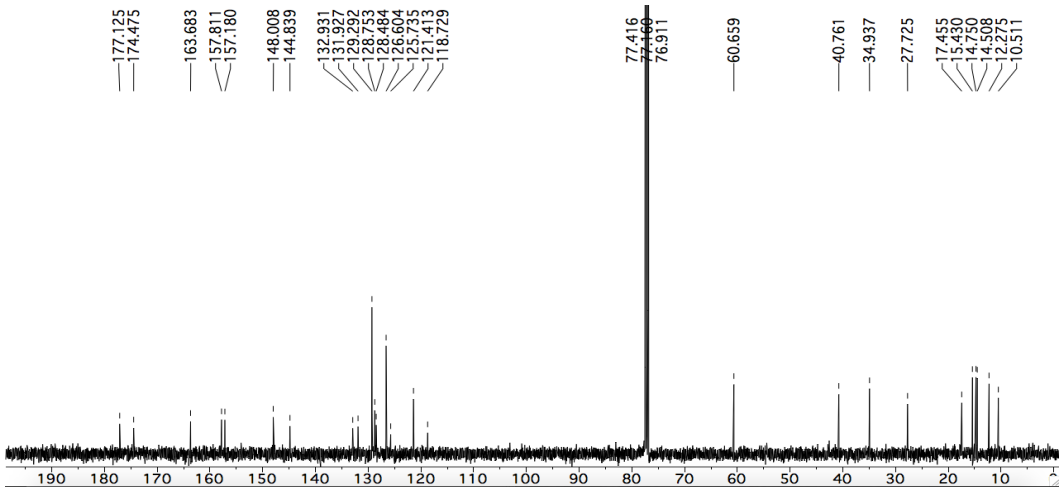
(*Z*)-Ethyl 5-((5-((2,5-dioxo-1-phenylpyrrolidin-3-yl)methyl)-4-ethyl-3-methyl-2*H*-pyrrol-2-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrole-3-carboxylate hydrobromide (3-19•HBr)



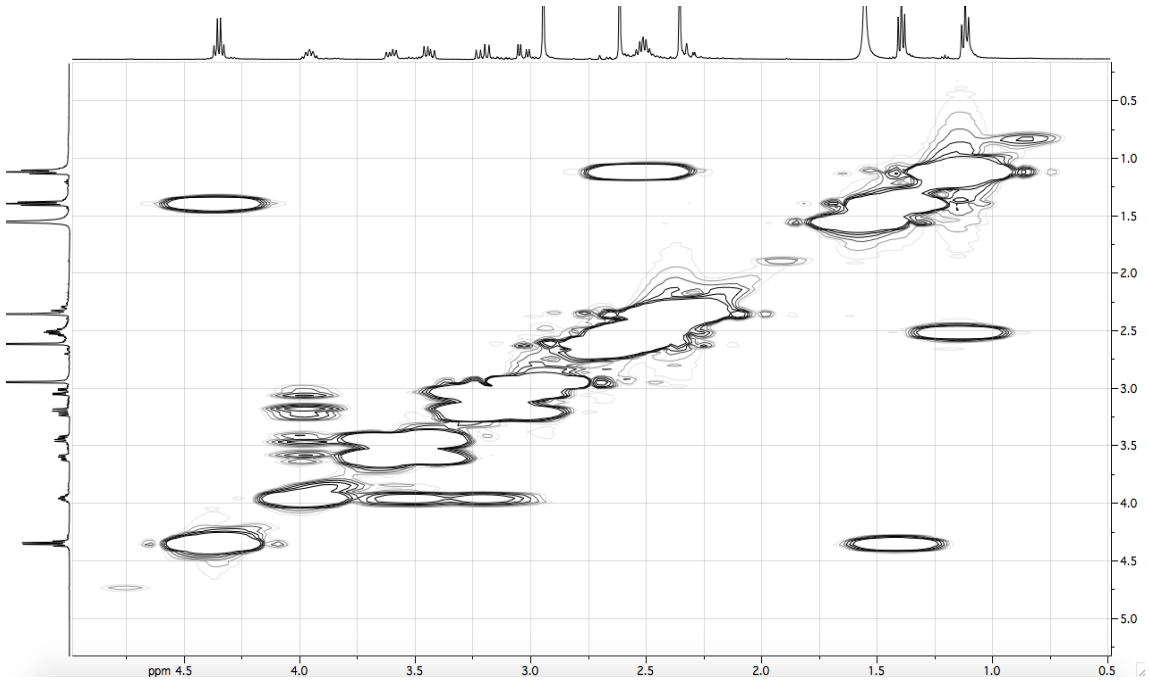
^{1}H NMR ($CDCl_3$, 500 MHz):



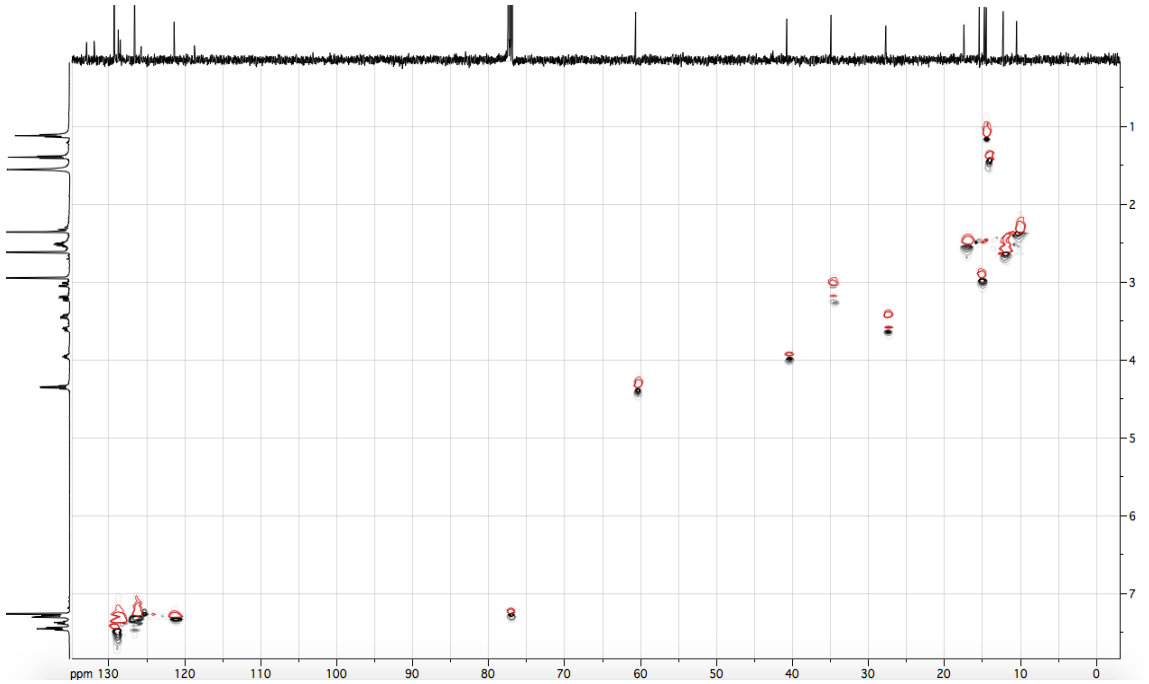
^{13}C UDEFT NMR ($CDCl_3$, 125 MHz):



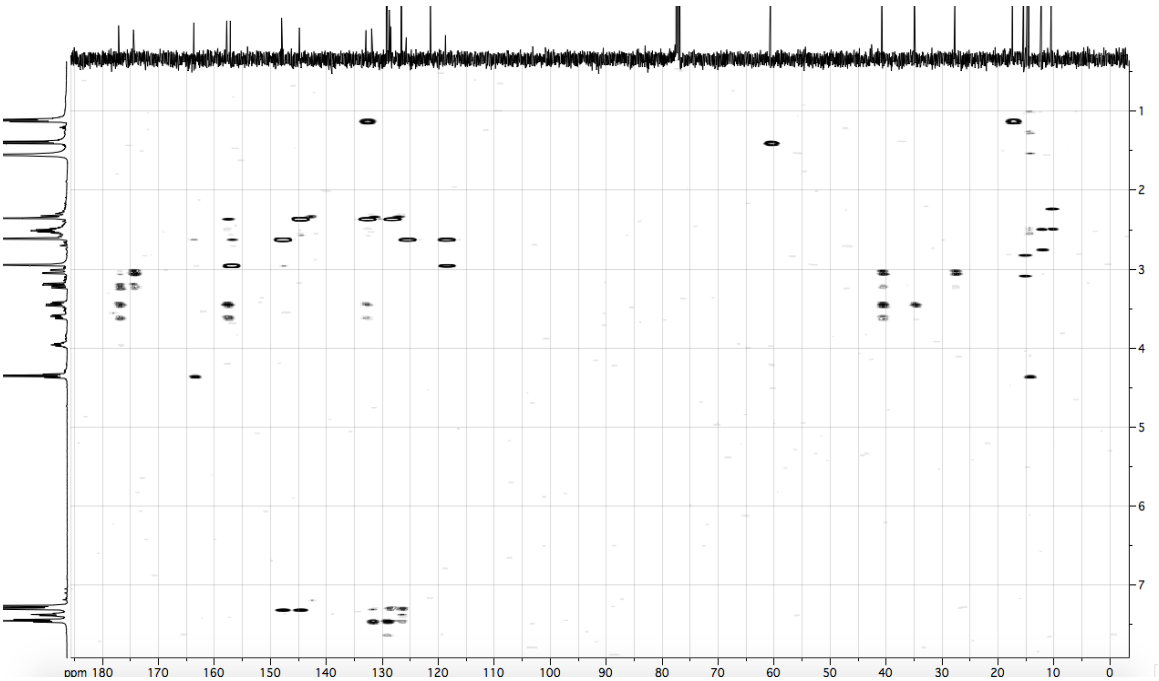
2D COSY ($CDCl_3$):



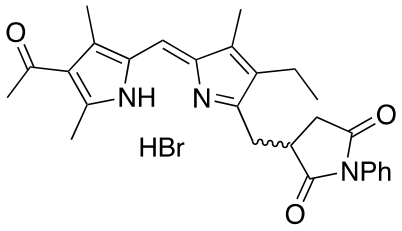
2D HSQC ($CDCl_3$):



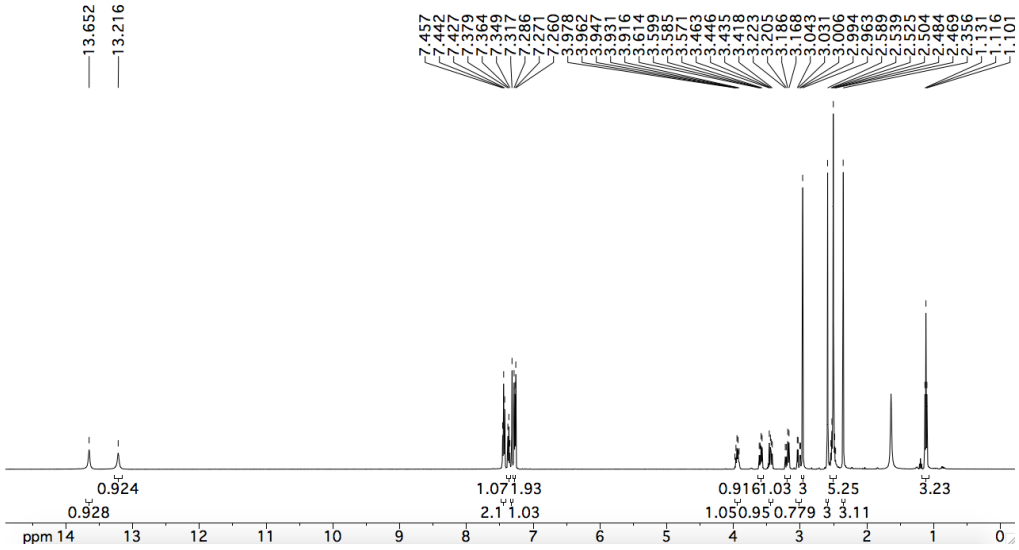
2D HMBC ($CDCl_3$):



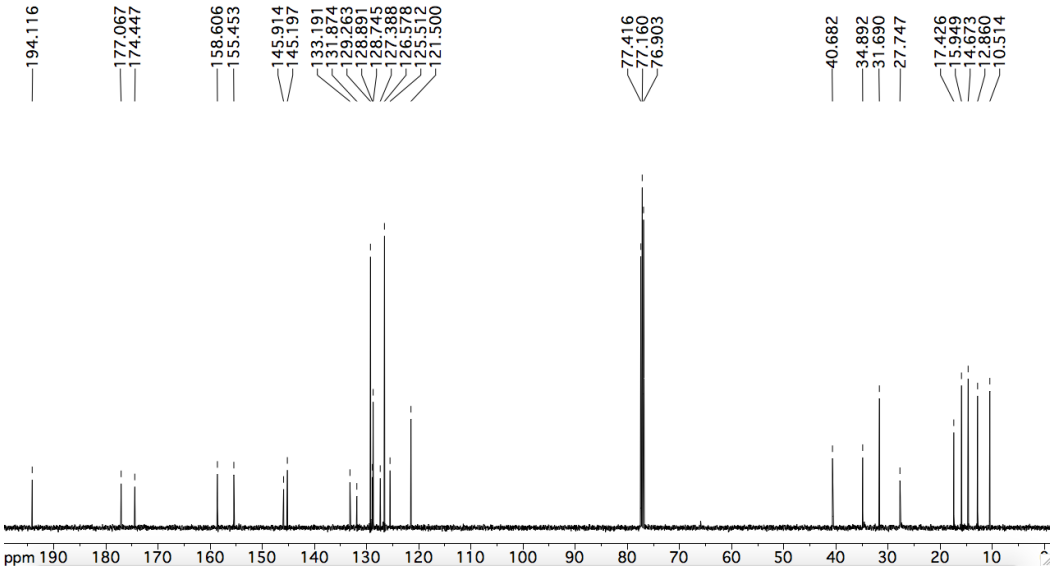
(*Z*)-3-((2-((4-Acetyl-3,5-dimethyl-1*H*-pyrrol-2-yl)methylene)-4-ethyl-3-methyl-2*H*-pyrrol-5-yl)methyl)-1-phenylpyrrolidine-2,5-dione hydrobromide (3-20•HBr)



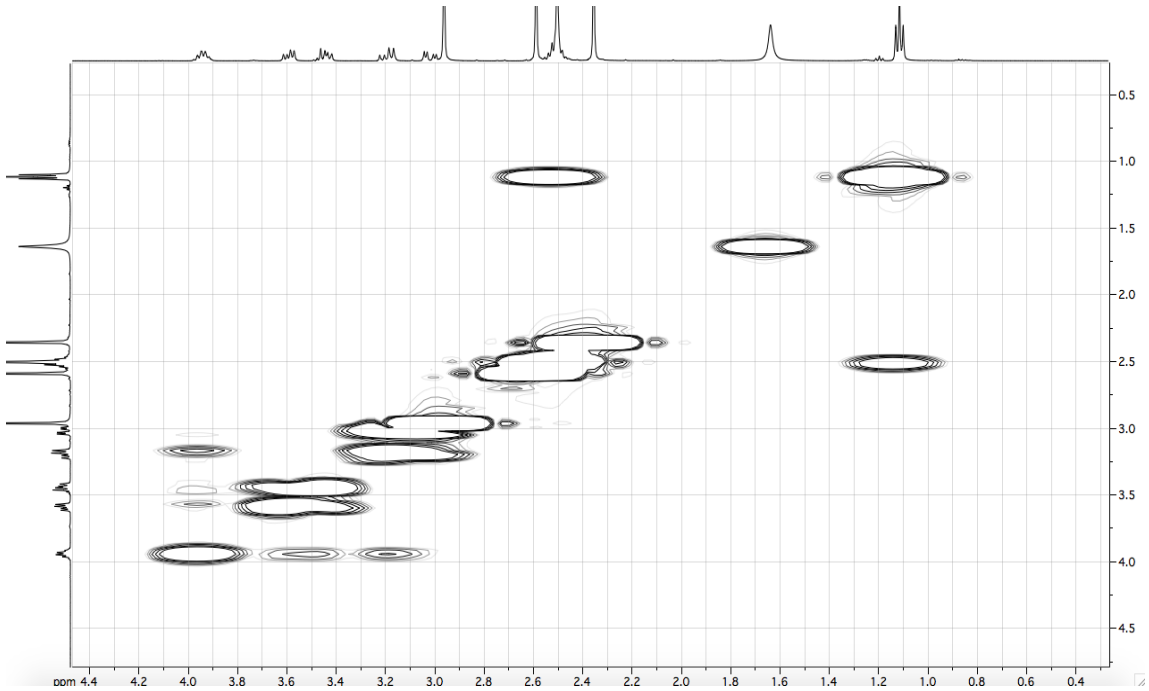
^{1}H NMR ($CDCl_3$, 500 MHz):



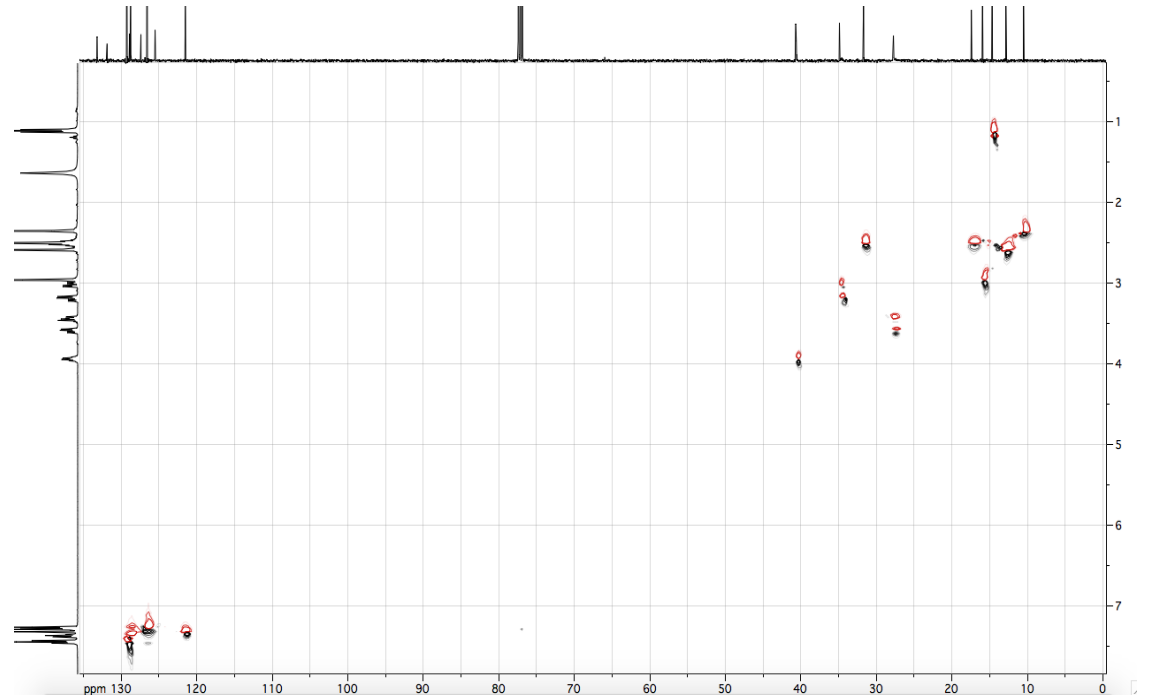
^{13}C UDEFT NMR ($CDCl_3$, 125 MHz):



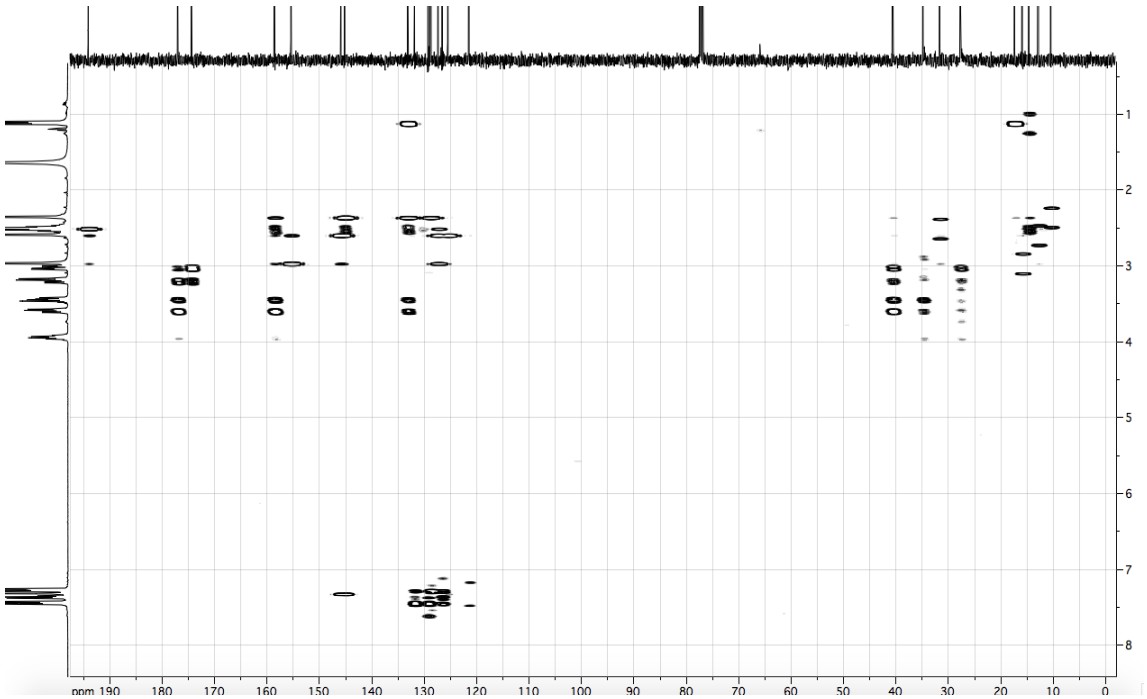
2D COSY ($CDCl_3$):



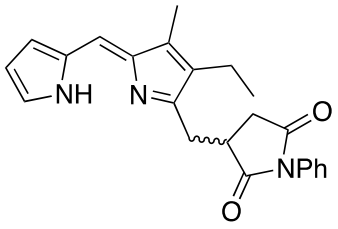
2D HSQC ($CDCl_3$):



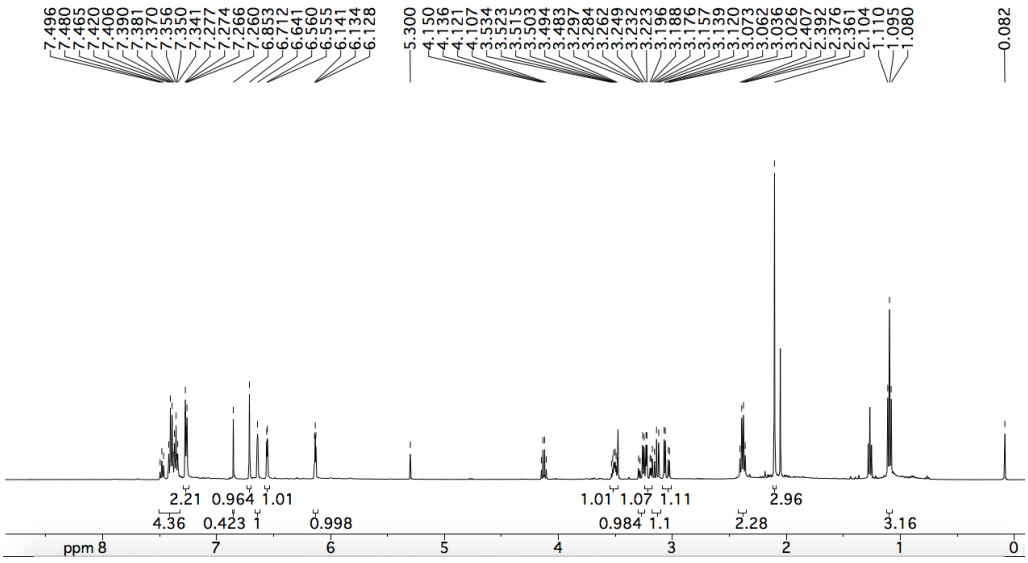
2D HMBC ($CDCl_3$):



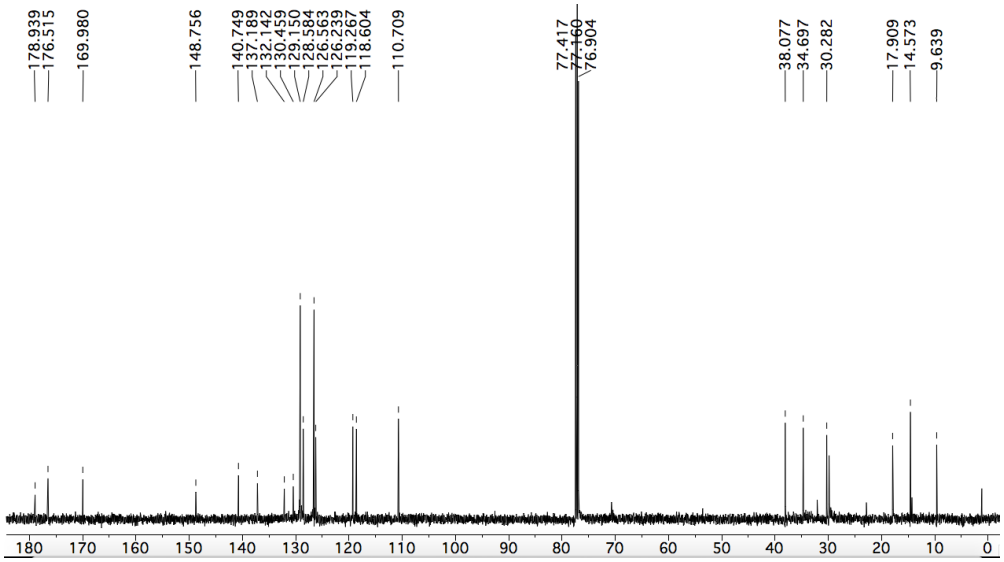
(*Z*)-3-((2-((1*H*-Pyrrol-2-yl)methylene)-4-ethyl-3-methyl-2*H*-pyrrol-5-yl)methyl)-1-phenylpyrrolidine-2,5-dione (3-21)



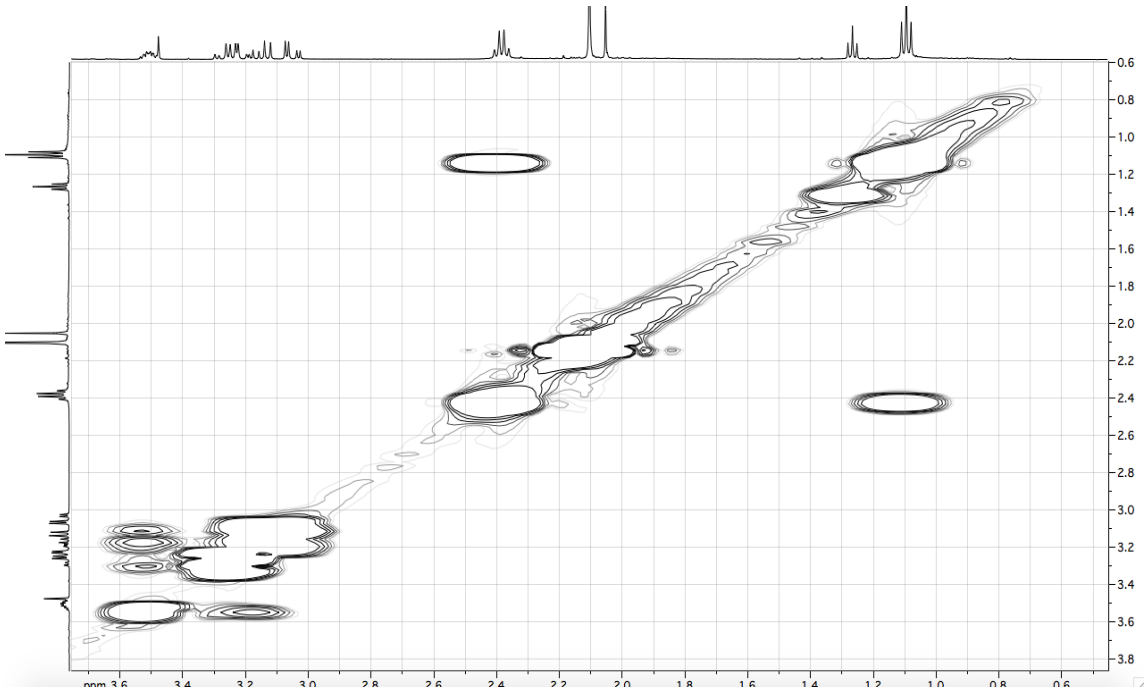
^{1}H NMR ($CDCl_3$, 500 MHz):



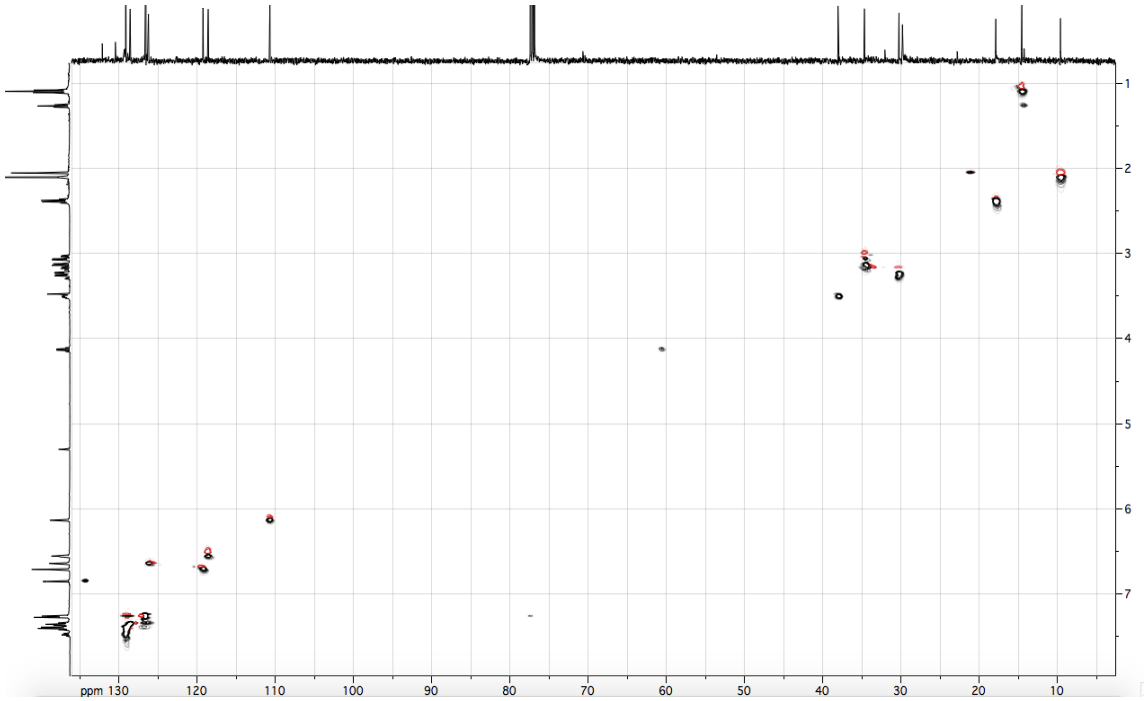
^{13}C UDEFT NMR ($CDCl_3$, 125 MHz):



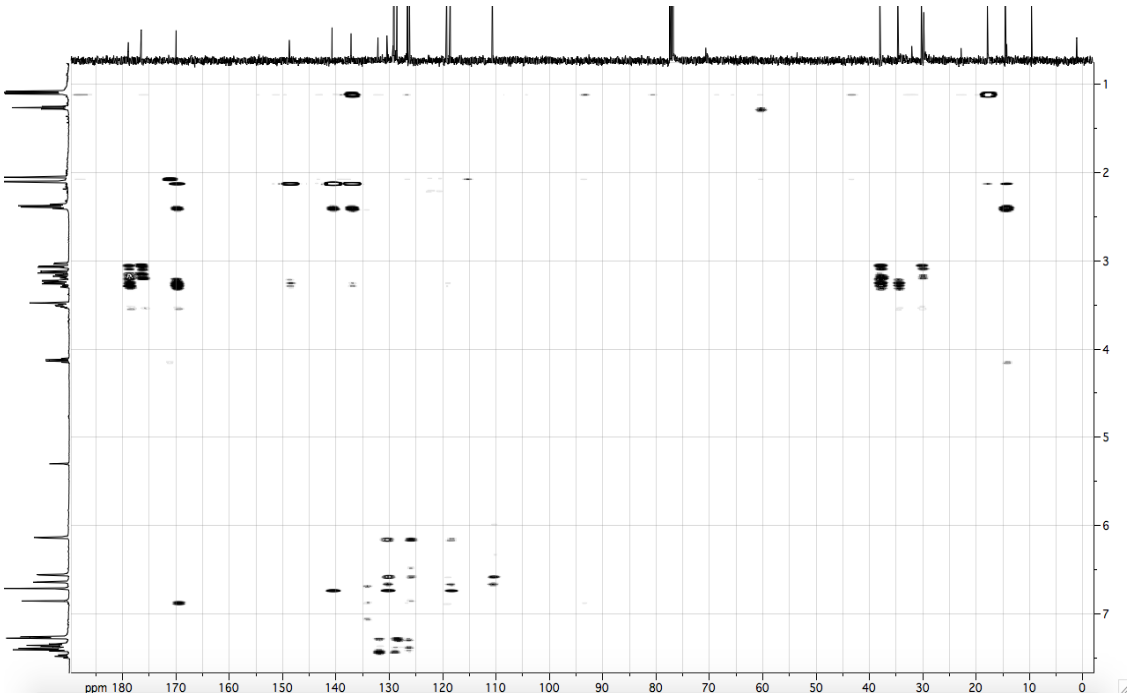
2D COSY ($CDCl_3$):



2D HSQC ($CDCl_3$):



2D HMBC ($CDCl_3$):

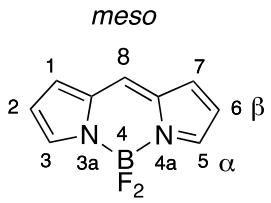


Chapter 4: *F*-BODIPYs: Studies in Stability and Synthesis

Section 4.1: Background information regarding *F*-BODIPYs

4,4-Difluoro-4-bora-3a,4a-diaza-*s*-indacenes, or *F*-BODIPYs, are the BF_2 complexes of dipyrrins, and these were first synthesized by Treibs and Kreuzer in 1968.[125] Nomenclature for *F*-BODIPYs is not consistent with the naming used for dipyrrins; rather, numbering begins at the β'-position and continues around the framework until reaching the adjoining *meso*-position (Figure 4-1). Like the parent dipyrrins, *F*-BODIPYs are intensely coloured compounds that absorb strongly in the visible and near infrared region of the electromagnetic spectrum. In addition to this absorbance, *F*-BODIPYs are exceptionally fluorescent materials. Fluorescent quantum yields of *F*-BODIPYs are typically very high, with photon-conversion ratios approaching 1.00 in many examples.[28]

Figure 4-1: **Nomenclature for *F*-BODIPYs**

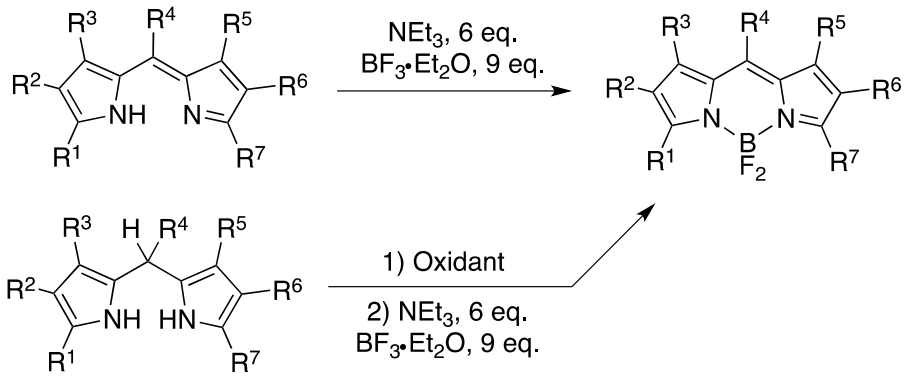


Despite their widespread use, and despite having first been reported nearly fifty years ago, *F*-BODIPYs spent twenty years in relative obscurity. During the 1970's and 80's, fewer than twenty reports of research relating to dipyrrin-boron complexes were described. During the late eighties and early nineties, however, a renaissance in *F*-BODIPY research transpired as the demand for stable, fluorescent materials became

increasingly critical for a variety of research purposes. Two fields led this surge, as *F*-BODIPYs were shown to be useful both as liquid based organic laser dyes,[126] and as fluorescent molecular probes for use in biological systems.[127] In the decades since, *F*-BODIPYs have flourished as synthetic targets for a wide array of practical applications. In addition to the traditional uses such as medical tagging and tunable dye lasers, *F*-BODIPYs have been used for such varied purposes as organic light emitting diodes,[128] organic dyes in dye-sensitized solar cells,[129] and solution-based metal-ion sensing.[130] The attractive optical properties of *F*-BODIPYs are complemented by the reported ruggedness of the molecules: relative to the parent dipyrrins from which *F*-BODIPYs are derived, the stability of these complexes is high.[28] Fluorine-substituted derivatives are generally stable to ambient atmospheric conditions, and they tolerate a wide array of temperatures and pH. More recent work, however, has highlighted the difficulties associated with performing chemical transformations on *F*-BODIPYs, as well as the ease with which the system can be converted back to the native dipyrrin and boron units.

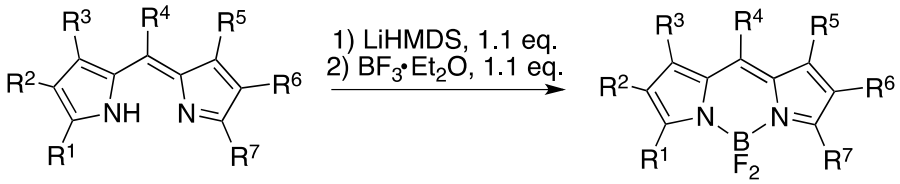
Synthesis of *F*-BODIPYs is classically performed using excess amounts of amine base and boron trifluoride diethyletherate (Scheme 4-1).

Scheme 4-1: **Classical synthesis of *F*-BODIPYs**



Treatment of a dipyrrin with six equivalents of amine and nine of BF_3•Et_2O yields *F*-BODIPYs in yields generally greater than eighty percent (Scheme 4-1, top).[28] Alternatively, one-pot conversion with *in situ* generation of the dipyrrin is also possible (Scheme 4-1, bottom).[131] Indeed, this second method is useful in trapping unstable dipyrrins as their *F*-BODIPYs. While these methods have been used to generate *F*-BODIPYs for over four decades, recent work has shown that boron complexation of dipyrrins can also be achieved in high yields using stoichiometric amounts of base (Scheme 4-2).[91] Deprotonation using a single equivalent of LiHMDS to generate the dipyrrinato anion, followed by subsequent treatment with a single equivalent of BF_3•Et_2O yields *F*-BODIPYs in good to quantitative yield, eliminating the requirement for excessive base and boron-containing species.

Scheme 4-2: **Stoichiometric synthesis of *F*-BODIPYs**



The reactivity of *F*-BODIPYs is highly dependent on the substituents attached to the pyrrolic rings. Typically, the most electrophilic position on the aromatic framework is at the *meso* position, and substitution to yield *meso*-aryl and alkyl compounds is possible.[132] Complicating this process is the electrophilicity of the boron atom: often, alkylating, arylating and alkoxylating reagents react preferentially at boron to produce a variety of products.[132,133] Alkyl, aryl and alkoxy derivatives (known colloquially as *C*- and *O*-BODIPYs, respectively) possess different reactivity and affect the optical properties of the compound.

Due to the favourable optical and physical properties inherent to *F*-BODIPYs, a staggering number of these compounds has been generated in recent decades. Although significant resources have been spent on target-oriented generation of new structures, much less research has been performed studying the fundamental aspects of the framework and its synthesis. The goal of the work reported herein is to explore the stability and synthesis of the unsubstituted *F*-BODIPY framework. Furthermore, a novel synthetic approach to the generation of *F*-BODIPYs using thiono-ester pyrroles generated using Lawesson's reagent is described.

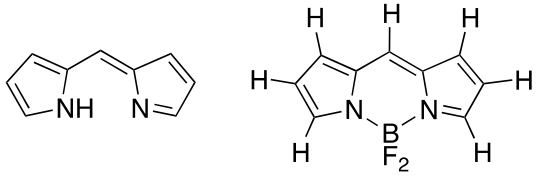
Section 4.2: Results and Discussions

4.2.1 Reactions of Fully Unsubstituted *F*-BODIPY

Complexation of unsubstituted dipyrrin **4-1** with boron trifluoride produces 4,4-difluoro-4-borato-3a-azonia-4a-aza-*s*-indacene, the fully unsubstituted *F*-BODIPY (**4-2**, Figure 4-2). This *F*-BODIPY was first reported by Tram *et al.* in 2007, and represents the first synthetic use of unsubstitued dipyrrin **4-1** since its inception in 1977.[134] Despite the unsubstituted structure of **4-1**, this compound-type was first reported over 60 years after Piloty's initial synthesis of dipyrrins in 1914.[135] This time gap is a consequence of the instability of the compound above -40 °C, and the subsequent challenges incurred with respect to synthesis and characterization.[123] Indeed, under ambient conditions, **4-1** is reported to rapidly degrade. Despite the instability of the dipyrrin, *F*-BODIPY **4-2** is a crystalline, red solid that is stable to atmospheric conditions. Compound **4-2** displays a quantum efficiency above 90% in many solvents;[134] this trait establishes **4-2** as a suitable target for development for use in practical applications, such as a biological tag or for use

in lasing media. Furthermore, the concept of using **4-2** as a fluorescent standard is appealing, due to favourable optical properties and nature of the compound as the simplistic core of all *F*-BODIPYs. Complexation with boron would also facilitate study of the otherwise unstable unsubstituted dipyrrinato framework.

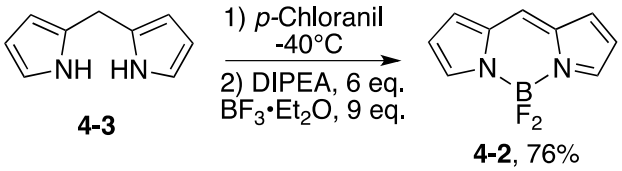
Figure 4-2: **Fully unsubstituted dipyrrin and *F*-BODIPY frameworks**



4-1 **4-2**

Until recently, synthesis of **4-2** had been performed on only small scale (50 mg) from unsubstituted dipyrromethane (**4-3**, Scheme 4-3) and with yields less than 10%.[28,136,137] Work reported by Dr. Sarah Crawford in her PhD dissertation improved this process; indeed, through alteration of reaction conditions, yields higher than 70% were attainable for the preparation of *F*-BODIPY **4-2**.[103] Following this procedure, the production of **4-2** was scaled to produce more than 400 mg per reaction (Scheme 4-3). With an accessible route to reasonable quantities of the *F*-BODIPY **4-2**, an investigation into modification of the structure for development of the framework for practical purposes was feasible.

Scheme 4-3: **Synthesis of *F*-BODIPY 4-2**

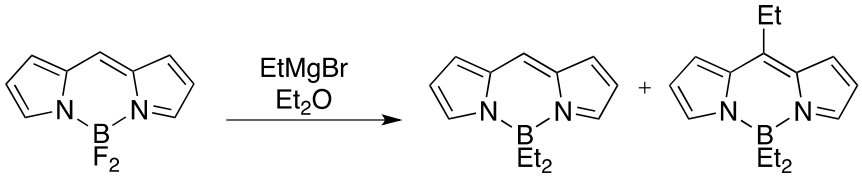


4-3 **4-2**, 76%

As the reactivity of **4-2** was of interest, and as maintenance of the unsubstituted nature of the dipyrrin frame was desired in order to maintain the photo-physical

properties of the core, substitution at the boron atom was explored. Indeed, reports regarding substitution of the fluorine atoms at boron to produce *B*-aryl, *B*-alkenyl, *B*-alkoxy and *B*-aryloxy derivatives have become increasingly common, with dozens of examples of this reactivity having been reported in the past several years. As the introduction of alkyl groups at the boron atom of other *F*-BODIPYs using Grignard reagents has been shown to be successful,[132] we set about investigating the synthesis of carbon-substituted BODIPYs (*C*-BODIPY) from *F*-BODIPY **4-2** (Table 4-1).

Table 4-1: **Alkyl *B*-substitution of *F*-BODIPY 4-2**



4-2 **4-4** **4-5**

Entry	EtMgBr (eq.)	t (h)	T (°C)	4-4 (%)	4-5 (%)
1	5	0.25	22	22	10
2	2.2	2	0	13	3
3	2.2	2	- 44	10	10

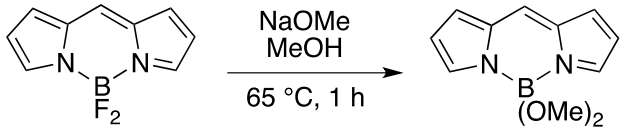
To a solution of **4-2**, five equivalents of ethyl magnesium bromide were added. A red precipitate quickly formed, but returned to solution after several minutes. Analysis of the reaction mixture using TLC revealed complete consumption of the starting material, as well as the formation of several fluorescent products. The reaction was quenched with water and, following phase separation and removal of organic eluent, the product mixture was purified via flash chromatography over silica. The fluorescent product obtained from this procedure was an inseparable mixture of the *C*-BODIPYs **4-4** and **4-5** in a 2.2:1

mixture (entry 1,Table 4-1). Previous studies have shown that *F*-BODIPYs bearing hydrogen at the *meso*-position are susceptible to reaction with alkyl or arylating reagents, to produce the corresponding *meso*-alkyl or *meso*-aryl products.[101] As such, it is unsurprising that products **4-4** and **4-5** were obtained. The products were sufficiently stable so as to enable purification over alumina (4:1 hexanes:ethyl acetate). However, exposure to atmospheric conditions over several hours resulted in decomposition of the materials both in a solution of $CDCl_3$, and as a solid on the benchtop. This decomposition is contrasted by the experimental stability of *C*-BODIPYs in more-substituted dipyrrinato frameworks.[132]

As an attempt to prevent the formation of *C*-BODIPY **4-5**, that is, to limit *meso*-substitution while promoting exchange at boron, the temperature and stoichiometry of the reaction were altered. As exchange at boron is preferred over substitution at the *meso*-position (as evidenced by the ratio of observed products at room temperature), the reaction temperature was cooled to 0 °C. Furthermore, as only two equivalents of EtMgBr should be required for substitution at boron, the amount of EtMgBr used for the reaction was reduced accordingly (Table 4-1, entry 2). While these conditions reduced production of the *meso*-ethyl compound **4-5** (generated in a 1:4 ratio relative to **4-4**), a notable decrease in the overall yield of reaction was also observed. A third reaction was performed at -44 °C (Table 4-1, entry 3) to determine whether the parent dipyrrin **4-2** was playing a role as an intermediate during halogen-alkyl exchange at boron. It was hoped that reducing the temperature below -40 °C would improve stability of the intermediates; however, this trial was unsuccessful in either improving the yield or the selectivity of the reaction.

Substitution at boron to synthesize the corresponding dimethoxy *O*-BODIPY was then investigated. These reactions are generally simple, providing high yields of *O*-BODIPYs when simple alkoxides are employed for exchange.[138] A solution of *F*-BODIPY **4-2** in methanol was treated with six equivalents of sodium methoxide, and the reaction mixture was stirred at room temperature. No reaction was observed by TLC after 30 minutes, and so the reaction was heated at reflux temperature. After an hour, consumption of the starting material was observed, and a new fluorescent product was produced as detected using TLC (Scheme 4-4).

Scheme 4-4: **Alkoxide *B*-substitution of *F*-BODIPY 4-2**



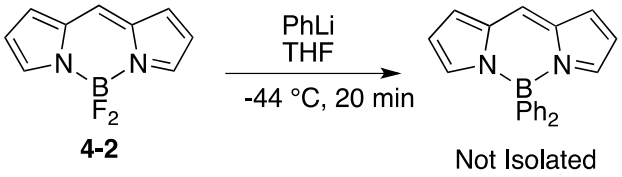
4-2 **4-6**

Repeated attempts to isolate this fluorescent product were made using flash chromatography over silica, as well as basic Brockman III alumina. Unfortunately, the compound proved unstable and decomposed within an hour in air at room temperature. In one instance, the reaction mixture was concentrated and then immediately filtered through a plug of alumina to give a mixture of *O*-BODIPY **4-6** (as identified using ^{1}H NMR and ^{11}B NMR spectroscopy) and two side-products, which could not be identified. The limited stability of *O*-BODIPY **4-6** prevented further characterization.

Synthesis of *B*-aryl BODIPYs from the parent unsubstituted compound **4-2** was also explored (Scheme 4-5).To a solution of **4-2** in THF at -44 °C, a 1.8 M solution of phenyllithium (PhLi, 2.2 equivalents) was added. The mixture was stirred for 20 minutes, after which no starting material could be detected using TLC analysis. The solution was quenched with water, and purified using flash chromatography over alumina. Only a trace

of a fluorescent product could be obtained, with the majority of the material consisting of red decomposition products. Neither *C*-BODIPYs nor *O*-BODIPYs have been singled out in the literature for their general instability, further hinting at the role the unsubstituted framework plays in decomposition of these products.[132]

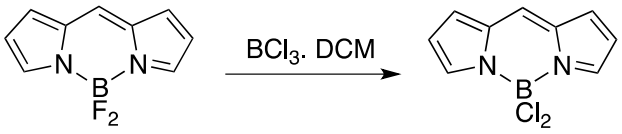
Scheme 4-5: **Attempted Phenyl *B*-substitution of *F*-BODIPY 4-2**



4-2 Not Isolated

With the results of these attempts in hand, a second approach to introducing alkyl and alkoxy substituents was explored. Introduction of chlorine atoms at boron is facilitated by treatment of *F*-BODIPYs with BCl_3 under anhydrous conditions.[101] *Cl*-BODIPYs have been shown to possess analogous reactivity at their boron atom, relative to *F*-BODIPYs. However, the conditions required to induce substitution are typically less harsh. In an attempt to determine whether reactivity might be induced using a *Cl*-BODIPY, the synthesis of the unsubstituted *Cl*-BODIPY **4-7** was carried out (Scheme 4-6).

Scheme 4-6: **Chloro *B*-substitution of *F*-BODIPY 4-2 to generate *Cl*-BODIPY 4-7**



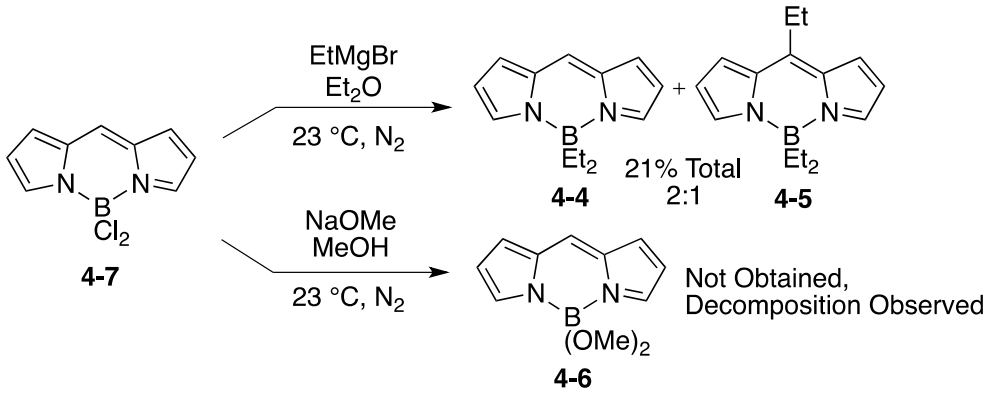
4-2 **4-7**, 99%

As *Cl*-BODIPYs are sensitive to moisture, they must be handled and stored in an inert environment to prevent decomposition. To produce *Cl*-BODIPY **4-7**, a solution of **4-2** in CH_2Cl_2 was prepared in the glove box, and charged with a single equivalent of BCl_3 (1.0 M in hexanes). The mixture was stirred for an hour, during which the solution

transitioned from a deep, red-purple colour to that of a lighter brick red. The mixture was filtered over Celite to remove a black, sticky precipitate that had formed. Evaporation of the solvent revealed the brick red *Cl*-BODIPY **4-7** in seemingly quantitative yield (99%). As is typical of *Cl*-BODIPYs, exposure to air over several hours lead to decomposition, and in this case, formation of a tar-like substance.

Formation of *C*- and *O*-BODIPYs **4-4** and **4-6** was thus attempted from the *Cl*-BODIPY starting material, **4-7**. In the glove box, two solutions of **4-7** were prepared such that the conditions for the methoxy and ethyl addition to *F*-BODIPY **4-2** were repeated (Scheme 4-7).

Scheme 4-7: **Attempted *B*-substitution of *Cl*-BODIPY 4-7**



It was hoped that addition of ethylmagnesium bromide to the *meso* position would be less preferred, due in-part to the increased lability of the chlorine atoms at the boron centre, relative to that of fluorine. Unfortunately, similar results were obtained, as the *meso*-H and *meso*-ethyl products (**4-4** and **4-5**) were obtained in approximately a 2:1 ratio (similar to the results obtained using *F*-BODIPY **4-2** as a starting material). In the case of formation of *O*-BODIPY **4-6** from **4-7**, the addition of sodium methoxide in dichloromethane at room temperature was sufficient to promote reaction. The brick-red

colour of solution was replaced by a dark, opaque solution. As with the reaction utilizing *F*-BODIPY **4-2** as a starting material, the fluorescent-product was unisolable, as decomposition hindered purification or analysis using NMR techniques.

As the di-methoxylation of **4-2** and **4-7** was unsuccessful, and as similar conditions can be used to generate *O*-BODIPYs from *F*-BODIPYs in more substituted systems, a NMR experiment was performed to ascertain the outcome of the reactants. As in Scheme 4-7, a sample of compound **4-7** was dissolved in MeOD in a NMR tube under a nitrogen atmosphere, and sodium methoxide was added as a solid. The NMR tube was then sealed, and the mixture was sonicated for 60 seconds such that both the *Cl*-BODIPY and methoxide were dissolved. The reaction was then monitored using ^{11}B NMR spectroscopy. In addition to the signal expected for the *Cl*-BODIPY, a second singlet was observed at 2.45 ppm corresponding to the *O*-BODIPY **4-6**. The ratio of this signal with respect to the *Cl*-BODIPY grew as time passed, until the 5-hour mark where the two signals were observed in approximately equal ratio. The signals then began to decrease relative to the baseline signal of the spectra, and after 24 hours only a small signal corresponding to **4-6** was visible. No signal corresponding to the *Cl*-BODIPY was present, and the formation of a black, tar-like film on the inside of the NMR tube was observed. This evidence demonstrates that despite *B*-methoxylation occurring on **4-6** relatively quickly, gradual decomposition of both the starting material and product also occurs on a reasonably short time-scale.

To summarise our experimental findings, BODIPYs of the unsubstituted dipyrrinato skeleton are significantly less stable than those of substituted variants:[28,125,137,139-141] our experimental work indicates a relative stability of F > Cl > C >

O with respect to substitution at boron. Although the decomposition of BODIPYs is documented,[142] theoretical studies for potential decomposition mechanisms are limited.[87] Thus, through collaboration with Dr. Chérif Matta and co-workers at Mount St. Vincent University, theoretical methods were employed[143] to examine the B–N bonds in compounds **4-2**, **4-4** and **4-6**, as well as pathways through which decomposition might occur. Several descriptors of the B–N bond strength in BODIPYs **4-2**, **4-4** and **4-6** were calculated at the B3LYP/6-311++G(d,p)//B3LYP/6-311++G(d,p) level of density functional theory (Table 4-2).

Table 4-2: **Calculated B–N bond descriptors of BODIPYs 4-2, 4-4 and 4-6**

Compound	Length (Å)	Frequency (cm^{-1})	Force Constant (millidyne/Å)	Ionicity (a.u.)
4-2 (F)	1.392	1165.5	5.265	3.630
4-4 (Et)	1.599	1126.4	3.023	3.233
4-6 (OMe)	1.603	1138.4	3.207	3.570

Ionicity of the bond is defined as: q(B) – q(N), the difference in the charges of the boron and nitrogen atoms.

These descriptors demonstrate the relatively strong and short B–N bond in **4-2**; within the other derivatives, the symmetric stretch vibrational frequencies (ν) reflect this trend. In addition, the force constants associated with these stretches indicate that the B–N bond in **4-2** is substantially more rigid (less deformable) than in the other compounds. These observations correlate well with our experimental results (*i.e.*, *F*-BODIPY is most stable), but these data are insufficient to account for the extreme instability of the *O*-BODIPY **4-6** (least stable experimentally) under both atmospheric and inert conditions, particularly since the calculated strengths of the B–N bonds in **4-4** and **4-6** are approximately equal.

To explore the formal loss of BX_2^+ for decomposition, the thermochemical properties of these compounds in their complexed and dissociated states were calculated (Table 4-3).

Table 4-3: **Calculated energies of the hypothetical dissociation reactions of BODIPYs 4-2, 4-4, and 4-6**

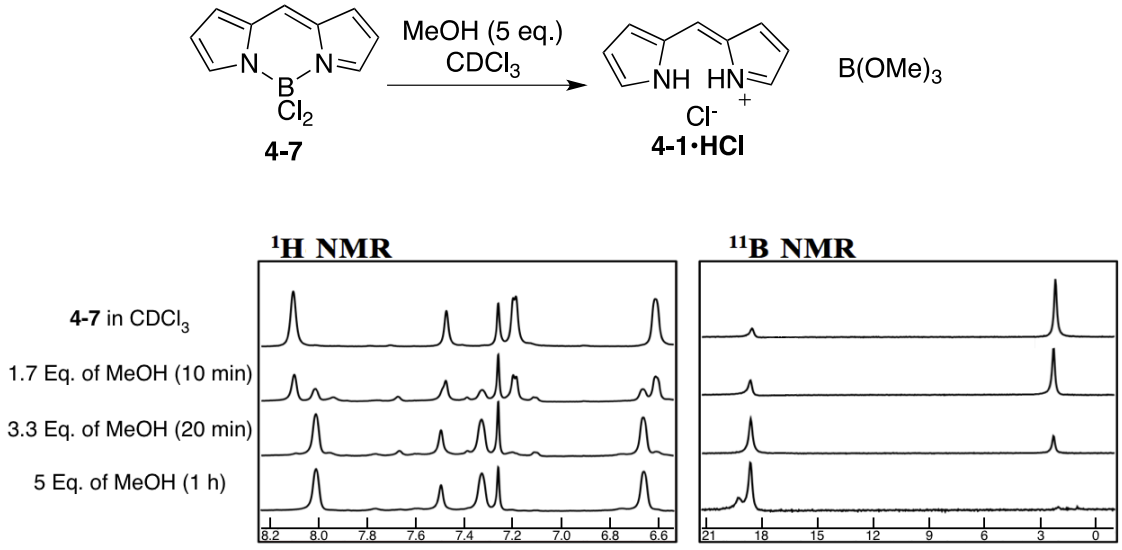
Compound	Δ***G*** (kcal/mol)	Δ***H*** (kcal/mol)	Δ***E*** (kcal/mol)
4-2 (F)	267.7	280.2	283.3
4-4 (Et)	183.7	201.0	205.9
4-6 (OMe)	174.2	192.6	195.5

As the B–N bond in the *F*-BODIPY **4-2** is chemically robust, the formal dissociation of BF_2^+ from **4-2** would be expected to be highly unfavoured. Indeed, the energy of dissociation is >80 kcal mol^{-1} higher for **4-2** than for **4-4**. Notably, the calculated trend indicates that the dimethoxy variant **4-6** exhibits the lowest energies of dissociation and that the *Et*-BODIPY **4-4** is intermediate in stability: thus F > C > O, which matches our experimental observations. While further studies are required to fully understand potential mechanism(s) of decomposition, these preliminary investigations offer rationale for the synthetic work.

During laboratory analysis of *Cl*-BODIPY **4-7**, a ^{11}B NMR spectrum was obtained using deuterated methanol (MeOD) as a solvent. In addition to the expected BODIPY signal, an additional small signal was observed at 18.5 ppm. This signal is shifted further downfield than has been reported for *O*-BODIPYs, and matches the expected shift for $B(OMe)_3$, which was itself was generated by addition of BCl_3 to excess

methanol over several minutes. The solution of **4-7** in MeOD was allowed to sit over a five-hour period. During this time, the ratio of *Cl*-BODIPY signal to the new $B(OMe)_3$ signal began to decrease. After twenty-four hours in solution, no trace of the chloro compound could be seen, and the signal at 18.5 ppm remained. To better visualize this change, methanol (5 equivalents) was added in four aliquots to a solution of **4-7** in $CDCl_3$, and ^1H and ^{11}B NMR spectra were acquired immediately following the addition of each aliquot (Figure 4-3).

Figure 4-3: **^1H and ^{11}B NMR spectra of addition to MeOH to 4-7 in $CDCl_3$**



The ^1H signals for **4-7** decreased, as a new set of peaks formed in the aromatic region accompanied by the emergence of an N–*H* signal at 14.6 ppm integrating for two protons. The signal at 14.6 ppm is consistent with those for N–*H* units within HX salts of dipyrrins. Concurrently, the ^{11}B singlet for $B(OMe)_3$ at 18.5 ppm appeared as the ^{11}B singlet at 2.26 ppm for **4-7** disappeared. A new set of peaks in the ^{13}C NMR spectrum was also obtained. These results were reproducible through the single addition of five equivalents of methanol to **4-7** with stirring for 30 minutes. These new signals are

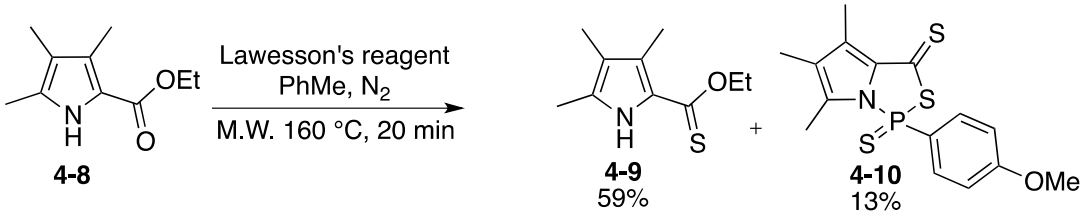
indicative of the unsubstituted dipyrrin salt **4-1•HCl**, presumably formed after the *Cl*-BODIPY **4-7** was converted to the dimethoxy variant **4-6**, which then decomplexed[100] to form **4-1**. Under these conditions, **4-1** was protonated to give the hydrochloride salt. As such salts are more stable than the corresponding free-base dipyrrins,[22,97] this method of accessing unsubstituted dipyrrin **4-1** facilitated the first NMR characterization of the compound. ESI^+ mass spectral analysis after 30 minutes revealed a base peak at 289.1 *m*/*z* corresponding to the protonated dimer $[2M + H]^+$ of **4-1**, plus signals for monomeric, trimeric and tetrameric ions. These results matched those obtained for the highly unstable free-base sample of **4-1** prepared by oxidation of dipyrromethane **4-3** (Scheme 4-3, step 1). Thus, methanol decomplexes *Cl*-BODIPY **4-2** to enable the synthesis and characterization of the HCl salt of the unsubstituted dipyrrin **4-1,** which is sufficiently stable to enable characterization in solution.

Finally, methanol (5 equivalents) was added to a solution of **4-7** in anhydrous dichloromethane under nitrogen. After 30 minutes, analysis using ^1H and ^{11}B NMR spectroscopy confirmed that decomplexation had occurred, and that **4-1•HCl** had again been formed. BCl_3 (5 equivalents) was then added, and the reaction mixture was stirred for an hour before work-up and analysis. The ^1H spectrum revealed two sets of pyrrolic signals: one for *Cl*-BODIPY **4-7** and another for the dipyrrin salt **4-1•HCl**. The ^{11}B spectrum featured the *Cl*-BODIPY **4-7** at 2.26 ppm, alongside signals for $B(OMe)Cl_2$, $B(OMe)_2Cl$ and $B(OMe)_3$, as well as two unassigned signals. This experiment demonstrates that, not only can the dipyrrin be generated from the *Cl*-BODIPY, but that there is potential for the formation of other BODIPYs subsequent to the *in situ* formation of **4-1**.

4.2.2 One-Pot Synthesis of *F*-BODIPYs from Knorr-Type Pyrroles

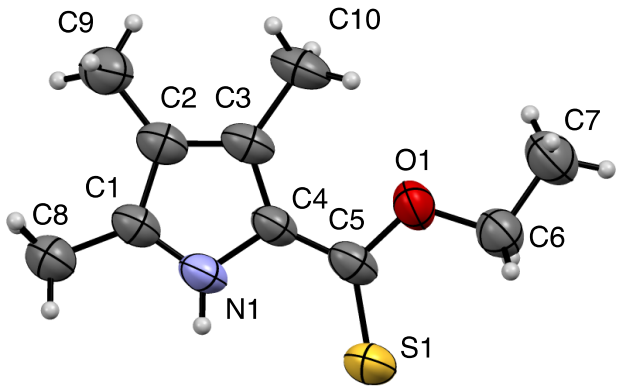
As mentioned earlier in this chapter, the synthesis of *F*-BODIPYs has remained largely unchanged for over forty years (Scheme 4-1). As such, novel methods for generating *F*-BODIPYs are of great interest to the synthetic community. One such synthetic method was discovered serendipitously during the optimization of another synthetic methodology, the sulfination of 2-pyrrole carboxylates (Scheme 4-8). Preliminary work for the 2-pyrrole sulfination reaction was performed by Dr. Deborah Smithen at Dalhousie University. For further contributions, including optimization and scope of the sulfination reaction, please refer to *RSC Adv.*, 2016, **6**, 69691-69697 (DOI: 10.1039/C6RA14809C).[144]

Scheme 4-8: **Generation of thionoester 4-9 and 1,3,2-thiazaphosphole 4-10**



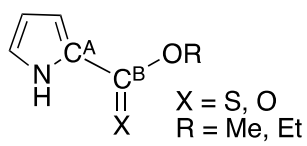
The sulfination work began with the reaction of ethyl 2-pyrrole carboxylate **4-8**, an alkyl substituted pyrrole readily available *via* Knorr-type condensation. Rather than endure the long reaction times often reported for successful thionation using Lawesson's reagent,[145] the transformation was expedited through the use of microwave-assisted heating. The outcome of this reaction, according to analysis using TLC, was complete consumption of the starting material and the generation of two new compounds. Upon isolation, one of these compounds was identified as the desired product **4-9**, isolated in a 59% yield. The structure of **4-9** was confirmed using X-ray crystallography (Figure 4-4).

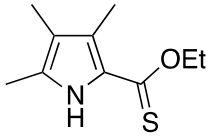
Figure 4-4: **ORTEP view of the molecular structure of pyrrolic 2-thionoester 4-9 with thermal elipsoids shown at 50%**



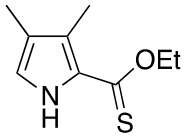
Selected bond lengths (pm) and angles (°): C4-C5: 141.8(4), C5-S1: 166.9(2), C5-O: 136.9(3), C4-C5-S1: 125.1(2), S-C5-O1: 123.8(2), C4-C5-O1: 118.6(2).

Table 4-4: **Selected geometric parameters of *O*-thionoesters and related starting materials**

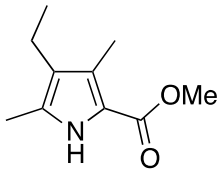




4-9



4-11



4-12

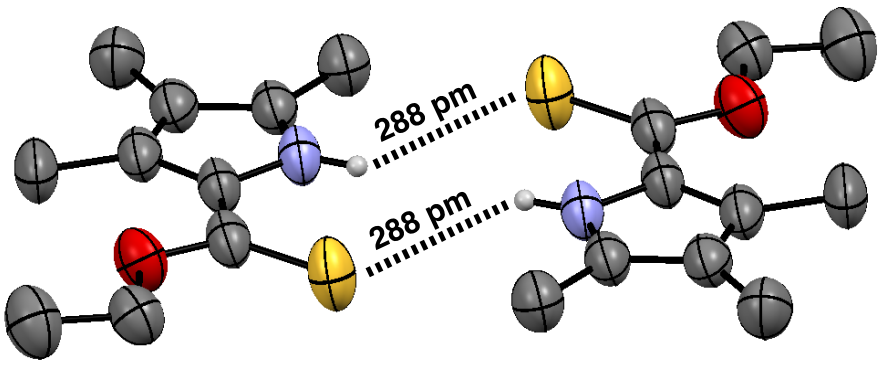
Pyrrole	C^A-C^B (pm)	C^B-X (pm)	C^B-O (pm)	C^A-C^B-X (°)	X-C^B-O (°)	C^A-C^B-O (°)
4-9	141.8(4)	166.9(2)	136.9(3)	125.1(2)	123.8(2)	118.6(2)
4-11	143.2(2)	164.98(16)	134.03(19)	124.48(12)	124.00(12)	111.52(13)
4-12	1.431(5)	121.4(4)	134.0(4)	125.6(3)	121.9(3)	112.5(3)

Only a single example of a pyrrolic 2-thionoester analogous to **4-9** is reported in the literature: the structure of this pyrrole is similar to **4-9**, save the replacement of the

distal, 5-methyl (C8) with a hydrogen atom (**4-11**, Table 4-4).[146] Selected geometric parameters of these *O*-thionoesters, as well as values for a related literature pyrrole, methyl 4-ethyl-3,5-dimethyl-1H-pyrrole-2-carboxylate (**4-12**),[147] are shown in Table 4-4.

There are significant structural differences between compound **4-9** and literature structures **4-11** and **4-12**. For example, the bond lengths between C^A and C^B, and C^B and O are significantly different in **4-11** and **4-12** as compared to **4-9**. This difference arises due to variations in crystal packing, as both reference compounds crystallized in monoclinic space groups (*P*21/*c* for **4-11** and *P*12/*n*1 for **4-12**), while **4-9** crystallized in the triclinic *P*(-1) space group. The reference compounds crystallized as sets of planar, centro-symmetric dimers that are bridged via hydrogen bond interactions between the *N*-H hydrogen and the carbonyl or thiocarbonyl groups of the adjacent molecule. The crystal structure of **4-9** displays the same N-H---S bridging pattern, but without the centro-symmetry present in the literature compounds.

Figure 4-5: **ORTEP view of dimeric bridging in the crystal lattice of pyrrolic 2-thionoester 4-9 with thermal elipsoids shown at 50%**

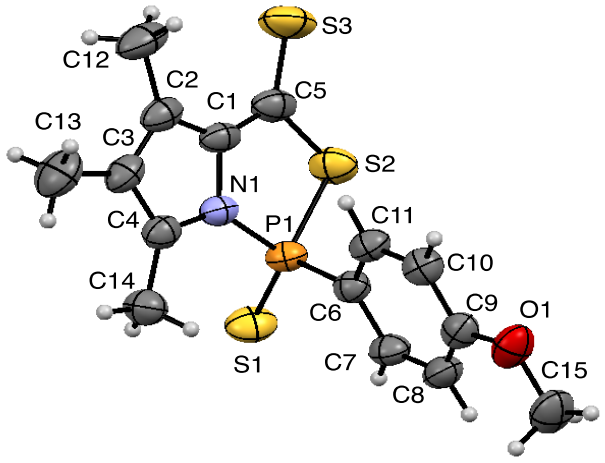


This type of non-centro-symmetric, N–H---S=C linked dimer has been previously described in the form of a related moropholine-dithione derivative.[148] This orientation is less-tightly packed relative to the monoclinic examples **4-11** and **4-12**. This is displayed

in the H---S bridging bond length: for reference, compound **4-11** exhibits a H---S hydrogen bond distance of 269.(2) pm within the crystal lattice, while **4-9** displays a H---S distance of 288.(3) pm. The C-S bond length of the thionyl group of **4-9** falls within expected parameters for Csp^2=S bonds,[149] and is in good agreement with the values observed for **4-11**. The bond angles surrounding C^B are much closer to ideal (120°) than is observed for either reference compounds, which is likely a result of reduced strain within the packing structure.

The second compound isolated from the original reaction, **4-10**, was more challenging to identify, with peaks in the NMR spectra that derived both from the pyrrole **4-8** and Lawesson's reagent starting materials. Fortunately, crystals suitable for X-ray crystallography were again obtained, enabling the unknown compound to be identified as 1,3,2-thiazaphosphole **4-10** (Figure 4-6).

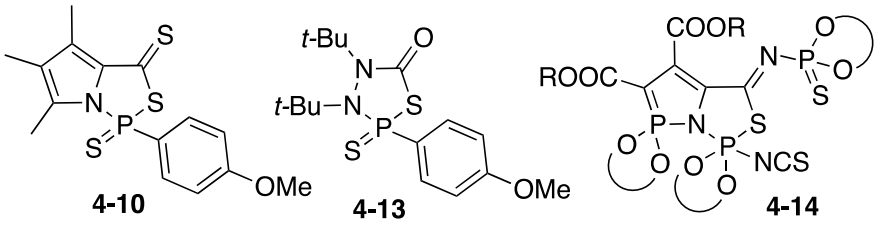
Figure 4-6: **ORTEP view of the molecular structure of 1,3,2-thiazaphosphole 4-10 with thermal ellipsoids shown at 50%**



Selected bond lengths (pm) and angles (°): P1-N1: 170.94(13), P1-S1: 192.35(6), P1-S2: 211.15(6), C1-C5: 139.7(2), C5-S2: 178.26(18), C5-S3: 165.10(18), N1-P1-S2: 92.81(5), P1-S2-C5: 96.50(6), S2-C5-C1: 113.28(12), C5-C1-N1: 117.55(14).

The thiazaphosphole functional group (N-P-S) is well described in the literature. However, no examples of pyrroles bearing this functionality could be found. Four, five and six-membered cyclic thiazaphospholes are well studied, and many related crystal structures are readily available from the Cambridge Crystallographic Data Centre (CCDC). X-ray crystal structures of the four-membered variety are typically obtained as metal complexes of the N-P-S bridging moiety. Molecules bearing main-group elements as the fourth atom of the ring are less common, but well described in the literature. However, no crystallographic data for these compounds were available for retrieval from the CCDC database. Five-membered thiazaphosphole rings are more frequently described than the four-membered variety. When limiting the fourth and fifth atoms of the ring to main group elements, and Lawesson's reagent as the sulfur source, dozens of known compounds can be found in the literature. Of these, only one compound (**4-13**) has been analyzed using X-ray crystallography. Table 4-5 contains selected geometric parameters for **4-10** and **4-13**,[150] as well as for the literature compound **4-14** that contains an analogous penta-carbothiazaphosphole ring.[151] **4-14** is derived from the phosphorous azide, $CH_2[6\text{-}t\text{-Bu-4-Me-}C_6H_2O]_2PN_3$. The bond parameters of compound **4-10** are within expected ranges for the carbothiazaphosphole system (Table 4-5). The Lawesson's reagent-derived compounds with tetra-coordinate phosphorous atoms, **4-10** and **4-13**, share similar N-P bond lengths of 170.94(13) and 170.8 pm, respectively. These values are quite long for bonds of the type $X_2\text{-}P(=X)\text{-}NX_2$, which are typically near 165 pm for compounds bearing sp^2 nitrogen atoms.[149]

Table 4-5: **Selected geometric parameters of compounds bearing five-membered thiazaphosphole rings**



Compound	N–P (pm)	P–S (pm)	N-P-S (°)	N-P-S-C (°)
4-10	170.94(13)	211.15(6)	92.81(5)	3.50
4-13	170.8[a]	210.8 [a]	94.93 [a]	30.93[a]
4-14	177.2(4)	210.1(2)	90.41[a]	20.03[a]

[A] Bond distances and angles were derived using raw coordinate data; error values were unreported in literature[150,151]

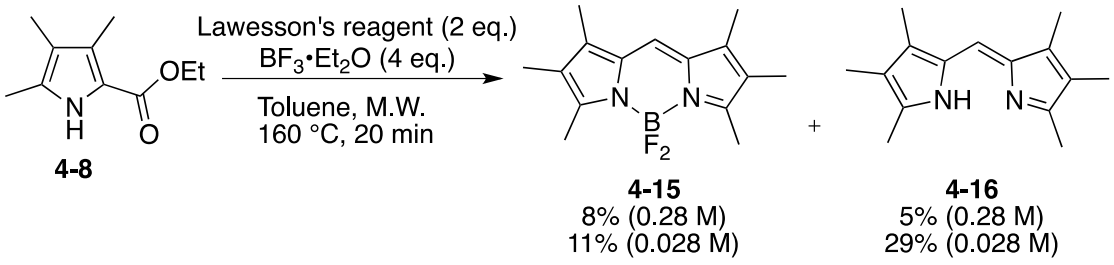
The penta-coordinate phosphorous atom in **4-14** has a longer P-N bond, at 177.2(4) pm, but is in a significantly different chemical environment. The length of the P-S bonds in all three compounds is relatively consistent, considering the significant differences in their surrounding environments, and is within expected values. The bite-angle of the N-P-S functionality in **4-10** falls within a reasonable value, being smaller than that found in **4-13**, but slightly larger than in **4-14**.

Unlike the literature examples, the penta-carbothiazaphosphole ring of **4-10** lays almost exactly in plane. This can be seen in the dihedral angles of the of the N-P-S-C atoms of the three compounds. **4-10** shows only a mild deviation from planarity (3.50°), while the other two systems differ significantly, adopting non-planar puckered conformations in their crystal structures. This planarity is likely due to the forced sp^2 geometry of the binding *N* atom in the pyrrole ring, which is not present in **4-13**, and is significantly reduced by the sp^3 nature of the neighbouring phosphoros atom in **4-14**.

Indeed, the bond angles surrounding the *N* and X^A atoms of **4-10** are closer to ideal for sp^2 hybridized atoms than in either **4-13** or **4-14**. The sum of the interior bond angles for the pentacarbothiazaphosphole ring of **4-10** is 539.73°, very close to the ideal value of 540° expected for a planar five-membered ring system. The pyrrole ring and the penta-carbothiazaphosphole rings are almost coplanar, with dihedral angles of no more than 3.5° between their atoms. The structural features of the pyrrole ring in **4-10** are not significantly different from expected values, and compare well with the pyrroles found in the crystal structures of **4-9** and **4-11** (Table 4-4).

With a firm understanding of the products of thionation in hand courtesy of Dr. Smithen, I attempted to optimize the thionation reaction through the inclusion of a Lewis acid. However, rather than enhance the yield of the thionation product **4-9**, the addition of $BF_3{\cdot}Et_2O$ resulted in the generation of a fluorescent material, alongside decomposition products. Cognizant of the rich chemistry offered by pyrroles, elucidation of the fluorescent material as *F*-BODIPY **4-15** was indeed satisfying (Scheme 4-9).

Scheme 4-9: **Generation of *F*-BODIPY 4-15 and dipyrrin 4-16 using Lawesson's reagent**



A slurry was prepared consisting of 100 mg of **4-8**, two equivalents of Lawesson's reagent and 1 mL of anhydrous toluene in a 5 mL microwave vial under nitrogen. Four equivalents of $BF_3{\bullet}Et_2O$ were added to the solution, and the mixture was

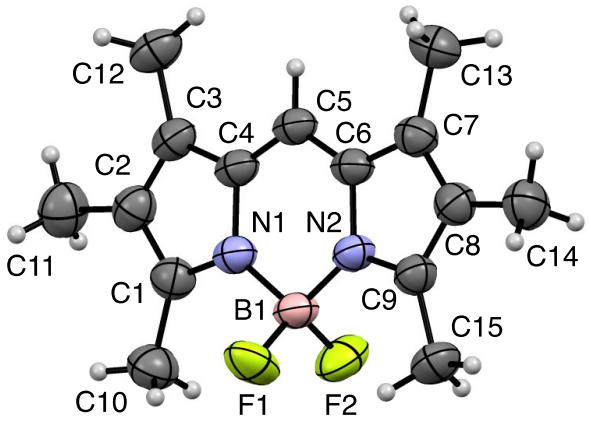
then subjected to microwave heating at 160 °C for 1.5 hours. Following the reaction, a large amount of precipitate had adhered to the walls of the vial. The previously pale white slurry had formed a black, sticky suspension. The precipitate was insoluble in most common solvents (toluene, hexane, ethyl acetate, dichloromethane, methanol), but could be dissolved in acetone. Analysis of the ^{1}H NMR spectrum revealed that the precipitate consisted of a complex mixture of Lawesson's based impurities, and had none of the characteristic signals of the starting material pyrrole.

TLC analysis of the filtrate revealed the presence of the desired *F*-BODIPY **4-15**. To isolate this material, the reaction mixture was diluted with 2 mL of ethyl acetate, sonicated for 5 minutes (to ensure breakup of precipitate and dissolution of any residual *F*-BODIPY), and then poured into ethyl acetate:hexanes (3:7). The mixture was then filtered through neutral alumina to remove the insoluble impurities. Purification was performed over neutral alumina using an eluent gradient consisting of dichloromethane:hexanes (5:95→20:80). Two impurities eluted with the *F*-BODIPY product, one at the head of the elution band and another at the tail. Thus, several chromatographic runs were required to obtain satisfactorily pure product. 1D and 2D NMR techniques, crystallization, and mass spectrometry were used in an attempt to elucidate the structure of the impurities, to no avail. The impurities bore structural features of Lawesson's reagent as well as BF_3•Et_2O, but not pyrrole. Attempts to recreate these products through combination of Lawesson's reagent with BF_3•Et_2O in the absence of pyrrole were not successful. Following the elution of all mobile substrates in the dichloromethane:hexane system, the solvent was changed to ethyl acetate:hexanes (1:19), and a small amount of the intermediate product dipyrrin **4-16** was isolated (5% yield).

Performing the same reaction at ten-fold dilution allowed for isolation of the symmetric free-base dipyrrin **4-16** in 29% yield. Unfortunately, the increase in isolable dipyrrin did not correlate to a significant increase in the yield of the desired *F*-BODIPY **4-15** (11%).

Despite the staggering number of known *F*-BODIPY structures in the crystal literature, compound **4-15** is as-yet unreported. Crystalline **4-15** was obtained via slow evaporation of layered dichloromethane and hexanes (Figure 4-7).

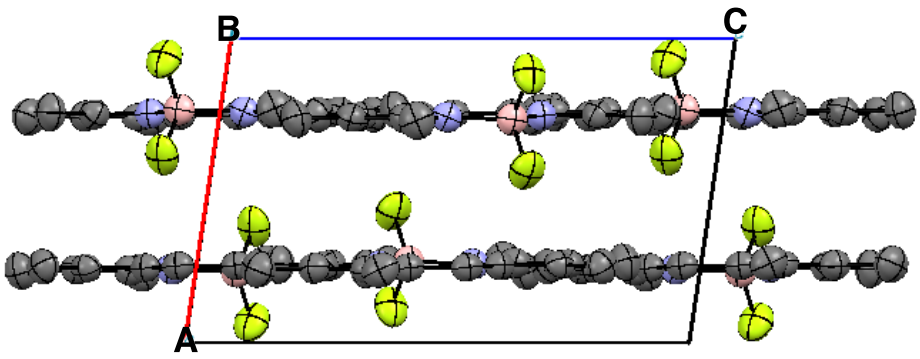
Figure 4-7: **ORTEP view of the molecular structure of *F*-BODIPY 4-15 with thermal elipsoids shown at 50%**



Selected bond lengths (pm) and angles (°): B1-F1: 139.5(2), B1-F2: 138.8(2), B1-N1: 154.9(3), B1-N2: 155.0(2), F1-B1-F2: 108.97(17), F1-B1-N1: 110.49(16), F1-B1-N2: 109.76(18), F2-B1-N1: 110.31(18), F2-B1-N2: 109.83(16), N1-B1-N2: 107.47(15)

The bond lengths and angles of **4-15** correlate well with literature values for related structures.[152] *F*-BODIPY **4-15** forms red crystals in the monoclinic space group $P2_1/n$. The carbon backbone is essentially flat, with little deviation from planarity (Figure 4-8).

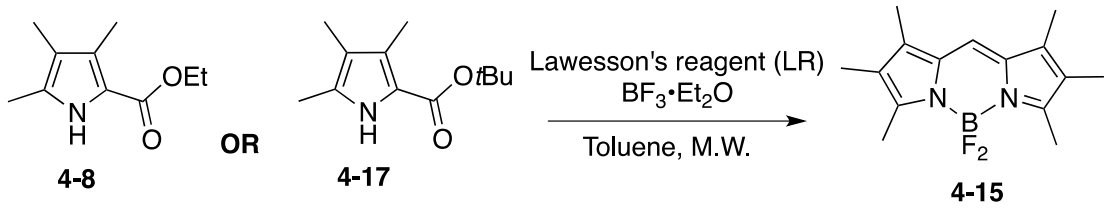
Figure 4-8: **ORTEP view of the molecular packing of *F*-BODIPY 4-15 along the *b*-axis, hydrogen atoms omitted for clarity**



As a result of molecular packing, the otherwise symmetric fluorine and nitrogen atoms are in different atomic environments, with B-F bond lengths of 139.5(2) and 138.8(2) pm, and B-N bond lengths of 154.9(3) and 155.0(2) pm. The *F*-BODIPY molecules exhibit π-π interactions, and stack in plane with one another to form channels along the *b*-axis of the crystal lattice.

Attempts were made to optimize the conditions of the reaction. During examination of the scope of reaction, it was discovered that pyrroles bearing a *t*-butyl ester, rather than an alkyl or benzyl ester, reacted more cleanly and the product mixture contained fewer insoluble, black side products. Rather, a sticky, red, insoluble film formed on the walls of the vessel, while the solution was clear and coloured a vibrant red. Unfortunately, the impurities described previously persisted. As reactions containing the *t*-butyl ester were more easily handled and purified, *t*-butyl 3,4,5-trimethylpyrrole-2-carboxylate, **4-17**, was used in conjunction with ethyl ester **4-8** to optimize the reaction conditions (Table 4-6).

Table 4-6: **Reaction optimization using pyrroles 4-8 and 4-17**



Entry	Pyrrole	T (°C)	t (min)	Vol. (mL)	LR (eq.)	$BF_3•Et_2O$ (eq.)	4-15 (%)
1	**4-17**	23	24 h	1	2	4	-[a]
2	**4-17**	100	20	1	2	4	< 1
3	**4-17**	120	20	1	2	4	5
4	**4-17**	140	20	1	2	4	12
5	**4-17**	160	20	1	2	4	12
6	**4-17**	180	20	1	2	4	10
7	**4-8**	160	20	0.5	2	4	-[b]
8	**4-8**	160	20	2	2	4	5
9	**4-17**	160	20	10	2	4	10
10	**4-17**	175	20	10	2	4	8
11	**4-17**	200	60	10	2	4	5
12	**4-17**	160	20	1	2	4	-[c]
13	**4-17**	160	20	1	2	4	-[d]
14	**4-17**	160	20	1	2	4	-[e]
15	**4-17**	160	20	10	2	4	-[f]
16	**4-17**	160	20	10	2	4	-[g]
17	**4-17**	160	20	10	2	10	8

Entry	Pyrrole	T (°C)	t (min)	Vol. (mL)	LR (eq.)	BF_3•Et_2O (eq.)	4-15 (%)
18	**4-8**	160	20	1	0	1.1	< 1
19	**4-8**	160	20	1	0	4	< 1
20	**4-8**	160	20	1	1	4	4

[a] Starting material was reclaimed without decomposition. [b] Decomposition of all pyrrolic products was observed. [c] THF was used as solvent. [d] DMSO was used as solvent. [e] $(CH_2OH)_2$ was used as solvent. [f] 1 equivalent of HCl (5 M, aqueous) added to reaction. [g] 1 equivalent of NaOH (5 M, aqueous) added to reaction.

As a control, **4-17** was combined with the reagents at room temperature in toluene without heating (Entry 1). No formation of *F*-BODIPY was observed and starting material was recovered, although addition of BF_3•Et_2O did result in a change of colour of the solution from colourless to yellow after several minutes. Allowing the reaction mixture to stir for 24 hours did not promote the reaction. As initial observation of a *F*-BODIPY had been seen at 160 °C (Scheme 4-9), the next trial was performed using microwave-promoted heating at 100 °C. While a small amount of *F*-BODIPY could be visualized after the reaction using TLC under long-wave irradiation (365 nm), none was isolable. The temperature was increased in 20 °C increments (Table 4-6, entries 2-6), and the product reached a yield (12%) that was comparable to the initial result for pyrrole **4-8** at 160 °C (Scheme 4-9). Further heating did not improve the yield of reaction and only resulted in thickening and blackening of the reaction mixture. Upon heating **4-17** at 180 °C, the reaction mixture became darker and the presence of insoluble Lawesson's-based decomposition products became problematic.

To determine whether concentration significantly affected the reaction, pyrrole **4-8** was reacted at twice the concentration (0.5 mL of solvent) at 160 °C for 20 minutes (entry 7). Under these conditions, all pyrrolic products were decomposed, and a black sticky substrate was obtained. Repeating this reaction using twice the dilution (entry 8)

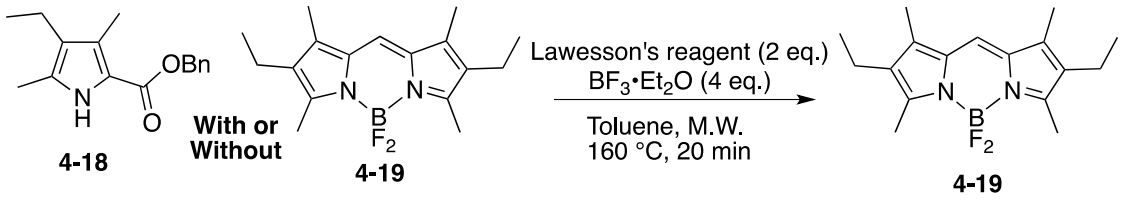
produced a 5% yield of **4-17**, similar to that obtained without dilution. In an effort to further reduce the formation of decomposition products, another trial was run using pyrrole **4-17** at 160 °C, but diluted 10 times (entry 9). This resulted in a dramatic decrease in the amount of precipitation products. Furthermore, a more facile workup could be achieved, such that dry loading of the reaction mixture directly onto the column was feasible (mitigating potential loss of *F*-BODIPY by adherence to the precipitates). However, the 10% yield of this reaction was comparable to that obtained under the more concentrated conditions. Another diluted reaction was run at 175 °C for 20 minutes, and another at 200 °C for an hour (entries 10 and 11). While formation of decomposition products was mitigated at 175 °C, it was not at 200 °C and the reaction vessel became black at this higher temperature, as with the reaction involving ethyl ester **4-8**. Neither set of conditions yielded greater amounts of product, and instead hindered formation of the *F*-BODIPY.

Several solvents were then explored for reaction. Using pyrrole **4-17**, a reaction was run in THF (entry 12). Only a trace amount of *F*-BODIPY was detectable when the reaction mixture was analyzed using TLC. High boiling point solvents were also explored. DMSO (aprotic, entry 13) and ethylene glycol (protic, entry 14) were tested. However, both solvents hindered the formation of *F*-BODIPY product. The addition of strong acids and bases (HCl and KOH) in single equivalent amounts (5 M aqueous solutions) did not aid in furthering the reaction (entries 15 and 16). Formation of fluorescent *F*-BODIPY product in these cases was inhibited entirely, most likely due to the aqueous conditions quenching the BF_3•Et_2O reagent.

Varying equivalents of Lawesson's reagent and BF_3•Et_2O were also explored (entries 17-20). Addition of excess BF_3•Et_2O (10 equivalents, entry 17) was explored, as typically excess is required for the synthesis of *F*-BODIPYs via traditional methods.[152] While this did not aid in improving the yield of the reaction (8%), it did not significantly reduce it. To determine whether the microwave-promoted conditions (160 °C, 20 min) were responsible for formation of **4-15**, and not necessarily the sulfur source, the reaction was repeated in the absence of Lawesson's reagent (entries 18 and 19). A trace amount of fluorescent material (reminiscent of *F*-BODIPY) was visible via TLC analysis. However, no isolable amount of product was obtained using either 1.1 or 4 equivalents of BF_3•Et_2O. These experiments confirm that the Lawesson's reagent is indeed responsible for inducing formation of the *F*-BODIPY product under these conditions. It should be noted that considerable effort was placed on attempting to generate *F*-BODIPY **4-15** from the thionoester **4-9** (Scheme 4-8), under conditions similar to those used to generate **4-15** from pyrrole **4-8**. Ultimately, this was not shown to provide any significant improvement to the yield of the reaction.

One possible cause for the poor yield of the *F*-BODIPYs is product loss due to instability under the reaction conditions. A series of experiments was run to determine the degree to which *F*-BODIPY degrades under microwave heating (Table 4-7). As a reference, a reaction using the 4-ethyl substituted, benzyl-ester pyrrole **4-18** was performed (15%, entry 1). This substrate was selected as a substantial quantity of the product *F*-BODIPY, **4-19**, was readily available for testing.

Table 4-7: **Reactions measuring product degradation under optimized conditions**

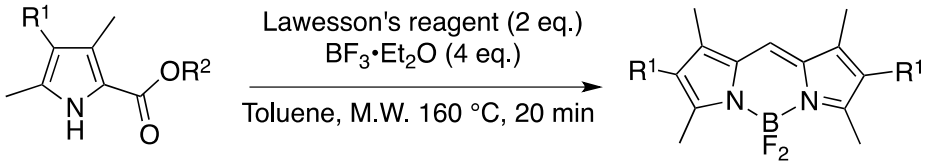


Entry	4-18 (mg)	4-19 In (mg)	Vol. (mL)	4-19 Out (mg)
1	100	0	1	12 (15%)
2	0	50	1	18 (36%)
3	100	50	1	27
4	0	100	1	trace
5	0	100	10	100

Subsequently, **4-19** was reacted under the same conditions to determine whether *F*-BODIPY can survive under these conditions (entry 2). Only 18 mg (36%) of the starting material was recovered. This indicates that, in the presence of Lawesson's reagent and BF_3•Et_2O, the *F*-BODIPY is not stable. A third reaction was run using both pyrrole and *F*-BODIPY starting material (entry 3). In this case, the isolated yield (27 mg) is approximately equal to the sum of the amounts of product we expected to be either generated from pyrrole, or to have survived the conditions based on the previous experiments (entries 1 and 2, 12 mg + 18 mg). Entries 4 and 5 demonstrate the significant effect that concentration has on reaction: doubling the concentration of **4-19** present prior to heating (relative to entry 2) resulted in near complete decomposition of the *F*-BODIPY (entry 4). Conversely, no deterioration of **4-19** was observed when the reaction was diluted by 10 times (entry 5).

The substrate scope of this reaction to produce *F*-BODIPYs was probed using a variety of readily available pyrroles (Table 4-8). The formation of *F*-BODIPY occurred in humble yields (between 9-18%) for the pyrroles bearing short-alkyl chain, ethyl, benzyl and *t*-butyl esters (entries 1-6). In general, the presence of a 3-ethyl substituent offered a slight benefit to yield, while the choice of ester substituent did not appear to have any significant effect. Unfortunately, the substrate scope seems limited to short-chain, alkyl-substituted pyrroles. Introduction of an aryl group or longer alkyl chain (entries 7 and 8) resulted in isolable fluorescent products, but in trace amounts and with poor purity. The presence of an acyl group was not tolerated (entry 9). β-Deacylation from pyrroles in the presence of BF_3 and ethanediol is a known reaction,[153] and likely interfered in the reaction of **4-25** with Lawesson's reagent and BF_3•Et_2O. Similarly, pyrroles bearing hydrogen, iodo and alkyl-alcohol bearing pyrroles (**4-26** to **4-28**, respectively) were not tolerated, and did not produce *F*-BODIPY products.

Table 4-8: **Substrate scope of Lawesson's reagent assisted *F*-BODIPY formation**



4-15 R^1 = Me
4-19 R^1 = Et

Entry	Starting Material	R^1	R^2	(%)
1	**4-8**	Me	Et	11
2	**4-20**	Me	Bn	11
3	**4-17**	Me	*t*-Bu	9
4	**4-21**	Et	Et	12
5	**4-18**	Et	Bn	15
6	**4-22**	Et	*t*-Bu	18
7	**4-23**	Ph	Bn	-[a]
8	**4-24**	$(CH_2)_7CH_3$	Et	-[a]
9	**4-25**	$COCH_3$	*t*-Bu	-[b]
10	**4-26**	H	Et	-[c]
11	**4-27**	I	*t*-Bu	-[c]
12	**4-28**	$(CH_2)_3CH_2OH$	Et	-[c]

[a] Impure *F*-BODIPY product isolable in trace amounts. [b] Competing deacylation reaction. [c] no isolable *F*-BODIPY

Section 4.3: Conclusions

In summary, the improved synthesis of unsubstituted *F*-BODIPY **4-2** has facilitated the study of alkylation, alkoxylation and chlorination of the boron atom in this

unstable framework. The electrophilic nature of the unsubstituted backbone hinders modular substitution in the case of alkylation, while the instability of the *O*-BODIPY hinders full analysis of the structure. Careful analysis of the reactivity of the chlorinated *Cl*-BODIPY has led to a novel pathway through which the sparsely reported dipyrrin **4-1** can be obtained as a hydrochloride salt. The methodology required to explore transformations to the unsubstituted dipyrrin in a controlled manner is better-developed, and the potential for use of the dipyrrin for other means is now greatly improved. This work has been published.[92]

Sulfination of Knorr pyrroles can be performed in good to excellent yield using Lawesson's reagent with microwave heating under inert conditions in toluene. In addition to the sulfination reaction, a small amount of a novel heterocycle, thiazaphosphole **4-10**, can also be obtained. Further studies will be required to optimize the synthesis of this compound, and a thorough study of conditions suitable for its isolation would be desirable. Researchers using Lawesson's reagent in the presence of Lewis acids and 1-ester pyrroles should be aware of the potential for formation of dipyrrin products.

Lawesson's reagent can also be used in conjunction with BF_3•Et_2O to generate *F*-BODIPYs from alkyl-substituted Knorr pyrroles under microwave heating conditions. The reaction suffers from low yield and difficult purification from byproducts, but represents a four-step, one-pot process (averaging around 65% yield per step) to form high-value products from simple starting materials. Several important questions remain pertaining to mechanism and the fate of the unaccounted-for pyrrolic material. This work has been published.[144]

Section 4.4: Experimental

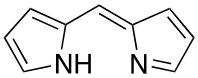
4.4.1 General Experimental

All chemicals were purchased and used as received unless otherwise indicated. Hexanes and dichloromethane (CH_2Cl_2) used for chromatography were obtained crude and purified via distillation under atmospheric conditions before use. Anhydrous solvents were used as received. Flash chromatography was performed using Silicycle ultra pure silica (230-400 mesh) or Brockmann III (150 mesh) activated basic or neutral alumina oxide as indicated. TLC was performed using glass-backed silica gel plates or on plastic-backed neutral alumina plates. Visualization of TLC plates was performed using UV light (254 nm) and/or vanillin stain when required. Moisture-sensitive reactions were performed in oven or flame-dried glassware under a positive pressure of nitrogen. Air and moisture-sensitive compounds were introduced via syringe. NMR spectra were recorded at the NMR-3 facility (Dalhousie University) using a Bruker 500 MHz or a Bruker 300 MHz spectrometer. ^{1}H and ^{13}C chemical shifts are expressed in parts per million (ppm) using, and use the solvent signal ($CDCl_3$ (^{1}H 7.26; ^{13}C 77.16 ppm), DMSO-d_6 (^{1}H 2.50; ^{13}C 39.52 ppm) to zero the spectra. ^{11}B and ^{19}F chemical shifts are expressed in parts per million (ppm) and were referenced using the absolute referencing procedure standard for Bruker digital spectrometers, with BF_3•Et_2O (15% in $CDCl_3$) and CCl_3F defining the 0 ppm position, respectively. All coupling constants (*J*) are reported in Hertz (Hz). Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Splitting patterns preceded by an “a” are defined as apparent signals. Description of atom assignments is made with consideration to the structure of the compound being labeled. All mass spectra were recorded by Mr. Xiao Feng using ion

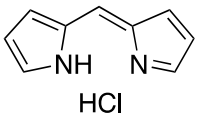
trap (ESI TOF) instruments. All microwave-promoted reactions were performed using a Biotage Initiator 8 laboratory microwave apparatus, 0–400 W power, 2.45 GHz. All X-Ray measurements were made using a Rigaku RAXIS RAPID imaging plate area detector with graphite monochromated Mo-Kα radiation. CCDC reference numbers for compounds used as literature comparisons are as follows: **4-11** 201149; **4-12** 667280; **4-13** 1267621; **4-14** 263350. Starting materials were prepared according to literature procedures as indicated in the experimental procedures.

Section 4.5: Synthesis

(*Z*)-2-((2*H*-Pyrrol-2-ylidene)methyl)-1*H*-pyrrole (4-1)



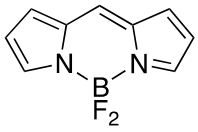
To a slurry of *p*-chloranil (184 mg, 0.75 mmol) in CH_2Cl_2 (10 mL) at -40 °C under nitrogen, a solution of di(1H-pyrrol-2-yl)methane **4-3**[154] (100 mg, 0.68 mmol) in CH_2Cl_2 (10 mL) was added drop-wise over several minutes. The reaction mixture was stirred for 3 hours, during which time the colour of the mixture turned from brown to bright yellow. The solvent was removed *in vacuo*, and the yellow material was characterized as a mixture of reaction products including **4-1** as its free-base according to ESI^+ mass spectral analysis.



Alternatively, to a solution of **4-7** (25 mg, 0.11 mmol) in CH_2Cl_2 (10 mL) under nitrogen, methanol (22 μL, 0.55 mmol) was added, and the mixture was then stirred for 30

minutes. The solvent was removed *in vacuo*, to give complete conversion to **4-1•HCl**. δ_H (500 MHz, $CDCl_3$) 6.66 (s, 2H, Pyr-H), 7.33 (s, 2H, Pyr-H), 7.50 (s, 1H, *meso*-H), 8.01 (s, 2H, pyr-H), 14.63 (bs, 2H, N-H); δ_C (125 MHz, $CDCl_3$): 117.8, 130.0, 133.2, 137.2, 144.5. ESI: $[2M+H]^+$ ($C_{18}H_{17}N_4$): 289.1448 (calculated); 289.1443 (experimental).

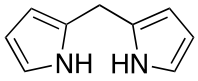
4,4-Difluoro-4-borato-3a-azonia-4a-aza-*s*-indacene (4-2)



To a slurry of *p*-chloranil (925 mg, 3.7 mmol) in CH_2Cl_2 (70 mL) at -40 °C under nitrogen, a solution of a di(1H-pyrrol-2-yl)methane (**4-3**,[154] 500 mg, 3.4 mmol) in CH_2Cl_2 (100 mL) under N_2 was added drop-wise over several minutes. The reaction mixture was stirred for 3 hours, during which the colour of the mixture turned from brown to bright yellow. After DIPEA (3.5 mL, 20.5 mmol) was added, the solution was stirred for 30 minutes. BF_3•OEt_2 (3.4 mL, 30.6 mmol) was then added slowly over several minutes, and the reaction mixture was stirred for 18 hours, during which time the temperature was allowed to rise to 22 °C. The fluorescent solution was sonicated for 30 minutes and then filtered through Celite to remove insoluble oxidation products: it was then washed with sat aq. $NaHCO_3$ and dried over $MgSO_4$. The solvent was removed *in vacuo*. Purification using basic Brockman III alumina (ethyl acetate/hexanes, 1:9 V/V) gave the title compound as a dark red solid (468 mg, 72 %). δ_H (500 MHz, $CDCl_3$) 6.55 (d, 2H, J = 4.0 Hz, Pyr-H), 7.15 (d, 2H, J = 4.0 Hz, Pyr-H), 7.42 (s, 1H, *meso*-H), 7.90 (bs, 2H, Pyr-H); δ_C (125 MHz, $CDCl_3$) 118.9, 131.4, 131.5, 135.3, 145.2; δ_B [^{1}H] (160 MHz, $CDCl_3$) 0.31

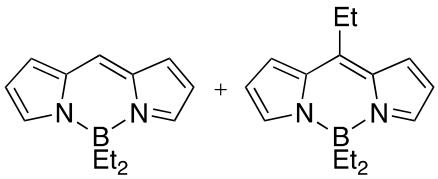
(t, $J_{B\text{-}F}$ = 29 Hz). ESI: $[M+Na]^+$ ($C_9H_7BF_2N_2Na$): 215.0586 (calculated); 215.0563 (experimental). These data matches reported literature values.[134]

Di(1H-pyrrol-2-yl)methane (4-3)



Di(1H-pyrrol-2-yl)methane was obtained either using Wang's method[154] as a crystalline, colourless solid, or as purchased from Frontier Scientific (the purchased sample contained grease impurities). δ_H (500 MHz, $CDCl_3$) 3.95 (s, 2H, Pyr_2-CH_2), 6.05 (s, 2H, Pyr-H), 6.17 (aq, 2H, J = 2.9 Hz,Pyr-H), 6.63 (aq, 2H, J = 2.1 Hz, Pyr-H), 7.74 (bs, 2H, N-H); δ_C (125 MHz, $CDCl_3$): 26.4, 106.6, 108.4, 117.5, 129.2. ESI: $[M+Na]^+$ ($C_9H_{10}N_2Na$): 169.0742 (calculated); 169.0736 (experimental). This data matched reported literature values.[154]

4,4-Diethyl-4-borato-3a-azonia-4a-aza-*s*-indacene (4-4) and 4,4-diethyl-8-ethyl-4-borato-3a-azonia-4a-aza-*s*-indacene (4-5)

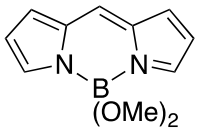


4-4 **4-5**

To a solution of **4-2** (50 mg, 0.26 mmol) in diethyl ether (20 mL) under nitrogen, a solution of ethyl magnesium bromide in diethyl ether (0.43 mL, 1.30 mmol) was added drop-wise and the reaction mixture stirred for 10 minutes. TLC analysis indicated complete consumption of starting material, and the reaction was quenched with water.

The product was extracted with CH_2Cl_2, and purified via flash chromatography on SiO_2 (ethyl acetate/hexanes, 2:8 V/V) to produce a brick-red solid. An inseparable mixture of products, **4-4** (11 mg, 22%) and **4-5** (7 mg, 10%) was isolated. Decomposition of the material was observed after several hours at room temperature, both in air and nitrogen environments. δ_H of **4-4** (500 MHz, $CDCl_3$) 0.42 (m, 6H, $BCH_2\mathit{CH_3}$), 0.60 (m, 4H, $B\mathit{CH_2}CH_3$), 6.56 (m, 2H, J = 4.2 Hz, Pyr-H), 7.07 (dd, 2H, J = 4.2, 0.9 Hz, Pyr-H), 7.45 (s, 1H, *meso*-H), 7.56 (d, 2H, J = 0.9 Hz, Pyr-H); δ_H of **4-5** (500 MHz, $CDCl_3$) 0.42 (m, 6H, $CH_2\mathit{CH_3}$), 0.60 (m, 4H, $\mathit{CH_2}CH_3$), 1.45 (t, 3H, J = 7.7 Hz, *meso*-$CH_2\mathit{CH_3}$), 3.01 (q, 2H, J = 7.7 Hz, *meso*-$\mathit{CH_2}CH_3$), 6.56 (m, 2H, Pyr-H), 7.23 (d, 2H, J = 4.2 Hz, Pyr-H), 7.52 (bs, 2H, Pyr-H) (note that peaks at 0.42, 0.60 and 6.56 contain signals from both **4-4** and **4-5**); δ_C of **4-4** and **4-5** (125 MHz, $CDCl_3$): 8.7, 8.8, 18.2, 24.8, 116.7, 117.5, 123.3, 127.0, 131.1, 134.2, 134.6, 141.2, 142.7, 151.4 (note that dipyrrin type peaks were not resolved; boron-substituted ethyl carbon peaks overlap in spectrum); δ_B (160 MHz, $CDCl_3$) 1.71 (**4-4**) and 1.04 (**4-5**).

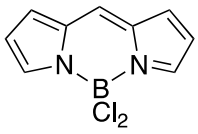
4,4-Dimethoxy-4-borato-3a-azonia-4a-aza-*s*-indacene (4-6)



To a solution of **4-2** (50 mg, 0.26 mmol) in methanol (10 mL) under nitrogen at 65 °C, NaOMe (117mg, 1.56 mmol) was added, and the reaction mixture stirred. After an hour, TLC analysis indicated complete consumption of starting material. The rapidly decomposing mixture was filtered through a plug of alumina, and the solvent removed *in vacuo* to produce a dark, red solid. The 4,4-dimethoxyBODIPY **4-6** was isolated (10 mg,

6%) with two unidentified side-products. δ_H (500 MHz, $CDCl_3$) 3.01 (s, 6H, OCH_3), 6.54 (m, 2H, *J* = 3.9 Hz, Pyr-H), 7.12 (d, 2H, *J* = 3.9 Hz, Pyr-H), 7.38 (s, 1H, *meso*-H), 7.83 (bs, 2H, Pyr-H); δ_B (160 MHz, $CDCl_3$) 5.20 (impurity), 2.45 (**4-6**), 1.29 (impurity). Product instability limited further characterization.

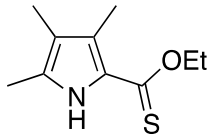
4,4-Dichloro-4-borato-3a-azonia-4a-aza-*s*-indacene (4-7)



To a solution of **4-2** (200 mg, 1.02 mmol) in CH_2Cl_2 (20 mL) under a nitrogen environment, a 1 M solution of BCl_3 (1.14 mL, 1.14 mmol) in CH_2Cl_2 was added drop-wise. The mixture was stirred for 30 minutes, during which time the dark red colour lightened significantly. The solution was filtered through Celite, and the solvent removed *in vacuo* to produce **4-7** as a brick-red solid (216 mg, 99%). δ_H (500 MHz, $CDCl_3$) 6.61 (s, 2H, Pyr-H), 7.19 (ad, 2H, *J* = 2.8 Hz, Pyr-H), 7.48 (s, 1H, *meso*-H), 8.10 (s, 2H, Pyr-H); δ_C (125 MHz, $CDCl_3$) 119.90, 131.41, 132.12, 133.90, 147.39; δ_B (160 MHz, $CDCl_3$) 2.28 (s). Mass spectral analysis was inconclusive, as is typical for 4,4-dichloroBODIPYs.[101]

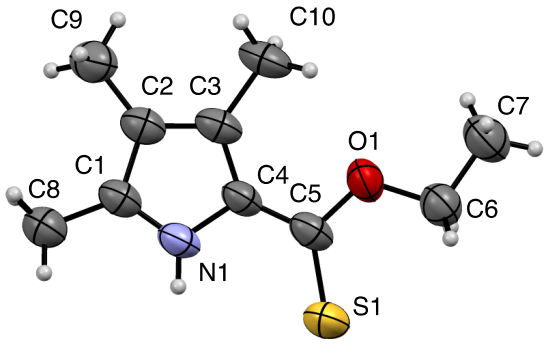
Alternatively, to a solution of **4-1•HCl** in CH_2Cl_2 under a nitrogen environment (generated from **4-7**, as per the second method for formation of **4-1**), 5 equivalents of BCl_3 were added, and the mixture was stirred for an hour. The solution was filtered through Celite, and the solvent removed *in vacuo*. Analysis via ^1H and ^{11}B NMR techniques revealed the presence of **4-7**, as well as several unidentifiable impurities.

***O*-Ethyl-3,4,5-trimethyl-1*H*-pyrrole-2-carbothioate (4-9)**



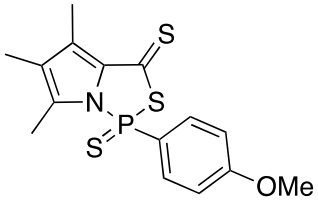
A suspension of pyrrolic ester **4-8**[155] (0.5 mmol) and Lawesson's reagent (0.3 mmol, 1.2 equivalents) in anhydrous *p*-xylene or anhydrous toluene (0.7 mL, 0.75 M), in a sealed flask under nitrogen, was placed in a sand bath preheated to 140 °C, and then heated with stirring for 1 hour. After this time, the reaction mixture was allowed to cool to room temperature before being diluted with ethyl acetate (1 mL) and the mixture then poured into 20% ethyl acetate/hexanes (20 mL), rinsing the flask with ethyl acetate (2 x 1 mL). The combined solution was then filtered through a short pad of silica, washing with 20% ethyl acetate/hexanes, and the filtrate concentrated to give the crude product, which was purified using column chromatography over silica, eluting with 5-10% ethyl acetate/hexanes to give thionoester **4-9** as a yellow solid (78 mg, 72% yield). Alternatively, a suspension of pyrrolic ester (0.5 mmol) and Lawesson's reagent (0.3 mmol, 1.2 equivalents) in anhydrous toluene (0.7 mL, 0.75 M), in a sealed microwave vial under nitrogen, was placed under microwave heating at 160 °C for 20 min. After this time, the reaction mixture was allowed to cool to room temperature before dilution with ethyl acetate (1 mL). The mixture was then poured into 20% ethyl acetate/hexanes (20 mL), rinsing the flask with ethyl acetate (2 x 1 mL). The combined solution was filtered through a short pad of silica, washing with 20% ethyl acetate/hexanes, and the filtrate was concentrated to give the crude product, which was purified using column chromatography over silica, eluting with 5% ethyl acetate/hexanes, to give **4-9** as a yellow solid (64 mg, 59%) Mp: 83-85 °C; δ_H ($CDCl_3$, 500 MHz) 1.46 (t, 3H, J = 7.2 Hz,

$CH_2\mathit{CH_3}$), 1.91 (s, 3H, Pyr-CH_3), 2.19 (s, 3H, Pyr-CH_3), 2.25 (s, 3H, Pyr-CH_3), 4.66 (q, 2H, J = 7.2 Hz, $\mathit{CH_2}CH_3$), 9.06 (bs, 1H, N-H); δ_C ($CDCl_3$, 125 MHz) 8.8, 12.0, 12.2, 14.3, 66.5, 119.2, 126.1, 128.6, 134.5, 199.5; ESI: $[M+Na]^+$ ($C_{10}H_{15}NSONa$): 220.0767 (calculated); 220.0775 (experimental).



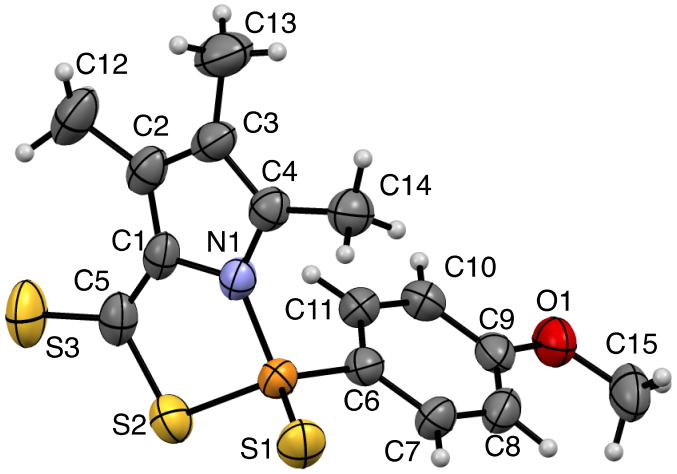
$C_{10}H_{15}NOS$, MM = 197.30 g/mol. Light-yellow plate crystal, dimensions 0.29 x 0.28 x 0.08 mm; triclinic space group, P_{-1} (#2); a = 7.215(2) Å, b = 8.581(3), c = 9.903(2) Å, α = 103.094(9)°, β = 93.3290(16)°, γ = 112.892(9)°, V = 542.8(3) $Å^3$; d = 1.207 g/cm^3, μ(Mo-Kα) = 2.609 cm^{-1}, 12478 reflections (4181 unique, R_{int} = 0.073), R = 0.0446, R_w = 0.0404, GOF = 1.062. CCDC deposition number: 1455753.

1-(4-Methoxyphenyl)-4,5,6-trimethylpyrrolo[1,2-c][1,3,2]thiazaphosphole-3(1H)-thione-1-sulfide (4-10)



A suspension of thionoester **4-9** (50 mg, 0.25 mmol) and Lawesson's reagent (77 mg, 0.19 mmol, 1.5 equivalents) in anhydrous *p*-xylene (0.5 mL), in a sealed flask under

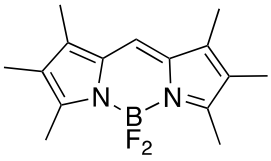
nitrogen, was placed in a sand bath preheated to 140 °C and heated with stirring for 1.5 hours. After this time, the reaction mixture was allowed to cool to room temperature before being poured into 30% ethyl acetate/hexanes (20 mL), rinsing the flask with ethyl acetate. The solution was then filtered, washing with 30% ethyl acetate/hexanes, and the filtrate concentrated to give the crude product, which was purified quickly using column chromatography over silica eluting with 15% ethyl acetate/hexanes, then again eluting with 45% CH_2Cl_2 in hexanes, if necessary, to give the title compound as an orange solid (30 mg, 33% yield). Mp: 125-127 °C; λ_{max} CH_2Cl_2 404 (ε 29 000), 279 (ε 20 000); δ_H ($CDCl_3$, 500 MHz) 1.94 (s, 3H, Pyr-CH_3), 2.13 (s, 3H, Pyr-CH_3), 2.43 (s, 3H, Pyr-CH_3), 3.88 (s, 3H, OCH_3), 6.99 (dd, 2H, J = 9.0, 3.5 Hz, Ar-H), 7.82 (dd, 2H, J = 15.2, 9.0 Hz, Ar-H); δ_C ($CDCl_3$, 125 MHz) 9.4, 11.3, 12.0, 55.8, 114.7 (d, J = 16.4 Hz), 124.0, 124.8, 130.2 (d, J = 6.0 Hz), 138.2 (d, J = 1.8 Hz), 139.5, 164.0, 194.0; δ_P ($CDCl_3$, 202 MHz) 63.4 (t, J = 15.2 Hz); ESI: $[M+Na]^+$ ($C_{15}H_{16}NPS_3ONa$): 376.0024 (calculated); 376.0014 (experimental).



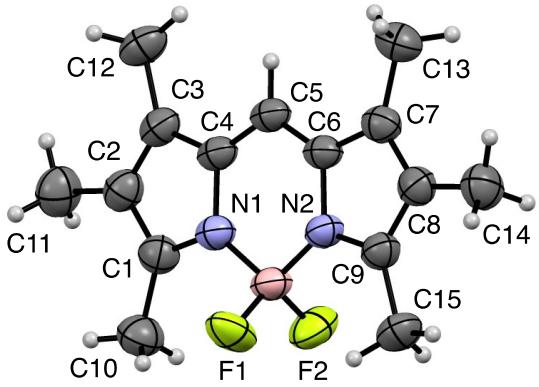
$C_{15}H_{16}NPS_3O$, MM = 353.46 g/mol. Orange plate crystal, dimensions 0.27 x 0.26 x 0.09 mm; monoclinic space group, $P2_1/n$; a = 7.4515(15) Å, b = 11.579(2), c = 19.631(3) Å, α

= 90 º, β = 97.168(6) º, γ = 90 º, V = 1680.5(5) Å^3; d = 1.397 g/cm^3, μ(Mo-Kα) = 5.33 cm^{-1}, 21248 reflections (5767 unique, R_{int} = 0.048), R = 0.0292, R_w = 0.0357, GOF = 1.096. CCDC deposition number: 1455752.

4,4-Difluoro-1,2,3,5,6,7-hexamethyl-8*H*-4-bora-3a,4a-diaza-s-indacene (4-15)

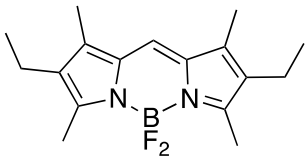


A mixture of **4-8**[155] (100 mg, 0.55 mmol) and Lawesson's reagent (223 mg, 0.55 mmol) was prepared in a 0.5-2.0 mL capacity microwave vial under nitrogen using a cap bearing a septum. A suspension was formed upon addition of toluene (1 mL) with vigorous stirring. BF_3•OEt_2 (0.27 mL, 2.2 mmol, 4 equivalents) was then added drop-wise, via the septum, and the vial was heated in a microwave reactor at 160 °C for 20 minutes before being allowed to cool to room temperature. The reaction mixture was diluted with ethyl acetate (2 mL), then poured into a 20% ethyl acetate/hexanes solution (30 mL). The solution was filtered through a short pad of silica, washing with 30% ethyl acetate/hexanes, and then concentrated. The crude product was purified over neutral alumina (Brockmann type III), eluting slowly with 5-20% CH_2Cl_2/hexanes, to give the title compound as a deep red crystalline solid (8 mg, 11% yield). δ_H ($CDCl_3$, 500 MHz) 1.93 (s, 6H, CH_3), 2.15 (s, 6H, CH_3), 2.48 (s, 6H, CH_3), 6.94 (s, 1H, *meso*-H); δ_B ($CDCl_3$, 160 MHz) 0.87 (t, J = 33 Hz); δ_F ($CDCl_3$, 470 MHz): -146.4 (q, J = 34 Hz); this data matches reported literature values.[123]



$C_{15}H_{19}N_2BF_2$, MM = 197.30 g/mol. Deep-red needle crystal, dimensions 0.42 x 0.19 x 0.08 mm; monoclinic space group, $P2_1/n$; a = 7.2351(6) Å, b = 16.6785(14), c = 11.8701(10) Å, α = 90 º, β = 98.682(4)°, γ = 90 º, V = 1416.0(2) $Å^3$; d = 1.295 g/cm^3, μ(Mo-Kα) = 0.940 cm^{-1}, 12329 reflections (3788 unique, R_{int} = 0.025), R = 0.0485, R_w = 0.0576 , GOF = 1.089. CCDC deposition number: 1468172.

2,6-Diethyl-4,4-difluoro-1,3,5,7-tertamethyl-8-H-4-bora-3a,4a-diaza-s-indacene (4-19)

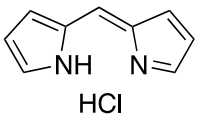


A mixture of **4-22**[156] (0.55 mmol, 1 equivalent) and Lawesson's reagent (223 mg, 0.55 mmol, 2 equivalents) was prepared in a 0.5-2.0 mL capacity microwave vial under nitrogen using a cap bearing a septum. A suspension was formed upon addition of toluene (1 mL) with vigorous stirring. BF_3•OEt_2 (0.27 mL, 2.2 mmol, 4 equivalents) was then added drop-wise, via the septum, and the vial was heated in a microwave reactor at 160 °C for 20 minutes before being cooled to room temperature. The mixture was diluted with ethyl acetate (2 mL), then poured into a 20% ethyl acetate/hexanes solution (30 mL).

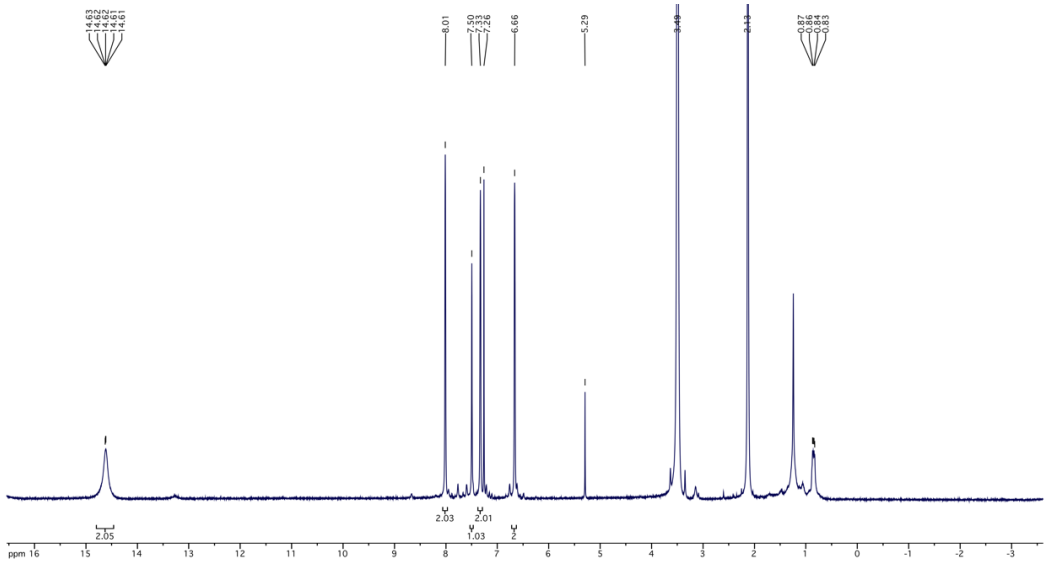
The solution was filtered through a short pad of silica, washing with 30% ethyl acetate/hexanes, and then concentrated. The crude product was purified over neutral alumina (Brockmann type III), eluting slowly with 5-20% CH_2Cl_2/hexanes, to give the title compound as a deep red crystalline solid (8 mg, 11% yield). δ_H ($CDCl_3$, 500 MHz) 1.06 (t, J = 7.6 Hz, 6H, 2 x $CH_2\mathit{CH_3}$), 2.16 (s, 6H, 2 x CH_3), 2.38 (q, J = 7.6 Hz, 4H, 2 x CH_2), 2.50 (s, 6H, 2 x CH_3), 6.95 (s, 1H, *meso*-H); δ_B NMR ($CDCl_3$, 160 MHz): 0.89 (t, J = 34 Hz); δ_F NMR ($CDCl_3$, 470 MHz): -146.3 (q, J = 34 Hz); this data matches reported literature values.[91]

Section 4.6: NMR Spectra

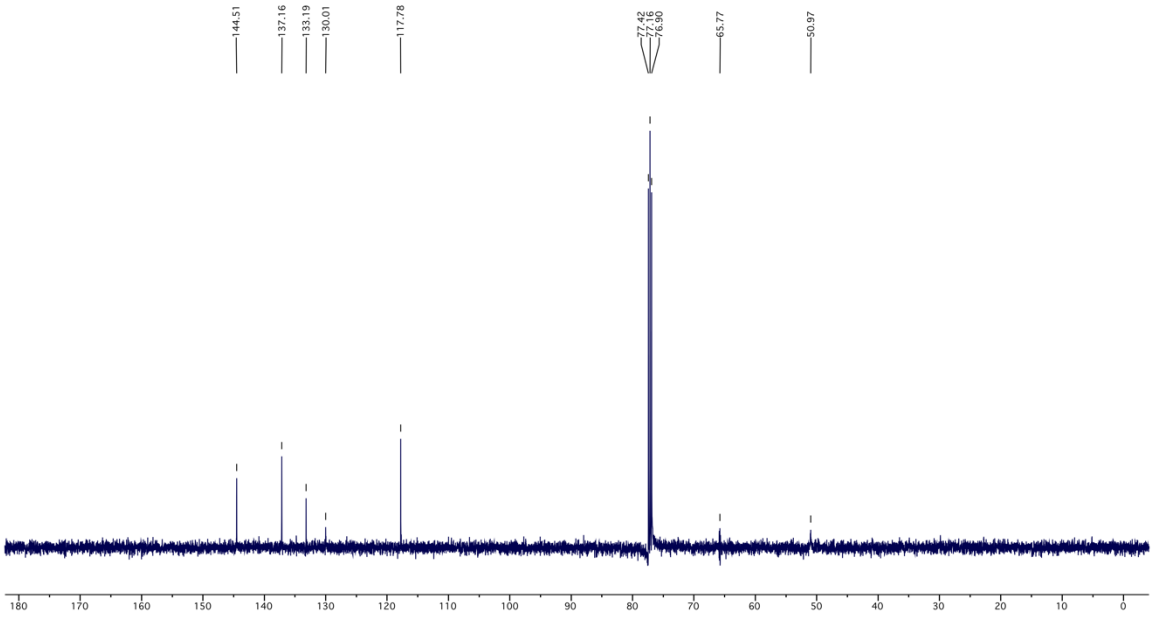
(Z)-2-((2*H*-Pyrrol-2-ylidene)methyl)-1*H*-pyrrole (4-1•HCl)



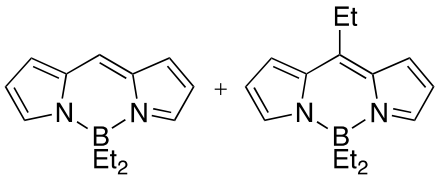
^{1}H NMR ($CDCl_3$, 500 MHz):



^{13}C UDEFT NMR ($CDCl_3$, 125 MHz):

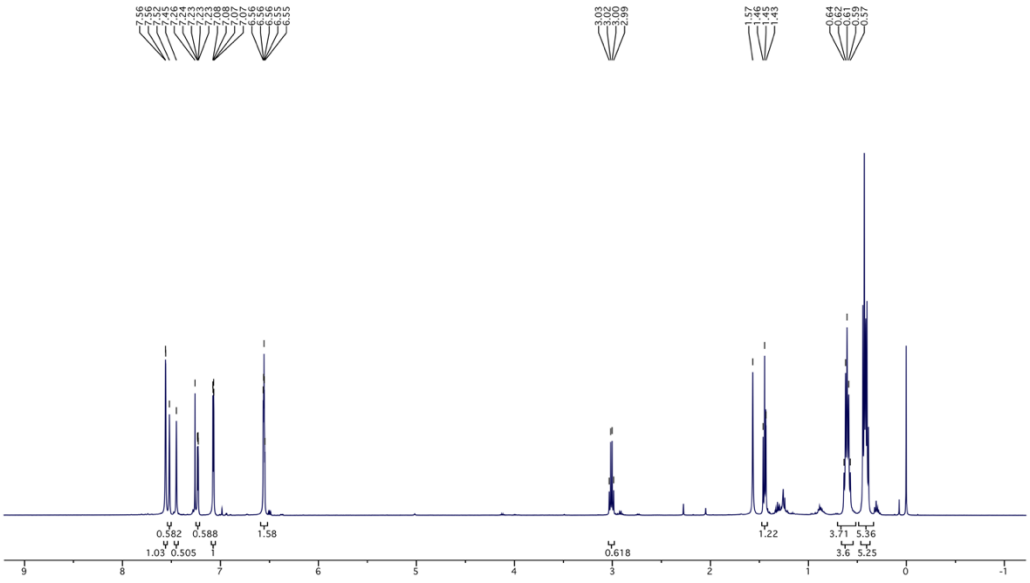


4,4-Diethyl-4-borato-3a-azonia-4a-aza-*s*-indacene (4-4) and 4,4-diethyl-8-ethyl-4-borato-3a-azonia-4a-aza-*s*-indacene (4-5)

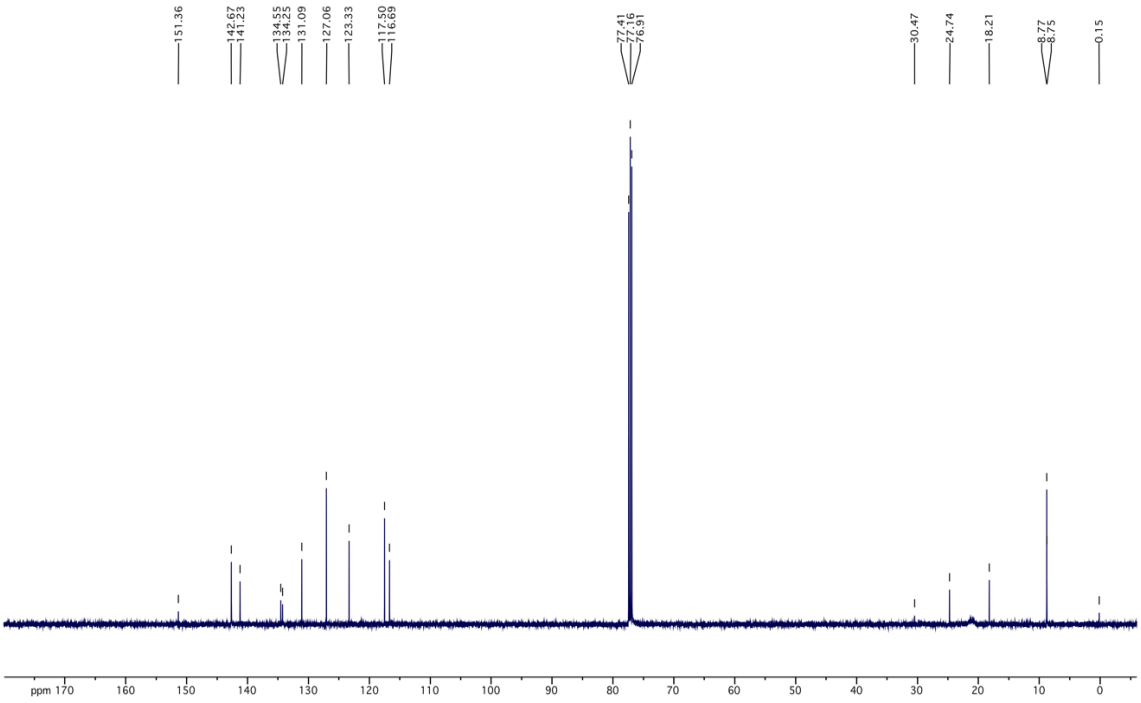


4-4 **4-5**

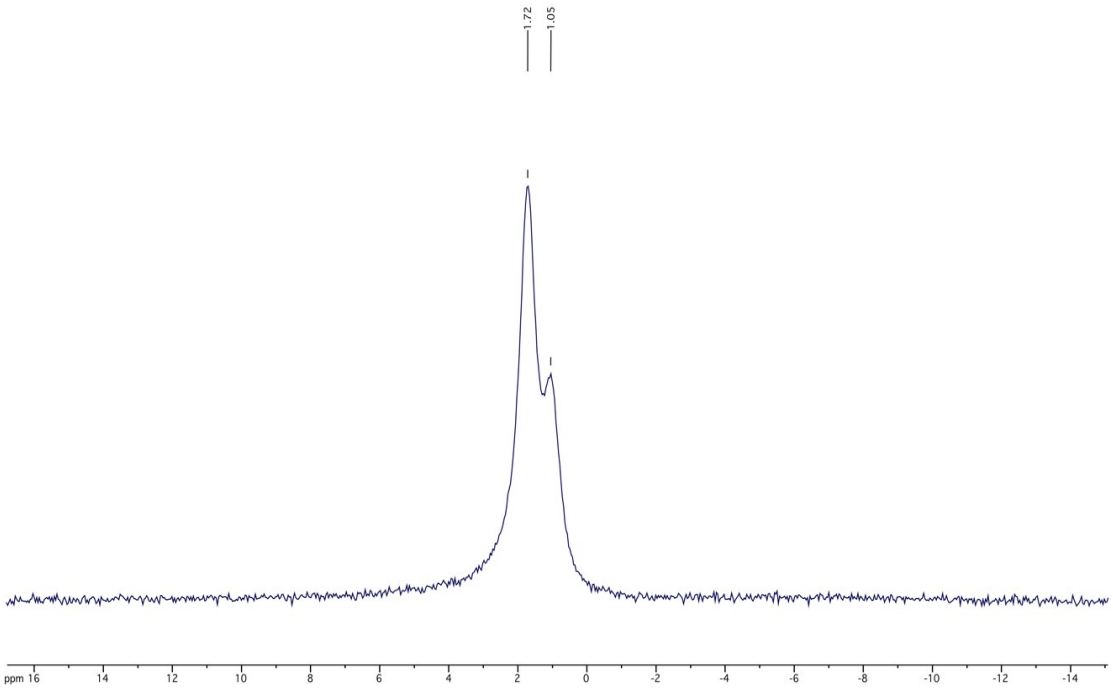
^{1}H NMR ($CDCl_3$, 500 MHz):



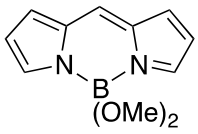
^{13}C UDEFT NMR ($CDCl_3$, 125 MHz):



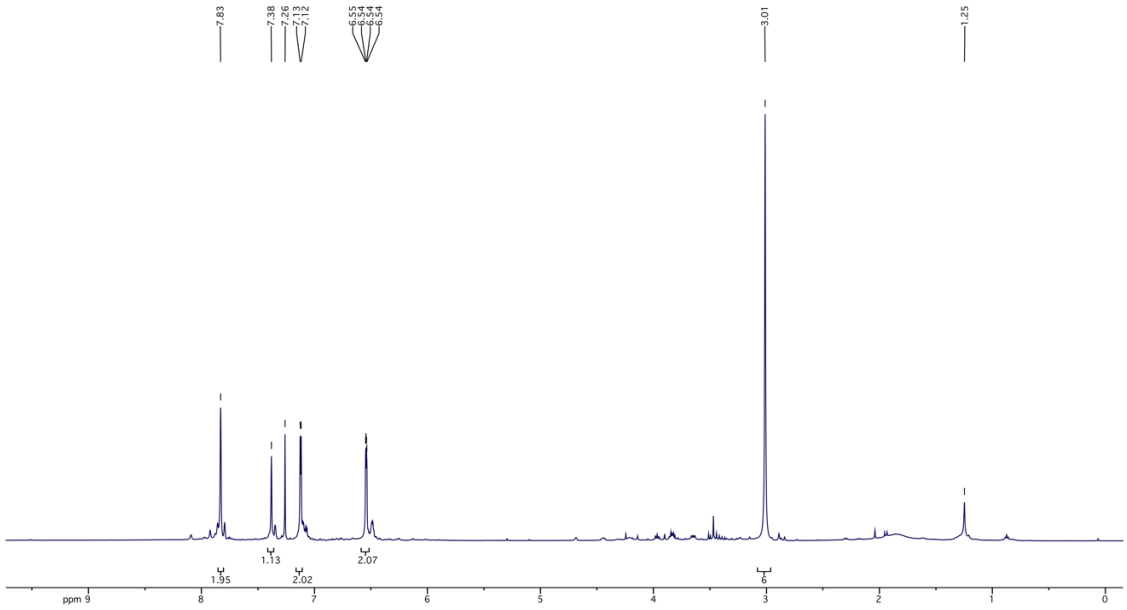
^{11}B NMR ($CDCl_3$, 160 MHz):



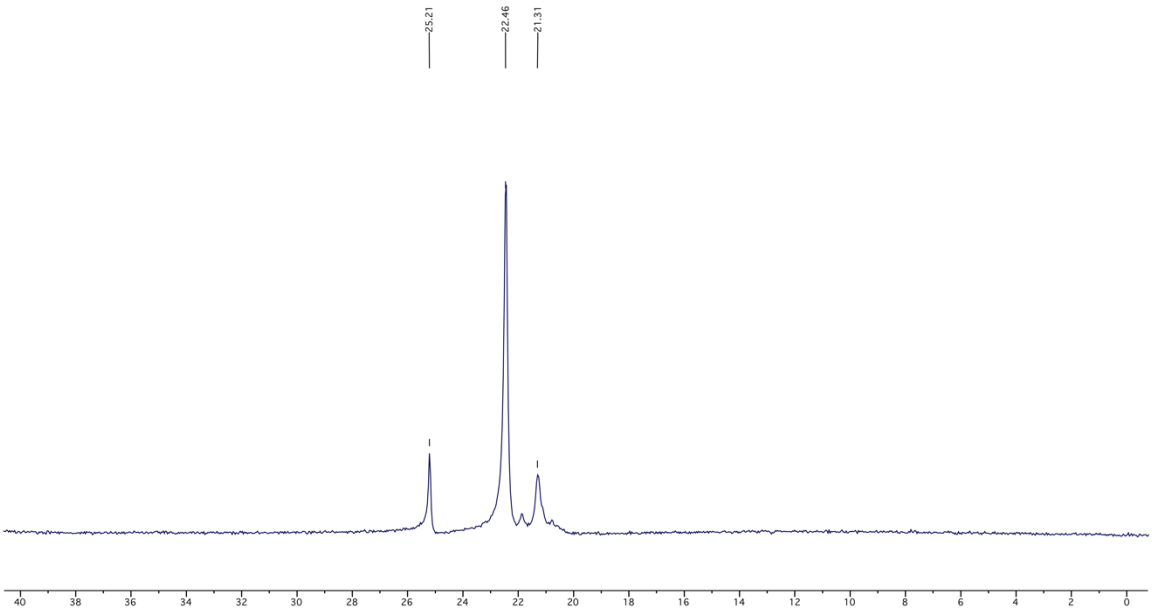
4,4-Dimethoxy-4-borato-3a-azonia-4a-aza-*s*-indacene (4-6; impure; unstable)



^{1}H NMR ($CDCl_3$, 500 MHz):

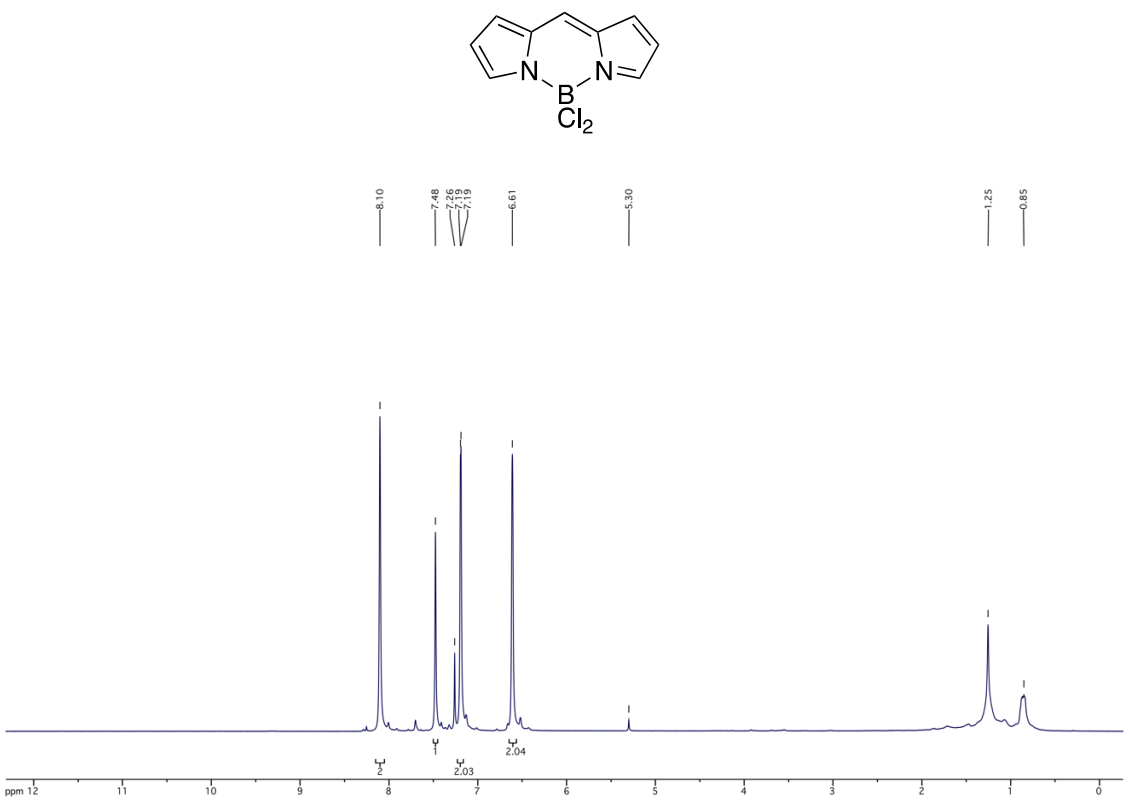


^{11}B NMR ($CDCl_3$, 160 MHz):

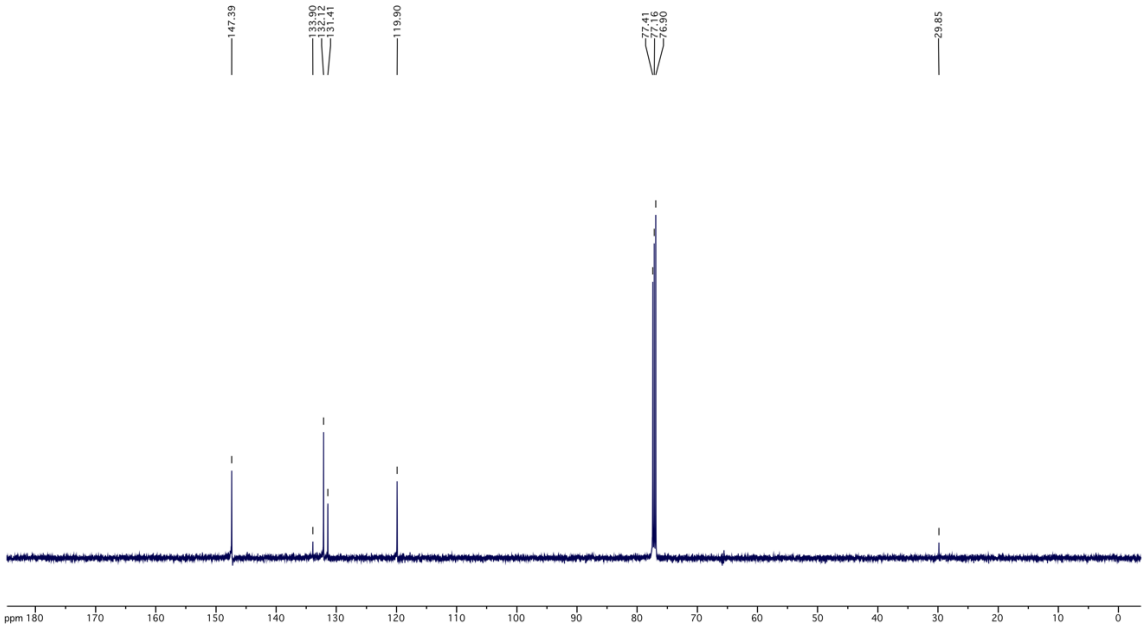


4,4-Dichloro-4-borato-3a-azonia-4a-aza-*s*-indacene (4-7)

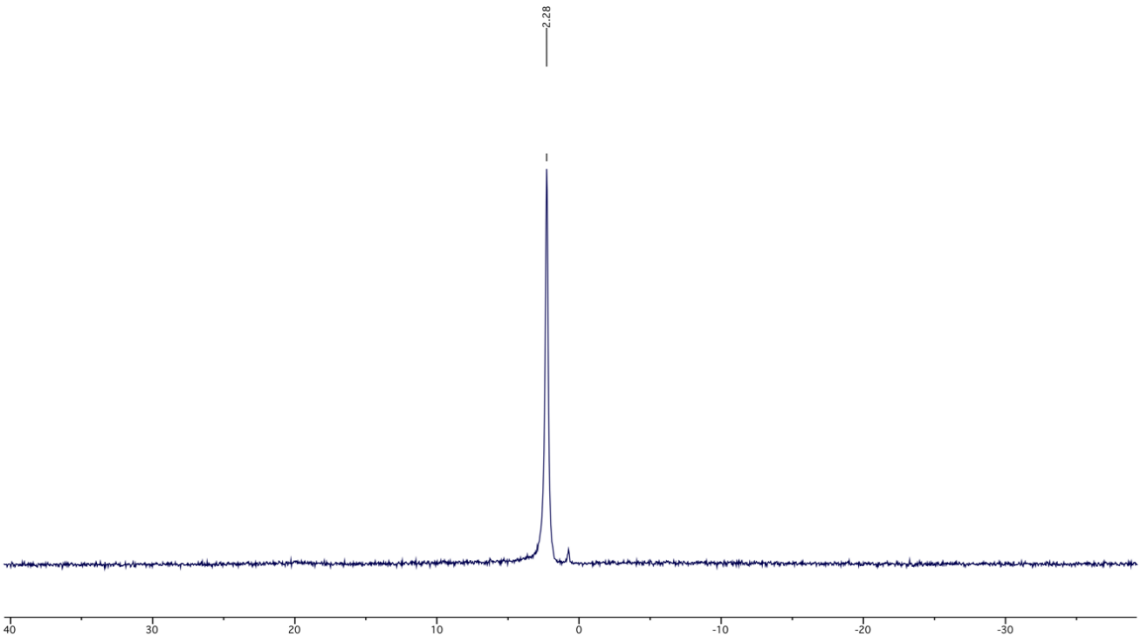
^{1}H NMR ($CDCl_3$, 500 MHz):



^{13}C UDEFT NMR ($CDCl_3$, 125 MHz):

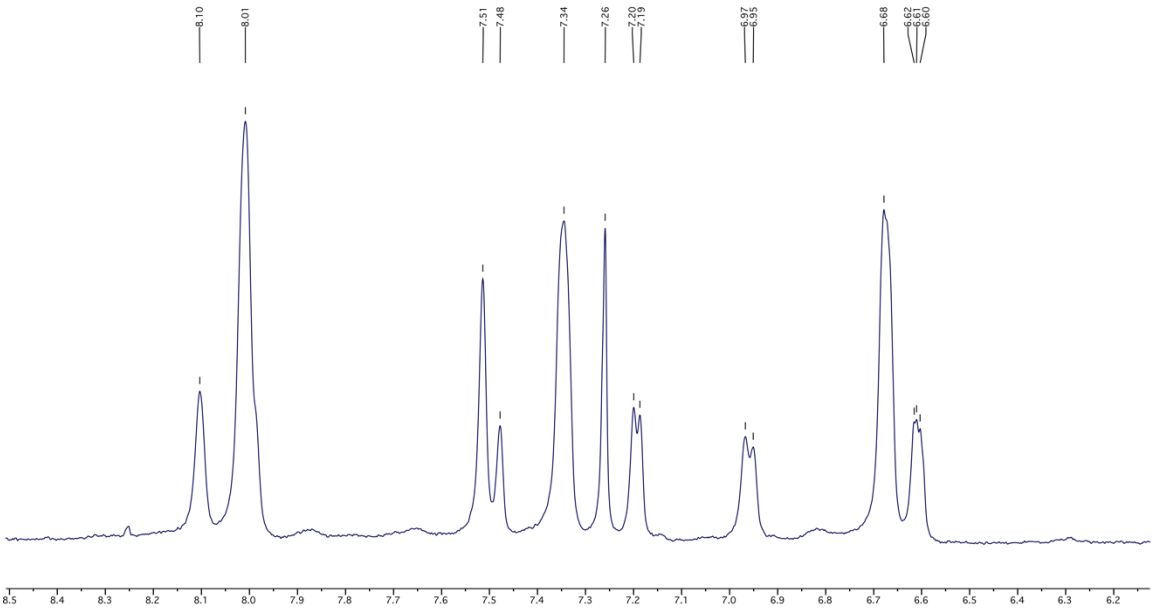


^{11}B NMR ($CDCl_3$, 160 MHz):

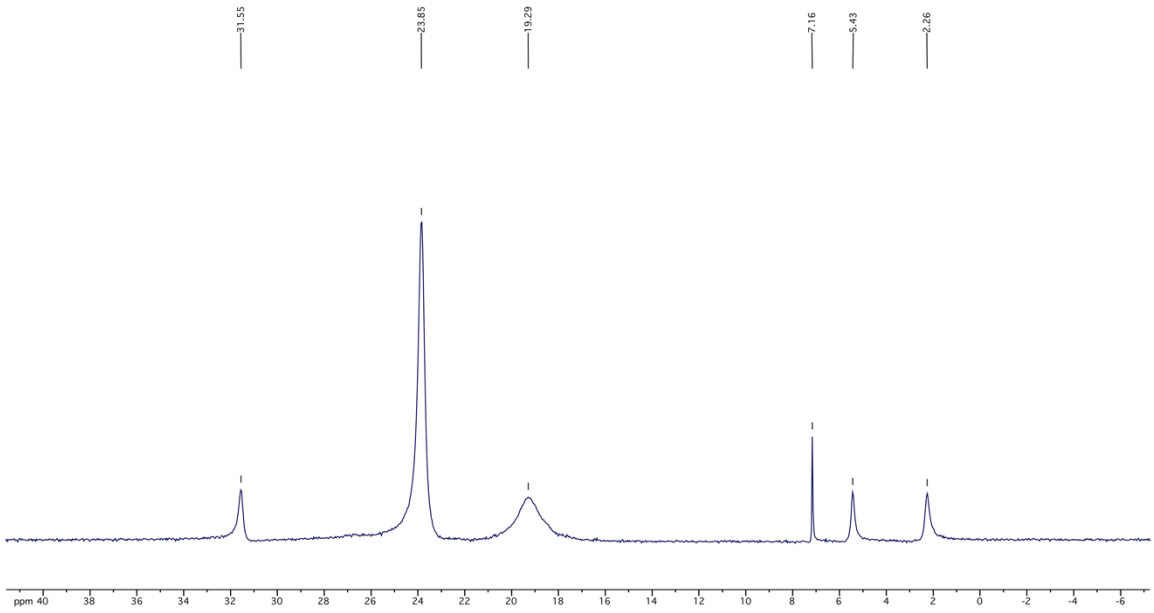


Mixture of 4-1•HCl and 4-7 synthesized via addition of BCl_3 to 4-1•HCl

^{1}H NMR ($CDCl_3$, 500 MHz):

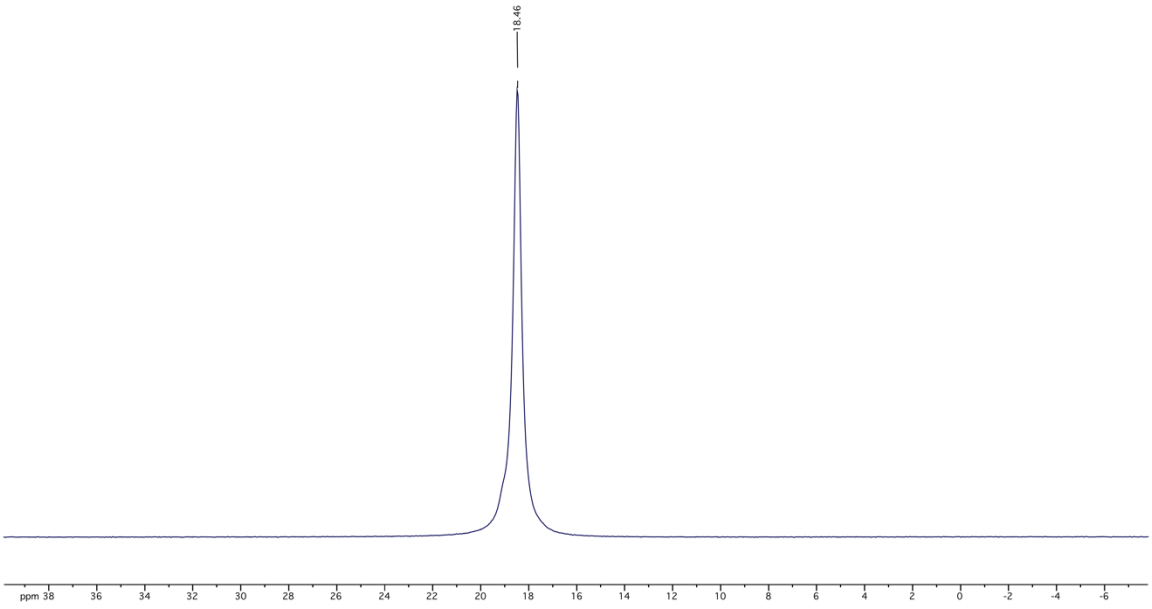


^{11}B NMR ($CDCl_3$, 160 MHz):

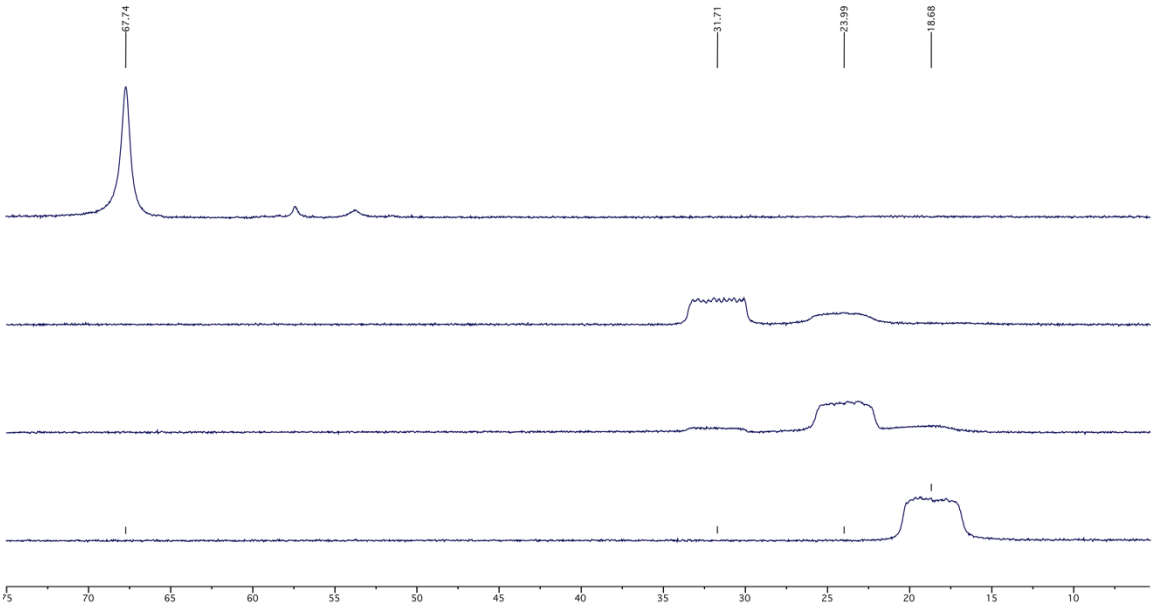


Trimethoxy borate generated via addition of excess MeOH to BCl_3 ($CDCl_3$)

^{11}B NMR ($CDCl_3$, 160 MHz):



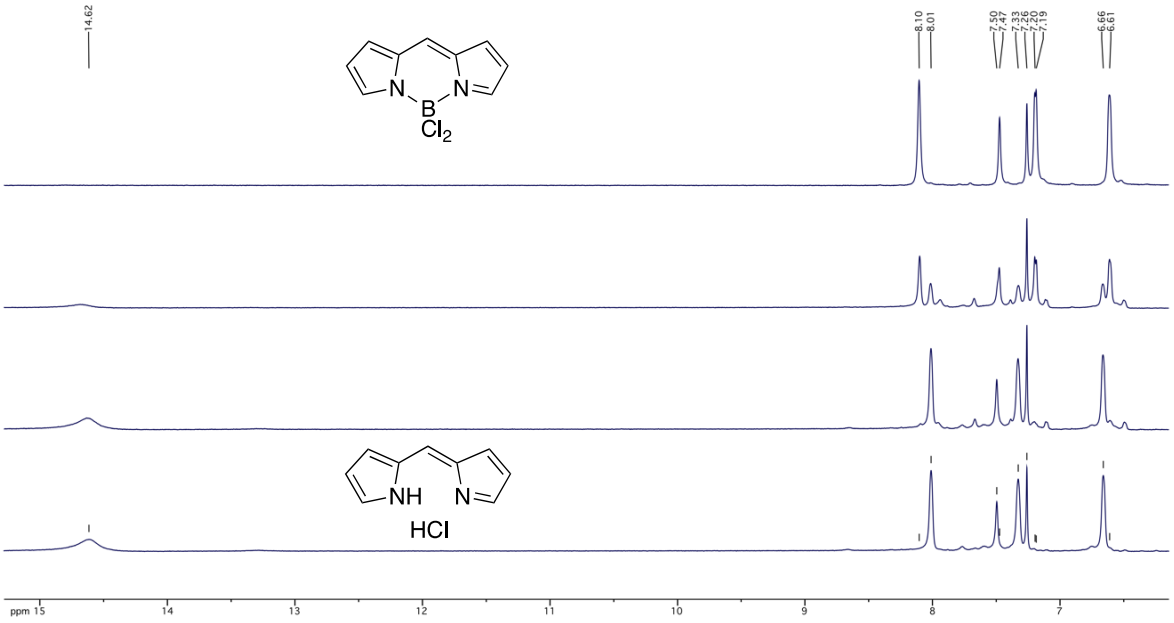
Trimethoxy borate generated via step-wise addition of three equivalents of MeOH to BCl_3 ($CDCl_3$)



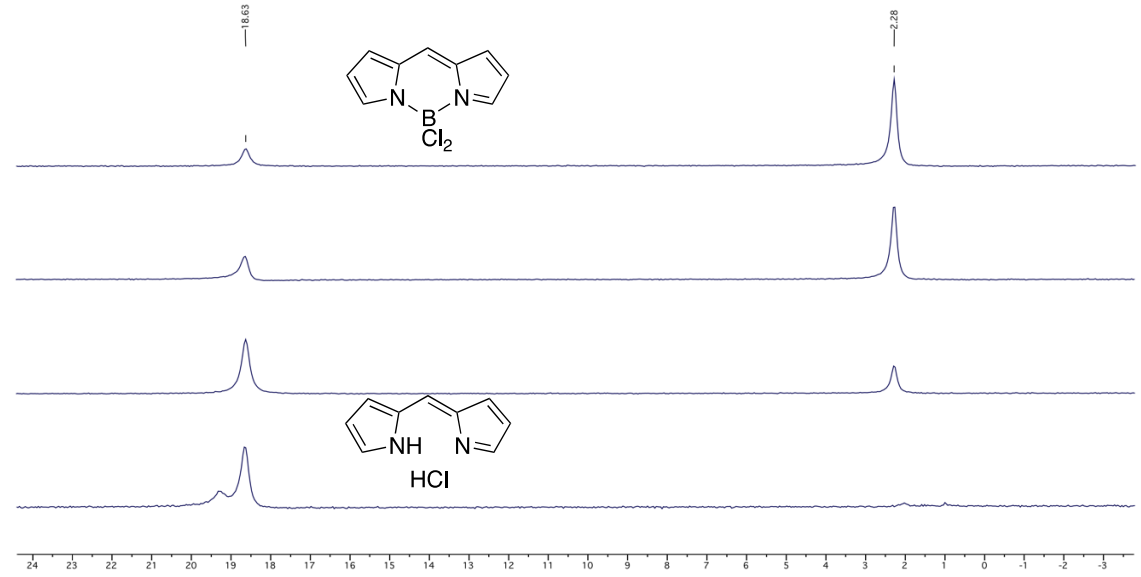
Formation of 4-1•HCl from 4-7

Spectra depicting formation (top to bottom) of **4-1•HCl** and $B(OMe)_3$ from **4-7** via addition of 5 equivalents of methanol (3 times addition of 1.5 μL) over 30 minutes (obtained every 10 min).

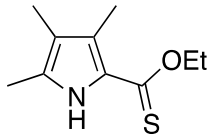
^{1}H NMR ($CDCl_3$, 500 MHz):



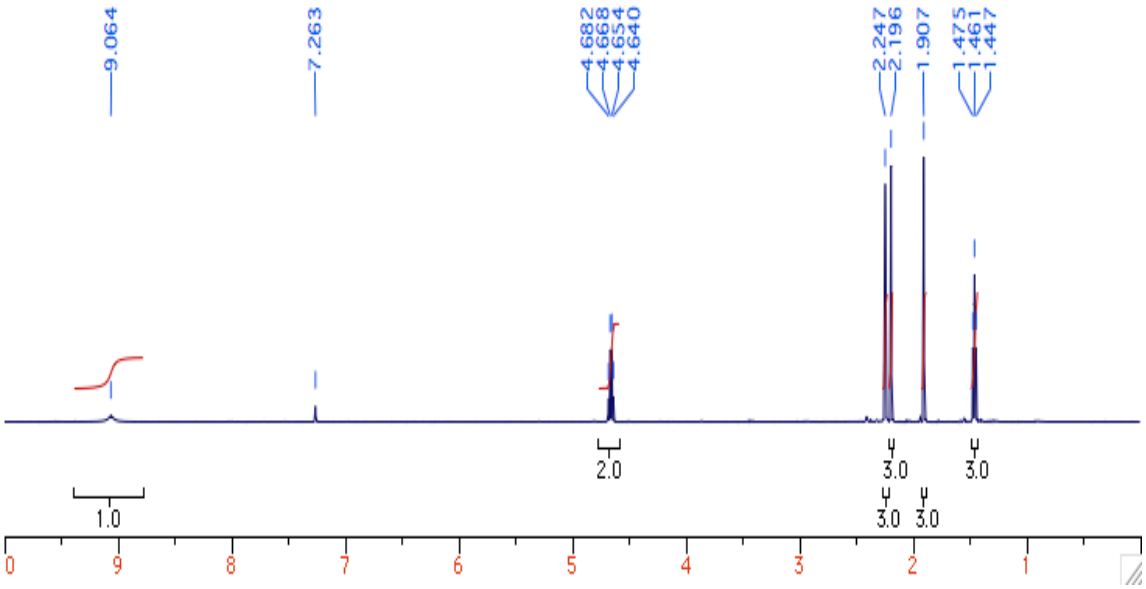
^{11}B NMR ($CDCl_3$, 500 MHz):



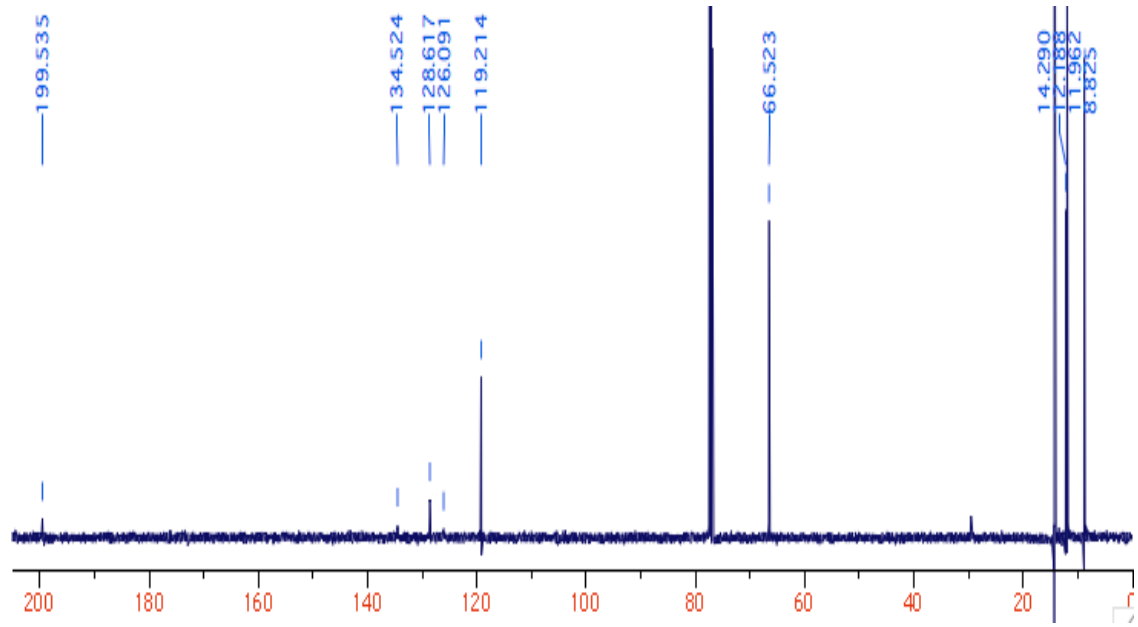
***O*-Ethyl-3,4,5-trimethyl-1H-pyrrole-2-carbothioate (4-11)**



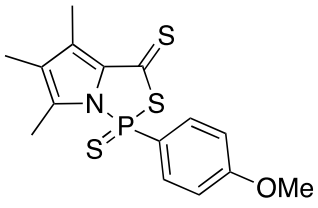
^{1}H NMR ($CDCl_3$, 500 MHz):



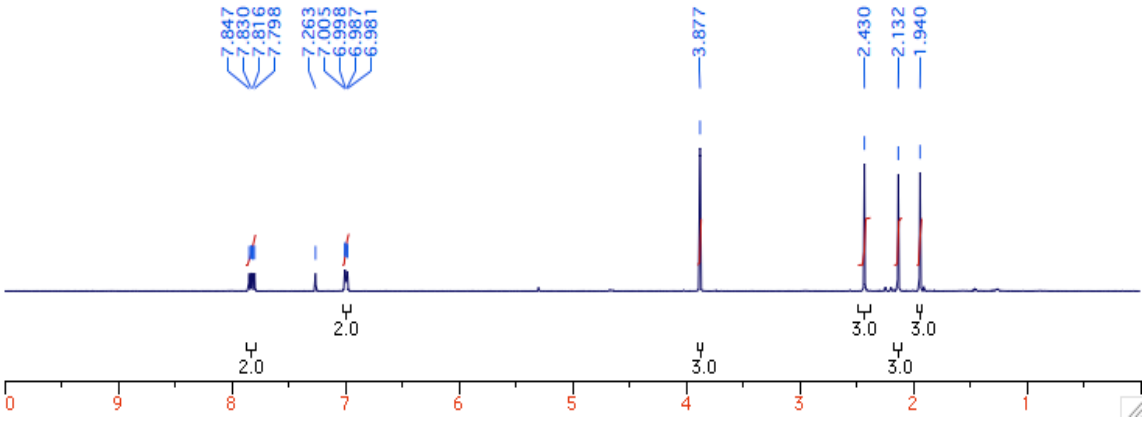
^{13}C UDEFT NMR ($CDCl_3$, 125 MHz):



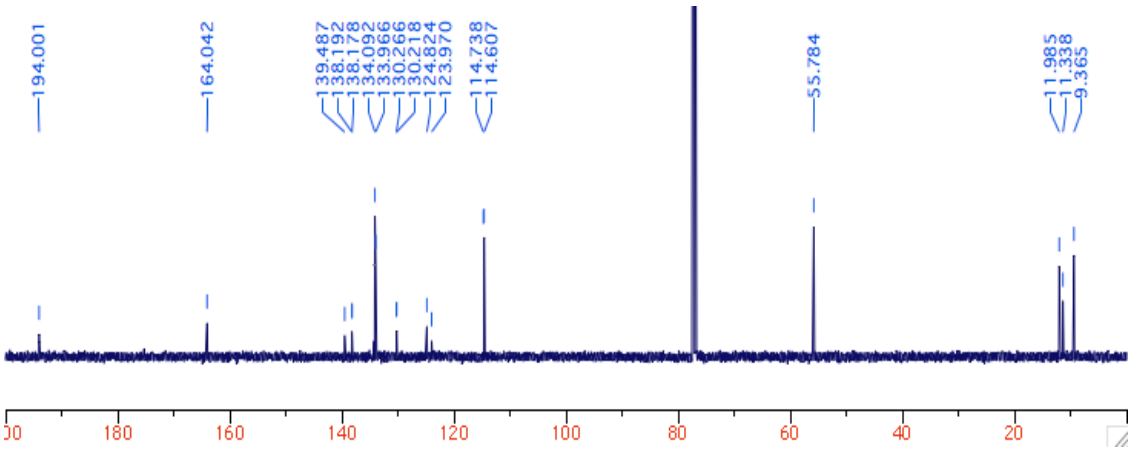
1-(4-Methoxyphenyl)-4,5,6-trimethylpyrrolo[1,2-c][1,3,2]thiazaphosphole-3(1H)-thione-1-sulfide (4-12)



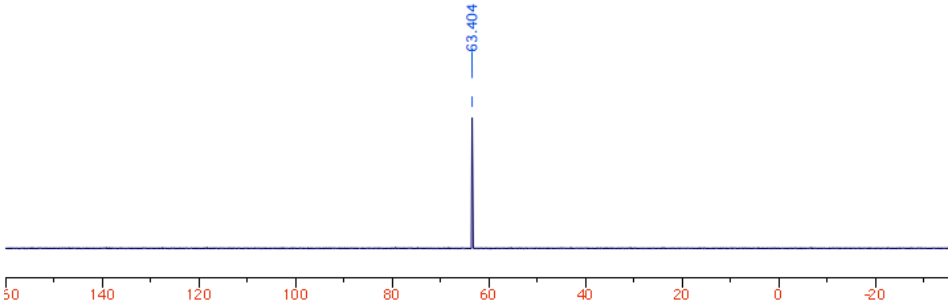
^{1}H NMR ($CDCl_3$, 500 MHz):



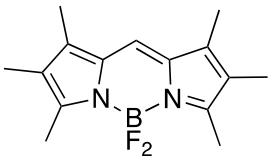
^{13}C UDEFT NMR ($CDCl_3$, 125 MHz):



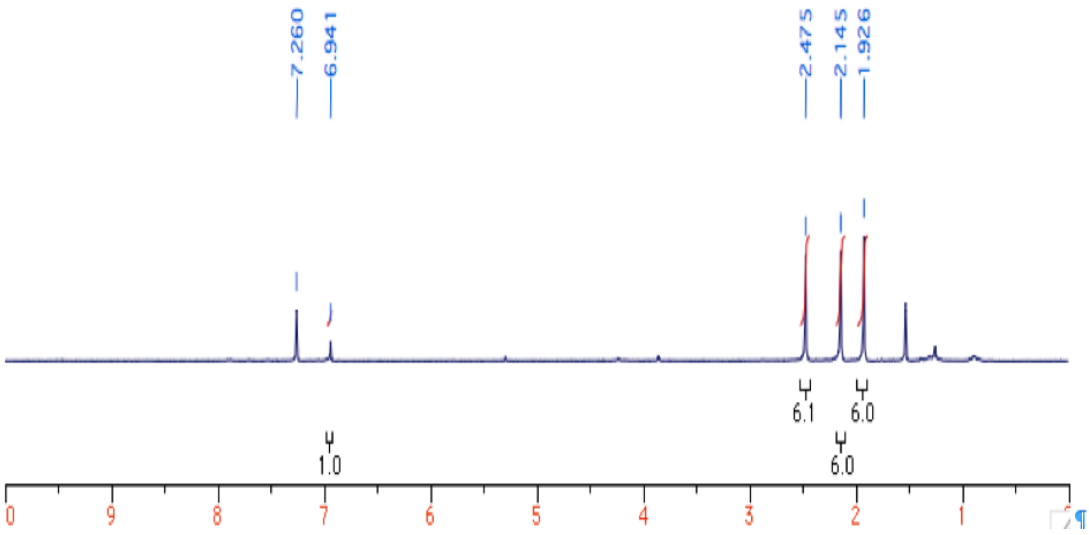
^{31}P NMR ($CDCl_3$, 202 MHz):



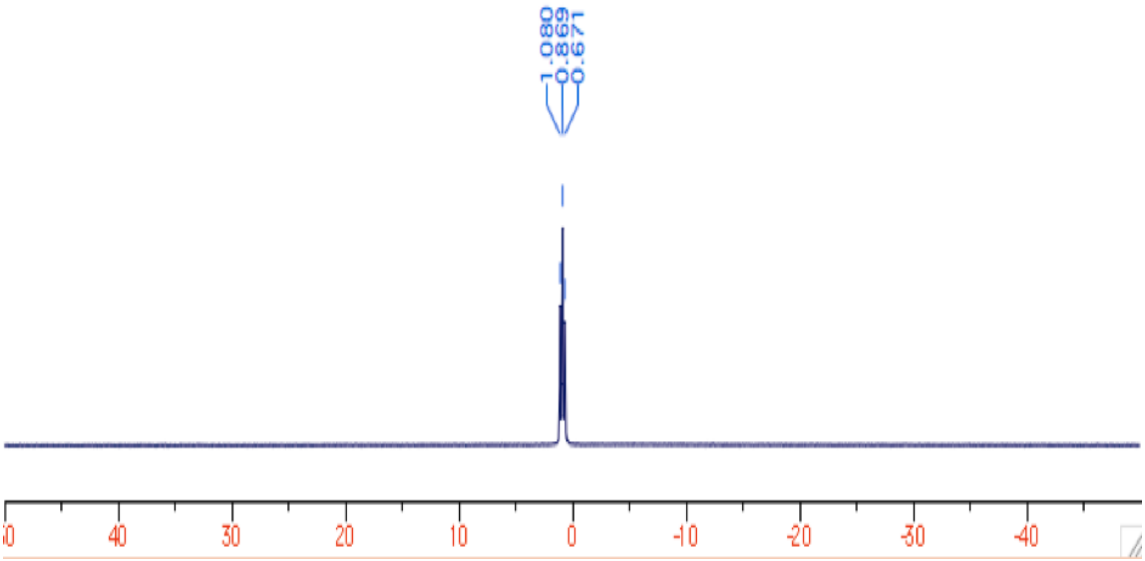
4,4-Difluoro-1,2,3,5,6,7-hexamethyl-8-H-4-bora-3a,4a-diaza-*s*-indacene (4-15)



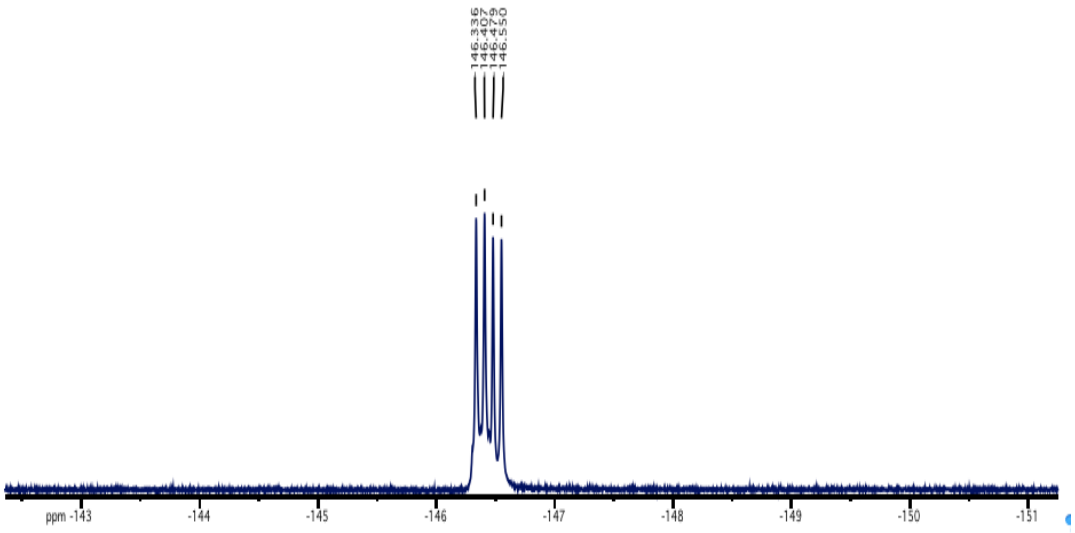
^{1}H NMR ($CDCl_3$, 500 MHz):



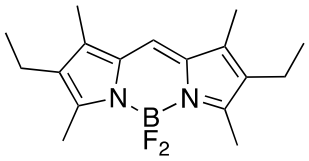
^{11}B NMR ($CDCl_3$, 160 MHz):



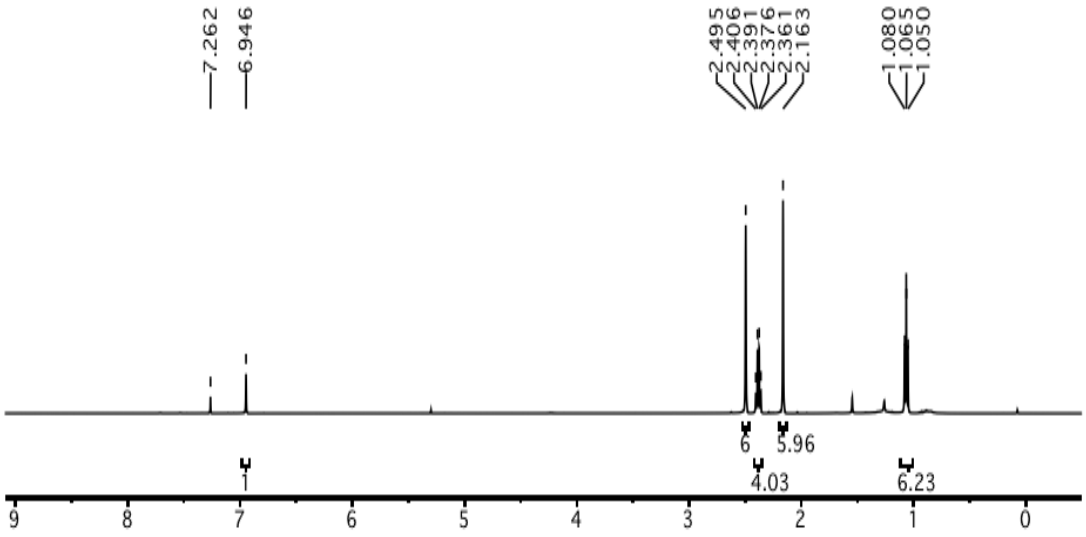
^{19}F NMR ($CDCl_3$, 470 MHz):



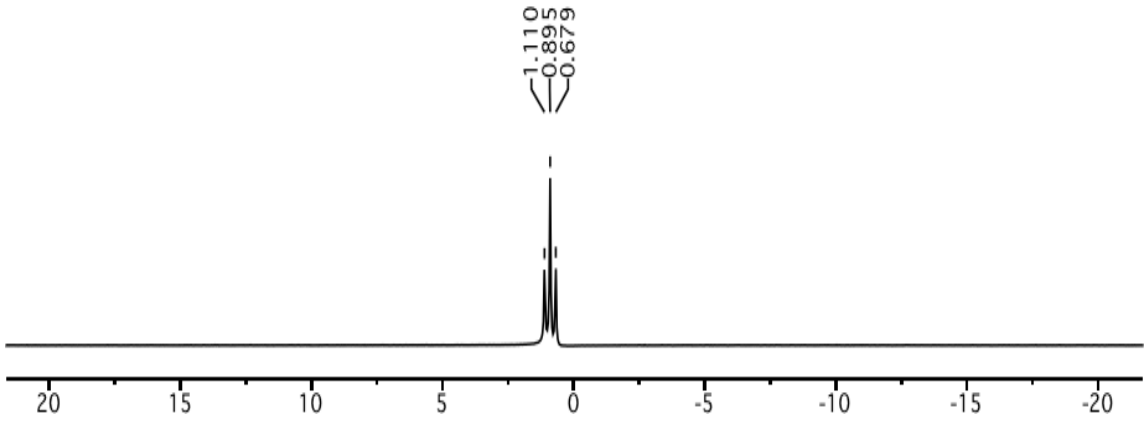
2,6-Diethyl-4,4-difluoro-1,3,5,7-tertamethyl-8-H-4-bora-3a,4a-diaza-*s*-indacene (4-19)



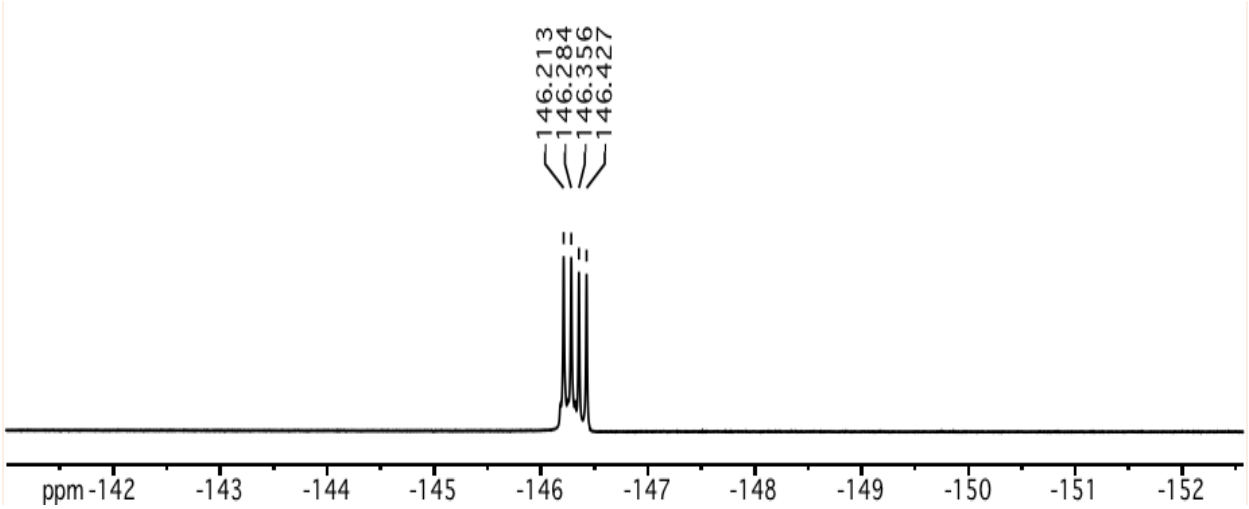
^{1}H NMR ($CDCl_3$, 500 MHz):



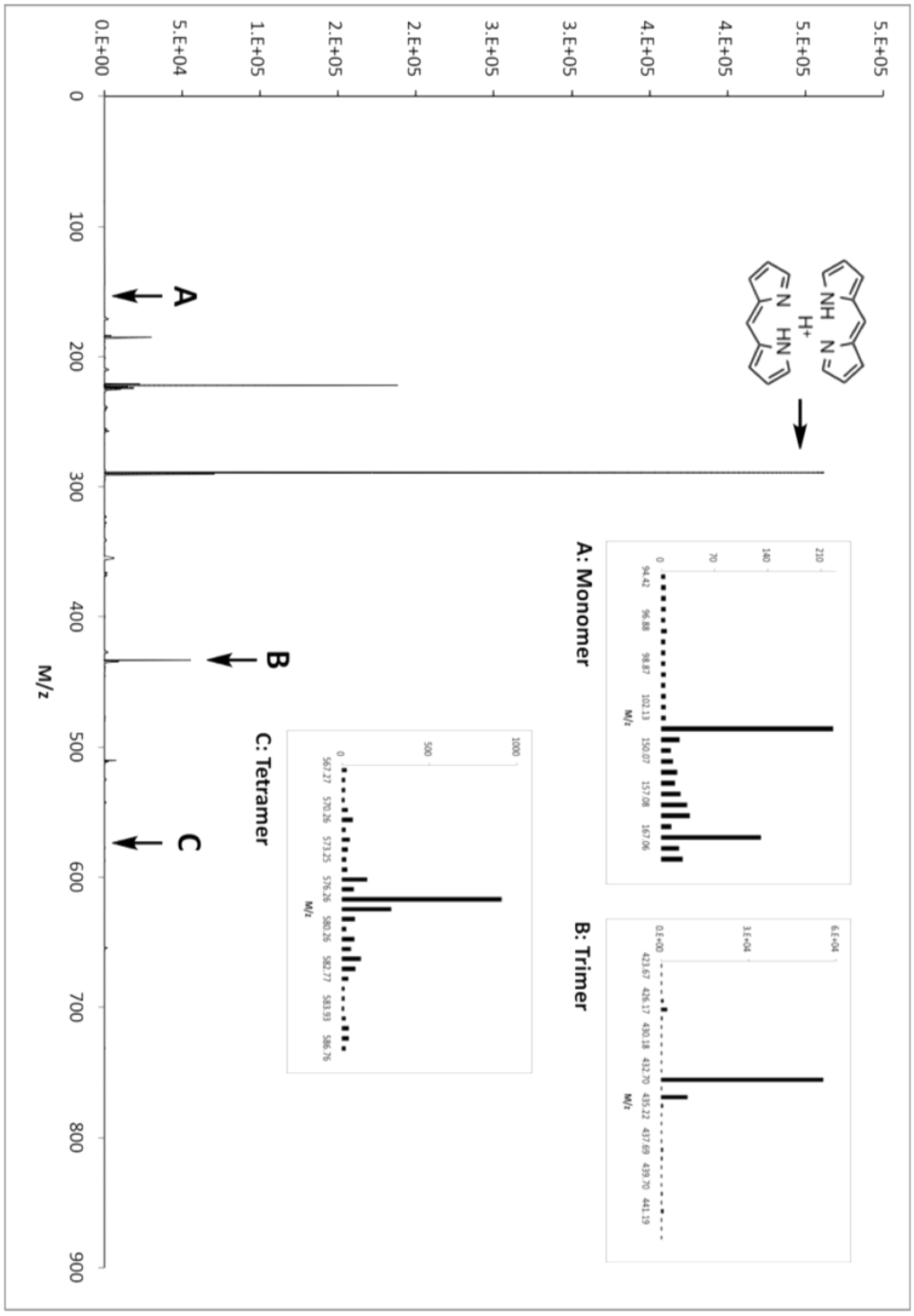
^{11}B NMR ($CDCl_3$, 160 MHz):



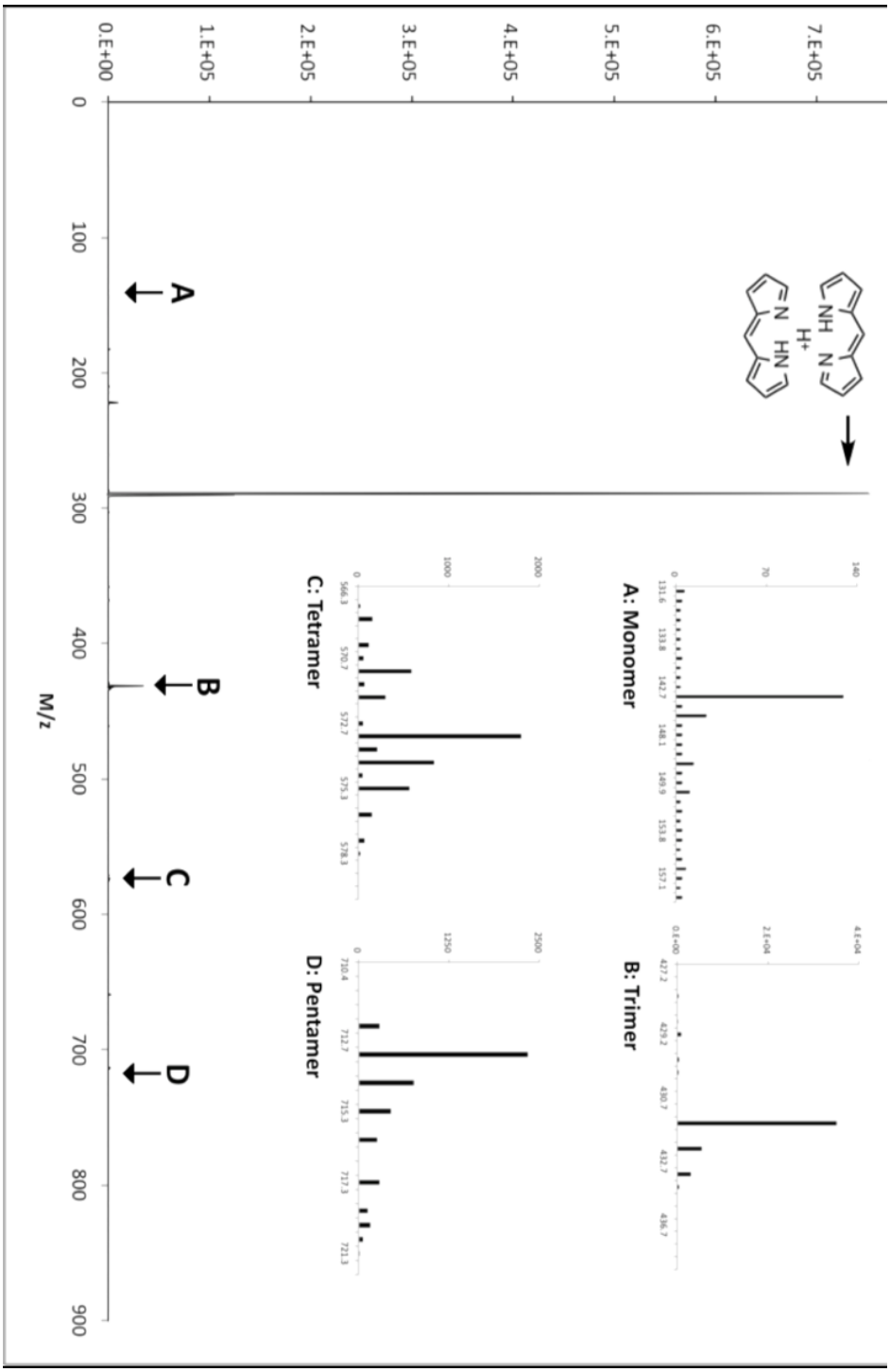
^{19}F NMR ($CDCl_3$, 470 MHz):



Section 4.7: Selected ESI$^+$ Spectra



Low resolution scan of *(Z)*-2-((2*H*-pyrrol-2-ylidene)methyl)-1*H*-pyrrole (**4-1**) produced via oxidation of di(1H-pyrrol-2-yl)methane



Low resolution scan of *(Z)*-2-((2*H*-pyrrol-2-ylidene)methyl)-1*H*-pyrrole (**4-1**) produced via deprotection from **4-2**

Chapter 5: Conclusion

Section 5.1: Conclusion

As the discussions found in Chapters 2, 3 and 4 are individually concluded in their respective sections, the Conclusion chapter of this thesis consists as a compilation of these previously-discussed segments.

5.1.1 Chapter 2 Conclusion

In summary, a novel set of prodigiosene analogues have been synthesized, adding to the library of compounds produced by members of the Thompson lab. The NCI, using their 60-cancer cell line panel, has subjected these derivatives to anti-proliferative analysis. The pentyl ester in particular, **2-39**, demonstrated considerable anti-proliferative properties and was synthesized on a larger scale for analysis using hollow fibre assays. Ultimately, the toxicological profile of the compound was deemed insufficient for testing using a traditional xenograft model. Collaborators working with Dr. Jeff Davis (Maryland) used **2-39** as a model against which to measure the basicity and ion-transport capabilities of ester-appended prodigiosenes. This work has been published.[61]

Decarboxylative coupling of 2-pyrrole carboxylic acids with aryl halides has been shown to be viable on *N*-methyl pyrroles bearing various acyl functionalities pendant at the 4- and 5- positions of the pyrrole ring. Although *N*-unprotected pyrroles did not undergo decarboxylative arylation, it is hoped that the use of reversible *N*-protection might be successful. Experimentation with a larger variety of dipyrrin carboxylic acids required, in order to ascertain if decarboxylative aryl-aryl coupling is viable.

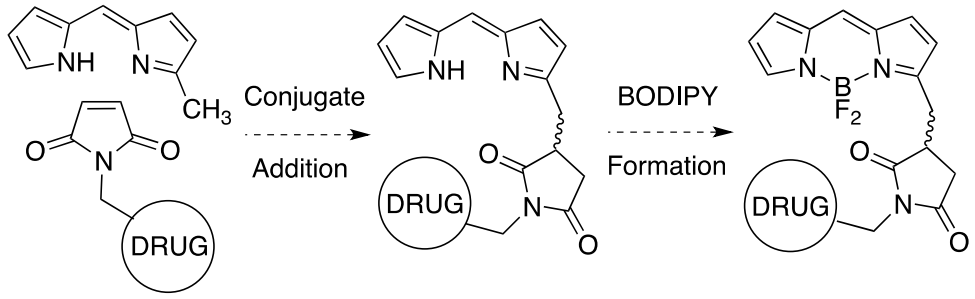
The activation of the 1-methyl moiety of free-base dipyrrins has been utilized to several ends. Firstly, the thermal decomposition products, 1-(pyrrolyl)-dipyrrin dimers, have been isolated and characterized for the first time since their proposal in 1978.[110] The stability of these compounds is certainly in question, and understanding the routes through which decomposition of dipyrrin frameworks occurs is important for a variety of reasons; for example, the increasing prevalence of dipyrrins for use as fluorescent tags in medical imaging, coupled with the realization that *F*-BODIPYs are not as stable as has been previously suggested,[100] means that frameworks such as compound **3-2** would need to be studied for biological effects before *F*-BODIPYs can be approved for use in human subjects. Further study regarding the biological interaction of **3-2**, with collaborators, would be of interest, provided an improved method of synthesis.

5.1.2 Chapter 3 Conclusion

Deuteration of the 1-methyl position on dipyrrins has been shown to be accessible following a simple procedure. As the 1-methyl substituent often serves as a synthetic handle for the synthesis of porphyrins,[121] this methodology allows for facile incorporation of a deuterium label at the *meso*-position of a porphyrin. Similarly, this deuteration phenomenon could have potential for the deuteration of a number of dipyrrin-containing constructs, including prodigiosenes, *F*-BODIPYs, and other dipyrrinato metal complexes that are desired for their optical properties. Furthermore, selective deuteration has been shown to occur where appropriate acyl functionalities are present. This allows for additional synthetic control of the labeling process. Further research on this topic will aim to expand on the effect of acyl functionalization at other positions of the dipyrrin on the deuteration process.

Finally, a methodology for the conjugate addition of *N*-phenylmaleimide to the 1-methyl position of free-base dipyrrins has been developed. This is the first literature report of direct C-C bond formation between the α-methyl group of a free-base dipyrrin and any other carbon source. The technique is applicable to both alkyl and mono-acyl substituted dipyrrins. However, reasonable yields are thus far only attainable with dipyrrins containing a stabilizing acyl functionality. Although the practical application of this chemistry is limited by the scope of reactive electrophiles, maleimides represent a class of compounds that are frequently studied for use in medicinal labeling chemistry.[122] Typically, a drug is attached to the *N*-terminal position of a maleimide. Sulfhydryl groups are then added across the maleimide double bond to form physiologically stable linkages. Conjugate addition of a 1-methyl dipyrrin to a maleimide-drug conjugate would allow for generation of drug-appended *F*-BODIPYs in as few as two synthetic steps (Figure 3-13).

Figure 5-1: **BODIPY tagging of pendant-maleimide drug molecules**



Although the barriers to this chemistry are present in the reluctance of maleimide-appended dipyrrins to complex with $BF_3{\cdot}Et_2O$, the potential for fast access to *F*-BODIPY labeled drug molecules via the procedures described here is alluring.

5.1.3 Chapter 4 Conclusion

In summary, the improved synthesis of unsubstituted *F*-BODIPY **4-2** has facilitated the study of alkylation, alkoxylation and chlorination of the boron atom in this unstable framework. The electrophilic nature of the unsubstituted backbone hinders modular substitution in the case of alkylation, while the instability of the *O*-BODIPY hinders full analysis of the structure. Careful analysis of the reactivity of the chlorinated *Cl*-BODIPY has led to a novel pathway through which the sparsely reported dipyrrin **4-1** can be obtained as a hydrochloride salt. The methodology required to explore transformations to the unsubstituted dipyrrin in a controlled manner is better-developed, and the potential for use of the dipyrrin for other means is now greatly improved. This work has been published.[92]

Sulfination of Knorr pyrroles can be performed in good to excellent yield using Lawesson's reagent with microwave heating under inert conditions in toluene. In addition to the sulfination reaction, a small amount of a novel heterocycle, thiazaphosphole **4-10**, can also be obtained. Further studies will be required to optimize the synthesis of this compound, and a thorough study of conditions suitable for its isolation would be desirable. Researchers using Lawesson's reagent in the presence of Lewis acids and 1-ester pyrroles should be aware of the potential for formation of dipyrrin products.

Lawesson's reagent can also be used in conjunction with $BF_3 \bullet Et_2O$ to generate *F*-BODIPYs from alkyl-substituted Knorr pyrroles under microwave heating conditions. The reaction suffers from low yield and difficult purification from byproducts, but represents a four-step, one-pot process (averaging around 65% yield per step) to form high-value products from simple starting materials. Several important questions remain

pertaining to mechanism and the fate of the unaccounted-for pyrrolic material. This work has been published.[144]

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