Dipyrrins, Pyrrolyldipyrrins, Prodigiosenes and Their Complexes

by

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

at

Dalhousie University
Halifax, Nova Scotia
September 2011

DALHOUSIE UNIVERSITY

DEPARTMENT OF CHEMISTRY

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DALHOUSIE UNIVERSITY

DATE: 29 September, 2011

AUTHOR: Sarah M. Crawford

TITLE: Dipyrrins, Pyrrolyldipyrrins, Prodigiosenes and Their Complexes

DEPARTMENT OR SCHOOL: Department of Chemistry

DEGREE: Ph.D. CONVOCATION: May YEAR: 2012

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Signature of Author

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ABSTRACT

Dipyrrins, pyrrolyldipyrrins and prodigiosenes are a closely related series of molecules: pyrrolyldipyrrins are dipyrrins with a pyrrolic substituent and prodigiosenes are a special class of pyrrolyldipyrrins with a methoxy substituent. Prodigiosenes are known for their anticancer activity, but although there have been a number of developments in their synthesis, chemical manipulation of prodigiosenes is rare. Development of a methodology for the chemical manipulation of prodigiosenes would allow a convergent synthesis of a closely related series of prodigiosenes ideal for investigations into structure activity relationships.

Chemical manipulation of dipyrrins is also rare, but this is largely overcome by first converting dipyrrins to dipyrrinato complexes. The same strategy could potentially apply to pyrrolyldipyrrins and prodigiosenes, but there are very few known pyrrolyldipyrrinato complexes. Three projects were undertaken in order to investigate the chemical manipulation of dipyrrins and pyrrolyldipyrrins.

The first project was to investigate the synthesis of a library of prodigiosenes by way of a convergent approach. The synthesis of a functionalized prodigiosene, with demonstrated anticancer activity, was optimized and many methods for functional group interconversion of an ester attached to the prodigiosene core were investigated. Ultimately, this method was unsuccessful in the synthesis of a library of prodigiosenes due to instability of prodigiosene intermediates.

The second project was to investigate the synthesis of pyrrolyldipyrrinato complexes. A series of pyrrolyldipyrrinato tin(IV) complexes with a previously unobserved binding mode for pyrrolyldipyrrins were successfully synthesized and one complex of the series was characterized using x-ray crystallography. Although fluorescent dipyrrinato complexes, with the exception of boron difluoride complexes, are rare, all of the pyrrolydipyrrinato tin(IV) complexes were highly fluorescent with fluorescence quantum yields between 0.28 to 0.61.

The third project was to develop a protection method for pyrrolyldipyrrins using dipyrrins as model compounds. A general, high yielding method was developed to remove the BF_2 group from a dipyrrinato borondifluoride complex to generate a dipyrrin. Preliminary application of this deprotection methodology to prodigiosene boron difluoride complexes shows promise. This deprotection methodology allowed for the development of a new methodology for the synthesis of *meso*-alkyl substituted dipyrrins *via meso*-modification of their corresponding boron difluoride complexes.

LIST OF ABBREVIATIONS USED

δ	Chemical shift
ε	Molar extinction coefficient
Φ_F	Fluorescence quantum yield
Ac_2O	Acetic anhydride
AcOH	Acetic acid
BME	Benzylmethyl ether
Bn	Benzyl
BOC	*tert*-Butylcarbonyl
F-BODIPY	4,4'-Difluoro-4-bora-3a,4a-diaza-*s*-indacene
br	Broad
d	Doublet
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyanobenzoquinone
dec.	Decomposition
DEF	Diethylformamide
DIPEA	Diisopropylethylamine
DMAP	4-(Dimethylamino)pyridine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic acid
2,4-DNP	2,4-Dinitrophenylhydrazone
dsDNA	Double stranded deoxyribonucleic acid
eq	Equivalents
ESI	Eletrospray ionization
Et	Ethyl
GI_{50}	Growth inhibition, 50%
h	Hour

HBTU	2-(1*H*-Benzotriazole-1-yl)-1,1,3,3-tetramethylaminium hexafluorophosphate
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
IUPAC	International Union of Pure and Applied Chemistry
J	Coupling constant
LC_{50}	Lethal concentration, 50%
lit	Literature
m	Multiplet
m.p.	Melting point
MIC	Minimum inhibitory concentration
min	Minute
MW	Microwave irradiation
NBS	*N*-Bromosuccinimide
NMR	Nuclear magnetic resonance
OAc	Acetate
Ph	Phenyl
ppm	Parts per million
q	Quartet
s	Singlet
SAR	Structure Activity Relationship
SEM	2-(Trimethylsilyl)ethoxymethyl
t	Triplet
TEA	Triethylamine
TEOF	Triethylorthoformate
THF	Tetrahydrofuran
TFA	Trifluoroacetic acid
Tf_2O	Trifluoromethanesulfonic anhydride
TGI	Total growth inhibition
TLC	Thin layer chromatography
TMOF	Trimethylorthoformate
UV/Vis	Ultraviolet-visible

ACKNOWLEDGEMENTS

"It is the dull eventless times that have no duration whatever. A time splashed with interest, wounded with tragedy, crevassed with joy- that's the time that seems long in the memory."

~ John Steinbeck (East of Eden)

I would first like to thank my supervisor, Prof. Alison Thompson for her support throughout my graduate studies. Under her guidance, I have developed many skills in chemical research, writing and teaching. I would also like to thank my committee members for their support and helpful suggestions during the course of this work. Financial support for my research was provided by the Natural Sciences and Research Council of Canada and Dalhousie University.

In addition, I am indebted to several members of the Department of Chemistry and would like to thank them for their assistance: Dr. T. Stanley Cameron, for solving the X-ray crystal structures of the compounds contained herein; Dr. Xiao Feng, for recording and processing the mass spectra of the compounds contained herein; Dr. Mike Lumsden for help troubleshooting ^{119}Sn and ^{15}N HMBC NMR experiments; Dr. Srinivasulu Bandi, Dr. David L. Jakeman and Dr. Susan E. Douglas for conducting the antimicrobial screening; and Dr. Neil Burford, for kindly providing laboratory space for me to work in from September 2010 to September 2011.

I would also like to acknowledge my fellow researchers and colleagues whom I have had the pleasure to know, interact with and learn from over the past four years: Dr. Adeeb Al-Sheikh Ali, Heather Cosh, Dr. H. Martin Gillis, Brandon Groves, Cassandra Hawco, Carla Jackson, Travis Lundrigan, Christy MacDonald, Dr. Estelle Marchal, Jennifer Melanson, Beth Pearce, Dr. Deborah Smithen, Dr. Srinath Thirumalairajan and

Dr. Md. Imam Uddin. I would also like to extend a special thanks to Dr. Adeeb Al-Sheikh-Ali for his help and guidance when I was a new graduate student. I would also like to extend a special thank-you to the current members of the Thompson group who have been very accommodating while I have been working in a separate laboratory space.

I have also had the opportunity to work with a volunteer and two summer students over the past four years and benefited greatly from the experience, as I hope they did. I would like to acknowledge Matthew White (for his work with the selective hydrolysis of pyrrole dicarboxylates), Lauren Longobardi (for her work with bis(dipyrrinato) *F*-BODIPY complexes), and Lloyd Tucker (for his work with bis(dipyrrinato) complexes).

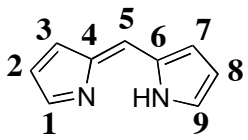
Lastly, I would like to thank my family. Thanks especially to my husband Nathan for his support, understanding and encouragement throughout my graduate studies. Finally, thanks to my parents, Stephen and Joan Bennett; my sister and brother, Elizabeth Bennett and Matthew Bennett; my parents in-law, Dale and Carol Crawford; and my grandparents in-law, Ken and Wendy Dickson for their support over the past four years.

CHAPTER 1 Introduction

1.1 Dipyrrins and Their Complexes

Dipyrrins are fully conjugated, planar molecules that consist of an azafulvene attached to a pyrrole through the 2-position. The structure and nomenclature of the dipyrrin skeleton, as recommended by IUPAC,[1] is depicted in Figure 1.

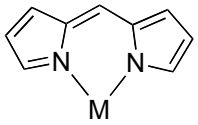
Figure 1. Structure and numbering of the dipyrrin unit



The 1- and 9-positions are commonly referred to as the α-positions, the 2-, 3-, 7- and 8-positions are commonly referred to as the β-positions and the 5-position is commonly referred to as the *meso*-position.

Dipyrrins have varying levels of stability, which correlate with the number, location and type of substituents. The fully unsubstituted dipyrrin (Figure 1) is not stable above -40 ˚C due to its susceptibility to both nucleophilic and electrophilic attack.[2] Alkyl substitution at the 1-, 2-, 3-, 7-, 8-, and 9-positions increases the stability of the resulting dipyrrin, but adding an aryl substituent at the 5-position greatly increases the stability. Dipyrrins without an aryl substituent in the 5-position are routinely isolated as their hydrochloride or hydrobromide salts, which are more stable than their corresponding free-base dipyrrins. The N*H* proton of a dipyrrin can be removed with a strong alkali base to give the dipyrrinato anion of the corresponding metal salt, which can coordinate to a metal centre, typically bound in a κ^2 fashion as shown in Figure 2.

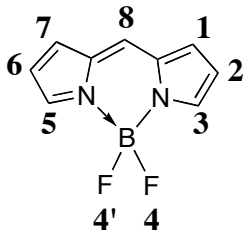
Figure 2. κ^2 Binding in a dipyrrinato complex



A wide variety of isolable dipyrrinato metal complexes have been synthesized, varying both in complexation geometry and metal ion.[3] Dipyrrinato complexes of select alkali metals, alkaline earth metals, transition metals and non-metals are all known.[3] The chemical manipulation of dipyrrinato complexes is far more commonly reported in the literature than the direct chemical manipulation of dipyrrins. This is presumably because in dipyrrinato complexes the nitrogen atoms of the dipyrrin are effectively protected by the metal cation to which they are coordinated.[3]

The most thoroughly studied dipyrrinato complexes are the borondifluoride complexes. These complexes have high thermal and photochemical stability, impressive chemical robustness and high fluorescence quantum yields, as well as tunable fluorescence properties. These properties are broadly exploited in their use as dyes, as fluorescent probes in biological systems, as materials for incorporation into electroluminescent devices, and as chemical sensors.[4, 5] These complexes are formally known as 4,4'-difluoro-4-bora-3a,4a-diaza-*s*-indacenes and commonly referred to as BODIPYs. The nomenclature of the structure is based on that of the analogous all-carbon tricyclic ring, and the numbering of the substituents follows that of indacene,[5] as highlighted in Figure 3.

Figure 3. BODIPY framework and numbering



The numbering scheme for BODIPYs is not consistent with the dipyrrin numbering scheme (Figure 1). It is useful to instead refer to the 5- and 3-positions as the α-positions, the 1-, 2-, 6-, and 7-positions as the β-positions and the 8-position as the *meso*-position when comparing a BODIPY with its parent dipyrrin, or to adopt the dipyrrin numbering scheme, in order to avoid confusion between the different numbering schemes. As the boron centre of the BODIPY can be substituted with groups other than fluoride, it is customary to add a prefix to the abbreviation to denote the type of substituent at boron: F for fluoro, O for oxygen, C for alkyl or aryl, E for alkynyl,[5] H for hydrido and X for the other halogens.

One area in this field that remains underexplored is the chemical modification and manipulation of dipyrrins, which is likely due to the inherent instability of the free-base dipyrrin unit. However, in the past ten years, there have been an increasing number of reports of direct chemical modification of dipyrrinato complexes. The majority of these examples involve simple functional group transformations remote to the dipyrrinato core, but there are also some reports of direct modification to the dipyrrinato core of a BODIPY. Another area in the field that remains underexplored is the synthesis of other dipyrrinato complexes with interesting optical properties: the majority of reported dipyrrinato complexes, with exception of BODIPYs, exhibit limited to no fluorescence.[3]

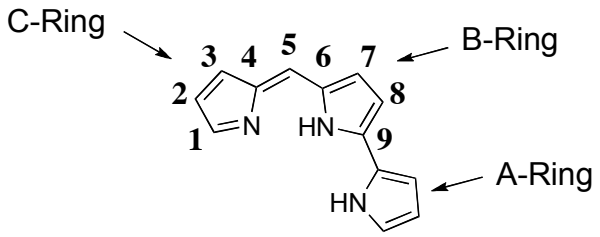
The work reported here aims to explore the existing methodologies and develop

new methodologies for the synthesis and chemical manipulation of *F*-BODIPYs, dipyrrins and their derivatives, and to investigate the properties of new dipyrrinato complexes.

1.2 Pyrrolyldipyrrins, Prodigiosenes and Their Complexes

Pyrrolyldipyrrins are a special class of dipyrrin in which a pyrrole is joined to the dipyrrin through the 9-position (Figure 4). The numbering system shown is adopted from the parent dipyrrin to avoid confusion, and a nomenclature for the different rings in the tripyrrolic system is also shown.

Figure 4. Pyrrolyldipyrrin skeleton and suggested nomenclature



The most well known member of the pyrrolydipyrrin family is the natural product prodigiosin. Members of the prodigiosin family (commonly called prodigioisenes) are pyrrolyldipyrrins with a methoxy substituent at the 7-position of the tripyrrolic skeleton. There have been a number of prodigioisenes isolated from natural sources and many others synthesized chemically in the laboratory, due to interest in their biological activity.[6, 7]

Although there have been many developments in the synthesis of pyrrolyldipyrrins of the prodigiosene family,[6] there has been little work to date on the direct chemical modification of the pyrrolyldipyrrin skeleton. Direct chemical modification of a prodigiosene could potentially allow for a convergent synthesis of a

library of closely related of prodigiosenes, ideal for exploring structure activity relationships. This work explores optimization of the synthesis of prodigiosenes and the feasibility of direct chemical modification of a prodigiosene in order to generate a library of closely related prodigiosenes for investigation of anticancer structure activity relationships.

Pyrrolyldipyrrins, including those of the prodigiosene family, are potentially interesting ligands because they can coordinate in the same fashion as a dipyrrinato ligand, but they have a potentially non-innocent substituent in the 9-position, which could coordinate to the metal centre. Aided by the chelate effect, the pyrrolic substituent could potentially coordinate to the metal through its nitrogen atom in a η^1 fashion or in a face-on η^5 interaction to give a π complex. This is an underexplored area as there are currently only Zn(II),[8-11] Cu(II),[11] and BF_2[12] complexes of pyrrolyldipyrrins known. The work reported herein will describe the synthesis and characterization of the first series of fluorescent pyrrolyldipyrrinato complexes.

1.3 Scope of Thesis

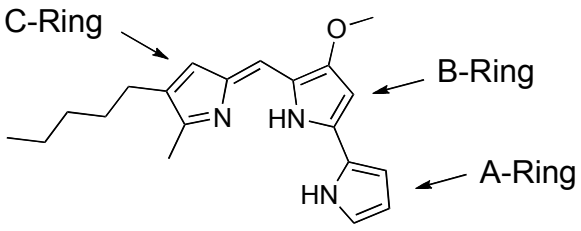
The overall goal of the projects contained herein is the exploration of the synthesis, reactivity and properties of dipyrrins, pyrrolyldipyrrins and prodigiosenes. CHAPTER 2 will discuss the synthesis and chemical manipulation of prodigiosenes. CHAPTER 3 will outline the synthesis of pyrrolyldipyrrin and prodigiosene complexes and investigations of their photophyscial properties. CHAPTER 4 will outline newly developed methodologies for the conversion of *F*-BODIPYs into dipyrrins, *meso*-substituted *F*-BODIPY synthesis, and dipyrrinato boronium cation synthesis.

CHAPTER 2 Prodigiosene Synthesis and Modification

2.1 Background

Prodigiosin (Figure 5) is a tripyrrolic, bright red pigment and the parent of a family of alkaloid natural products characterized by a common 4-methoxypyrrolyldipyrrin core unit.[6] These bright red pigments are secondary metabolites produced by certain bacteria, including those of the *Serratia* and *Streptomyces* genera. Like many bacterial strains, these bacteria prefer starch-rich growth media and the colonies they produce have a distinct bright red color due to the production of prodigiosene pigments.

Figure 5. Prodigiosin



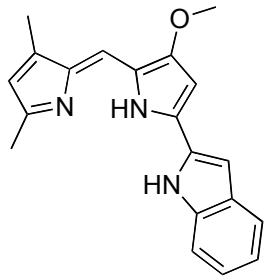
There are many reports of "bleeding" food found in the historical literature that have since been attributed to the growth of these bacterial colonies. In 322 BCE, during Alexander the Great's siege of Tyre, Macedonian seers interpreted the "blood" a solider found on the inside of his piece of bread as an indication that the city, which they were about to besiege, would fall. In 1263, at the Church of Saint Christina near Bolsena, a priest, feeble in faith, was celebrating mass and observed "blood" dripping from the sacramental bread. His faith was restored and this miracle is commemorated today as the festival of Corpus Christi and is the most famous example of "bleeding" food on record.[6]

Although the scientific nature of these "miracles" is understood today, prodigiosenes remain a compound class of interest because they exhibit immunosuppressive, antimicrobial, antifungal, antiprotozoal, antimalarial and anticancer properties.[6, 7] An early chemotherapeutic, Coley's toxin,[13] which consisted of a mixture of sterilized cultures of *Streptococcus* species and *Serratia marcescens*, was used to treat cancerous tumors from 1893 to 1963, before it was banned by the FDA. One can speculate that the presence of prodigiosin in the sterilized cultures contributed to the efficacy of this chemotherapeutic. Prodigiosin itself is not suitable for clinical development as an anticancer pharmaceutical because it exhibits systemic toxicity at effective anticancer doses. In contrast, prodigiosenes (synthetic derivatives of the natural product prodigiosin) are considered to be attractive targets for development as anticancer chemotherapeutics as they are able to induce apoptosis in several human cancer cell lines and also show *in vitro* cytotoxicity for several cell lines.[14]

The diverse molecular mechanisms by which prodigiosenes induce apoptosis are still under widespread investigation. However, the anticancer activity of prodigiosenes is currently thought to arise from their abilities to interfere with protein kinase C isozymes, interfere with the Bcl-2 family of intrinsic apoptotic regulation proteins, damage and intercalate into DNA, and modify the pH of cellular organelles.[6] Prodigiosenes are able to raise intracellular pH by acting as rapid and reversible symporters of H^+ and Cl^-,[15-18] which may trigger apoptosis. In structure activity relationship (SAR) studies, the tripyrrolic core has been determined to be essential to this symport mechanism as protonation of the basic site allows for the formation of a tight ion pair that allows transmembrane transport of the H^+/Cl^- ion pair.[18] Prodigiosenes bind to double stranded

DNA (dsDNA) through intercalation into the minor groove, and oxidatively cleave dsDNA in a copper-mediated reaction.[19, 20] All of the nitrogen atoms in the tripyrrolic structure bind to Cu(II) in a complex where the C-ring of prodigiosin has been oxidized, making the tripyrrolic core essential for this mode of activity.[11] Published SAR studies all confirm that the triheterocyclic core of prodigiosenes, featuring either a pyrrolic or an indolic A-ring, is essential for anticancer activity.[21-24] Obatoclax (GX15-070), shown in Figure 6, is an A-ring indole prodigiosene that functions as a Bcl-2 inhibitor to induce apoptosis.[25]

Figure 6. Obatoclax (GX15-070)

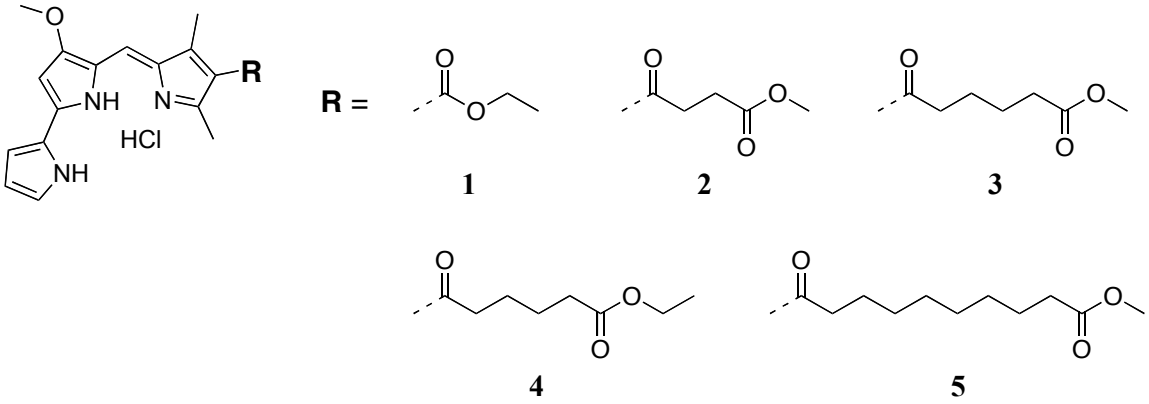


Obatoclax, developed by Gemin X and recently acquired by Cephalon, is currently in Phase 2b clinical trials against extensive stage small cell lung cancer.[26] Other SAR studies of prodigiosenes have shown that the methoxy group on the B-ring is essential for cytotoxicity.[27, 28] With this knowledge, future SAR studies should focus on modifying the A- and C-rings of the tripyrrolic prodigiosene core structure.

Recently, the Thompson group has reported the synthesis of C-ring modified prodigiosenes that have pendant ester groups (Figure 7)[29] attached to the prodigiosene core *via* either an ester or a ketone linkage. Incorporation of ester functionality on the C-ring has two major benefits: (i) the placement of a carbonyl group adjacent to the heterocyclic skeleton has been found to have a stabilizing effect that serves to facilitate

synthesis and isolation; and (ii) the ester group, be it directly conjugated to the prodigiosene core or pendant to it, provides opportunity for further functionalization of the prodigiosene.

Figure 7. C-Ring modified prodigiosenes



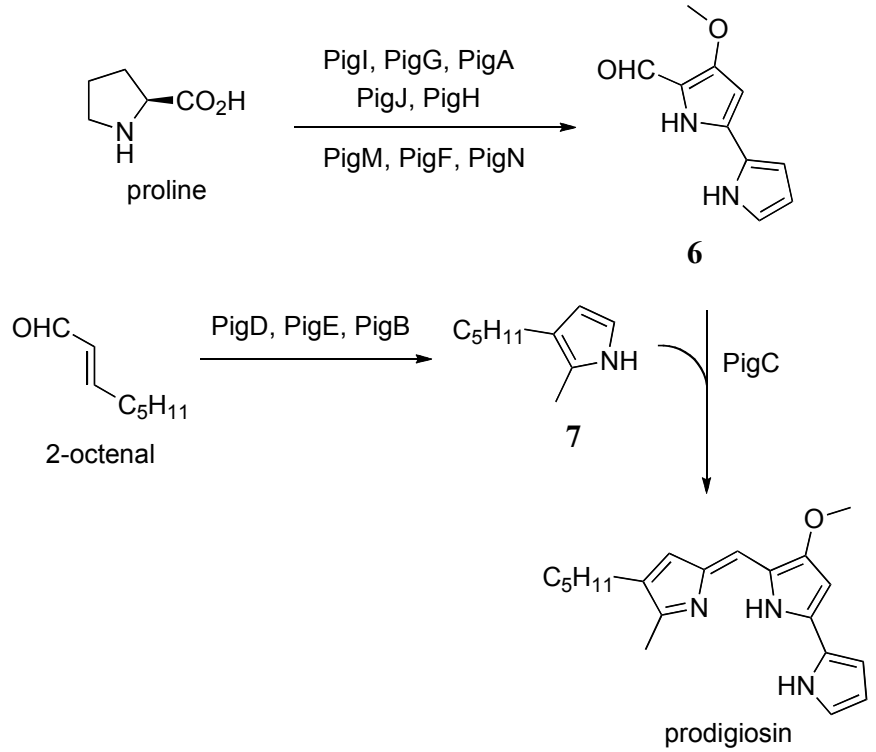
Of the synthetic C-ring modified prodigiosenes synthesized in the Thompson laboratory **1** through **5** exhibited significant H^+/Cl^- transmembrane transport,[15] although the introduction of the carbonyl group adjacent to the pyrrolic skeleton decreased transport efficiency, relative to prodigiosin itself. The synthetic prodigiosenes were shown to maintain the oxidative, copper-mediated DNA cleavage ability of the parent prodigiosene, although at a slightly slower rate than the parent prodigiosin.[15] Of the synthetic C-ring esters, prodigiosene **1** exhibited the best combination of activity in both H^+/Cl^- transmembrane transport and copper-mediated DNA cleavage ability and also showed decoupled growth inhibition and cytotoxicity properties *in vitro*, making it an interesting target for further investigation.

2.2 THE CHEMISTRY OF PRODIGIOSENES

2.2.1 Synthetic Approaches to Prodigiosenes Reported in the Literature

In nature, prodigiosenes are synthesized by way of an enzyme-catalyzed condensation reaction between proline-derived 3-methoxy-5,5'-bipyrrole-2-carbaldehyde (**6**) and 2-methyl-3-pentylpyrrole (**7**), the latter derived from 2-octenal (Scheme 1).[30]

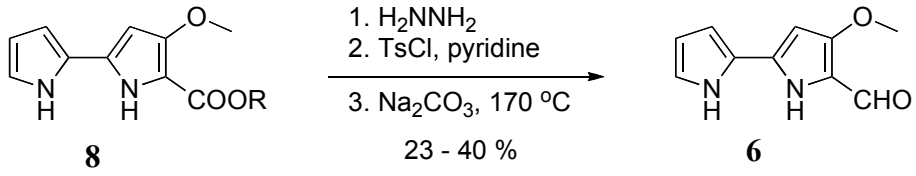
Scheme 1. Outline of the biosynthesis of prodigiosin



In the laboratory, prodigiosenes have been synthesized using a variety of methods. The routes can be divided into two main categories: those involving a biomimetic condensation between bipyrrole carbaldehyde **6** and a pyrrole as the final synthetic step, and those involving a carbon-carbon bond forming cross-coupling reaction as the final synthetic step.

The very first total synthesis of prodigiosin, in 1962, relied on a biomimetic condensation step[31] and this method remained the most popular for some time. The methods used to generate the bipyrrolic aldehyde precursor varied, but the final step of each method relied on a low-yielding McFayden-Stevens reduction of an ester (**8**) to generate bipyrrole aldehyde **6** (Scheme 2).[6]

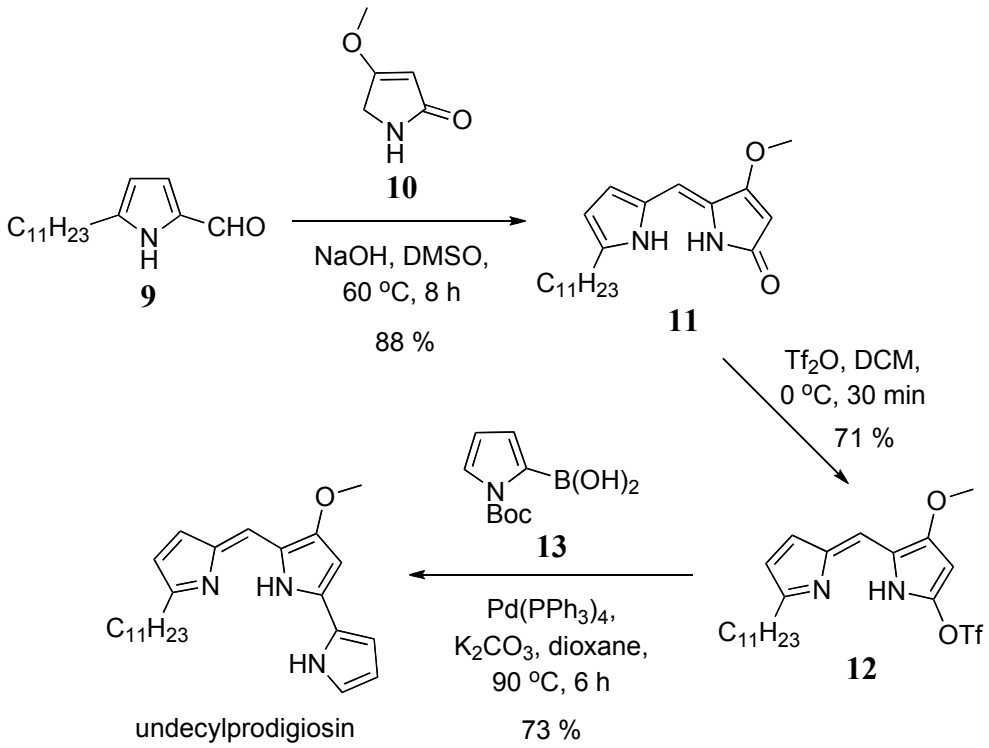
Scheme 2. General McFayden-Stevens reduction of bipyrrole ester **8**



8 **6**

In 1996, D'Alessio and co-workers reported an alternate synthetic route, which avoided the synthesis of bipyrrole aldehyde **6** (Scheme 3). The reaction relied on the formation of a dipyrrinone (**11**) from the base-catalyzed condensation of the 2-formyl pyrrole **9** with the commercially available pyrrolinone **10**. The dipyrrinone was converted to its corresponding triflate (**12**), which was then converted to undecylprodigiosin by way of a one-pot Suzuki coupling and BOC deprotection.[32] This method represented an improvement over all of the other synthetic routes as it was both scalable and higher yielding.

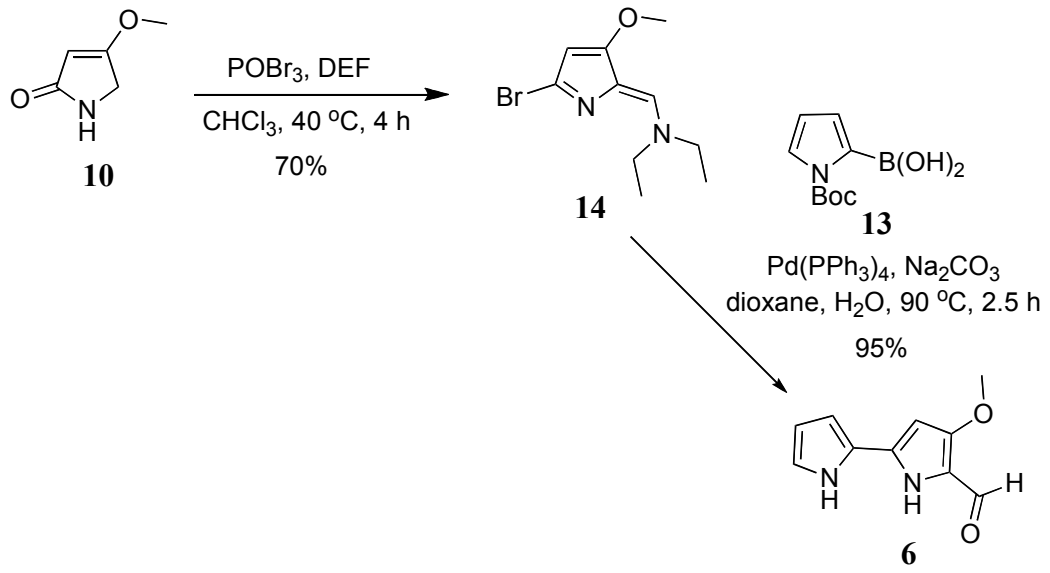
Scheme 3. D'Alessio's methodology for the synthesis of prodigiosenes



Many syntheses of prodigiosin itself and synthetic derivatives of the prodigiosene family rely on this methodology.[22, 33-37] A modified version of D'Alessio's methodology has been implemented in the synthesis of prodigiosenes in the Thompson group.[29] The modification involves using potassium hydroxide as the base and tetrahydrofuran as the solvent in the condensation step to form pyrrolinone. These modifications were adopted because they were found to give higher, and more reproducible, yields than the original method.

In 2006, Dairi and coworkers from Gemin X Biotechnologies Inc. published a high-yielding synthesis of bipyrrole aldehyde **6** (Scheme 4), which made the biomimetic condensation a feasible synthetic route to prodigiosenes. The procedure involved the synthesis of a bromopyrrole enamine followed by a Suzuki coupling with *N*-Boc-pyrrole-2-boronic acid (**13**).[38]

Scheme 4. Dairi's synthesis of bipyrrole aldehyde **6**

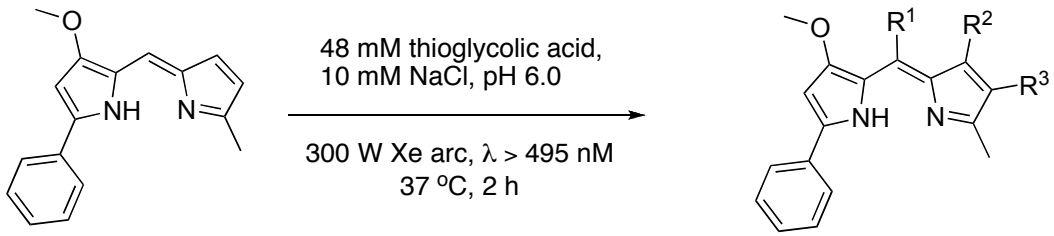


This methodology is gaining popularity in prodigiosene synthesis[30, 39, 40] and has also been adapted for use in the large scale production of Obatoclax.[41] Unfortunately, other researchers who have implemented this synthetic route reported modified protocols to prepare both bromoenamine **14** and bipyrrole carbaldehyde **6**, suggesting that this route suffers from unreliable results.[42, 43]

2.2.2 The Chemical Modification of Prodigiosenes

Very little work has been published to date on the direct modification of prodigiosenes. One literature report detailed the photoinduced redox reaction of an A-ring modified prodigiosene derivative with thioglycolic acid to generate a series of thiolated prodigiosenes (Scheme 5).[37]

Scheme 5. Synthesis of thioglycolic acid substituted prodgiosenes



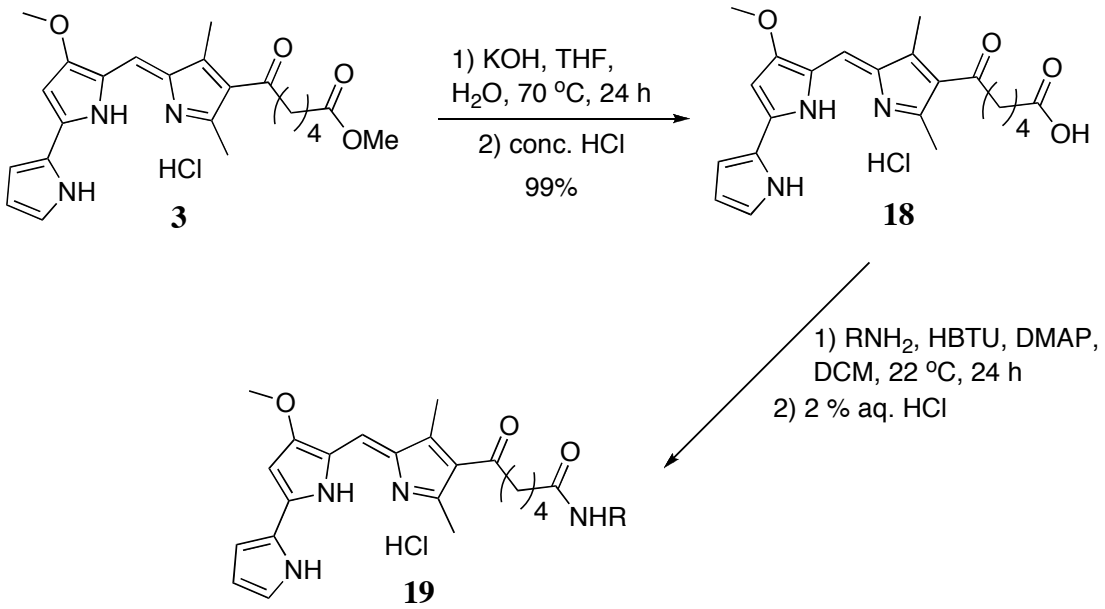
15

16 $R^1 = H, R^2 = SCH_2CO_2H, R^3 = H$
17 $R^1 = R^2 = SCH_2CO_2H, R^3 = H$
18 $R^1 = R^2 = R^3 = SCH_2CO_2H$

The thioglycolic conjugates (**16**, **17**, and **18**) formed in sequential fashion, with the monothioglycolic conjugate (**16**) forming first followed by the di- and trithyoglycolic conjugates (**17**, **18**). This route is not a synthetically viable route as it produces multiple products in low yields. Also worthy of note is the fact that when the phenyl A-ring of **15** is replaced with a pyrrole the resulting tripyrrolic compound does not react to give thioadducts under the same reaction conditions. For this reason, the synthetic manipulation of **15** can be considered a direct modification of a dipyrrin, rather than that of a prodigiosene.

Another route to the functionalization of prodigiosenes was developed by Rosa I. Sáez Díaz, a former post-doctoral fellow in the Thompson group.[9] This method involved the base-catalyzed hydrolysis of an ester to give a carboxylic acid followed by a coupling reaction to generate a series of alkyl, aryl and allyl amide-functionalized prodigiosenes. This method is outlined in Scheme 6.

Scheme 6. Synthesis of amido functionalized prodigiosenes



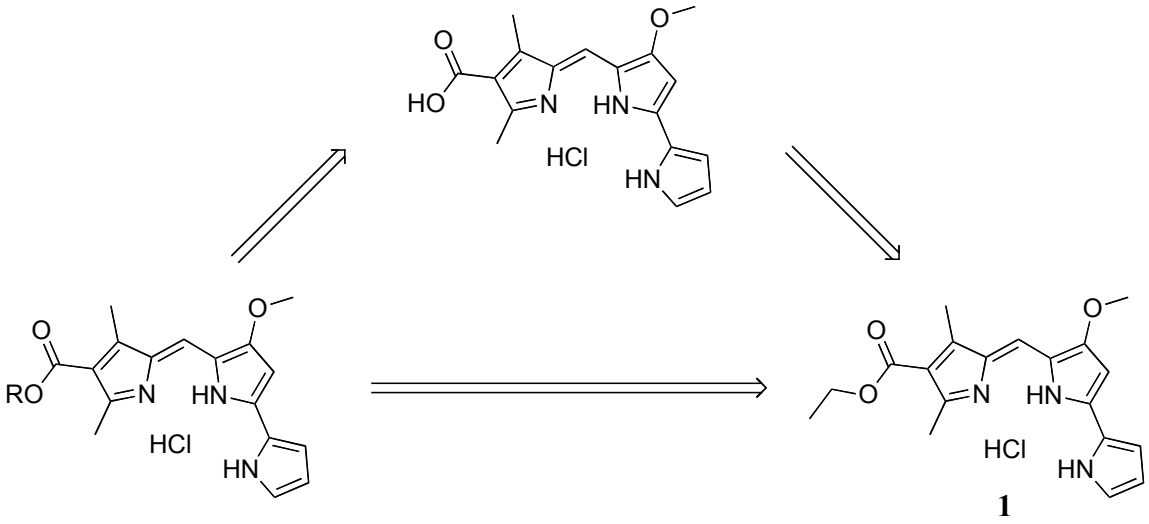
19a R = Ph, 58%
19b R = Bn, 34%
19c R = $CH_2CH{=}CH_2$, 61%
19d R = Et, 60%
19e R = *t*Bu, 82%

To our knowledge, these are the only reports in the literature of direct chemical modification of prodigiosenes. The core of the prodigiosene skeleton contains a dipyrrin and although there is some precedent in the literature for the chemical manipuation or dipyrrins and dipyrrinato complexes, this area is also underexplored.[3] The synthesis and chemical manipulation of the dipyrrin unit will be discussed in more detail in CHAPTER 4.

The overall goal of this project was to synthesize and evaluate the biological activity of derivatives of the ethyl ester prodigiosene **1**. Initially, the goal was to synthesize and evaluate a small library of derivatives where the alkyl group of the ester had been replaced with other alkyl, benzyl and aryl groups. Two approaches were investigated for the synthesis of prodigiosene esters. In the first approach to derivatives

of **1** (Figure 8), the synthesis of ethyl ester prodigiosene **1**, using a modified version of D'Alessio's method,[29] needed to be optimized and then an investigation of the direct derivitization of ethyl ester prodigiosene **1** needed to be undertaken.

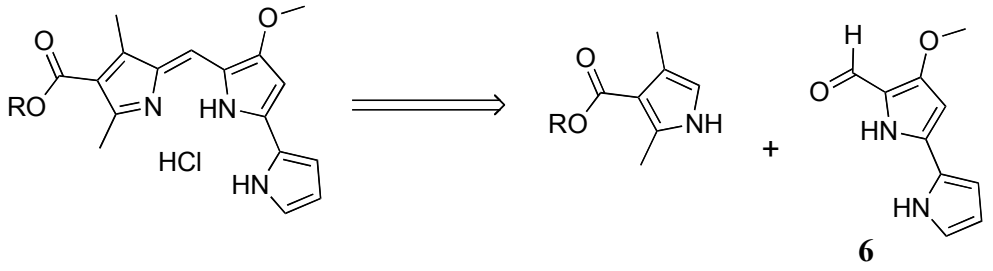
Figure 8. Retrosynthesis for the first approach to prodigiosene derivatives



To our knowledge, there was no literature precedent for the hydrolysis or transesterification of an ester directly attached to the tripyrrolic core of prodigiosin or the hydrolysis of an ester directly attached to a dipyrrin or dipyrrinato complex. However, the acid- or base-promoted hydrolysis of esters directly attached to the tetrapyrrolic core of porphyrins and metalloporphyrrins has been reported.[44-46] In a slight modification of the first approach, prodigiosene **1** could be converted to a metal or boron complex prior to hydrolysis. The addition of a complexation step could serve to both protect and modify the electronic structure of the prodigiosene ligand to render the ester group more susceptible to hydrolysis.

In the second approach to derivatives of **1** (Figure 9), different functionalized 3-carboxylate pyrroles would be joined to the bipyrrole aldehyde **6** by means of a condensation reaction, thus synthesizing the prodigiosene derivatives directly.

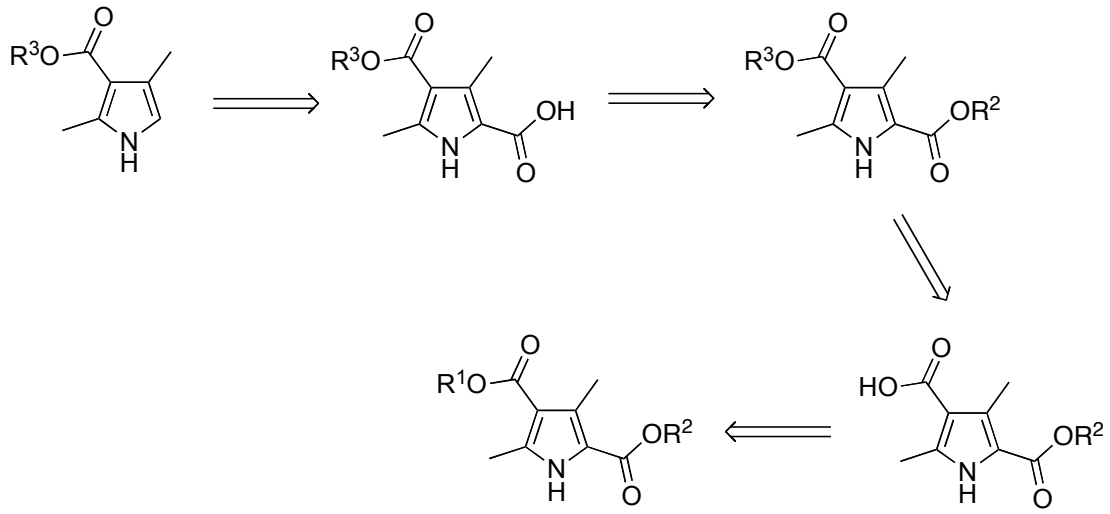
Figure 9. Retrosynthesis for the second approach to prodigiosene derivatives



6

Here, the modified pyrrole that would become the C-ring of the prodigiosene derivative could be synthesized starting from a Knorr pyrrole. A selective deprotection and esterfication strategy followed by a decarboxylation reaction could be utilized to arrive at the desired 3-carboxylate pyrrole products as outlined in Figure 10.

Figure 10. Retrosynthesis of ester-functionalized pyrroles to be incorporated into prodigiosene derivatives



Hydrolysis of 2,4-pyrrole diesters is selective, with acidic conditions favoring hydrolysis of various alkyl groups on the ester at 4-position and basic conditions favoring the hydrolysis of the various alkyl groups on the ester at the 2-position, and there are several recent examples of selective hydrolysis of 2,4-pyrrole dicarboxylates.[9, 47-49] This ability to selectively hydrolyze ester groups in the 2- and 4-positions of pyrroles allows for the preparation of a variety of pyrrole derivatives featuring different esters at the 4-position for incorporation into the prodigiosene skeleton.

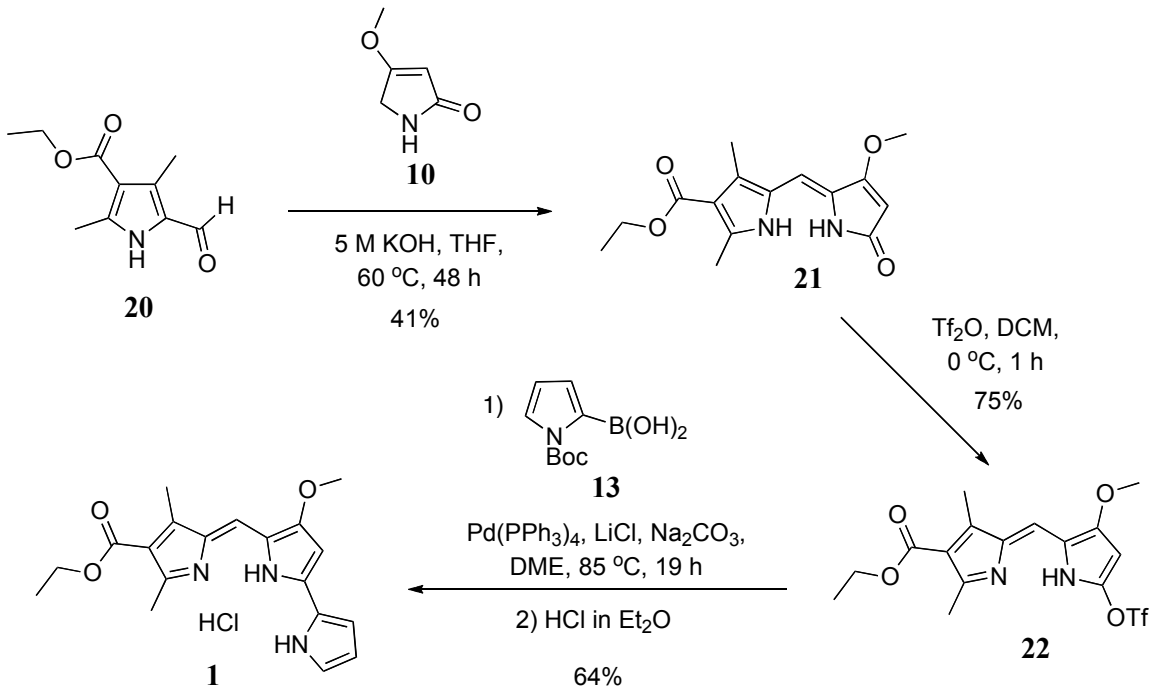
With two promising synthetic strategies with which to access C-ring modified prodigiosenes, the synthesis of a small library of derivatives where the alkyl group of the ester has been replaced by other alkyl, benzyl and aryl groups was undertaken as part of this project. Once isolated and characterized, the biological activity of these derivatives were to be evaluated in order to determine if modification at this position is tolerated in terms of maintaining anticancer and H^+/Cl^- transport.

2.3 Results and Discussion

2.3.1 Optimization of the Synthesis of Ethyl Ester Prodigiosene **1**

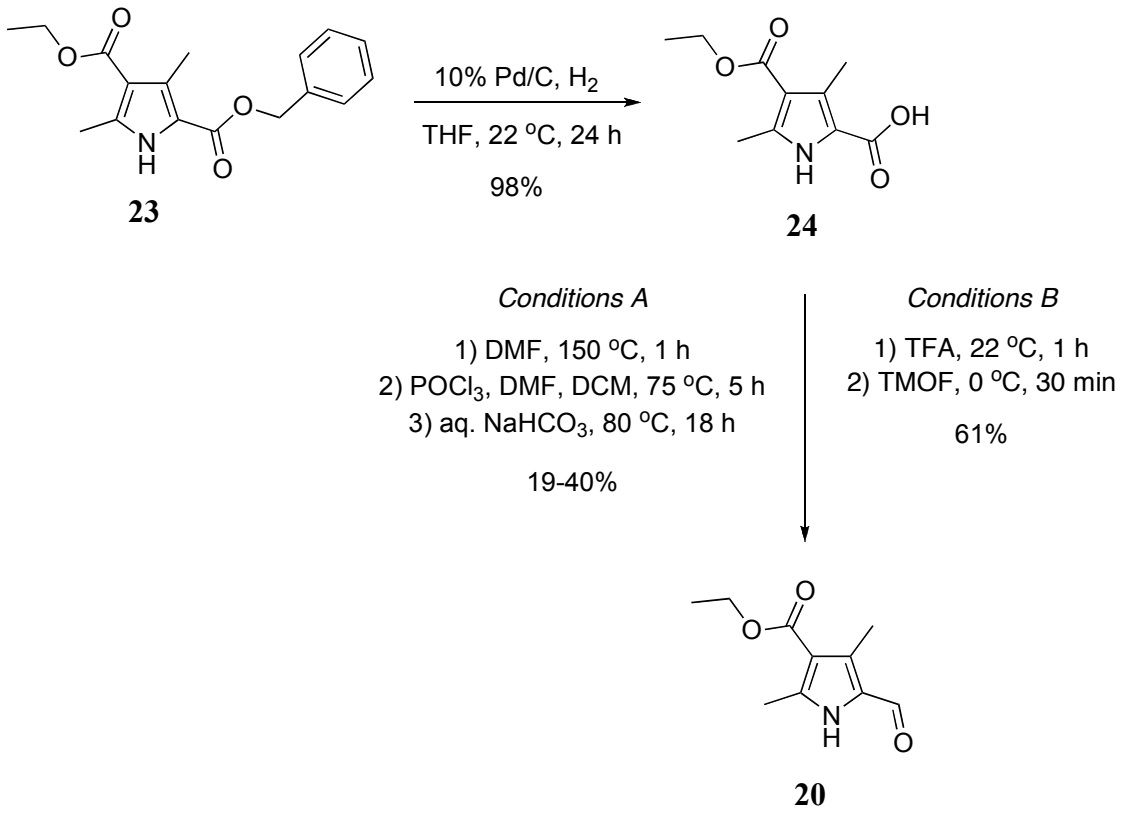
In order to investigate the transesterification and hydrolysis of the ethyl ester prodigiosene **1**, its synthesis had to be optimized in terms of efficiency and scalability, such that multi-gram quantities were available. The Thompson group had previously reported the synthesis of **1** as outlined in Scheme 7.[29]

Scheme 7. Reported synthesis of prodigiosene **1**[29]



This synthesis[29] was in need of improvement as it was low yielding (20% over the three steps shown in Scheme 7), but one of the major difficulties in its optimization was the synthesis of pyrrole **20**. The benzyl group of pyrrole **23**,[50] the product of a Knorr reaction between benzyl acetoacetate and ethyl acetoacetate, may be removed in quantitative yields by hydrogenolysis over palladium on carbon. Pyrrole **20**[51] may be synthesized from the resulting pyrrole-2-carboxylic acid **24**[52] by way of a decarboxylation followed by a formylation with both steps conducted in one pot under two different sets of conditions (A or B), as shown in Scheme 8. The one-pot procedure for installing a formyl group in the α-position of substituted pyrroles removes the necessity for the isolation of α-unsubstituted pyrroles, which, depending on substitution patterns, can be unstable.

Scheme 8. Synthesis of pyrrole **20**

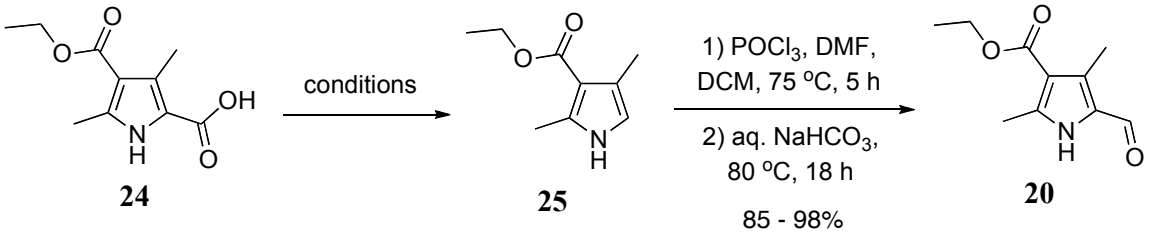


In the first method (Conditions A), pyrrole carboxylate **24** is heated in DMF, to effect decarboxylation, followed by treatment with the Vilsmeier reagent to give 2-formyl pyrrole **20**.[53] Unfortunately, this one-pot procedure gave low and variable yields of **20**. In the second method (Conditions B), pyrrole carboxylate **24** is treated with TFA, to affect the decarboxylation, and then trimethylorthoformate, which acts as a formylating reagent, to give pyrrole **20** in 61% yield. This second strategy was higher yielding and more reproducible than the first, though the yield was still low for such an early point in the synthesis. Recently, α-unsubstituted pyrrole **25** has been reported in the literature to be air and water stable[54] and so it was believed that the decarboxylation and

formylation steps could be implemented independently in this case in order to obtain higher yields of 2-formyl pyrrole **20**.

The synthesis of 2-formyl pyrrole **20** was therefore broken down into two steps, with the isolation of the decarboxylation product **25** preceding the Vilsmeir reaction. Several decarboxylation conditions were investigated as outlined in Scheme 9 and Table 1.

Scheme 9. Modified synthesis of pyrrole **20**



24 **25** **20**

Table 1. Investigation of decarboxylation conditions for **24**

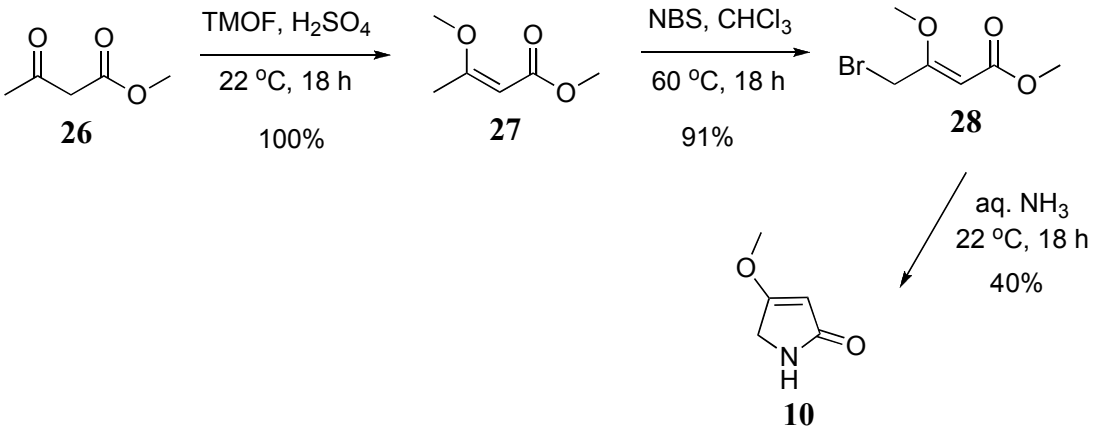
Entry	**Conditions**	**Isolated Yield of 25** /%
1	DMF, 150 ºC, 1 h	40
2	DMF, 150 ºC, 12 h	49
3	MeOH, *p*-toluenesulfonic acid, 65 ºC, 3 h	40
5	215 ºC (neat), 15 min	98

The first attempted one-pot procedure to provide **20** involved first heating a solution of **24** in DMF at 150 ºC for 1 h (Table 1, entry 1).[53] When the product mixture of this reaction was isolated and purified, the required decarboxylated product **25** was obtained in 40% yield and the carboxylic acid starting material **24** was recovered in 58% recovery. Heating carboxylic acid **24** in DMF for 12 h or in methanol with an acid catalyst[55] did not give substantial increases in yield of pyrrole **25** (Table 1, entries 2 and 3). The highest yielding method involved heating the neat pyrrole-2-carboxylate **24** past its melting point

and waiting for the evolution of carbon dioxide gas to cease.[56] These conditions lead to quantitative purified yields of **25** (Table 1, entry 5). When **25** was subjected to the Vilsmeir formylation conditions, **20** precipitated out of solution and was isolated as an off-white powder using suction filtration. Using the newly developed two-step procedure, purified yields of **20** were consistently between 85 and 98%; this represents a great improvement over the previous purified yield range of 19 to 40% using the one-pot decarboxylation and formylation method.[53]

A previously reported three-step procedure[57] was implemented to generate 4-methoxy-3-pyrrolin-2-one (**10**) from commercially available methyl acetoacetate (**26**). As shown in Scheme 10, methyl acetoacetate was treated with trimethylorthoformate under acidic conditions, to give **27** in quantitative yields after purification *via* vacuum distillation. Compound **27** was then brominated using NBS in the presence of benzoyl peroxide to give **28** in a 91% yield after purification *via* vacuum distillation. Compound **28** was then stirred at room temperature in aqueous ammonium hydroxide to give pyrrolinone **10**, after extraction with dichloromethane and crystallization from methanol, in a 40% yield. This final step posed some difficulty, as pyrrolinone **10** is quite soluble in aqueous media. Heating the reaction mixture to 65 ˚C did not improve the overall yield and performing the reaction in a solution of methanolic ammonia led to an unidentified byproduct.[58] Further investigations into the isolation of the product found that the yield could be improved by approximately 15 to 20% by continuously extracting the aqueous reaction mixture with dichloromethane over four days. This new method allows for the isolation of multi-gram quantities of pyrrolinone **10**.[58]

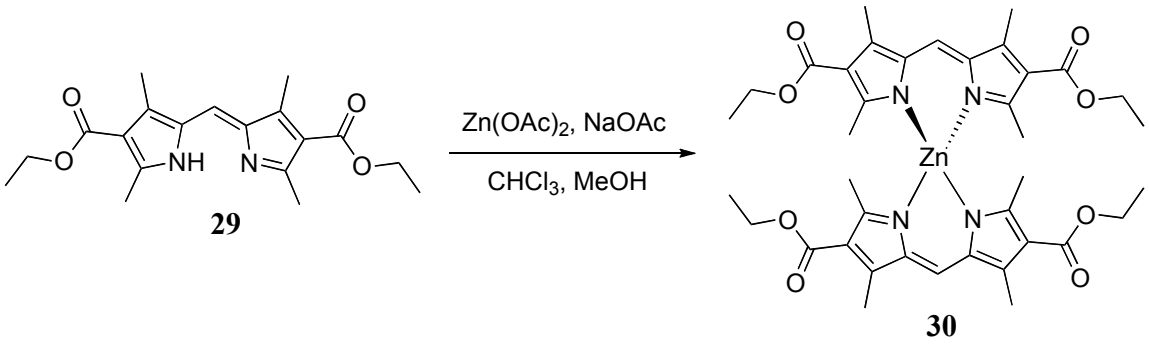
Scheme 10. Synthesis of pyrrolinone **10**



26 **27** **28** **10**

The condensation of pyrrole **20** with pyrrolinone **10** (Scheme 7) was reported to produce dipyrrinone **21** in a 41% yield.[29] This yield was improved by 20% by increasing the nitrogen degassing time from 10 minutes to 40 minutes. The synthesis of triflate **22** from dipyrrinone **21** also proved problematic. Once isolated and purified, **22** was found to be unstable on the bench top and was either used immediately or stored in the freezer under an atmosphere of nitrogen to prevent decomposition. Triflation reactions of different dipyrrolic analogues of dipyrrinone **21** are reported in the literature and all use similar conditions with reported yields ranging from 65 to 94%,[20, 36, 37] indicating that it should be possible to obtain high yields of **22**. Rigorous drying of solvents and reagents is necessary as the presence of water lowers the yield of the reaction to 40-60% through the production of a byproduct that was identified, *via* spectroscopic methods, as symmetrical dipyrrin **29**. In order to confirm the identity of dipyrrin **29**, a tetrahedral zinc(II) complex was generated according to a previously published procedure,[59, 60] as shown in Scheme 11.

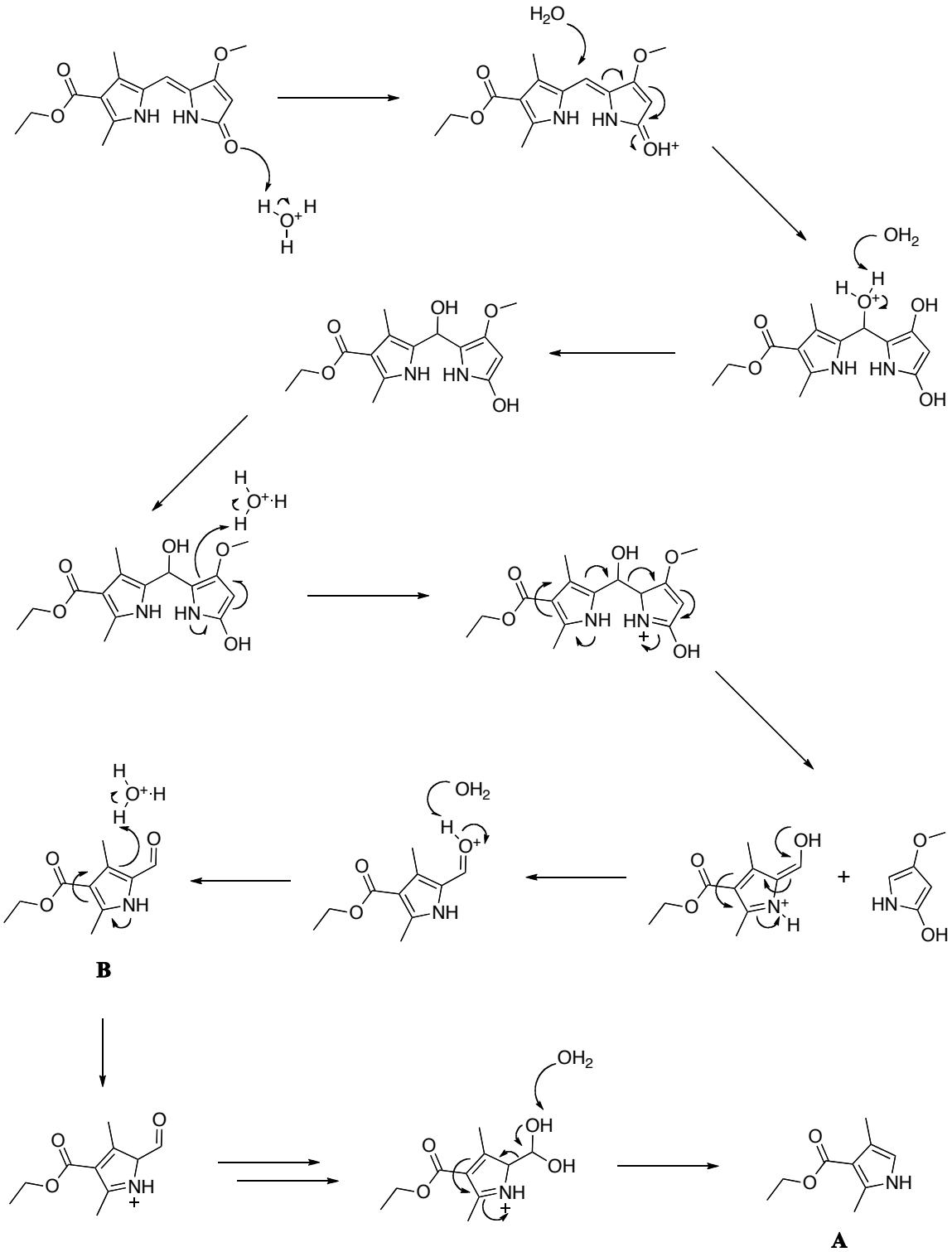
Scheme 11. Synthesis of dipyrrin zinc complex

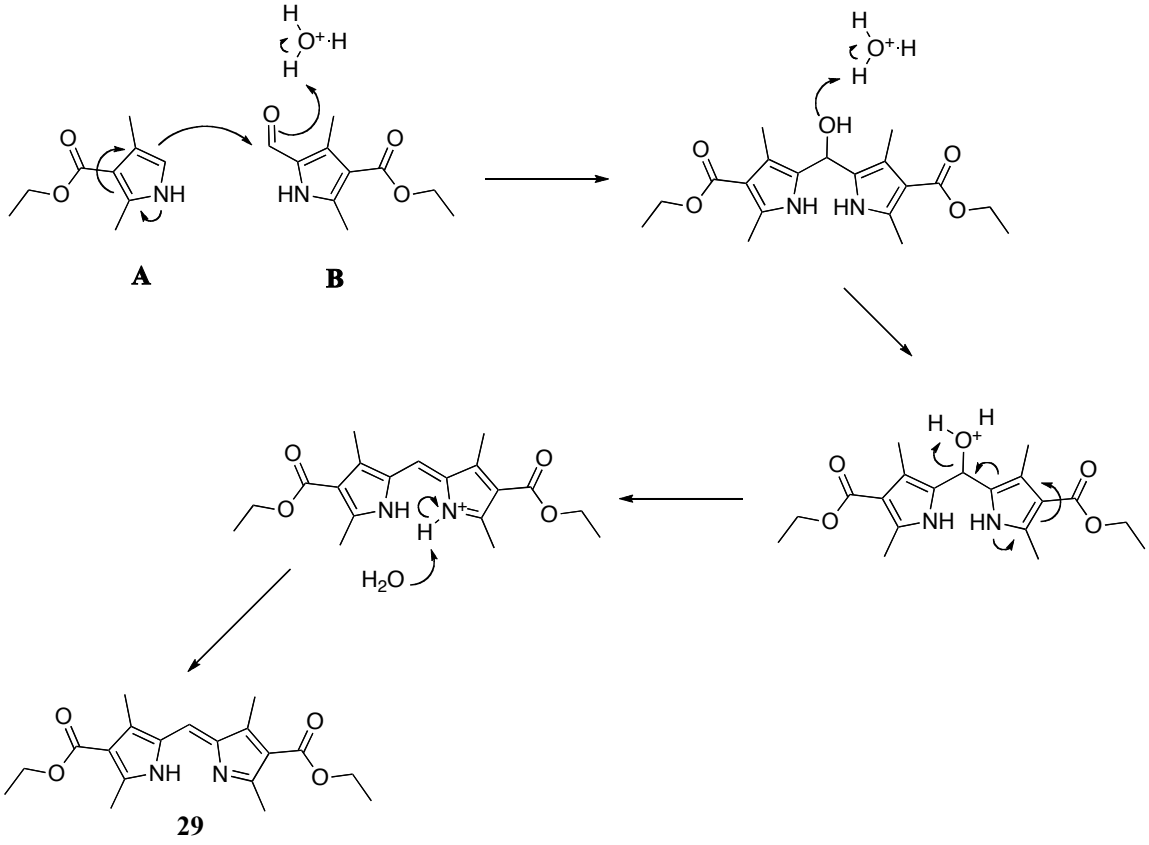


29 **30**

Characterization using NMR spectroscopy and mass spectrometry indicated that the tetrahedral zinc complex **30** had been successfully synthesized, confirming the identity of dipyrrin **29**. Figure 11 depicts a possible mechanism for the generation of this dipyrrin byproduct. The byproduct is thought to arise from the hydrolysis of dipyrrinone **21** to a 2-formyl pyrrole and an α-free pyrrole. The self-condensation of two molecules of ethyl 2,4-dimethyl-pyrrole-3-carboxylate would lead to dipyrrin **29**.

Figure 11**.** Mechanism for the formation of dipyrrin **29**




A
B
29

This proposed mechanism accounts for the fact that the reaction to produce dipyrrin **29** took place under acid catalysis in the presence of water. Some other mechanistic possibilities, not illustrated in Figure 11 are that dipyrrin **29** was generated from the acid catalyzed coupling of two molecules of **B** with the loss of formaldehyde. Now, rigorously dried solvents are used in the triflation procedure, and purified yields of triflate **22** are thus routinely 85% and higher.

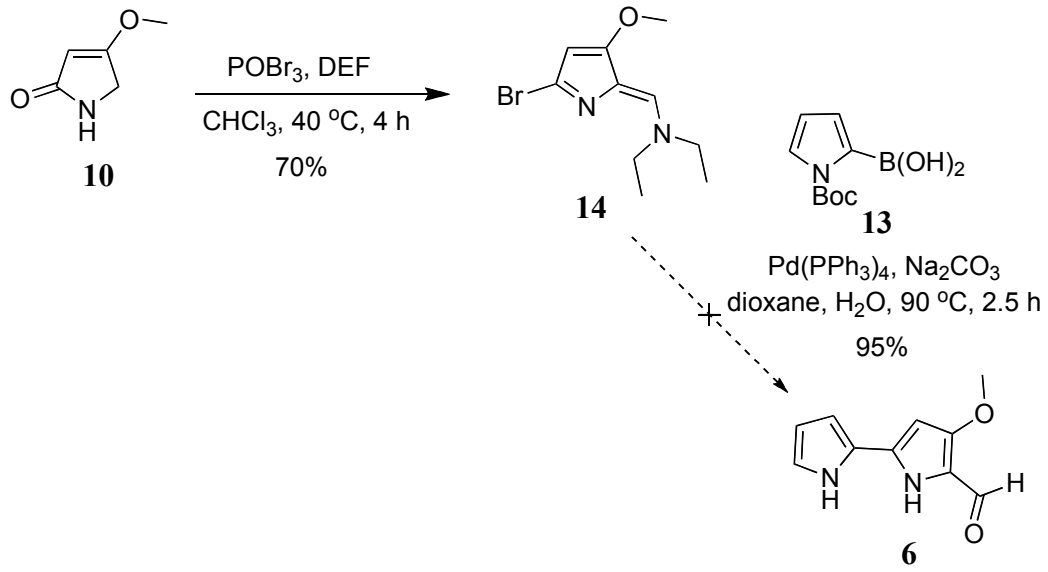
Once the triflation procedure was optimized, the Suzuki coupling of the triflate **22** with *N*-BOC protected pyrrole-2-boronic acid (Scheme 7) was investigated. It was noted that the yield of prodigiosene **1**, could be increased from 60% to greater than 80% when the reaction was conducted on a scale of 300 milligrams or larger. This is likely due to catalyst deactivation, which has a greater effect on the small scale reaction.

Using an optimized version of a synthetic scheme already used for the production of prodigiosenes in the Thompson laboratory, ethyl ester prodigiosene **1** can now be routinely synthesized in six steps with an average overall yield of 34%. With a robust route to **1** in hand, efforts were then focused upon its chemical modification.

2.3.2 Biomimetic Synthesis of Prodigiosenes

Before we proceeded with the direct chemical modification of the prodigiosenes, we wanted to investigate the feasibility of the second method in synthesizing C-ring modified prodigiosenes. One popular, recently reported route to prodigiosenes and other realated natural products involves the synthesis of the bipyrrole aldehyde **6** followed by a condensation of a pyrrole, in a biomimetic step, to give the desired prodigiosene. Bipyrrole aldehyde **6** can be synthesized from the pyrrolinone **10** using a reported method as shown in Scheme 12.[38]

Scheme 12. Synthesis of bipyrrole aldehyde **6**



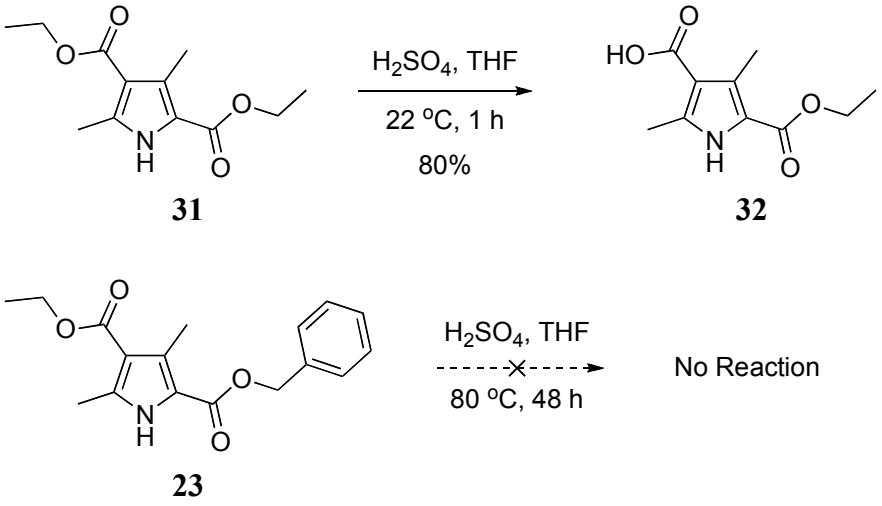
The synthesis of the bromopyrrole enamine **14** proved more difficult than anticipated. The literature procedure involved generating a Vilsmeir reagent from diethylformamide and phosphorous oxybromide, adding it to a solution of pyrrolinone **10** and heating the reaction mixture for several hours. Reportedly, the reaction mixture was poured on ice, the pH adjusted to neutral and the precipitate formed was isolated *via* suction filtration to give **6**. Under these work-up conditions, no product could be isolated in our hands. When the reaction mixture was subjected to aqueous work-up, dried, concentrated and a series of triturations with hexanes and dichloromethane were performed a white powder resulted. A broad singlet at 14.0 ppm in the ^{1}H NMR spectrum of this isolated material indicated the presence of an HBr salt of **14**. Due to this result, the literature procedure[38] was modified to include a basic pH adjustment in the work-up. This modification allowed for the isolation of **14** in a 45% yield. Although the original literature procedure reported a yield of 70%, three recent publications that use this procedure for the production of **14** reported yields closer to 50%.[30, 40, 61]

The Suzuki coupling of the bromopyrrole enamine **14** with *N*-BOC protected pyrrole-2-boronic acid **13** to produce bipyrrole **6** has been attempted multiple times, but has not been successfully accomplished to date, despite the fact that four published procedures[30, 38, 40, 61] report quantitative yields of **6**. Over the course of the reaction, under all the attempted conditions, the bromopyrrole enamine **14** is consumed, and monitoring using TLC shows the production of six new products. However, the NMR spectrum of the crude material indicates that the desired product is not present. These products, when isolated using column chromatography, are a minor proportion of the overall mass of the crude material. The reaction has been carried out with a number of variations. For example, the tetrakis triphenylphosphine palladium catalyst has been generated *in situ* using palladium acetate and triphenylphosphine, and purchased tetrakis triphenylphosphine has been added to the reaction as a solid; dimethoxyethane and dioxane have both been used as solvents; the sodium carbonate base has been replaced with sodium methoxide; and lithium bromide has been added. The time of the reaction has also been modified with reaction times from one to eighteen hours. These experimental variations all give similar results. One recently published procedure[61] reports a much longer reaction time and the addition of sodium methoxide in the last thirty minutes of the reaction indicating that there are difficulties with the originally reported procedure and personal correspondence with other researchers who have used this procedure[42, 43] also indicates that this procedure suffers from reproducibility difficulties.

Concurrently to the investigations of the synthesis of the bipyrrole aldehyde **6**, the development of a selective hydrolysis methodology for the synthesis of pyrrole

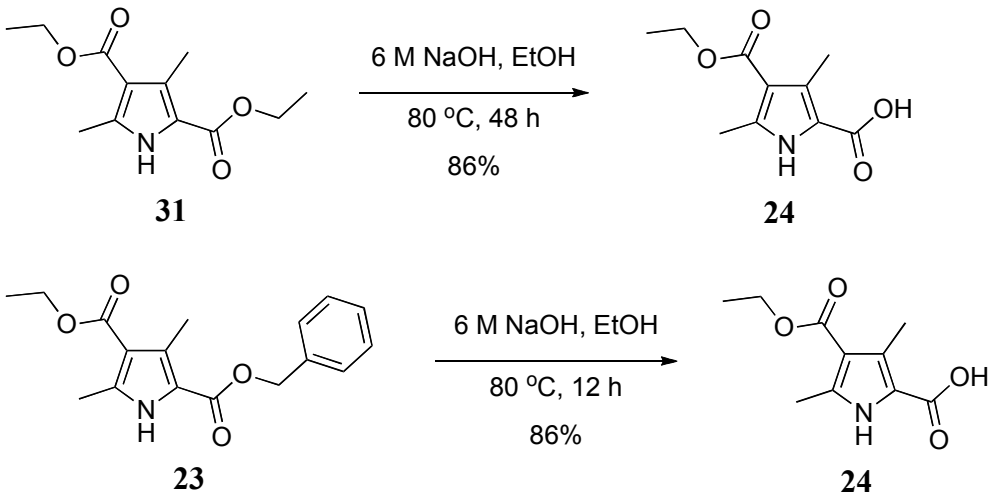
carboxylates, to be incorporated as a prodigiosene C-ring, was explored in some detail. Few specific procedures were published in the literature for the selective hydrolysis of 2,4-pyrrole diesters. However it was found, as alluded to in a communication,[48] that the hydrolysis of the ester at the 2-position of 2,4-pyrrole diesters can be accessed selectively using basic conditions and the ester at the 4-position can be accessed using acidic conditions. Another interesting point of note is that the nature of the R group of the ester appears to affect the success and progress of the hydrolysis reaction. This effect is showcased by the use of similar acidic hydrolysis conditions, on two different 2,4-pyrrole diesters shown in Scheme 13.

Scheme 13. Attempted hydrolysis of 2,4-pyrrole diesters under acidic conditions



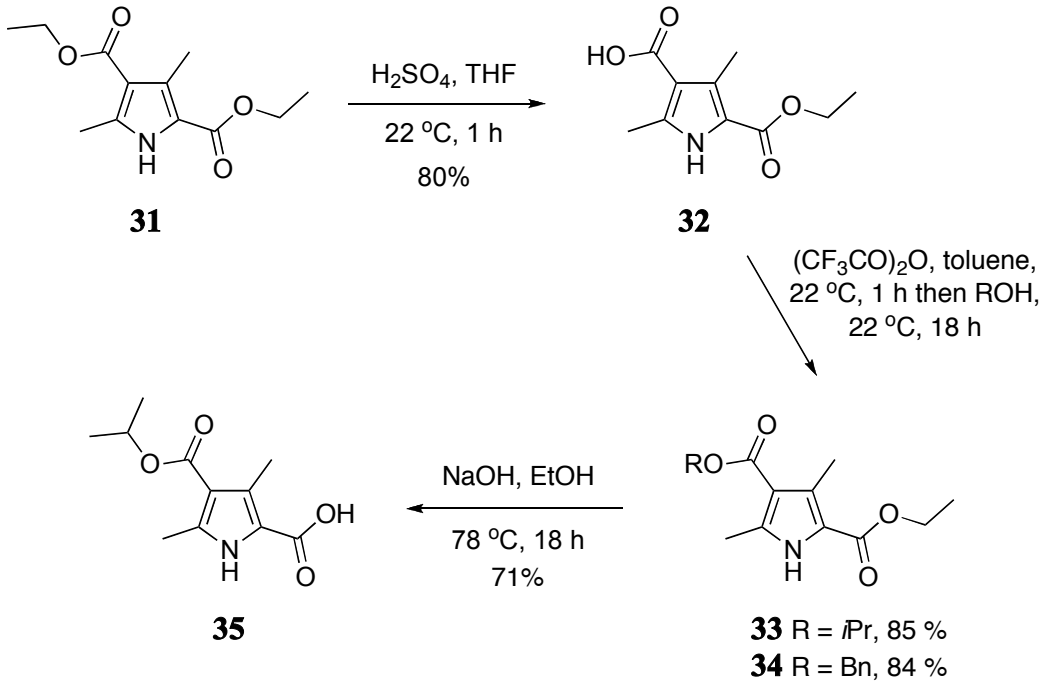
These results seem to suggest that the benzyl ester at the 2-position deactivates the reactivity towards hydrolysis of the ethyl ester in the 4-position. Under basic hydrolysis conditions, both the benzyl and ethyl groups of the ester at the 2-position were hydrolyzed, as shown in Scheme 14. The hydrolysis of the ethyl ester required a longer period of time than that of the benzyl ester.

Scheme 14. Attempted hydrolysis of 2,4-pyrrole diesters under basic conditions



Due to the success of the selective hydrolysis, a synthesis of a modified C-ring pyrrole was conducted as shown in Scheme 15.

Scheme 15. Synthesis of a modified C-ring using a selective hydrolysis method



This method involved a selective hydrolysis of the ester in the 4-position of the pyrrole diester **31**. This was followed by an esterification procedure, adapted from the

literature,[48] to give pyrrole diesters **33** and **34** in good yields. As a further proof of concept, a selective hydrolysis of the ester in the 2-position of pyrrole diester **33** gave pyrrole carboxylate **35**. The corresponding α-free pyrrole could then be generated from **35** through a decarboxylation reaction, presumably using conditions similar to the decarboxylation conditions described in the first method. This pyrrole could then be condensed with the bipyrrole aldehyde **6** to give a prodigiosene derivative.

Although the synthesis of substituted pyrroles with different esters in the 4-position was quite successful, difficulties in the synthesis of the bipyrrole aldehyde **6** made this biomimetic method less favorable for use in the synthesis of C-ring modified prodigiosenes. The method described previously, by which prodigiosene ethyl ester **1** is chemically modified, was therefore chosen for the synthesis of C-ring modified prodigiosene derivatives. It should be noted that pyrrole esters, such as **35**, could be converted into pyrrole aldehydes and be used to generate new prodigiosene derivatives in the method used for the synthesis of ethyl ester **1**.

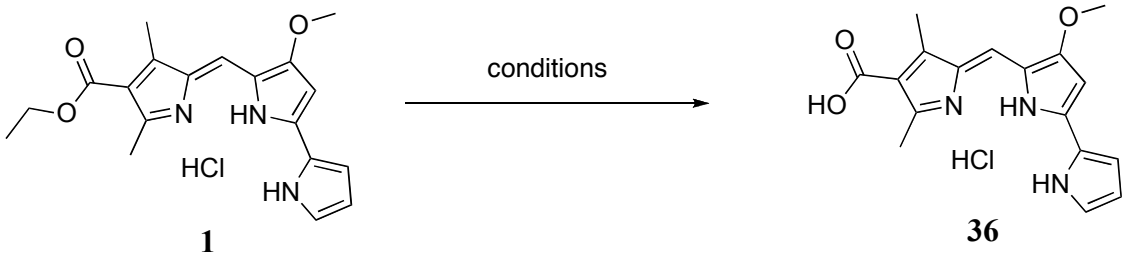
2.3.3 Hydrolysis of Ethyl Ester Prodigiosene **1**

The majority of reported ester hydrolysis reactions are conducted using acid or base catalysis.[62] Acids catalyze the reaction by making the carbonyl carbon atom more electropositive and, therefore, more susceptible to nucleophilic attack. Typical acid catalysts for ester hydrolysis include sulfuric, sulfonic, phosphoric and hydrochloric acids. Bases catalyze the reaction by providing a more powerful nucleophile than water, the hydroxide anion. Unless a molecule is base-sensitive, ester hydrolysis is almost always conducted under base-mediated conditions because it allows formation of the salt of the acid and thus drives the equilibrium towards the desired product.[62] Typical bases

used for ester hydrolysis include aqueous potassium and sodium hydroxide in tetrahydrofuran, ethanol, dimethylformamide or pyridine. Methods for ester hydrolysis have been reviewed in detail.[62-64]

Acid- and base-catalyzed hydrolysis conditions were employed in initial attempts for the hydrolysis of the ester of **1**. The hydrolysis of **1**, shown in Scheme 16, proved to be more difficult than anticipated and attempts to hydrolyze the ester using acid- and base-catalyzed hydrolysis are summarized in Table 2.

Scheme 16. Attempted hydrolysis of prodigiosene **1**



1 **36**

Table 2. Hydrolysis conditions for prodigiosene **1**

Entry	Conditions	Results
1	H_2SO_4, THF (1:1), 22 ˚C, 18 h	Starting material decomposes
2	H_2SO_4, TFA (1:1), 22 ˚C, 1 h	Starting material recovered
3	H_2SO_4, TFA (1:1), 22 ˚C, 18 h	Starting material decomposes
4	HCl, MeOH (1:10), reflux, 18 h	Starting material recovered
5	HCl, MeOH (1:10), reflux, 72 h	Starting material decomposes
6	5 M KOH, THF (1:1), reflux, 48 h	Starting material recovered
7	6 M KOH, EtOH (1:10), reflux, 48 h	MS (ESI^+) shows **36**
8	5 M KOH, pyridine (1:10), reflux, 96 h	Starting material recovered

A variety of acid-catalyzed hydrolysis conditions were attempted (Table 2, entries 1 through 5). Prodigiosene **1** was treated with H_2SO_4 in both tetrahydrofuran and trifluoracetic acid (Table 2, entries 1 through 3). At room temperature the starting

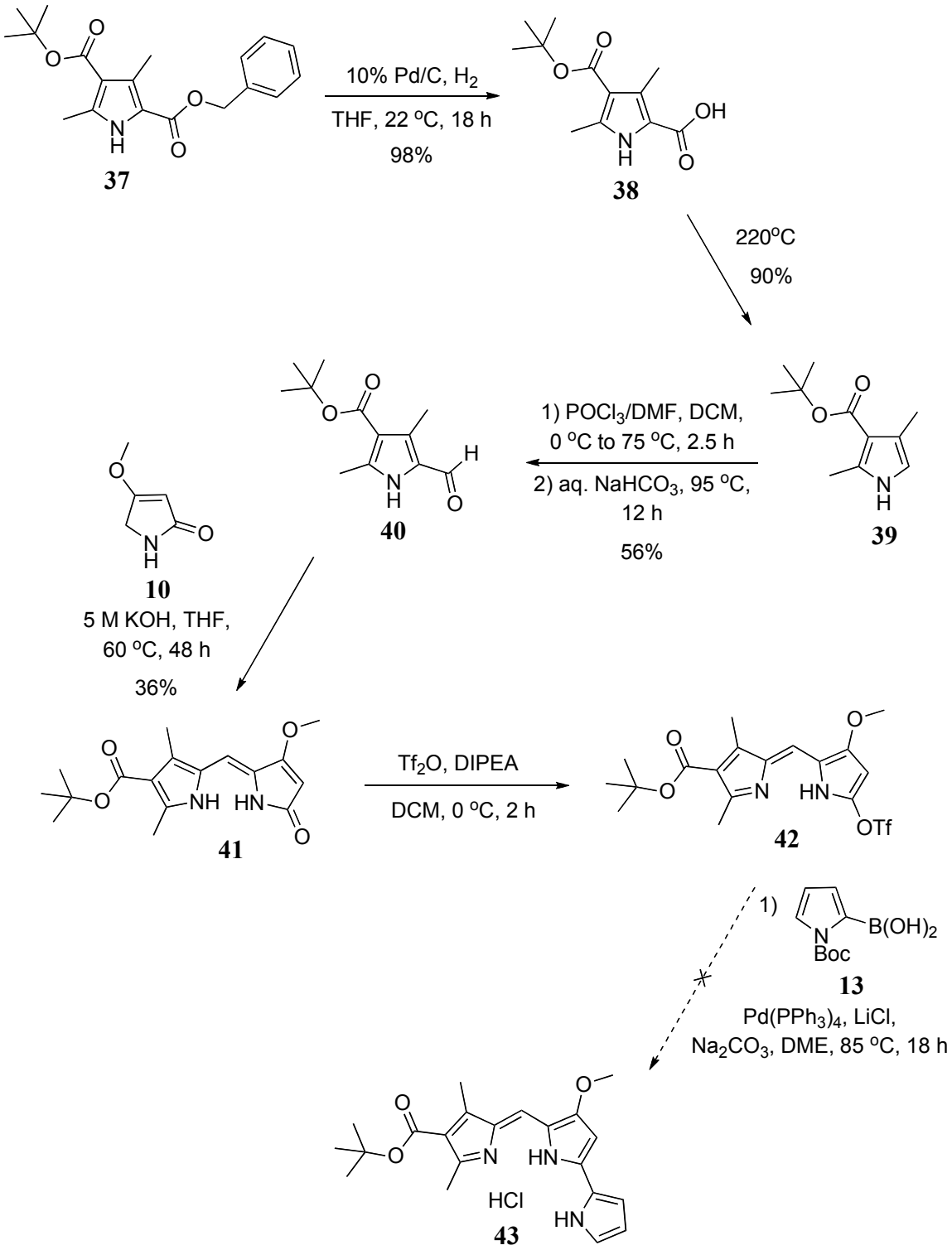
material was found to decompose under these conditions if left for greater than 12 hours. In contrast, if the reaction was quenched before decomposition, the starting material could be recovered nearly quantitatively. Similar results were obtained using HCl in methanol (Table 2, entries 4 and 5). The isolated material was still red in color, indicating the possible presence of the tripyrrolic core of prodigiosene. The isolated material was sparingly soluble in water and had low solubility in common organic solvents. The components of these decomposition mixtures could not be identified using NMR spectroscopy or mass spectrometry and purification was not possible due to the poor solubility of the mixtures.

Several sets of base-catalyzed hydrolysis conditions were also used (Table 2, entries 6 through 8). Heating solutions of prodigiosene **1** in mixtures of 5 M potassium hydroxide and tetrahydrofuran or pyridine to reflux temperature for 2 days resulted in a quantitative recovery of starting material (Table 2, entries 6 and 8). Heating solutions of prodigiosene **1** in a 1:10 mixture of 6 M potassium hydroxide:ethanol to reflux temperature, appeared to generate the desired carboxylic acid **37** (Table 2, entry 7), according to mass spectrometry data obtained using the crude product. Unfortunately, this result could not be confirmed using NMR spectroscopy due to difficulties in the isolation and purification of the product. The crude product was sparingly soluble in methanol and water, and attempts to recrystallize the crude product from these solvents were not successful. Subjection of the crude reaction mixture to trifluoroacetic anhydride followed by the addition of an alcohol, esterification conditions that have been shown to be effective for pyrroles substituted with carboxylic acids in the 4-position,[48] did not lead to an esterified product. Repeated manipulations of the crude product led to increasingly

intractable dark purple material indicating that the product may also be of limited stability.

Due to the difficulty of the hydrolysis of the ethyl ester, attempts were made to synthesize *tert*-butyl ester prodigiosene **43**, as shown in Scheme 17. Because the *tert*-butyl group is acid labile,[63] this prodigiosene has the potential to be hydrolyzed easily, which would be ideal in the prodigiosene. There is also the potential that hydrolysis could occur through a different mechanism. There are two commonly observed mechanisms for the acid-catalyzed hydrolysis of esters. The second, and less commonly observed, mechanism is the $A_{AL}1$ mechanism;[62] an S_N1 mechanism that involves alkyl-oxygen cleavage. This mechanism is only operative when the ester has a tertiary alkyl, allylic or benzylic group which can leave as a stable carbocation, as in the case of the *tert*-butyl ester but not the ethyl ester.[62] A route for the synthesis of the *tert*-butyl ester prodigiosene is outlined in Scheme 17. The synthetic sequence is very similar to the synthesis of the ethyl ester prodigiosene **1** and differs only in the starting Knorr pyrrole **37**. There is some risk associated with carrying the *tert*-butyl group through so many synthetic steps as it is relatively labile and carboxylic acid derivatives of the desired products may be generated, thus leading to lower overall yields. However, if the ester group is particularly labile at one particular step this may provide an opportunity for esterification at an alternate step in the synthesis.

Scheme 17. Synthesis of *tert*-butyl ester prodigiosene **43**



Hydrogenolysis of Knorr pyrrole **37** gave carboxylic acid **38** in excellent yield, which was then decarboxylated in excellent yield to give pyrrole **39**. Pyrrole **39** was then submitted to Vilsmeir reaction conditions to give formyl pyrrole **40** in low yield. Formyl pyrrole **40** was then condensed with pyrrolinone **10** to give dipyrrinone **41** in low yield. The triflation of dipyrrinone **41** was difficult. When the reaction was performed in dichloromethane using triflic anhydride, ^{1}H NMR spectroscopy and mass spectrometry showed the presence of three products: the desired triflate **42**, the carboxylic acid of triflate **42** and the carboxylic acid derivative of **41**. All purification attempts resulted in decomposition and loss of material. When the reaction was buffered with excess diisopropylethylamine, triflate **42** was the major product along with a small amount of the carboxylic acid of pyrrole **40**. As purification proved difficult, the crude material was subjected to the Suzuki coupling conditions, upon which decomposition of the starting material occurred without the production of prodigiosene. Analysis of the crude material by ESI mass spectrometry did not show any of the desired prodigiosene ester (**43**) or the corresponding prodigiosene acid (**37**).

As dipyrrinone **41** appeared to be easily hydrolyzed, we thought to perform the hydrolysis and subsequent esterification at this stage of the synthesis. Treating **41** with TFA generated the desired carboxylic acid derivative of **41**. A ^{1}H NMR recorded in DMSO-*d6* indicates the generation of the desired carboxylic acid, but the insolubility of the derivative in any available deuterated solvents including D_2O prevented any further characterization. Subjection of the crude material to esterification conditions used for simple pyrroles[65] was similarily unsuccessful.

In summary, all attempts to hydrolyze esters directly attached to the prodigiosene core were unsuccessful. Although the crude reaction mixture from the hydrolysis with potassium hydroxide in ethanol appeared to contain some hydrolysis product, the product could not be isolated and had limited stability. Due to the failure of the hydrolysis approach, investigations were undertaken to develop a transesterification methodology for the generation of ester analogues of prodigiosene **1**.

2.3.4 Transesterification of Ethyl Ester Prodigiosene **1**

Transesterification is a process in which one ester is transformed directly into another ester. This is the favorable method of modifying one ester into another, as it requires a single step compared to the two-step hydrolysis and esterification procedure. Transesterification reactions are normally carried out using nucleophiles, enzymes, and metal complexes as catalysts. While metal complexes such as aluminum halides, titanium tetraalkoxides and organotin compounds are the most widely used for transesterification in the literature,[64] they are not ideal for the transesterification of prodigiosenes because prodigiosenes are potentially good ligands for metals. Nucleophiles used for transesterification include sulfides, selenides, halides, cyanides and alkali metal alkoxides. Methods for transesterification have been extensively reviewed.[64]

It has been reported that a combination of DBU and lithium bromide in the presence of molecular sieves in an alcoholic solvent is an effective transesterification system.[66] Using this combination of reagents in the presence of *n*-butanol the free-base of prodigiosene **1** was not transesterified; instead, 97% of the starting material was recovered. Another report indicated that potassium *tert*-butoxide is an effective catalyst for transesterification.[67, 68] Employing these conditions,[67, 68] a mixture of the free-base of

prodigiosene **1** along with *n*-butylacetate and potassium *tert*-butoxide was stirred under aspirator vacuum at 65 °C. Although no transesterified project was isolated, 95% of the starting material was recovered.

Microwave-promoted esterifications have proved successful for pyrrole substrates in the past.[69] Both ambient pressure and high-pressure microwave-promoted reaction conditions were used for the transesterification of prodigiosene **1** to generate the methyl ester prodigiosene **44.** This transformation is shown in Scheme 18 with investigated conditions highlighted in Table 3.

Scheme 18. Microwave-promoted transesterification of prodigiosene **1**

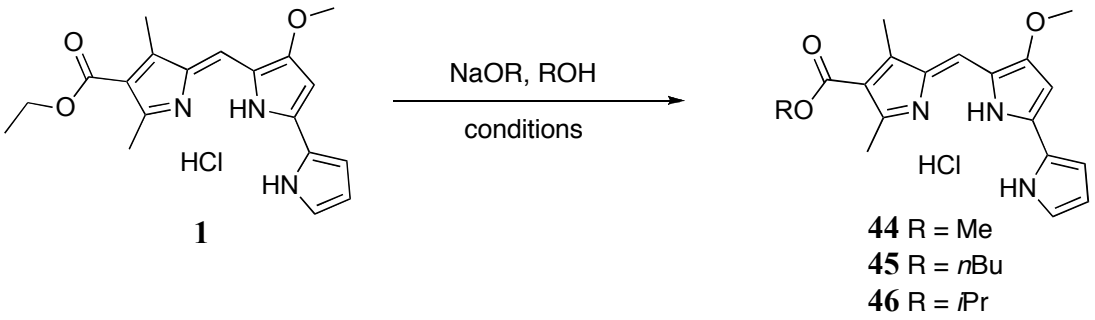


Table 3. Conditions for transesterification of prodigiosene **1**

Entry	R	Conditions	Results
1	Me	1.2 eq NaOMe, MeOH, MW, 125°C, 10 min	Mixture of **1** and **44**
2		1.5 eq NaOMe, MeOH, MW, 125°C, 20 min	**44** (75-87%)
3		1.5 eq NaOMe, MeOH, reflux, 20 min	**1** recovered
4	*n*Bu	15 eq NaO*n*Bu, *n*BuOH, MW, 200˚C, 40 min	1 : 1 Mixture of **1** and **45**
5	*i*Pr	125 eq NaO*i*Pr, *i*PrOH, MW, 140˚C, 40 min	1 : 1 Mixture of **1** and **46**

Methyl ester **44** was successfully synthesized using 1.5 equivalents of sodium methoxide and heating to 125 °C for 20 minutes in methanol (Table 3, entry 2). Using fewer equivalents of sodium methoxide (Table 3, entry 1) or using conventional heating methods (Table 3, entry 3) did not result in the isolation of the transesterified product **44**.

When this method was adapted to *n*-butyl and *iso*-propyl alcohols (Table 3, entries 4 and 5), ^{1}H NMR spectra of the crude reaction mixtures after work-up showed the formation of the desired product along with the starting material in 1:1 ratios. Re-subjecting these mixtures to the reaction conditions did not improve the ratio of starting material to product. The product mixtures were inseparable by column chromatography and decomposed on attempted conversion of the free-bases to HCl salts. Although the reaction with methanol was reproducible, the reactions with *iso*-propanol and *n*-butanol suffered from poor reproducibility, making optimization practically impossible. Although this method produced the methyl ester derivative in good yields, it is not a general method and no further investigations into optimization were undertaken.

With limited success in the nucleophilic and microwave-promoted transesterification methods, we attempted to investigate metal-based transesterification methods. Titanium tetraalkoxides and organotin reagents are the most common metal catalyst for transesterification reactions although copper and rare earth metal alkoxides are known to catalyze the reaction as well.[64] We began by investigating the milder organotin reagents as catalysts for transesterification of **1**. Dibutyltin oxide is a reagent that has been shown to be an effective, mild transesterification catalyst.[70] In this method, the alcohol, ester and 10 mole percent of dibutyltin oxide are typically heated at reflux temperature for 12 hours to give the transesterified product. When prodigiosene **1** was subjected to these conditions, a highly fluorescent product was formed in low yields. ^{1}H NMR spectroscopy and mass spectrometry data indicated that this material was not the transesterified product, but rather the dibutyltin complex of prodigiosene **1**. Resubjection of the complex to the original transesterification conditions did not result in the isolation

of any transesterified product. Further investigations into the synthesis, structure and properties of these prodigiosene tin complexes will be detailed in CHAPTER 3.

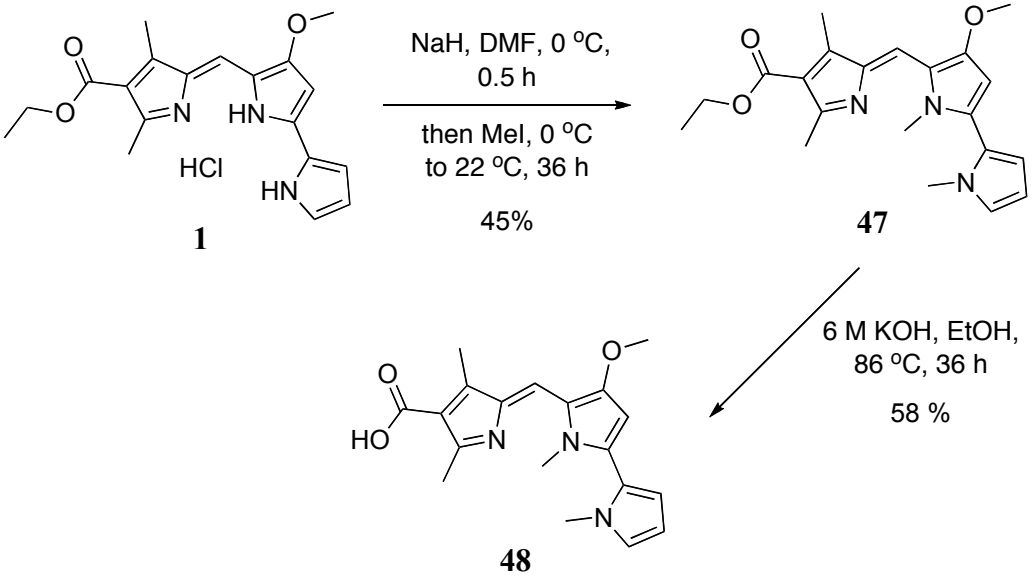
2.3.5 Investigation of Prodigiosene Protection Methods

The hydrolysis, esterification and transesterification of prodigiosene **1** proved difficult. Acid- and base-promoted hydrolysis reactions did not result in the isolation of carboxylic acid and, although a microwave-promoted transesterification method was found for the generation of methyl ester prodigiosene **44**, it was not generalizable to other esters. The solubility and stability of isolated hydrolysis products also proved quite unpredictable and the adoption of a strategy which stabilizes and enhances the solubility of the products would be ideal. This could potentially be accomplished by *N*-protection of the prodigiosene or by appending an alkyl or removable thioalkyl chain[71] at the C-2 position of the prodigiosene A-ring. A-ring modification was less favourable because it would introduce one or more extra steps in the overall synthesis and, therefore, *N*-protection was investigated.

N-Protection strategies for the ester-functionalized prodigiosenes had to be carefully designed due to the fact that acidic and basic conditions are used in hydrolysis and esterification. Traditional pyrrole protection strategies could involve using the 2-(trimethylsilyl)ethoxymethyl (SEM) protecting group, which is resistant to reductive, oxidative, acidic and basic conditions and may be removed in two steps[72] or the benzylmethyl ether (BME) protecting group, which is stable to acidic and basic conditions and can be removed in two steps.[72] Because both of these strategies required expensive reagents and the addition of three steps to the synthesis, *N*-methylation was first investigated as a test case as several examples of *N*-monomethyl and *N*-monobenzyl

substituted prodigiosenes have been synthesized successfully in the past.[73] *N,N*-Dimethylated prodigiosene **47** was synthesized and isolated, according to Scheme 19, in 45% yield along with an amphiphilic byproduct.

Scheme 19. Synthesis and hydrolysis of *N*-methylated prodigiosene **48**

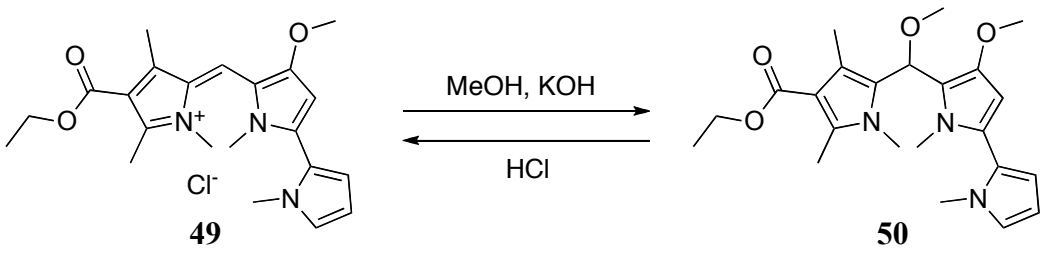


Subjection of the *N*-protected product (**47**) to 6 M sodium hydroxide in ethanol led to hydrolysis product **48**, according to preliminary results deduced from ^{1}H NMR spectra. Purification of the product using reverse-phase chromatography was difficult, as was characterization due to the low solubility and general instability of the product. It is interesting to note that **48** is partially soluble in water.

The isolation of the amphiphilic byproduct from the methylation reaction using normal- and reverse-phase chromatography was not successful. Previous work regarding the *N,N*-methylation of dipyrrins[74] indicates that the structure of the amphiphilic byproduct likely corresponds to that of compound **49**. When the crude reaction mixture

was treated with potassium hydroxide in methanol, the solution of the ampiphilic byproduct went from deep purple to colorless, indicating the disappearance of the dipyrrin chromophore and formation of the corresponding dipyrrylcarbinol ether (**50**) as shown in Scheme 20.

Scheme 20. *N,N,N*-Trimethylprodigiosene dipyrrilcarbinol ether equilibrium



49 **50**

Dipyrrlcarbinol ether **50** was converted to *N,N,N*-trimethylprodigiosene **49** upon treatment with HCl. Unfortunately, compound **50** was of limited stability and could not be isolated. Based on the methylation test reaction, applying traditional pyrrole *N*-protection to prodigiosene **1** was anticipated to be difficult and to require a significant amount of optimization. Both the BME and SEM protecting groups are introduced *via* a reaction with a sodium pyrrolyl anion and may result in amphiphilic products, similar to those isolated in the methylation case. The *N,N*-dimethylated prodigiosene carboxylic acid (**48**) was not investigated further as such derivatives are known to be biologically inactive[73] and the methyl groups can only be removed under harsh reducing conditions incompatible with the ligand.[72]

A final possibility for prodigiosene *N*-protection relied upon complex formation. Because there are very few prodigiosene metal complexes known, before this method could be investigated in detail it was necessary to undertake a general study of the

complexation behaviour of prodigiosenes. This approach will be discussed in more detail in CHAPTER 3.

2.4 Conclusions and Implications

The goal of this project was to synthesize and evaluate the biological activity of a small library of derivatives of ethyl ester prodigiosene **1** where the alkyl group of the ester has been modified. Two methods were investigated for the synthesis of the library of derivatives.

The first approach involved the synthesis of ethyl ester prodigiosene **1** followed by direct chemical modification to afford derivatives. The first step of this approach involved optimization of the synthesis prodigiosene **1**: prodigiosene **1** can now routinely be synthesized in six steps with an average overall yield of 34%. The second approach involved a biomimetic condensation of bipyrrole aldehyde and a 4-pyrrole ester to directly generate the prodigiosene derivatives with various appended esters. Although a successful method has been found for the convergent synthesis of a variety of C-4 ester substituted pyrroles, bipyrrole aldehyde **6** could not be successfully isolated, despite a systematic investigation of the reaction parameters. For these reasons, the first approach was adopted to generate the prodigiosene derivatives.

The second step of the first approach involved direct chemical modification of the prodigiosene ethyl ester **1** by hydrolysis followed by esterification or transesterification. Unfortunately, this proved to be difficult. Although base-mediated hydrolysis of prodigiosene **1** and its *N,N*-dimethyl protected derivative gave somewhat promising results initially, this method was largely unsuccessful predominantly due to the poor stability and solubility of the isolated materials which translated to insurmountable

difficulties in the isolation of the products. Transesterification methods also proved largely unsuccessful in generating modified prodigiosene esters with one exception. Ethyl ester prodigiosene **1** was successfully transformed into methyl ester prodigiosene **44** by way of reaction with sodium methoxide in methanol using microwave irradiation in a closed vessel at high pressure. This method was found to be reproducible and high yielding for the synthesis of the methyl ester prodigiosene (**44**), but it was not widely applicable to generation of esters *via* alternate alkoxide reagents.

In conclusion, the direct hydrolysis or transesterification of ethyl ester prodigiosene **1** and its *N,N*-dimethyl protected derivative **47** proved largely unsuccessful due to the poor stability of the carboxylic acid (**36**). Due to the inherent instability of the carboxylic acid (**36**), it was concluded that the proposed convergent method, by which **1** was chemically transformed, was not suitable for providing access to a library of prodigiosenes with modified ester alkyl groups.

CHAPTER 3 Synthesis and Investigations into Pyrrolyldipyrrinato Complexes

3.1 Background

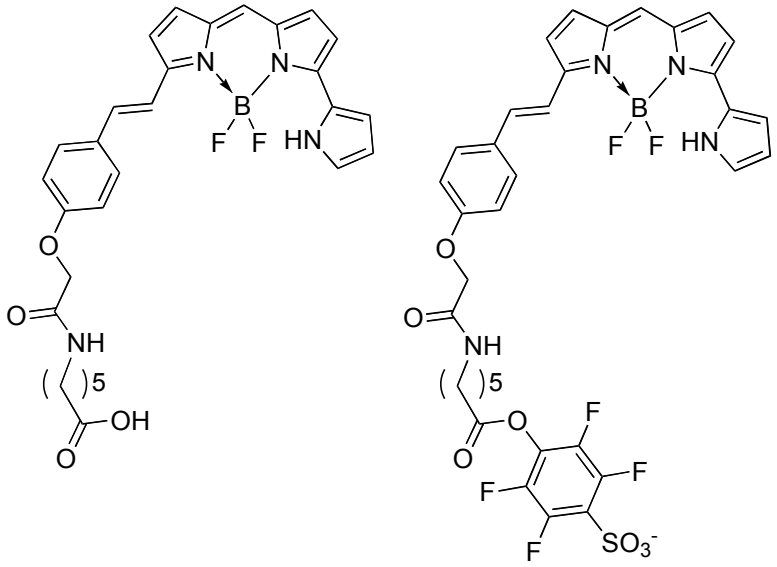
3.1.1 Prodigiosene Complexation

Due to our difficulties in directly modifying an ester appended to the prodigiosene core (0, Section 2.3), we sought to investigate complexation strategies as a method for stabilizing the prodigiosene core. There are numerous examples of dipyrrinato complexes in the literature and metal complexation is often employed as a purification strategy for free-base dipyrrins which can be difficult to isolate and/or have limited stability.[3] Prodigiosenes and pyrrolyldipyrrins, which do not contain the 7-methoxy substituent, are potentially interesting dipyrrinato type ligands because they can coordinate in the same fashion as a dipyrrinato ligand but have a potentially non-innocent substituent in the 9-position, which could also coordinate to the metal centre. Aided by the chelate effect, the pyrrolic substituent could potentially coordinate to the metal through its nitrogen atom in a η^1 fashion or it could coordinate in a face on, η^5 interaction to give a π complex.

The literature contains only three types of prodigiosene metal complexes and in these examples the prodigiosene only exhibits two modes of binding. The first example is a homoleptic zinc(II) complex where the two dipyrrinato units of two identical prodigiosenes bind to the zinc metal centre. These are the most common examples of prodigiosene metal complexes in the literature and there are four reported examples, one employing prodigiosin itself as a ligand[11] and the others employing different synthetic prodigiosenes as ligands.[8-10] Notably, a zinc(II) prodigiosene protection strategy has also been utilized in prodigiosene synthesis.[9]

The second example is a boron difluoride complex of a synthetic pyrrolyldipyrrin where the dipyrrinato unit of a single pyrrolyldipyrrin binds a boron difluoride unit. There is currently one pyrrolyldipyrrinato boron difluoride complex which is commercially available from Invitrogen™ for use as a fluorescent probe for biological systems.[12] A derivative of this *F*-BODIPY, where the carboxylic acid group of the pyrrolyldipyrrin has been esterified to give a 4-sulfotetrafluorophenyl ester, has also been reported.[75] These complexes are shown in Figure 12. To our knowledge, these are the only two examples of fluorescent pyrrolyldipyrrinato complexes reported in the literature prior to our work.

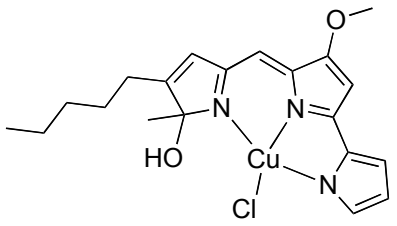
Figure 12. Known boron difluoride complexes of pyrrolyldipyrrins



The last example is a copper(II) complex of prodigiosin in which the C-ring is oxidized. In this complex, all of the nitrogen atoms in the tripyrrolic structure bind copper(II), which is also coordinated to a chloride ligand,[11] as shown in Figure 13. To our knowledge, this is the only example of a prodigiosene-type ligand that coordinates a metal centre through all three of its nitrogen atoms. However, because the prodigiosin C-

ring is oxidized, the tripyrrolic core is no longer a pyrrolyldipyrrin and the ligand is monoanionic.

Figure 13. Cu(II) complex of C-ring oxidized prodigiosin



In two of the three reported types of prodigiosene metal complexes, the metal ion coordinates to the prodigiosene solely through its dipyrrinato unit. Therefore, in these complexes, a prodigiosene ligand can essentially be considered a dipyrrinato ligand with a pyrrolic substituent in the 9-position.

Although there are relatively few examples of pyrrolyldipyrrinato metal complexes in the literature, there are many examples of dipyrrinato metal complexes. A wide variety of isolable dipyrrinato metal complexes have been synthesized varying both in complexation geometry and in metal ion.[3] The geometry at the metal centre in these complexes is largely influenced by the steric interactions between the substituents in the 1- and 9-positions of the dipyrrinato ligands, which are brought in close proximity to one another upon complex formation.

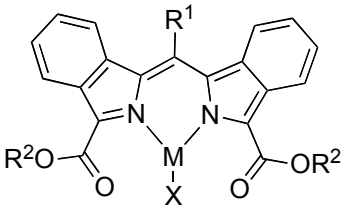
3.1.2 Fluorescent Dipyrrinato Complexes

With the exception of the BODIPY class, dipyrrinato metal complexes do not generally exhibit detectable fluorescence emission.[3] There is currently great interest in developing new fluorescent dipyrrinato metal complexes for use in electroluminescent devices and there are several recent examples in the literature of fluorescent dipyrrinato complexes.

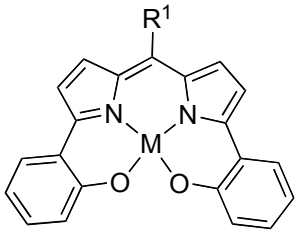
Several weakly fluorescent, homoleptic dipyrrinato complexes (ML_2) with rotationally restricted *meso*-aryl groups have been isolated and characterized. A zinc(II) complex of this type has the highest quantum yield ($\Phi_F = 0.36$),[76] but complexes of indium(III) and gallium(III) have also been found to exhibit weak fluorescence ($\Phi_F = 0.02 - 0.07$).[77] Another homoleptic rhodium(III) complex (ML_3) with rotationally unrestricted *meso*-aryl groups has been found to exhibit very weak fluorescence (Φ_F not determined).[78] Some coordination polymers containing zinc(II) dipyrrinato complexes bridged by various rigid *meso*-phenylethynyl spacers are also reported to weakly fluoresce (Φ_F not determined).[79]

Recently there has also been enhanced interest in the synthesis of heteroleptic dipyrrinato complexes (MLX_n). An unusual dimeric zinc(II) complex, featuring a *meso*-pyridyl moiety which is rotationally restricted by coordination of the pyridyl nitrogen to the zinc metal centre of a neighbouring complex, has been reported to be weakly fluorescent ($\Phi_F = 0.06$).[80] More recently, several fluorescent dipyrrinato zinc(II) and calcium(II) dipyrrinato complexes (MLX) have also been reported ($\Phi_F = 0.58 - 0.70$).[81] In these complexes, the dipyrrinato ligand was π extended and contained either a rotationally unrestricted *meso*-aryl group or was *meso*-unsubstituted. The metal centre was also coordinated to an acetate group, as shown in Figure 14, and the authors also indicated that fluorescent complexes can be obtained using yttrium(III), lanthanum(III) and gallium(III), but these species have not been isolated or characterized.[81]

Figure 14. Highly fluorescent dipyrrinato metal complexes



R^1 = H; R^2 = Et; M = Zn; X = OAc; Φ_F = 0.70
R^1 = H; R^2 = Et; M = Ca; X = OAc; Φ_F = 0.64
R^1 = 4-$MeO_2CC_6H_4$; R^2 = t-Bu; M = Zn; X = OAc; Φ_F = 0.65
R^1 = 4-$MeO_2CC_6H_4$; R^2 = t-Bu; M = Ca; X = OAc; Φ_F = 0.58



R^1 = Ph; M = Al; Φ_F = 0.23
R^1 = mesityl; M = Al; Φ_F = 0.72

More recently, several fluorescent dipyrrinato aluminium(III) complexes (MLX_2) have been reported (Φ_F = 0.23 - 0.72).[82] In these complexes, the dipyrrinato ligands have two pendant phenolic groups, whose phenolates coordinate to the metal, and either a rotationally unrestricted *meso*-aryl group (Φ_F = 0.23) or a rotationally restricted *meso*-aryl group (Φ_F = 0.72), as shown in Figure 14. A fluorescent tin(II) dipyrrinato complex (MLX) has also been isolated (Φ_F = 0.42).[83] In this complex the dipyrrinato ligand contains a rotationally restricted *meso*-aryl group and the metal centre bears an additional triflate ligand. The precursor to this fluorescent tin complex contains a chloride ligand and exhibits only weak fluorescence (Φ_F = 0.04). There is also one example of a platinum(II) dipyrrinato complex with a rotationally restricted *meso*-aryl group which exhibits very weak fluorescence (Φ_F = 0.01)[84] and several iridium(II) complexes which exhibit solid state phosphorescence (Φ_P = 0.06 - 0.12).[85]

With these few examples, the development of fluorescent dipyrrinato metal complexes is still under explored. Several trends seem to emerge from the known fluorescent dipyrrinato complexes: in order to obtain high fluorescence quantum yields,

the ligand must be rigidified by additional coordination sites and the dipyrrinato unit must either be *meso*-unsubstituted or *meso*-substituted with a rotationally restricted aryl group. Pyrrolyldipyrrins, which contain a potential extra site of metal coordination, are therefore good ligand candidates for the development of fluorescent dipyrrinato complexes.

3.2 The Chemistry of Pyrrolyldipyrrinato Complexes

In the literature there are only two examples of the direct modification of a pyrrolyldipyrrinato complex. Both of these examples involve the hydrolysis and esterification of an ester remote to the pyrrolyldipyrrin core, one on a pyrrolyldipyrrinato zinc complex[9] and the other on a pyrrolyldipyrrinato boron difluoride complex.[75] The limited number of examples highlighting the reactivity of pyrrolyldipyrrinato metal complexes emphasizes the need to further explore their synthesis and reactivity.

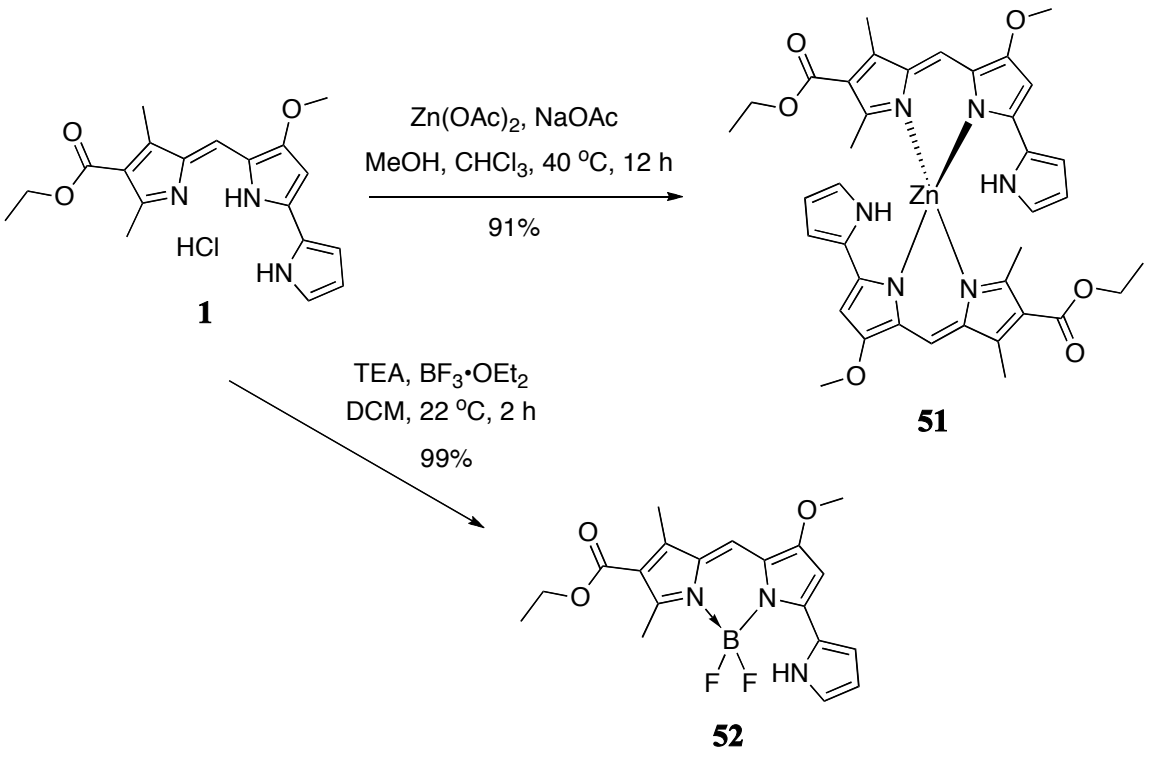
3.3 Results and Discussion

3.3.1 The Synthesis and Chemical Manipulation of Precedented Pyrrolyldipyrrinato Complexes

As zinc(II) and boron difluoride complexes of prodigiosenes are known, we began our explorations into complexation by synthesizing these complexes of prodigiosene ethyl ester **1**. The zinc complex was synthesized according to a previously published procedure[59, 60] and was monitored using UV/Vis spectroscopy: the starting material had a wavelength of maximum absorption at 475 nm, while the complex had a wavelength of maximum absorption at 519 nm. The boron difluoride complex was also synthesized using a common procedure for dipyrrinato boron difluoride complex formation.[4, 5] The synthetic scheme for both complexes is shown in Scheme 21. Both complexes were

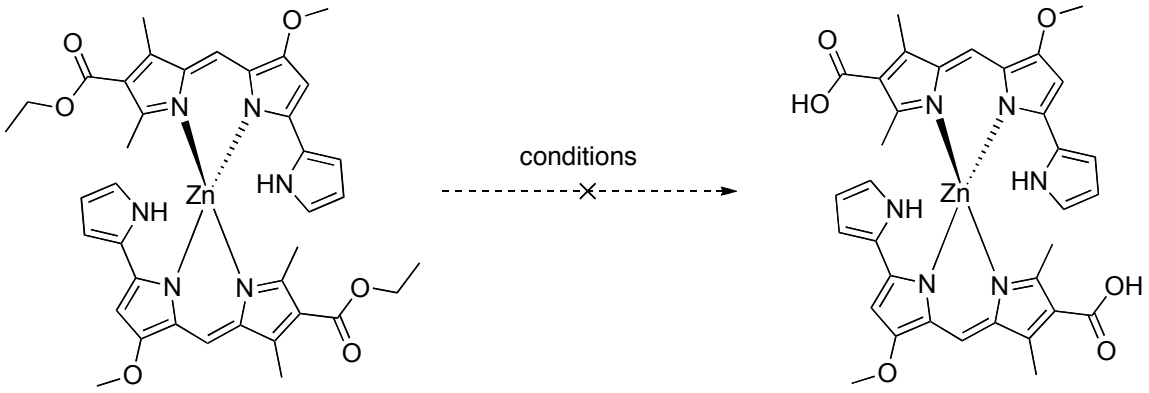
bench stable crystalline materials that could be purified over silica, in contrast to the corresponding free-base, which could not be purified over silica.

Scheme 21. Synthesis of zinc (**51**) and boron (**52**) complexes of prodigiosene **1**



Once both complexes were in hand we attempted to investigate the hydrolysis of the ethyl ester, hoping that complexation would facilitate isolation of the elusive carboxylate product. We started with chemical manipulation of the zinc complex as there is one previously reported hydrolysis of an ester remotely attached to a prodigiosene zinc(II) complex.[9] Because acid facilitates decomplexation of the ligand from the zinc, the hydrolysis of **51**, shown in Scheme 22, was only attempted under basic conditions, as summarized in Table 4.

Scheme 22. Attempted hydrolysis of zinc complex **51**



51 **53**

Table 4. Conditions for hydrolysis of zinc complex **51**

Entry	Conditions	Results
1	5 M KOH, THF (1:1), 7 days, reflux	Starting material recovered
2	5 M KOH, pyridine (1:10), 4 days, reflux	Starting material decomposed
3	6 M KOH, EtOH (1:10), 2 days, reflux	Starting material decomposed

From the base-catalyzed hydrolysis attempts, it appears that protection *via* zinc complexation does not facilitate the isolation of a hydrolyzed prodigiosene carboxylate. Zinc complex **51** was subjected to the same conditions that were successful in generating the transient, unstable prodigiosene carboxylate (**36**) from prodigiosene **1** (Table 4, entry 3). Zinc complex **51** did not withstand these conditions and analysis of the crude reaction mixtures by mass spectrometry showed multiple products that did not contain zinc. These decomplexed products were only sparingly soluble in water and methanol, solubility properties that are similar to those of the products of the attempted hydrolysis of unprotected prodigiosene **1**. More recently, Dr. Md. Imam Uddin has synthesized a prodigiosene bearing a benzyl ester on the C-ring.[58] Formation of a prodigiosene zinc complex followed by hydrogenolysis of the benzyl ester over palladium on carbon generates zinc complex **53** *in situ*, but the complex could not be isolated or characterized

as it decomposed readily. It can be trapped *in situ* following hydrogenolysis, *via* a coupling reaction with both esters and amides, but the resulting products are isolated in yields under 12% with complete consumption of starting material, indicating that the esterification reaction is in competition with the decomposition reaction.[58]

Attempts were also made to hydrolyze the ethyl ester of prodigiosene *F*-BODIPY **52** using 6 M KOH in ethanol. These conditions resulted in the complete consumption of starting material and a mixture of highly polar products, one of which was identified to be the unstable prodigiosene carboxylate **36** from a mass spectrum of the crude reaction mixture after aqueous work-up. A ^{11}B NMR spectrum of the same material indicated that the crude material did not contain boron and, although the mass spectrum indicated the presence of one other compound, it could not be identified. Purification of the crude material over neutral alumina was unsuccessful as the material adhered strongly to the alumina and could not be removed.

The base-catalyzed hydrolysis of methyl esters directly attached to the aryl group of *meso*-phenyl dipyrrin ligands coordinated to cobalt(III) has been previously reported,[86] consequently, the synthesis of the cobalt(III) complexes of prodigiosene **1** was attempted according to the published procedure, using commercially available $Na_3[Co(NO_2)_6]$. This reaction initially proved unsuccessful and a repeated attempt, monitored using UV/Vis spectroscopy, showed the slow disappearance of starting material without the corresponding formation of another UV active species, indicating that no complexation occurred, although the starting material was consumed, presumably *via* a decomposition pathway. It may be that prodigiosene **1** generates a ligand that is too sterically demanding to form an octahedral Co(**1**)$_3$ complex, or that it is oxidized in a redox couple with the

Co(III). Synthesis of the analogous iron(III) complex also proved unsuccessful, providing further evidence that prodigiosene **1** does not form stable octahedral metal complexes.

Although complexation was not a viable method for the chemical manipulation of prodigiosenes under basic conditions, zinc(II) and BF_2 complexes of prodgiosene **1** could be isolated in high yields. Our next goal was to investigate the synthesis of previously unreported complexes in order to explore the binding modes and properties of prodigiosene and pyrrolyldipyrrinato complexes.

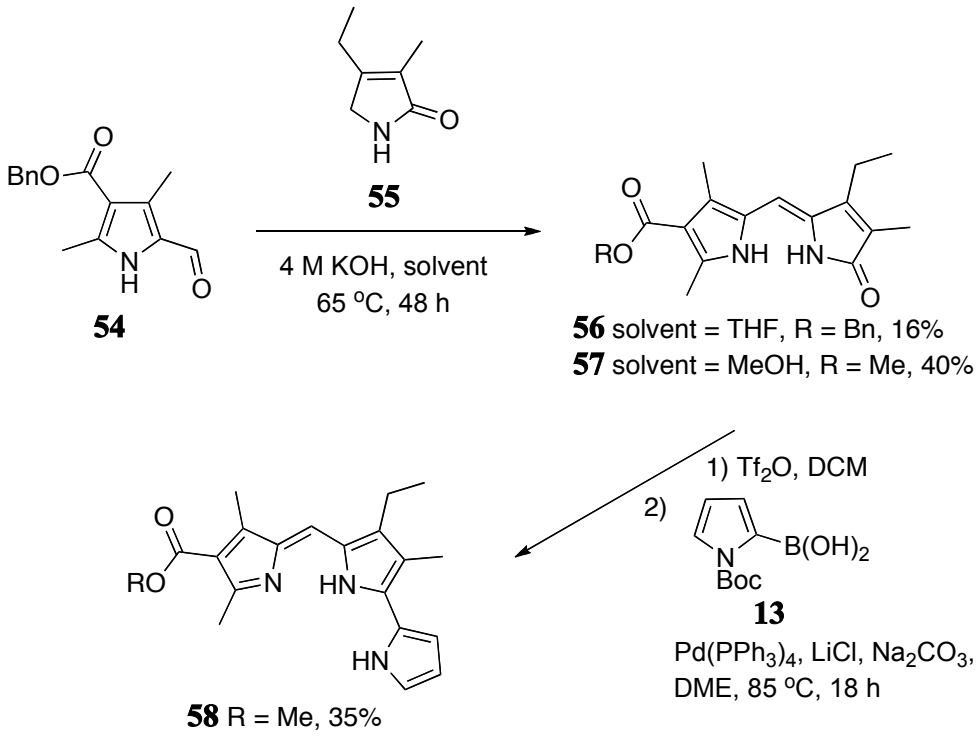
3.3.2 Synthesis of Additional Pyrrolyldipyrrins for Complexation

The synthesis of pyrrolyldipyrrins of the prodigiosene family has been previously discussed in detail (0, Section 2.3). However, in order to investigate the complexation of pyrrolyldipyrrins as a general class, it was necessary to synthesize a variety of pyrrolyldipyrrins and prodigiosenes with substituents, varying in electronic and steric properties, around the C-ring and the A-ring. In order to do a preliminary study, efforts were focused on synthesizing three classes of pyrrolyldipyrrins: C-ring ester and B-ring alkyl substituted, C-ring alkyl and B-ring methoxy substituted, and B- and C-ring alkyl substituted.

We began by focusing on the synthesis of pyrrolyldipyrrins without the methoxy group characteristic to the prodigiosene family. Although common to pyrrolyldipyrrins, a methoxy group in the 7-position is uncommon in dipyrrrins and, to our knowledge, there are no examples of dipyrrinato complexes that contain an aryloxy or alkoxy substituent at this position. In order to synthesize these derivatives, we used a modified version of D'Alessio's methodology that was previously optimized for the synthesis of ethyl ester prodigiosene **1**, but in place of 4-methoxy-3-pyrrolin-2-one, we used 4-ethyl-3-methyl-3-

pyrrolin-2-one as it contains alkyl substituents, which are common to both dipyrrins and dipyrrinato ligands. Two pyrrolyldipyrrins were synthesized using this methodology, as shown in Scheme 23.

Scheme 23. Synthesis of B-ring alkyl pyrrolyldipyrrins

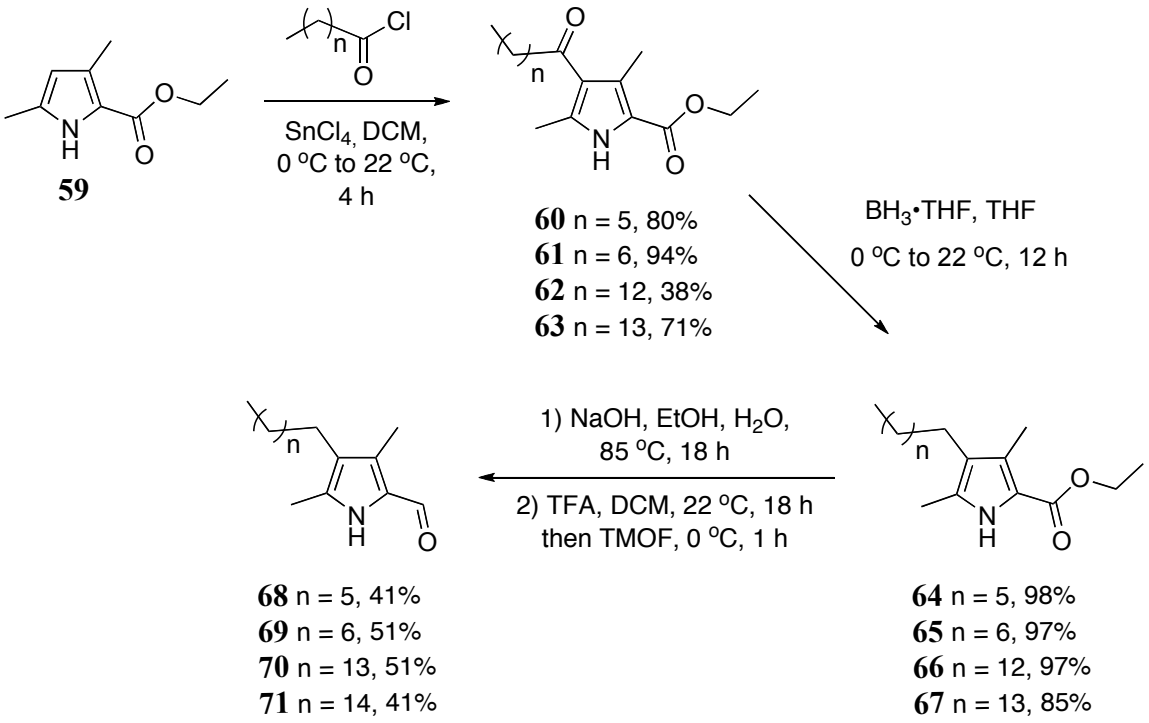


In this procedure, benzyl 5-formyl-2,4-dimethyl-1*H*-pyrrole-3-carboxylate (**54**),[87] is condensed with 4-ethyl-3-methyl-3-pyrrolin-2-one (**55**) in the presence of 4 M KOH. When this condensation is conducted in tetrahydrofuran, dipyrrinone **56** is isolated in a low yield of 16 %. In attempts to optimize the reaction, the solvent was changed to methanol. This change resulted in the isolation of the transesterified methyl ester dipyrrinone **57** in 40 % yield. Dipyrrinone **57** was converted into its corresponding triflate and, as the resulting triflate was observed to be unstable in solution, it was subjected to a Suzuki coupling reaction with *N*-BOC-pyrrole-2-boronic acid (**13**) immediately following work-up. Conversion of the product of the Suzuki coupling into

its corresponding HCl salt *via* work-up with aqueous hydrochloric acid gave pyrrolyldipyrrin **58** in a 35% yield. Dipyrrinone **56** was also converted into a pyrrole dipyrrin *via* a Suzuki coupling, but was transformed directly into its corresponding metal complex. As the instability of the triflate was thought to be a major contributor to the low yield of the Suzuki coupling step, attempts were made to synthesize a bromodipyrrin derivative of **57** using phosphorous oxybromide, as bromodipyrrins have been found to be more stable to air and temperature than triflates.[88] The bromination of the dipyrrinone **57** was not a viable synthetic step because the reaction was sluggish, even with continual addition of new phosphorous oxybromide, and resulted in multiple products that were difficult to separate using column chromatography.

Secondly, our focus moved to the synthesis of C-ring alkyl, B-ring methoxy substituted pyrrolyldipyrrins. Alkyl groups directly attached to the dipyrrin core are found more commonly in dipyrrinato complexes than ester groups. Before synthesis of the alkyl-substituted prodigiosenes was attempted a series of alkyl-substituted pyrrole-2-carbaldehydes with varying alkyl chain lengths had to be synthesized as precursors as shown in Scheme 24.

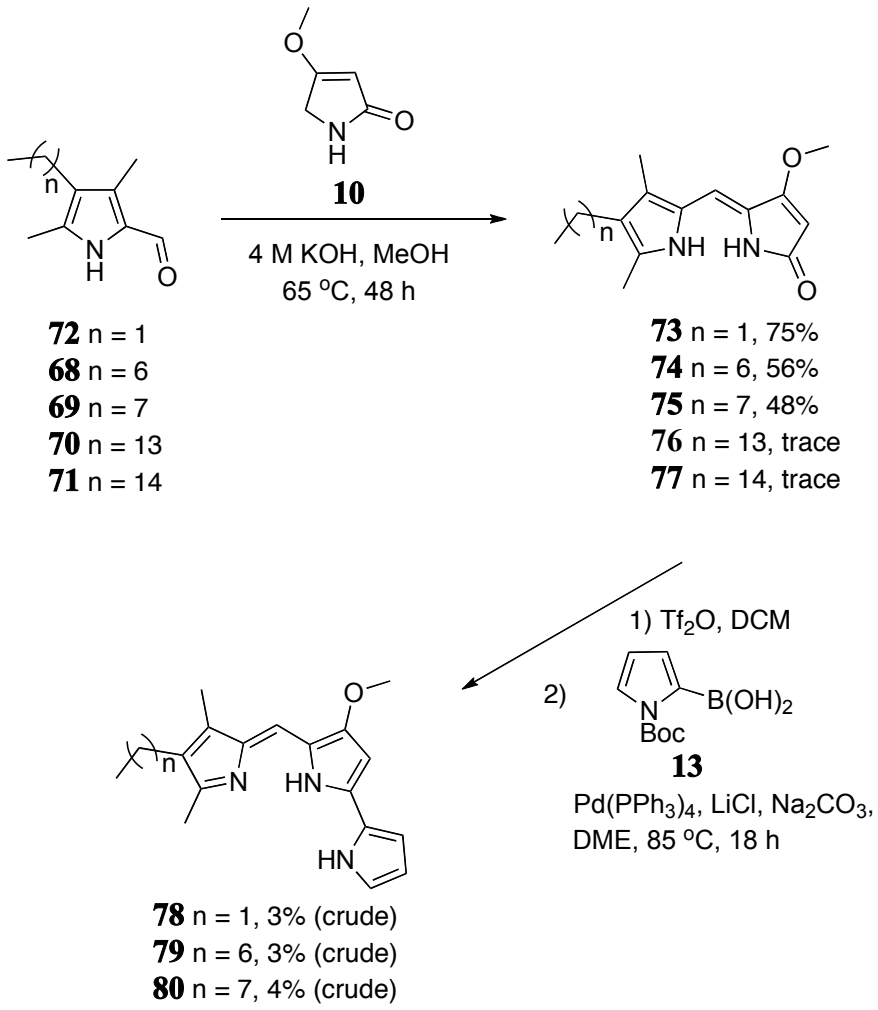
Scheme 24. Synthesis of C-ring alkyl substituted pyrroles



In this method, ethyl 3,5-dimethyl-1*H*-pyrrole-2-carboxylate[89] is alkylated using a series of acid chlorides to give the 2,4-pyrrole carboxylates (**60** - **63**). Reduction of the ketone directly attached to the pyrrole with BH_3•THF gave the corresponding 4-alkyl-pyrrole-2-carboxylates (**64** - **67**) in high yields. Hydrolysis of the ethyl ester under basic conditions followed by decarboxylation and formylation resulted in the isolation of the desired 4-alkyl-pyrrole-2-carbaldehydes (**68** - **71**) in moderate yields over two steps. An additional pyrrole-2-carbaldehyde with an 4-ethyl group (**72**)[90] was generated *via* the Vilsmeier formylation of commercially available kryptopyrrole.

With the pyrrole starting materials in hand, attempts were made to synthesize several prodigiosene derivatives with different alkyl chain lengths as shown in Scheme 25.

Scheme 25. Synthesis of C-ring alkyl prodigiosenes



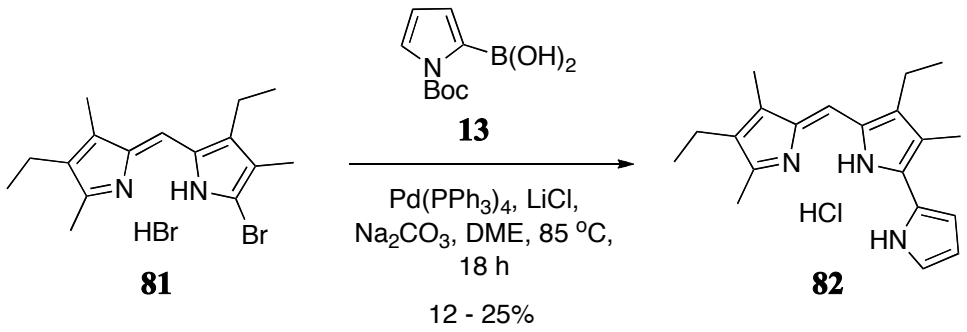
In this method, 4-alkyl-pyrrole-2-carbaldehydes were condensed with 4-methoxy-3-pyrrolin-2-one under basic conditions in methanol. Yields of the dipyrrinone ranged from good (**73**) to moderate (**74**, **75**) for dipyrrinones with short alkyl chains. There were no other products generated in these reactions and some starting material was recovered. The synthesis of dipyrrinones **76** and **77** was not successful. Even after increased reaction times, starting material was recovered. Trace amounts of product were isolated, but could not be separated from the pyrrole-2-carbaldehyde starting materials using crystallization or column chromatography. The poor solubility of these derivatives in refluxing

methanol was a concern, but changing the solvent to lower polarity tetrahydrofuran did not result in an improvement in the yield. Dipyrrinones **73**, **74** and **75** were converted into their corresponding triflates, in crude yields over 90%, and subsequently underwent a Suzuki coupling to give prodigiosenes **78**-**80**. The crude yields of these products were all under 4% and, despite repeated attempts to purify these products over neutral and basic alumina, impurities remained. Although these yields were low, no triflate starting material could be isolated from any of the crude reaction mixtures and no other pyrrole-containing compounds were isolated by way of column chromatography over basic alumina.

Attempts were also made to synthesize a bromodipyrrin from dipyrrinone **75** using $POBr_3$, with hopes that higher yields could be obtained in the Suzuki coupling reaction starting from this material as opposed to the dipyrrin triflate. The reaction was sluggish and after 2 weeks at reflux temperature and the addition of a total of 10 equivalents of $POBr_3$ the majority of the starting material still remained. This method was not a viable method for synthesizing C-ring alkyl substituted prodigiosenes and there was insufficient material to use these ligands in the pyrrolyldipyrrin complexation investigations.

Finally, attempts were made to synthesize a pyrrolyldipyrrin with both B- and C-ring alkyl substitution. Unsymmetrical bromodipyrrin **81** can be synthesized in high yields from *tert*-butyl 4-ethyl-3,5-dimethyl-2-pyrrole-carboxylate,[91] which can be generated from the corresponding 4-acetyl pyrrole.[92, 93] Bromodipyrrin **81** was converted into pyrrolyldipyrrin **82** *via* the typical Suzuki coupling reaction, as shown in Scheme 26.

Scheme 26. Synthesis of fully alkyl substituted pyrrolyldipyrrin **82**



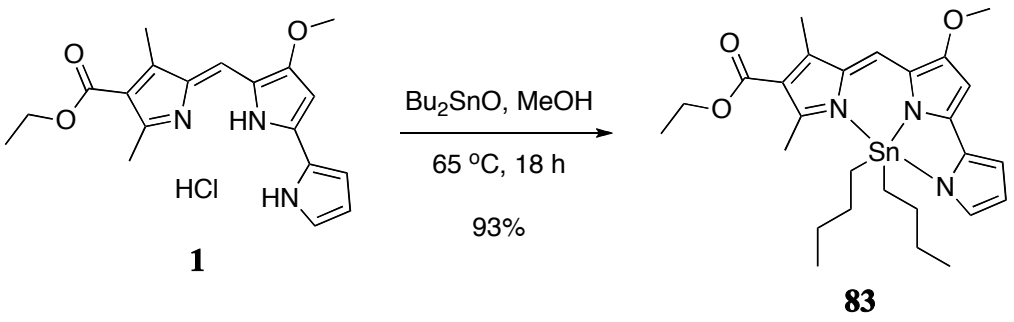
Pyrrolydipyrrin **82** was isolated in low yields and was difficult to isolate in pure form as it had limited stability on silica, neutral alumina and basic alumina. This reaction also suffered from poor reproducibility and the product was isolated in yields ranging from 12 to 25%.

With a series of differentially substituted pyrrolyldipyrrins in hand, including some prodigiosenes, investigations into the synthesis, stability and properties of pyrrolyldipyrrinato complexes could begin.

3.3.3 Synthesis and Structural Determinaton of a Series of Pyrrolyldipyrrinato Tin(IV) Complexes

In attempts to transesterify ethyl ester prodigiosene **1** using a literature procedure that employed catalytic amounts of dibutyltin oxide,[70] a small amount of a highly fluorescent material was isolated. When this reaction was repeated using a stoichiometric amount of dibutyltin oxide, tin complex **83** was isolated in 93% yield, as shown in Scheme 27.

Scheme 27. Synthesis of a tin complex of ethyl ester prodigiosene **1**



1 **83**

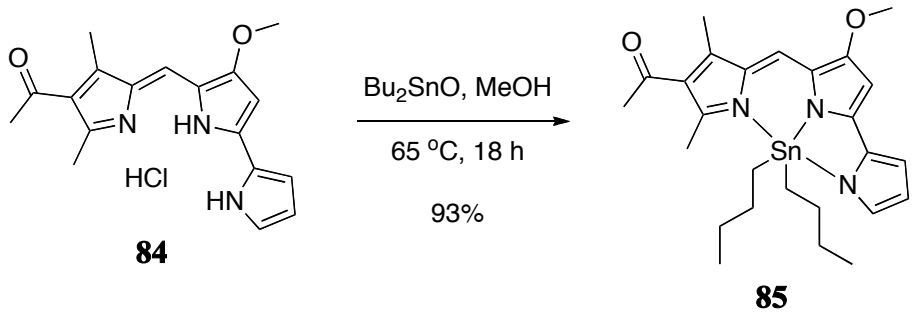
It was postulated that **83** was a five-coordinate, prodigiosene tin(IV) complex. In this postulated structure, the prodigiosene is a dianionic ligand (LX_2) and the tin metal centre is coordinated to all three nitrogen atoms of the tripyrrolic prodigiosene core. In the only other reported prodigiosene complex, where all three nitrogen atoms of the tripyrrolic prodigiosene core coordinate to a metal, the C-ring of the prodigiosene is oxidized so the prodigiosene is no longer a dianionic ligand (LX_2), but a monoanionic (L_2X) ligand.[11] Although it was postulated that the pyrrole ring in complex **83** coordinates and stabilizes the tin center, it is also feasible that the carbonyl group could stabilize the tin of a neighboring complex through an intermolecular interaction in the solid state.

Although no prodigiosene tin(IV) complexes have been reported to our knowledge, dibutyltin(IV) complexes of 1,9-diacyldipyrromethanes have been extensively investigated. In these complexes, the carbonyl groups in the 1- and 9-positions of the dipyrromethane are required to stabilize the tin centre.[94-97] The omission of a carbonyl group in either the 1- or 9-position prevents the formation of the complex.[97] Reactions of pyrrole with tin sources are known and have been exploited for the synthesis of *N*-tributylstannyl pyrrole, which is prepared *via* the azeotropic dehydration of bis(tributyltin) oxide and pyrrole, or heating tributyltin methoxide with pyrrole.[98]

In order to investigate the structure and bonding in these complexes, it was necessary to obtain an X-ray crystal structure. Attempts to grow crystals of suitable quality for X-ray diffraction using slow evaporation, solvent diffusion, vapor diffusion and slow cooling resulted only in small (< 1 mm length) fractal crystals of **83**. These difficulties in crystallization led us to the synthesis of derivatives with functionalities that could potentially increase the crystallinity of the corresponding tin complexes.

In order to increase the overall crystallinity of the tin complexes, investigations focused on appending alternate functionality to the prodigiosene core. In the first attempt, prodigiosene **84**[29] was converted into its tin complex in high yields as shown in Scheme 28.

Scheme 28. Synthesis of prodigiosene dibutyltin complex **85**

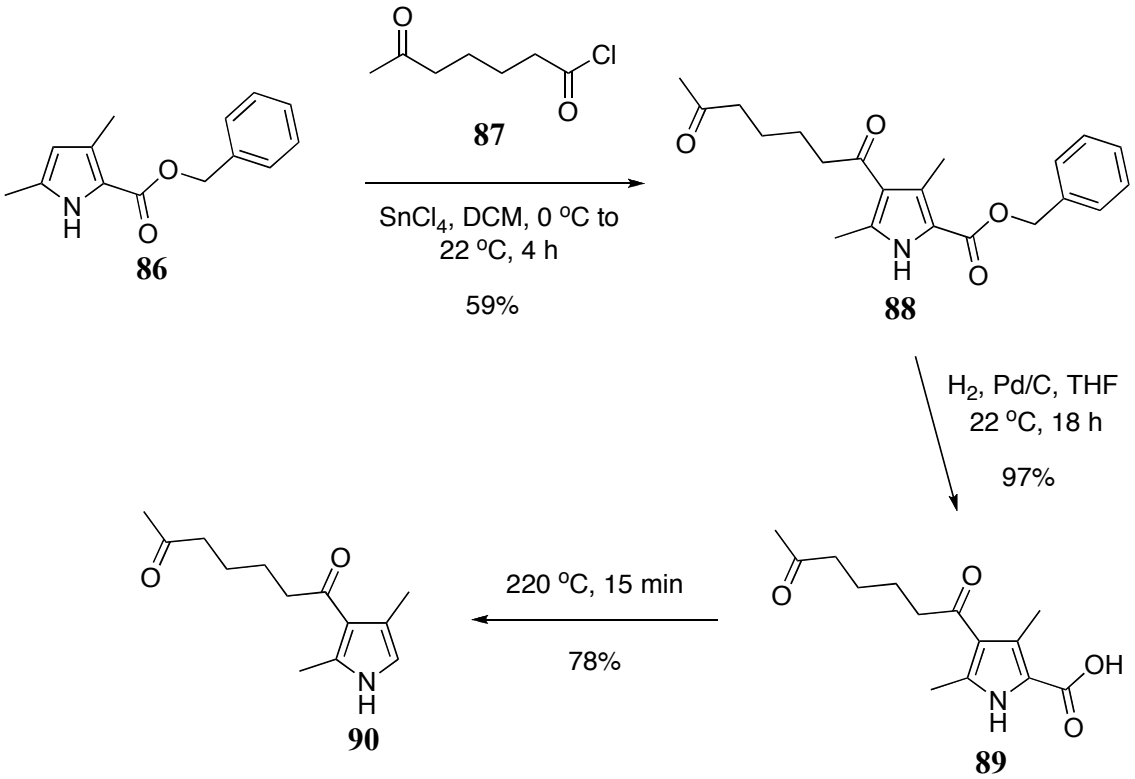


Although difficulties were encountered in crystallizing **85**, it was hoped that by introducing hydrazone functionality, which is known generally to exhibit high crystallinity and low solubility, *via* the attached ketone, crystallization could be facilitated. Attempts to convert **85** to its 2,4-DNP hydrazone using 2,4-DNP and acetic acid in ethanol resulted in loss of fluorescence and recovery of the parent prodigiosene **84**[29] indicating that the complexes are acid sensitive. Attempts to convert prodigiosene **84**[29] to its 2,4-DNP hydrazone prior to tin complexation led to an insoluble product.

When this crude product was subjected to tin complexation conditions, it gave a fluorescent product that unfortunately decomposed upon purification and upon standing in solution.

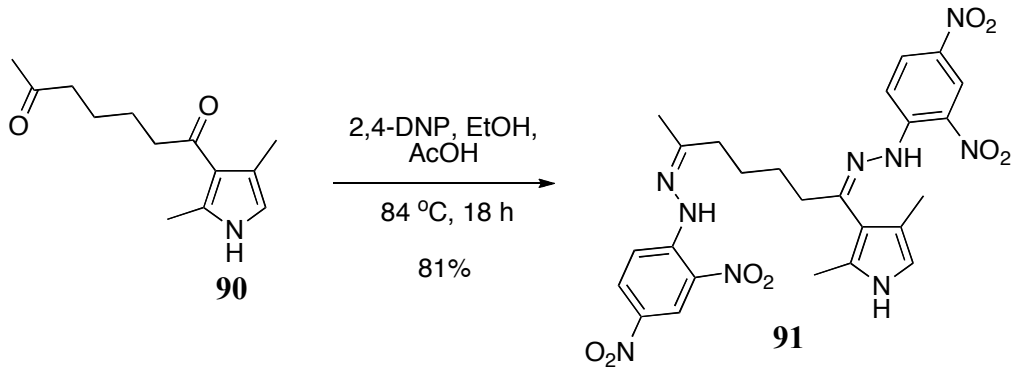
In a second attempt to generate a crystalline complex, a new prodigiosene with a ketone incorporated on a 6-carbon chain attached to the C-ring was proposed. This compound, or an intermediate in its synthesis, could then be converted into its corresponding hydrazone for increased crystallinity. This synthesis, outlined in Scheme 29, began with a Lewis acid-mediated acylation of pyrrole **86**,[99] with functionalized acid chloride **87**[100] to give pyrrole **88**. Hydrogenolysis over palladium followed by decarboxylation gave α-free pyrrole **90**, which could later be incorporated into a prodigiosene as a C-ring.

Scheme 29. Pyrrole diketone synthesis



Once pyrrole diketone **90** was generated, attempts were made to formylate the 2-position of the pyrrole using Vilsmeier formylation conditions and also using trifluoroacetic acid (TFA) and triethylorthoformate (TEOF).[101, 102] These attempts led to mixtures of multiple products. It is proposed that the diketone may cyclize under the acidic conditions and so the ketone was converted into its 2,4-dinitrophenylhydrazone, as shown in Scheme 30, prior to formylation.

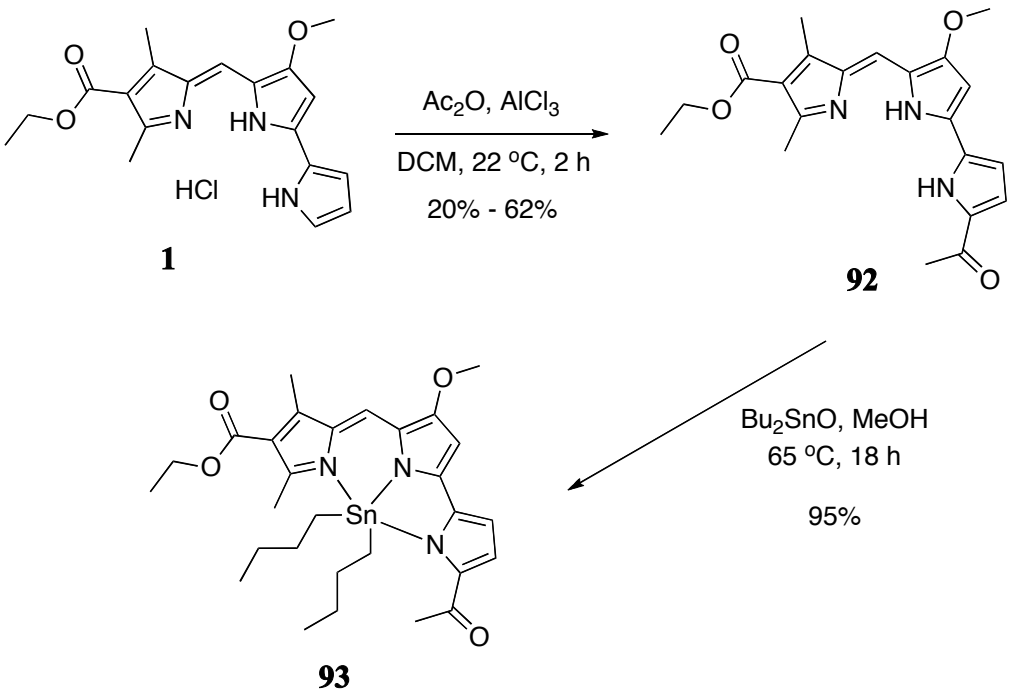
Scheme 30. Synthesis of a hydrazone derivative of **90**



Formylation of **91** using Vilsmeier reaction conditions resulted in decomposition of the starting material. Formylation using a modified literature procedure employing TFA and TEOF[101] appeared to be successful, from the analysis of NMR spectra of the crude material. As expected, the material was very insoluble and attempts at purification by crystallization were unsuccessful. Due to the added difficulty in synthesis upon introducing the additional ketone functionality, focus was moved to a third strategy.

In a third attempt to isolate crystals of a prodigiosene tin complex, an extra carbonyl group was introduced to the A-ring of **1** according to a literature procedure.[22] Although the reaction was not very reproducible and gave variable yields, **93** was isolated following tin complexation as shown in Scheme 31.

Scheme 31. Synthesis of a crystalline tin complex **93**

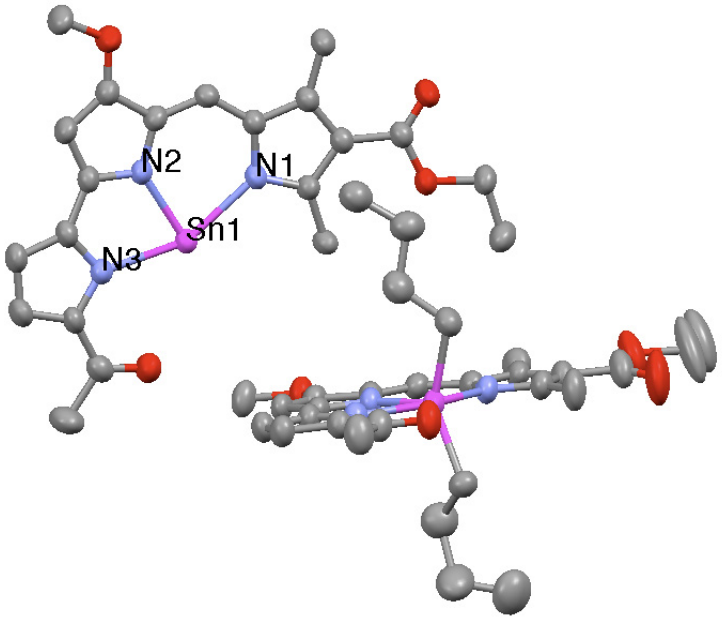


Many thanks to Dr. Adeeb Al-Sheikh Ali who successfully generated an X-ray diffraction quality crystal of prodigiosene dibutyltin complex **93** *via* slow evaporation from a dichloromethane solution in the presence of a few drops of methanol.

All crystals in the sample were found to be non-merohedral twins and solving the X-ray crystal structure first with twinned data led to the possible location of the composite plane, which allowed for dissection of a fragment of untwinned crystal, as shown in Figure 15. The disorder still present in the crystal is likely dynamic as the crystal survives cooling to -73 ˚C, but shatters after some time, when cooled to -93 ˚C. The structure shows a pentacoordinate tin atom with distorted trigonal bipyramidal geometry. All three nitrogen atoms of the pyrrolyldipyrrin are coordinated to the tin center making this structure, to the best of our knowledge, the first example of a

pyrrolyldipyrrinato complex, which binds through all three of its pyrrolic nitrogen atoms and behaves as a dianionic, LX_2 ligand.

Figure 15. Thermal ellipsoid diagram (50%) of **93**



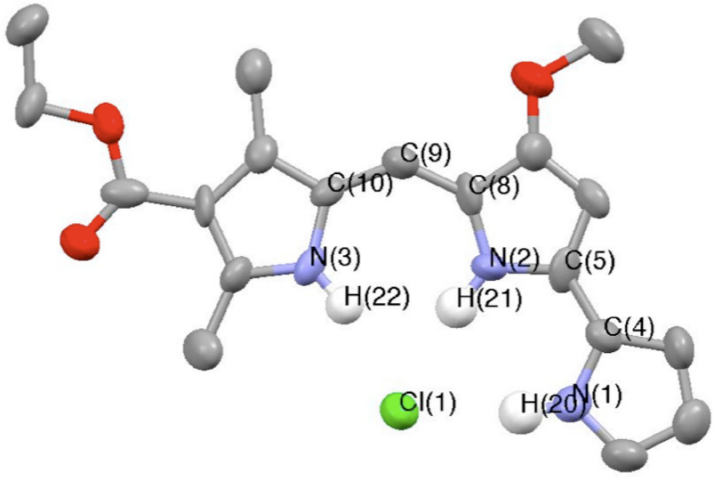
Sn(1) butyl groups and all hydrogen atoms removed for clarity. Selected bond distances (Å): Sn(1)-N(1), 2.309(2); Sn(1)-N(2), 2.128(2); Sn(1)-N(3), 2.239(2). Selected bond angles (deg): N(1)-Sn(1)-(N2), 81.46(9); N(1)-Sn(1)-N(3), 155.25(10); N(2)-Sn(1)-N(3), 73.85(10); C(43)-Sn(1)-C(47), 137.84(14) (C(43) and C(47) are the carbon atoms of each attached butyl group respectively).

The N(3)-Sn(1)-N(1) bond angle of 155.25(10)˚ is the largest of the angles involving the tin center, suggesting that N(1) and N(3) are occupying the pseudoaxial positions in the complex. However, the C(43)-Sn(1)-C(47) bond angle is larger than the 120˚ degrees normally separating equatorial substituents in a trigonal bipyramidal complex with a value of 137.84(14)˚. The bond angles between N(1)-Sn(1) or N(3)-Sn(1) and the equatorial atoms (N(2), C(43), C(47)) range from 73˚ to 95˚ while the bond angles between C(43)-Sn(1) or C(47)-Sn(1) and N(1), N(2) or N(3) range from 93˚ to 112˚. The trigonal pyramidal geometry is significantly distorted in the complex, likely

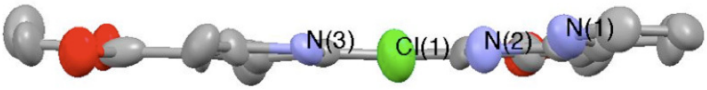
due to the restrictions imposed by the rigid pyrrolyldipyrrinato ligand framework. The tin-nitrogen bond lengths in complex **93** range from 2.128 to 2.309 Å. These bond lengths are within the reported ranges of other nitrogen tin bonds in neutral, pentacoordinate tin(IV) complexes.[103-105]

The coordinated pyrrolyldipyrrinato unit is essentially planar in complex **93**. In the X-ray crystal structure of the hydrochloride salt of ethyl ester prodigiosene **1**, which contains a similar pyrrolyldipyrrinato unit to **93** (differing only in an acyl group on the pyrrole ring), the pyrrolydipyrrin is also planar, as shown in Figure 16.

Figure 16. Thermal elipsoid diagram (50%) of **1**



Front View

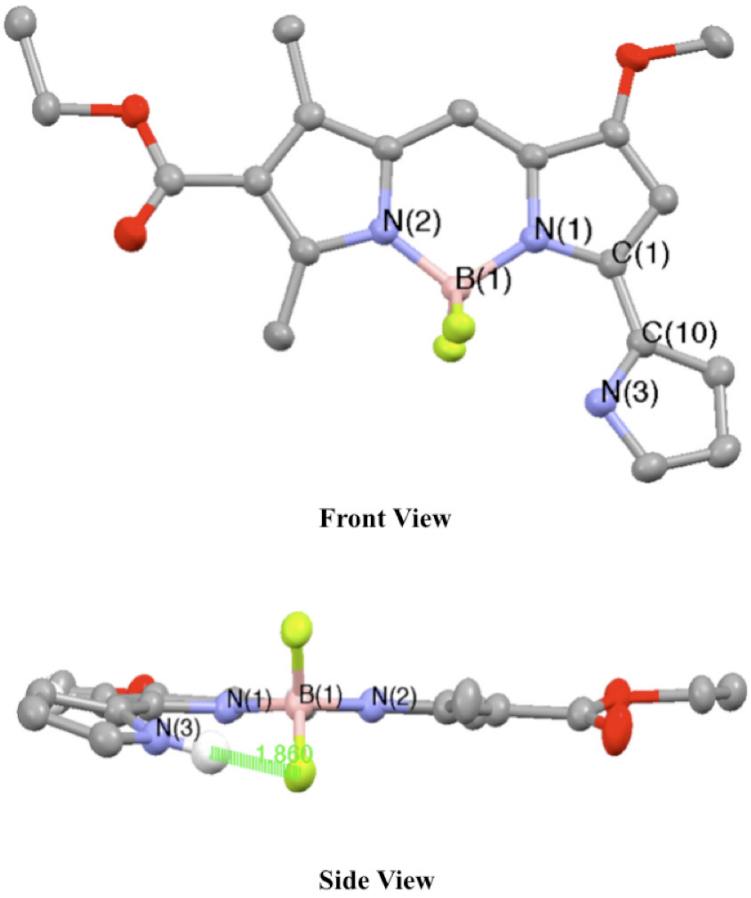


Side View

Hydrogen atoms removed for clarity. Selected bond angles (deg): C(10)-C(9)-C(8) 132.6(5); Selected contact distances (Å): H(22)-Cl(1) 2.195, H(21)-Cl(1) 2.169, H(20)-Cl(1) 2.226; Selected torsional angle (deg): N(1)-C(4)-C(5)-N(2) -2.8(9).

This planarity has also been observed in other crystal structures of pyrrolyldipyrrin hydrochloride salts and is enforced by hydrogen bonds between the chloride counteranion and the pyrrolyldipyrrin,[106] but not all hydrochloride salts exhibit this planarity.[18] X-ray diffraction quality crystals of *F*-BODIPY **52** were isolated by slow evaporation of a dichloromethane solution in the presence of a few drops of methanol. Interestingly, in *F*-BODIPY **52**, the uncoordinated pyrrole unit is 16˚ out of the plane of the coordinated dipyrrinato unit as shown in Figure 17. This twist is likely to accommodate a hydrogen bond between the hydrogen attached to the pyrrolic nitrogen atom and the fluorine atom below the dipyrrinato plane with a contact distance of 1.860 Å. In a published X-ray crystal structure of the zinc(II) complex of prodigiosin, which coordinates to zinc through its dipyrrinato ligand alone, the dipyrrinato portion of the ligand is planar but, in a similar fashion to the *F*-BODIPY complex, the uncomplexed pyrrole unit is twisted 20.6˚ out of the plane of the dipyrrin.[11]

Figure 17. Thermal ellipsoid diagram (50%) of **52**



Hydrogens removed for clarity. Selected bond distances (Å): B(1)-N(1), 2.309(2); B(1)-N(2), 2.128(2); Selected bond angle (deg): N(1)-B(1)-(N2), 81.46(9); Selected torsional angle (deg): N(1)-C(1)-C(10)-(N3), -16.09; Contact distance (Å): N(3)-H···F(1) 1.860.

With success in the synthesis and confirmation of the bonding mode in these complexes, attempts were focused on synthesizing other examples of pyrrolyldipyrrinato tin complexes. The pyrrolyldipyrrins were converted to their corresponding dibutyltin complexes by heating a methanolic solution of each pyrrolyldipyrrin with an excess of dibutyltinoxide at reflux temperature for a period of 18 h, as shown in Scheme 32, Table 5. Similarly, several pyrrolyldipyrrins were converted into their corresponding diphenyltin complexes by heating a methanolic solution of pyrrolyldipyrrin with an excess of diphenyltin oxide at reflux temperature, as shown in Scheme 32, Table 5.

Scheme 32. General synthetic scheme for the synthesis of pyrrolyldipyrrinato tin(IV) complexes

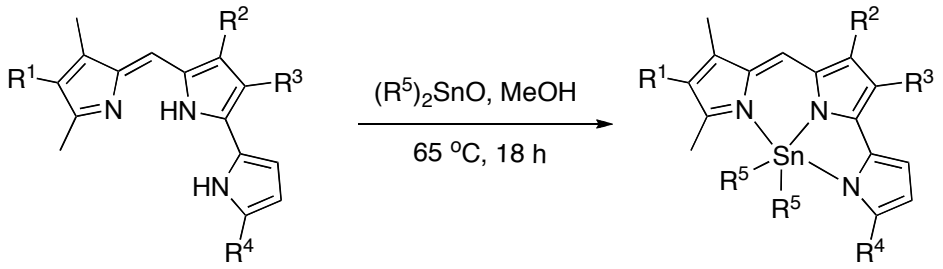


Table 5. Yields of pyrrolyldipyrrinato tin(IV) complexes

Starting Material	Product	R^1	R^2	R^3	R^4	R^5	Isolated yield /%
1	**83**	CO_2Et	OMe	H	H	^{n}Bu	93
92	**93**	CO_2Et	OMe	H	C(O)Me	^{n}Bu	95
94	**95**	CO_2Bn	OMe	H	H	^{n}Bu	90
56	**96**	CO_2Bn	Et	Me	H	^{n}Bu	86
82	**97**	Et	Et	Me	H	^{n}Bu	22
94	**98**	CO_2Bn	OMe	H	H	Ph	82
58	**99**	CO_2Me	Et	Me	H	Ph	84
82	**100**	Et	Et	Me	H	Ph	33

The conversion of the pyrrolyldipyrrins to the corresponding tin(IV) complexes was quantitative in all cases according to analysis using TLC, and the isolated yields of the pyrrolyldipyrrinato dibutyl and diphenyl tin(IV) complexes were generally high with the exception of the fully alkyl substituted derivatives **97** and **100** (Table 5). The diphenyltin complexes (**98-100**) exhibited some decomposition to return the pyrrolyldipyrrin starting material upon purification over neutral or basic alumina, a procedure that was utilized to remove the excess diphenyltin oxide. Attempts to optimize the reaction and subsequent purification were conducted using pyrrolyldipyrrin **94**. Unfortunately, if only 1 equivalent of diphenyltin oxide was used in the reaction of **94** the reaction was sluggish and small amounts of unreacted **94** remained in the reaction

mixture after four days at reflux temperature. Attempts to use crystallization as a purification strategy were similarly unsuccessful.

Notably, the diphenyltin complexes are less stable in solution than their corresponding dibutyltin complexes and decompose to free pyrrolyldipyrrins slowly over the period of a week. The diphenyltin and dibutyltin complexes are sensitive to acid and the corresponding pyrrolyldipyrrin HCl salts are generated rapidly and quantitatively after adding aqueous hydrochloric acid to a solution of the corresponding tin complex in a 1:1 solution of dichloromethane and methanol. This is not unsurprising as protic acids with a pKa less than about 25 are known to cleave the Sn-N bond.[98]

Attempts were also made to synthesize a diphenylsilicon complex of prodigiosene **94** using dichlorodiphenylsilane. Although the reaction appeared to be successful in generating a single, highly fluorescent compound according to analysis using TLC, isolation proved difficult under standard conditions as quenching the dichlorodiphenylsilane resulted in decomplexation. The complex is, unsurprisingly, both air and moisture sensitive. Further studies into silicon complexes would need be undertaken under air and moisture free conditions in a glovebox.

3.3.4 Investigations into the Optical and Biological Properties of Pyrrolyldipyrrinato Tin(IV) Complexes

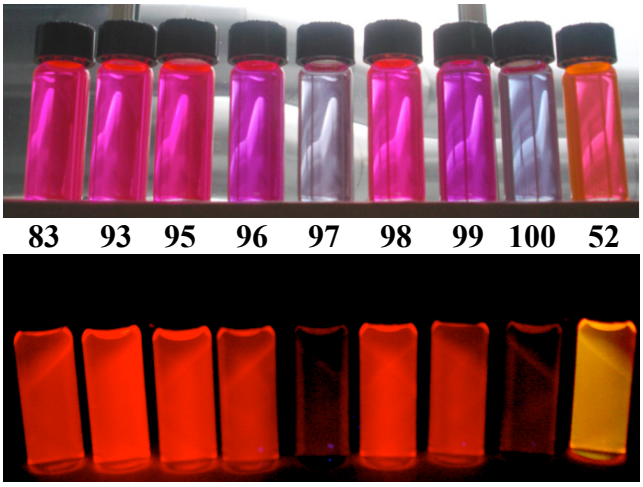
Although the pyrrolyldipyrrin ligands do not display detectable fluorescence, all of the synthesized tin complexes exhibit appreciable fluorescence quantum yields (Φ_F = 0.28 to 0.61) in dichloromethane with maximum wavelengths of emission in the orange region (584 and 622 nm). The complexes also exhibit broad absorption bands between 550 and 625 nm (ε 7-11 x 10^4 M^{-1} cm^{-1}) (Table 6, Figure 18).

Table 6. Optical properties of tin pyrrolyldipyrrinato complexes and *F*-BODIPY complex **52** in DCM at 22 ˚C

Complex	**Absorbance λ_{max}** /nm	**ε** /10^{-4} M^{-1} cm^{-1}	**Emission λ_{max}** /nm	**Φ_F**
83	561	8.78	584	0.53[a]
93	570	11.6	582	0.61[a]
95	561	8.82	584	0.53[a]
96	585	8.69	607	0.52[b]
97	599	11.6	617	0.28[b]
98	561	7.40	583	0.55[a]
99	587	8.63	609	0.51[b]
100	603	8.70	622	0.32[b]
52	543	10.5	559	0.92[a]

[a] Relative to rhodamine 6G in EtOH (Φ_F = 0.94); [b] Relative to rhodamine 101 in EtOH (Φ_F = 0.96).

Figure 18. Pyrrolyldipyrrinato complexes in dichloromethane solution (~7.0 x 10^{-5} M) visualized under ambient light (top) and long wave UV irradiation (bottom)



The *F*-BODIPY pyrrolyldipyrrinato complex (**52**) has the highest fluorescence quantum yield of all of the compounds (Φ_F = 0.92) and this value is comparable to the fluorescence quantum yields of other strongly emitting *F*-BODIPYs.[4] The pyrrolyldipyrrinato tin complexes show an interesting pattern in their quantum yields based on the substitution pattern about the ligand. When the ligand contains a conjugated

ester substituent (**83**, **93**, **95**, **96**, **98** and **99**) the fluorescence quantum yield was high (Φ_F > 0.50). However, when the ligand contained only alkyl substituents (**97** and **100**) the fluorescence quantum yields were much lower (Φ_F < 0.32). The Stokes shifts of the complexes were small and range from 435 to 833 cm^{-1}.

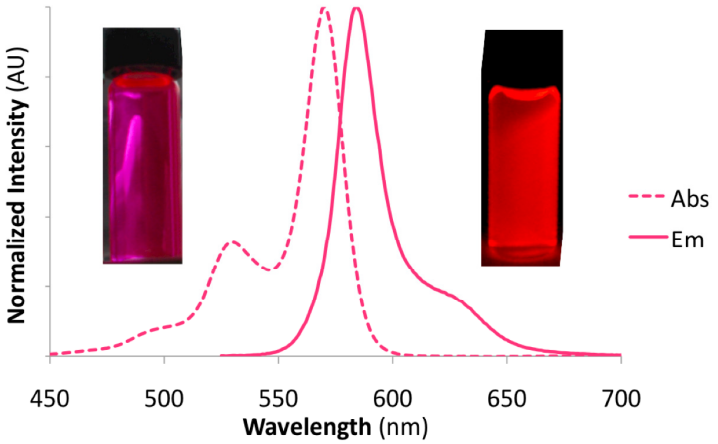
These complexes displayed similar fluorescence properties to several recently reported fluorescent dipyrrinato metal complexes. There have been two recent reports of π-extended dipyrrinato complexes of Ca(II) and Zn(II) (Φ_F = 0.58 - 0.70)[81] and a tetradentate N_2O_2-type dipyrrinato Al(III) complex (Φ_F = 0.23)[82] which display moderate to high fluorescence quantum yields. In the case of the aluminum complex, the ligand is held in a rigid position by the additional coordination of phenolic oxygens. In the case of the π-extended dipyrrinato complexes, the ligands contain esters in the 1- and 9-positions and the proximate carbonyl oxygen atoms likely play a role in ligand-metal bond stabilization. This series of pyrrolyldipyrrinato tin(IV) complexes is a further example of dipyrrinato-type complexes which exhibit high fluorescence quantum yields. The added rigidity induced through coordination of the A-ring pyrrole reduces the number of pathways for non-radiative decay, allowing for higher observed fluorescence quantum yields than those of traditional dipyrrinato complexes with only two coordination sites. *F*-BODIPY **52** has the highest fluorescence quantum yield of the synthesized complexes. Although the pyrrolide unit is not bound to the boron centre in this complex, the pyrrolyldipyrrin rigidity is due to the presence of the hydrogen bond between the unbound pyrrole N*H* and the neighboring fluorine atom.

The effects of changing the substituents around the pyrrolydipyrrinato core of the complexes are evident after analysis of the wavelengths of maximum absorption. When

the pyrrolyldipyrrin ligand contained both ester and methoxy groups (**83** and **95**) the wavelength of maximum absorption was 561 nm (**83** and **95**). When the methoxy group was replaced with an alkyl group (**96**), the wavelength of maximum absorption shifted 24 nm bathochromically and when the ester group was also replaced with an alkyl group (**97**) the wavelength of maximum absorption was bathochromically shifted 14 nm. The same trend is observable for the diphenyltin complexes. When the pyrrolyldipyrrinato ligand was not modified, but the groups on the tin center were changed from butyl to phenyl, there was little to no effect on the wavelength of maximum emission or the quantum yields of fluorescence for the related complexes (compare **95** and **97** with butyl substituents to **98** and **100** with aryl substituents).

All of the absorption spectra have a similar band structure in the visible region: a large peak with a shoulder. This band structure is commonly observed for dipyrrinato complexes.[76, 107] For each complex, the emission spectrum is approximately the mirror image of the absorption spectrum, but the vibronic features are less prominent in the emission spectrum. The normalized absorption and emission spectrum of tin complex **93** is shown in Figure 19 as a representative example.

Figure 19. Normalized absorption (- -) and emission (—) spectra of **93** obtained using 520 nm excitation in DCM at 22 ˚C



This high yielding route to dibutyltin complexation and decomplexation allows for a potential new pyrrolyldipyrrin purification strategy, similar to that used for 1,9-carbonyl substituted dipyrromethanes.[97] Many pyrrolyldipyrrins of the prodigiosene family are generated *via* a Suzuki coupling reaction with a boronic acid-containing pyrrole. If the reaction is not clean, the resulting mixture is often difficult to purify, and thus tin complexation has promise as a useful purification strategy.

Currently, the most popular use of fluorescent ligand-metal complexes is as chemical sensors in solution. In order to develop complexes as fluorescent sensors for tin(IV), the ligand would need to be modified so that the material was highly stable in solution and the reaction conditions would need to be modified so that the complexation reaction occurs at an appreciable rate at room temperature.

Neutral tin(IV) complexes are well known in the literature for their antimicrobial activity and have also found use in biocidal paints for ships.[108] Dialkyl or aryl substituted tin complexes are of intermediate toxicity to trialkyl or aryl and monoalkyl or aryl.[109] The toxicity of the complexes appears to correlate with their total molecular surface area and

their overall hydrophobicity.[108] Although the mechanisms of action of tin(IV) complexes on microbial processes are still poorly understood, many bacterial membrane functions can be inhibited by organotin complexes. Many organotin(IV) complexes with nitrogen-containing ligands exhibit antimicrobial activity.[108] Pyrrolyldipyrrinato complex **83** was submitted and tested for antimicrobial activity against several *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Pseudomonas aeruginosa*, *Enterococcus faecalis* and *Bacillus subtilis* strains. The minimum inhibitory concentrations can be found in Table 7.

Table 7. MIC data ($\mu g mL^{-1}$) for prodigiosene tin complexes **83**

	MIC ($\mu g mL^{-1}$)		
	83	*Erythromycin*	*Vancomycin*
Staphylococcus aureus C622; ATCC 25923	16	0.5	1
Staphylococcus aureus C623	2	>128	1
Staphylococcus aureus 305	8	0.125	0.5
Staphylococcus aureus Becker CP8 stanis	4	0.25	0.5
Staphylococcus aureus Becker Lyc12 CP336 stanislaus	32	0.125	0.5
Staphlyococcus epidermidis C960; ATCC14990	>128	0.125	1
Pseudomonas aeruginosa H188	>128	64	>128
Salmonella enteric s. Typhimurium C587	128	64	>128
Escherichia coli C498	32	32	>128
Enterococcus faecalis C625; ATCC 29212	8	1	2
Bacillus subtilis C971; ATCC 6633	2	0.125	0.125

The erythromycin control had comparable or better activity against all of the strains with the exception of *S. aureus* 623 (a clinical methicillin resistant *Staphylococcus aureus* isolate);[110] compound **83** was found to have a MIC of 2 $\mu g\ mL^{-1}$ against *S. aureus* C623,

while the erythromycin control had a MIC of > 128 μg mL^{-1}. Further investigation of the antimicrobial activity of **83** or the other pyrrolyldipyrrinato complexes was not undertaken.

As previously discussed in 0, pyrrolyldipyrrins of the prodigiosin family are known to exhibit anticancer activity through several different mechanisms, some of which require complexation of the tripyrrolic core to a metal or anion.[6] In addition, there are also examples of neutral, 5-coordinate tin complexes, which exhibit *in vitro* anticancer activity.[105, 109] Because several of the prodigiosenes used in this complexation study are known to exhibit anticancer activity,[15, 29] investigations on the effect of tin complexation on anticancer activity were undertaken. Complexes **95** and **98** were selected for cell inhibition studies against the NIH/NCI 60 cancer cell lines. The results are summarized along with those of the free ligand (**94**) in Table 8.

Table 8. Mean *in vitro* activity of prodigiosenes and their complexes over 60 human cancer cell lines

Compound	Log_{10}mean GI_{50}	Log_{10}mean TGI	Log_{10}mean LC_{50}
Prodigiosin[a]	-7.85	-5.68	-6.65
94[a]	-7.02	-5.82	-5.00
95[a]	-7.53	-6.27	-5.43
98	-8.07	-5.84	-4.90

[a]Average of 2 repeat screens

Compared to the free ligand (**94**), complexes **95** and **96** show growth inhibition and total growth inhibition similar or larger in value to that of prodgiosin. Both complexes show lower lethal concentrations than prodigiosin, which is too cytotoxic to be used as a therapeutic. These biological results are preliminary as further studies are necessary to address the stability of the tin-nitrogen bonds under the test conditions.

Preliminary comparison of the activity data of complexes **95** and **98** to the free ligand **94**, appear to suggest that the observed activities are not due to the free ligand alone. Although the observed biological activities may be complex specific, they could alternatively be due to the nonspecific action of hydrolyzed R_2Sn^+ moieties, known for their undersirable neurotoxicity and immune suppression,[109] in conjunction with the free ligand.

3.4 Conclusions and Implications

A series of previously unreported pyrrolyldipyrrinato tin complexes have been prepared. The bonding mode in these complexes was determined using X-ray crystallographic analysis for a representative complex. The series of compounds have been analyzed using UV/Visible and fluorometric analysis in order to discover the effects on fluorescence of modifying substiuents on the ligand and substituents at the tin(IV) centre. The complexes are all highly fluorescent with quantum yields ranging between 0.23 and 0.61. The series of complexes show larger quantum efficiencies of fluorescence when the ligand contains an electron-withdrawing group conjugated to the C-ring. Substitution on the B-ring has a much smaller effect. Several of the synthesized derivatives have also been tested for antimicrobial activity. Two derivatives were selected for cell inhibition studies against the NIH/NCI 60 cancer cell lines and the results of these experiments, although preliminary, are interesting. In-house cell-inhibition studies would need to be done in order to determine the stability of the Sn-N bonds under the experimental conditions.

In the future, the synthesis of other prodigiosene metal complexes should be attempted as their remains very little known about prodigiosene metal complexes, their binding modes and their biological activity. Particularly of interest would be the synthesis

of palladium, platinum, and zirconium pyrrolyldipyrrinato complexes, which could have potential applications in catalysis. Before a detailed investigation of pyrrolyldipyrrinato complexation can be undertaken, a more efficient method for the synthesis of non-prodigiosene pyrrolyldipyrrins would also need to be developed, as the current one is not sufficient for the generation of moderate to high yields of the desired pyrrolyldipyrrins.

It would also be interesting to investigate the possible applications of the prodigiosene tin complexes. Some biological testing has already been conducted on the prodigiosene tin complexes, but there are also potential applications of these pyrrolyldipyrrinato complexes in the field of materials given the their high fluorescence quantum yields.

CHAPTER 4 BODIPY SYNTHESIS, DEPROTECTION and MODIFICATION

4.1 BACKGROUND

Dipyrrins are historically noted to be difficult to manipulate and purify, presumably due to the azafulvenium and pyrrolic nitrogen moieties contained within.[3] Strategies have been developed to protect dipyrrins and thus concurrently facilitate their purification. Most of these involve converting the dipyrrin to its corresponding metal complex prior to functionalization.[3] While a wide variety of synthetic modifications can be carried out on the resulting dipyrrinato complexes, strongly acidic and reductive conditions must be avoided to prevent decomplexation.[3]

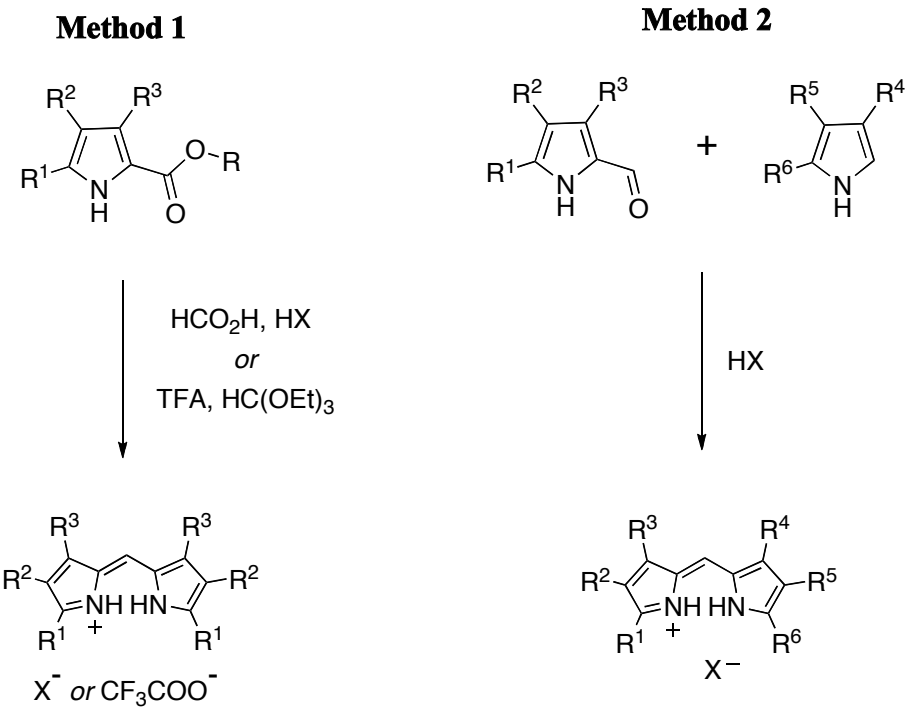
In contrast, when a dipyrrin is converted to its BF_2 complex, the resulting compounds have high thermal and photochemical stability, good solubility and are chemically robust. They also emit sharp fluorescence peaks with high quantum yields. *F*-BODIPYs are routinely synthesized in high yields by trapping the parent dipyrrin as its BF_2 complex. Ideally, dipyrrins could be protected as stable *F*-BODIPY compounds, chemically modified, purified, and then deprotected to give functionalized dipyrrins. To our knowledge, a general methodology for the removal of the boron center from a *F*-BODIPY to generate the parent dipyrrin has not been investigated. This chapter will focus on the development of a methodology to remove the boron center from *F*-BODIPYs, the development of a methodology to alkylate the *meso*-position of *F*-BODIPYs and initial attempts to synthesize a new class of halogenated BODIPYs (*X*-BODIPYs).

4.2 THE CHEMISTRY OF BODIPYS

4.2.1 Synthesis of Dipyrrins, Dipyrrinato Complexes and *F*-BODIPYs

Methods for the synthesis of dipyrrins have been reviewed in detail.[3] *meso*-Unsubstituted dipyrrins are commonly generated through the acid-catalyzed condensation of pyrroles as shown in Figure 20.

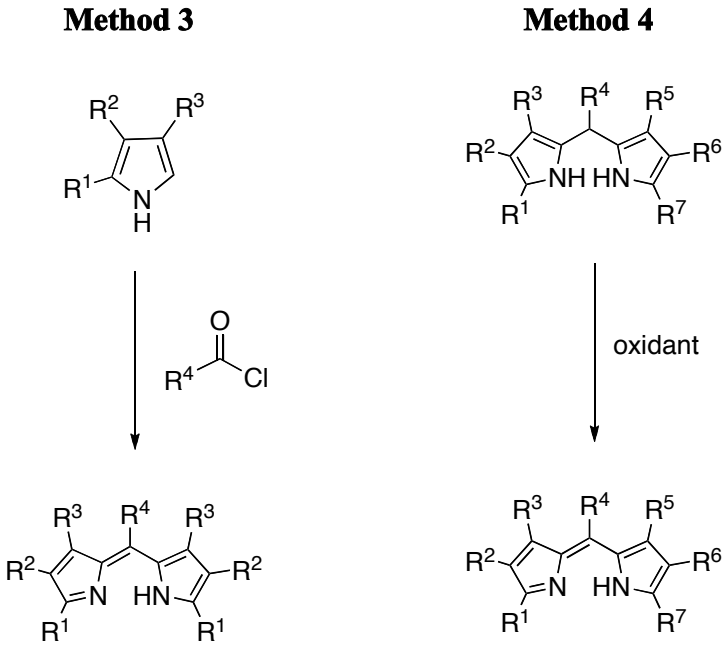
Figure 20. Synthesis of *meso*-unsubstituted dipyrrins



In Method 1, an α-unsubstituted pyrrole, usually generated *in situ* from a pyrrole with an α-carboxylic ester, is treated with formic acid and hydrobromic acid or TFA and triethylorthoformate to generate symmetrical *meso*-unsubstituted dipyrrins. In Method 2, a pyrrole with an α-formyl group is combined with an α-unsubstituted pyrrole in the presence of a strong acid, usually hydrobromic acid, to generate unsymmetrical *meso*-unsubstituted dipyrrins.

To produce *meso*-substituted dipyrrins, one can condense two equivalents of an α-unsubstituted pyrrole with an acid chloride (Method 3) or oxidize a dipyrromethane to the corresponding dipyrrin (Method 4) as outlined in Figure 21.

Figure 21. Synthesis of *meso*-substituted dipyrrins



Method 3 is limited to the synthesis of symmetrical dipyrrins while Method 4 is currently limited to the synthesis of dipyrrins with *meso*-H or *meso*-aryl substituents. Dipyrrins with *meso*-alkyl substituents can be synthesized from alkyl acid chlorides. These compounds are generally isolated as their corresponding BF_2 complexes, most likely due to the fact that *meso*-alkyl dipyrrins are unstable: they posses an allylic acidic proton and can therefore undergo a base-promoted isomerization to give the corresponding dipyrrinylethenes.[111] Yields for the the synthesis of *meso*-alkyl *F*-BODIPYs are either unreported[115] or below 20%.[112-114] The synthesis of *meso*-alkyl substituted *F*-BODIPYs is an area that requires further exploration.

A wide variety of isolable dipyrrinato metal complexes have been synthesized, varying both in complexation geometry and metal ion.[3] They are most commonly synthesized from purified dipyrrins. Similarily, *F*-BODIPYs are routinely synthesized in high yields from crude or purified dipyrrins. According to a recently reported procedure, symmetrical *F*-BODIPYs can also be generated from α-formyl pyrroles in one pot, without isolation of the parent dipyrrin.[116] Methods for the synthesis of dipyrrinato complexes[3] and *F*-BODIPY complexes of dipyrrins[4, 5] have both been reviewed in detail.

4.2.2 Modification of the Dipyrrin Core

There are relatively few examples of the direct modification of dipyrrins. Most of these transformations involve the interconversion of functional groups installed prior to dipyrrin synthesis and are carried out exclusively on dipyrrinato and *F*-BODIPY complexes.[3] The remaining few examples involve the direct modification of the dipyrrin core.

Substituents can be appended directly to the dipyrrin core of an *F*-BODIPY in the 2- and 6-positions by way of electrophilic substitution. This type of reactivity has been exploited to synthesize *F*-BODIPYs that are sulfonated,[117] chlorinated,[118] brominated[119, 120] and iodinated[121] in the 2- and 6-positions. A recent report indicates that substituents can also be directly appended to the dipyrrin core of an *F*-BODIPY in the 3- and 5-positions by way of oxidative nucleophilic hydrogen substitution; however, the reaction is currently limited to carbon and nitrogen centered nucleophiles.[122]

Methyl substituents at the 3- and 5-positions of *F*-BODIPYs can be deprotonated under mild conditions and undergo a Knoevenagel condensation with a variety of aldehydes, oxidized to their corresponding ketones and aldehydes using DDQ, or

oxidized to their corresponding acetates using lead tetraaceate.[123, 124] If good leaving groups are incorporated at the 3- and 5-positions of the *F*-BODIPY, carbon, oxygen, nitrogen and sulfur based nucleophiles can be introduced at these positions by direct nucleophilic subtitution.[125-127]

4.2.3 *meso*-Modification of Dipyrrinato Complexes

There are many examples in the literature of the modification of functional groups appended to *meso*-aryl groups of *F*-BODIPYs and dipyrrinato complexes. These examples include hydrogenation of nitro substituents,[86] hydrolysis of esters,[86] esterification of carboxylic acids,[86] copper-mediated azide-alkyne coupling[128] and, most commonly, conversion of aryl halides *via* palladium catalyzed aryl-aryl coupling to species with new carbon-carbon bonds.[3] These examples emphasize that molecules containing the dipyrrin core can undergo multiple chemical manipulations while protected as *F*-BODIPYs or as dipyrrinato complexes.

Examples of direct nucleophilic or electrophilic substitution at the *meso*-position of dipyrrins, dipyrrinato complexes or *F*-BODIPYs are rarely reported in the literature. *meso*-Cyano dipyrrins can be directly generated from *meso*-unsubstituted dipyrrins through cyanide anion attack at the *meso*-position, followed by protonation, to give the corresponding dipyrromethane, which can then be oxidized back to the dipyrrin.[124] There are several examples in the literature of the reactions of various bile pigments[129, 130] and a prodigiosin analogue[37]with sulfur-based nucleophiles to give *meso*-substituted derivatives. Bile pigments are also reported to undergo electrophilic substitution to give the corresponding bromo and nitro *meso*-substituted derivatives using elemental bromine, nitronium tetrafluoroborate and nitric acid.[131, 132] Direct *meso*-modification of *F*-

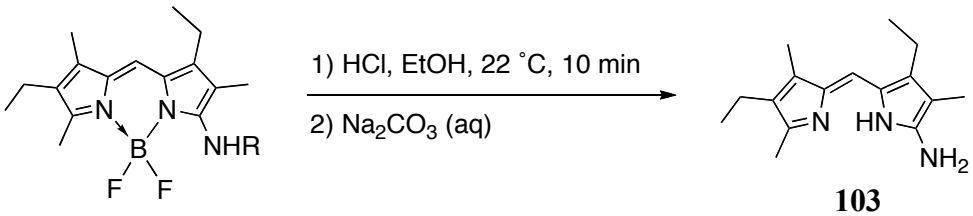
BODIPYs is limited to *F*-BODIPYs that possess a *meso*-thioalkyl substituent. The *meso*-thioalkyl group of the *F*-BODIPY can be displaced by nitrogen-based nucleophiles to generate other *meso*-substituted *F*-BODIPYs.[133, 134] This approach has been limited to symmetrical BODIPYs as the *meso*-thioalkyl BODIPY is generated by the reaction of thiophosgene with two equivalents of a substituted pyrrole to give the corresponding dipyrrolthione, which is then alkylated to give the thioalkyl dipyrrin and trapped as its BF_2 complex.[134] The *meso*-thioalkyl group of the *F*-BODIPY can also be coupled in the Liebeskind−Srögl cross-coupling reaction with aryl and alkenyl boronic acids to generate *meso*-aryl and *meso*-alkenyl substituted *F*-BODIPYs.[135]

4.2.4 Modification of the Boron Centre of *F*-BODIPYs

Use of substituents other than fluorine at the boron center of the BODIPY core is currently under wide investigation with the goal of identifying BODIPYs with exotic spectroscopic properties. A variety of *B*-aryl, *B*-alkyl (*C*-BODIPY) and *B*-alkynyl (*E*-BODIPY) derivatives have been synthesized utilizing organolithium or Grignard reagents.[136-142] *B*-Dialkyl *C*-BODIPYs have additionally been synthesized directly from their corresponding dipyrrins using bromodimethylborane, dibutylboron triflate and 9-BBN triflate.[107] In addition, *B*-dialkoxy and *B*-diaryloxy derivatives (*O*-BODIPYs) have been synthesized *via* fluorine displacement with either alkoxides or alcohols in the presence of Lewis acids.[143-145] In these procedures, alkyl, cyclic and aryl alcohols can displace the fluorine atoms of *F*-BODIPY complexes to give *O*-BODIPYs.

There is one example in the literature where the BF_2 unit is removed from an *F*-BODIPY to generate the corresponding dipyrrin[146] as shown in Scheme 33.

Scheme 33. Removal of the BF_2 unit from an *F*-BODIPY

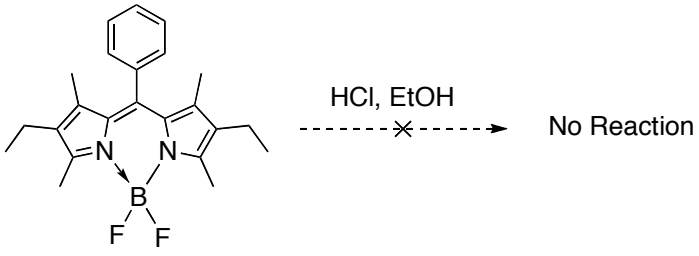


101 R = H
102 R = Ac

103

In this example, an *F*-BODIPY with an amine or acylated amine in the 3-position was subjected to treatment with hydrochloric acid in ethanol to generate the corresponding dipyrrin.[146] The authors were primarily interested in the synthesis of new *F*-BODIPY analogues and did not attempt to explore the general applicability of this method for BF_2 removal or investigate the mechanism of the reaction. Attempts to apply this methodology to *F*-BODIPY **104**, as shown in Scheme 34, failed and *F*-BODIPY **104** was quantitatively recovered in spite of increases to both reaction temperature and time. Presumably, the amino groups of **101** and **102** have a participating role in the deprotection, making this a method of limited utility.

Scheme 34. Attempted deprotection of *F*-BODIPY **104**



104

Several synthetic approaches to the deprotection of *F*-BODIPYs to regenerate the parent dipyrrin are envisioned: (i) protonation of the dipyrrinato nitrogen atoms followed by release of the BF_2 moiety, (ii) nucleophilic attack at the boron center and cleavage of the boron-nitrogen bonds to give the dipyrrinato anion which could be subsequently

protonated, or (iii) nucleophilic attack at the *meso*-position and cleavage of the N-B bonds, with subsequent protonation and elimination of the nucleophile to return the dipyrrin.

4.3 Results and Discussion

4.3.1 Development of *F*-BODIPY Deprotection Methodology

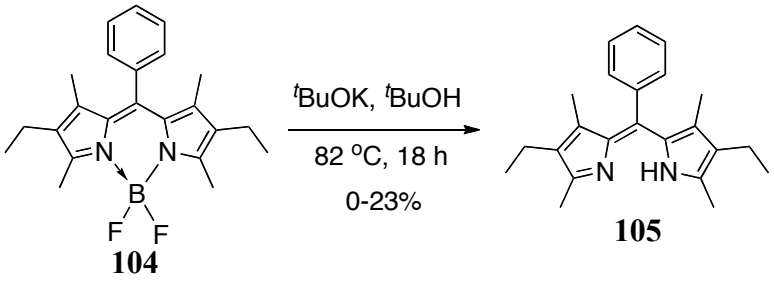
As protonation of the dipyrrinato ligand using ethanolic hydrochloric acid proved unsuccessful for removal of the BF_2 group of *F*-BODIPY **104**, focus was shifted to a strategy involving nucleophillic attack at the boron centre for boron removal. This approach necessitated the use of a reagent that would potentially preferentially bond to boron, displacing the dipyrromethene. Alkoxides, nitrogen bases and carbenes were proposed as possible reagents to effect this transformation as they would form strong bonds with boron. As boron-oxygen bonds are the only boron-element bond stronger than the boron-fluorine bond,[147] we began by investigating the use of oxygen-based reagents to deprotect *F*-BODIPYs. It was envisioned that a borophilic, oxygen-based, sterically hindered nucleophile would attack at the boron centre, break the dative boron-nitrogen bond and prevent its reformation due to steric effects. This would then lead to further attack at the boron centre and eventual release of the dipyrrinato anion. *F*-BODIPYs are known to undergo nucleophilic displacement of the fluoride atoms from boron in the presence of alkoxides in alcoholic solvents at high temperatures,[143] or in the presence of Lewis acid catalysts in alcoholic solvents.[145] For this reason, *tert*-butoxide, a moderate to poor nucleophile with high steric bulk, was selected.

It was thought that if the *tert*-butoxide could attack at the boron centre, the boron-nitrogen formally dative bond would break and have difficulty reforming through

displacement of the *tert*-butoxide due to the steric bulk of the *tert*-butoxide group and the superior strength of the boron-oxygen bond compared to that of the boron-nitrogen bond. These factors made *tert*-butoxide a good choice as a starting point for the investigation of *F*-BODIPY deprotection. In order to test possible deprotection methods, *F*-BODIPY **104** with a *meso*-aryl substituent was chosen because the deprotected product would be a *meso*-aryl dipyrrin: *meso*-aryl dipyrrins are generally more stable than *meso*-unsubstituted dipyrrins and would be easier to isolate and purify following BF_2 deprotection.

In the first deprotection trial, *F*-BODIPY **104**[148] was treated with 6 equivalents of potassium butoxide in *tert*-butanol at 82 ˚C as shown in Scheme 35. After 18 h the reaction mixture was no longer fluorescent and upon aqueous work-up the desired dipyrrin (**105**) was isolated in 23% yield along with a variety of unidentified decomposition products.

Scheme 35. *F*-BODIPY deprotection with potassium *tert*-butoxide

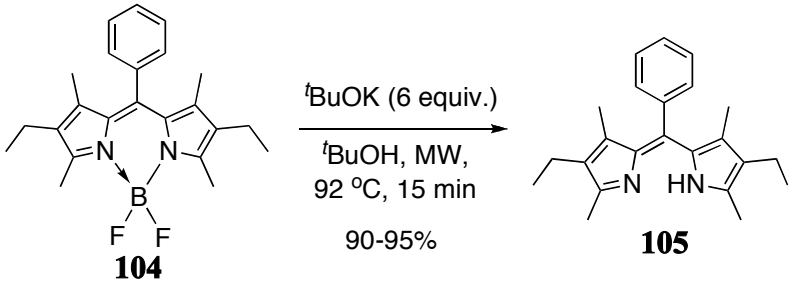


104 **105**

This extremely encouraging preliminary result indicated that the boron centre could be removed from the *F*-BODIPY and prompted further investigations. Disappointingly, the reaction was not reproducible and attempts to optimize the reaction condition, by varying the temperature and equivalents of potassium *tert*-butoxide used, all led to decomposition of the starting materials without the generation of the deprotected product (**105**). When

the reaction was carried out under microwave irradiation, the deprotected product, dipyrrin **105**, could be generated in reproducibly high yield. This procedure involved heating a sealed mixture of *F*-BODIPY **104** and 6 equivalents of potassium *tert*-butoxide in *tert*-butanol to 92 °C under 600 W microwave irradiation for 15 minutes (Scheme 36), followed by an aqueous work-up with a saturated solution of sodium bicarbonate to give the deprotected product (**105**). The crude material isolated from this reaction was of sufficient purity to carry forward in a synthetic sequence and any boron-containing byproducts were easily removed by work-up by treatment with a saturated solution of sodium bicarbonate.

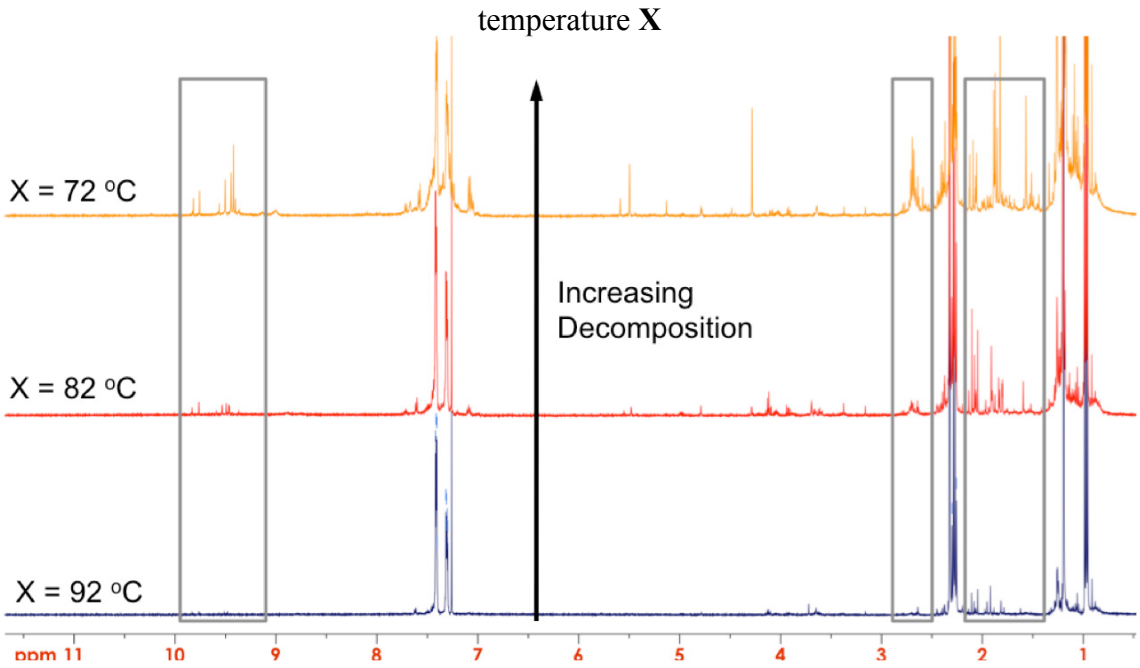
Scheme 36. Microwave-promoted deprotection of *F*-BODIPY **104**



104 **105**

Attempts to optimize this reaction focused on adjustments to the temperature of the reaction, the time of the reaction and and number of equivalents of potassium *tert*-butoxide utilized. The purity of the crude material was found to be dependent on the reaction temperature. Heating the reaction mixture to 92, 82 and 72 ˚C under 600 W of microwave irradiation resulted in the complete consumption of the *F*-BODIPY starting material (**104**), but, as the temperature was decreased, the degree of decomposition increased. This effect could be best observed by comparing proton NMR spectra of the crude product from reactions conducted at varying temperatures as shown in Figure 22.

Figure 22. Crude ^{1}H NMR spectra of dipyrrin **105** isolated from reactions conducted at



This increase in decomposition is clearly seen in the regions between 9.0 and 10.0 ppm, 1.5 to 2.0 ppm and 2.5 to 3.0 ppm. When the reaction was conducted at 92 ˚C, these regions of the crude proton NMR were essentially free of signals, but as the temperature of reaction was decreased there became a visible increase in the number of signals in these regions. This trend of increasing of decomposition with decreasing in temperature is unusual. In spite of the decomposition at lower temperatures, the product could be isolated in pure form from these reaction mixtures using column chromatography over basic alumina. It was essential to use basic alumina as the dipyrrin adheres strongly to both silica and neutral alumina. The additional products produced at lower temperatures were difficult to isolate because they were produced in such small quantities and could not be characterized.

In order to investigate the role of potassium *tert*-butoxide in the reaction, attempts were made*tert*-butoxide to use other reagents in the deprotection reaction. The results of these investigations are outlined in Table 9.

Table 9. Optimization of the microwave-promoted deprotection of *F*-BODIPY **104**

Reagent	**Solvent**	**Temperature** /^{o}C	**Time** /min	**Yield** /%
^{t}BuOK (6 eq)	^{t}BuOH	92	15	92
^{t}BuOK (3 eq)	^{t}BuOH	92	15	0[a]
NaH (6 eq)	DMF	92	15	0[b]
NaH (6 eq)	DMF	165	15	0[b]
LiHMDS (6 eq)	DMF	165	15	0[b]
KI (6 eq)	DMF	120	120	0[a]

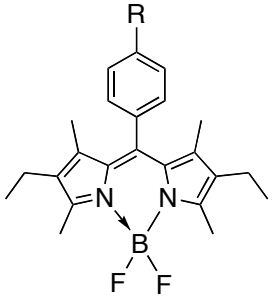
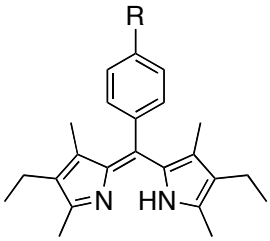
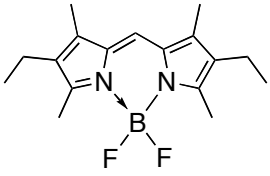
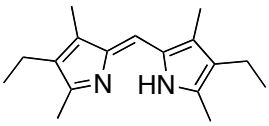
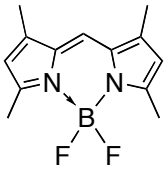
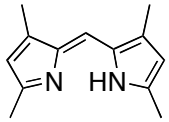
[a]starting material recovered; [b]decomposition

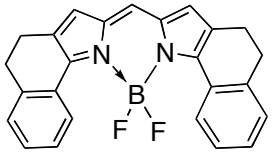
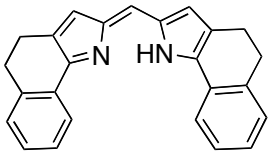
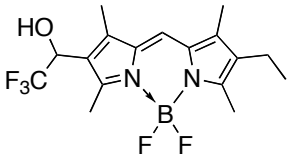
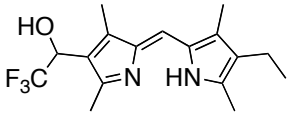
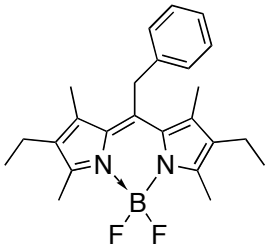
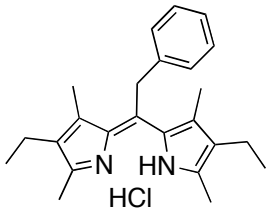
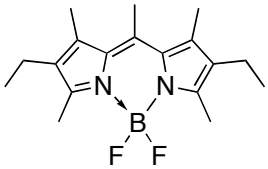
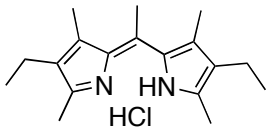
The use of three equivalents of *tert*-butoxide, rather than six equivalents, resulted in the isolation of only starting material. Lithium hexamethyldisilazane and sodium hydride were used in place of potassium *tert*-butoxide, as non-oxygen based non-nucleophilic bases; however, in both cases, NMR spectroscopic analysis indicated the formation of only trace amounts of the deprotected product **105**, alongside many decomposition products. Replacement of the potassium *tert*-butoxide in *tert*-butanol with sodium isopropoxide in *iso*-propanol gave the *O*-BODIPY with two *B*-isopropoxide groups in 47% yield, along with trace amounts of the desired deprotected product. Attempts to separate the *B*-isopropoxide derivative from the trace amounts of deprotected product using column chromatography over basic alumina were unsuccessful. These results indicate that a sterically bulky alkoxide is necessary to accomplish the deprotection.

Potassium iodide was also used in place of potassium *tert*-butoxide in the reaction. This was done to test the hypothesis that deprotection could occur through a nucleophilic attack at the *meso*-position and subsequent loss of the BF_2 group. Iodide is a good nucleophile and could potentially operate through attack at the *meso*-position. After an increased reaction time of 2 hours, only starting material was present in the reaction mixture indicating that nucleophilic attack at the *meso*-position is not a viable deprotection route to pursue.

The optimized method was then tested for its general applicability to *F*-BODIPY deprotection. To investigate the scope of the reaction, a series of *F*-BODIPYs (**106**, **108**, **110**, **112**, **114**, **116**) were synthesized from their corresponding dipyrrin HBr or HCl salts, using 9 equivalents of boron trifluoride diethyl etherate and 6 equivalents of triethylamine according to a common procedure found in the literature.[4] To successfully deprotect *meso*-unsubstituted *F*-BODIPYs, a reaction time of 40 minutes was required and this extended reaction time was adopted when investigating the scope of the reaction. A series of *F*-BODIPYs were successfully deprotected using the new methodology as shown in Table 10.

Table 10. Microwave-assisted deprotection of *F*-BODIPY derivatives in the presence of 6 equivalents of potassium *tert*-butoxide in *tert*-butanol at 92 ˚C for 40 minutes

Entry	**Starting Material**	**Product**	**Isolated Yield** /%
1	 **104** R = H **106** R = CF_3	 **105** R = H **107** R = CF_3	**105** 91 **107** 90
2	 **108**	 **109**	86
3	 **110**	 **111**	92[a]

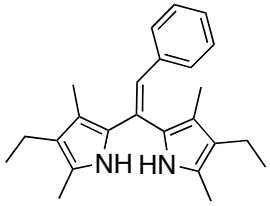
Entry	Starting Material	Product	Isolated Yield /%
4	 **112**	 **113**	51
5	 **114**	 **115**	93
6	 **116**	 **117**	88
7	 **118**	 **119**	85

[a]Compound isolated as its zinc complex as the dipyrrin is a sternutator

The symmetrical *meso*-aryl *F*-BODIPYs, **104** and **106,** and the *meso*-unsubstituted *F*-BODIPY **108,** were deprotected in high yields (Table 10, entries 1 and 2), along with unsymmetrical *meso*-unsubstituted *F*-BODIPY **114** (Table 10, entry 5). The β- and *meso*-unsubstituted *F*-BODIPYs **110** and **112** were also deprotected to give dipyrrins **111** and **113** (Table 10, entries 3 and 4). The low yield of dipyrrin **113** can possibly be attributed to the sterically bulky substituents in the α-positions of the dipyrrin, which may shield the boron centre from approach of the *tert*-butoxide anion. No starting material was recovered from the reaction mixture. The *meso*-benzyl **116** and *meso*-methyl **118** *F*-BODIPYs were deprotected in high yield to generate the corresponding

unstable *meso*-substituted dipyrrins (Table 10, entries 6 and 7).[111] These compounds were isolated as their HCl salts to prevent tautomerization to the vinylic dipyrroles, which are known to be unstable in air.[111] This was accomplished by adding a dilute hydrochloric acid wash as the final step in the extraction procedure. Removal of trace amounts of *tert*-butanol from the HCl salt **117** resulted in conversion to the vinylic dipyrrole **120** (Figure 23), which was, unsurprisingly, unstable in solution.

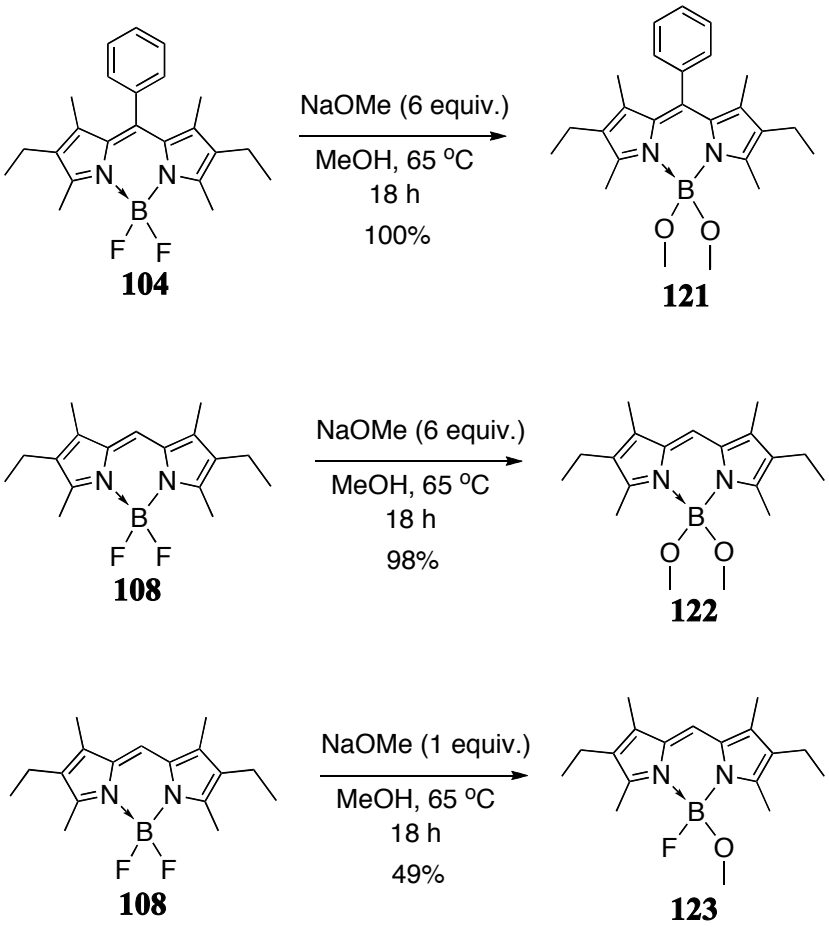
Figure 23. Vinylic dipyrrole byproduct



120

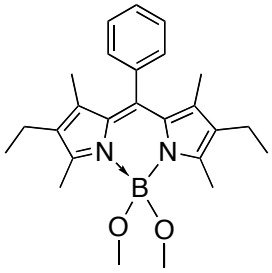
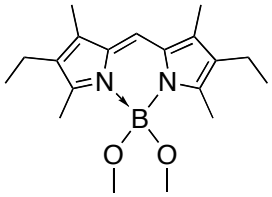
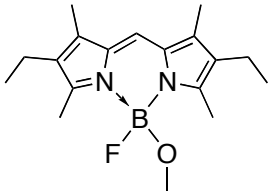
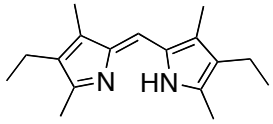
As the reaction had been so successful with *F*-BODIPYs, a series of BODIPYs with oxygen and carbon based substituents on the boron center were investigated to explore the scope of the deprotection reaction. The *O*-BODIPYs were synthesized from their corresponding *F*-BODIPYs through nucleophilic displacement of the fluoride atoms from boron in the presence of alkoxides.[143] The synthesis of the *O*-BODIPYs is shown in Scheme 37.

Scheme 37. *O*-BODIPY synthesis



Once the *O*-BODIPYs were in hand, they were subjected to the optimized deprotection conditions, as shown in Table 11.

Table 11. *O*-BODIPY deprotection

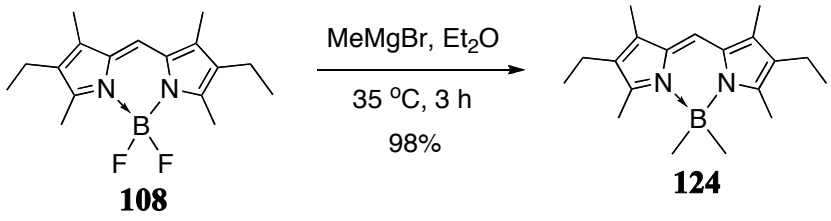
Entry	Starting Material	Product	Isolated Yield /%
1	 **121**	-	0[a]
2	 **122**	-	0[a]
3	 **123**	 **109**	75

[a] Starting material recovered quantitatively

The *O*-BODIPYs **121** and **122**, with two *B*-alkoxy substituents, could not be deprotected under the optimized conditions, and starting material was quantitatively recovered even after an extended reaction time. Interestingly, *O*-BODIPY **123**, with one *B*-alkoxy substituent, was deprotected successfully to obtain dipyrrin **109** in an isolated yield of 75%. This result again infers the importance of a steric component to the success of the deprotection.

A *C*-BODIPY was synthesized using an alkyl Grignard reagent according to literature procedures as outlined in Scheme 38.

Scheme 38. Synthesis of *C*-BODIPY **124**

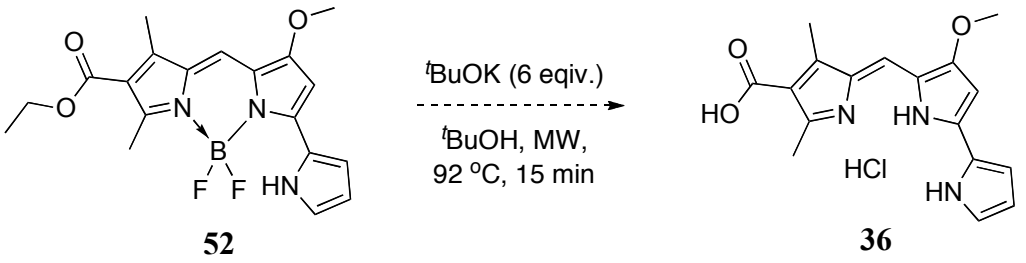


Unsurprisingly, *C*-BODIPY **124** with two *B*-methyl groups could not be deprotected using this methodology, which further serves to highlight the importance of a steric component to the success of the deprotection.

This methodology represents the first general method for the removal of the boron centre from a *F*-BODIPY to generate the corresponding dipyrrin. This methodology has been successfully applied to a series of *meso*-unsubstituted, *meso*-substituted, symmetrical and unsymmetrical *F*-BODIPYs to generate the corresponding dipyrrins in high yields. The methodology is currently limited to *F*-BODIPYs with at least one fluorine substituent on the boron centre.

Application of the methodology to the deprotection of prodigiosene *F*-BODIPYs has also been attempted. The *F*-BODIPY of prodigiosene **1** (**52**) has been subjected to the standard deprotection conditions, as shown in Scheme 39. The starting material (**52**) was completely consumed during the course of the reaction and a mass spectrum (ESI^+) of the crude reaction mixture after work-up indicated that prodigiosene carboxylate **36** had formed. This result indicates that the *F*-BODIPY deprotection was successful but that the ethyl ester was hydrolyzed under the basic reaction conditions. Due to the inherent instability of prodigiosene carboxylate **36**, it was not isolated.

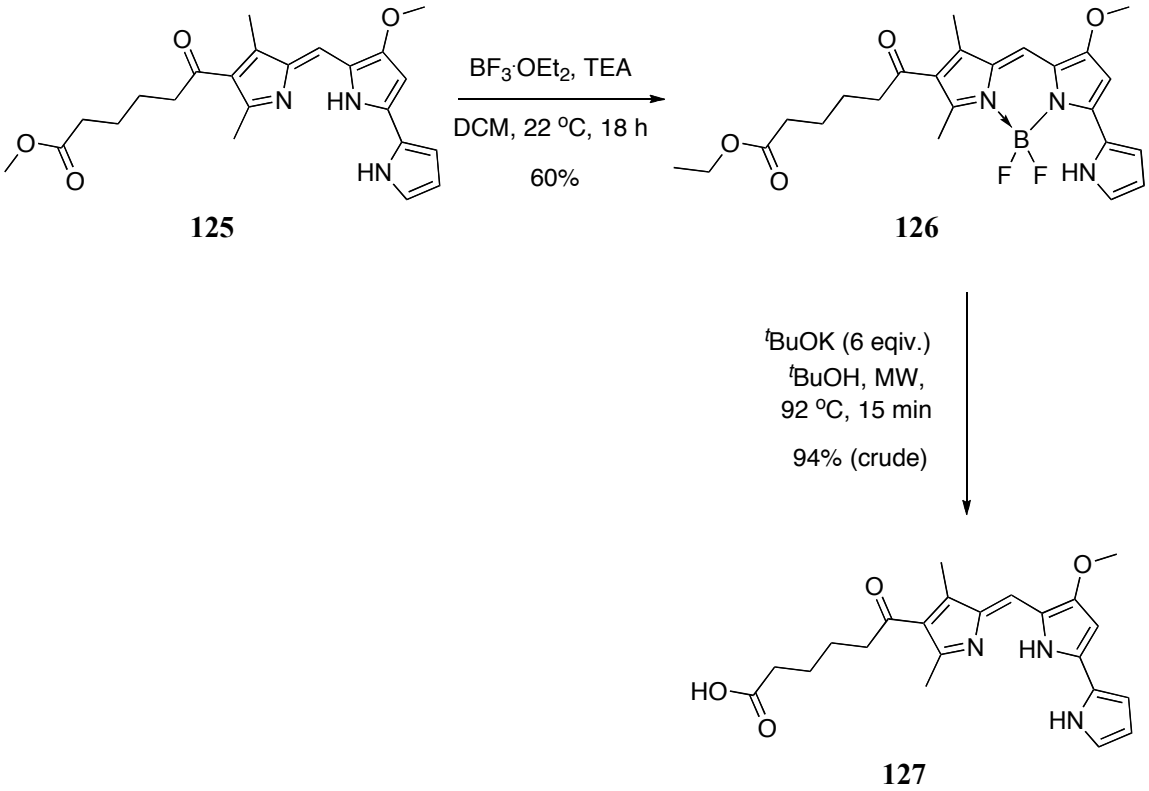
Scheme 39. Attempted deprotection of *F*-BODIPY **52**



52 **36**

To further explore the applicability of this methodology to *F*-BODIPY prodigiosene deprotection, a prodigiosene without an ester directly attached to the C-ring (**125**)[29] was selected for further deprotection trials. The corresponding *F*-BODIPY (**126**) was synthesized in moderate yield and the derivative was successfully deprotected under the general deprotection conditions, as highlighted in Scheme 40.

Scheme 40. Synthesis and deprotection of prodigiosene *F*-BODIPY **126**



125 **126** **127**

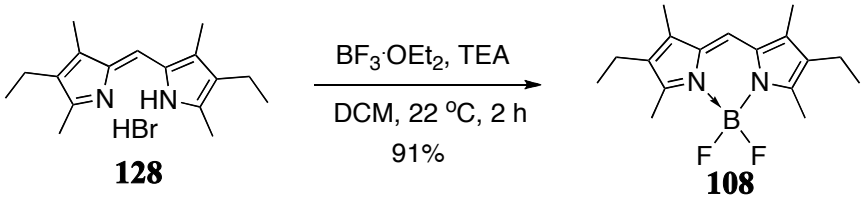
The basic reaction conditions used for the deprotection also hydrolyzed the pendant ester

of the prodigiosene and the resulting prodigiosene carboxylate (**127**) had limited solubility, impeding characterization. Further optimization of the synthesis of *F*-BODIPY **126**, which currently suffers from low yields, and investigations into a method to quantitatively esterify the resulting prodigiosene carboxylate **127** in high yields, for characterization purposes, will be necessary before this deprotection methodology can have general utility in prodigiosene synthesis.

4.3.2 *meso*-Modification of *F*-BODIPYs and Improvements to the Synthesis of the Fully Unsubstituted *F*-BODIPY

Many procedures exist in the literature for the functionalization of *F*-BODIPYs; however, most require a *F*-BODIPY with a modifiable functional group and focus on functionalization of the substituents appended to the BODIPY core. In order to design a methodology for the *meso*-modification of BODIPY compounds, a symmetrical, easily synthesized *F*-BODIPY **108**[116, 149] was chosen as a test compound. This compound was chosen as it can be synthesized on a 5 g scale in near-quantitative yields, according to the procedure shown in Scheme 41.

Scheme 41. Synthesis of *F*-BODIPY test compound



With **108** in hand, electrophilic substitution at the *meso*-position was investigated. Reports of electrophilic bromination of bile pigments (containing multiple dipyrrin units)[123, 131] and porphyrins are common in the literature.[150] Attempted bromination of *F*-BODIPY **108** with elemental bromine, elemental bromine and iron(III) chloride, and

NBS at several temperatures all resulted in the formation of complex mixtures of five or more products, which could not be separated using column chromatography over silica or alumina. The large number of products indicates that the alkyl substituents of the dipyrrin are likely being brominated in competing reactions. The exploitation of electrophilic iodination, using bis(trifluoroacetoxy)iodobenzene and iodine, conditions optimized for porphyrins,[151] was not successful and only the starting material was recovered. Attempts to react **108** with benzoyl chloride were similarily unsuccessful.

The possibility of using *F*-BODIPY **108** in a Heck coupling reaction with bromobenzene was also investigated. It should be noted that *meso*-aryl substituted BODIPYs with pendant halogen atoms on the *meso*-aryl groups are commonly elaborated using palladium-catalyzed carbon-carbon bond forming reactions in the literature.[3] In the current case, the reactions were carried out in DMF, using 1.2 equivalents of bromobenzene, 10 mole percent palladium catalyst (tris(dibenzylideneacetone)-dipalladium(0) or palladium(II) acetate) and 20 mole percent phosphine ligand (tri-2-furylphosphine, tri-*t*-butyl phosphonium tetrafluoroborate, triphenylphosphine, tri-*o*-tolylphosphine, 1,3-bis(diphenylphosphino)propane, tricyclohexylphosphine, or 1,1-bis(diphenylphosphino)ferrocene). None of the ligand-catalyst combinations resulted in production of the *meso*-substituted *F*-BODIPY after heating to 90 ^{o}C for 19 hours. A series of test reactions proved that our catalyst systems were successful in mediating the Heck coupling between bromobenzene and methyl acrylate and that *F*-BODIPY **108** did not poison the palladium catalyst.

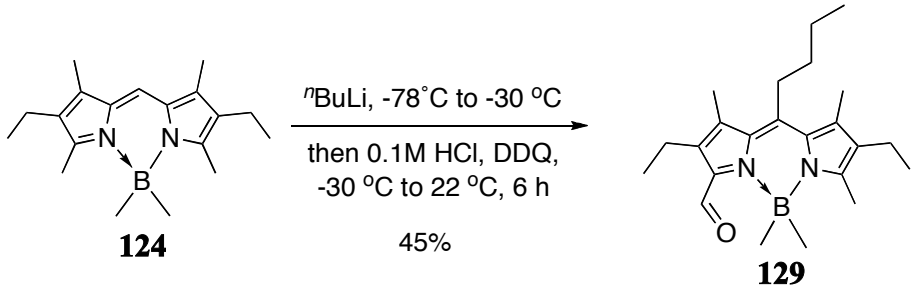
Porphyrins and their metal complexes are susceptible to nucleophilic substitution at the *meso*-position and the resulting intermediate may then be oxidized in one pot to

generate *meso*-substituted porphyrins.[152, 153] Aryl and alkyl lithium reagents are the commonly used nucleophiles in these reactions, which could potentially pose a problem in the case of *F*-BODIPYs. Aryl, alkyl and alkynyl lithium complexes have been used to generate *C*-BODIPYs (BODIPYs in which the boron-fluorine bonds have been replaced with boron-carbon bonds), starting from *meso*-alkyl, *meso*-aryl and *meso*-H *F*-BODIPY compounds;[141] however, it should be noted that the yields of the corresponding *C*-BODIPYs are all under 45% and that the yield in the single example of a *meso*-H C-BODIPY synthesized from a *meso*-H *F*-BODIPY is only 20%. In another case, the reaction of a *meso*-H *F*-BODIPY with 2 equivalents of a perfluorinated aryl lithium reagent (prepared from reacting the perfluorinated bromobenzene with *n*-butyllithium) resulted in the isolation of a small amount of a *meso*-butyl substituted *F*-BODIPY compound.[154] The authors proposed that this was the result of the second equivalent of aryl lithium reagent deprotonating the *meso*-position and reacting with residual *n*-butyl bromide, present in the reaction mixture as a byproduct from the generation of the perfluorinated aryl lithium reagent with *n*-butyllithium.[154]

In order to investigate the scope of the nucleophilic substitution of BODIPY compounds, a test compound that could not undergo nucleophilic attack at the boron centre was selected in hopes of preventing the formation of multiple products. *B*-Dimethyl *C*-BODIPY **124** was chosen as a suitable test compound as the methyl groups would block nucleophlic attack at the boron centre and it could also be synthesized in high yields (Scheme 38). When an ethereal solution of **124** was subjected to *n*-butyllithium at - 78 ˚C, followed by DDQ oxidation after warming to room temperature,

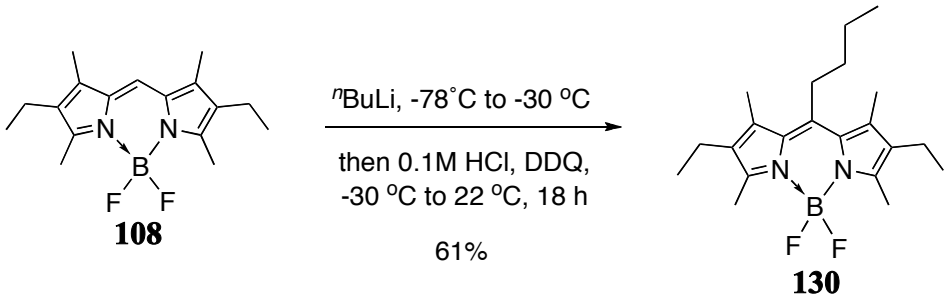
the *meso*-butyl *C*-BODIPY with a single methyl group oxidized to the corresponding aldehyde (**129**) was isolated in 45% yield as shown in Scheme 42.

Scheme 42. *meso*-Alkylation of *C*-BODIPY **124**



The oxidation of the α-methyl group using DDQ is a known reaction for dipyrrinones[155] and one *F*-BODIPY.[156] Dipyrrins are also known to undergo a similar reaction under Mn(II) oxidation.[157] Despite the undesired oxidation, this unoptimized reaction was encouraging and the same alkylation protocol was attempted on *F*-BODIPY **108** to determine if the alkylation was selective for the *meso*-position over the boron center. Under similar conditions, *meso*-butylated product **130** was isolated in 61% yield as shown in Scheme 43.

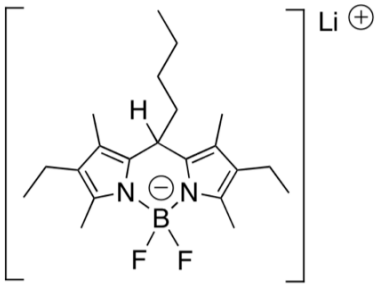
Scheme 43. *meso*-Alkylation of *F*-BODIPY **108**



This result was exciting as it represents a new method for the synthesis of alkyl substituted *F*-BODIPYs and dipyrrins in better yields that the existing published methods.[112-115] The color changes observed during the course of the reaction also serve to give some indication of the mechanism. The solution of *F*-BODIPY **108** in

dichloromethane was bright orange and fluorescent, but once the *n*-butyllithium was added the solution went light yellow and clear. The loss of color indicated the disruption of the dipyrrin chromophore. This is likely caused by the nucleophilic attack of the butyl anion at the *meso*-position to give a charged dipyrromethane intermediate as shown in Figure 24.

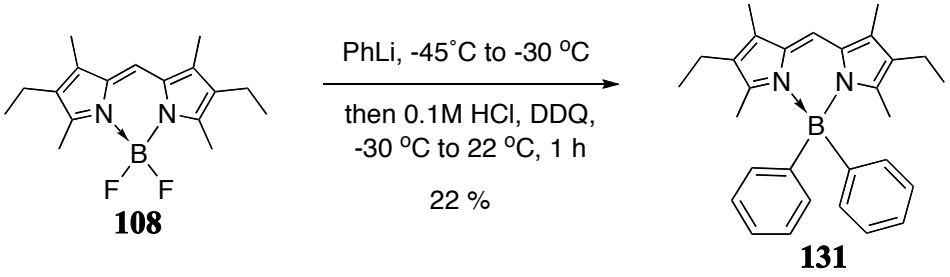
Figure 24. Postulated alkylation intermediate



This proposed intermediate is structurally and electronically related to the intermediate proposed for nucleophilic *meso*-substitution of porphyrrins.[153]

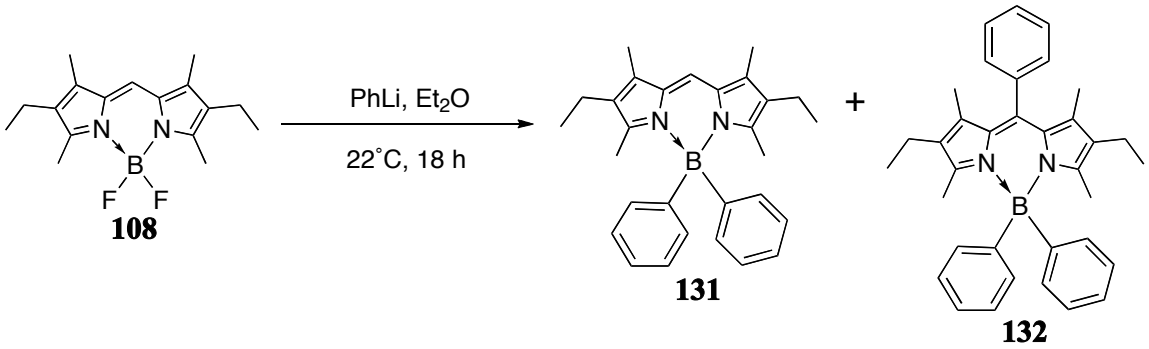
The reaction of *F*-BODIPY **108** under similar conditions using phenyl lithium did not result in the isolation of any *meso*-phenyl product, but rather the isolation of *C*-BODIPY **131**, with no *meso*-substituted product, as shown in Scheme 44.

Scheme 44. Arylation of *F*-BODIPY **108** at -45 °C



When the same reaction was conducted at room temperature, in the absence of DDQ, a mixture of *C*-BODIPY **131** and *C*-BODIPY **133**, with the desired *meso*-phenyl substituent, were generated as shown in Scheme 45.

Scheme 45. Arylation of *F*-BODIPY **108** at 22 °C



Although the mixture of *C*-BODIPY **131** and *C*-BODIPY **132** could not be separated using column chromatography, integrations of signals in the proton NMR spectrum revealed that the two compounds were present in a 1.0 to 0.2 ratio respectively. The lack of *F*-BODIPY products isolated from the reaction mixture when the reaction was carried out at both low and room temperature indicates that nucleophilic attack at the boron centre occurs preferentially to nucleophilic attack at the *meso*-position with the use of phenyllithium as a nucleophile. This reactivity has been exploited in the synthesis of *C*-BODIPYs from *meso*-substituted *F*-BODIPYs, but the products are generally isolated in yields below 50 %.[141] The preferential substitution at boron over the *meso*-positon also presents a problem in using this *F*-BODIPY *meso*-modification methodology for a new synthetic route to dipyrrins, as the microwave-promoted deprotection of BODIPYs is currently limited to the deprotection of *F*-BODIPYs. The absence of DDQ in the reaction conducted at room temperature also indicates that this transformation may be occurring through an alternate mechanism than the analogous *meso*-alkylation. The color changes observed in the analogous alkylation reaction could not be observed in the arylation reaction, as the phenyllithium reagent was orange in color and was used in excess.

In *F*-BODIPY **108**, two methyl groups effectively shield the meso-position and may hinder the substitution reaction. In order to investigate the steric requirements of the nucleophilic *meso*-alkylation and *meso*-arylation of *F*-BODIPYs, *F*-BODIPY **133** and *F*-BODIPY **135** were chosen as test compounds. *F*-BODIPY **135** has only one methyl group shielding the *meso*-position and **133** has no methyl groups shielding the *meso*-position.

While *F*-BODIPY **135** is easily synthesized using traditional methods,[158] the synthesis of *F*-BODIPY **133** has only recently been reported.[159-161] Of the three syntheses published, one involves a four-step procedure,[159] while the other two methods are one-pot reactions, which involve trapping an unstable dipyrrin intermediate,[4, 5] with reported yields under 10 percent.[160, 161] These low yields are attributed to the instability of the dipyrrin, which has been reported to decompose above -40 ˚C.[2] The authors were primarily interested in the fluorescence properties of *F*-BODIPY **133** and so yield was not their greatest concern, but in order for this one-pot method to be synthetically viable in our hands, the yields needed to be drastically increased. Unsubstituted dipyrromethane **134** was synthesized using Wang's method[162] or purchased from Frontier Scientfic. Using modifications of the procedure developed by Tram and coworkers,[161] a series of trials were conducted in order to optimize the oxidant used in the dipyrrin formation reaction and the base used in the *F*-BODIPY formation reaction. The synthesis and optimization of the *F*-BODIPY forming reaction is outlined in Scheme 46 and Table 12.

Scheme 46. Optimization of the synthesis of *F*-BODIPY **133**

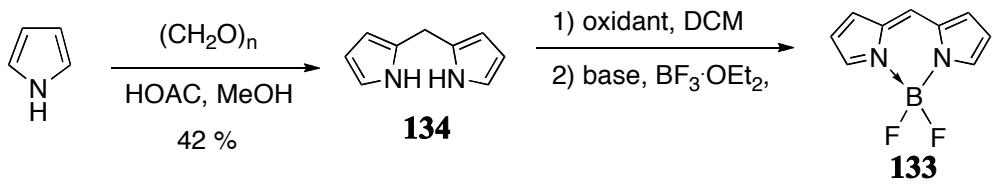


Table 12. Optimization of the synthesis of *F*-BODIPY **97**

Entry	Oxidant	Base	Oxidation Reaction		BODIPY Formation Reaction		Isolated Yield /%
			T / ˚C	Time / h	T / ˚C	Time / h	
1	DDQ	TEA	-78	1	-78 to -30	3	0[a]
2		DIPEA	-78	1	-78 to -30	3	0.76
3		DBU	-78	1	-78 to -30	3	0.61
4	*p*-chloranil	DIPEA	-78	1	-78 to -30	3	29
5			-78	1	-78 to -30	3	23
6			-78	1	-78 to -30	3	10
7			-40	3	-40 to 22	18	76
8			-40	3	-40 to 22	18	70
9			-40	3	-40 to 22	18	72

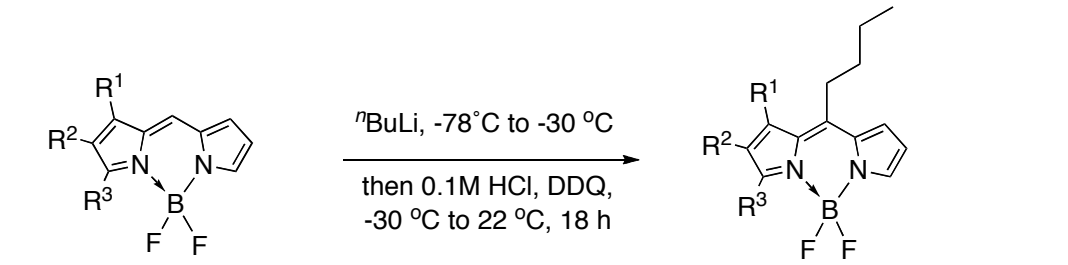
[a] No product observed in the reaction mixture

It was found that using sterically hindered amine bases and changing the oxidant from DDQ to the milder *p*-chloranil gave a substantial increase in the yield of *F*-BODIPY **133**; however, this procedure suffered from varying yields between 10 and 29 % (Table 12, entries 4 through 6). Increasing the oxidation time period to 3 h, the oxidation temperature to -40 ˚C and allowing the BODIPY formation reaction to warm to room temperature over a period of 18 h before work-up (Table 12, entries 7 through 9) substantially increased the yield of *F*-BODIPY **133** and improved the reproducibility of the reaction. The increased temperature and reaction time for the dipyrromethane oxidation appear to be key to the increase in yield of the product *F*-BODIPY. The yield of *F*-BODIPY **133** can now be increased to 72 % ± 4 % (95 % confidence, based on Table 12, entries 7 through 9). Notably, the solvent can be changed from DCM to toluene

and *F*-BODIPY **133** can be generated in 72 % ± 6 % (95 % confidence, 3 trials). This represents a significant improvement over the reported literature methods involving *in situ* oxidation of dipyrromethane **134** followed by *F*-BODIPY formation, which report yields under 10%.[160, 161] The majority of trials (Table 12, entries 1 through 8) were conducted on a 0.5 to 0.6 mmol scale of **134**, while one trial (Table 12, entry 9) was conducted on a 3.4 mmol scale, indicating the scalability of the procedure. With a reproducible and high yielding method to synthesize *F*-BODIPY **133** developed, further explorations into the *meso*-alkylation and *meso*-arylation of *F*-BODIPYs were possible.

The reaction of *F*-BODIPY **133** with *n*-butyllithium gave *F*-BODIPY **136** in 26% yield and the reaction of *F*-BODIPY **135** with *n*-butyllithium gave *F*-BODIPY **137** in 42% yield, as shown in Scheme 47.

Scheme 47. Alkylation of *F*-BODIPY **133** and *F*-BODIPY **135**



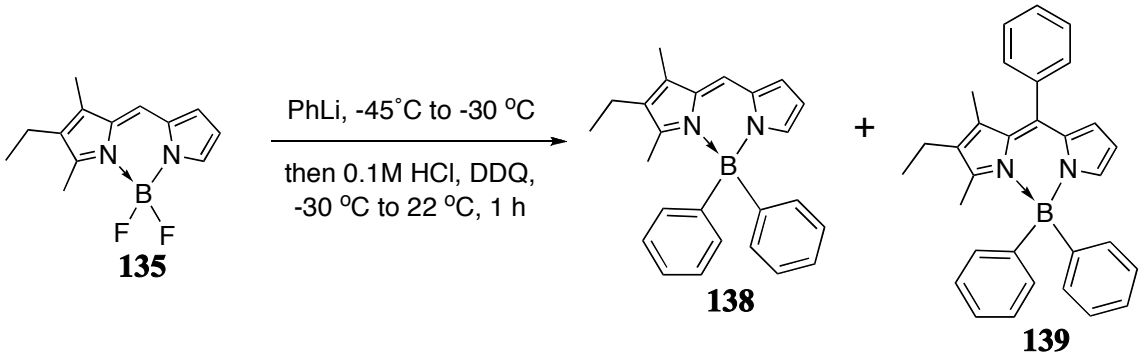
133 $R^1 = R^2 = R^3 = H$
135 $R^1 = R^3 = Me$, $R^2 = Et$

136 $R^1 = R^2 = R^3 = H$, 26%
137 $R^1 = R^3 = Me$, $R^2 = Et$, 42%

While the reactivity of these compounds is similar to that of *F*-BODIPY **108**, the yields of the *meso*-alkylated product were found to decrease as the substitution around the *F*-BODIPY core decreases. This decrease in yield may be due to the fact that the charged dipyrromethane-type boron-containing intermediate decreases in stability as the substitution about the dipyrrin core decreases, in a fashion similar to the analogous dipyrrin series.[3, 4]

Explorations into the reaction of aryllithium reagents with *meso*-unsubstituted BODIPYs **133** and **135**, as a method for the synthesis of aryl-substituted *F*-BODIPYs were also of interest. It was found that the reaction of *F*-BODIPY **135** with phenyllithium gave the *C*-BODIPY **138** and the *C*-BODIPY **139** in a 1.0 to 0.67 ratio as shown in Scheme 48. This ratio is slightly larger than that observed from the reaction of *F*-BODIPY **108** with phenyl lithium (1 to 0.20) and indicates that steric crowding of the *meso*-position is indeed a deterrent in BODIPY *meso*-substitution.

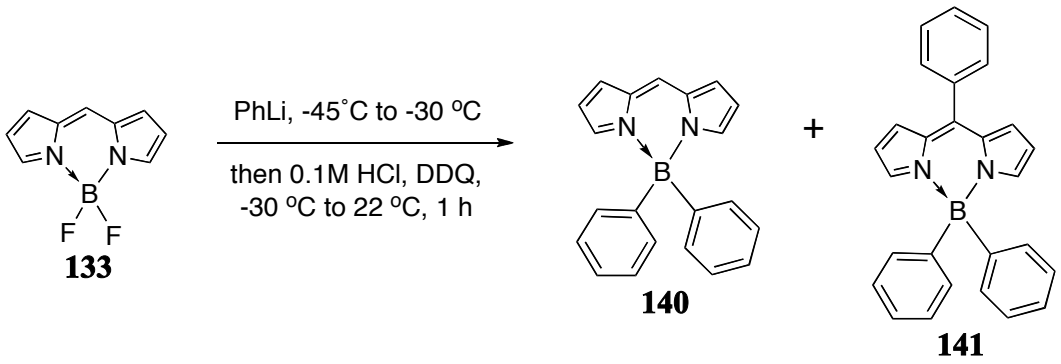
Scheme 48. Arylation of *F*-BODIPY **135**



135 **138** **139**

The reaction of *F*-BODIPY **133** with phenyl lithium resulted in two products that could not be separated using column chromatography, partially due to the small amount of material isolated, and, therefore, characterization using NMR spectroscopy and mass spectrometry was carried out on the mixture. A broad singlet in the boron NMR spectrum of the mixture indicated that the products formed were *C*-BODIPYs and the mass spectrum (ESI^+) indicated that the isolated material was a mixture of *C*-BODIPY **140** and *C*-BODIPY **141**, as shown in Scheme 49.

Scheme 49. Arylation of *F*-BODIPY **133**



133 **140** **141**

A comparison of the relative integrations of the pyrrolic hydrogen peaks in the proton NMR spectrum of the product indicated that *C*-BODIPY **140** and *C*-BODIPY **141** were present in a 1.0 to 0.61 ratio respectively. This ratio is similar to the ratio of *C*-BODIPY **138** to *C*-BODIPY **139** (1 to 0.67 ratio), formed under the same reaction conditions, and indicates that there is no increase in *meso*-arylated product going from *F*-BODIPY **135**, with a single methyl group blocking the *meso*-position, to *F*-BODIPY **133**, with no methyl groups blocking the *meso*-position.

4.3.3 Explorations into *X*-BODIPY Synthesis

Substitution of the fluorine atoms at the boron centre to give *B*-aryl, *B*-alkenyl, *B*-alkoxy and *B*-aryloxy derivatives has been accomplished successfully to generate a wide variety of *C*-BODIPY[137-140] and *O*-BODPY[143-145, 163] compounds. Recently, more exotic BODIPY derivatives have been synthesized as well,[164, 165] including a *H*-BODIPY;[166] however, to our knowledge, BODIPY analogues of the heavier halogens have not been reported. This is not unsurprising as boron-halogen bond strengths decrease in the order F >> Cl > Br > I and, consequently, B-Cl, B-Br and B-I bonds are much more labile than B-F bonds.[167] It was expected that changing the substitution at the *F*-BODIPY boron centre from fluorine to the heavier halogens will have a significant effect on the

fluorescence properties of the resulting *X*-BODIPYs. The presence of the heavier halogens will likely facilitate quenching by internal conversion, intersystem crossing, or charge transfer and enhance the non-radiative decay pathways by increasing spin-orbit coupling.

There is only one reported BODIPY analogue that contains a B-X bond. In this example, a *meso*-methyl substituted dipyrrinato sodium complex is treated with $PhBCl_2$ to produce the *C,Cl*-BODIPY analogue bearing one chloride and one phenyl substituent at the boron centre.[168] There is only one other example in the literature of the reaction of a dipyrrin or dipyrrinato complex with a boron trihalide other than a BF_3 adduct. In this example, a dipyrrin bearing a catechol-functionalized *meso*-position is treated with BCl_3. This reaction results in a series of three cyclic oligomers where the boron centre links one dipyrrin to another by binding to the dipyrrin moiety of one molecule and the catechol moiety of the second molecule.[169]

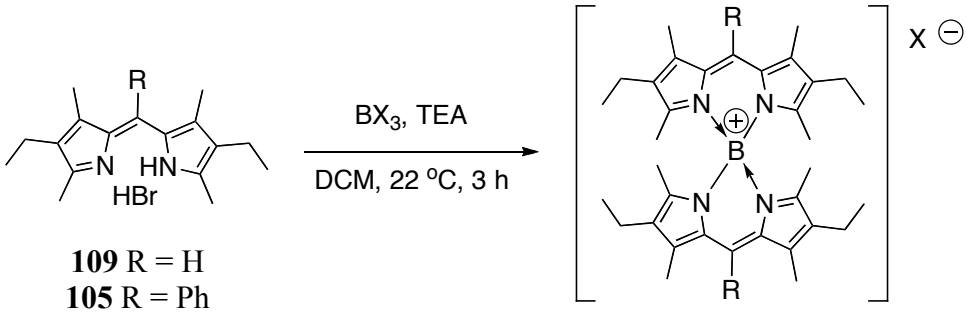
Although BODIPY analogues of the heavier halogens have not been isolated, BCl_2, BBr_2 and BI_2 β-diketiminato complexes, which are structurally related to dipyrrins, can be generated *via* treatment of a silyl protected β-diketiminate with BCl_3, BBr_3 and BI_3.[170, 171] All of these complexes were prepared and manipulated in a dry and oxygen-free atmosphere and were characterized using single-crystal X-ray diffraction studies.[170, 171] Similarly, structurally related diboryl BF_2, BCl_2 and BBr_2 complexes of porphyrins are known.[172]

F-BODIPYs are synthesized from dipyrrins or dipyrrin salts *via* reaction with excess triethylamine and BF_3•OEt_2. Following this method, the formation of the *X*-BODIPYs of the heavier halogens of the symmetrical dipyrrins **105** and **109** were

investigated by carrying out the reactions under the same conditions, but replacing BF_3•OEt_2 with BCl_3, BBr_3 or BI_3. Following the general proedure for the formation of *F*-BODIPY derivatives, triethylamine was added to a solution of the dipyrrin hydrobromide salt in dichloromethane followed by the addition of nine equivalents of the boron trihalide as a 1.0 M solution in dichloromethane (in the case of BCl_3 and BBr_3) or as a solid (in the case of BI_3). After 24 h, the solution was treated with methanol. The resulting deep red solution was subjected to an aqueous work-up and the resulting crude products were purified over neutral alumina. Due to the presence of water in the work-up procedure, isolation of the heavier halogen *X*-BODIPYs themselves would be unlikely, but some derivatives thereof (i.e. *O*-BODIPYs) would be possible to isolate.

As expected, the heavier halogen *X*-BODIPY analogues were not isolated from the reaction mixtures on aqueous work-up and neither were the expected *O*-BODIPYs. However, the previously unknown boronium salts **142** and **143** were isolated in various yields from the corresponding boron trihalides, as shown in Scheme 50.

Scheme 50. Synthesis of boronium cations using boron trihalides, BX_3 (X = Cl, Br, I)

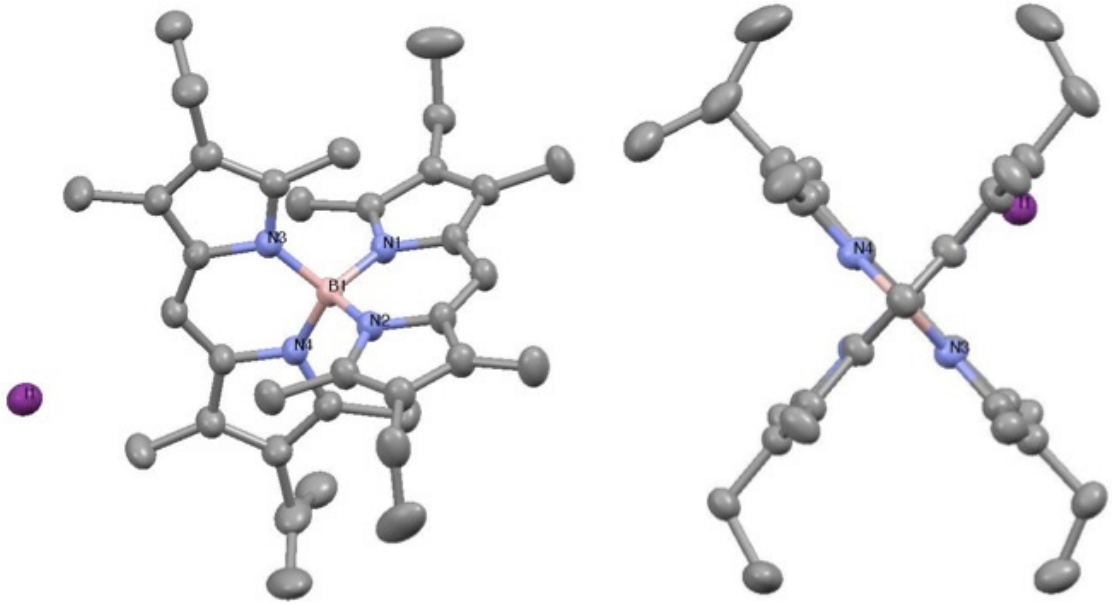


109 R = H
105 R = Ph

142Cl R = H, X = Cl; 8%
142Br R = H, X = Br; 12%
142I R = H, X = I; 56%
143I R = Ph, X = I; 60%

X-ray diffraction quality crystals of **142I**, containing an iodide counterion, were grown and analyzed. The X-ray crystal structure can be found in Figure 25.

Figure 25. Thermal ellipsoid diagram (50%) of **142I**.



Hydrogen atoms removed for clarity.

The environment around the boron is tetrahedral with N-B-N angles ranging from 106.67˚ to 112.07˚ and the B-N bond lengths range from 1.547 Å to 1.550 Å, which is within the sum of covalent radii for the B and N atoms (1.55 Å).[173] The two dipyrrinato units are nearly orthogonal to each other as the angles between the planes made up by the dipyrrinato units are 95˚ and 85˚ respectively. This orthoganality of dipyrrinato ligands is a common feature of homoleptic dipyrrinato complexes and is enforced by the steric crowding of the methyl groups in the 1- and 9-positions of the dipyrrinato ligand.[3] There is some observable disorder in an ethyl group attached to one of the dipyrrinato ligands.

Conversion of dipyrrins without substituents in the α-positions into their corresponding boronium cations was unsuccessful and led to intractable products. There

are many examples of boronium cations with nitrogen donors.[174-176] Recent advances in boronium cation chemistry include the use of boronium cations as catalysts in propylene oxide polymerization and Diels-Alder reactions.[174] In light of these possible applications, attempts were made to synthesize chiral variants of our boronium cations using bis(dipyrrin)s, attached by alkyl and ester linkages, to the corresponding boronium cations. In the case of the alkyl linked dipyrrins, no boronium salts were isolated and in the case of the ester linked dipyrrins, the ester linkages were cleaved to give the corresponding diol, but no boronium salts could be isolated from the reaction mixture.

4.4 Conclusions and Implications

A methodology has been developed to remove the boron centre from *F*-BODIPYs to regenerate the corresponding dipyrrins. This methodology has been successfully applied to a series of *meso*-unsubstituted, *meso*-substituted, symmetrical and unsymmetrical *F*-BODIPYs to generate the corresponding dipyrrins in high yields. The methodology is currently limited to BODIPYs with at least one fluorine substituent on the boron centre and it requires the use of a bulky alkoxide. Attempts to deprotect *C*-BODIPYs and *O*-BODIPYs with two alkoxy, alkyl, or aryl substituents of the boron centre were unsuccessful.

The development of this methodology is significant because it allows the BF_2 moiety of the *F*-BODIPY to be conceptualized as a protecting group for a dipyrrin and could potentially have widespread use in the synthesis and purification of dipyrrins. Ideally, a dipyrrin could be protected as its more stable and more easily purified *F*-BOIDPY and then chemically modified, purified and deprotected using the new microwave-promoted deprotection methodology to give the desired dipyrrin. The

methodology is also extremely efficient as the majority of the crude dipyrrin products obtained using the microwave-promoted deprotection method are clean according to proton NMR spectral data and do not require any purification after work-up. One drawback of the methodology is that the scale of the microwave-promoted reaction is limited by the size of the sealed microwave vessels available: our reactions were conducted using sealed, quartz lined vessels that held a maximum volume of 30 mL.

Investigations into the direct chemical modification of a *F*-BODIPY unfunctionalized at the *meso*-position were undertaken. *F*-BODIPYs have been successfully monoalkylated at the *meso*-position using *n*-butyllithium. This new method to generate these compounds in moderate yields represents an improvement to the current methods used to generate symmetrical, *meso*-alkylated *F*-BODIPYs. It also allows for the synthesis of the previously unaccessible unsymmetrical, *meso*-alkylated *F*-BODIPYs. This methodology could potentially be extended to other alkyl lithium reagents to generate a variety of different *meso*-substituted *F*-BODIPYs, potentially with additional sites for further functionalization.

Attempts to extend the *meso*-modification methodology to *meso*-arylation were not straightforward. Phenyllithium was found to preferentially attack at the boron centre of the *F*-BODIPY to generate *B*-diaryl *C*-BODIPYs before attacking at the *meso*-position to generate the desired *meso*-arylated derivative. Under modified conditions, the *meso*-unsubstituted and *meso*-aryl *B*-diaryl *C*-BODIPYs could be isolated with the ratio of the products corresponding to the steric accessibility of the *meso*-position.

Initial attempts to synthesize *X*-BODIPYs from BX_3 boron sources resulted in the isolation of previously unknown boronium cations. These boronium cations could be

isolated from all BX_3 boron sources with the highest yield (56%) isolated using BI_3 and the lowest yield (6%) isolated using BCl_3. Attempts were made to synthesize boronium cations from α-free dipyrrins, bis(dipyrrin)s and chiral linked bisdipyrrins; however, these attempts were largely unsuccessful. The synthesis of *X*-BODIPYs under air- and moisture-free conditions in a glove box is currently under investigation by Thompson group member Travis Lundrigan.

CHAPTER 5 EXPERIMENTAL SECTION

5.1 GENERAL EXPERIMENTAL

All ^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz), ^{11}B NMR (160 MHz), and ^{119}Sn NMR (186 MHz) spectra were recorded on a Bruker Avance AV-500 spectrometer.^{19}F NMR (235.2 MHz) were recorded on Bruker AC-250 spectrometer. Chemical shifts are expressed in parts per million (ppm) using the solvent signal [$CDCl_3$ (^{1}H 7.26 ppm, ^{13}C 71.23 ppm); DMSO-*d6* (^{1}H 2.50 ppm, ^{13}C 39.52 ppm); MeOD-*d4* (^{1}H 3.31ppm, ^{13}C 49.00 ppm); Acetone-*d6* (^{1}H 2.05 ppm, ^{13}C 29.84 ppm)] as an internal reference for ^{1}H and ^{13}C, BF_3•OEt_2 as an external reference for ^{11}B, $C_6H_5CF_3$ as an external reference for ^{19}F, and $Sn(CH_3)_4$ as an external reference for ^{119}Sn. Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. All coupling constants (*J*) are reported in Hertz (Hz). Mass spectra were obtained using ion trap (ESI) instruments operating in positive or negative mode, as indicated. Melting points are uncorrected.

Two microwave systems were used in the deprotection experiments. A CEM MARS-X microwave reaction system equipped with quartz lined QXP-1500Plus vessels, an RTP-300Plus Fiber Optic Temperature Control Sensor, and an ESP-1500Plus Internal Pressure Sensor was used in the transesterificaiton and deprotection experiments. A Biotage Initiator microwave reaction system with EXP vessels was also used in one deprotection experiment.

Column chromatography was performed using 230-400 mesh ultra pure silica; 150 mesh Brockmann III activated, neutral alumina oxide; 150 mesh Brockmann III activated, basic alumina oxide; or 230-400 mesh Reversed Phase C18 ultra pure silica as

indicated. Crude solvents for column chromatography and work-up, were distilled under 1 atm of air prior to use. All other chemicals were used as received. 1-(*tert*-Butoxycarbonyl)-1*H*-pyrrol-2-ylboronic acid (**13**) was purchased form Frontier Scientific and 4-ethyl-3-methyl-1*H*-pyrrol-2(5*H*)-one (**55**), hexanoyl chloride, octanoyl chloride, tetradecanoyl chloride, pentadecanoyl chloride, 3-ethyl-2,4-dimethylpyrrole and 6-oxovaleric acid, were purchased from Aldrich. Compound **112**[116] was a gift from Dr. Kevin Burgess and Liangxing Wu (Texas A & M University), compound **94**[88] was a gift from Dr. Md. Imam Uddin, and compound **125**[29] was a gift from Dr. Estelle Marchal. Compounds **10**,[57], **23**,[177] **27**[57] **28**,[57] **31**,[178] **37**,[179] **59**,[69] **81**,[91] **86**,[69] **87**,[100] **105**,[180] **107**,[180] **109HBr**,[149] **111HBr**,[181] **114**,[182] **117HCl**,[111] **119HCl**,[111] and **128**[183] were synthesized according to the reported procedures.

5.2 Absorbance and Fluorescence Measurements

The absorbance measurements were performed using a CARY 100 Bio UV/Visible spectrophotometer. The fluorescence measurements were performed using a Shimadzu RF-5301PC Spectrofluorimeter. A 10 mm quartz cuvette was used in all measurements. For the fluorescence experiments, the slit width was 3 nm for both excitation and emission. Relative quantum efficiencies of derivatives were obtained by comparing the areas under the emission spectra of the test with that of a solution of rhodamine 101 in ethanol ($\Phi_F = 0.96$) or rhodamine 6G in ethanol ($\Phi_F = 0.94$).[184] The excitation wavelength was 520 nm for rhodamine 6G and the compounds measured against it. The excitation wavelength was 546 nm for rhodamine 101 and the compounds measured against it. Quantum yields were determined using Equation 1.[185]

$$\phi_X = \phi_{st}\left(\frac{I_X}{I_{st}}\right)\left(\frac{A_{st}}{A_X}\right)\left(\frac{\eta_X^2}{\eta_{st}^2}\right)$$ …Equation 1

Where ϕ_{st} is the reported quantum yield of the standard, I is the area from the integrated emission spectra, A is the absorbance at the excitation wavelength and η is the refractive index of the solvent used. The X subscript denotes the unknown, and "st" denotes the standard.

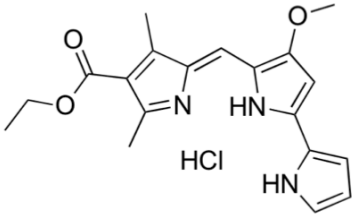
5.3 Biological Activities

Mean *in vitro* activities of pyrrolyldipyrrinato complexes **94**, **95**, **98** against the National Cancer Institute 60 human tumor cell line anticancer drug screen (NCI60) were measured at the National Cancer Institute (NCI) of the National Institute of Health (NIH). Details of the screening experiments can be found online[14] and details of the development and utility of the screen have been reviewed in detail.[186]

MIC values of pyrrolyldipyrrinato complex **83**, in DMSO solution, were determined by Dr. Srinivasulu Bandi in collaboration with Dr. David L. Jakeman and Dr. Susan E. Douglas.[110]

5.4 Experimental Procedures

5.4.1 Ethyl (*Z*)-2-((4-methoxy-1*H*,1'*H*-2,2'-bipyrrol-5-yl)methylene)-3,5-dimethyl-2*H*-pyrrole-4-carboxylate hydrochloride (**1**)[29]

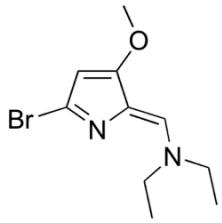


This compound was synthesized according to a published procedure.[29] Compound **22**[29] (571 mg, 1.35 mmol) was dissolved in dimethoxyethane (30 mL) and LiCl (172 mg, 4.06

mmol), 1-*N*-Boc-pyrrole-2-boronic acid (**13**) (569 mg, 2.70 mmol), and $Pd(PPh_3)_4$ (156 mg, 0.135 mmol) were added. The resulting solution was purged by bubbling with nitrogen for 10 min then a solution of Na_2CO_3 (2 M, 2.71 mL, 5.41 mmol) was added, and the reaction mixture was stirred at 85 °C for 18 h. The crude reaction mixture was poured onto a saturated aqueous solution of sodium bicarbonate (50 mL). Extraction with ethyl acetate (3 x 30 mL), followed by washing of the combined organic fractions with brine (30 mL), drying over anhydrous sodium sulfate and removal of the solvent under reduced pressure gave the crude product. The crude product was purified using flash chromatography on basic alumina with ethyl acetate:hexane (30:70) as an eluent, concentrated *in vacuo* and dissolved in HPLC grade acetone (3 mL). 1 M HCl in diethyl ether (2 mL) was added to the solution and a fine red precipitate formed which was isolated using suction filtration and rinsed with ether (3 x 2 mL) to give **1** as a bright pink solid (432 mg, 1.15 mmol, 85%). m.p. = 230-231 ˚C; δ_H (500 MHz, $CDCl_3$) 13.00 (1H, bs), 12.76 (1H, bs), 12.69 (1H, bs), 7.30 (1H, s), 7.13 (1H, s), 7.02-7.00 (1H, m), 6.40-6.39 (1H, m), 6.11 (1H, s), 4.32 (2H, q, *J*=7), 4.06 (3H, s), 2.82 (3H, s), 2.52 (3H, s), 1.38 (3H, t, *J*=7). δ_C (125 MHz, $CDCl_3$) 166.8, 164.6, 150.5, 150.1, 140.6, 128.5, 123.6, 122.6, 122.2, 119.1, 116.0, 113.0, 112.5, 93.5, 60.0, 59.2, 14.9, 14.6, 11.9. The recorded ^{13}C NMR data matches (within 0.2 ppm) the reported data for the compound.[29] UV/Vis (DCM, 22 ˚C) λ_{max} = 528 nm (ε = 87200 mol L^{-1} cm^{-1}); *m/z* ESI^+ found 340.1665 $[M+H]^+$ calculated for $C_{19}H_{22}N_3O_3$ 340.1656. A crystal suitable for X-ray crystallography was obtained from a slow evaporation of a solution of compound **1** in dichloromethane in the presence of few drops of methanol. Data for **1**: $C_{19}H_{22}N_3O_3Cl$, M = 375.85 g, deep-red, needle, 0.39 x 0.10 x 0.01 mm, primitive orthorhombic, Pbca (#61), a = 7.9121(3) Å, b =

19.2314(8) Å, c = 24.6951(10) Å, V = 3757.6(3) $Å^3$, Z = 4, T = 293(1) K, ρ = 1.329 g cm^{-3}, μ(MoKα) = 2.268 cm^{-1}, 35806 reflections (5492 unique, R_{int} = 0.224), R = 0.0457, Rw = 0.0426, GOF = 1.134.

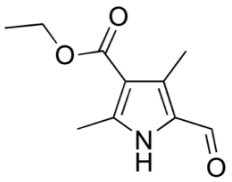
5.4.2 *N*-((5-Bromo-4-methoxy-2H-pyrrol-2-ylidene)methyl)-*N*-ethylethanamine (**14**)[38]



This compound was synthesized using a modified literature procedure.[38] A solution of phosphorous oxybromide (12.6 g, 44 mmol) in chloroform (15 mL) was added dropwise to a mixture of diethylformamide (5.8 mL, 53 mmol) in chloroform (5 mL) at 0 ˚C. The resulting suspension was stirred at 0˚C for 30 min and the solvent was then removed *in vacuo*. After pumping dry over 20 min, chloroform (20 mL) was added and the resulting suspension was cooled to 0 ˚C. A solution of **10**[57] (2 g, 17.7 mmol) in chloroform (10 mL) was added dropwise and the mixture was warmed to room temperature and then heated at 60 ˚C for 5 h. The mixture was poured onto ice (75 mL), and the pH of the aqueous solution was adjusted to pH 14 by treatment with 6 M NaOH. The aqueous layer was extracted with EtOAc (3 x 75 mL). The organic layers were combined, washed with 6 M NaOH (2 x 150 mL), dried over sodium sulfate and the solvent was then removed *in vacuo*. Purification over silica gel using ethyl acetate:hexane (30:70) gave **14** as a yellow oil which solidified on standing (2.02 g, 8.0 mmol, 45%). m.p. = 35-37 ˚C; δ_H (500 MHz, $CDCl_3$) 6.99 (1H, s), 5.59 (1H, s), 4.12 (2H, q, *J*=7), 3.76 (3H, s), 3.39 (2H, q, *J*=7), 1.27-1.31 (6H, m). The recorded ^{1}H NMR data matches (within 0.03 ppm) the reported data

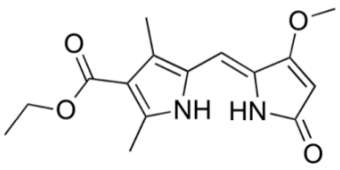
for the compound.[38] *m/z* ESI^+ found 259.0453, 261.0424 $[M+H]^+$ calculated for $C_{10}H_{16}{}^{79}BrN_2O$ 259.0441.

5.2.3 Ethyl 5-formyl-2,4-dimethyl-1H-pyrrole-3-carboxylate (**20**)[187, 188]



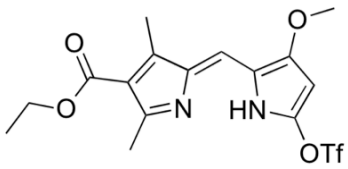
$POCl_3$ (4 mL) was added dropwise to a solution of dimethylformamide (4 mL) in anhydrous dichloromethane (4 mL) stirring at 0 ºC under nitrogen. The solution was stirred for 20 min at 0 ºC. This solution was added dropwise by syringe to a solution of **25** (770 mg, 4.6 mmol) in anhydrous dichloromethane (4 mL). The resulting solution was heated at reflux temperature for 2 h and then allowed to cool to room temperature. The cooled mixture was poured slowly onto a solution of sodium bicarbonate (8 g) in water (60 mL) and the solution was heated at reflux temperature for 12 h. The resulting beige precipitate was isolated *via* suction filtration and pumped dry overnight to give **20** as a beige solid (909 mg, 4.6 mmol, 99%). m.p. = 164-166 ˚C (lit. 165 ˚C);[188] δ_H (500 MHz, $CHCl_3$) 10.42 (1H, bs), 9.60 (1H, s), 4.30 (2H, q, *J*=7), 2.58 (3H, s), 2.55 (3H, s), 1.36 (3H, t, *J*=7). δ_C (125 MHz, $CHCl_3$) 177.5, 165.1, 143.9, 136.5, 128.4, 114.3, 59.8, 14.6, 14.4, 10.8. *m/z* ESI^+ found 218.0786 $[M+Na]^+$ calculated for $C_{10}H_{13}NNaO_3$ 218.0788. Previously reported ^1H and ^{13}C NMR data was recorded in DMSO-*d6*.[187]

5.4.4 Ethyl (Z)-5-((3-methoxy-5-oxo-1*H*-pyrrol-2(5*H*)-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrole-3-carboxylate (**21**)[29]



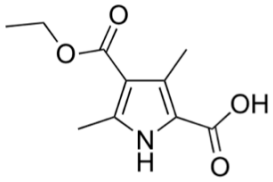
This compound was synthesized using a modified literature procedure.[29] A solution of **10**[57] (871 mg, 7.7 mmol) in tetrahydrofuran (40 mL) was purged with N_2 for 20 min. To this solution was added a purged solution of aqueous potassium hydroxide (4 M, 4.5 mL, 17.9 mmol). This solution was stirred at 60 °C for 1 h and then **27** (1.0 g, 4.5 mmol) was added and the solution stirred under N_2 for 2 days at 60 °C. Methanol:dichloromethane (9:1, 400 mL) and water (300 mL) were added to the residue. The layers were separated, the aqueous layer was washed with methanol:dichloromethane (9:1, 3 x 300 mL), the combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to give **21** as a bright yellow solid (1.04 g, 3.6 mmol, 70%). m.p. = 279-281 ˚C; δ_H (500 MHz, DMSO-d_6) 10.91 (1H, bs), 9.72 (1H, bs), 6.02 (1H, s), 5.26 (1H, s), 4.17 (2H, q, J=7), 3.85 (3H, s), 2.46 (3H, s), 2.22 (3H, s), 1.27 (3H, t, J=7). δ_C (125 MHz, DMSO-d_6) 170.7, 166.8, 164.7, 139.0, 125.2, 123.9, 122.0, 111.4, 94.4, 91.3, 58.7, 58.4, 14.3, 13.5, 10.8. This ^{13}C NMR data matches (within 0.6 ppm) the reported data for the compound.[29] *m/z* ESI^+ found 291.1330 $[M+H]^+$ calculated for $C_{15}H_{19}N_2O_4$ 291.1339.

5.4.5 Ethyl (*Z*)-2-((3-methoxy-5-(trifluoromethylsulfonyloxy)-1*H*-pyrrol-2-yl)methylene)-3,5-dimethyl-2*H*-pyrrole-4-carboxylate (**22**)[29]



This compound was synthesized using a literature procedure.[29] Tf_2O (1.2 mL, 6.7 mmol) was slowly added to a solution of **21** (1.3 g, 4.5 mmol) in dry dichloromethane (225 mL), under nitrogen at 0 ˚C. The reaction mixture was stirred for 2 h at 0 ˚C and then poured onto a saturated aqueous solution of sodium bicarbonate. The layers were separated, the aqueous layer was extracted with dichloromethane (3 x 60 mL) and the combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. Purification over silica gel using ethyl acetate:hexane (10:90) as an eluent resulted in **22** as a bright yellow solid (1.64 g, 3.9 mmol, 86%). δ_H (500 MHz, $CHCl_3$) 10.99 (1H, bs), 7.13 (1H, s), 5.43 (1H, s), 4.31 (2H, q, *J*=7), 3.90 (3H, s), 2.57 (3H, s), 2.43 (3H, s), 1.37 (3H, t, *J*=7). The ^{1}H NMR data matches (within 0.01 ppm) that of the reported compound.[29] Further characterization was avoided due to the general instability of the derivative.

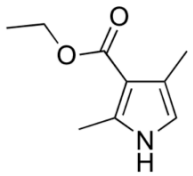
5.4.6 4-(Ethoxycarbonyl)-3,5-dimethyl-1*H*-pyrrole-2-carboxylic acid (**24**)[56]



Triethylamine (0.1 mL, 0.66 mmol) and palladium on activated carbon (10 % by wt., 1 g) and were added to a solution of **23** (10 g, 33 mmol) in tetrahydrofuran (100 mL). The reaction mixture was stirred for 16 h under 1 atm of hydrogen gas, diluted with methanol

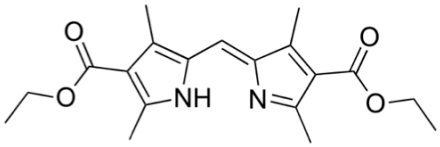
(50 mL) and filtered through a plug of Celite, rinsing with methanol (2 x 25 mL), to give **24** as a white crystalline solid (6.30, 30 mmol, 90 %). m.p. = 204-205 ˚C (lit. 203-204 ˚C);[56] δ_H (500 MHz, DMSO-*d6*) 12.37 (1H, bs), 11.73 (bs, 1H), 4.16 (2H, q, *J*=7), 2.45 (3H, s), 2.39 (3H, s), 1.26 (3H, t, *J*=7). δ_C (125 MHz, DMSO-*d6*) 164.7, 162.2, 138.8, 129.0, 118.2, 112.1, 58.6, 14.3, 13.4, 11.7. *m/z* ESI^+ found 234.0733 $[M]^+$ calculated for $C_{10}H_{13}NNaO_4$ 234.0737. The previously reported ^1H NMR data for this compound were recorded in pyridine-*d5*.[56]

5.4.7 Ethyl 2,4-dimethyl-1*H*-pyrrole-3-carboxylate (**25**)[92, 187]



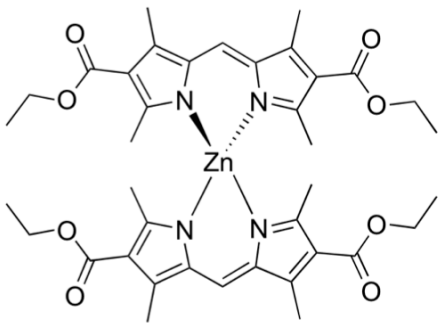
4-(Ethoxycarbonyl)-3,5-dimethyl-1*H*-pyrrole-2-carboxylic acid (**24**)[56] (1.0 g, 4.7 mmol) was placed in a round-bottom flask and the flask was then equipped with a condenser. The round-bottom flask was placed in a heating mantle preheated to 215 ºC until the solid melted and bubbling ceased (approximately 15 min). The flask was then removed from the heating mantle and the contents allowed to cool to room temperature. Purification over silica gel using ethyl acetate:hexane (2:1) as an eluent followed by the removal of solvent *in vacuo* gave **25** as a beige powder (909 mg, 4.6 mmol, 97%). m.p. = 69-70 ˚C (lit. 75-76 ˚C);[92] δ_H (500 MHz, $CDCl_3$) 8.19 (1H, bs), 6.35 (1H, q, *J*=1), 4.27 (2H, q, *J*=7), 2.48 (3H, s), 2.24 (3H, d, *J*=1), 1.35 (3H, t, *J*=7). δ_C (125 MHz, $CDCl_3$) 166.5, 136.1, 121.7, 114.3, 110.8, 59.2, 14.6, 14.2, 12.7. *m/z* ESI^+ found 190.0845 $[M+Na]^+$ calculated for $C_9H_{13}NNaO_2$ 190.0838. The previously reported ^1H and ^{13}C NMR data for this compound were recorded in DMSO-*d6*.[187]

5.4.8 Ethyl (Z)-5-((4-(ethoxycarbonyl)-3,5-dimethyl-2*H*-pyrrol-2-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrole-3-carboxylate (**29**)



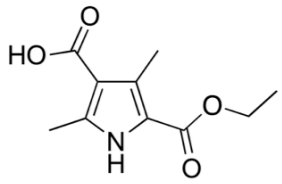
Tf_2O (0.9 mL, 5.3 mmol) was slowly added to a solution of ethyl-(*Z*)-5-((3-methoxy-5-oxo-1*H*-pyrrol-2(5*H*)-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrole-3-carboxylate (**21**) (1.03 g, 3.5 mmol) in wet dichloromethane (60 mL) at 0 ˚C under nitrogen. The reaction mixture was stirred for 2 h at 0 ˚C and then poured onto a saturated aqueous solution of sodium bicarbonate. The layers were separated, the aqueous layer was extracted dichloromethane (3 x 60 mL) and the combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. Purification over silica gel using ethyl acetate:hexane (0:100 to 15:85) as an eluent resulted in **29** as a bright orange powder (600 mg, 1.7 mmol, 49 %). m.p. = 133 ˚C dec.; δ_H (500 MHz, $CDCl_3$) 8.50 (s, 1H), 7.00 (s, 1H), 4.30 (q, 4H, *J*=*7*), 2.58 (s, 6H), 2.47 (s, 6H), 1.37 (t, 6H, *J*=*7*); δ_C (125 MHz, $CDCl_3$) 165.2, 156.9, 144.6, 137.6, 120.1, 119.5, 59.9, 17.5, 14.6, 12.0; UV/Vis (DCM, 22 ˚C) λ_{max} = 454 nm (ε = 16 300 mol L^{-1} cm^{-1}); *m/z* ESI^+ found 345.1776 $[M]^+$ calculated for $C_{19}H_{24}N_2O_4$ 345.1809.

5.4.9 Zn(**29**)$_2$ (**30**)



A solution of zinc acetate dihydrate (115 mg, 0.52 mmol) and sodium acetate (71 mg, 0.52 mmol) in methanol (5 mL) was added to a solution of **29** (75 mg, 0.22 mmol) in chloroform (5 mL). The reaction mixture was stirred 12 h at room temperature and the resulting dark yellow solution was diluted with dichloromethane (30 mL) and poured onto water (40 mL). The layers were separated and and the organic fraction was dried over sodium sulfate, filtered and concentrated *in vacuo*. Purification over silica gel using ethyl acetate:hexane (35:65) as an eluent gave **30** as a bright yellow crystalline powder (128 mg, 0.18 mmol, 81%). m.p. = 201-202 ˚C; δ_H (500 MHz, $CDCl_3$) 7.41 (1H, s), 4.27 (4H, q, *J*=7), 2.60 (6H, s), 2.21 (6H, s), 1.34 (6H, t, *J*=7); δ_C (125 MHz, $CDCl_3$) 165.1, 161.8, 148.3, 136.5, 125.4, 119.5, 59.6, 17.5, 14.4, 14.2; UV/Vis (DCM, 22 ˚C) λ_{max} = 487 nm (ε = 224 000 mol L^{-1} cm^{-1}); *m/z* ESI^+ found 773.2465 $[M+Na]^+$ calculated for $C_{38}H_{46}N_4NaO_8Zn$ 773.2516.

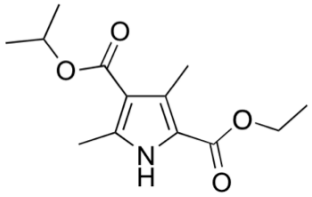
5.4.10 5-(Ethoxycarbonyl)-2,4-dimethyl-1*H*-pyrrole-3-carboxylic acid (**32**)[189]



Concentrated sulfuric acid (0.9 mL) was added dropwise to a solution of **31**[178] (100 mg, 0.42 mmol) in tetrahydrofuran (10 mL) at room temperature. The resulting solution was stirred for 1 h and then distilled water (5 mL) was slowly added to the reaction mixture. The resulting white precipitate was isolated by suction filtration to give **32** as a white solid (70 mg, 0.33 mol, 80%). m.p. = 227 ˚C dec. (lit. 123-124);[189] δ_H (500 MHz, DMSO-*d*6) 11.76 (1H, bs), 4.23 (2H, q), 2.45 (3H, s), 2.39 (3H, s), 1.28 (3H, t); δ_C (125 MHz,

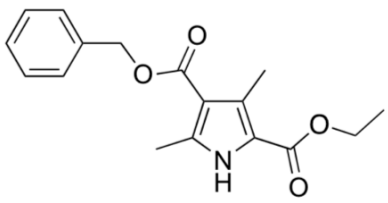
DMSO-*d*6) 166.3, 160.7, 139.4, 129.8, 117.4, 112.9, 59.4, 14.4, 13.5, 11.8; *m/z* ESI^+ found 234.0737 $[M+Na]^+$ calculated for $C_{10}H_{13}NNaO_4$ 234.0737. Full characterization data for this compound has not been reported previously.

5.4.11 2-Ethyl 4-isopropyl 3,5-dimethyl-1*H*-pyrrole-2,4-dicarboxylate (**33**)



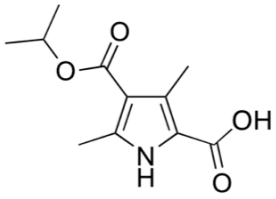
Trifluoroacetic anhydride (48 μL, 0.68 mmol) was added dropwise to a suspension of **32** (60 mg, 0.28 mmol) in dry toluene (5 mL) under nitrogen and the resulting solution was stirred for 30 min. Isopropyl alcohol (60 μL, 0.34 mmol) was added and the mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with dichloromethane (10 mL) and then washed with 1 M NaOH (2 x 20 mL). The organic layer was dried over sodium sulfate and the solvent was removed *in vacuo* to give **33** as a light yellow powder (63 mg, 0.25 mmol, 85%). m.p. = 124-125 ˚C; δ_H (250 MHz, $CDCl_3$) 8.92 (1H, bs), 5.19 (1H, p), *J*=*7*), 4.33 (2H, q, *J*=*7*), 2.56 (3H, s), 2.51 (3H, s), 1.33-1.40 (9H, m); δ_C (125 MHz, $CDCl_3$) 165.1, 161.7, 138.7, 131.0, 118.0, 114.2, 67.0, 60.4, 22.4, 14.64, 14.56, 12.1; *m/z* ESI^+ found 276.1198 $[M+Na]^+$ calculated for $C_{13}H_{19}NNaO_4$ 276.1206.

5.4.12 2-Ethyl-4-benzyl-3,5-dimethyl-1*H*-pyrrole-2,4-dicarboxylate (**34**)[189]



Trifluoroacetic anhydride (74 μL, 0.53 mmol) was added dropwise to a suspension of **32** (93 mg, 0.44 mmol) in dry toluene (5 mL) and stirred for 30 min. Benzyl alcohol (65 μL, 0.53 mmol) was added and the mixture was stirred at room temperature for 18 h. The reaction mixture was diluted with ethyl acetate (10 mL) and then washed with 1 M NaOH (2 x 20 mL). The organic layer was dried over sodium sulfate and the solvent was removed *in vacuo* to give **34** as a light yellow powder (111 mg, 0.37 mmol, 84%). m.p. = 144-146 ˚C (lit. 151-152);[189] δ_H (250 MHz, $CDCl_3$) 8.97 (s, 1H), 7.42-7.30 (m, 5H), 5.30 (s, 2H), 4.32 (q, 2H, *J*=*7*), 2.57 (s, 3H), 2.50 (s, 3H), 1.36 (t, 3H, *J*=*7*); δ_C (125MHz, $CDCl_3$) 165.3, 161.7, 139.1, 136.7, 131.1, 128.7, 128.2, 128.1, 118.2, 113.5, 65.6, 60.5, 14.7, 14.6, 12.2; *m/z* ESI^+ found 324.1192 $[M+Na]^+$ calculated for $C_{17}H_{19}NNaO_4$ 324.1206. Full characterization data for this compound has not been reported previously.

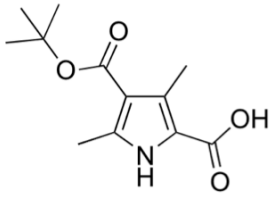
5.4.13 4-(*iso*Propoxycarbonyl)-3,5-dimethyl-1*H*-pyrrole-2-carboxylic acid (**35**)



6 M NaOH (160 μL, 0.94 mmol) was added to a solution of **33** (61 mg, 0.24 mmol) in ethanol (4 mL) and the reaction mixture was heated at 80 ºC for 48 h. The reaction mixture was diluted with dichloromethane (10 mL) and 1 M NaOH (10 mL) and the layers were separated. The aqueous layer was then extracted with dichloromethane (3 x 20 mL). The basic layer was acidified with 1 M HCl and then extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to give **35** as a light brown powder (38 mg, 0.17 mmol,

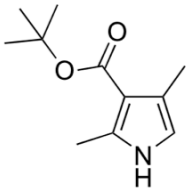
71%). m.p. = 184-185 ˚C; δ_H (500 MHz, CD_3OD) 5.12 (1H, p, *J*=*7*), 2.52 (3H, s), 2.44 (3H, s), 1.33 (6H, d, *J*=7) (O*H* and N*H* not observed); δ_C (125MHz, DMSO-*d6*) 164.3, 162.3, 138.8, 129.0, 118.1, 112.4, 65.9, 22.0, 13.5, 11.8; *m/z* ESI^+ found 248.0885 $[M+Na]^+$ calculated for $C_{11}H_{15}NNaO_4$ 248.0893.

5.4.14 4-(*tert*-Butoxycarbonyl)-3,5-dimethyl-1*H*-pyrrole-2-carboxylic acid (**38**)



Palladium on activated carbon (10 % by wt., 400 mg) was added to a solution of **37**[25, 179] (4.0 g, 12.1 mmol) in ethyl acetate (40 mL). The reaction mixture was stirred for 16 h under 1 atm of hydrogen gas, diluted with methanol (40 mL), and filtered through a pad of Celite, rinsing with methanol (2 x 15 mL), to give **38** as a white crystalline solid. This material was transformed directly into **39** without further purification or characterization.

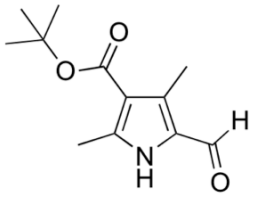
5.4.15 *tert*-Butyl 2,4-dimethyl-1H-pyrrole-3-carboxylate (**39**)



4-(*tert*-Butoxycarbonyl)-3,5-dimethyl-1*H*-pyrrole-2-carboxylic acid (**38**) (2.71 g, 11.4 mmol) was placed in a round-bottom flask and the flask was then equipped with a condenser. The round-bottom flask was placed in a heating mantle preheated to 215 ºC until the solid melted and bubbling ceased (approximately 15 min). The flask was then removed from the heating mantle and the contents allowed to cool to room temperature.

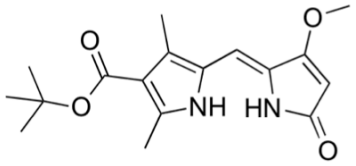
The resulting beige solid was dissolved in dichloromethane (50 mL) and washed with 2 M NaOH (3 x 50 mL). The organic fractions were combined, dried with sodium sulfate, and concentrated *in vacuo* to give **39** as a beige, crystalline solid (1.97 g, 10.1 mmol, 89%). δ_H (500 MHz, $CDCl_3$) 8.25 (1H, s), 6.32 (1H, s), 2.45 (3H, s), 2.21 (3H, s), 1.56 (9H, s); δ_C (125 MHz, $CDCl_3$) 166.0, 135.5, 121.4, 114.2, 112.2, 79.4, 28.7, 14.2, 12.9; *m/z* ESI^+ found 218.1151 $[M+Na]^+$ calculated for $C_{11}H_{17}NO_2Na$ 218.1157.

5.4.16 *tert*-Butyl 5-formyl-2,4-dimethyl-1H-pyrrole-3-carboxylate (**40**)



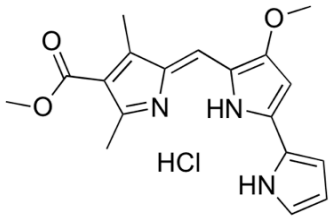
$POCl_3$ (9 mL) was added dropwise to a solution of dimethylformamide (9 mL) in anhydrous dichloromethane (9 mL) stirring at 0 ºC under N_2. The solution was stirred for 20 min at 0 ºC. This solution was added dropwise *via* syringe to a solution of **39** (1.76 g, 9 mmol) in anhydrous dichloromethane (9 mL). The resulting solution was heated at reflux temperature for 2 h and then allowed to cool to room temperature. The cooled mixture was poured slowly onto a solution of sodium bicarbonate (40 g) in water (500 mL) and the solution was heated at reflux temperature for 12 h. The resulting beige precipitate was isolated *via* filtration and pumped dry overnight in a vacuum oven to give **40** (1.11 g, 5 mmol, 56%). m.p. = 129-130 ˚C; δ_H (500 MHz, $CDCl_3$) 9.61 (1H, s), 9.21 (1H, s), 2.52 (6H, s), 1.57 (9H, s); δ_C (125 MHz, $CDCl_3$) 177.2, 164.2, 142.3, 135.2, 128.1, 115.5, 80.4, 28.5, 14.5, 10.7; *m/z* ESI^+ found 246.1101 $[M+Na]^+$ calculated for $C_{12}H_{17}NNaO_3$ 246.1106.

5.4.17 *tert*-Butyl (*Z*)-5-((3-methoxy-5-oxo-1*H*-pyrrol-2(5*H*)-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrole-3-carboxylate (**41**)



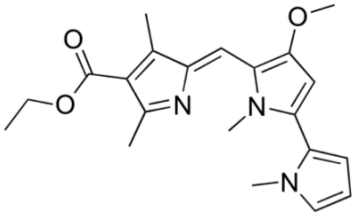
A solution of **10**[57] (760 mg, 6.8 mmol) in tetrahydrofuran (40 mL) was purged with N_2 for 20 min. To this solution was added a purged solution of aqueous potassium hydroxide (4 M, 3.9 mL, 15.8 mmol). This solution was stirred at 60 °C for 1 h and then **40** (1.0 g, 4.5 mmol) was added and the solution stirred under N_2 for 2 days at 60 °C. The crude reaction mixture was concentrated *in vacuo* and the resulting brown solid was crystallized from hot methanol, isolated *via* filtration, and dried in a vacuum oven to give **41** as a bright yellow solid (350 mg, 1.1 mmol, 24%). Concentration of the mother liquor followed by a second crystallization from methanol resulted in the isolation of an additional 170 mg of product to give 520 mg, 1.6 mmol, 36% overall. m.p. = 274-276 ˚C; δ_H (500 MHz, DMSO-d_6) 6.02 (1H, s), 5.24 (1H, s), 3.85 (3H, s), 2.43 (3H, s), 2.19 (3H, s), 1.49 (9H, s); δ_C (125 MHz, DMSO-d_6) 170.7, 166.8, 164.2, 139.0, 124.9, 124.0, 122.2, 112.7, 94.8, 91.2, 78.7, 58.3, 28.2, 13.8, 10.9; *m/z* ESI^+ found 341.1472 $[M+Na]^+$ calculated for $C_{17}H_{22}N_2NaO_4$ 341.1477.

5.4.18 Methyl (*Z*)-2-((4-methoxy-1*H*,1'*H*-2,2'-bipyrrol-5-yl)methylene)-3,5-dimethyl-2*H*-pyrrole-4-carboxylate hydrochloride (**44**)



Sodium methoxide (1 M solution in MeOH, 50 μL, 0.05 mmol) was added to a solution of **1** (12 mg, 0.03 mmol) in methanol (8 mL). The reaction mixture was heated to 125°C, in a microwave, over a period of 10 min and then held at 125°C for a further 10 min. The reaction mixture was cooled for 20 min and the resulting orange solution was poured onto a 1 M aqueous solution of HCl (10 mL) and extracted with dichloromethane (3 x 10 mL). The organic fractions were combined, dried with sodium sulfate, and concentrated *in vacuo* to give **44** as a red powder (10 mg, 0.26 mmol, 87%). m.p. = 257 ˚C dec.; δ_H (500 MHz, $CDCl_3$) 12.97 (1H, s), 12.75 (1H, s), 12.68 (1H, s), 7.30 (1H, s), 7.11 (1H, s), 7.00 (1H, s), 6.39-6.38 (1H, m), 6.10-6.09 (1H, m), 4.05 (3H, s), 3.85 (3H, s), 2.81 (3H, s), 2.51 (3H, s); δ_C (125 MHz, $CDCl_3$) 166.8, 165.1, 150.5, 150.3, 140.6, 128.7, 123.6, 122.7, 122.2, 119.1, 115.8, 113.0, 112.6, 93.5, 59.1, 51.2, 14.9, 12.0; UV/Vis (DCM, 22 ˚C) λ_{max} = 525 nm (ε = 86 100 mol L^{-1} cm^{-1}); *m/z* ESI^+ found 326.1499 $[M+H]^+$ calculated for $C_{18}H_{20}N_3O_3$ 326.1505.

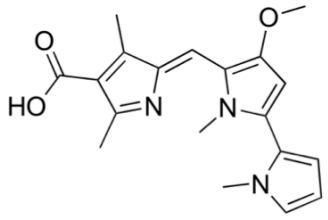
5.4.19 Ethyl (*Z*)-2-((4-methoxy-1,1'-dimethyl-1*H*,1'*H*-2,2'-bipyrrol-5-yl)methylene)-3,5-dimethyl-2*H*-pyrrole-4-carboxylate (**47**)



Sodium hydride (60% in mineral oil, 89 mg, 2.24 mmol) was added to a solution of **1** (105 mg, 0.28 mmol) in DMF (10 mL). The reaction mixture was stirred at 0 ˚C for 30 min and then iodomethane (0.17 mL, 2.80 mmol) was added slowly and the reaction mixture was allowed to warm to room temperature and stirred for three days. The purple solution was diluted with diethyl ether (20 mL) and poured onto a brine solution (20 mL).

The layers were separated, the aqueous layer was extracted with ether (3 x 15 mL), then the combined organic fractions were dried over sodium sulfate and concentrated *in vacuo*. Purification over silica gel using ethyl acetate:hexane (9:20) with 1.5% triethylamine as an eluent and removal of the solvent *in vacuo* gave **47** as an orange solid. (45 mg, 0.12 mmol, 45%). m.p. = 110-111 ˚C; δ_H (500 MHz, $CDCl_3$) 6.83 (1H, s), 6.79 (1H, t, *J=2*), 6.71 (1H, d of d, *J=2, 4*), 6.19 (1H, d of d, *J=3, 4*), 5.93 (1H, s), 4.30 (2H, q, *J=7*), 4.10 (3H, s), 3.91 (3H, s), 3.78 (3H, s), 2.57 (3H, s), 2.46 (3H, s), 1.36 (3H, t, *J=7*); δ_C (125 MHz, $CDCl_3$) 167.9, 166.0, 161.9, 144.3, 141.1, 129.0, 128.8, 127.9, 127.4, 115.6, 113.3, 113.1, 108.6, 97.2, 59.4, 58.5, 37.7, 33.3, 14.6, 13.0, 12.5. UV/Vis (DCM, 22 ˚C) λ_{max} = 525 nm (ε = 50 300 mol L^{-1} cm^{-1}); *m/z* ESI^+ found 368.1951 $[M+H]^+$ calculated for $C_{21}H_{26}N_3O_3$ 368.1969.

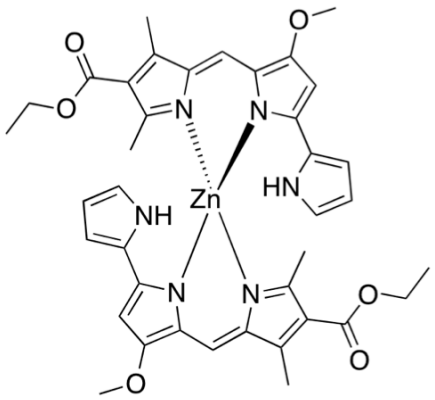
5.4.20 (*Z*)-2-((4-Methoxy-1,1'-dimethyl-1*H*,1'*H*-2,2'-bipyrrol-5-yl)methylene)-3,5-dimethyl-2*H*-pyrrole-4-carboxylate (**48**)



An aqueous KOH solution (5 M, 0.5 mL, 2.5 mmol) was added to a solution of **47** (20 mg, 0.05 mmol) in EtOH (5 mL). The reaction mixture was stirred at 86 ˚C for 3 days. The reaction mixture was poured onto 1 M NaOH (20 mL) and dichloromethane (30 mL) was added. The layers were separated and the aqueous layer was acidified to pH 3 using a 2 M aqueous HCl solution. The resulting solution was extracted with a solution of dichloromethane:methanol (9:1, 6 x 30 mL). The organic fractions were combined, dried over sodium sulfate, and concentrated *in vacuo*. Purification over reversed phase silica

gel (C-18 Reversed Phase, 16 % C) using methanol:water (30:70) as an eluent gave **48** as a deep purple film. (10 mg, 0.02 mmol, 58%). δ_H (500 MHz, D_2O) 7.38 (1H, s), 7.34 (1H, br s), 7.26-7.25 (1H, m) 6.54 (1H, s), 6.46-6.45 (1H, m), 4.17 (3H, s), 3.99 (3H, s), 3.61 (3H, s), 2.57 (3H, s), 2.42 (3H, s). Further characterization was prevented by the instability and insolubility of the compound.

5.4.21 Zn(**1**)$_2$ (**51**)

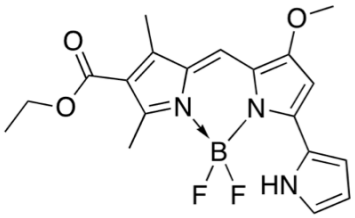


51

To a solution of **1** (100 mg, 0.27 mmol) in chloroform (3 mL) was added a solution of zinc(II) acetate dihydrate (292 mg, 1.33 mmol) and sodium acetate (181 mg, 1.33 mmol) in methanol (3 mL). The resulting solution was stirred at 40 ˚C overnight. The resulting dark red solution was poured onto water (10 mL) and extracted with dichloromethane (3 x 10 mL). The organic fractions were combined, dried with sodium sulfate, filtered and concentrated *in vacuo*. Purification over basic alumina using dichloromethane as the eluent gave **22** as a bright red crystalline powder (100 mg, 0.27 mmol, 99%). m.p. = 241-243 ˚C; δ_H (500 MHz, $CDCl_3$) 9.23 (1H, s), 7.34 (1H, s), 6.59 (1H, s), 6.48-6.49 (1H, m), 6.09-6.10 (1H, m), 6.04 (1H, s), 4.21 (2H, q, *J*=*7*), 3.97 (3H, s), 2.54 (3H, s), 2.18 (3H, s), 1.29 (3H, t, *J*=7); δ_C (125 MHz, $CDCl_3$) 166.7, 165.6, 156.4, 155.0, 141.0, 132.9, 131.4, 126.4, 122.7, 117.8, 117.0, 113.9, 110.4, 95.8, 59.1, 58.3, 16.9, 14.4, 12.0; UV/Vis

(DCM, 22 ˚C) λ_{max} = 523 nm (ε = 152 100 mol L^{-1} cm^{-1}); *m/z* ESI^+ found 741.2374 $[M]^+$ calculated for $C_{38}H_{41}N_6NaO_8Zn$ 741.2379.

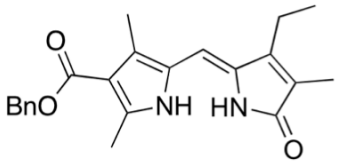
5.4.22 (**1**)BF_2 (**52**)



Triethylamine (0.2 mL, 1.4 mmol, 21 eq) was added to a solution of **1** (25 mg, 0.07 mmol) in dry dichloromethane, under a nitrogen atmosphere. The resulting reaction mixture was stirred for 10 min and then BF_3•OEt_2 (0.2 mL, 1.1 mmol, 17 eq) was added slowly and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was poured into a 5% aqueous solution of citric acid (20 mL) and extracted with diethyl ether (20 mL). The organic layer was washed with 5 % aqueous citric acid (3 x 20 mL), dried over sodium sulfate and concentrated *in vacuo*. Filtration over a pad of silica eluting with dichloromethane followed by concentration *in vacuo* gave **52** as a purple, crystalline solid (28 mg, 0.07 mmol, 100%). m.p. = 210-211 ˚C; δ_H (500 MHz, $CDCl_3$) 10.5 (1H, s), 7.15-7.13 (1H, m), 7.13 (1H, s), 6.94-6.92 (1H, m), 6.39-6.37 (1H, m), 6.14 (1H, s), 4.31 (2H, q, *J=7*), 3.99 (3H, s), 2.80 (3H, s), 2.43 (3H, s), 1.37 (3H, t, *J=7*); δ_C (125 MHz, $CDCl_3$) 165.4, 164.3, 152.9, 151.4, 136.5, 129.4, 129.3, 126.4, 123.5, 118.6, 117.8, 115.0, 111.7, 97.2, 59.7, 58.7, 14.6, 14.4, 11.8; δ_B (80.25 MHz, $CDCl_3$) 1.06 (t, J_{BF}*=36*); δ_F (235.2 MHz, $CDCl_3$) -139 (q, J_{FB}*=31*); ^{15}N HMBC δ_N ($CDCl_3$) -198.3, -221.6. UV/Vis (DCM, 22 ˚C) λ_{max} (nm) (ε (mol L^{-1} cm^{-1})): 536 (184 000). Fluorescence (DCM, 22 ˚C) λ_{max} (nm): 551, Φ_F: 0.92. *m/z* ESI^+ found 410.1458 $[M+Na]^+$ calculated for $C_{19}H_{20}BF_2N_3O_3Na$ 410.1463. A crystal suitable for X-ray crystallography was obtained

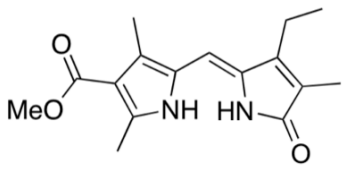
from a slow evaporation of a solution of compound **52** in dichloromethane. Data for **52**: $C_{19}H_{20}N_3O_3BF_2$, M = 387.19 g, dark-red, needle, 0.39 x 0.13 x 0.08 mm, primitive monoclinic, P21/c (#14), a = 7.3029(4) Å, b = 25.1293(11) Å, c = 9.7763(5) Å, V = 1779.52(15) $Å^3$, Z = 4, T = 123(1) K, ρ = 1.445 g cm^{-3}, μ(MoKα) = 1.116 cm^{-1}, 52752 reflections (19174 unique, R_{int} = 0.074), R = 0.0441, Rw = 0.0557, GOF = 1.022.

5.4.23 Benzyl (*Z*)-5-((3-ethyl-4-methyl-5-oxo-1*H*-pyrrol-2(5*H*)-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrole-3-carboxylate (**56**)



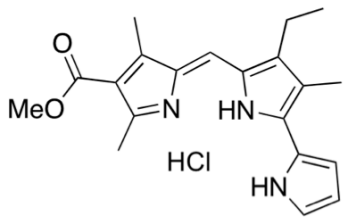
A solution of 4-ethyl-3-methyl-1*H*-pyrrol-2(5*H*)-one (1.5 g, 5.9 mmol) in tetrahydrofuran (50 mL) was purged with N_2 for 20 min. To this solution was added a purged solution of aqueous potassium hydroxide (4 M, 5.2 mL, 21 mmol). This solution was stirred at 70°C for 1 h and then benzyl 5-formyl-2,4-dimethyl-1*H*-pyrrole-3-carboxylate[87] (1.1 g, 8.9 mmol) was added and the solution was stirred under N_2 for 2 days at 70°C. The crude reaction mixture was concentrated *in vacuo*. The resulting bright yellow solid was isolated using filtration, and the residue was rinsed with cold methanol (2 x 10 mL) and dried in a vacuum oven to give **56** as a bright yellow solid (340 mg, 0.93 mmol, 16%). m.p. = 223-224 ˚C; δ_H (500 MHz, DMSO-d_6) 10.95 (1H, br s), 9.85 (1H, br s), 7.44-7.33 (5H, m), 5.95 (1H, s), 5.23 (2H, s), 2.46 (3H, s), 2.26 (3H, s), 2.25 (2H, q, *J*=*8*) 2.08 (3H, s), 1.00 (3H, t, *J*=*8*); δ_C (125 MHz, DMSO-d_6) 171.8, 164.6, 141.2, 139.1, 136.9, 131.7, 130.7, 128.5, 127.81, 127.78, 123.4, 122.9, 111.0, 96.6, 64.5, 16.4, 13.8, 13.4, 11.2, 9.3; *m/z* ESI^+ found 365.1865 $[M+H]^+$ calculated for $C_{22}H_{25}N_2O_3$ 365.1860.

5.4.24 Methyl (*Z*)-5-((3-ethyl-4-methyl-5-oxo-1*H*-pyrrol-2(5*H*)-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrole-3-carboxylate (**57**)



A solution of 4-ethyl-3-methyl-1*H*-pyrrol-2(5*H*)-one (704 mg, 5.6 mmol) in methanol (32 mL) was purged with N_2 for 20 min. To this solution was added a purged solution of aqueous potassium hydroxide (4 M, 3.3 mL, 13.1 mmol). This solution was stirred at 70°C for 1 h, and then benzyl 5-formyl-2,4-dimethyl-1*H*-pyrrole-3-carboxylate[87] (965 mg, 3.8 mmol) was added. The solution was stirred under N_2 for 2 days at 70 °C. The crude reaction mixture was concentrated *in vacuo* and the resulting bright yellow solid was isolated *via* filtration, and the residue was rinsed with cold methanol (2 x 10 mL) and dried in a vacuum oven to give **57** as a bright yellow solid (555 mg, 1.5 mmol, 40%). m.p. = 298 ˚C (dec); δ_H (500 MHz, DMSO-d_6); 10.92 (1H, s), 9.84 (1H, s), 5.95 (1H, s), 3.70 (3H, s), 2.45 (3H, s), 2.08 (3H, s), 2.25 (3H, s), 2.25 (2H, q, *J* = *7*), 1.01 (3H, t, *J* = *7*) δ_C (125 MHz, DMSO-d_6) 171.8, 165.3, 141.2, 138.8, 131.5, 130.7, 123.3, 122.9, 111.2, 96.6, 50.4, 16.4, 13.6, 13.4, 11.1, 9.3; ESI^+ found 311.1365 $[M+Na]^+$ calculated for $C_{16}H_{20}N_2NaO_3$ 311.1366.

5.4.25 Methyl (*Z*)-2-((4-ethyl-3-methyl-1*H*,1'*H*-2,2'-bipyrrol-5-yl)methylene)-3,5-dimethyl-2*H*-pyrrole-4-carboxylate (**58**)

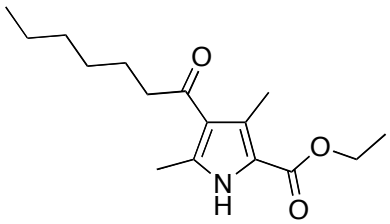


Triflic anhydride (0.28 mL, 1.6 mmol) was slowly added to a solution of **57** (400 mg, 1.1 mmol) in dichloromethane (25 mL). The reaction mixture was stirred at room temperature for 2 h and then poured onto a saturated aqueous solution of sodium bicarbonate (25 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (2 x 25 mL), and the combined organic layers were dried over sodium sulfate and concentrated *in vacuo*.

The crude solid was dissolved in dimethoxyethane (20 mL) and LiCl (0.13 g, 3.1 mmol), 1-*N*-Boc-pyrrole-2-boronic acid (0.33 g, 1.5 mmol), and $Pd(PPh_3)_4$ (0.12 mg, 0.10 mmol) were then added. The resulting solution was purged by bubbling with nitrogen for 10 min, then a solution of Na_2CO_3 (2 M, 2.04 mL, 4.1 mmol) was added and the reaction mixture was stirred at 90 °C for 19 h. The crude reaction mixture was filtered through Celite and poured onto a saturated aqueous solution of sodium bicarbonate (25 mL). Extraction with ethyl acetate (3 x 20 mL), followed by washing of the combined organic fractions with brine (20 mL), drying over anhydrous sodium sulfate, and removal of the solvent *in vacuo* gave the crude product. Purification using flash chromatography on basic alumina with a gradient of ethyl acetate:hexane (0:100 to 20:80) as eluent and removal of the solvent *in vacuo* furnished **58** as an orange film. The film was dissolved in ethyl acetate (20 mL) and washed with 0.5 M HCl (20 mL). The organic layer was dried

over sodium sulfate and concentrated *in vacuo* to give **58HCl** as a purple solid (160 mg, 0.39 mmol, 35%). m.p. = 206-209 ˚C; δ_H (500 MHz, $CDCl_3$) 13.11 (1H, s), 12.94 (1H, s), 12.55 (1H, s), 7.34 (1H, s), 7.13 (1H, s), 7.01 (1H, s), 6.44 (1H, s), 3.85 (3H, s), 2.82 (3H, s), 2.74 (2H, q, *J = 7*), 2.53 (3H, s), 2.32 (3H, s), 1.21 (3H, t, *J = 7*); δ_C (125 MHz, $CDCl_3$) 165.0, 151.6, 148.4, 145.2, 141.8, 132.3, 130.2, 128.3, 124.6, 121.6, 119.1, 116.2, 115.5, 112.9, 51.2, 18.9, 15.0, 13.5, 12.1, 10.2; UV/Vis (DCM, 22 ˚C) λ_{max} = 535 nm (ε = 78 900 mol L^{-1} cm^{-1}); *m/z* ESI^+ found 338.1870 $[M+H]^+$ calculated for $C_{20}H_{24}N_3O_2$ 338.1863.

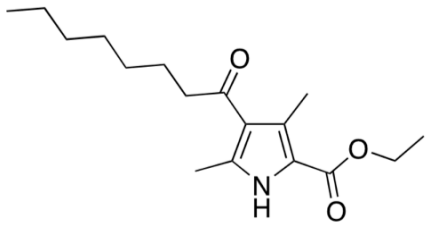
5.4.26 Ethyl 4-(1-oxoheptanoyl)-3,5-dimethyl-1*H*-pyrrole-2-carboxylate (**60**)



Heptanoyl chloride (5.1 mL, 33 mmol) was added to a solution of **59**[69] (5.0 g, 30 mmol) in dry dichloromethane (100 mL) at 0 ˚C under a nitrogen atmosphere. Tin(IV) chloride (3.9 mL, 33 mmol) was added dropwise *via* syringe and the reaction mixture was stirred for 3 h while warming to room temperature. The reaction mixture was poured onto an aqueous 1 M HCl solution (100 mL) and stirred for 20 min. The phases were separated, the aqueous phase was extracted with dichloromethane (2 x 50 mL) and the combined organic phases were dried over sodium sulfate and concentrated *in vacuo*. The resulting yellow solid was recrystallized from hot ethanol, and isolated using suction filtration to give **60** as a white crystalline solid (6.79 g, 24 mmol, 80%). m.p. = 94-95 ˚C; δ_H (500 MHz, $CDCl_3$) 9.45 (1H, s), 4.32 (2H, q, *J*=*7*), 2.71 (2H, t, *J*=*7*), 2.57 (3H, s), 2.51 (3H,

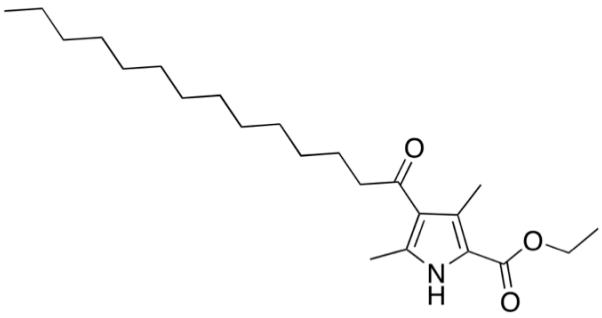
s), 1.67 (2H, pentet, *J*=*7*), 1.38-1.28 (9H, m), 0.87 (3H, t, *J*=*7*); δ_C (125 MHz, $CDCl_3$) 198.7, 162.0, 138.1, 129.2, 123.6, 118.0, 60.5, 43.0, 31.9, 29.3, 24.4, 22.7, 15.2, 14.6, 14.2, 12.9; *m/z* ESI^+ found 302.1723 $[M+Na]^+$ calculated for $C_{16}H_{25}NNaO_3$ 302.1727.

5.4.27 Ethyl 3,5-dimethyl-4-(1oxooctanoyl)-1*H*-pyrrole-2-carboxylate (**61**)[190]



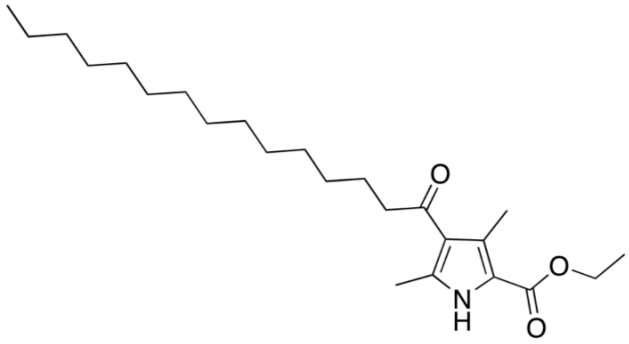
Octanoyl chloride (5.6 mL, 33 mmol) was added to a solution of **59**[69] (5 g, 30 mmol) in dry dichloromethane (100 mL) at 0 ˚C under a nitrogen atmosphere. Tin(IV) chloride (3.9 mL, 33 mmol) was added dropwise *via* syringe and the reaction mixture was stirred for 3 h while warming to room temperature. The reaction mixture was poured onto an aqueous 1 M HCl solution (100 mL) and stirred for 20 min. The phases were separated, the aqueous phase was extracted with dichloromethane (2 x 50 mL) and the combined organic phases were dried over sodium sulfate and concentrated *in vacuo*. The resulting yellow solid was recrystallized from hot ethanol, and isolated using suction filtration to give **61** as a white crystalline solid (8.2 g, 28 mmol, 94%). m.p. = 79-80 ˚C (lit. 79-81);[190] δ_H (500 MHz, $CDCl_3$) 9.49 (s, 1H), 4.32 (q, 2H, *J*=*7*), 2.71 (t, 2H, *J*=*7*), 2.57 (s, 3H), 2.51 (s, 3H), 1.67 (pentet, 2H, *J*=*7*), 1.37-1.23 (m, 11H), 0.86 (t, 3H, *J*=*7*); δ_C (125 MHz, $CDCl_3$) 198.7, 162.1, 138.1, 129.2, 123.6, 118.0, 60.5, 43.0, 31.9, 29.5, 29.37, 29.42, 22.7, 15.2, 14.6, 14.2, 12.9. The ^{13}C NMR data matches (within 0.2 ppm) the previously reported data.[190] *m/z* ESI^+ found 316.1885 $[M+Na]^+$ calculated for $C_{17}H_{27}NNaO_3$ 316.1883.

5.4.28 Ethyl 3,5-dimethyl-4-(1-oxotetradecanoyl)-1*H*-pyrrole-2-carboxylate (**62**)



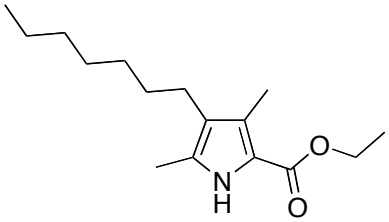
Tetradecanoyl chloride (12.3 g, 50 mmol) was added to a solution of **59**[69] (7.5 g, 45 mmol) in dry dichloromethane (100 mL) at 0 ˚C under a nitrogen atmosphere. Tin(IV) chloride (5.8 mL, 50 mmol) was added dropwise *via* syringe and the reaction mixture was stirred for 3 h while warming to room temperature. The reaction mixture was poured onto an aqueous 1 M HCl solution (100 mL) and stirred for 20 min. The phases were separated, the aqueous phase was extracted with dichloromethane (2 x 50 mL) and the combined organic phases were dried over sodium sulfate and concentrated *in vacuo*. The resulting yellow solid was recrystallized from hot ethanol, and isolated using suction filtration to give **62** as a white crystalline solid (6.5 g, 17 mmol, 38%). m.p. = 80-82 ˚C; δ_H (500 MHz, $CDCl_3$) 9.21 (1H, s), 4.33 (2H, q, *J*=*7*), 2.71 (2H, t, *J*=*7*), 2.59 (3H, s), 2.51 (3H, s), 1.67 (2H, pentet, *J*=*7*), 1.38-1.30 (23H, m), 0.87 (3H, t, *J*=*7*); δ_C (125 MHz, $CDCl_3$) 198.7, 161.9, 137.9, 129.2, 123.7, 118.0, 60.5, 43.1, 32.1, 29.82, 29.81, 29.79, 29.73, 29.68, 29.62, 29.5, 24.4, 22.8, 15.3, 14.6, 14.3, 12.9 (2 CH_2 signals not resolved). *m/z* ESI^+ found 400.2818 $[M+Na]^+$ calculated for $C_{23}H_{39}NO_3Na$ 400.2822.

5.4.29 Ethyl 3,5-dimethyl-4-(1-oxopentadecanoyl)-1*H*-pyrrole-2-carboxylate (**63**)



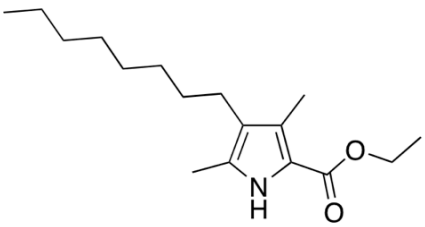
Pentadecanoyl chloride (13.0 g, 50 mmol) was added to a solution of **59**[69] (5 g, 45 mmol) in dry dichloromethane (100 mL) at 0 ˚C under a nitrogen atmosphere. Tin(IV) chloride (5.8 mL, 50 mmol) was added dropwise *via* syringe and the reaction mixture was stirred for 3 h while warming to room temperature. The reaction mixture was poured onto an aqueous 1 M HCl solution (100 mL) and stirred for 20 min. The phases were separated, the aqueous phase was extracted with dichloromethane (2 x 50 mL) and the combined organic phases were dried over sodium sulfate and concentrated *in vacuo*. The resulting yellow solid was recrystallized from hot ethanol, and isolated using suction filtration to give **63** as a white crystalline solid (12.4 g, 32 mmol, 71%). m.p. = 93-94 ˚C; δ_H (500 MHz, $CDCl_3$) 9.10 (1H, s), 4.33 (2H, q, *J*=*7*), 2.72 (2H, t, *J*=*7*), 2.58 (3H, s), 2.51 (3H, s), 1.67 (2H, pentet, *J*=*7*), 1.39-1.28 (25H, m), 0.87 (3H, t, *J*=*7*); δ_C (125 MHz, $CDCl_3$) 198.7, 161.8, 137.8, 129.2, 123.7, 118.0, 60.51, 43.1, 32.1, 29.84, 29.82, 29.80, 29.78, 29.74, 29.69, 29.62, 29.5, 24.4, 22.8, 13.4, 14.6, 14.3, 12.9 (1 CH_2 signal not resolved). *m/z* ESI^+ found 392.3146 $[M]^+$ calculated for $C_{24}H_{42}NO_3$ 392.3159.

5.4.30 Ethyl 3,5-dimethyl-4-heptyl-1*H*-pyrrole-2-carboxylate (**64**)



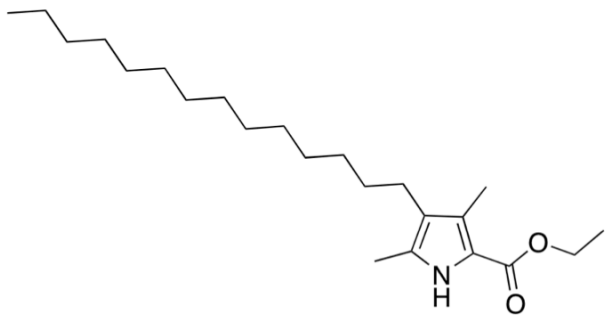
Ethyl 4-heptanoyl-3,5-dimethyl-1*H*-pyrrole-2-carboxylate (**60**) (4.28 g, 15 mmol) was suspended in anhydrous tetrahydrofuran (43 mL) under N_2 and cooled to 0 ˚C. BH_3•THF (1 M in THF, 34 mL, 34 mmol) was added slowly dropwise to the stirred solution by way of a dropping funnel and the reaction mixture was stirred for 18 h and allowed to warm to room temperature. The reaction mixture was cooled to 0 ˚C and water (30 mL) and an aqueous 1 M HCl solution (30 mL) were added sequentially by way of a dropping funnel. The resulting solution was stirred for 30 min at 0 ˚C and then concentrated *in vacuo*, poured onto water (30 mL), extracted with dichloromethane (3 x 60 mL), dried over sodium sulfate and concentrated *in vacuo* to give **64** as a white solid (4.11 g, 15 mmol, 98%). m.p. = 51-53 ˚C; δ_H (500 MHz, $CDCl_3$) 8.74 (1H, s), 4.29 (2H, q, *J*=*7*), 2.34 (2H, t, *J*=*7*), 2.26 (3H, s), 2.19 (3H, s), 1.40 (2H, pentet, *J*=*7*), 1.38-1.27 (11H, m), 0.88 (3H, t, *J*=*7*); δ_C (125 MHz, $CDCl_3$) 161.9, 129.6, 127.2, 122.5, 116.8, 59.7, 32.0, 31.0, 29.6, 29.4, 24.2, 22.8, 14.7, 14.2, 11.6, 10.8; *m/z* ESI^+ found 288.1920 $[M+Na]^+$ calculated for $C_{16}H_{27}NNaO_2$ 288.1934.

5.4.31 Ethyl 3,5-dimethyl-4-octyl-1*H*-pyrrole-2-carboxylate (**65**)[190]



Ethyl 4-octanoyl-3,5-dimethyl-1*H*-pyrrole-2-carboxylate (**61**) (5.22 g, 18 mmol) was suspended in anhydrous tetrahydrofuran (52 mL) under N_2 and cooled to 0 ˚C. BH_3•THF (1 M in THF, 39 mL, 39 mmol) was added slowly dropwise to the stirred solution by way of a dropping funnel and the reaction mixture was stirred for 18 h and allowed to warm to room temperature. The reaction mixture was cooled to 0 ˚C and water (30 mL) and an aqueous 1 M HCl solution (30 mL) were added sequentially by way of a dropping funnel. The resulting solution was stirred for 30 min at 0 ˚C and then concentrated *in vacuo*, poured onto water (30 mL), extracted with dichloromethane (3 x 60 mL), dried over sodium sulfate and concentrated *in vacuo* to give **64** as a white solid (4.90 g, 18 mmol, 97%). m.p. = 55-56 ˚C (lit. 55-57);[190] δ_H (500 MHz, $CDCl_3$) 8.78 (1H, s), 4.29 (2H, q, *J*=*7*), 2.33 (2H, t, *J*=*7*), 2.27 (3H, s), 2.20 (3H, s), 1.41 (2H, pentet, *J*=*7*), 1.39-1.26 (13H, m), 0.88 (3H, t, *J*=*7*); δ_C (125 MHz, $CDCl_3$) 161.9, 129.6, 127.2, 122.5, 116.8, 59.7, 32.0, 31.0, 29.7, 29.6, 29.5, 24.2, 22.8, 14.7, 14.2, 11.6, 10.8. The ^{13}C NMR data matches (within 0.3 ppm) the recorded data for the compound.[190] *m/z* ESI^+ found 280.2264 $[M+H]^+$ calculated for $C_{17}H_{30}NNaO_2$ 280.2271.

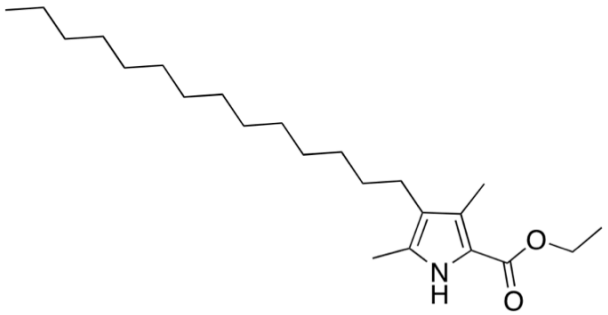
5.4.32 Ethyl 3,5-dimethyl-4-tetradecyl-1*H*-pyrrole-2-carboxylate (**66**)[191]



Ethyl 4-tetradecanoyl-3,5-dimethyl-1*H*-pyrrole-2-carboxylate (**62**) (3.0 g, 8.0 mmol) was suspended in anhydrous tetrahydrofuran (30 mL) under N_2 and cooled to 0 ˚C. BH_3•THF

(1 M in THF, 17.5 mL, 17.5 mmol) was added slowly dropwise to the stirred solution by way of a dropping funnel and the reaction mixture was stirred for 18 h and allowed to warm to room temperature. The reaction mixture was cooled to 0 ˚C, water (20 mL) and an aqueous 1 M HCl solution (20 mL) were added sequentially by way of a dropping funnel and the solution was stirred for 30 min at 0 ˚C. The resulting white precipitate was isolated using suction filtration to give **66** as a white solid (2.80 g, 7.7 mmol, 97%). m.p. = 64-65 ˚C; δ_H (500 MHz, $CDCl_3$) 8.66 (1H, s), 4.29 (2H, q, *J*=*7*), 2.35 - 2.32 (2H, m), 2.26 (3H, s), 2.19 (3H, s), 1.40 (2H, pentet, *J*=*7*), 1.36-1.26 (25H, m), 0.88 (3H, t, *J*=*7*); δ_C (125 MHz, $CDCl_3$) 161.9, 129.5, 127.2, 122.6, 116.8, 59.7, 32.1, 31.0, 29.83, 29.80, 29.7, 29.6, 29.5, 24.2, 22.8, 14.8, 14.3, 11.7, 10.8 (4 CH_2 signals not resolved). *m/z* ESI^+ found 386.3030 $[M+Na]^+$ calculated for $C_{23}H_{41}NNaO_2$ 386.3030.

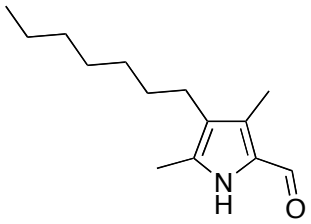
5.4.33 Ethyl 3,5-dimethyl-4-pentadecyl-1*H*-pyrrole-2-carboxylate (**67**)



Ethyl 4-pentadecanoyl-3,5-dimethyl-1*H*-pyrrole-2-carboxylate (**63**) (6.0 g, 815 mmol) was suspended in anhydrous tetrahydrofuran (50 mL) under N_2 and cooled to 0 ˚C. BH_3•THF (1 M in THF, 31 mL, 31 mmol) was added slowly dropwise to the stirred solution by way of a dropping funnel and the reaction mixture was stirred for 18 h and allowed to warm to room temperature. The reaction mixture was cooled to 0 ˚C, water (30 mL) and an aqueous 1 M HCl solution (30 mL) were added sequentially by way of a

dropping funnel and the solution was stirred for 30 min at 0 ˚C. The resulting white precipitate was isolated using suction filtration to give **67** as a white solid (4.9 g, 13 mmol, 85%). m.p. = 69-71 ˚C; δ_H (500 MHz, $CDCl_3$) 8.57 (1H, s), 4.29 (2H, q, *J*=*7*), 2.35-2.32 (2H, m), 2.26 (3H, s), 2.19 (3H, s), 1.40 (2H, pentet, *J*=*7*), 1.37-1.25 (25H, m), 0.88 (3H, t, *J* = *7*); δ_C (125 MHz, $CDCl_3$) 161.8, 129.5, 127.2, 122.6, 116.8, 59.7, 32.1, 31.0, 29.9, 29.83, 29.81, 29.7, 29.6, 29.5, 24.3, 22.8, 14.8, 14.3, 11.7, 10.7 (4 CH_2 signals not resolved); *m/z* ESI^+ found 400.3178 $[M+Na]^+$ calculated for $C_{24}H_{43}NNaO_2$ 400.3186.

5.4.34 3,5-Dimethyl-4-heptyl-1*H*-pyrrole-2-carbaldehyde (**68**)

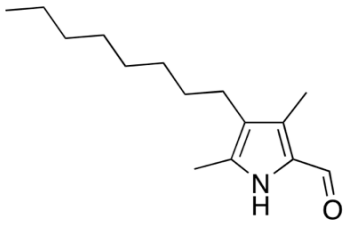


Water (7 mL) and sodium hydroxide (995 mg, 23.6 mmol) were added to a stirred suspension of ethyl 3,5-dimethyl-4-heptyl-1*H*-pyrrole-2-carboxylate (**64**) (3.0 g, 11.3 mmol) in 95% ethanol (30 mL). The solution was heated with stirring at 85 ˚C for 18 h and then poured onto water (75 mL). The solution was acidified using an aqueous 2 M HCl solution, which resulted in the separation of a brown oil. Dichloromethane (75 mL) was added and the layers were separated. The aqueous layer was extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried over sodium sulfate and then concentrated *in vacuo* to give a brown oil (1.57 g) which solidified on standing.

The brown oil was dissolved in dichloromethane (150 mL) at 0 ˚C under N_2. TFA (5.4 mL, 73 mmol) was added dropwise to the stirred solution. The reaction mixture was

then warmed to room temperature and stirred for 18 h. The reaction mixture was cooled to 0 ˚C and TMOF (3.6 mL, 15 mmol) was added dropwise. The resulting solution was stirred for 1 h at 0 ˚C and then poured onto an aqueous 1 M NaOH solution (100 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (2 x 100 mL) and the combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. Purificiation over silica gel eluting with ethyl acetate:hexanes (20:80) gave **68** as a beige solid (1.00 g, 4.5 mmol, 41%). m.p. = 84-85 ˚C; δ_H (500 MHz, $CDCl_3$) 10.0 (1H, s), 9.44 (1H, s), 2.34 (2H, t, *J=7*), 2.254 (3H, s), 2.248 (3H, s), 1.41 (2H, pentet, *J=7*), 1.32-1.24 (8H, m), 0.88 (3H, t, *J=7*); δ_C (125 MHz, $CDCl_3$) 175.7, 136.3, 132.6, 127.9, 123.6, 32.0, 30.7, 29.6, 29.4, 23.9, 22.8, 14.2, 11.8, 9.0; *m/z* ESI^+ found 244.1669 $[M+Na]^+$ calculated for $C_{14}H_{23}NNaO$ 244.1672.

5.4.35 3,5-Dimethyl-4-octyl-1*H*-pyrrole-2-carbaldehyde (**69**)

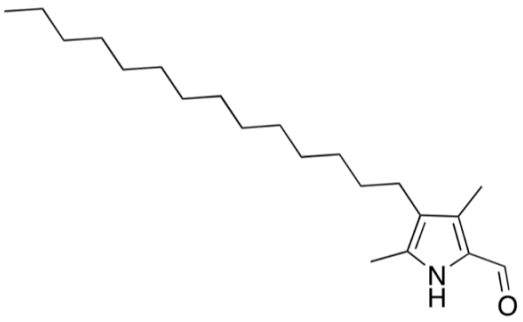


Water (7 mL) and sodium hydroxide (944 mg, 23.6 mmol) were added to a stirred suspension of ethyl 3,5-dimethyl-4-octyl-1*H*-pyrrole-2-carboxylate (**65**) (3.0 g, 10.7 mmol) in 95% ethanol (30 mL). The solution was heated with stirring at 85 ˚C for 18 h and then poured onto water (75 mL). The solution was acidified using an aqueous 2 M HCl solution, which resulted in the separation of a brown oil. Dichloromethane (75 mL) was added and the layers were separated. The aqueous layer was extracted with dichloromethane (3 x 30 mL). The combined organic layers were then dried over sodium

sulfate and concentrated *in vacuo* to give a brown oil (1.54 g) which solidified on standing.

The brown oil was disolved in dichloromethane (150 mL) at 0 ˚C under N_2. TFA (5.4 mL, 73 mmol) was added dropwise to the stirred solution. The reaction mixture was warmed to room temperature and stirred for 18 h. The reaction mixture was cooled to 0 ˚C and TMOF (3.6 mL, 15 mmol) was added dropwise. The resulting solution was stirred for 1 h at 0 ˚C and then poured onto an aqueous 1 M NaOH solution (100 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (2 x 100 mL) and the combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. Purificiation over silica gel eluting with ethyl acetate:hexanes (20:80) gave **69** as a beige solid (1.28 g, 5.4 mmol, 51%). m.p. = 81-82 ˚C; δ_H (500 MHz, $CDCl_3$) 10.0 (1H, s), 9.44 (1H, s), 2.34 (2H, t, *J=7*), 2.254 (3H, s), 2.248 (3H, s), 1.41 (2H, pentet, *J=7*), 1.32-1.24 (8H, m), 0.88 (3H, t, *J=7*); δ_C (125 MHz, $CDCl_3$) 175.7, 136.3, 132.6, 127.9, 123.6, 32.0, 30.7, 29.6, 29.4, 23.9, 22.8, 14.2, 11.8, 9.0; *m/z* ESI^+ found 244.1669 $[M+Na]^+$ calculated for $C_{14}H_{23}NNaO$ 244.1672.

5.4.36 3,5-Dimethyl-4-tetradecyl-1*H*-pyrrole-2-carbaldehyde (**70**)

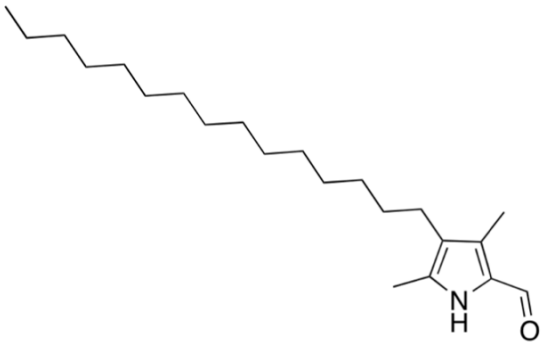


Water (5 mL) and sodium hydroxide (363 mg, 8.2 mmol) were added to a stirred suspension of ethyl 3,5-dimethyl-4-tetradecyl-1*H*-pyrrole-2-carboxylate (**66**) (1.5 g, 4.1

mmol) in 95% ethanol (20 mL). The solution was heated with stirring at 85 ˚C for 18 h and then poured onto water (50 mL). The solution was acidified using an aqueous 2 M HCl solution, which resulted in the precipitation of a white solid. The solid was isolated using suction filtration and dried overnight before use in the formylation reaction.

The dry solid was dissolved in dichloromethane (100 mL) at 0 ˚C under N_2. TFA (2.4 mL, 33 mmol) was added dropwise to the stirred solution. The reaction mixture was warmed to room temperature and then stirred for 1 h. The reaction mixture was cooled to 0 ˚C and TMOF (1.6 mL, 15 mmol) was added dropwise. The resulting solution was stirred for 30 min at 0 ˚C and then poured onto an aqueous 1 M NaOH solution (100 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (2 x 100 mL) and the combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. Purification over silica gel eluting with ethyl acetate:dichloromethane (20:80) gave **70** as a light green solid (665 mg, 2.1 mmol, 51%). m.p. = 99-101 ˚C; δ_H (500 MHz, $CDCl_3$) 9.91 (1H, s), 9.44 (1H, s), 2.34 (2H, t, *J=7*), 2.254 (3H, s), 2.247 (3H, s), 1.41 (2H, pentet, *J=7*), 1.28-1.25 (22H, m), 0.88 (3H, t, *J=7*); δ_C (125 MHz, $CDCl_3$) 175.7, 136.1, 132.6, 127.9, 123.6, 32.1, 30.7, 29.8, 29.7, 29.6, 29.5, 23.9, 22.8, 14.3, 11.8, 9.0 (5 CH_2 signals not resolved); *m/z* ESI^+ found 320.2941 $[M+H]^+$ calculated for $C_{21}H_{38}NO$ 320.2948.

5.4.37 3,5-Dimethyl-4-pentadecyl-1*H*-pyrrole-2-carbaldehyde (**71**)

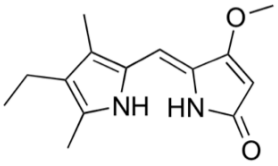


Water (10 mL) and sodium hydroxide (528 mg, 13 mmol) were added to a stirred suspension of ethyl 3,5-dimethyl-4-pentadecyl-1*H*-pyrrole-2-carboxylate (**67**) (2.5 g, 6.6 mmol) in 95% ethanol (40 mL). The solution was heated with stirring at 85 ˚C for 18 h and then poured onto water (100 mL). The solution was acidified using an aqueous 2 M HCl solution, which resulted in the precipitation of a white solid. The solid was isolated by way of suction filtration.

The dry solid was disolved in dichloromethane (200 mL) at 0 ˚C under N_2. TFA (4.7 mL, 63 mmol) was added dropwise to the stirred solution. The reaction mixture was warmed to room temperature and then stirred for 1 h. The reaction mixture was cooled to 0 ˚C and TMOF (3.1 mL, 29 mmol) was added dropwise. The resulting solution was stirred for 30 min at 0 ˚C and then poured onto an aqueous 1 M NaOH solution (100 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (2 x 100 mL) and the combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. Purificiation over silica gel eluting with ethyl acetate:dichloromethane (20:80) gave **71** as a light green solid (885 mg, 2.7 mmol, 41%). m.p. = 103-104 ˚C; δ_H (500 MHz, $CDCl_3$) 9.95 (1H, s), 9.44 (1H, s), 2.34 (2H, t, *J*=*7*), 2.254 (3H, s), 2.248 (3H, s), 1.41 (2H, pentet, *J*=*7*), 1.29-1.27 (24H, m), 0.88 (3H, t,

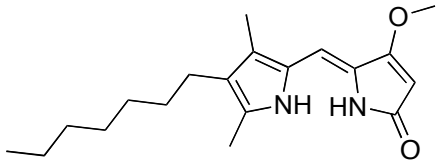
J=7); δ_C (125 MHz, $CDCl_3$) 175.7, 136.2, 132.6, 127.9, 123.6, 32.1, 30.7, 29.8, 29.7, 29.6, 29.5, 23.9, 22.8, 14.3, 11.8, 9.0 (6 CH_2 signals not resolved); *m/z* ESI^+ found 334.3108 $[M+H]^+$ calculated for $C_{22}H_{40}NO$ 334.3104.

5.4.38 3(*Z*)-5-((3,5-Dimethyl-4-ethyl-1*H*-pyrrol-2-yl)methylene)-4-methoxy-1*H*-pyrrol-2(5*H*)-one (**73**)



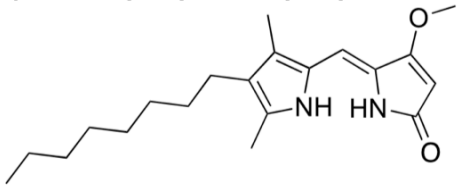
Aqueous potassium hydroxide (4 M, 6.1 mL, 24.4 mmol) was added to a solution of 3-methoxy-1*H*-pyrrol-2(5*H*)-one (1.18 g, 10.4 mmol) in methanol (50 mL) and the resulting solution was purged with nitrogen for 20 min and then stirred at 60 ˚C for 1 h. 4-Ethyl-3,5-dimethyl-1*H*-pyrrole-2-carbaldehyde[90] (1.05 g, 6.96 mmol) was added and the solution was stirred under nitrogen for 2 days at 84 ˚C. The crude reaction mixture was concentrated *in vacuo* and poured onto water (50 mL). The resulting yellow solid was isolated using suction filtration to give **73** as a yellow solid (1.28 g, 5.20 mmol, 75%). m.p. = 279-280 ˚C; δ_H (500 MHz, $CHCl_3$) 10.90 (1H, br s), 10.19 (1H, br s), 6.37 (1H, s), 5.09 (1H, s), 3.89 (3H, s), 2.39 (2H, q, *J*=7), 2.35 (3H, s), 2.12 (3H, s), 1.06 (3H, t, *J*=7); δ_C (125 MHz, $CHCl_3$) 173.2, 167.9, 131.9, 125.6, 123.2, 121.7, 121.5, 100.8, 89.7, 58.2, 17.6, 15.5, 11.5, 9.6; *m/z* ESI^+ found $[M+H]^+$ 247.1442 calculated for $C_{14}H_{19}N_2O_2$ 247.1441.

5.4.39 (3*Z*)-5-((3,5-dimethyl-4-heptyl-1*H*-pyrrol-2-yl)methylene)-4-methoxy-1*H*-pyrrol-2(5*H*)-one (**74**)



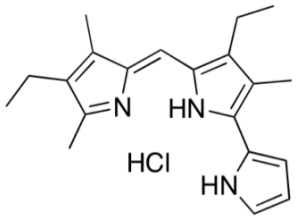
Aqueous potassium hydroxide (4 M, 2.0 mL, 7.9 mmol) was added to a solution of 3-methoxy-1*H*-pyrrol-2(5*H*)-one (384 mg, 3.4 mmol) in methanol (20 mL) and the resulting solution was purged with nitrogen for 20 min and then stirred at 60°C for 1.5 h. 4-Heptyl-3,5-dimethyl-1*H*-pyrrole-2-carbaldehyde (**68**) (500 mg, 2.3 mmol) was added and the solution stirred under nitrogen for 2 days at 84°C. The crude reaction mixture was concentrated *in vacuo* and poured onto water (20 mL). The resulting orange solid was isolated using suction filtration. Purification over basic alumina eluting with a gradient of ethyl acetate:hexanes (20:80 to 100:0) gave **74** as an orange solid (409 mg, 1.3 mmol, 56%). m.p. = 155-157 ˚C; δ_H (500 MHz, $CDCl_3$) 10.94 (1H, bs), 10.20 (1H, bs), 6.37 (1H, s), 5.09-5.08 (1H, m), 3.89 (3H, s), 2.36 (2H, q, *J*=7), 2.34 (3H, s), 2.11 (3H, s), 1.57 (2H, pentet, *J*=7), 1.13-1.27 (8H, m), 0.88 (3H, t, *J*=7); δ_C (125 MHz, $CDCl_3$) 173.1, 167.9, 132.4, 126.0, 121.74, 121.69, 121.4, 100.9, 89.6, 58.2, 32.1, 31.1, 29.7, 29.4, 24.4, 22.9, 14.3, 11.6, 9.7; *m/z* ESI^+ found 317.2216 $[M+H]^+$ calculated for $C_{19}H_{39}N_2O_2$ 317.2224.

5.4.40 (3*Z*)-5-((3,5-dimethyl-4-octyl-1*H*-pyrrol-2-yl)methylene)-4-methoxy-1*H*-pyrrol-2(5*H*)-one (**75**)



Aqueous potassium hydroxide (4 M, 1.9 mL, 7.42 mmol) was added to a solution of 3-methoxy-1*H*-pyrrol-2(5*H*)-one (360 mg, 2.12 mmol) in methanol (20 mL) and the resulting solution was purged with nitrogen for 20 min and then stirred at 60°C for 1.5 h. 4-Octyl-3,5-dimethyl-1*H*-pyrrole-2-carbaldehyde (**69**) (1.05 g, 6.96 mmol) was added and the solution stirred under nitrogen for 2 days at 84°C. The crude reaction mixture was concentrated *in vacuo* and poured onto water (20 mL). The resulting orange solid was isolated by suction filtration. Purification over basic alumina eluting with a gradient of ethyl acetate:hexane (0:100 to 20:80) gave **75** as an orange solid (340 mg, 1.02 mmol, 48%). m.p. = 175-177 ˚C; δ_H (500 MHz, $CDCl_3$) 10.94 (1H, s), 10.21 (1H, s), 6.37 (1H, s), 5.08 (1H, s), 3.89 (3H, s), 2.31 (2H, t, *J*=*7*), 2.34 (3H, s), 2.11 (3H, s), 1.41 (2H, pentet, *J*=*7*), 1.29-1.27 (10H, m), 0.88 (3H, t, *J*=7); δ_C (125 MHz, $CDCl_3$) 173.1, 167.9, 132.4, 126.0, 121.74, 121.69, 121.4, 100.9, 89.6, 58.2, 32.1, 31.1, 29.74, 29.70, 29.5, 24.4, 22.8, 14.3, 11.6, 9.7; *m/z* ESI^+ found 331.2401 $[M+H]^+$ calculated for $C_{20}H_{31}N_2O_2$ 331.2380.

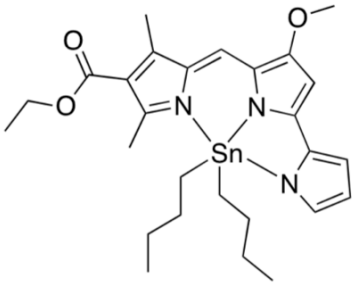
5.4.41 (*Z*)-4-Ethyl-5-((4-ethyl-3,5-dimethyl-2*H*-pyrrol-2-ylidene)methyl)-3-methyl-1*H*,1'*H*-2,2'-bipyrrole (**82**)



Unsymmetrical bromodipyrrin **81**,[91] LiCl (47 mg, 1.12 mmol), 1-*N*-Boc-pyrrole-2-boronic acid (0.16 g, 0.74 mmol), and $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) were dissolved in dimethoxyethane (10 mL) and the solution was purged by bubbling with nitrogen for 10 min. A solution of Na_2CO_3 (2 M, 0.75 mL, 1.49 mmol) was added, and the reaction

mixture was stirred at 90 °C for 19 h and then poured into water (20 mL). The crude reaction mixture was filtered through Celite and poured onto a saturated aqueous solution of sodium bicarbonate (25 mL). Extraction with ethyl acetate (3 x 20 mL), followed by washing of the combined organic fractions with brine (20 mL), drying over anhydrous sodium sulfate, and removal of the solvent under reduced pressure gave the crude product. Purification using flash chromatography on basic alumina with a gradient of ethyl acetate:hexane (0:100 to 20:80) as eluent furnished **82** as an orange film after removal of the solvent *in vacuo* (78 mg, 16%). m.p. = 153-155 ˚C; δ_H (500 MHz, $CDCl_3$): 12.97 (1H, s), 12.70 (1H, s), 12.28 (1H, s), 7.24 (1H, s), 6.97 (1H, s), 6.90 (1H, s), 6.38 (1H, s) 2.69 (2H, q, *J* = *8*), 2.58 (3H, s), 2.42 (2H, q, *J* = *8*), 2.26 (3H, s), 2.25 (3H, s), 1.19 (3H, t, *J* = *8*), 1.07 (3H, t, *J* = *8*); δ_C (125 MHz, $CDCl_3$) 149.8, 149.3, 145.2, 138.8, 129.4, 126.7, 125.8, 125.7, 122.8, 122.6, 116.4, 115.3, 111.5, 18.2, 17.4, 16.3, 14.8, 12.7, 11.6, 10.1; UV/Vis (DCM, 22 ˚C) λ_{max} = 560 nm (ε = 68 100 mol L^{-1} cm^{-1}); *m/z* ESI^+ found 308.2112 $[M+H]^+$ calculated for $C_{20}H_{26}N_3$ 308.2121.

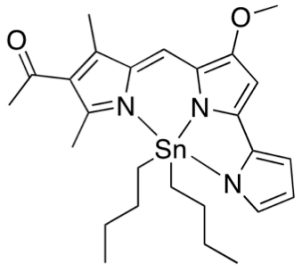
5.4.42 $(Bu)_2$(**1**)Sn(IV)(**83**)



Dibutyltin oxide (15 mg, 0.059 mmol) was addd to a solution of prodigiosene **1** (20 mg, 0.05 mmol) in methanol (5 mL). The resulting solution was stirred at 65 °C for 18 h and then concentrated *in vacuo*. The residue was dissolved in ethyl acetate and poured onto a saturated aqueous solution of sodium bicarbonate (20 mL) and extracted with ethyl

acetate (3 x 20 mL). The organic fractions were combined, dried with sodium sulfate, and the solvent removed *in vacuo* to give the crude product. Purification over basic alumina using dichloromethane as an eluent and removal of the solvent *in vacuo* gave **82** as a purple film (26 mg, 0.046 mmol, 93%). m.p. = 115-117 ˚C; δ_H (500 MHz, $CDCl_3$) 6.97-6.95 (2H, m), 6.82 (1H, d, *J=3*), 6.43 (1H, dd, *J=2,3*), 6.06 (1H, s), 4.29 (2H, q, *J=7*), 4.00 (3H, s), 2.64 (3H, s), 2.45 (3H, s), 1.65-1.18 (15H, m), 0.75 (6H, t, *J=7*); δ_C (125 MHz, $CDCl_3$) 168.5, 166.1, 157.2, 152.1, 137.3, 133.4, 132.1, 132.0, 129.5, 115.7, 114.1, 113.8, 112.3, 92.7, 59.4, 58.6, 27.0, 26.4, 24.0, 17.3, 14.7, 13.6, 12.2; δ_{Sn} (186 MHz, $CDCl_3$) -245.9; δ_N (50.7 MHz, $CDCl_3$) -229.9, -165.5; UV/Vis (DCM) λ_{max} (nm) ε (mol $L^{-1}{\cdot}cm^{-1}$)): 568 (85 000). Fluorescence (DCM, 22 ˚C) λ_{max} (nm): 579, Φ_F: 0.57. *m/z* ESI^+ found 594.1749 $[M+Na]^+$ calculated for $C_{27}H_{37}N_3NaO_3Sn$ 594.1755.

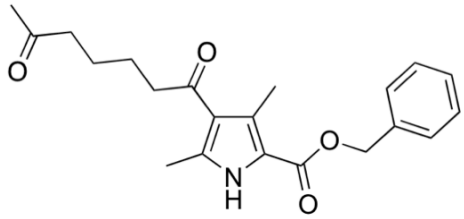
5.4.43 $(Bu)_2$(**84**)Sn(IV) (**85**)



Dibutyltin oxide (22 mg, 0.09 mmol) was addd to a solution of prodigiosene **1** (25 mg, 0.07 mmol) in methanol (5 mL). The resulting solution was stirred at 65 °C for 18 h and then concentrated *in vacuo*. The residue was dissolved in ethyl acetate and poured onto a saturated aqueous solution of sodium bicarbonate (20 mL) and extracted with ethyl acetate (3 x 20 mL). The organic fractions were combined, dried with sodium sulfate, and the solvent removed *in vacuo* to give the crude product. Purification over silica using ethyl acetate:dichloromethane:triethylamine (20:78.5:1.5) as an eluent and removal of the

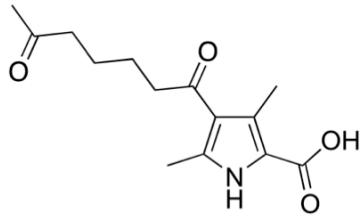
solvent *in vacuo* gave **84** as a purple film (35 mg, 0.065 mmol, 93%). δ_H (500 MHz, $CDCl_3$) 6.875-6.878 (2H, m), 6.74 (1H, dd, *J=1,3*), 6.34 (1H, dd, *J=2,3*), 5.97 (1H, s), 3.91 (3H, s), 2.54 (3H, s), 2.374 (3H, s), 2.366 (3H, s), 1.46-1.28 (8H, m), 1.11 (4H, sextet, *J=7*), 0.65 (6H, t, *J=7*); δ_C (125 MHz, $CDCl_3$) 195.4, 168.6, 157.5, 151.9, 134.7, 133.5, 132.4, 132.0, 130.0, 125.9, 114.3, 113.5, 112.7, 92.8, 58.6, 31.6, 27.0, 26.4, 24.1, 18.2, 13.6, 13.1; δ_{Sn} (186 MHz, $CDCl_3$) -245.0; δ_N (50.7 MHz, $CDCl_3$) -230.4, -165.1; *m/z* ESI^+ found 542.1824 $[M+H]^+$ calculated for $C_{26}H_{36}N_3O_2Sn$ 542.1829.

5.4.44 Benzyl 3,5-dimethyl-4-(6-oxoheptanoyl)-1*H*-pyrrole-2-carboxylate (**88**)



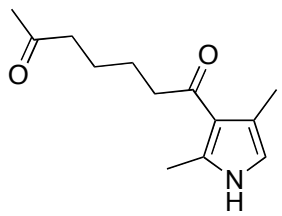
Compound **42**[100] (8.13g, 50 mmol) was added slowly to a solution of **87**[69] (10.3 g, 45 mmol) in dichloromethane (100 mL) and the solution was cooled to 0˚C. $SnCl_4$ (5.9 mL, 50 mmol) was added dropwise and the reaction mixture was warmed to room temperature and then stirred for 4 h. The reaction mixture was poured onto aqueous 0.1 M NaOH (250 mL) and filtered through Celite to remove the white precipitate. The layers were separated and the organic layers was dried over sodium sulfate and concentrated *in vacuo* to give a red solid which was crystallized from dichloromethane:hexanes (2:1) to give **88** as a beige powder (10.4 g, 27 mmol, 59%). δ_H (125 MHz, $CDCl_3$) 9.03 (1H, s), 7.42 -7.34 (5H, m), 5.32 (2H, s), 2.74 (2H, t, *J=7*), 2.59 (3H, s), 2.49 (3H, s), 2.47 (2H, t, *J=7*), 2.13 (3H, s), 1.70-1.61 (4H, m); δ_c (125 MHz, $CDCl_3$) 209.0, 197.8, 161.3, 138.2, 136.1, 129.8, 128.8, 128.5, 128.4, 123.7, 117.7, 66.3, 43.8, 42.7, 30.1, 23.8, 23.7, 15.4, 13.0; *m/z* ESI^+ found 378.1676 $[M+Na]^+$ expected for $C_{21}H_{25}NO_4Na$ 378.1681.

5.4.45 3,5-Dimethyl-4-(6-oxoheptanoyl)-1*H*-pyrrole-2-carboxylic acid (**89**)



Palladium on activated carbon (10% by weight, 1.0 g) was added to a solution of **88** (10.2 g, 29 mmol) in tetrahydrofuran (150 mL) and the reaction mixture was then stirred under 1 atm of hydrogen for 18 h. Methanol (150 mL) was added to the reaction mixture and the resulting solution was filtered over Celite, and concentrated *in vacuo* to give a brown solid. This solid was crystallized from hot methanol to give **89** as a beige powder (6.6 g, 25 mmol, 86%). m.p. = 164-166 ˚C; δ_H (500 MHz, DMSO-*d6*) 12.41 (1H, s), 11.68 (1H, s), 2.60 (2H, t, *J*=*7*), 2.47 (3H, s), 2.43 (2H, t, *J*=*7*), 2.42 (3H, s), 2.07 (3H, s), 1.54-1.45 (4H, m); δ_c (125 MHz, DMSO-*d6*) 208.4, 196.7, 162.4, 137.7, 128.0, 122.3, 118.0, 42.7, 41.6, 29.6, 23.3, 23.0, 14.3, 12.3. *m/z* ESI^- found 264.1262 $[M-H]^-$ calculated for $C_{14}H_{18}NO_4$ 264.1241.

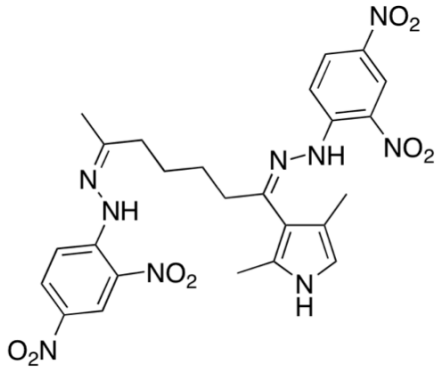
5.4.46 1-(2,4-Dimethyl-1*H*-pyrrol-3-yl)heptane-1,6-dione (**90**)



Compound **89** (3.01 g, 11.4 mmol) was placed in a round-bottom flask and the flask was then equipped with a condenser. The round-bottom flask was placed in a heating mantle preheated to 220 ºC until the solid melted and bubbling ceased (approximately 15 min). The flask was then removed from the heating mantle and the contents allowed to cool to

room temperature. Purification over silica gel using ethyl acetate:hexane (13:20) as an eluent and removal of the solvent *in vacuo* gave **90** as a white powder (2.0 g, 9.1 mmol, 80%). m.p. = 69-71 ˚C; δ_H (500 MHz, $CDCl_3$) 8.06 (1H, s), 6.36-6.35 (1H, m), 2.73 (2H, t, *J=7*), 2.49 (3H, s), 2.48 (2H, t, *J=7*), 2.27 (3H, d, *J=1*), 2.14 (3H, s), 1.73-1.62 (4H, m); δ_C (125 MHz, $CDCl_3$) 209.2, 197.6, 135.5, 120.9, 120.5, 114.9, 53.6, 43.9, 42.2, 30.1, 23.9, 15.5, 14.0; *m/z* ESI^+ found 244.1308 $[M+Na]^+$ expected for $C_{13}H_{19}NO_2Na$ 244.1313.

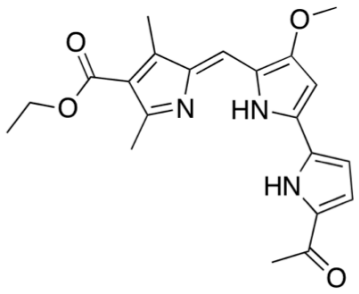
5.4.47 3-((1*Z*,6*Z*)-1,6-Bis(2-(2,4-dinitrophenyl)hydrazono)heptyl)-2,4-dimethyl-1*H*-pyrrole (**91**)



Acetic acid (0.2 mL) was added to a solution of **90** (100 mg, 0.38 mmol) and 2,4-dinitrophenylhydrazine (224 mg, 1.03 mmol) in ethanol (5 mL) and the reaction mixture was stirred at 85˚C for 18 h. The solvent was removed *in vacuo* to give a brown solid, which was crystallized from hot ethyl acetate to give **91** as a purple solid (178 mg, 0.31 mmol, 81%). m.p = 175-177 ˚C; δ_H (500 MHz, DMSO-*d6*) 11.30 (1H, s), 10.77 (1H, s), 10.69 (1H, s), 8.82 (1H, d, *J=3*), 8.78 (1H, d, *J=3*), 8.32 (1H, dd, *J=3, 10*), 8.24 (1H, dd, *J=3, 10*), 7.83 (1H, d, *J=10*), 7.73 (1H, d, *J=10*), 6.45-6.44 (1H, m), 2.81 (2H, t, *J=7*), 2.48 (2H, t, *J=7*), 2.37 (3H, s), 2.17 (3H, s), 2.04 (3H, s), 1.78-1.66 (4H, m); δ_C (125 MHz, DMSO-*d6*) 159.7, 158.0, 144.5, 144.3, 136.6, 136.1, 130.1, 129.9, 129.3, 128.8,

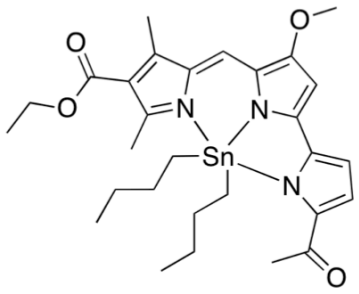
128.4, 123.0, 122.9, 117.1, 116.6, 115.9, 115.7, 115.2, 37.6, 29.1, 25.3, 24.4, 15.8, 14.0, 13.3. *m/z* ESI^- found 580.1885 $[M-H]^-$ calculated for $C_{22}H_{25}N_2O_3$ 580.1910.

5.4.48 (*Z*)-Ethyl 2-((5'-acetyl-4-methoxy-1H,1'H-2,2'-bipyrrol-5-yl)methylene)-3,5-dimethyl-2H-pyrrole-4-carboxylate (**92**)



Compound **92** was prepared according to a modified literature procedure.[22] Ac_2O (0.100 mL, 1.06 mmol) and solid $AlCl_3$ (157 mg, 1.18 mmol) were added to a solution of **1** (100 mg, 0.226 mmol) in CH_2Cl_2 (30 mL) and the resulting solution was stirred at room temperature for 2 h. The resulting solution was washed with aqueous 0.5 N HCl (100 mL) and then 2 M NaOH (100 mL). The organic layer was dried over sodium sulfate and concentrated *in vacuo*. Purification over neutral alumina using ethyl acetate:hexanes (20:80) as an eluent and removal of the solvent *in vacuo* gave **92** as an orange film (63 mg, 0.165 mmol, 62%). δ_H (500 MHz, $CDCl_3$) 7.00 (1H, s), 6.95 (1H, d, *J=4.0*), 6.68 (1H, d, *J=4.0*), 5.95 (1H, s), 4.31 (2H, q, *J=7.0*), 3.92 (3H, s), 2.65 (3H, s), 2.48 (3H, s), 2.44 (3H, s), 1.38 (3H, t, *J=7.0*). δ_C (125 MHz, $CDCl_3$) 188.1, 168.6, 165.5, 157.9, 143.9, 141.3, 133.8, 133.5, 133.4, 127.2, 117.8, 115.4, 114.1, 112.9, 95.6, 59.7, 58.6, 25.8, 15.2, 14.6, 11.7; *m/z* ESI^+ found 382.1764 $[M+H]^+$ calculated for $C_{21}H_{23}N_3O_4$ 382.1761.

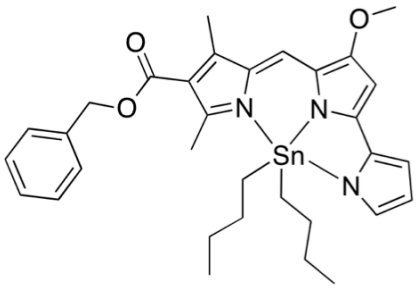
5.4.49 ($(Bu)_2$(**92**)Sn(IV) (**93**)



Dibutyltin oxide (13 mg, 0.052 mmol) was added to a solution of prodigiosene **92** (20 mg, 0.050 mmol) in methanol (10 mL). The resulting solution was stirred at 65 °C for 18 h and then concentrated *in vacuo*. The residue was dissolved in ethyl acetate and poured onto a saturated aqueous solution of sodium bicarbonate (20 mL) and then extracted with ethyl acetate (3 x 20 mL). The organic fractions were combined, dried with sodium sulfate, and the solvent removed *in vacuo* to give the crude product. Purification over neutral alumina using ethyl acetate:hexanes (5:95) as an eluent and removal of the solvent *in vacuo* gave **93** as a purple film (29 mg, 0.047 mmol, 95%). m.p. = 162-164 ˚C; δ_H (500 MHz, $CDCl_3$) 7.18 (1H, s), 6.99 (1H, d, *J=3.5*), 6.64 (1H, d, *J=3.5*), 6.13 (1H, s), 4.30 (2H, q, *J=7.5*), 4.00 (3H, s), 2.66 (3H, s), 2.50 (3H, s), 2.56 (3H, s), 1.66-1.49 (4H, m), 1.38 (3H, t, *J=7.5*), 1.12-0.97 (8H, m), 0.59 (6H, t, *J=7*); δ_C (125 MHz, $CDCl_3$) 189.6, 167.6, 165.8, 156.0, 153.9, 142.5, 139.6, 137.6, 135.3, 128.3, 120.0, 118.3, 117.5, 110.5, 93.0, 59.6, 58.6, 27.1, 25.8, 25.6, 23.9, 17.3, 14.7, 13.5, 12.3; δ_{Sn} (186 MHz, $CDCl_3$) -221.9; UV/Vis (DCM) λ_{max} (nm) (ε (mol L^{-1}·cm^{-1})): 568 (85 000). Fluorescence (DCM, 22 ˚C) λ_{max} (nm): 579, Φ_F: 0.57. *m/z* ESI^+ found 614.1993 $[M+H]^+$ calculated for $C_{29}H_{39}N_3O_4Sn$ 614.2035. A crystal suitable for X-ray crystallography was obtained from a slow evaporation of a solution of compound **93** in dichloromethane in the presence of few drops of methanol. Data for **93**: $C_{29}H_{38}N_3O_4Sn$, M = 611.34 g, dark-red needle, 0.42

x 0.23 x 0.12 mm^3, primitive triclinic, space group P-1 (#2), a = 12.1339 Å, b = 13.04640(10) Å, c = 19.65300(10) Å, V = 2903.79(3) $Å^3$, Z = 4, T = 200(1) K, ρ = 1.398 gcm^{-3}, μ(MoKα) = 9.167 cm^{-1}, 106009 reflections (22429 unique, R_{int} = 0.065), R = 0.0358, Rw = 0.0439, GOF = 1.082.

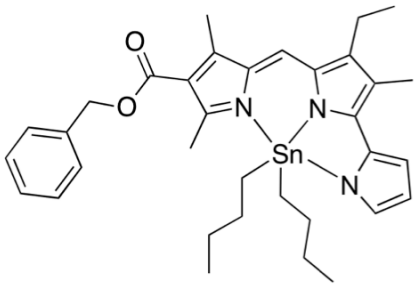
5.4.50 $(Bu)_2$(**94**)Sn(IV) (**95**)



Dibutyltin oxide (62 mg, 0.25 mmol) was added to a solution of prodigiosene **94** (40 mg, 0.1 mmol) in methanol (6 mL). The resulting solution was stirred at 65 °C for 18 h and then concentrated *in vacuo*. The residue was dissolved in dichloromethane (15 mL), washed with a saturated aqueous solution of sodium bicarbonate (2 x 15 mL), dried over sodium sulfate and concentrated *in vacuo*. Purification over basic alumina using dichloromethane as an eluent and removal of the solvent *in vacuo* gave **95** as a purple film (57 mg, 0.09 mmol, 90%). m.p. = 120-122 ˚C; δ_H (500 MHz, $CDCl_3$) 7.46-7.44 (2H, m) 7.40-7.37 (2H, m), 7.34-7.31 (1H, m), 6.95-6.94 (1H, m), 6.94 (1H, s), 6.83 (1H, dd, *J=1,3*), 6.43 (1H, dd, *J=2,3*), 6.13 (1H, s), 5.30 (2H, s), 4.00 (3H, s), 2.63 (3H, s), 2.45 (3H, s), 1.52-1.39 (8H, m), 1.22-1.18 (4H, m), 0.75 (6H, t, *J=8*); δ_C (125 MHz, $CDCl_3$) 168.6, 165.8, 157.4, 152.2, 137.3, 137.1, 133.4, 132.2, 132.2, 132.0, 129.6, 128.6, 128.2, 128.0, 115.3, 114.2, 113.7, 112.5, 65.4, 58.6, 27.0, 26.4, 24.0, 17.4, 13.6, 12.3; δ_{Sn} (186 MHz, $CDCl_3$) -209.5; UV/Vis (DCM) λ_{max} (nm) (ε ($mol\,L^{-1}\cdot cm^{-1}$)): 561(88 000).

Fluorescence (DCM, 22 ˚C) λ_{max} (nm): 584, Φ_F: 0.53. *m/z* ESI^+ found 634.2082 $[M+H]^+$ calculated for $C_{32}H_{40}N_3O_3Sn$ 634.2086.

5.4.51 $(Bu)_2$((*Z*)-Methyl 2-((4-ethyl-3-methyl-1*H*,1'*H*-2,2'-bipyrrol-5-yl)methylene)-3,5-dimethyl-2*H*-pyrrole-4-carboxylate)Sn(IV) (**96**)



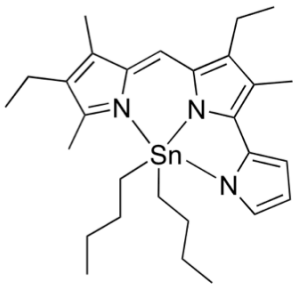
Triflic anhydride (0.23 mL, 1.4 mmol) was slowly added to a solution of **56** (340 mg, 0.93 mmol) in dichloromethane (25 mL). The reaction mixture was stirred at room temperature for 2 h and then poured onto a saturated aqueous solution of sodium bicarbonate (25 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (2 x 25 mL), and the combined organic layers were dried over sodium sulfate and concentrated *in vacuo*.

The crude solid was dissolved in dimethoxyethane (10 mL) and LiCl (0.12 g, 2.8 mmol), 1-*N*-Boc-pyrrole-2-boronic acid (0.30 g, 1.4 mmol), and $Pd(PPh_3)_4$ (0.11 mg, 0.009 mmol) were added. The resulting solution was purged by bubbling with nitrogen for 10 min then a solution of Na_2CO_3 (2 M, 1.86 mL, 3.7 mmol) was added, and the reaction mixture was stirred at 90 °C for 19 h. The crude reaction mixture was filtered through Celite and poured onto a saturated aqueous solution of sodium bicarbonate (25 mL). Extraction with ethyl acetate (3 x 20 mL), followed by washing of the combined organics with brine (20 mL), drying over anhydrous sodium sulfate and removal of the

solvent under reduced pressure gave the crude product. Purification using flash chromatography on basic alumina with a gradient of dichloromethane:hexane (40:60) as gave an orange film after removal of the solvent *in vacuo*.

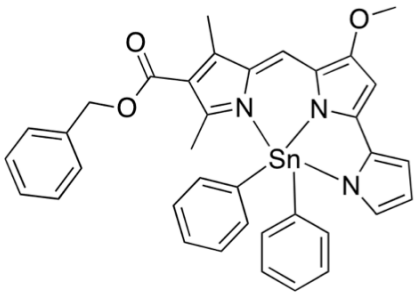
Dibutyltin oxide (231 mg, 0.93 mmol) was added to a solution of the orange film in methanol (10 mL). The resulting solution was stirred at 65 °C for 18 h and then concentrated *in vacuo*. The residue was dissolved in ethyl acetate and poured onto a saturated aqueous solution of sodium bicarbonate (20 mL) and extracted with ethyl acetate (3 x 20 mL). The organic fractions were combined, dried with sodium sulfate, and the solvent removed *in vacuo* to give the crude product. The residue was dissolved in dichloromethane and filtered through basic alumina eluting with dichloromethane and the solvent was removed *in vacuo*. Purification over basic alumina using dichloromethane:hexanes (1:1) as an eluent and removal of the solvent *in vacuo* gave **96** as a dark purple solid (36 mg, 0.056 mmol, 86%). m.p. = 91-93 ˚C; δ_H (500 MHz, $CDCl_3$) 7.47-7.45 (2H, m), 7.40-7.38 (2H, m), 7.35-7.32 (1H, m), 6.99 (1H, m), 6.93 (1H, dd, *J=2,3*), 6.83 (1H, s), 6.47 (1H, dd, *J=2,3*), 5.32 (2H, s), 2.74 (2H, q, *J=7*), 2.65 (3H, s), 2.48 (3H, s) 2.27 (3H, s), 1.49-1.41 (8H, m), 1.26-1.18 (7H, m), 0.75 (6H, t, *J=8*); δ_C (125 MHz, $CDCl_3$) 165.8, 157.2, 152.7, 144.6, 138.2, 137.8, 137.1, 134.2, 132.0, 131.8, 131.3, 128.6, 128.2, 128.0, 115.6, 115.5, 114.2, 113.0, 65.4, 27.0, 26.5, 23.9, 18.5, 17.4, 14.2, 13.6, 12.4, 9.9; δ_{Sn} (186 MHz, $CDCl_3$) -214.2; UV/Vis (DCM) λ_{max} (nm) ε (mol L^{-1}·cm^{-1})): 585 (87 000). Fluorescence (DCM, 22 ˚C) λ_{max} (nm): 607, Φ_F: 0.52. *m/z* ESI^+ found 645.2473 $[M+H]^+$ calculated for $C_{34}H_{44}N_3O_2Sn$ 645.2450.

5.4.52 $(Bu)_2$(**82**)Sn(IV) (**97**)



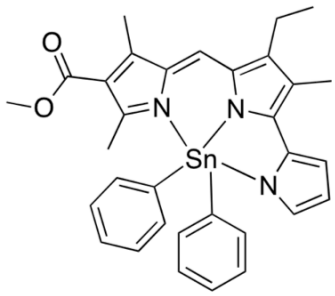
Dibutyltin oxide (45 mg, 0.18 mmol) was added to a solution of prodigiosene **82** in methanol (10 mL). The resulting solution was stirred at 65 °C for 18 h and then concentrated *in vacuo*. The residue was dissolved in ethyl acetate and poured onto a saturated aqueous solution of sodium bicarbonate (20 mL) and extracted with ethyl acetate (3 x 20 mL). The organic fractions were combined, dried with sodium sulfate, and the solvent removed *in vacuo* to give the crude product. Purification over basic alumina using an eluent gradient of hexanes:ethyl acetate (100:0 to 10:90) and removal of the solvent *in vacuo* gave **97** as a blue film (17 mg, 0.049 mmol, 22%). m.p. = 99-101 ˚C; δ_H (500 MHz, $CDCl_3$) 6.91-6.90 (1H, m), 6.79 (1H, dd, *J=1,3*) 6.75 (1H, s), 6.43 (1H, dd, *J=2,3*), 2.65 (2H, q, *J=7)*, 2.41 (2H, q, *J=7)*, 2.37 (3H, s), 2.26 (3H, s), 2.02 (3H, s), 1.49-1.38 (9H, m), 1.26-1.18 (9H, m), 1.07 (3H, t, *J=7)*, 0.78 (3H, t, *J=7*); δ_C (125 MHz, $CDCl_3$) 153.9, 150.3, 149.0, 135.1, 134.52, 134.50, 132.4, 129.7, 129.3, 121.2, 115.8, 112.7, 109.8, 27.1, 26.7, 23.3, 18.2, 17.9, 16.4, 15.2, 14.7, 13.6, 10.4, 10.0; δ_{Sn} (186 MHz, $CDCl_3$) -253.3; UV/Vis (DCM, 22 ˚C) λ_{max} (nm) (ε (mol $L^{-1}\cdot cm^{-1}$)): 599 (120 000). Fluorescence (DCM, 22 ˚C) λ_{max} (nm): 617, Φ_F: 0.28. *m/z* ESI^+ found 540.2354 $[M+H]^+$ calculated for $C_{28}H_{42}N_3Sn$ 540.2395.

5.4.53 $(Ph)_2$(**94**)Sn(IV) (**98**)



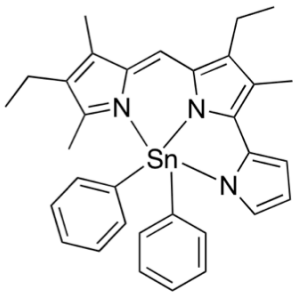
Diphenyltin oxide (54 mg, 0.22 mmol) was added to a solution of prodigiosene **94** (29 mg, 0.07 mmol) in methanol (5 mL) and dichloromethane (5 mL). The resulting solution was stirred at 65 °C for 18 h and then concentrated *in vacuo*. The residue was dissolved in ethyl acetate and poured onto a saturated aqueous solution of sodium bicarbonate (20 mL) and extracted with ethyl acetate (3 x 20 mL). The organic fractions were combined, dried with sodium sulfate, and the solvent removed *in vacuo* to give the crude product. Purification over basic alumina using dichloromethane as an eluent and removal of the solvent *in vacuo* gave **98** as a purple film (40 mg, 0.059 mmol, 82%). m.p. = 262 -264 ˚C; δ_H (500 MHz, $CDCl_3$) 7.61-7.59 (4H, m, tin satellites at 7.69-7.67 and 7.52-7.51, ^3J *(^{119}Sn-^1H) = 40*), 7.44-7.31 (12H, m), 7.12 (1H, s), 6.82 (1H, dd, *J=1,3*), 6.49 (1H, dd, *J=2,3*), 6.04 (1H, s), 5.29 (2H, s), 3.98 (3H, s), 2.58 (3H, s), 2.14 (3H, s); δ_C (125 MHz, $CDCl_3$) 168.9, 165.8, 157.1, 154.3, 141.0, 138.1, 137.4, 136.9, 135.4, 134.2, 133.5, 131.6, 130.1, 129.9, 129.2, 128.9, 128.8, 128.6, 128.3, 128.0, 127.4, 127.3, 115.9, 114.8, 113.7, 93.0, 65.5, 58.7, 18.1, 12.6. δ_{Sn} (186 MHz, $CDCl_3$) 367.1; UV/Vis (DCM) λ_{max} (nm) (ε (mol L^{-1}·cm^{-1})): 561 (74 000). Fluorescence (DCM, 22 ˚C) λ_{max} (nm): 583, Φ_F: 0.55. *m/z* ESI^+ found 674.1465 $[M+H]^+$ calculated for $C_{36}H_{32}N_3O_3Sn$ 674.1460.

5.4.54 $(Ph)_2$(**58**)Sn(IV) (**99**)



Diphenyltin oxide (49 mg, 0.17 mmol) was added to a solution of prodigiosene **94** (35 mg, 0.08 mmol) in methanol (6 mL) and dichloromethane (1 mL). The resulting solution was stirred at 65 °C for 18 h and then concentrated *in vacuo*. The residue was dissolved in ethyl acetate and poured onto a saturated aqueous solution of sodium bicarbonate (20 mL) and extracted with ethyl acetate (3 x 20 mL). The organic fractions were combined, dried with sodium sulfate, and the solvent removed *in vacuo* to give the crude product. Filtration through basic alumina eluting with dichloromethane, purification over basic alumina using dichloromethane:hexanes (1:1) as an eluent and removal of the solvent *in vacuo* gave **99** as a dark purple film (41 mg, 0.06 mmol, 75%). m.p. = 254-256 ˚C; δ_H (500 MHz, $CDCl_3$) 7.60-7.59 (4H, m, tin satellites at 7.69-7.67 and 7.52-7.51, *^3J (^{119}Sn-^{1}H) = 40*), 7.52-7.51 (1H, m), 7.36-7.31 (6H, m), 6.99 (1H, s), 6.92-6.91 (1H, m), 6.52 (1H, dd, *J=2,3*), 3.81 (3H, s), 2.68 (2H, q, *J=8*), 2.60 (3H, s), 2.27 (3H, s), 2.12 (3H, s), 1.19 (3H, t, *J=8*); δ_C (125 MHz, $CDCl_3$) 166.5, 156.9, 154.7, 145.0, 141.1, 138.7, 138.3, 135.4, 135.0, 133.3, 132.1, 131.0, 130.0, 129.2, 116.5, 115.6, 114.9, 113.9, 50.8, 18.5, 18.0, 14.1, 12.4, 9.9; ^{15}N HMBC δ_N ($CDCl_3$) -178.2, -217.9. δ_{Sn} (186 MHz, $CDCl_3$) 363.5; UV/Vis (DCM) λ_{max} (nm) ε (mol L^{-1}·cm^{-1})): 587 (86 000). Fluorescence (DCM, 22 ˚C) λ_{max} (nm): 609, Φ_F: 0.51. *m/z* ESI^+ found 610.1524 $[M+H]^+$ calculated for $C_{32}H_{32}N_3O_2Sn$ 610.1511.

5.4.55 $(Ph)_2$(**82**)Sn(IV) (**100**)



Diphenyltin oxide (38 mg, 0.13 mmol) was added to a solution of prodigiosene **82** (20 mg, 0.07 mmol) in methanol (5 mL) and dichloromethane (1 mL). The resulting solution was stirred at 65 °C for 18 h and then concentrated *in vacuo*. The residue was dissolved in ethyl acetate and poured onto a saturated aqueous solution of sodium bicarbonate (20 mL) and extracted with ethyl acetate (3 x 20 mL). The organic fractions were combined, dried with sodium sulfate, and the solvent removed *in vacuo* to give the crude product. Filtration through basic alumina eluting with dichloromethane, purification over basic alumina using dichloromethane:hexanes (1:5) as an eluent and removal of the solvent *in vacuo* gave **100** as a blue film (13 mg, 0.022 mmol, 33%). m.p. = 225-227 ˚C; δ_H (500 MHz, $CDCl_3$) 7.64-7.62 (4H, m, with tin satellites at 7.72-7.70 and 7.56-7.54 ^3J (^{119}Sn-^1H) = *40*), 7.40-7.31 (7H, m), 6.90 (1H, s), 6.77 (1H, dd, *J=1,3*), 6.47 (1H, dd, *J=2,3*), 2.66 (2H, q, *J=7*), 2.39 (2H, q, *J=7*), 2.32 (3H, s), 2.20 (3H, s), 1.79 (3H, s), 1.21 (3H, t, *J=7*), 1.05 (3H, t, *J=7*); δ_C (125 MHz, $CDCl_3$) 153.5, 152.7, 149.4, 141.8, 136.1, 135.8, 135.6, 134.8, 132.0, 131.0, 130.0, 129.7, 128.9, 121.7, 115.8, 113.4, 110.8, 18.3, 17.9, 16.3, 15.3, 15.2, 10.3 (1 CH_2 unresolved alkyl region); δ_{Sn} (186 MHz, $CDCl_3$) 363.0; UV/Vis (DCM) λ_{max} (nm) ε (mol L^{-1}·cm^{-1})): 603 (87 000). Fluorescence (DCM, 22 ˚C) λ_{max} (nm): 622, Φ_F: 0.32. *m/z* ESI^+ found 579.1694 $[M]^+$ calculated for $C_{32}H_{33}N_3Sn$ 579.1691.

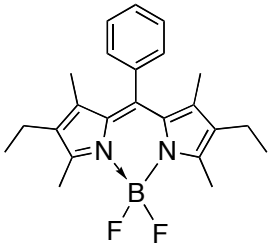
5.1.56 General procedure for the synthesis of BODIPY compounds (GP1)

A solution of dipyrrin HCl or HBr salt (250 mg) and triethylamine (6 eq) in CH_2Cl_2 (60 mL) was stirred under nitrogen at room temperature for 10 min. Boron trifluoride etherate (9 eq) was then added slowly over 5 min. The resulting solution was stirred for 2 h and then concentrated *in vacuo*. The residue was diluted with diethyl ether (50 mL), washed with 1 N HCl (3 x 100 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The resulting material was filtered through a pad of silica, eluting with dichloromethane and the solvent was removed *in vacuo*.

5.1.57 General procedure for the deprotection of BODIPY compounds (GP2)

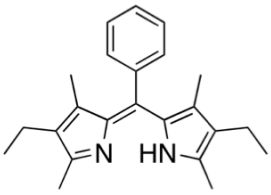
Potassium *tert*-butoxide (6 eq) and BODIPY (50 mg) were suspended in *tert*-butanol (15 mL) in a QXP vessel. The mixture was heated in the microwave for 40 min. (power = 600 W, ramp time = 2 min, ramp to temperature = 92 ˚C, hold time = 40 min, stirring = medium). The reaction mixture was allowed to cool to room temperature, diluted with diethyl ether (25 mL) and poured onto a saturated aqueous solution of sodium bicarbonate (75 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried over anhydrous sodium sulfate and the solvent was removed *in vacuo*.

5.4.58 1,3,5,7-Tetramethyl-2,6-diethyl-8-phenyl-4-bora-3a,4a-diaza-*s*-indacene (**104**)[148]



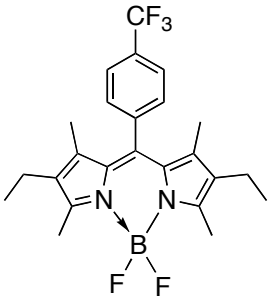
Synthesized from **105HBr** using the general *F*-BODIPY procedure (GP1) to give **104** as a bright orange solid (214 mg, 83%). m.p. = 172-173 ˚C (lit: not reported); δ_H (500 MHz, $CDCl_3$) 7.49-7.46 (m, 3H), 7.30-7.28 (m, 2H), 2.55 (s, 6H), 2.31 (q, J = 7, 4H), 1.29 (s, 6H), 0.99 (t, J = 7, 6H); δ_C (125 MHz, $CDCl_3$) 153.7, 140.3, 138.5, 135.9, 132.8, 130.9, 129.1, 128.8, 128.4, 17.2, 14.7, 12.6, 11.7. The ^{13}C NMR data matches (within 0.1 ppm) the reported data for the compound.[148] δ_B (160 MHz, $CDCl_3$) 0.65 (t, J_{BF} = 32); *m/z* ESI^+ found 403.2128 $[M+Na]^+$ calculated for $C_{23}H_{27}BF_2N_2Na$ 403.2133.

5.4.59 (*Z*)-3-ethyl-5-((4-ethyl-3,5-dimethyl-2H-pyrrol-2-ylidene)(phenyl)methyl)-2,4-dimethyl-1H-pyrrole (**105**)



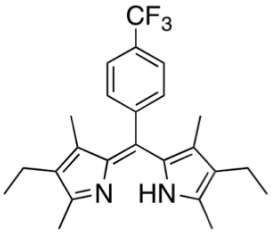
Synthesized from **104**[148] using the general deprotection procedure (GP2) to give **105** as a yellow-orange solid (44 mg, 91%). δ_H (500 MHz, $CDCl_3$) 7.42-7.41 (m, 3H), 7.32-7.30 (m, 2H), 2.33 (s, 6H), 2.28 (q, J = 7.5, 4H), 1.20 (s, 6H), 0.97 (t, J = 7.0, 6H); δ_C (125 MHz, $CDCl_3$) 150.3, 138.9, 137.9, 135.9, 135.1, 131.5, 129.8, 128.6, 128.2, 17.7, 15.0, 14.4, 11.9; *m/z* ESI^+ found 333.2320 $[M+H]^+$ calculated for $C_{23}H_{29}N_2$ 333.2325.

5.4.60 2,6-Diethyl-8-(4-trifluoromethylphenyl)-1,3,5,7-tetramethyl-4-bora-3a,4a-diaza-*s*-indacene (**106**)



Synthesized from **107HBr** using the general *F*-BODIPY procedure (GP1) to give **106** as a bright orange solid (215 mg, 84%). m.p. = 193-194 ˚C; δ_H (500 MHz, $CDCl_3$) 7.77 (d, *J* =7.5, 2H), 7.46 (d, *J* = 7.5, 2H), 2.54 (s, 6H), 2.30 (q, *J* = 7.5, 4H), 1.25 (s, 6H), 0.98 (t, *J* = 7.5, 6H); δ_C (125 MHz, $CDCl_3$) 154.6, 139.9, 138.1, 133.4, 131.4 (q, J_{CF} = *32.5*), 130.5, 129.2, 126.1 (q, J_{CF} = 4.0), 125.1, 123.0, 17.2, 14.7, 12.7, 12.0; δ_B (160 MHz, $CDCl_3$) 0.65 (t, J_{BF} = 32); *m/z* ESI^+ found 471.2001 $[M+Na]^+$ calculated for $C_{24}H_{26}BF_5N_2$ 471.2007.

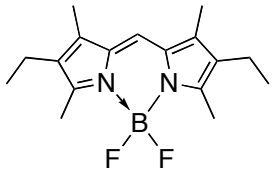
5.4.61 (*Z*)-3-Ethyl-5-((4-ethyl-3,5-dimethyl-2*H*-pyrrol-2-ylidene)(4-(trifluoromethyl)phenyl)methyl)-2,4-dimethyl-1*H*-pyrrole (**107**)



Synthesized from **106** using the general deprotection procedure (GP2). The crude product was dissolved in pentane, filtered through basic alumina eluting with ethyl acetate:pentane (2:98), and concentrated *in vacuo* to give **105** as an orange solid (40 mg, 90%). δ_H (500 MHz, $CDCl_3$) 7.65 (d, *J* = 8.0, 2H), 7.42 (d, *J* = 8.0, 2H), 2.28 (s, 6H), 2.23 (q, *J* = 7.5, 4H), 1.11 (s, 6H), 0.93 (t, *J* = 7.5, 6H); δ_C (125 MHz, $CDCl_3$) 150.9,

142.86, 135.8, 135.5, 134.4, 131.9, 130.4, 125.5 (q, J_{CF} = 4.0), 125.4, 123.3, 17.7, 15.0, 14.6, 12.1; *m/z* ESI$^+$ found 401.2199 $[M+H]^+$ calculated for $C_{24}H_{28}F_3N_2$ 401.2205.

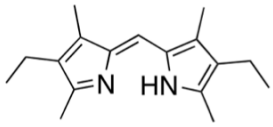
5.4.62 2,6-Diethyl-1,3,5,7-tetramethyl-8*H*-4-bora-3a,4a-diaza-*s*-indacene (**108**)[116, 192]



Synthesized from **109HBr**[149] using the general *F*-BODIPY procedure (GP1) to give **108** as a bright orange solid (201 mg, 89%). m.p. = 176-178 ˚C (lit: 187-188 ˚C);[149] δ_H (500 MHz, $CDCl_3$) 6.94 (s, 1H), 2.50 (s, 6H), 2.37 (q, *J* = 7.5, 4H), 2.15 (s, 6H), 1.06 (t, *J* = 8, 6H); δ_C (125 MHz, $CDCl_3$) 154.7, 136.7, 132.5, 131.7, 118.7, 17.4, 14.7, 12.6, 9.4; δ_B (160 MHz, $CDCl_3$) 0.76 (t, J_{BF} = 32); *m/z* ESI$^+$ found 327.1815 $[M+Na]^+$ calculated for $C_{17}H_{23}BF_2N_2$ 327.1820.

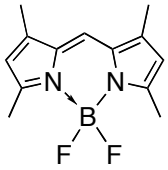
Compound **108** was also synthesized on large scale according to the following procedure. A solution of dipyrrin HBr salt[183] (5 g) and triethylamine (10 eq) in CH_2Cl_2 (120 mL) was stirred under N_2 at room temperature for 10 min. Boron trifluoride etherate (15 eq) was then added slowly over 5 min. The resulting solution was stirred for 2 h and then concentrated *in vacuo*. The residue was diluted with diethyl ether (200 mL), washed with 1 N HCl (3 x 200 mL), dried over anhydrous sodium sulfate, filtered and the filtrate evaporated to dryness. The resulting material was filtered through a pad of silica eluting with dichloromethane and the solvent was removed *in vacuo* to give **108** as a bright orange solid (4.10 g, 91%).

5.4.63 (*Z*)-3-Ethyl-5-((4-ethyl-3,5-dimethyl-2*H*-pyrrol-2-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrole (**109**)



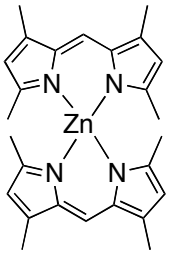
Synthesized from **108** or **123** using the general deprotection procedure (GP2). The crude product was dissolved in pentane, filtered through basic alumina eluting with ethylacetate:pentane (6:94), and concentrated *in vacuo* to give an orange solid (40 mg, 96% (starting from **108**); 26 mg, 75% (starting from **123**)). δ_H (500 MHz, $CDCl_3$) 9.51 (bs, 1H), 6.64 (s, 1H), 2.37 (q, J = 7.5, 4H), 2.30 (s, 6H), 2.13 (s, 6H), 1.06 (t, J = 7.5, 6H); δ_C (125 MHz, $CDCl_3$) 151.3, 136.8, 133.3, 130.0, 115.4, 17.9, 15.0, 14.5, 9.6; *m/z* ESI^+ found 257.2003 $[M+H]^+$ calculated for $C_{17}H_{25}N_2$ 257.2012.

5.4.64 1,3,5,7-Tetramethyl-8*H*-4-bora-3a,4a-diaza-*s*-indacene (**110**)[116]



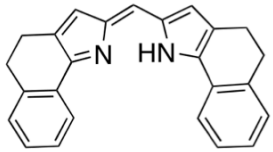
Synthesized from **111HBr**[181] using the general *F*-BODIPY procedure (GP1) to give a bright orange solid (208 mg, 94%). m.p. = 202-203 ˚C (lit: not reported); δ_H (500 MHz, $CDCl_3$) 7.04 (s, 1H), 6.05 (s, 2H), 2.53 (s, 6H), 2.25 (s, 6H); δ_C (125 MHz, $CDCl_3$) 156.9, 141.3, 133.5, 120.2, 119.2, 14.8, 11.4; δ_B (160 MHz, $CDCl_3$) 0.76 (t, J_{BF} = 32); *m/z* ESI^+ found 271.1189 $[M+Na]^+$ calculated for $C_{13}H_{15}BF_2N_2$ 271.1194.

5.4.65 Zinc[k^2-(3,3′,5,5′-tetramethyl-meso-*H*-dipyrrinato)] **(111Zn)**[149]



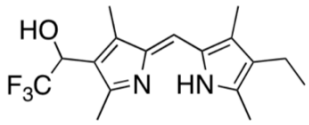
CAUTION! **111** is a powerful sternutator and must be handled only under adequate ventilation.[193] For this reason, **111** was converted *in situ* to its zinc(II) complex **111Zn**. *F*-BODIPY **110** (50 mg, 0.20 mmol) and potassium *tert*-butoxide (135 mg, 1.2 mmol) and were suspended in *tert*-butanol (15 mL) in a QXP vessel. The mixture was heated in the microwave for 40 min. (Power = 600 W, ramp time = 2 min, ramp to temperature = 92 ˚C, hold time = 40 min, stirring = medium). The reaction mixture was allowed to cool to room temperature, and zinc acetate dihydrate (398 mg, 1.81 mmol) was added and the reaction mixture was allowed to stir for 30 min. The mixture was diluted with diethyl ether (25 mL) and poured onto a saturated aqueous solution of sodium bicarbonate (75 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried over anhydrous sodium sulfate and the solvent was removed *in vacuo*. The crude product was dissolved in pentane, filtered through basic alumina eluting with ethyl acetate:pentane (6:94), and concentrated *in vacuo* to give **111Zn** as an orange solid (88 mg, 96%). δ_H (500 MHz, $CDCl_3$) 7.03 (s, 1H), 5.99 (s, 2H), 2.32 (s, 6H), 1.96 (s, 6H); δ_C (125 MHz, $CDCl_3$) 157.8, 142.0, 136.6, 121.9, 116.8, 16.5, 11.9. The ^{13}C NMR data corresponds (within 0.1 ppm) to that previously reported for the compound.[149] *m/z* ESI^+ found 462.1756 $[M+H]^+$ calculated for $C_{26}H_{30}N_4Zn$ 462.1762.

5.4.66 (*Z*)-2-((4,5-Dihydro-1*H*-benzo[*g*]indol-2-yl)methylene)-4,5-dihydro-2*H*-benzo[*g*] indole **(113)**



Synthesized from **112**[116] using the general deprotection procedure (GP2). The crude material was dissolved in hexane, filtered through basic alumina eluting with hexane:ethyl acetate (91:9), and concentrated *in vacuo* to give a purple solid (22 mg, 51%). δ_H (500 MHz, $CDCl_3$) 9.68 (bs, 1H), 7.85 (d, J = 7.5, 2H), 7.41-7.37 (m, 2H), 7.28-7.27 (m, 4H), 6.75 (s, 1H), 6.64 (s, 2H), 2.98 (t, J = 7.5, 4H), 2.84 (t, J = 7.5, 4H); δ_C (125 MHz, $CDCl_3$) 150.8, 141.8, 138.7, 130.0, 129.7, 128.7, 128.5, 127.1, 123.6, 122.8, 122.2, 29.8, 22.2; *m/z* ESI^+ found 349.1699 $[M+H]^+$ calculated for $C_{25}H_{21}N_2$ 349.1705.

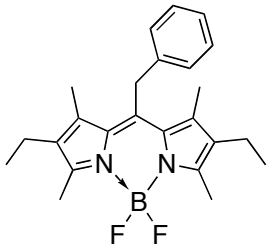
5.4.67 (*Z*)-1-(2-((4-Ethyl-3,5-dimethyl-1*H*-pyrrol-2-yl)methylene)-3,5-dimethyl-2*H*-pyrrol-4-yl)-2,2,2-trifluoroethanol (**115**)



Synthesized from **114**[182] using the general deprotection procedure (GP2). The crude material was dissolved in hexane, filtered through basic alumina eluting with ethyl acetate:hexane (1:1), and concentrated *in vacuo* to give a yellow solid (41 mg, 93%). δ_H (500 MHz, $CDCl_3$) 6.66 (s, 1H), 5.30 (bs, 1H), 4.98 (q, J = 7.0, 1H), 2.36 (q, J = 7.5, 2H), 2.35 (s, 3H), 2.31 (s, 3H), 2.22 (s, 3H), 2.12 (s, 3H), 1.06 (t, J = 7.5, 3H); δ_H (125 MHz, $CDCl_3$) 164.0, 141.8, 138.0, 134.9, 130.6, 126.4, 124.2, 116.1, 115.5, 67.6 (q, J_{CF} =*34*), 29.9, 18.1, 16.0, 14.6, 13.9, 10.0, 9.7; *m/z* ESI^+ found 327.1687 $[M+H]^+$ calculated

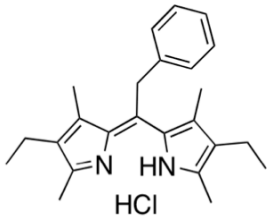
for $C_{17}H_{22}OF_3N_2$ 327.1684.

5.4.68 8-Benzyl-2,6-diethyl-1,3,5,7-tetramethyl-4-bora-3a,4a-diaza-*s*-indacene (**116**)



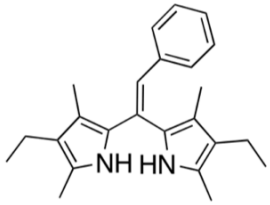
Synthesized from **117HCl**[111] using the general *F*-BODIPY procedure (GP1) to give **116** as a bright orange solid (219 mg, 85%). m.p. = 246-248 ˚C; δ_H (500 MHz, $CDCl_3$) 7.31-7.20 (m, 5H), 4.39 (s, 2H), 2.55 (s, 6H), 2.35 (q, J = 7.5, 4H), 2.07 (s, 6H), 1.02 (t, J = 7.5, 6H); δ_C (125 MHz, $CDCl_3$) 153.0, 139.2, 137.2, 136.7, 132.7, 132.2, 129.0, 127.9, 126.6, 34.0, 17.2, 14.9, 13.1, 12.6; δ_B (160 MHz, $CDCl_3$) 0.65 (t, J_{BF} = 32); *m/z* ESI^+ found 417.2284 $[M+Na]^+$ calculated for $C_{24}H_{29}BF_2N_2$ 417.2290.

5.4.69 (*Z*)-3-Ethyl-5-(1-(4-ethyl-3,5-dimethyl-2*H*-pyrrol-2-ylidene)-2-phenylethyl)-2,4-dimethyl-1*H*-pyrrole hydrochloride (**117**)



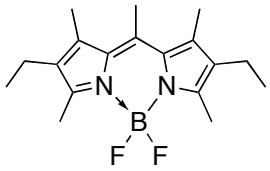
F-BODIPY **116** (50 mg, 0.13 mmol) and potassium *tert*-butoxide (85 mg, 0.76 mmol) were suspended in *tert*-butanol (15 mL) in a QXP vessel. The mixture was heated in the microwave for 40 min. (Power = 600 W, ramp time = 2 min, ramp to temperature = 92 ˚C, hold time = 40 min, stirring = medium). The reaction mixture was allowed to cool to room temperature, diluted with diethyl ether (25 mL) and poured onto a 1 M HCl solution (75 mL). The layers were separated and the aqueous layer was extracted with

diethyl ether (3 x 20 mL). The combined organic fractions were dried over anhydrous sodium sulfate and the solvent was removed *in vacuo* to give **117** as an orange solid (43 mg, 88%). δ_H (500 MHz, $CDCl_3$) 12.2 (bs, 2H), 7.15 (d, J = 7.5, 2H), 7.07 (t, J = 7.5, 2H), 7.00 (t, J = 7.5, 1H), 4.66 (s, 2H), 2.38 (s, 6H), 2.33 (q, J = 7.5, 4H), 2.0 (s, 6H), 1.02 (t, J = 7.5, 6H); δ_C (125 MHz, $CDCl_3$) 150.0, 147.7, 138.6, 137.3, 132.3, 131.3, 128.8, 128.2, 126.0, 40.0, 17.6, 14.5, 12.4, 12.2; *m/z* ESI^+ found 347.2482 $[M+H]^+$ calculated for $C_{24}H_{31}N_2$ 347.2487. The ^{13}C and ^1H NMR spectrum show that residual *t*BuOH is present. Attempts to remove the *t*BuOH resulted in the formation of the vinylic bipyrrole **120** (as shown below). δ_H (500 MHz, $CDCl_3$) 7.61 (bs, 1H), 7.40 (bs, 1H), 7.19-7.00 (m, 5H), 6.45 (s, 1H), 2.48-2.34 (m, 4H), 2.18 (s, 3H), 2.16 (s, 3H), 2.04 (s, 3H), 1.60 (s, 3H), 1.11 (t, *J=7.5*, 3H), 1.06 (t *J=7.5*, 3H).



120

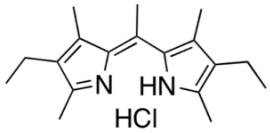
5.4.70 2,6-Diethyl-1,3,5,7,8-pentamethyl-4-bora-3a,4a-diaza-*s*-indacene (**118**)



Synthesized from **119HCl**[111] using the general *F*-BODIPY procedure (GP1) to give **118** as a bright orange solid (231 mg, 89%). m.p. = 209-211 ˚C; δ_H (500 MHz, $CDCl_3$) 2.56 (s, 3H), 2.45 (s, 6H), 2.35 (q, J = 7.5, 4H), 2.29 (s, 6H), 1.00 (t, J = 7.5, 6H); δ_C (125

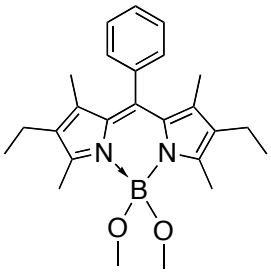
MHz, $CDCl_3$) 152.0, 139.9, 136.5, 132.6, 131.9, 17.4, 17.2, 15.1, 14.6, 12.6; δ_B (160 MHz, $CDCl_3$) 0.46 (t, *J* = 32); *m/z* ESI^+ found 341.1971 $[M+Na]^+$ calculated for $C_{18}H_{25}BF_2N_2Na$ 341.1977.

5.4.71 (*Z*)-3-Ethyl-5-(1-(4-ethyl-3,5-dimethyl-2*H*-pyrrol-2-ylidene)-2-methyl)-2,4-dimethyl-1*H*-pyrrole hydrochloride (**119**)



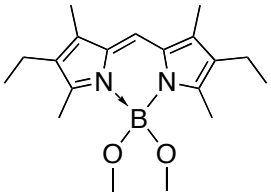
BODIPY **118** (50 mg, 0.16 mmol) and potassium *tert*-butoxide (106 mg, 0.94 mmol) were suspended in *tert*-butanol (15mL) in a QXP vessel. The mixture was heated in the microwave for 40 min. (Power = 600 W, ramp time = 2 min, ramp to temperature = 92 ˚C, hold time = 40 min, stirring = medium). The reaction mixture was allowed to cool to room temperature, diluted with diethyl ether (25 mL) and poured onto a 1 M HCl solution (75 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried over anhydrous sodium sulfate and the solvent was removed *in vacuo* to give **119** as an orange solid (41 mg, 85%). δ_H (500 MHz, $CDCl_3$) 12.40 (bs, 2H), 2.78 (s, 3H), 2.49 (s, 6H), 2.37 (q, *J* = 7.5, 4H), 2.05 (s, 6H), 1.04 (t, *J* = 7.5, 6H); δ_C (125 MHz, $CDCl_3$) 149.1, 146.9, 136.9, 132.0, 131.5, 24.0, 17.6, 14.6, 12.43, 12.40; *m/z* ESI^+ found 271.2169 $[M+H]^+$ calculated for $C_{18}H_{28}N_2$ 271.2174.

5.4.72 2,6-Diethyl-4,4'-dimethoxy-1,3,5,7-tetramethyl-8-phenyl-4-bora-3a,4a-diaza-*s*-indacene (**121**)



Compound **121** was synthesized using a modified literature procedure.[143] Sodium methoxide (46 mg, 0.81 mmol) was added to a solution of **104** (50 mg, 0.13 mmol) in methanol (5 mL) and the reaction mixture was stirred at reflux temperature for 18 h. The reaction mixture was then poured into water (20 mL) and extracted with ethyl acetate (20 mL). The organic layer was washed with water (2 x 20 mL) and the combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to give **121** as an orange crystalline solid (52 mg, 100%). m.p. = 149-151 ˚C; δ_H (500 MHz, $CDCl_3$) 7.48-7.45 (3H, m), 7.32-7.28 (2H, m), 2.94 (6H, s), 2.53 (6H, s), 2.32 (4H, q, J = 7.5), 1.29 (6H, s), 1.00 (6H, t, J = 7.5); δ_C (125 MHz, $CDCl_3$) 154.0, 140.1, 136.6, 136.3, 132.3, 128.9 (2C), 128.6, 128.5, 49.2, 17.2, 14.8, 12.3, 11.8; δ_B (160 MHz, $CDCl_3$) 2.46 (s); *m/z* ESI^+ found 427.2527 $[M+Na]^+$ calculated for $C_{25}H_{33}BN_2O_2Na$ 427.2533.

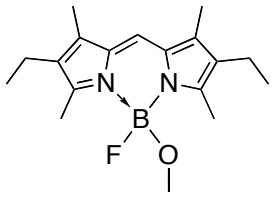
5.4.73 2,6-Diethyl-4,4'-dimethoxy-1,3,5,7-tetramethyl-8*H*-4-bora-3a,4a-diaza-*s*-indacene (**122**)



Compound **122** was synthesized using a modified literature procedure.[143] Sodium methoxide (145 mg, 2.68 mmol) was added to a solution of **108** (129 mg, 0.42 mmol) in

methanol (10 mL) and the reaction mixture was stirred at reflux temperature for 18 h. The reaction mixture was then poured into water (20 mL) and extracted with ethyl acetate (20 mL). The organic layer was washed with water (2 x 20 mL) and the combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to give **122** as an orange crystalline solid (130 mg, 98%). m.p. = 138-140 ˚C; δ_H (500 MHz, $CDCl_3$) 6.90 (s, 1H), 2.84 (s, 6H), 2.47 (s, 6H), 2.38 (q, *J* = 7.5, 4H), 2.17 (s, 6H), 1.06 (t, *J* = 7.5, 6H); δ_C (125 MHz, $CDCl_3$) 154.9, 134.6, 133.8, 131.2, 118.4, 49.3, 17.5, 14.9, 12.3, 9.5; δ_B (160 MHz, $CDCl_3$) 2.66 (s); *m/z* ESI^+ found 351.2214 $[M+Na]^+$ calculated for $C_{19}H_{29}BN_2O_2Na$ 351.2220.

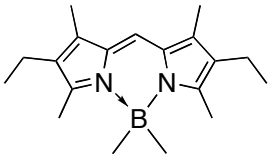
5.4.74 2,6-Diethyl-4-fluoro-4-methoxy-1,3,5,7-tetramethyl-8*H*-4-bora-3a,4a-diaza-*s*-indacene (**123**)



Compound **123** was synthesized using a modified literature procedure.[143] Sodium methoxide (18 mg, 0.33 mmol) was added to a solution of **108** (100 mg, 0.33 mmol) in methanol (10 mL) and the reaction mixture was stirred at reflux temperature for 18 h. The reaction mixture was then poured into water (20 mL) and extracted with ethyl acetate (20 mL). The organic layer was washed with water (2 x 20 mL) and the combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. Purification over silica gel eluting with a gradient of ethyl acetate:hexanes (10:90 to 70:30) and removal of the solvent *in vacuo* gave **123** as an orange crystalline solid (51 mg, 49%). m.p. = 184-185 ˚C; δ_H (500 MHz, $CDCl_3$) 6.92 (s, 1H), 2.88 (s, 3H), 2.48 (s, 6H), 2.37 (q, *J* = 7.5, 4H), 2.16 (s, 6H), 1.05 (t, *J* = 7.5, 6H); δ_C (125 MHz, $CDCl_3$) 154.8, 135.8,

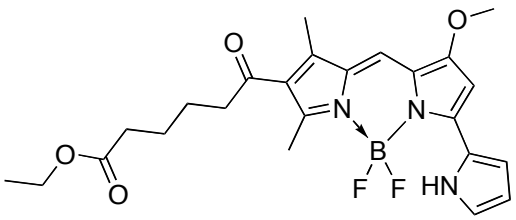
133.2, 131.5, 118.6, 49.3 (d, *J=6.3*), 17.5, 14.8, 12.5, 9.5; δ_B (160 MHz, $CDCl_3$) 1.86 (d, *J* = 25); *m/z* ESI^+ found 339.2014 $[M+Na]^+$ calculated for $C_{18}H_{26}BFN_2ONa$ 339.2020.

5.4.75 2,6-Diethyl-1,3,4,4'-5,7-hexamethyl-8*H*-4-bora-3a,4a-diaza-*s*-indacene (**124**)



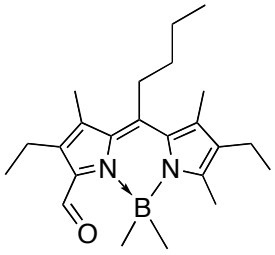
Compound **124** was synthesized using a modified literature procedure.[128] Methyl magnesium bromide (1.30 mL, 3.0 M, 3.9 mmol) was added to a solution of **104** (250 mg, 0.82 mmol) in anhydrous diethyl ether (25 mL) and the reaction mixture was stirred at reflux temperature for 3 h. The reaction mixture was then poured into water (50 mL) and the layers were separated. The aqueous layer was extracted with diethyl ether (3 x 20 mL) and the combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. Purification over silica gel eluting with ethyl acetate:hexanes (17:83) and removal of the solvent *in vacuo* gave **124** as a red crystalline solid (240 mg, 98%). m.p. = 100-102 ˚C; δ_H (500 MHz, $CDCl_3$) 7.00 (s, 1H), 2.43 (s, 6H), 2.40 (q, *J=7.5*, 4H), 2.18 (s, 6H), 1.07 (t, *J=7.5*, 6H), 0.20 (s, 6H); δ_C (125 MHz, $CDCl_3$) 151.6, 132.3, 131.2, 130.7, 119.2, 17.8, 14.9, 14.2, 9.3 (1 CH_3 missing (B*CH*$_3$)); δ_B (160 MHz, $CDCl_3$) -0.54 (s); *m/z* ESI^+ found 319.2316 $[M+Na]^+$ calculated for $C_{19}H_{29}BN_2Na$ 319.2321.

5.4.76 (**125**)BF_2 (**126**)



Triethylamine (0.09 mL, 0.66 mmol) was added to a solution of **125**[29] (48 mg, 0.11 mmol) in dry dichloromethane, under a nitrogen atmosphere and the resulting reaction mixture was stirred for 10 min. BF_3•OEt_2 (0.10 mL, 0.99 mmol) was added slowly and the resulting mixture was stirred at room temperature for 18 h. The reaction mixture was poured into an aqueous 1 M solution of HCl (20 mL) and extracted with dichloromethane (20 mL). The organic layer was washed with an aqueous 1 M solution of HCl (3 x 20 mL), dried over sodium sulfate and concentrated *in vacuo.* Purification over silica gel eluting with a solvent gradient of ethyl acetate:hexanes (1:1 to 4:1) and removal of the solvent *in vacuo* gave **126** as a purple, crystalline solid (32 mg, 0.07 mmol, 60%). m.p. = 169-170 ˚C; δ_H (500 MHz, $CDCl_3$) 10.49 (1H, bs), 7.20-7.18 (1H, m), 7.15 (1H, s), 6.99-6.97 (1H, m), 6.39-6.37 (1H, m), 6.13 (1H, s), 4.13 (2H, q, *J*=7), 3.98 (3H, s), 2.78 (3H, s), 2.76 (2H, t, *J*=7) 2.41 (3H, s), 2.31 (2H, t, *J*=7), 1.72- 1.65 (4H, m), 1.25 (3H, t, *J*=7); δ_C (125 MHz, $CDCl_3$) 197.6, 173.7, 164.3, 151.8, 151.6, 133.8, 129.7, 129.4, 127.3, 126.6, 123.4, 118.9, 114.8, 111.8, 97.3, 60.4, 58.8, 42.8, 34.4, 24.9, 23.8, 15.2, 14.4, 12.6; δ_B (160 MHz, $CDCl_3$) 1.22 (t, J_{BF}=31); UV/Vis (DCM, 22 ˚C) λ_{max} (nm) (ε (mol L^{-1}·cm^{-1})): 546 (100 000). *m/z* ESI^+ found 494.2011 $[M+Na]^+$ calculated for $C_{24}H_{28}BF_2N_3NaO_4$ 494.2033.

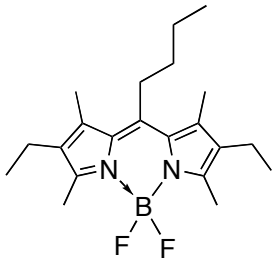
5.4.77 2,6-Diethyl-1,3,5,7-tetramethyl-8*H*-4-bora-3a,4a-diaza-*s*-indacene (**129**)



n-Butyllithium (0.51 mL of a 0.95 M solution in hexanes, 0.48 mmol) was slowly added

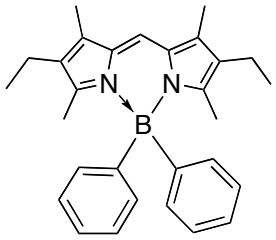
under a nitrogen atmosphere to a round-bottom flask containing a solution of **124** (109 mg, 0.29 mmol) in tetrahydrofuran (15 mL) at -78 ˚C. The solution was allowed to stir while slowly warming to room temperature over 3 h. At room temperature, a 0.1 M aqueous solution of HCl (7 mL) was added dropwise and the mixture was stirred for 5 min. 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone (658 mg, 4.8 mmol) was then added and the reaction mixture was stirred for 6 h at room temperature. The reaction mixture was diluted with dichloromethane (75 mL) and water (150 mL). The layers were separated and the organic layer was washed with water (3 x 150 mL). The combined organic layers were dried over anhydrous sodium sulfate and the solvent was removed *in vacuo*. Purification over silica gel eluting with a slow gradient of dichloromethane:hexanes (40:60 to 60:40) and removal of the solvent *in vacuo* gave **129** as a bright orange solid (58 mg, 0.13 mmol, 45%). δ_H (500 MHz, $CDCl_3$) 10.41 (s, 1H), 3.13-3.15 (m, 2H), 2.86-2.82 (m, 2H), 2.49 (s, 3H), 2.43 (q, *J = 7.5*, 2H), 2.41 (s, 3H), 2.36 (s, 3H) 1.75-1.54 (m, 4H), 1.12 (t, *J = 7.5*, 3H), 1.08 (t, *J = 7.5,* 3H), 1.02 (t, *J = 7.5*, 3H), 0.34 (s, 6H); δ_C (125 MHz, $CDCl_3$) 186.1, 159.2, 146.6, 137.33, 137.26, 137.1, 136.6, 134.8, 131.3, 127.2, 33.9, 28.8, 23.3, 18.1, 17.5, 15.2, 14.9, 14.3, 14.2, 13.9, 12.3 (1 signal missing (B*CH₃*)); δ_B (160 MHz, $CDCl_3$) -1.47 (broad s); m/z ESI+ found 367.2929 $[M+H]^+$ calculated for $C_{23}H_{36}BN_2O$ 367.2915.

5.4.78 8-Butyl-2,6-diethyl-1,3,5,7-tetramethyl-4-bora-3a,4a-diaza-*s*-indacene (**130**)



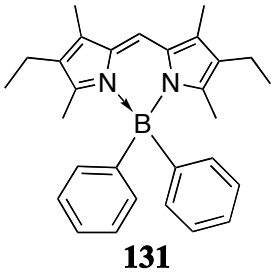
n-Butyllithium (1.06 mL of a 0.95 M solution in hexanes, 1.1 mmol) was slowly added under a nitrogen atmosphere to a round-bottom flask containing a solution of **108** (100 mg, 0.33 mmol) in tetrahydrofuran (15 mL) at -78 ˚C (dry ice/acetone bath). The solution was allowed to stir while slowly warming to room temperature. At room temperature, a 0.1 M aqueous solution of HCl (5mL) was added dropwise and the mixture was stirred for 5 min. 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone (749 mg, 3.3 mmol) was then added and the reaction mixture was allowed to stir for 18 h at room temperature.The reaction mixture was diluted with dichloromethane (75 mL) and water (150 mL). The layers were separated and the organic layer was washed with water (3 x 150 mL). The combined organics were dried over anhydrous sodium sulfate and the solvent was removed *in vacuo*. Purification over silica gel eluting with a slow gradient of dichloromethane:hexanes (20:80 to 60:40) and removal of the solvent *in vacuo* gave **130** as a bright orange solid (72 mg, 0.20 mmol, 61%). m.p. = 159-161 ˚C; δ_H (500 MHz, $CDCl_3$) 2.99-2.96 (m, 2H), 2.50 (s, 6H), 2.41 (q, J = 7.5, 4H), 2.33 (s, 6H), 1.66-1.59 (m, 2H), 1.53 (sextet, J = 7.5, 2H), 1.05 (t, J = 7.5, 6H), 1.00 (t, J = 7.5, 3H); δ_C (125 MHz, $CDCl_3$) 152.0, 145.2, 135.8, 132.6, 131.0, 33.8, 28.3, 23.5, 17.3, 15.0, 13.9, 13.4, 12.5; δ_B (160 MHz, $CDCl_3$) 0.46 (t, J = 32); *m/z* ESI^+ found 383.2441 $[M+Na]^+$ calculated for $C_{21}H_{31}BF_2N_2Na$ 383.2446 .

5.4.79 2,6-Diethyl-1,3,5,7-tetramethyl-4,4′-diphenyl-8*H*-4-bora-3a,4a-diaza-*s*-indacene (**131**)

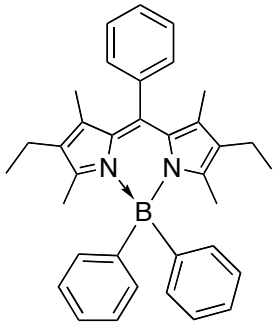


Phenyl lithium (1.83 mL of a 1.8 M solution in di-*n*-butyl ether, 3.3 mmol) was slowly added under a nitrogen atmosphere to a round-bottom flask containing a solution of **108** (100 mg, 0.33 mmol) in tetrahydrofuran (15 mL) at -45 ˚C. The solution was stirred for 30 min and then the cooling bath was removed and the mixture was stirred at room temperature 1 h. A 0.1 M aqueous solution of HCl (5 mL) was added dropwise and the reaction mixture was allowed to stir for 5 min. 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone (749 mg, 10 mmol) was added and the reaction mixture was allowed to stir for 1 h at room temperature. The reaction mixture was filtered through a pad of neutral alumina, dried over sodium sulfate, and concentrated *in vacuo* to give a brown oil. Purification over silica gel eluting with ethyl acetate:hexanes (7:93) and removal of the solvent *in vacuo* gave **131** as a bright orange solid (31 mg, 0.08 mmol, 22%). m.p. = 241-242 ˚C; δ_H (500 MHz, $CDCl_3$) 7.29-7.16 (m, 10H), 2.32 (q, *J = 7.5*, 4H), 2.21 (s, 6H), 1.75 (s, 6H), 0.98 (t, *J = 7.5*, 6H); δ_C (125 MHz, $CDCl_3$) 154.0, 134.1, 133.9, 133.8, 132.3, 131.6, 127.3, 125.7, 119.5, 17.7, 14.9, 14.4, 9.5; δ_B (160 MHz, $CDCl_3$) 0.18 (t, *J=32*); *m/z* ESI^+ found 459.2368 $[M+K]^+$ calculated for $C_{21}H_{31}BF_2N_2K$ 459.2374.

5.4.80 2,6-Diethyl-1,3,5,7-tetramethyl-4,4'-diphenyl-8*H*-4-bora-3a,4a-diaza-*s*-indacene (**131**) and 2,6-diethyl-1,3,5,7-tetramethyl-4,4',8-triphenyl-4-bora-3a,4a-diaza-*s*-indacene (**132**)



131

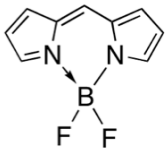


132

Phenyl lithium (4.6 mL of a 1.8 M solution in di-*n*-butyl ether, 8.2 mmol) was slowly added under a nitrogen atmosphere to a round-bottom flask containing a solution of **108** (250 mg, 0.82 mmol) in diethyl ether (15 mL) at 25 ˚C. The solution was stirred at room temperature for 18 h. Methanol (5 mL) was added dropwise and the reaction mixture was concentrated *in vacuo* to give an orange oil. Purification over silica gel eluting with ethyl acetate:hexanes (4:96) and removal of the solvent *in vacuo* gave a mixture of **131** and **132** as an orange solid (**131**: 28 mg, 0.06 mmol, 7%, and **132**: 142 mg, 0.24 mmol, 29%). δ_H (500 MHz, $CDCl_3$) 7.49-7.47 (m, 3H, **132**), 7.42-7.40 (m, 4H, **132**), 7.36-7.34 (m, 2H, **132**), 7.30-7.16 (m, 8.5H, **131** and **132**), 7.13 (s, 0.20H, **131**), 2.33 (q, *J = 7*.0, 0.84H, **131**), 2.22 (m, *J = 7*, 5H, **131** and **132**), 1.77-1.76 (m, 6.7H, **131** and **132**), 1.31 (s, 6H, **132**), 0.99 (t, *J = 7*, 1.3H, **131**), 0.90 (t, *J = 7*, 6H, **132**); δ_C (125 MHz, $CDCl_3$) 154.03, 153.97, 140.9, 140.8, 137.1, 135.4, 134.1, 133.9, 133.8, 132.9, 131.6, 130.9, 129.0, 128.9, 128.5, 127.29, 127.26, 125.7, 125.6, 119.5, 17.7, 17.5, 14.91, 14.89, 14.7, 14.5, 12.1, 9.5 (2 C missing (B*C* **131** and B*C* **132**)); δ_B (160 MHz, $CDCl_3$) -0.34 (broad s); *m/z*

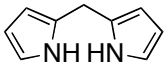
ESI^+ $[M+Na]^+$ 443.3, 519.3. Although this mixture could not be separated, assignments are based on those of a pure sample of *C*-BODIPY **131**.

5.4.81 4-Bora-3a,4a-diaza-*s*-indacene (**133**)[159-161]



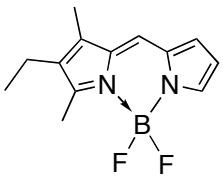
A suspension of 2,3,5,6-tetrachloro-*p*-benzoquinone (173 mg, 0.55 mmol) in dichloromethane (10 mL) under a nitrogen atmosphere was added dropwise to a stirred solution of **134**[162] (73 mg, 0.50 mmol) in dichloromethane (15 mL) at -40 ˚C under nitrogen. Once the addition was complete, the solution was stirred at -40 ˚C for 3 h. Diisopropylethylamine (0.52 mL, 3.0 mmol) was added dropwise to the reaction mixture and the solution was stirred 1 h at -40 ˚C. $BF_3{\cdot}OEt_2$ (0.50 mL, 4.5 mmol) was added dropwise to the reaction mixture and the solution was stirred for 18 h while warming to room temperature. The reaction mixture was filtered through Celite and the solvent was removed *in vacuo*. The crude solid was purified over silica gel eluting with ethyl acetate:hexanes (3:7) and concentrated *in vacuo* to give **133** as a red solid (70 mg, 0.36 mmol, 73%). m.p. = 156-157 ˚C; δ_H (500 MHz, $CDCl_3$) 7.90 (s, 2H), 7.42 (s, 1H), 7.16 (d, J = *4.0*, 2H), 6.55 (d, J = 4.5, 2H); δ_C (125 MHz, $CDCl_3$) 145.2, 135.0, 131.5, 131.4, 118.9. The ^{13}C NMR data matches (within 0.1 ppm) the data reported for the compound.[159] δ_B (160 MHz, $CDCl_3$) 0.15 (t, J_{BF} = 30); *m/z* ESI^+ found 215.0564 $[M+Na]^+$ calculated for $C_9H_7BF_2N_2Na$ 215.0568.

5.4.82 Di(1*H*-pyrrol-2-yl)methane (**134**)[162]



Compound **134** was synthesized using a modification of a literature procedure.[162] Paraformaldehyde (216 mg, 7.2 mmol) was added to a stirred solution of pyrrole (20 mL, 288 mmol) in methanol (10 mL) and acetic acid (30 mL) under nitrogen. The solution was stirred for 20 h at room temperature and then poured onto dichloromethane (100 mL). A saturated solution of sodium bicarbonate was added to adjust the pH to neutral and the layers were separated. The organic layer was washed with an aqueous saturated sodium bicarbonate solution (3 x 75 mL), dried over sodium sulfate and concentrated *in vacuo* to give an off-white solid. Purification over neutral alumina gave **134** as a white solid (434 mg, 2.97 mmol, 41%). m.p. = 73-74 ˚C (lit 73-74);[162] δ_H (500 MHz, $CDCl_3$) 7.67 (1H, bs), 6.63-6.62 (1H, m), 6.19-6.17 (1H, m), 6.07-6.05 (1H, m), 3.95 (2H, s); δ_C (125 MHz, $CDCl_3$) 129.2, 117.4, 108.4, 106.6, 26.4; The ^{13}C NMR data matches (within 0.2 ppm) the reported data for the compound. *m/z* ESI^+ found 169.0736 $[M+Na]^+$ calculated for $C_9H_{10}N_2Na$ 169.0736.

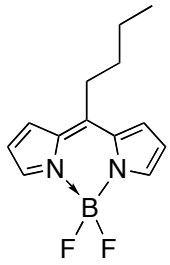
5.4.83 2-Ethyl-1,3-dimethyl-8*H*-4-bora-3a,4a-diaza-*s*-indacene (**135**)[158]



Synthesized from 2-ethyl-1,3,7,9-tetramethyldipyrromethene hydrobromide[192] using the general *F*-BODIPY procedure (GP1) to give **135** as a bright red solid (196 mg, 89%). m.p. = 134-136 ˚C; δ_H (500 MHz, $CDCl_3$) 7.57 (s, 1H), 7.11 (s, 1H), 6.84 (d, J = 4.0, 1H) 6.39-6.37 (m, 1H,), 2.56 (s, 3H), 2.39 (q, J = 7.5, 2H), 2.16 (s, 3H), 1.07 (t, J = 7.5, 3H).

δ_C (125 MHz, $CDCl_3$) 163.4, 141.2, 137.8, 136.2, 134.9, 132.4, 125.3, 123.6, 115.6, 17.3, 13.4, 14.3, 9.5. The ^{13}C NMR data matches (withn 0.03 ppm) the data reported for the compound.[158] δ_B (160 MHz, $CDCl_3$) 0.42 (t, J = 32); *m/z* ESI^+ found 271.1178 $[M+Na]^+$ calculated for $C_{13}H_{15}BF_2N_2Na$ 271.1194.

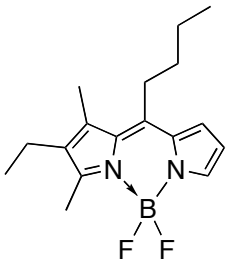
5.4.84 8-Butyl-4-bora-3a,4a-diaza-*s*-indacene (**136**)



n-Butyllithium (1.9 mL of a 1.6 M solution in hexanes, 3.1 mmol) was slowly added under a nitrogen atmosphere to a round-bottom flask containing a solution of **133** (60 mg, 0.31 mmol) in tetrahydrofuran (10 mL) at -78 ˚C. The solution was stirred while slowly warming to -30 ˚C. At -30 ˚C, methanol (2 mL) was added dropwise followed by a 0.1 M aqueous solution of HCl (2 mL) and the mixture was stirred for 10 min. The flask was removed from the cooling bath and 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (541 mg, 2.4 mmol) was added and the reaction mixture was stirred for 3 h at room temperature. The reaction mixture was diluted with dichloromethane (75 mL) and water (150 mL). The layers were separated and the organic layer was washed with water (3 x 150 mL), dried over anhydrous sodium sulfate and the solvent was removed *in vacuo*. Filtration through a pad of silica eluting with dichloromethane, purification over silica gel eluting with dichloromethane:hexanes (1:1) and removal of the solvent *in vacuo* gave **136** as an orange solid (20 mg, 0.08 mmol, 26%). m.p. = 156 ˚C dec.; δ_H (500 MHz, $CDCl_3$) 7.85

(s, 2H), 7.27-7.28 (m, 2H), 6.53-6.54 (m, 2H), 2.95-2.92 (m, 2H), 1.81-1.75 (m, 2H), 1.47 (sextet, *J* = *7.5*, 2H), 0.97 (t, *J* = *7.5*, 3H); δ_C (125 MHz, $CDCl_3$) 151.4, 143.4, 135.3, 127.9, 118.1, 36.1, 31.3, 23.3, 13.9; δ_B (160 MHz, $CDCl_3$) 0.02 (t, J_{BF} = 30); *m/z* ESI^+ found 271.1178 $[M+Na]^+$ calculated for $C_{13}H_{15}BF_2N_2Na$ 271.1194.

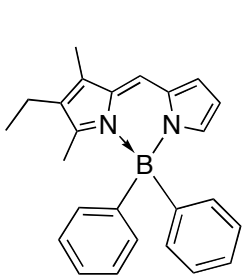
5.4.85 8-Butyl-2-ethyl-1,3-dimethyl-4-bora-3a,4a-diaza-*s*-indacene (**137**)



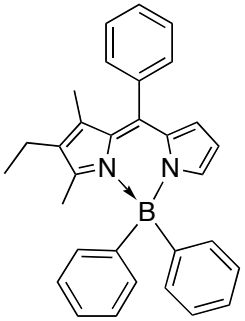
n-Butyllithium (2.5 mL of a 1.6 M solution in hexanes, 4.0 mmol) was slowly added under a nitrogen atmosphere to a round-bottom flask containing a solution of **135** (100 mg, 0.40 mmol) in tetrahydrofuran (15 mL) at -78 ˚C (dry ice/acetone bath). The solution was stirred while slowly warming to -30 ˚C. At -30 ˚C, methanol (2.5 mL) was added dropwise followed by a 0.1 M aqueous solution of HCl (2.5 mL) and the mixture was stirred for 15 min. The mixture was removed from the cooling bath and 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone (700 mg, 7.7 mmol) was added and the reaction mixture was allowed to stir for 3 h at room temperature. The reaction mixture was diluted with dichloromethane (75 mL) and water (150 mL). The layers were separated and the organic layer was washed with water (3 x 150 mL). The combined organics were dried over anhydrous sodium sulfate and the solvent was removed *in vacuo*. Purification over silica gel eluting with ethyl acetate:hexanes (25:75) and removal of the solvent *in vacuo* gave **137** as a red solid (51 mg, 0.17 mmol, 42%). m.p. = 85-86 ˚C; δ_H (500 MHz, $CDCl_3$) 7.55 7.54 (m, 1H), 7.00 (d, *J* = 3.5, 1H), 6.40-6.39 (m, 1H), 2.93-2.90 (m, 2H), 2.57 (s, 3H),

2.42 (q, J = 7.5, 2H), 2.34 (s, 3H), 1.71-1.65 (m, 2H), 1.52 (sextet, J = 7.5, 2H), 1.06 (t, J = 7.5, 3H), 0.98 (t, J = 7.5, 3H); δ_C (125 MHz, $CDCl_3$) 160.6, 145.9, 140.2, 136.3, 135.5, 133.8, 133.6, 122.3, 115.0, 34.9, 29.6, 23.5, 17.2, 14.6, 13.9, 13.3, 13.2; δ_B (160 MHz, $CDCl_3$) 0.20 (t, J = 32); *m/z* ESI^+ found 327.1815 $[M+Na]^+$ calculated for $C_{17}H_{23}BF_2N_2Na$ 327.1820.

5.4.86 2-Ethyl-1,3-dimethyl-4,4′-diphenyl-8*H*-4-bora-3a,4a-diaza-*s*-indacene (**138**) and 2-ethyl-1,3-dimethyl-4,4′,8-triphenyl-4-bora-3a,4a-diaza-*s*-indacene (**139**)



138

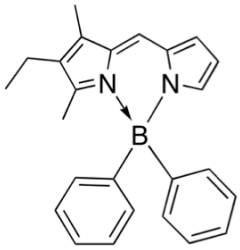


139

Phenyllithium (2.2 mL of a 1.8 M solution in di-*n*-butyl ether, 4.0 mmol) was slowly added under a nitrogen atmosphere to a round-bottom flask containing a solution of **135** (100 mg, 0.40 mmol) in tetrahydrofuran (15 mL) at -45 ˚C. The solution was stirred for 30 min and then the cooling bath was removed and the mixture was stirred at room temperature for 1 h. A 0.1 M aqueous solution of HCl (5 mL) was added dropwise and the reaction mixture was stirred for 5 min. 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone (908 mg, 10 mmol) was added and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was filtered through a pad of neutral alumina, dried over sodium sulfate, and concentrated *in vacuo* to give a brown oil. Purification over silica gel eluting with ethyl acetate:hexanes (2:98) and removal of the solvent *in vacuo* gave a mixture of **138** and **139** as a bright orange solid. The mixture was purified over

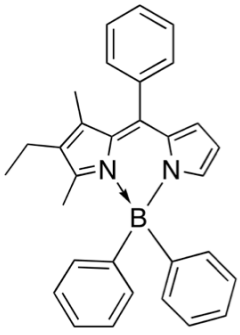
silica gel elutng with a gradient of ethyl acetate:hexanes (0:100 to 2:98) and concentrated *in vacuo* to give a mixture of **138** and **139** as a bright orange solid (**138**: 14 mg, 0.04 mmol, 10% and **139**: 10 mg, 0.02 mmol, 6%). The mixture of **138** and **139** was again purified over silica eluting with a gradient of hexanes to ethyl acetate:hexanes (0:100 to 2:98) and the pure fractions concentrated *in vacuo* to give **138** as orange solid and **139** as an orange solid.

2-Ethyl-1,3-dimethyl-4,4'-diphenyl-8*H*-4-bora-3a,4a-diaza-*s*-indacene (**138**)



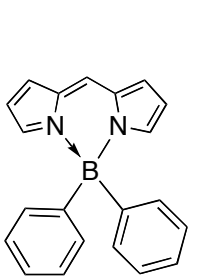
m.p. = 203-204 ˚C; δ_H (500 MHz, $CDCl_3$) 7.29 (s, 1H), 7.23-7.14 (m, 11H), 6.89 (d of d, *J = 1.0, 4.0*, 1H), 6.31 (d of d, *J = 1.0, 4.0*, 1H), 2.41 (q, *J = 7.5*, 2H), 2.26 (s, 3H), 1.84 (s, 3H), 1.06 (t, *J = 7.5*, 3H); δ_C (125 MHz, $CDCl_3$) 139.6, 138.0, 136.1, 134.2, 133.3, 132.0, 127.4, 126.0, 124.3, 123.6, 114.9, 105.6, 17.7, 15.0, 14.7, 9.6 (1 C missing; B*C*); δ_B (160 MHz, $CDCl_3$) 0.19 (broad s); *m/z* ESI^+ found 387.1985 $[M+Na]^+$ calculated for $C_{25}H_{25}BN_2Na$ 387.2003.

2-Ethyl-1,3-dimethyl-4,4',8-triphenyl-4-bora-3a,4a-diaza-*s*-indacene (**139**)

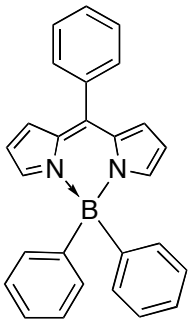


m.p. = 155-156 ˚C; δ_H (500 MHz, $CDCl_3$) 7.48-7.46 (m, 3H), 7.39-7.37 (m, 2H), 7.28-7.23 (m, 8H, overlaps with $CHCl_3$ solvent signal), 7.21-7.17 (m, 3H), 6.36 (d of d, *J = 1.0, 4.0*, 1H), 6.24 (d of d, *J = 1.0, 4.0*, 1H), 2.34 (q, *J = 7.5*, 2H), 1.85 (s, 3H), 1.50 (s, 3H), 1.00 (t, *J = 7.5*, 3H); δ_C (125 MHz, $CDCl_3$) 160.3, 142.4, 139.2, 139.0, 135.6, 135.4, 134.2, 133.5, 133.3, 129.2, 128.9, 128.3, 127.4, 125.9, 124.1, 114.6, 17.6, 15.3, 14.7, 12.7 (1 C missing; B*C*); δ_B (160 MHz, $CDCl_3$) - 0.09 (broad s); *m/z* ESI^+ found 463.2288 $[M+Na]^+$ calculated for $C_{31}H_{29}BN_2Na$ 463.2316.

5.4.87 4,4′-Diphenyl-8*H*-4-bora-3a,4a-diaza-*s*-indacene (**140**) and 4,4′8-triphenyl-4-bora-3a,4a-diaza-*s*-indacene (**141**)



140

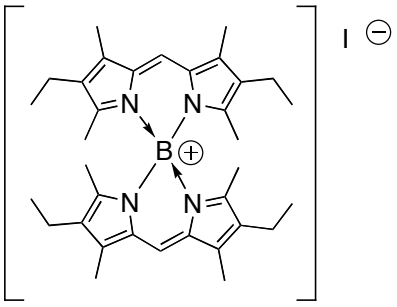


141

Phenyl lithium (0.65 mL of a 1.8 M solution in di-*n*-butyl ether, 1.2 mmol) was slowly added under a nitrogen atmosphere to a round-bottom flask containing a solution of **133** (56 mg, 0.29 mmol) in tetrahydrofuran (11 mL) at -45 ˚C. The solution was stirred for 30 min and then the cooling bath was removed and the mixture was stirred at room temperature 1 h. A 0.1 M aqueous solution of HCl (4 mL) was added dropwise and the reaction mixture was stirred for 5 min. 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone (658 mg, 10 mmol) was added and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was filtered through a pad of neutral alumina, dried over sodium sulfate, and concentrated *in vacuo* to give a brown oil. Filtration through silica gel eluting with ethyl acetate:hexanes (15:85), purification over silica eluting with a

slow gradient of ethyl acetate:hexanes (1:99 to 3:97) and concentration *in vacuo* gave a mixture of **140** (3.4 mg, 0.01 mmol, 4%) and **141** (2.1 mg, 0.005 mmol, 2%) as an orange solid. δ_H (500 MHz, $CDCl_3$) 7.55-7.54 (m, 1H), 7.52-7.51 (m, 0.5H), 7.50-7.49 (m, 0.5H), 7.40-7.39 (m, 0.5H), 7.31 (d, *J = 4,* 0.50H), 7.25-7.17 (m, 4H), 7.13-7.11 (m, 2H), 7.07-7.01 (m, 6H), 6.91-6.87 (m, 2H), 6.59 (d, *J = 4.5*, 0.5H), 6.53 (d of d, *J = 2.0, 4.0*, 1H), 6.40 (d of d, *J = 1.5, 4.0*, 0.5H); δ_C (125 MHz, $CDCl_3$) 145.9, 144.5, 136.9, 135.0, 132.8, 132.4, 131.4, 130.6, 129.8, 129.3, 129.2, 128.4, 128.1, 127.6, 127.2, 127.1, 126.4, 126.0, 125.3, 121.2, 117.92, 117.86; δ_B (160 MHz, $CDCl_3$) 0.80 (broad s); *m/z* ESI^+ found 331.1375 $[M+Na]^+$ calculated for $C_{21}H_{17}BN_2Na$ 331.1382 (**140**) and found 407.1675 $[M+Na]^+$ calculated for $C_{27}H_{21}BN_2Na$ 407.1695 (**141**).

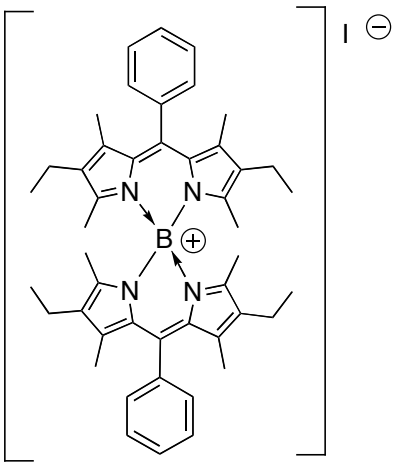
5.4.88 κ^2-(4,4′-Diethyl-3,3′,5,5′-tetramethyldipyrrinato) boronium iodide (**142I**)



To a solution of 4,4’-diethyl-3,3’,5,5’-tetramethyldipyrrin hydrochloride[183] (100 mg, 0.30 mmol) in anhydrous dichloromethane (15 mL) under nitrogen was added triethylamine (0.25 mL, 1.80 mmol) and the solution was stirred for 10 min. Solid BI_3 (1.04 g, 2.70 mmol) was added in parts, slowly, and the resulting solution was stirred for 18 h at room temperature. The reaction mixture was cooled to 0 ˚C and methanol (4 mL) was added dropwise. The reaction mixture was diluted with dichloromethane (25 mL) and distilled water (25 mL) and the layers were separated. The aqueous layer was extracted with

dichloromethane (2 x 25 mL) and the combined organic fractions were dried over sodium sulfate and concentrated *in vacuo* to give a red solid. Purification over neutral alumina eluting with a gradient of dichloromethane:methanol (100:0 to 95:5) and removal of the solvent *in vacuo* gave **142I** as a red solid (55 mg, 0.08 mmol, 56%). m.p. = > 300 ˚C; δ_H (500 MHz, CD_3OD) 7.80 (s, 2H), 2.40 (q, 8H, *J*=7), 2.35 (s, 12H), 1.75 (s, 12H), 1.01 (t, 12H, *J*=7); δ_C (125 MHz, CD_3OD) 157.5, 141.2, 136.5, 135.2, 122.4, 17.9, 14.9, 11.6, 9.6. δ_B (160 MHz, CD_3OD) -2.79. UV/Vis (CH_3CN) λ (nm), ε ($mol\,L^{-1}cm^{-1}$): 386 (15 600), 531 (57 000). *m/z* ESI^+ found 521.3784 $[M]^+$ calculated for $C_{34}H_{46}N_4B$ 521.3810. A crystal suitable for X-ray crystallography was obtained from a slow evaporation of a solution of compound **142I** in a 1:1 solution of pentane to dichloromethane. Data for **142I**: $C_{34}H_{46}N_4BI$, M = 648.48 g, deep-red plate, 0.41 x 0.22 x 0.09 mm^3, primitive monoclinic, space group P21/c (#14), a = 10.9061(4) Å, b = 14.5040(5) Å, c = 21.2718(7) Å, V = 3295.91(20) $Å^3$, Z = 4, T = 173(1) K, ρ = 1.307 gcm^{-3}, μ(MoKα) = 9.997 cm^{-1}, 25370 reflections (11930 unique, R_{int} = 0.042), R = 0.0361, Rw = 0.0414, GOF = 1.040.

5.4.89 κ^2-(4,4′-Diethyl-3,3′,5,5′-tetramethyl-*meso*-phenyl-dipyrrinato) boronium iodide (**143I**)



To a solution of 4,4'-diethyl-3,3',5,5'-tetramethyl-*meso*-phenyl-dipyrrin (**105**) (100mg, 0.30 mmol) in anhydrous dichloromethane (15 mL) under nitrogen was added triethylamine (0.25 mL, 1.80 mmol) and the solution was then stirred for 10 min. Solid BI_3 (1.04 g, 2.70 mmol) was added in parts, slowly, and the resulting solution was stirred for 18 h at room temperature. The reaction mixture was cooled to 0 ˚C and methanol (4 mL) was added dropwise. The reaction mixture was diluted with dichloromethane (25 mL) and distilled water (25 mL) and the layers were separated. The aqueous layer was extracted with dichloromethane (2 x 25 mL) and the combined organic fractions were dried over sodium sulfate and concentrated *in vacuo* to give a brown solid. The solid was suspended in methanol, stirred 30 min at room temperature and isolated using suction filtration to give **143I** as a brown solid (72 mg, 0.09 mmol, 60%). m.p. = 256-257 ˚C; δ_H (500 MHz, acetone-*d6*) 7.70-7.68 (m, 6H), 7.50-7.48 (m, 4H), 2.36 (q, 8H, *J=7*), 2.06 (s, 12H), 1.46 (s, 12H), 0.93 (t, 12H, *J=7*). δ_C (125 MHz, acetone-*d6*) 156.9, 142.8, 141.6, 136.1, 135.4, 134.8, 130.61, 130.58, 128.9, 17.5, 14.9, 12.3, 11.8. δ_B (160 MHz, acetone-*d6*) 2.41. UV/Vis (CH_3CN) λ (nm), ε ($mol\,L^{-1}\cdot cm^{-1}$): 356 (15 200), 514 (63 400). *m/z* ESI^+ found 673.4411 $[M]^+$ calculated for $C_{46}H_{54}BN_4$ 673.4436.

CHAPTER 6 Conclusions

The overall goals of this graduate research were to investigate routes to the chemical manipulation of dipyrrins, pyrrolydipyrrins and prodigiosenes. The first project was to investigate the synthesis of a library of prodigiosenes by way of a convergent approach involving the synthesis of a functionalized prodigiosene, with demonstrated anticancer activity, and subsequent functional group interconversion of an ester attached to the prodigiosene core. The second project was to investigate the synthesis of pyrrolyldipyrrinato complexes. The third project was to develop a protection method for pyrrolyldipyrrins using dipyrrins as model compounds.

The first approach involved the synthesis of ethyl ester prodigiosene **1** followed by direct chemical modification to afford derivatives. The first step of this method involved optimization of the synthesis prodigiosene **1**: prodigiosene **1** can now routinely be synthesized in six steps with an average overall yield of 34%. Functional group modification of the prodigiosene ethyl ester **1** by hydrolysis followed by esterification or transesterification was the next step. A prodigiosene ethyl ester was successfully generated under microwave promoted transesterification conditions, but the reaction was not applicable to the synthesis of other derivatives. Unfortunately, the hydrolysis approach was also largely unsuccessful predominantly due to the poor stability and solubility of prodigiosene carboxylate **36**. Due to this inherent instability, it was concluded that the proposed convergent method, to derivatives of **1**, was not suitable for providing access to a library of prodigiosenes with modified ester alkyl groups.

The second project involved the synthesis of new pyrrolyldipyrrinato complexes. A methodology was developed for the synthesis of previously unreported

pyrrolyldipyrrinato tin(IV) complexes. A series of previously unreported pyrrolyldipyrrinato tin complexes have been prepared and the bonding mode in these complexes was determined using X-ray crystallographic analysis of a representative complex. The complexes are all highly fluorescent with quantum yields ranging between 0.23 and 0.61. The series of complexes show increasing quantum efficiencies of fluorescence when the ligand contains an electron-withdrawing group on the C-ring. Substitution on the B-ring has a much smaller effect. Investigations into the biological activity of these derivatives is ongoing and in-house cell-inhibition studies would need to be conducted in order to determine the stability of the Sn-N bonds under the experimental conditions. In the future, the synthesis of other prodigiosene metal complexes should be attempted as there is very little known about these complexes, their binding modes and their biological activity.

The third project was to develop a protection method for pyrrolyldipyrrins using dipyrrins as model compounds. A microwave-promoted methodology has been developed to remove the boron centre from *F*-BODIPYs to regenerate the corresponding dipyrrins. This methodology has been successfully applied to a series of *F*-BODIPYs to generate the corresponding dipyrrins in high yields, but it is limited to BODIPYs with at least one fluorine substituent on the boron centre. This methodology allows the BF_2 moiety of the *F*-BODIPY to be conceptualized as a protecting group for a dipyrrin and could potentially have a widespread use in the synthesis and purification of dipyrrins. The synthesis of the fully unsubstituted *F*-BODIPY was optimized and thus it can now be routinely synthesized in high yields of 72% ± 6% (95% confidence). A methodology to alkylate the meso-position *F*-BODIPYs using *n*-butyllithium has also been successfully

developed. This method represents an improvement to the current methods used to generate *meso*-alkylated *F*-BODIPYs and could potentially be extended to other alkyl lithium reagents to generate a variety of different *meso*-substituted *F*-BODIPYs, with additional sites for functionalization. Attempts to extend the *meso*-modification methodology to *meso*-arylation were not successful. Initial attempts to synthesize *X*-BODIPYs from BX_3 sources were made and resulted in the isolation of previously unreported dipyrrinato boronium cations.

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APPENDIX A X-RAY ANALYSIS DATA

APPENDIX A.1 (*Z*)-Ethyl 2-((4-methoxy-1H,1'H-2,2'-bipyrrol-5-yl)methylene)-3,5-dimethyl-2H-pyrrole-4-carboxylate hydrochloride (**1**)

A. Crystal Data

Empirical Formula	$C_{19}H_{22}N_3O_3Cl$
Formula Weight	375.85
Crystal Color, Habit	deep red, needle
Crystal Dimensions	0.39 X 0.10 X 0.01 mm
Crystal System	orthorhombic
Lattice Type	Primitive
Indexing Images	4 oscillations @ 300.0 seconds
Detector Position	127.40 mm
Pixel Size	0.100 mm
Lattice Parameters	a = 7.9121(3) Å b = 19.2314(8) Å c = 24.6951(10) Å V = 3757.6(3) Å^3
Space Group	Pbca (#61)
Z value	8
D_{calc}	1.329 g/cm^3
F_{000}	1584.00
μ(MoKα)	2.268 cm^{-1}

B. Intensity Measurements

Diffractometer	Rigaku RAXIS-RAPID
Radiation	MoKα (λ = 0.71070 Å) graphite monochromated
Data Images	45 exposures
ω oscillation Range (χ=0.0, φ=0.0)	160.0 - 190.0°
Exposure Rate	360.0 sec./°
ω oscillation Range (χ=0.0, φ=180.0)	113.8 - 118.8°
Exposure Rate	360.0 sec./°
ω oscillation Range (χ=0.0, φ=0.0)	51.0 - 175.0°
Exposure Rate	360.0 sec./°
Detector Position	127.40 mm
Pixel Size	0.100 mm
$2\theta_{max}$	60.1°
No. of Reflections Measured	Total: 35806 Unique: 5492 (R_{int} = 0.224)
Corrections	Lorentz-polarization Absorption (trans. factors: 0.773 - 0.998)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares on F
Function Minimized	Σ w (|Fo| - |Fc|)^2
Least Squares Weights parameters	Chebychev polynomial with 3 11.2043,-9.0996,8.5992
$2\theta_{max}$ cutoff	52.0˚
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	2931
No. Variables	257
Reflection/Parameter Ratio	11.40
Residuals: R (I>3.00σ(I))	0.0457
Residuals: Rw (I>3.00σ(I))	0.0426
Goodness of Fit Indicator	1.134
Max Shift/Error in Final Cycle	0.000
Maximum peak in Final Diff. Map	0.74 e$^-$/Å^3
Minimum peak in Final Diff. Map	-0.64 e$^-$/Å^3

APPENDIX A.2 (**1**)BF_2 (**52**)

A. Crystal Data

Empirical Formula	$C_{19}H_{20}N_3O_3BF_2$
Formula Weight	387.19
Crystal Color, Habit	dark-red, needle
Crystal Dimensions	0.39 X 0.13 X 0.08 mm
Crystal System	monoclinic
Lattice Type	Primitive
Indexing Images	4 oscillations @ 300.0 seconds
Detector Position	127.40 mm
Pixel Size	0.100 mm
Lattice Parameters	a = 7.3029(4) Å b = 25.1293(11) Å c = 9.7763(5) Å β = 97.313(3) ° V = 1779.52(15) Å^3
Space Group	$P2_{1/c}$ (#14)
Z value	4
D_{calc}	1.445 g/cm^3
F_{000}	808.00
μ(MoKα)	1.116 cm^{-1}

B. Intensity Measurements

Diffractometer	Rigaku RAXIS-RAPID
Radiation	MoKα (λ = 0.71070 Å) graphite monochromated
Data Images	48 exposures
ω oscillation Range (χ=0.0, φ=0.0)	160.0 - 190.0°
Exposure Rate	540.0 sec./°
ω oscillation Range (χ=0.0, φ=180.0)	20.0 - 110.0°
Exposure Rate	540.0 sec./°
ω oscillation Range (χ=0.0, φ=0.0)	22.5 - 112.5°
Exposure Rate	540.0 sec./°
Detector Position	127.40 mm
Pixel Size	0.100 mm
$2\theta_{max}$	144.5°
No. of Reflections Measured	Total: 52752 Unique: 19174 (R_{int} = 0.074)
Corrections	Lorentz-polarization Absorption (trans. factors: 0.821 - 0.991)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SHELX97)
Refinement	Full-matrix least-squares on F
Function Minimized	Σ w (|Fo| - |Fc|)^2
Least Squares Weights parameters	Chebychev polynomial with 3 13.1802,0.2626, 11.1166
$2\theta_{max}$ cutoff	60.0˚
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	3160
No. Variables	333
Reflection/Parameter Ratio	9.49
Residuals: R (I>3.00σ(I))	0.0441
Residuals: Rw (I>3.00σ(I))	0.0557
Goodness of Fit Indicator	1.022
Max Shift/Error in Final Cycle	0.000
Maximum peak in Final Diff. Map	0.36 e$^-$/Å^3
Minimum peak in Final Diff. Map	-0.21 e$^-$/Å^3

APPENDIX A.3 ($(Bu)_2$(**92**)Sn(IV) (**93**)

B. Crystal Data

Empirical Formula	$C_{29}H_{38}N_3O_4Sn$
Formula Weight	611.33
Crystal Color, Habit	dark-red, needle
Crystal Dimensions	0.42 X 0.23 X 0.12 mm
Crystal System	triclinic
Lattice Type	Primitive
Indexing Images	4 oscillations @ 300.0 seconds
Detector Position	127.40 mm
Pixel Size	0.100 mm
Lattice Parameters	a = 12.1339 Å b = 13.04640(10) Å c = 19.65300(10) Å α = 82.876(3) ° β = 78.432(3) ° γ = 72.742(2) ° V = 2903.79(3) Å^3
Space Group	P-1 (#2)
Z value	4
D_{calc}	1.398 g/cm^3
F_{000}	1260.00
μ(MoKα)	9.167 cm^{-1}

B. Intensity Measurements

Diffractometer	Rigaku RAXIS-RAPID
Radiation	MoKα (λ = 0.71070 Å) graphite monochromated
Data Images	75 exposures
ω oscillation Range (χ=0.0, φ=0.0)	20.0 - 200.0°
Exposure Rate	444.0 sec./°
ω oscillation Range (χ=0.0, φ=180.0)	20.0 - 200.0°
Exposure Rate	444.0 sec./°
ω oscillation Range (χ=0.0, φ=0.0)	20.0 - 35.0°
Exposure Rate	444.0 sec./°
Detector Position	127.40 mm
Pixel Size	0.100 mm
$2\theta_{max}$	71.6°
No. of Reflections Measured	Total: 106009 Unique: 22429 (R_{int} = 0.065)
Corrections	Lorentz-polarization Absorption (trans. factors: 0.776 - 0.896) Secondary Extinction (coefficient: 1.65990e+002)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SHELX97)
Refinement	Full-matrix least-squares on F
Function Minimized	Σ w (|Fo| - |Fc|)^2
Least Squares Weights parameters	Chebychev polynomial with 3 7.9089,-3.2881,6.5045,
$2\theta_{max}$ cutoff	52.5˚
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	8120
No. Variables	696
Reflection/Parameter Ratio	11.67
Residuals: R (I>3.00σ(I))	0.0358
Residuals: Rw (I>3.00σ(I))	0.0439
Goodness of Fit Indicator	1.082
Max Shift/Error in Final Cycle	0.000
Maximum peak in Final Diff. Map	1.01 e$^-$/Å^3
Minimum peak in Final Diff. Map	-0.57 e$^-$/Å^3

APPENDIX A.4 κ^2-(4,4′-Diethyl-3,3′,5,5′-tetramethyldipyrrinato) boronium iodide (**142I**)

A. Crystal Data

Empirical Formula	$C_{34}H_{46}N_4BI$
Formula Weight	648.48
Crystal Color, Habit	deep-red, plate
Crystal Dimensions	0.41 X 0.22 X 0.09 mm
Crystal System	monoclinic
Lattice Type	Primitive
Indexing Images	4 oscillations @ 300.0 seconds
Detector Position	127.40 mm
Pixel Size	0.100 mm
Lattice Parameters	a = 10.9061(4) Å b = 14.5040(5) Å c = 21.1718(7) Å β = 100.2156(19) ° V = 3295.91(20) Å^3
Space Group	$P2_{1/c}$ (#14)
Z value	4
D_{calc}	1.307 g/cm^3
F_{000}	1344.00
μ(MoKα)	9.997 cm^{-1}

B. Intensity Measurements

Diffractometer	Rigaku RAXIS-RAPID
Radiation	MoKα (λ = 0.71070 Å) graphite monochromated
Data Images	79 exposures
ω oscillation Range (χ=0.0, φ=0.0)	50.0 - 180.0°
Exposure Rate	540.0 sec./°
ω oscillation Range (χ=0.0, φ=180.0)	48.5 - 178.5°
Exposure Rate	540.0 sec./°
ω oscillation Range (χ=0.0, φ=0.0)	47.5 - 182.5°
Exposure Rate	540.0 sec./°
Detector Position	127.40 mm
Pixel Size	0.100 mm
$2\theta_{max}$	71.5°
No. of Reflections Measured	Total: 25370 Unique: 11930 (R_{int} = 0.042)
Corrections	Lorentz-polarization

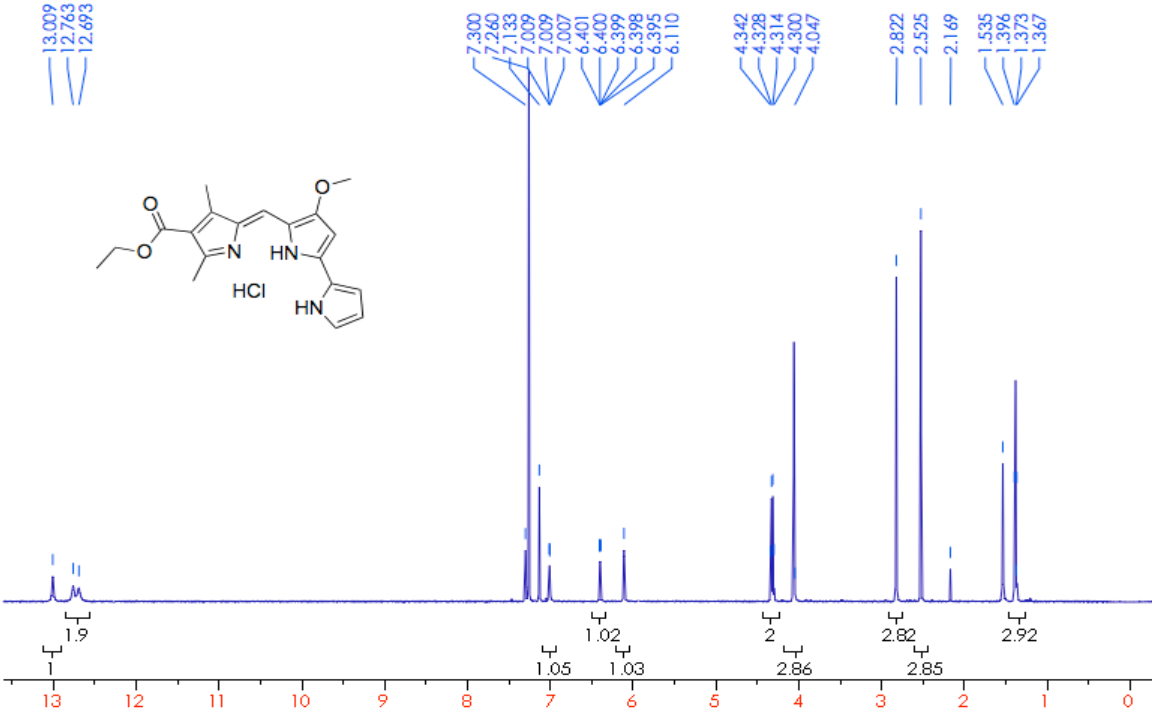
C. Structure Solution and Refinement

Structure Solution	Direct Methods (SHELX97)
Refinement	Full-matrix least-squares on F
Function Minimized	Σ w (|Fo| - |Fc|)^2
Least Squares Weights parameters	Chebychev polynomial with 3 13.0520,-4.8971, 10.6057
$2\theta_{max}$ cutoff	60.0˚
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	6538
No. Variables	373
Reflection/Parameter Ratio	17.53
Residuals: R (I>3.00σ(I))	0.0361
Residuals: Rw (I>3.00σ(I))	0.0414
Goodness of Fit Indicator	1.040
Max Shift/Error in Final Cycle	0.000
Maximum peak in Final Diff. Map	0.67 e$^-$/Å^3
Minimum peak in Final Diff. Map	-0.49 e$^-$/Å^3

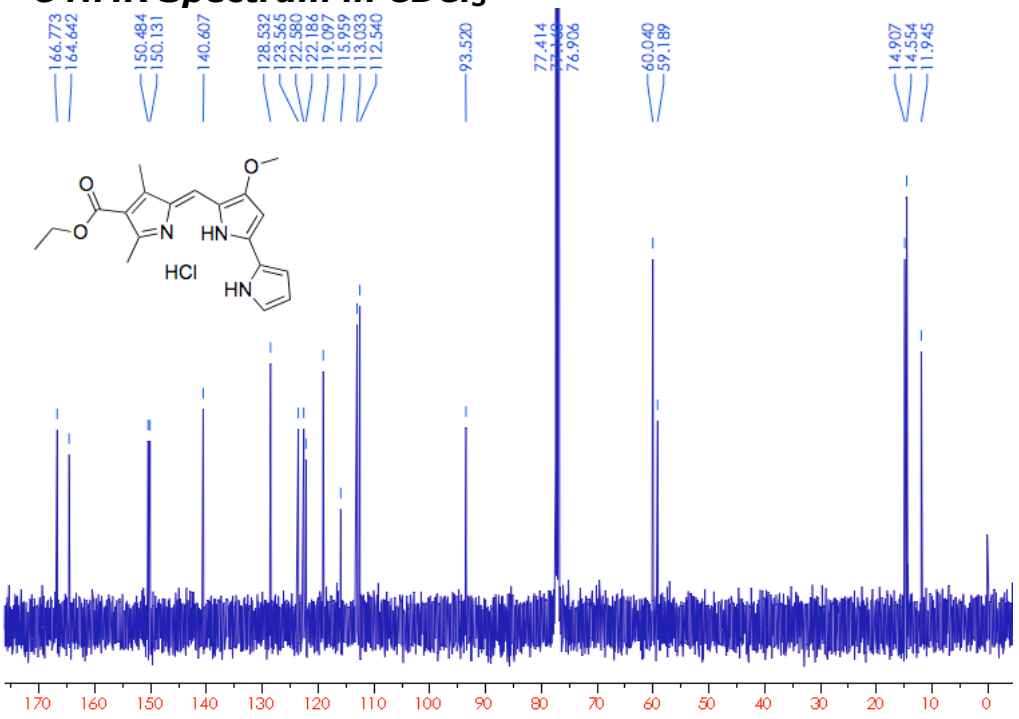
APPENDIX B NMR Data for Synthesized Compounds

APPENDIX B.1 (*Z*)-Ethyl 2-((4-methoxy-1H,1'H-2,2'-bipyrrol-5-yl)methylene)-3,5-dimethyl-2H-pyrrole-4-carboxylate hydrochloride (**1**)[29]

^{1}H NMR Spectrum in $CDCl_3$

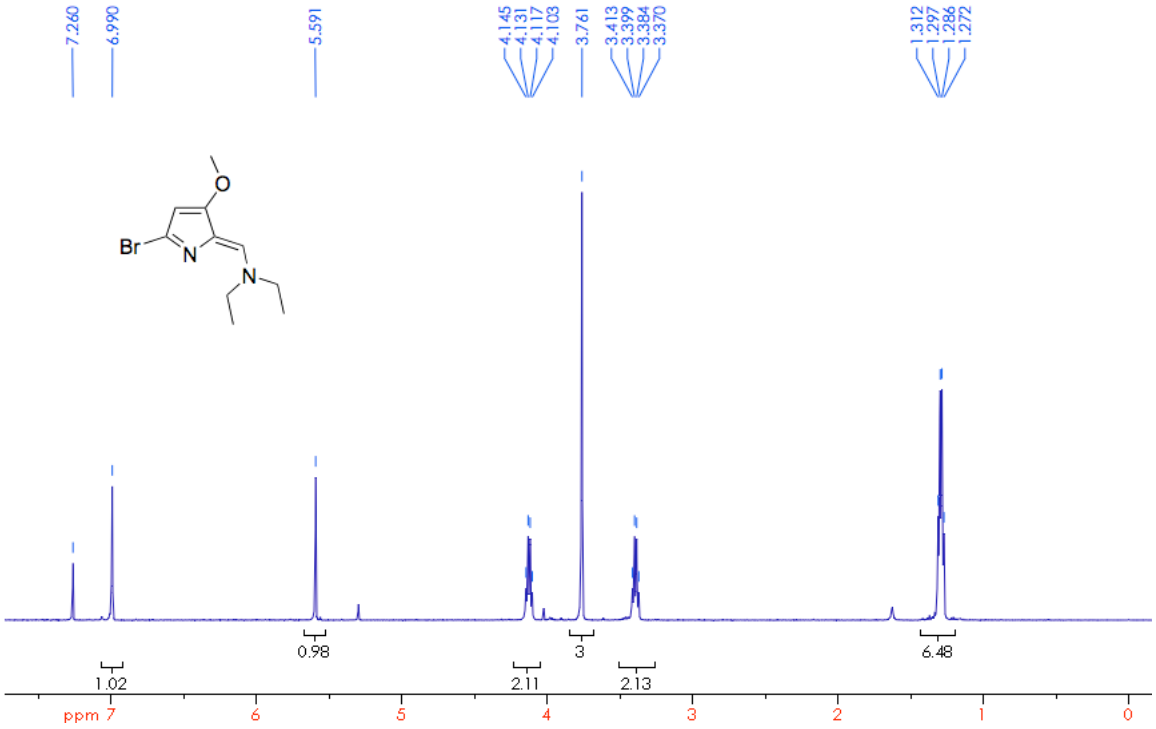


^{13}C NMR Spectrum in $CDCl_3$



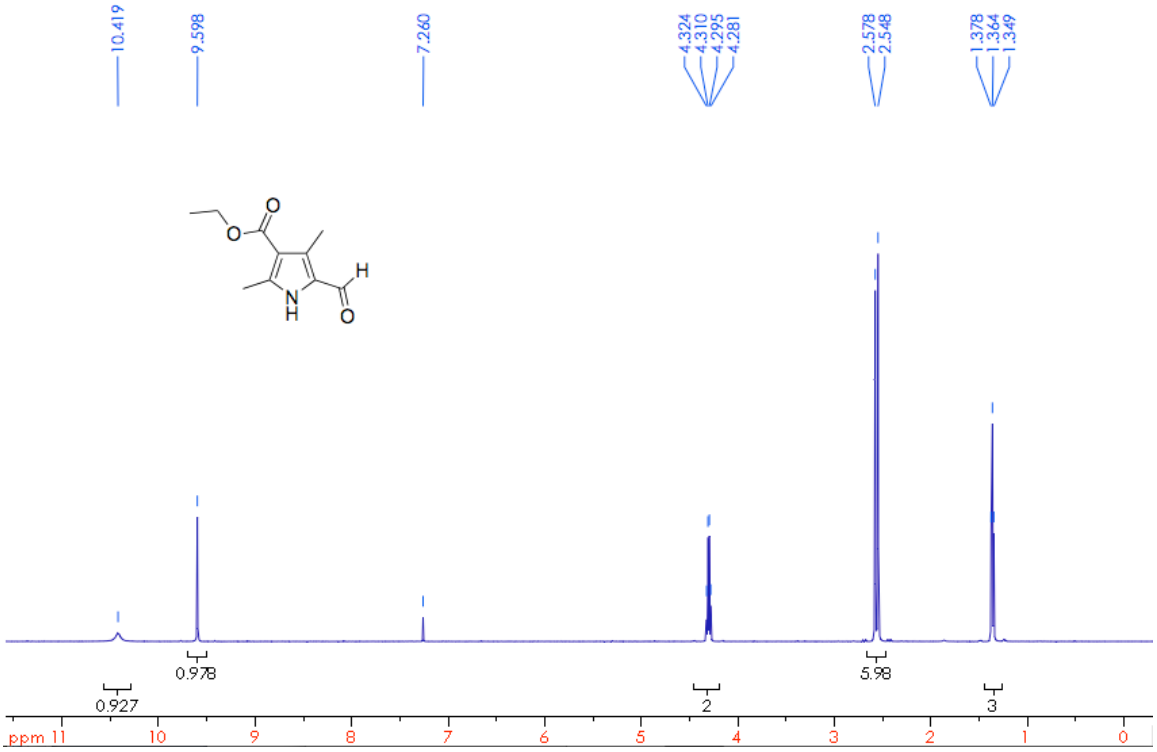
APPENDIX B.2 *N*-((5-Bromo-4-methoxy-2H-pyrrol-2-ylidene)methyl)-*N*-ethylethanamine (**14**)[38]

^{1}H NMR Spectrum in $CDCl_3$

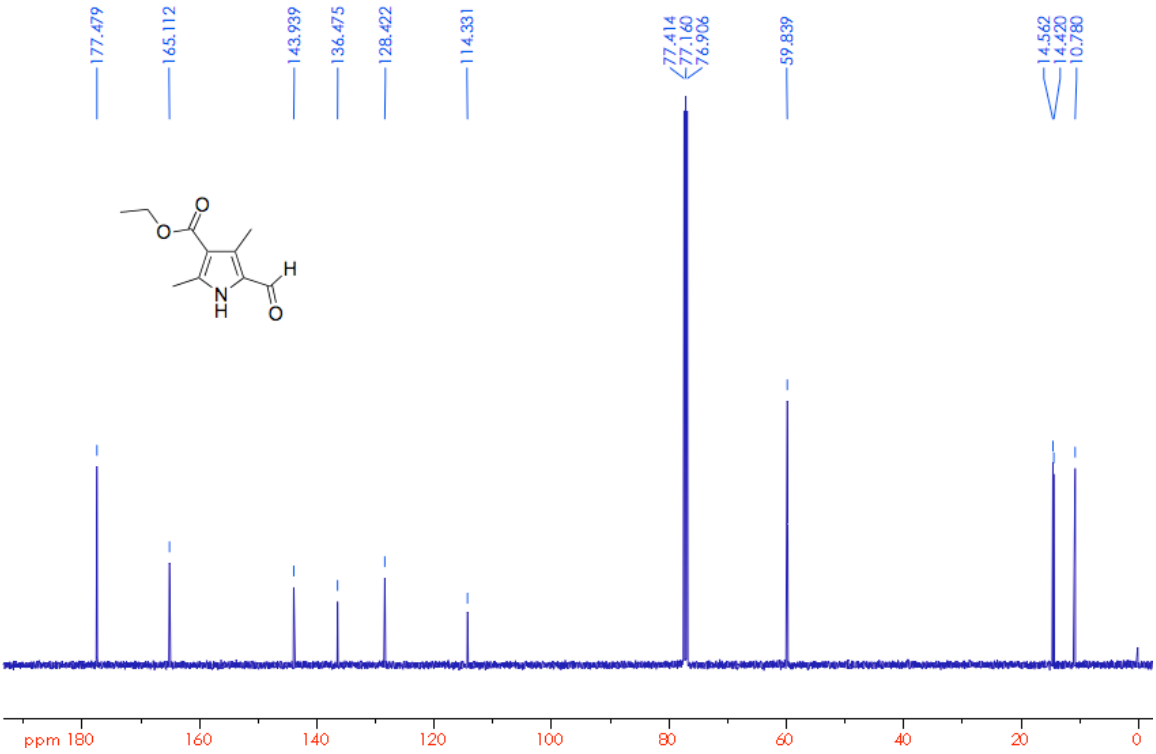


APPENDIX B.3 Ethyl 5-formyl-2,4-dimethyl-1H-pyrrole-3-carboxylate (**20**)[187, 188]

^{1}H NMR Spectrum in $CDCl_3$

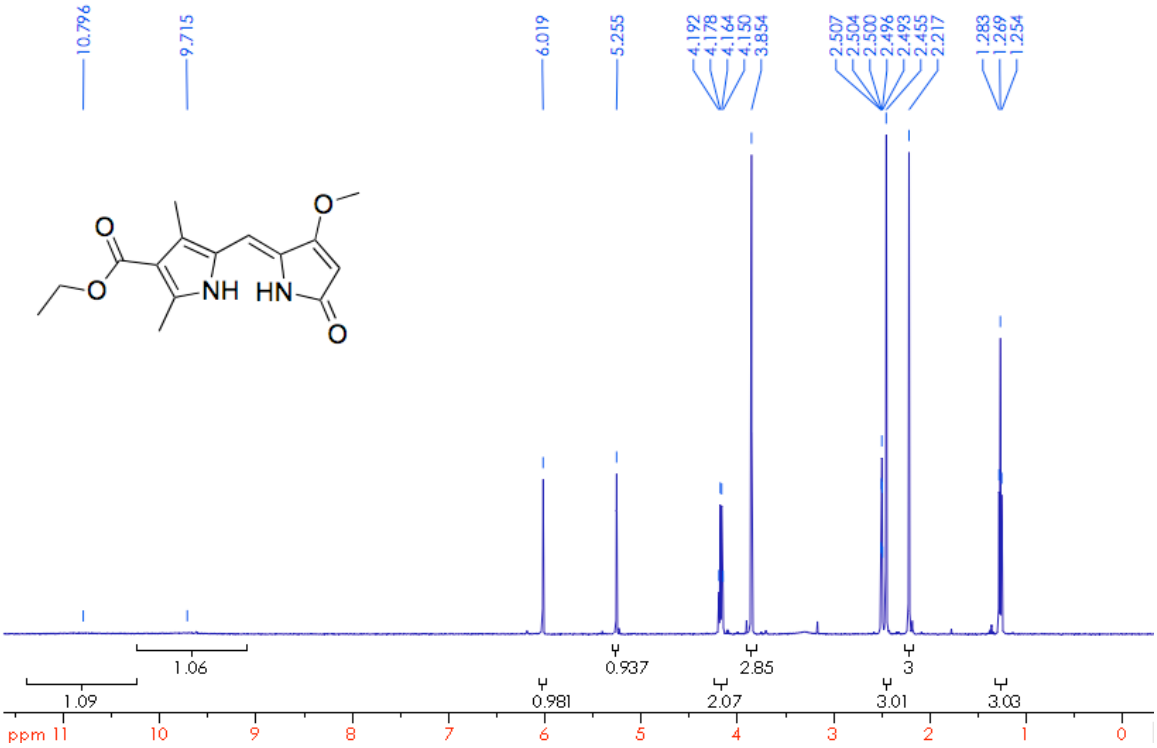


^{13}C NMR Spectrum in $CDCl_3$

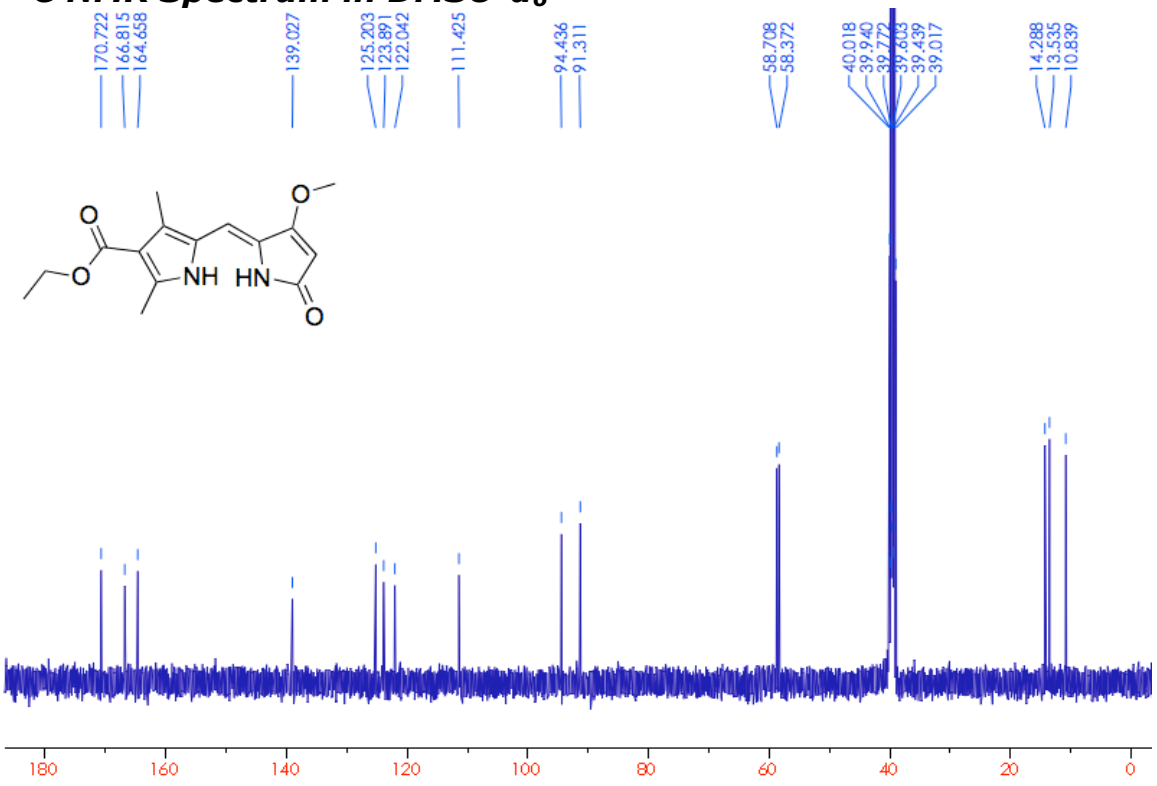


APPENDIX B.4 (*Z*)-Ethyl-5-((3-methoxy-5-oxo-1*H*-pyrrol-2(5*H*)-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrole-3-carboxylate (**21**)[29]

^{1}H NMR Spectrum in DMSO-d_6

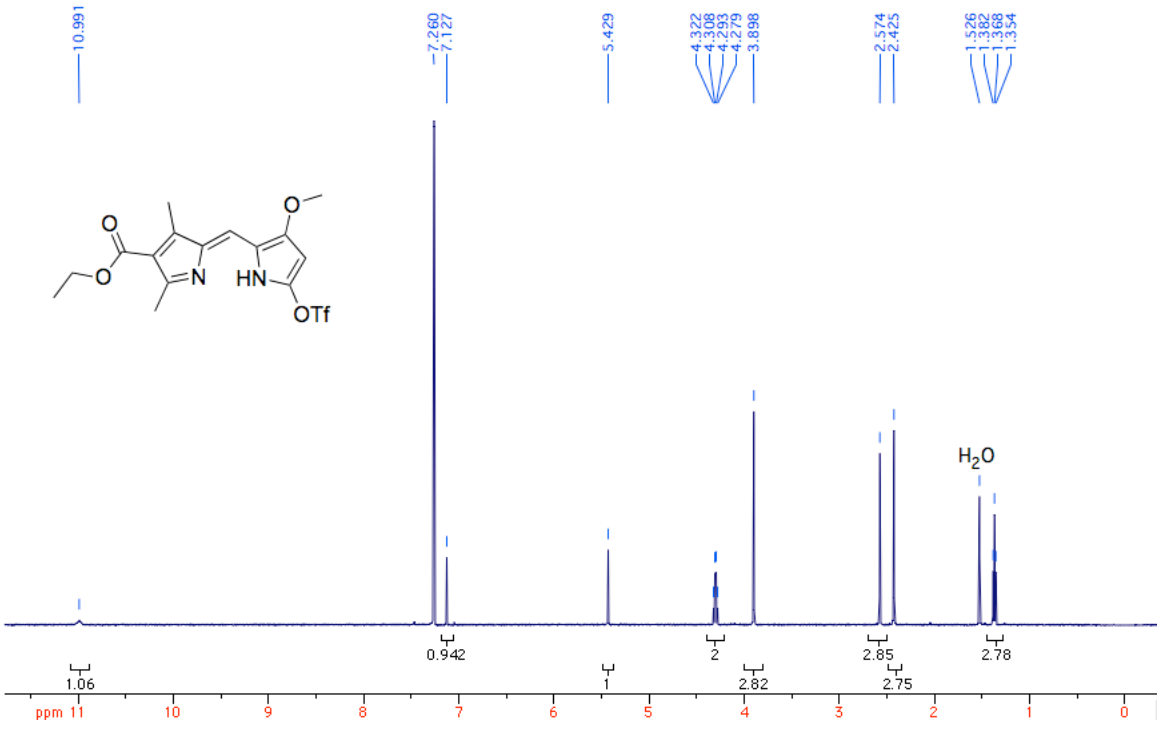


^{13}C NMR Spectrum in DMSO-d_6



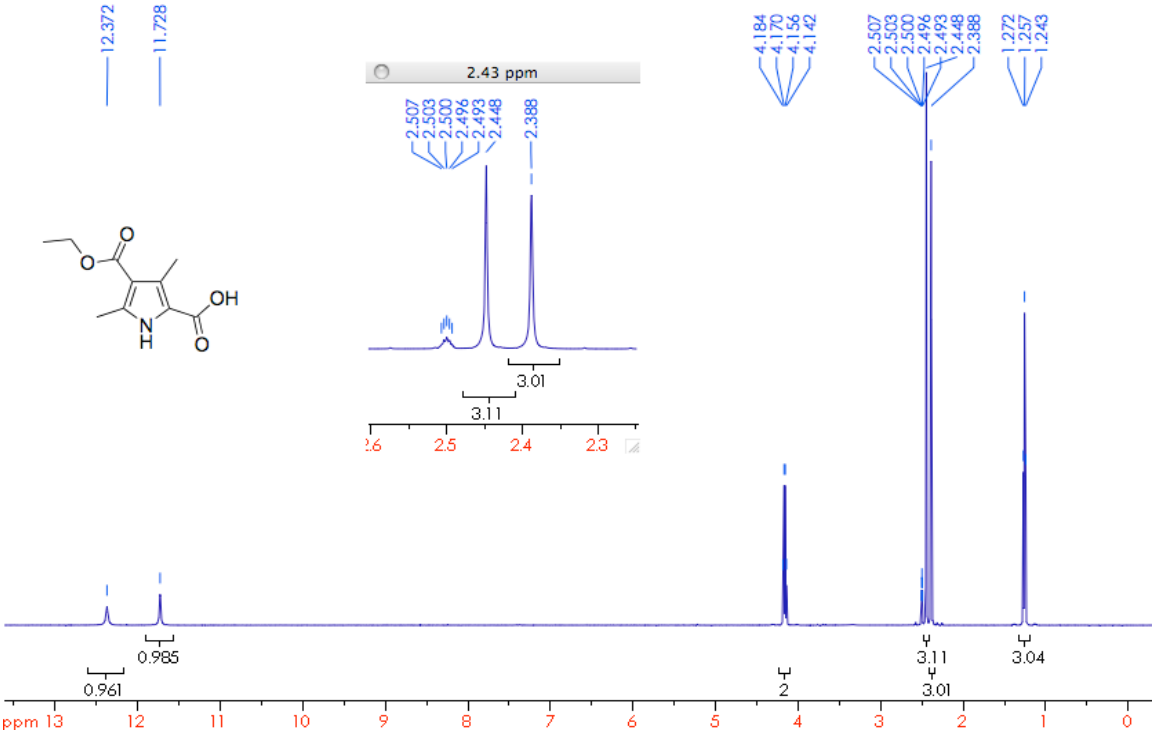
APPENDIX B.5 (*Z*)-ethyl 2-((3-methoxy-5-(trifluoromethylsulfonyloxy)-1*H*-pyrrol-2-yl)methylene)-3,5-dimethyl-2*H*-pyrrole-4-carboxylate (**22**)[29]

^{1}H NMR Spectrum in $CDCl_3$

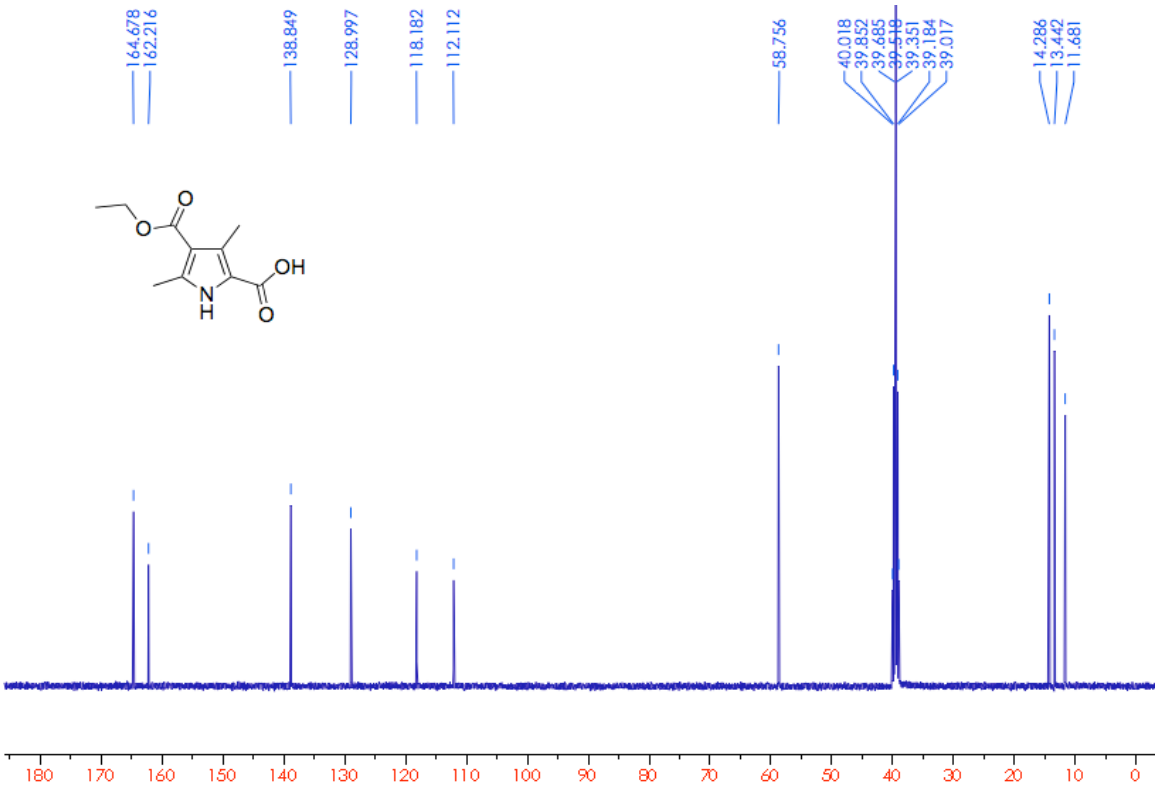


APPENDIX B.6 4-(Ethoxycarbonyl)-3,5-dimethyl-1*H*-pyrrole-2-carboxylic acid (**24**)[48]

^{1}H NMR Spectrum in DMSO-d_6

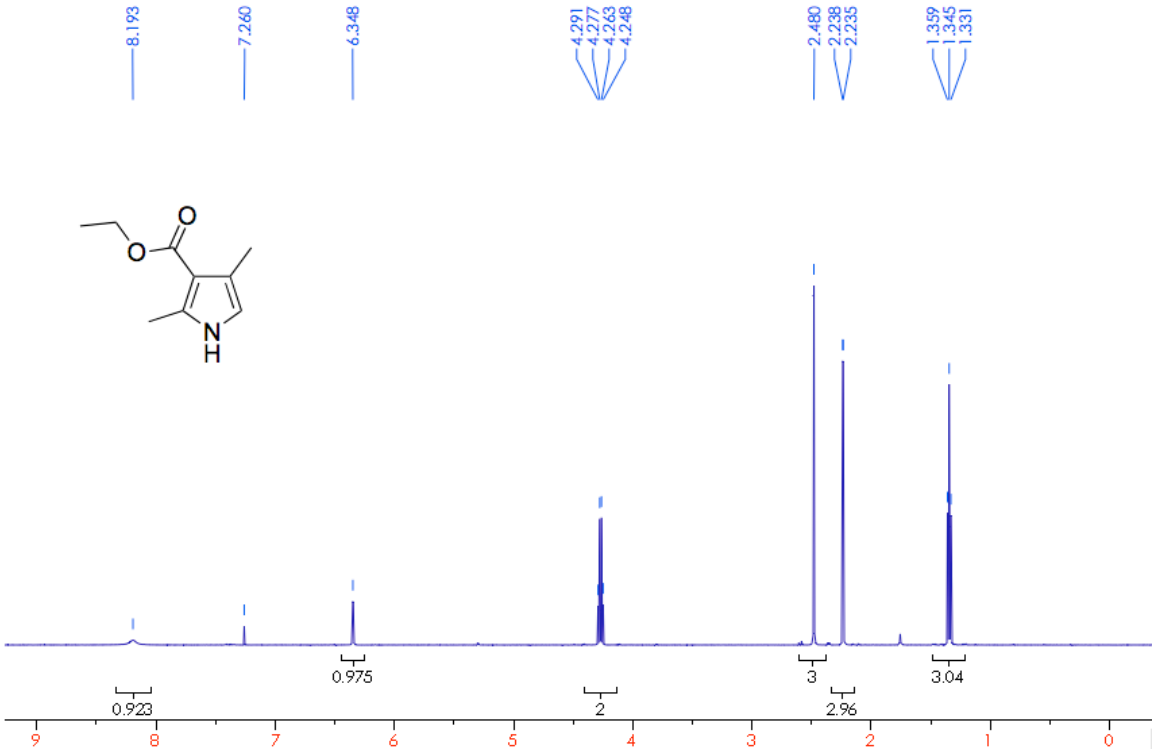


^{13}C NMR Spectrum in DMSO-d_6

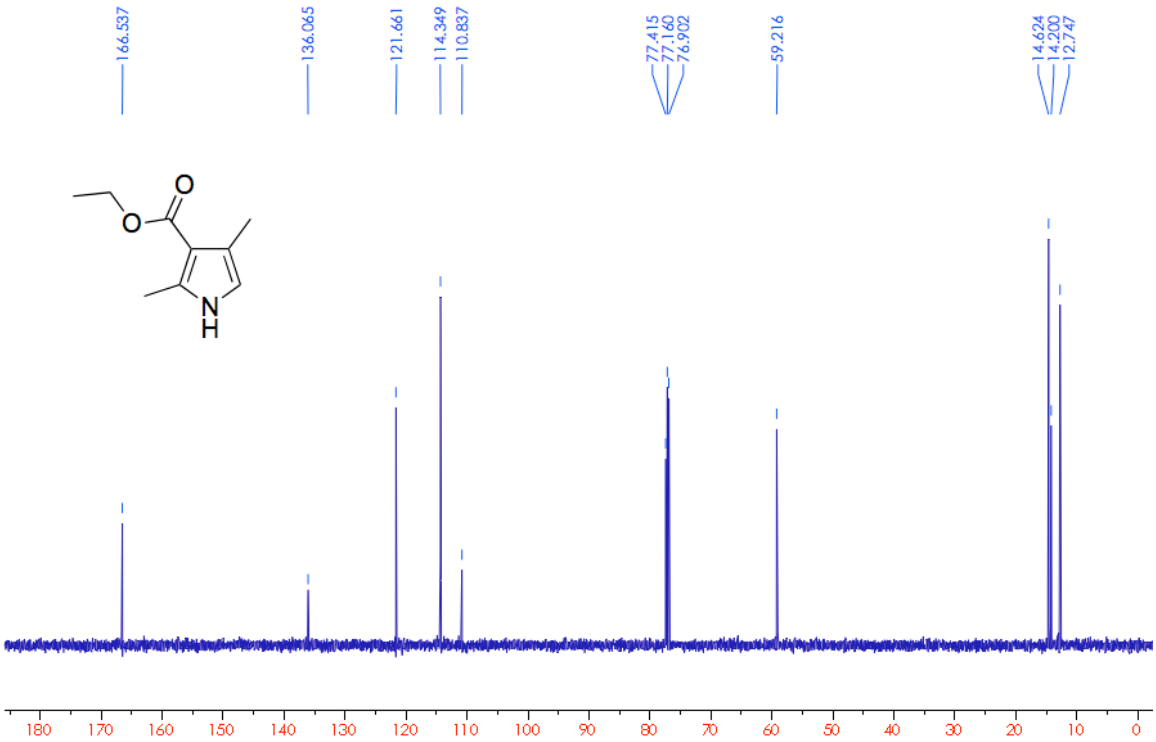


APPENDIX B.7 Ethyl 2,4-dimethyl-1H-pyrrole-3-carboxylate (**25**)[92, 187]

^{1}H NMR Spectrum in $CDCl_3$

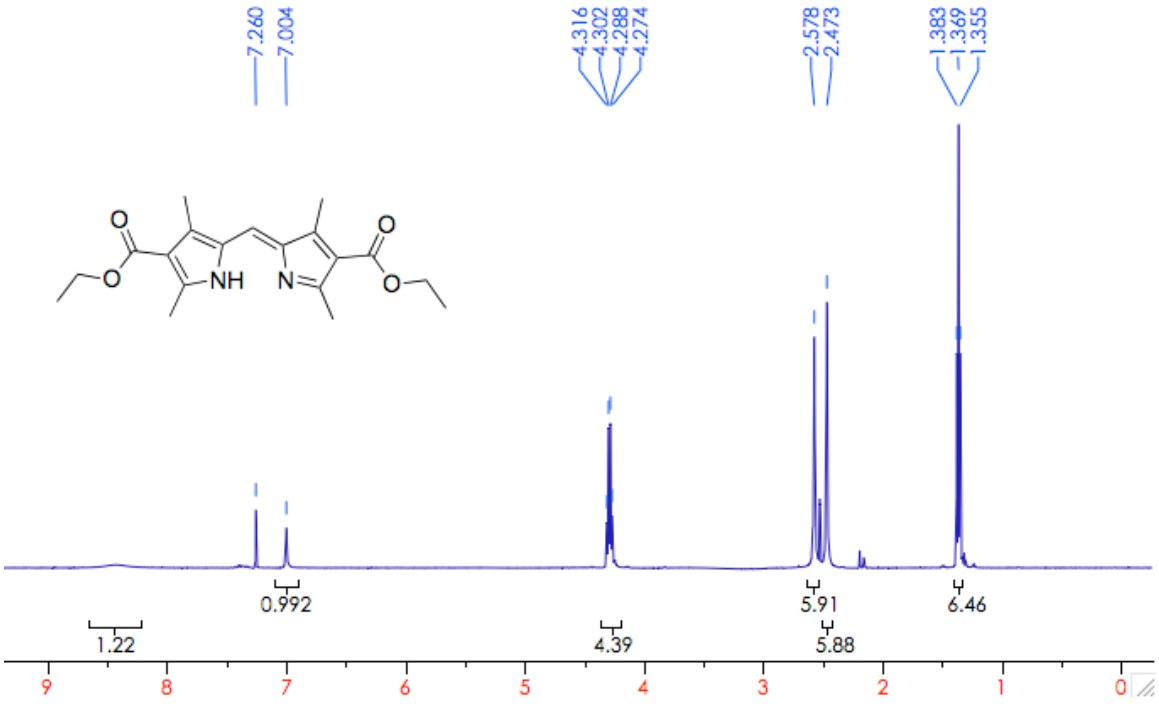


^{13}C NMR Spectrum in $CDCl_3$

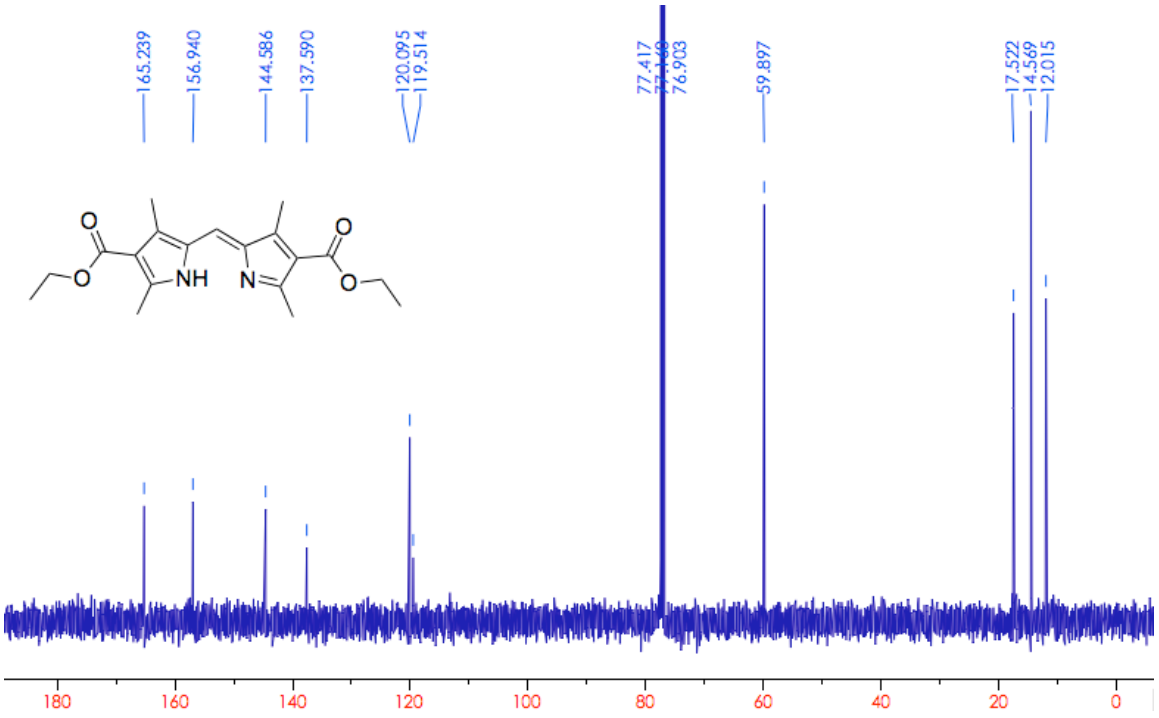


APPENDIX B.8 (*Z*)-Ethyl 5-((4-(ethoxycarbonyl)-3,5-dimethyl-2H-pyrrol-2-ylidene)methyl)-2,4-dimethyl-1H-pyrrole-3-carboxylate (**29**)[102]

^{1}H NMR Spectrum in $CDCl_3$

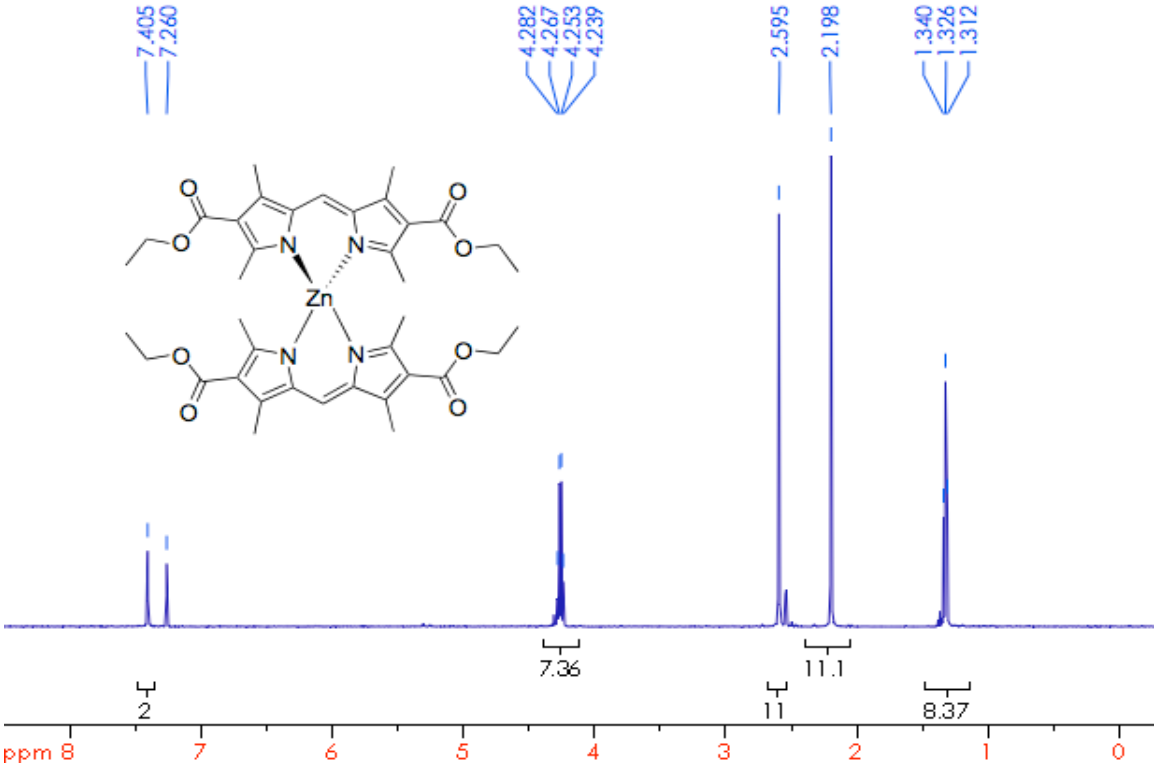


^{13}C NMR Spectrum in $CDCl_3$

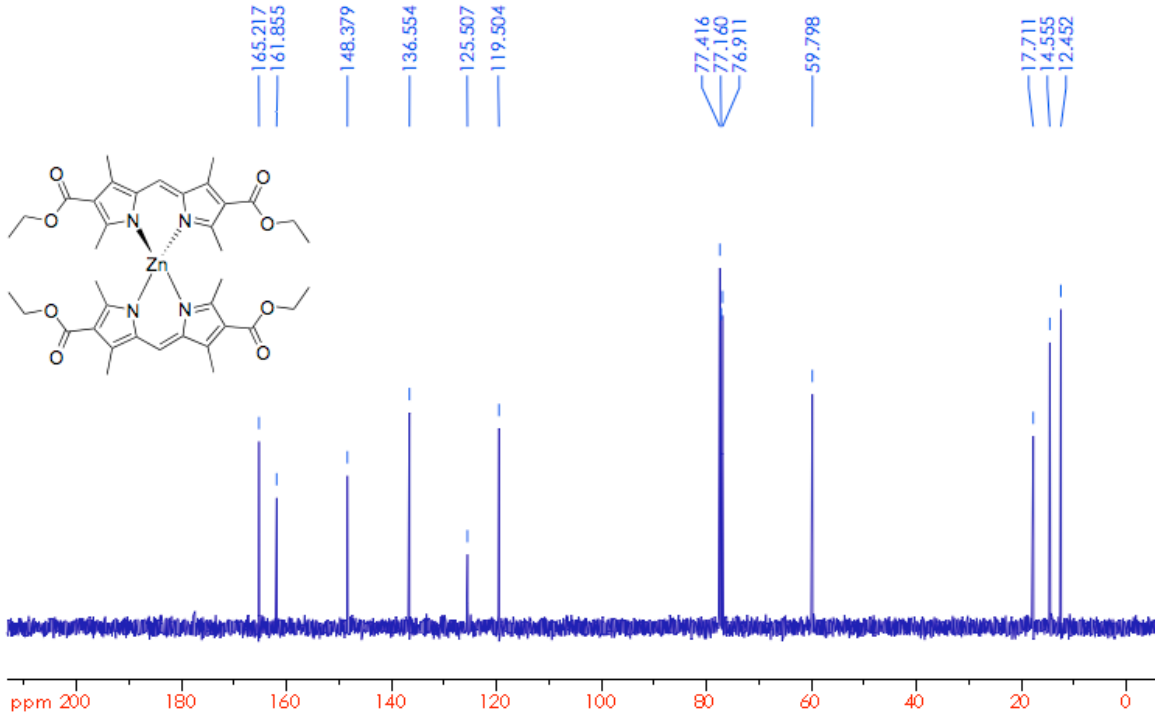


APPENDIX B.9 Zn(**29**)$_2$ (**30**)

^{1}H NMR Spectrum in $CDCl_3$

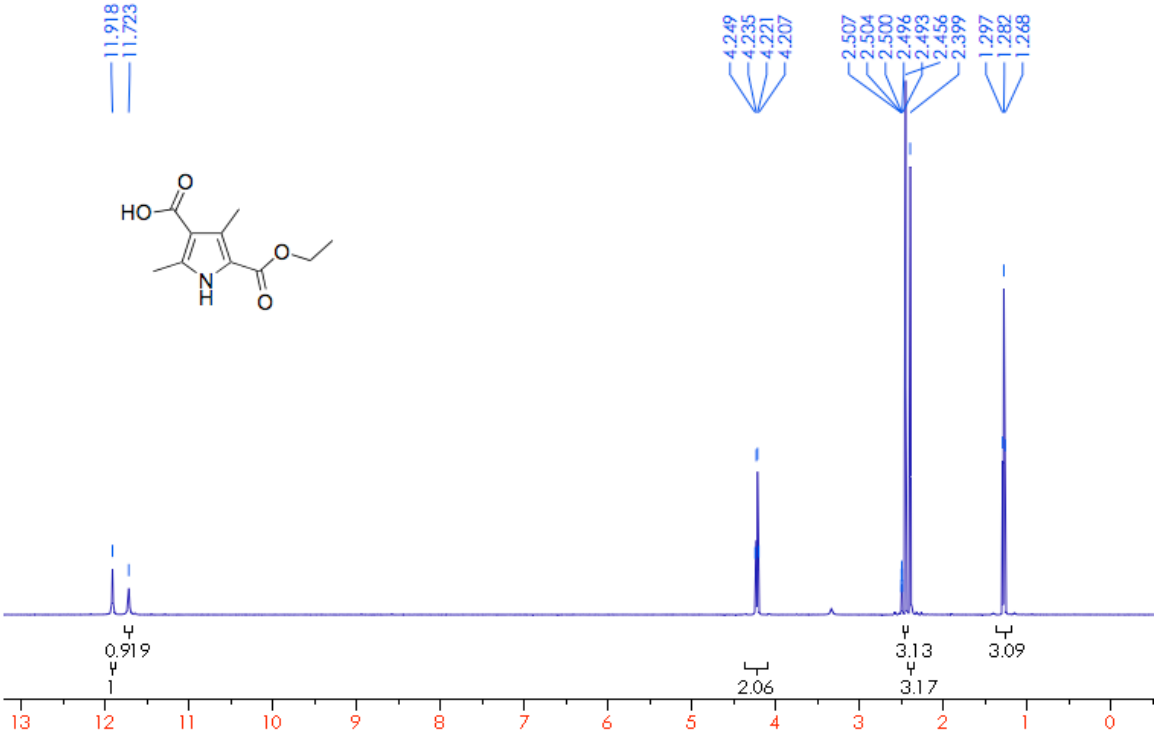


^{13}C NMR Spectrum in $CDCl_3$

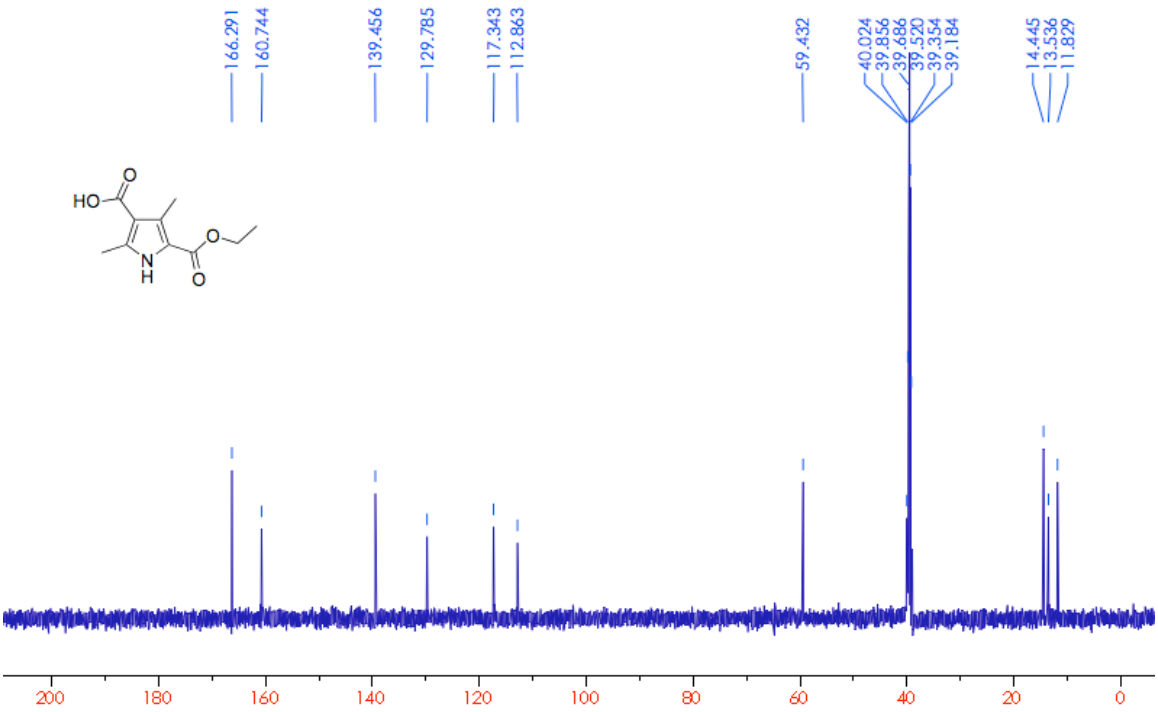


APPENDIX B.10 5-(Ethoxycarbonyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (**32**)[189]

^{1}H NMR Spectrum in DMSO-d_6

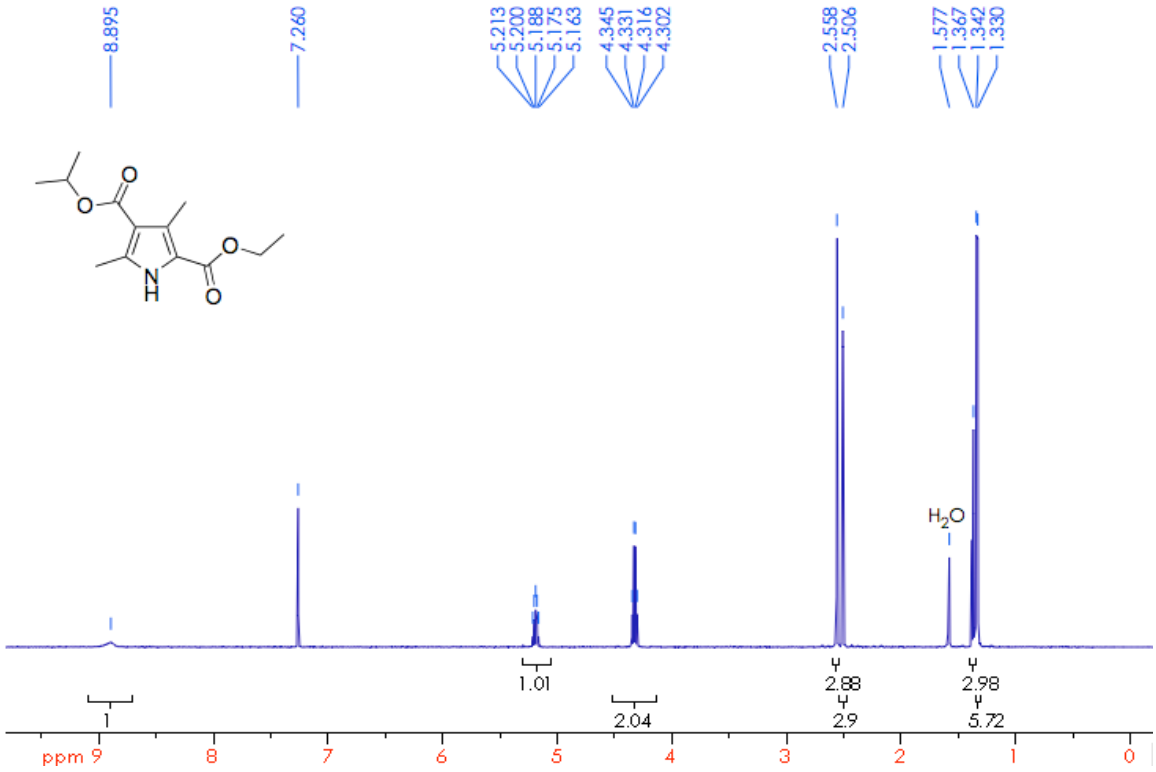


^{13}C NMR Spectrum in DMSO-d_6

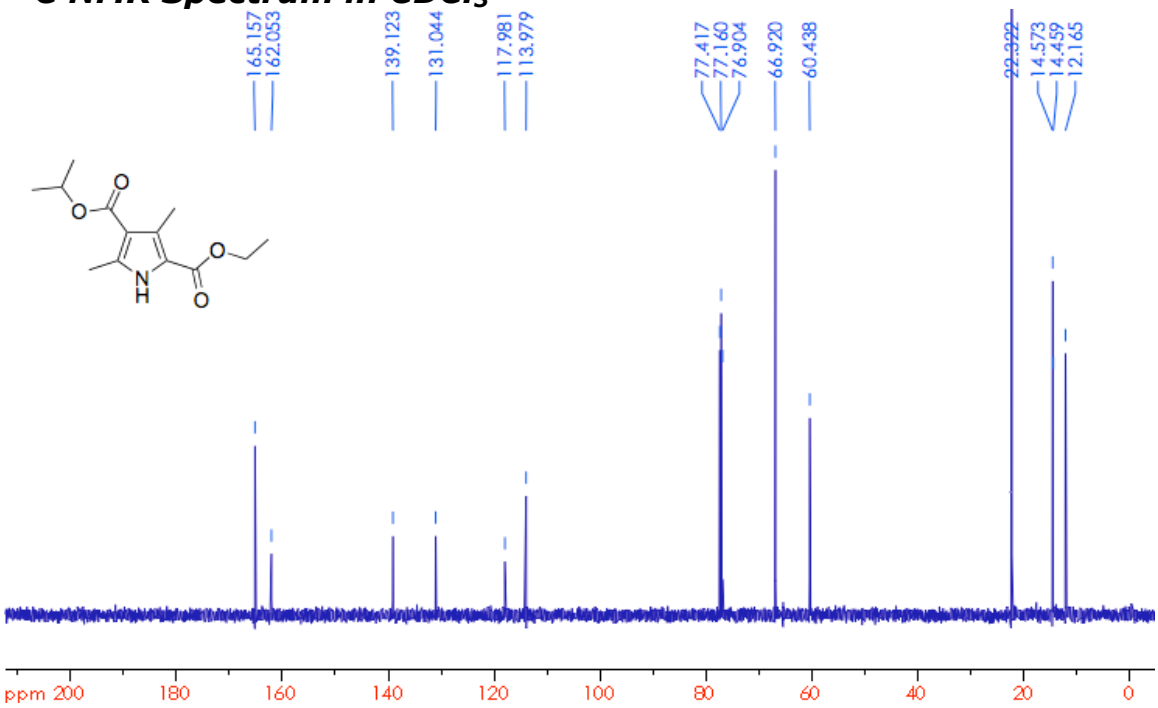


APPENDIX B.11 2-Ethyl 4-isopropyl 3,5-dimethyl-1H-pyrrole-2,4-dicarboxylate (**33**)

^{1}H NMR Spectrum in $CDCl_3$

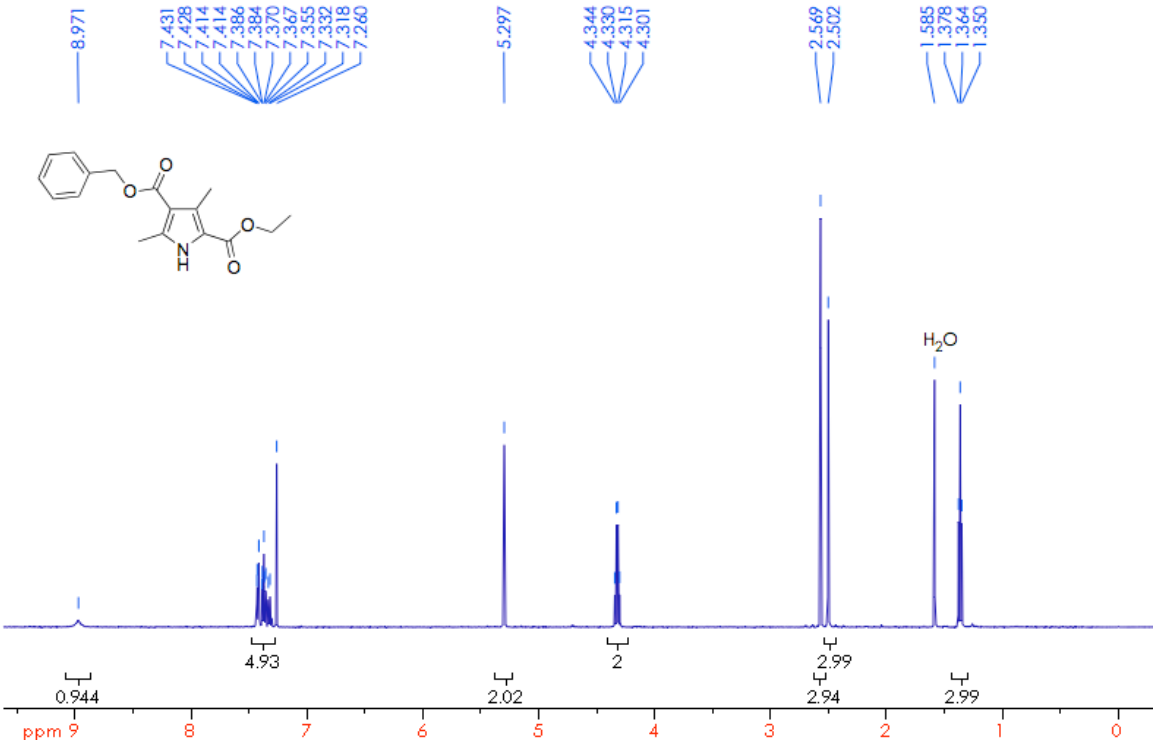


^{13}C NMR Spectrum in $CDCl_3$

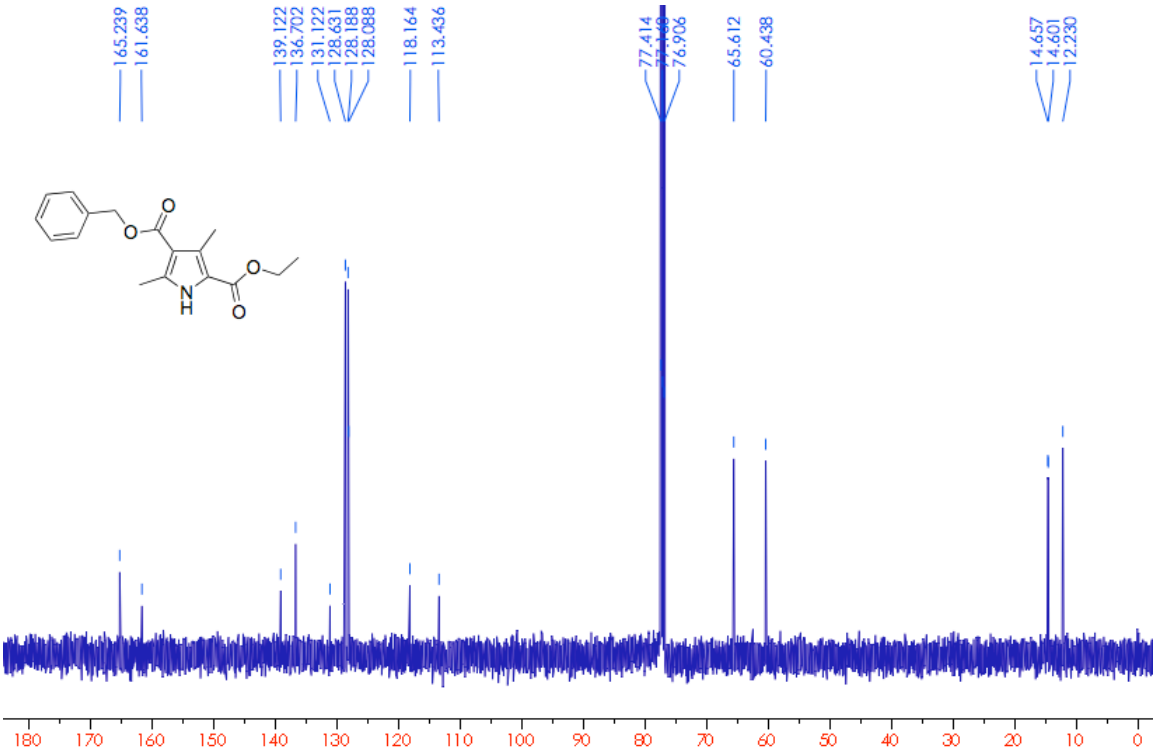


APPENDIX B.12 2-Ethyl 4-benzyl 3,5-dimethyl-1H-pyrrole-2,4-dicarboxylate (**34**)[189]

^{1}H NMR Spectrum in $CDCl_3$

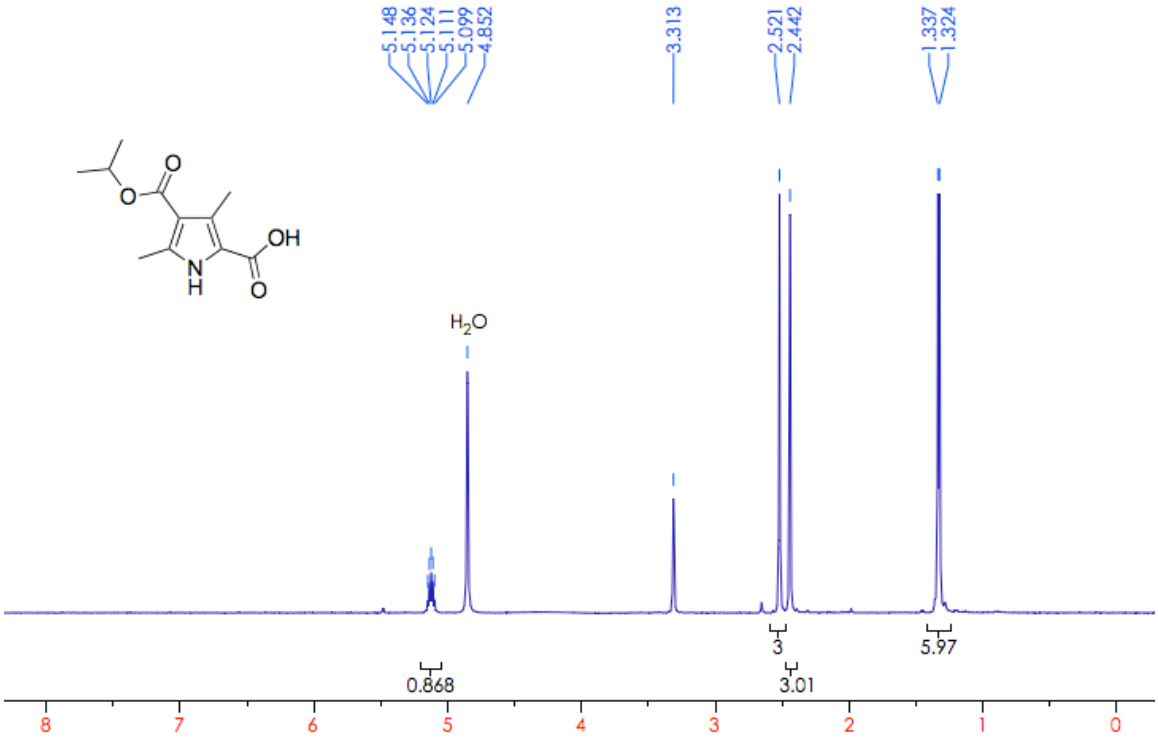


^{13}C NMR Spectrum in $CDCl_3$

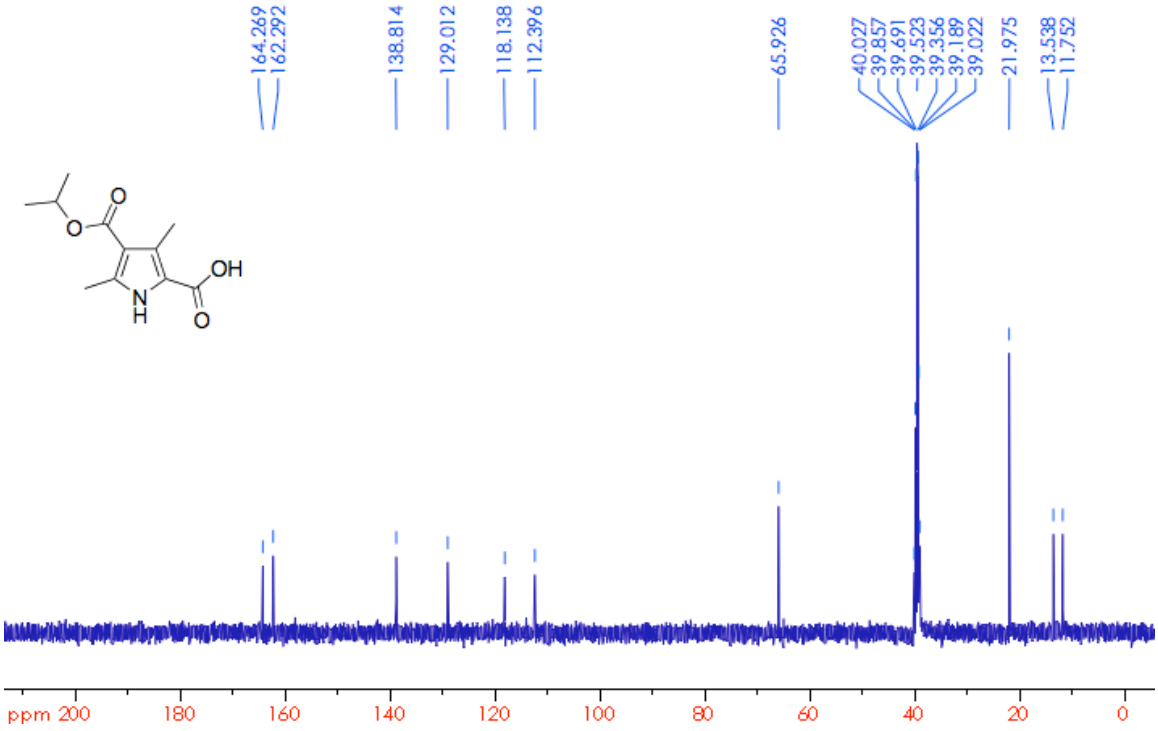


APPENDIX B.13 4-(*iso*Propoxycarbonyl)-3,5-dimethyl-1H-pyrrole-2-carboxylic acid (**35**)

^{1}H NMR Spectrum in CD_3OD

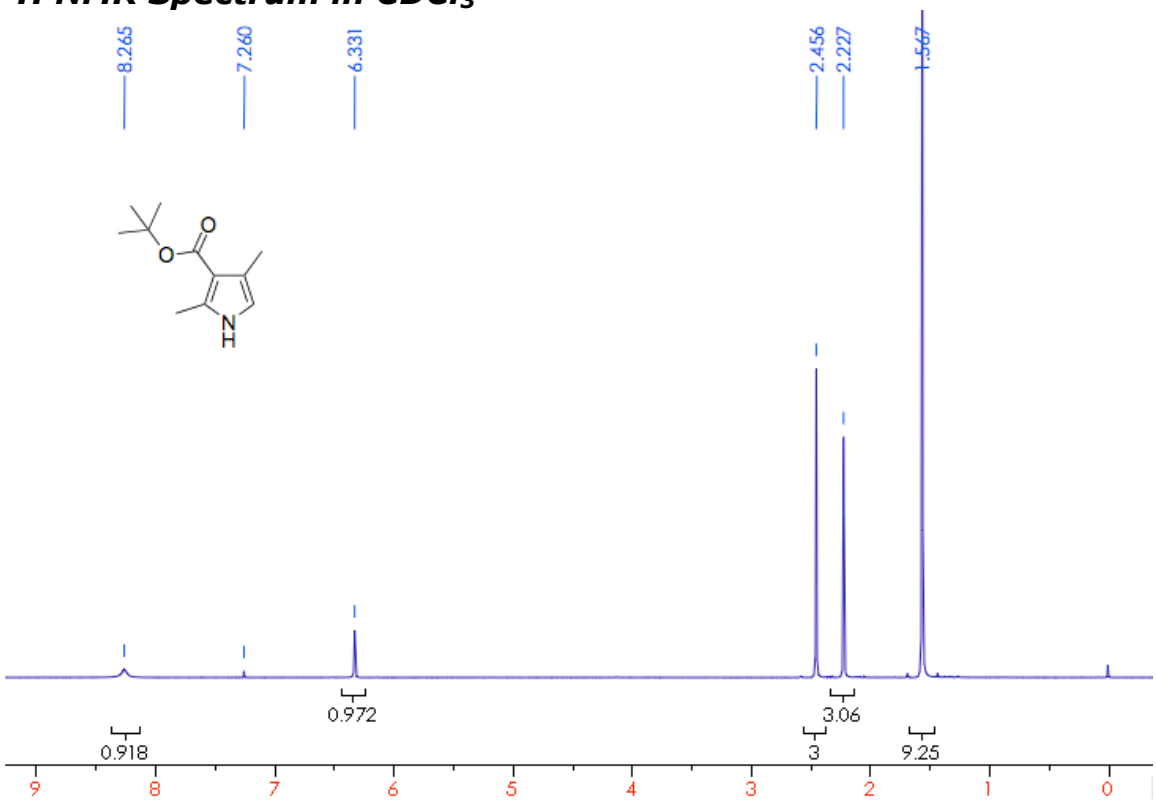


^{13}C NMR Spectrum in DMSO-d6

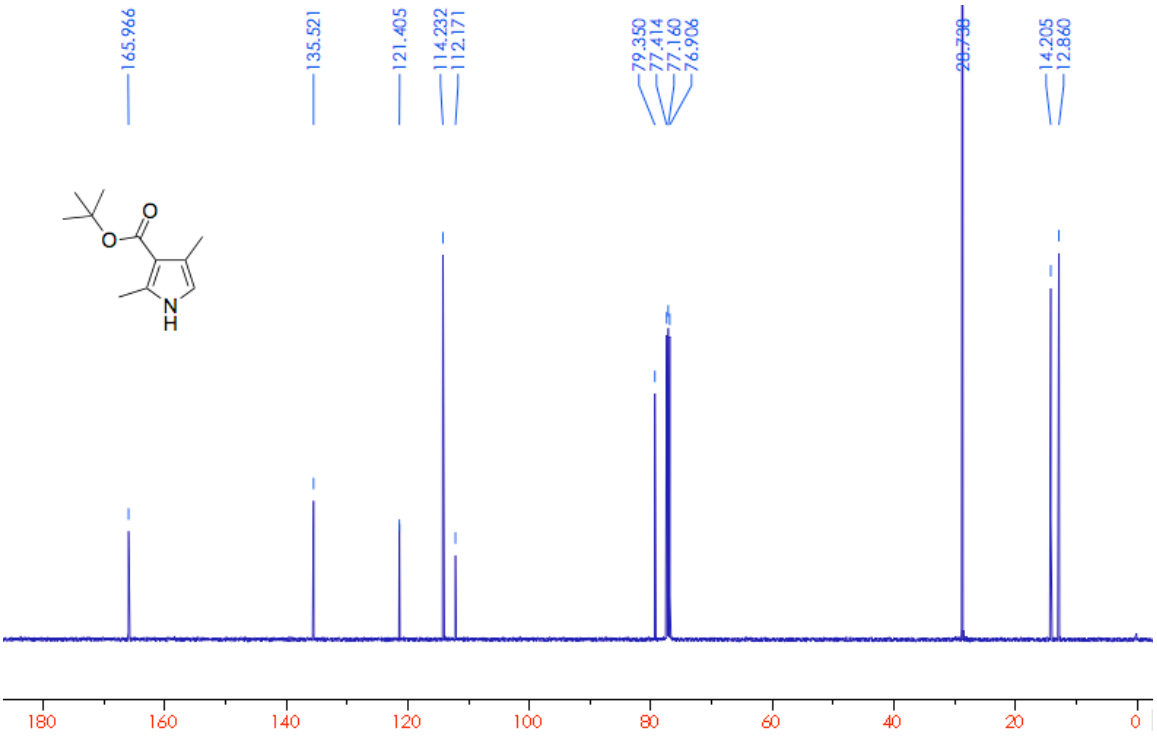


APPENDIX B.14 *tert*-Butyl 2,4-dimethyl-1H-pyrrole-3-carboxylate (**39**)

^{1}H NMR Spectrum in $CDCl_3$

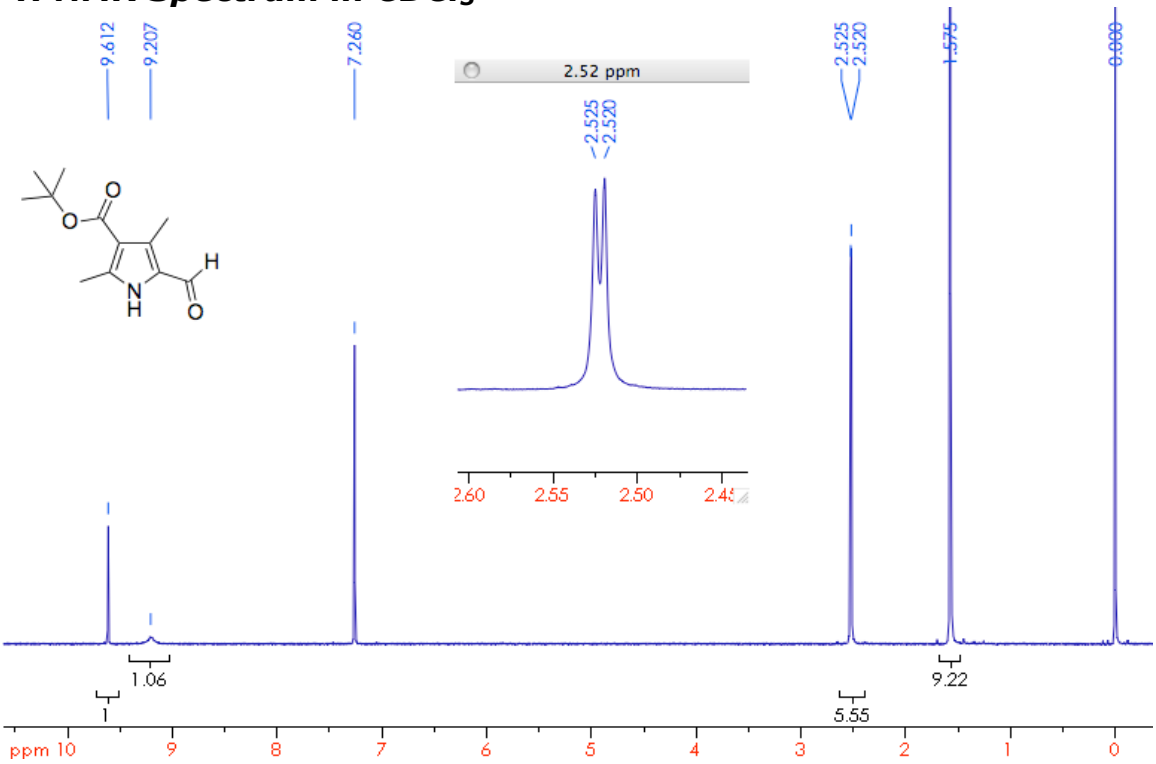


^{13}C NMR Spectrum in $CDCl_3$

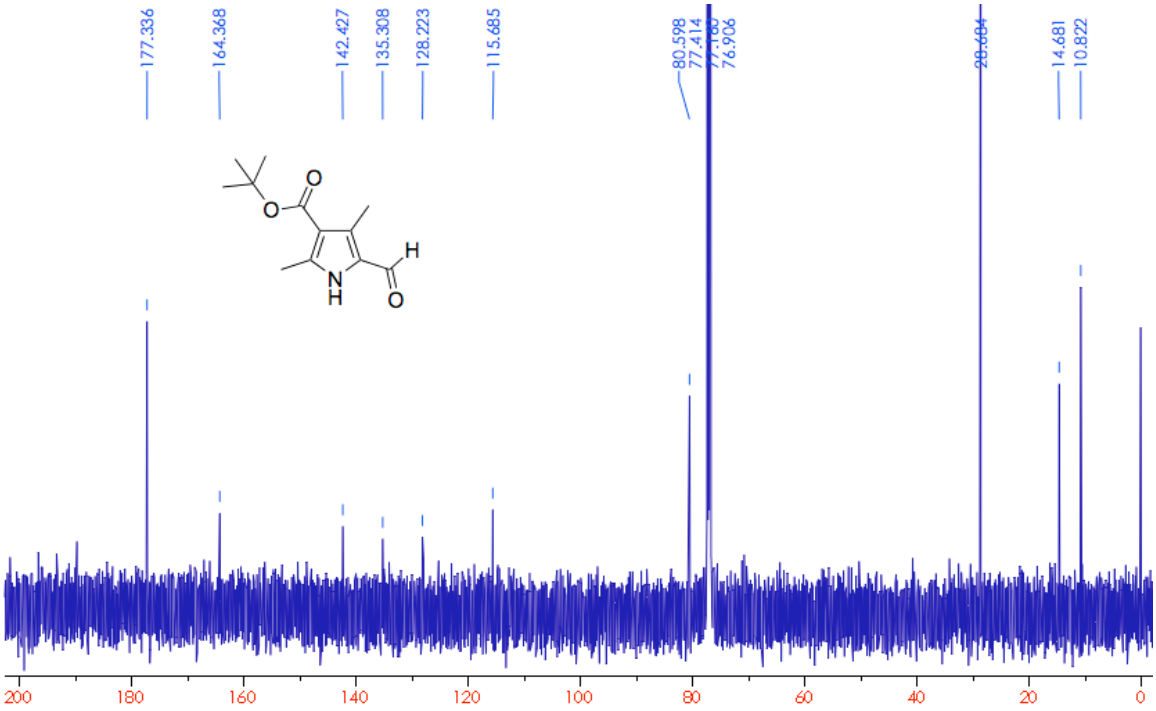


APPENDIX B.15 *tert*-Butyl 5-formyl-2,4-dimethyl-1*H*-pyrrole-3-carboxylate (**40**)

^{1}H NMR Spectrum in $CDCl_3$

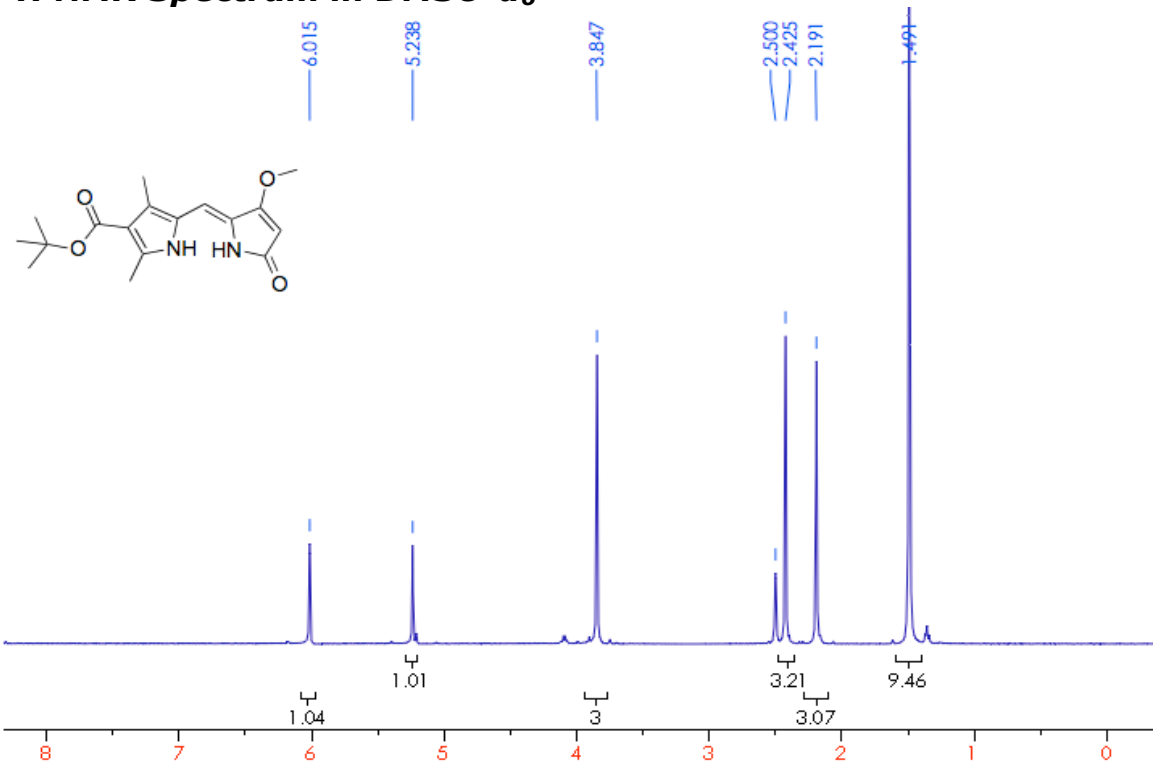


^{13}C NMR Spectrum in $CDCl_3$

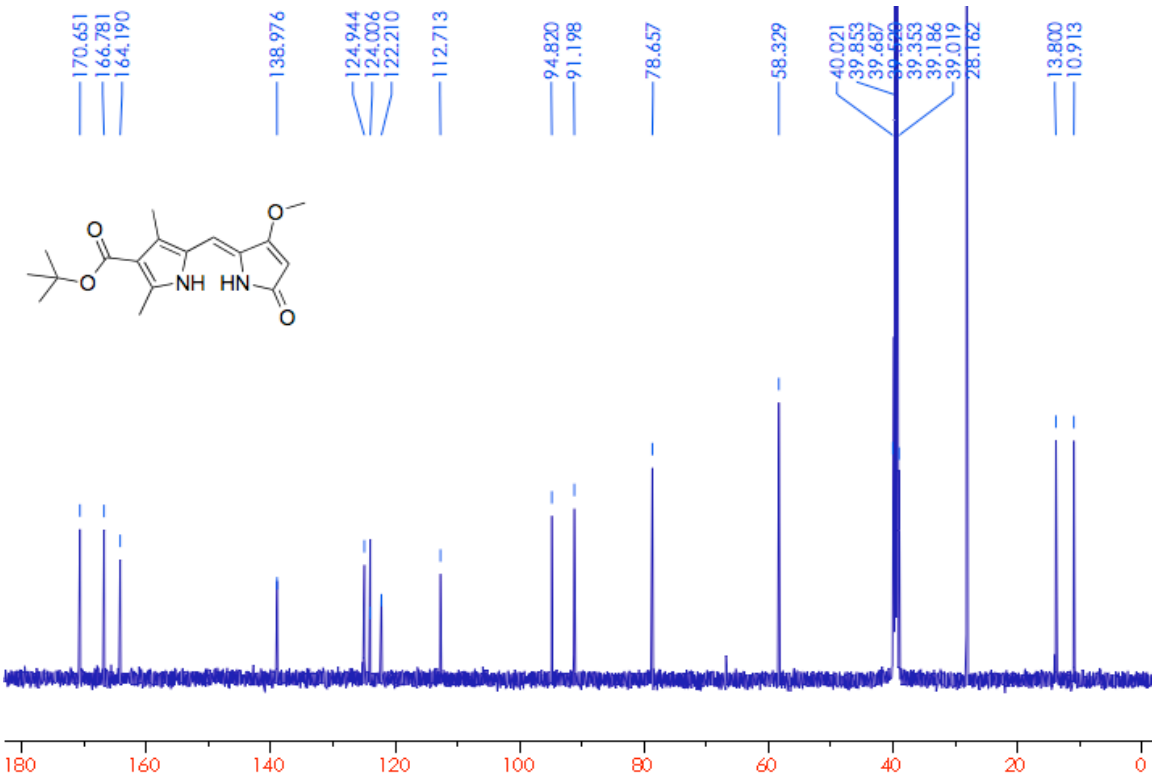


APPENDIX B.16 (*Z*)-*tert*-Butyl 5-((3-methoxy-5-oxo-1*H*-pyrrol-2(5*H*)-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrole-3-carboxylate (**41**)

^{1}H NMR Spectrum in DMSO-d_6

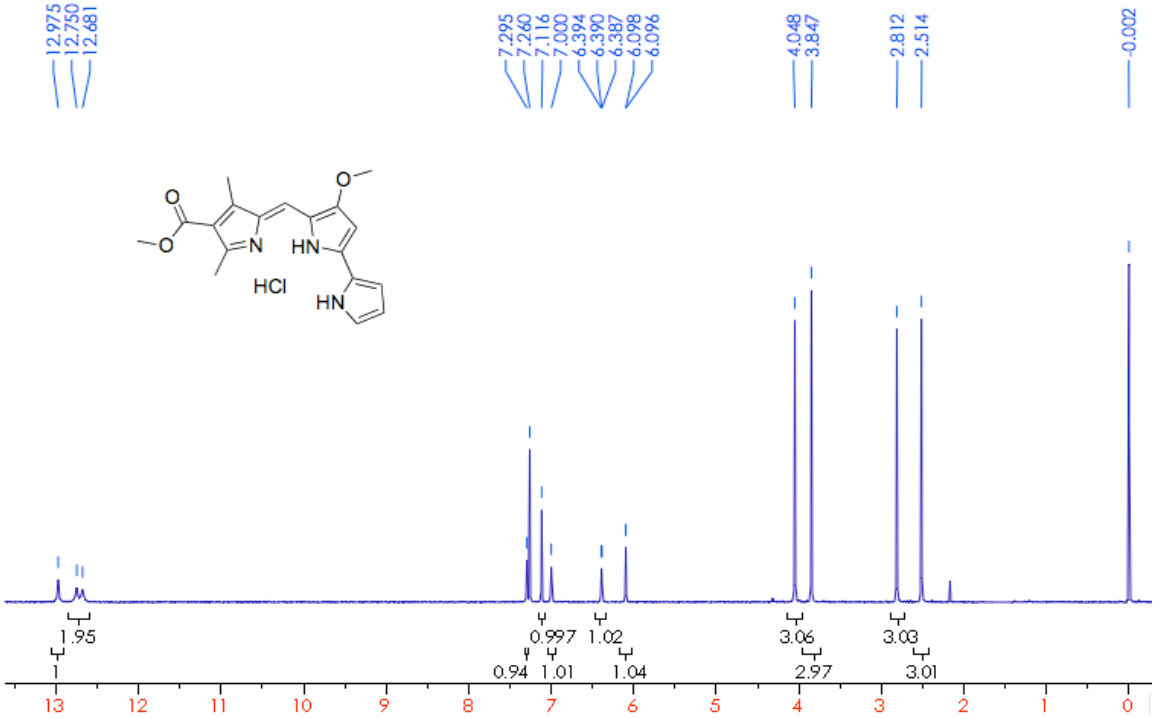


^{13}C NMR Spectrum in DMSO-d_6

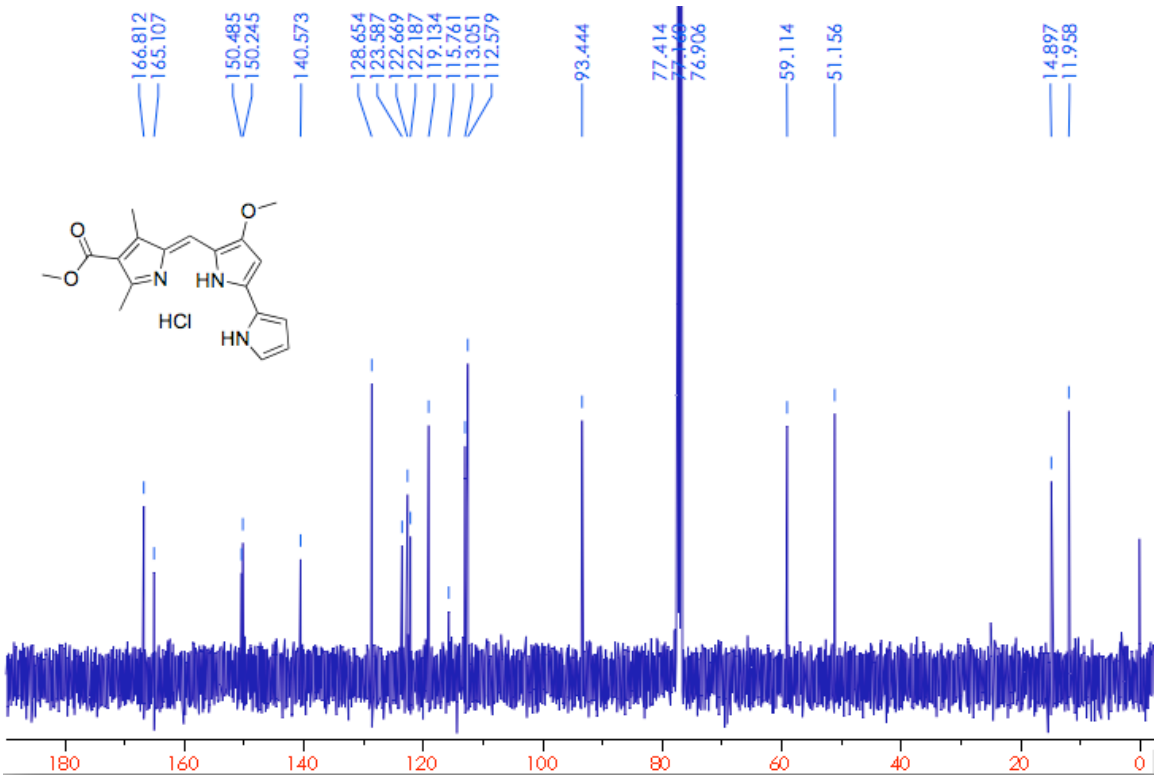


APPENDIX B.17 (*Z*)-Methyl 2-((4-methoxy-1H,1'H-2,2'-bipyrrol-5-yl)methylene)-3,5-dimethyl-2H-pyrrole-4-carboxylate hydrochloride (**44**)

^{1}H NMR Spectrum in $CDCl_3$

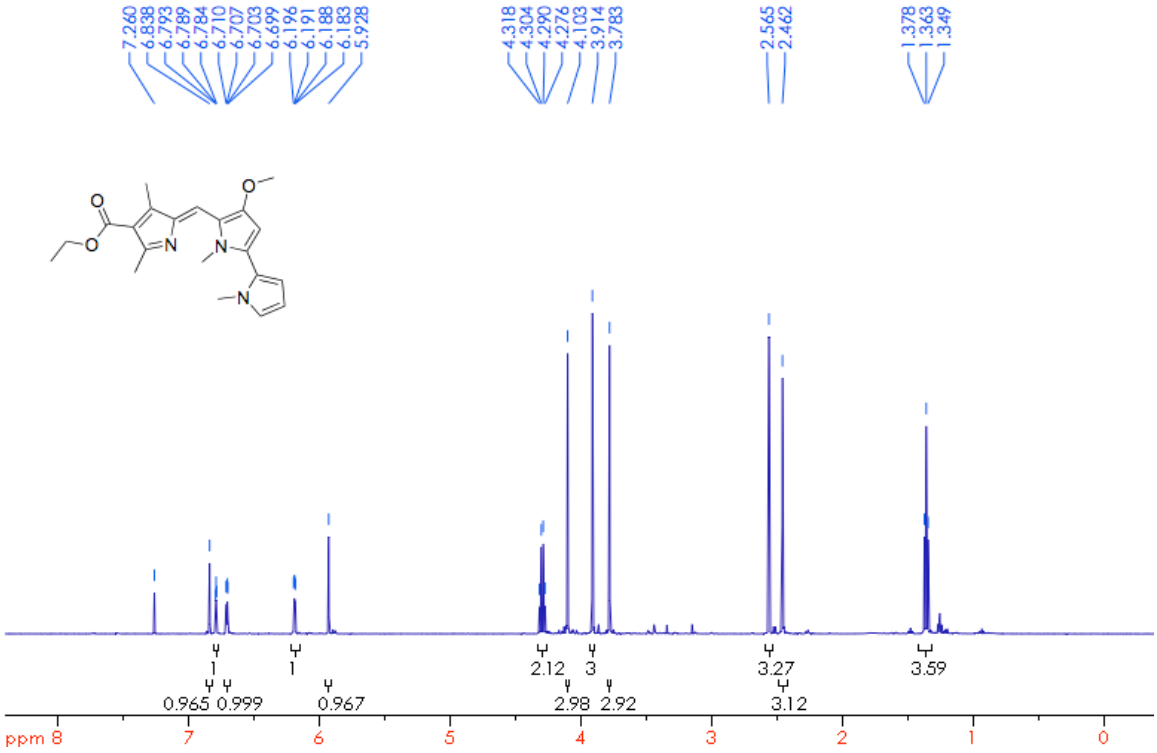


^{13}C NMR Spectrum in $CDCl_3$

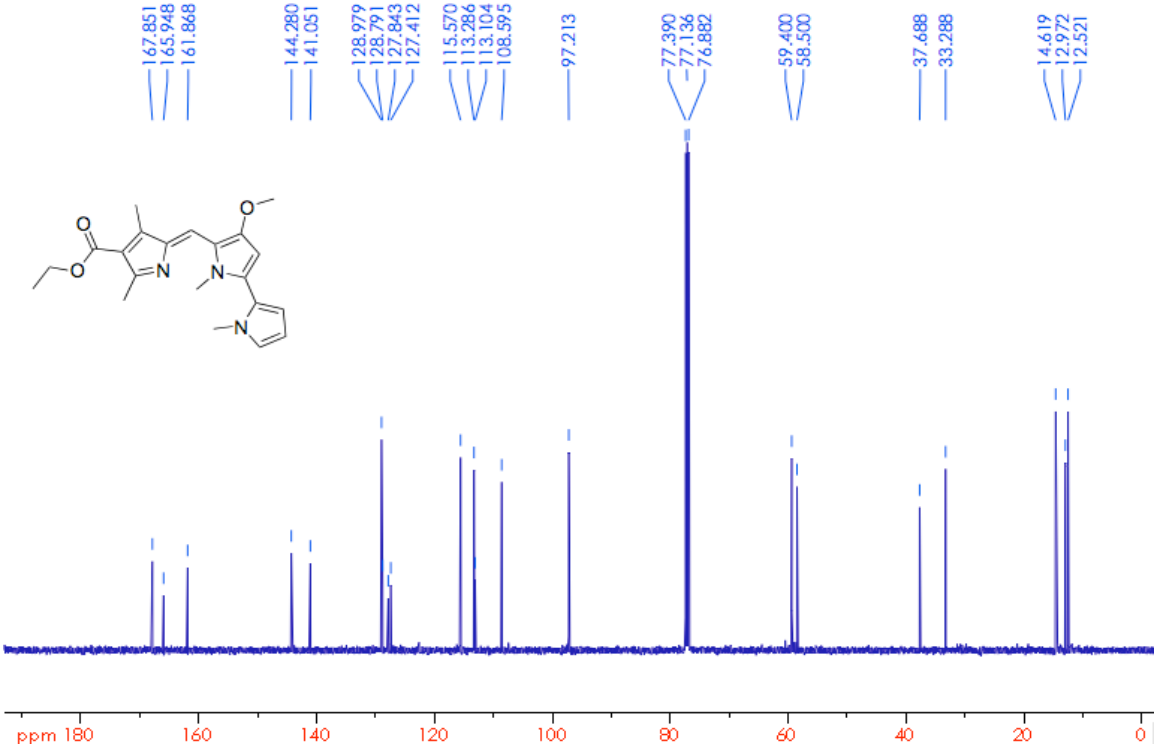


APPENDIX B.18 (*Z*)-Ethyl 2-((4-methoxy-1,1'-dimethyl-1*H*,1'*H*-2,2'-bipyrrol-5-yl)methylene)-3,5-dimethyl-2*H*-pyrrole-4-carboxylate (**47**)

^{1}H NMR Spectrum in $CDCl_3$

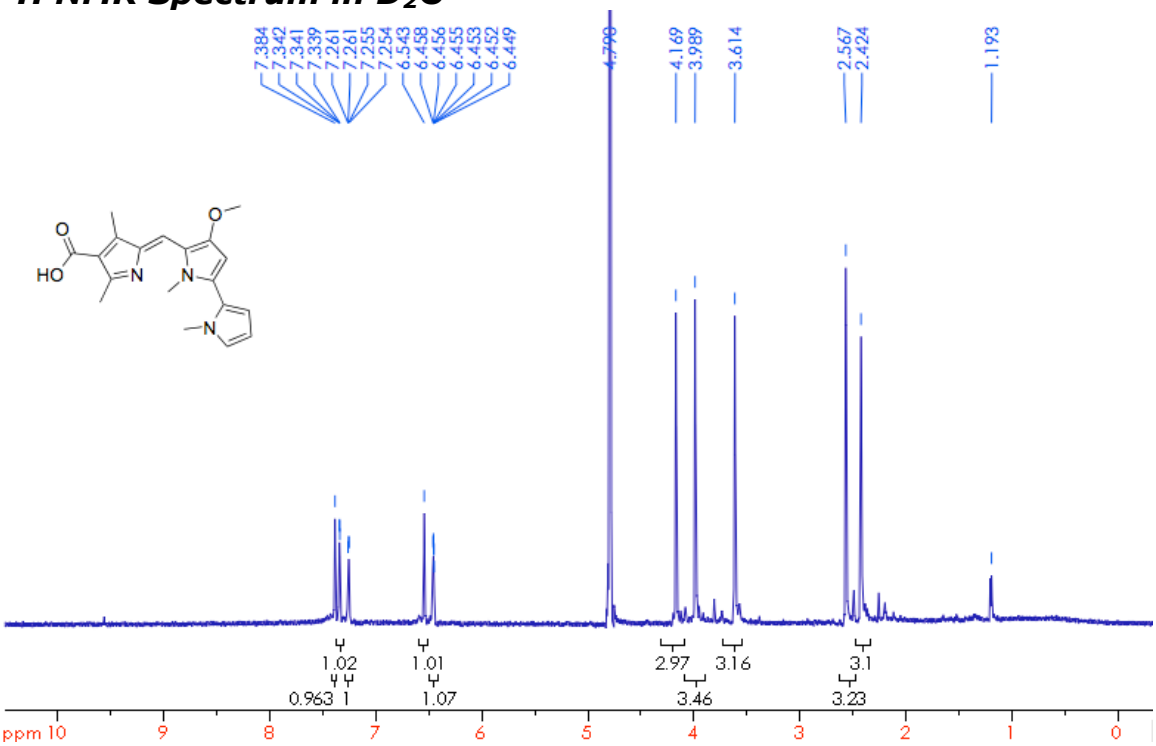


^{13}C NMR Spectrum in $CDCl_3$



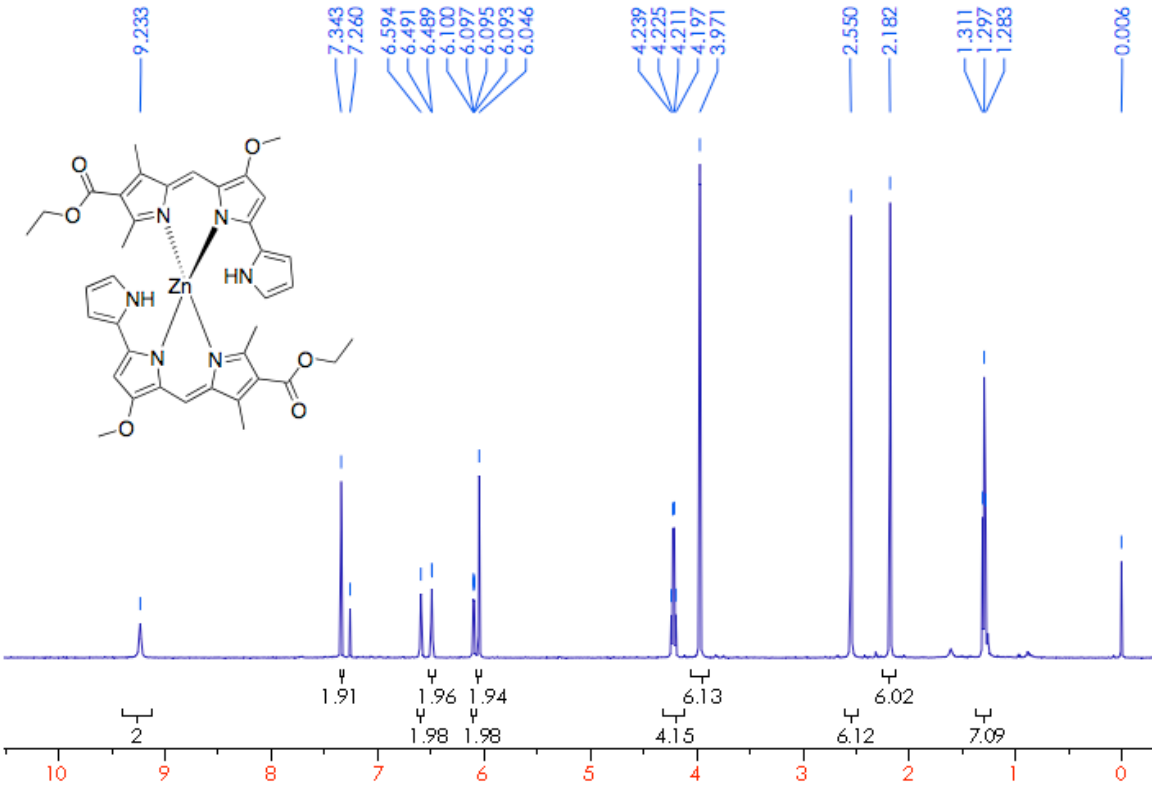
APPENDIX B.19 (*Z*)-2-((4-methoxy-1,1'-dimethyl-1*H*,1'*H*-2,2'-bipyrrol-5-yl)methylene)-3,5-dimethyl-2*H*-pyrrole-4-carboxylate (**48**)

^{1}H NMR Spectrum in D_2O

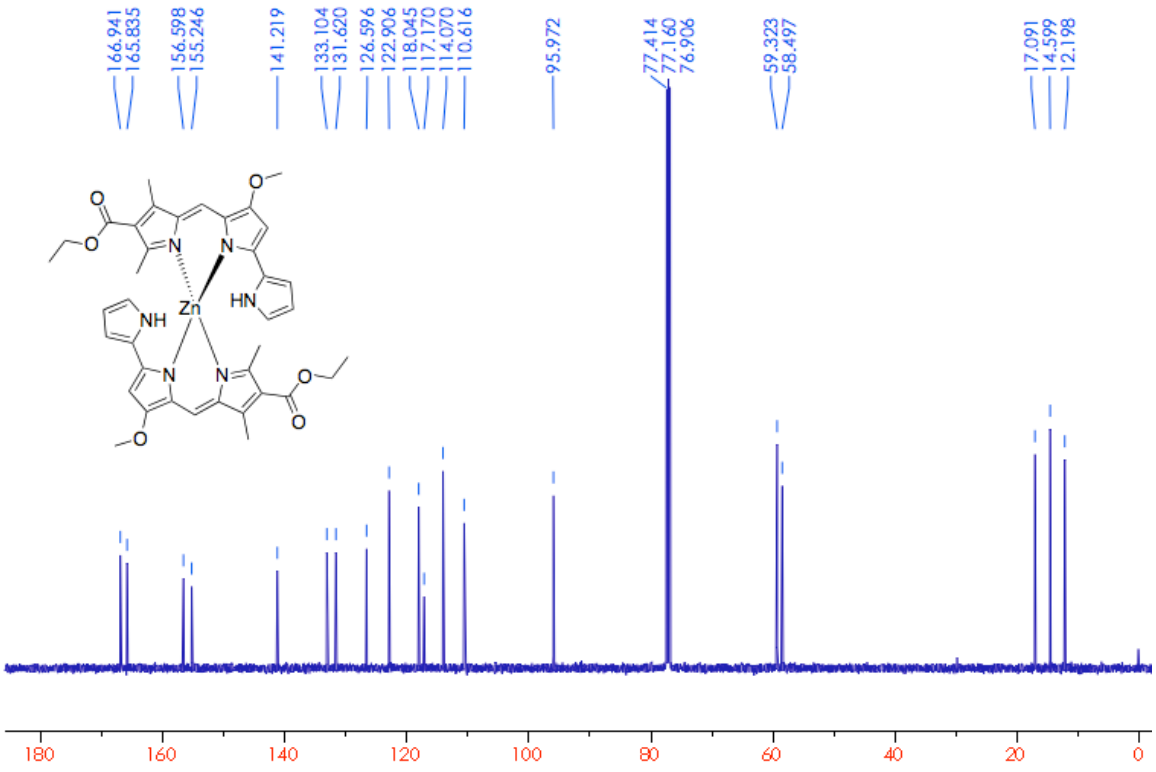


APPENDIX B.20 Zn(**1**)$_2$ (**51**)

^{1}H NMR Spectrum in $CDCl_3$

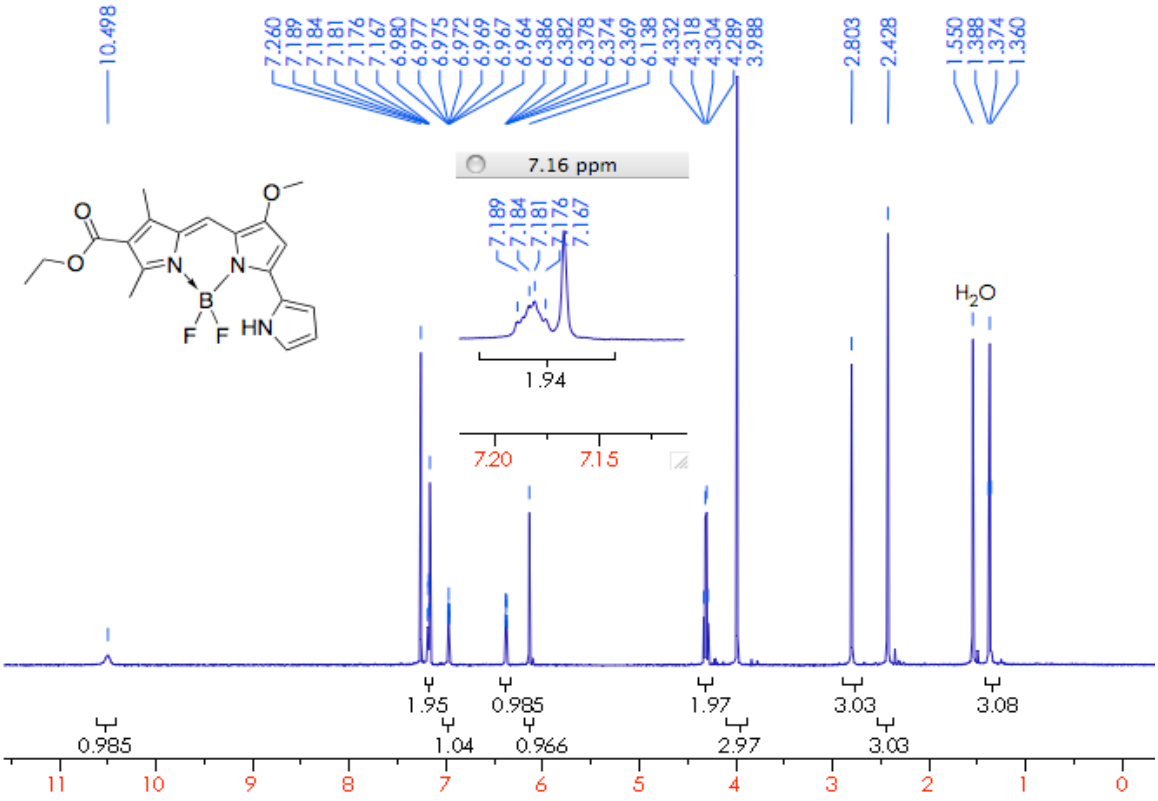


^{13}C NMR Spectrum in $CDCl_3$

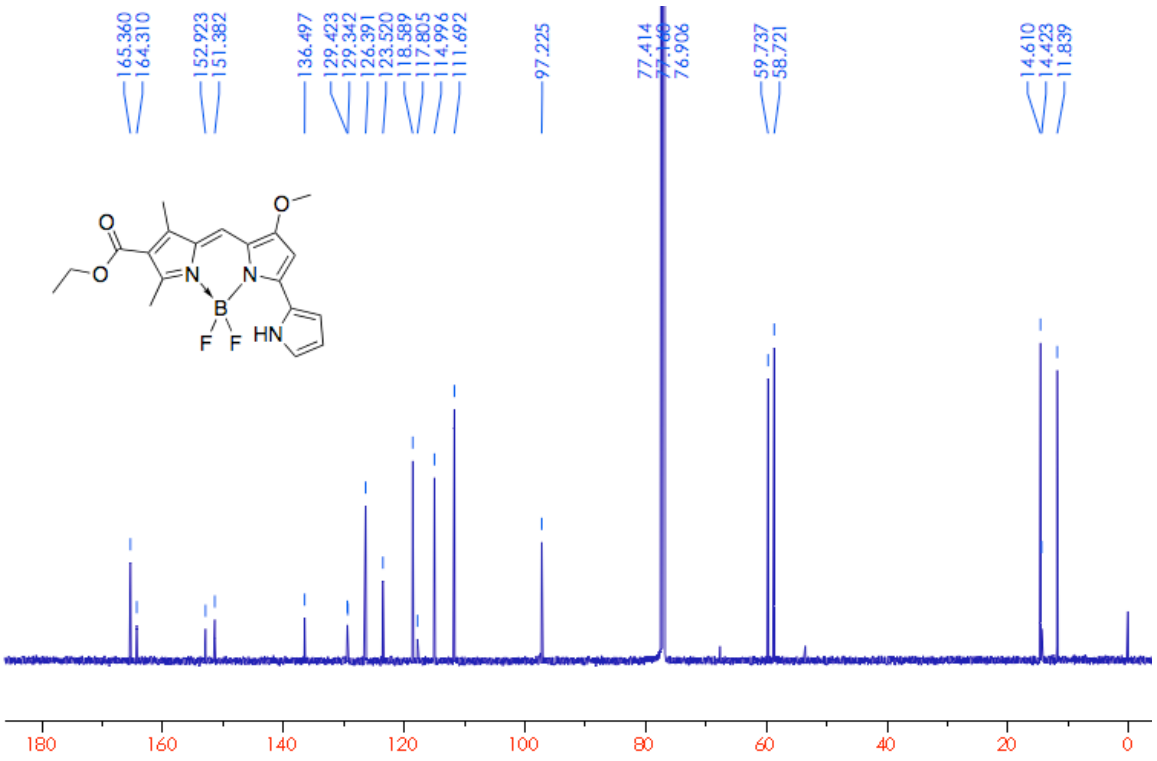


APPENDIX B.21 (**1**)BF_2 (**52**)

^{1}H NMR Spectrum in $CDCl_3$

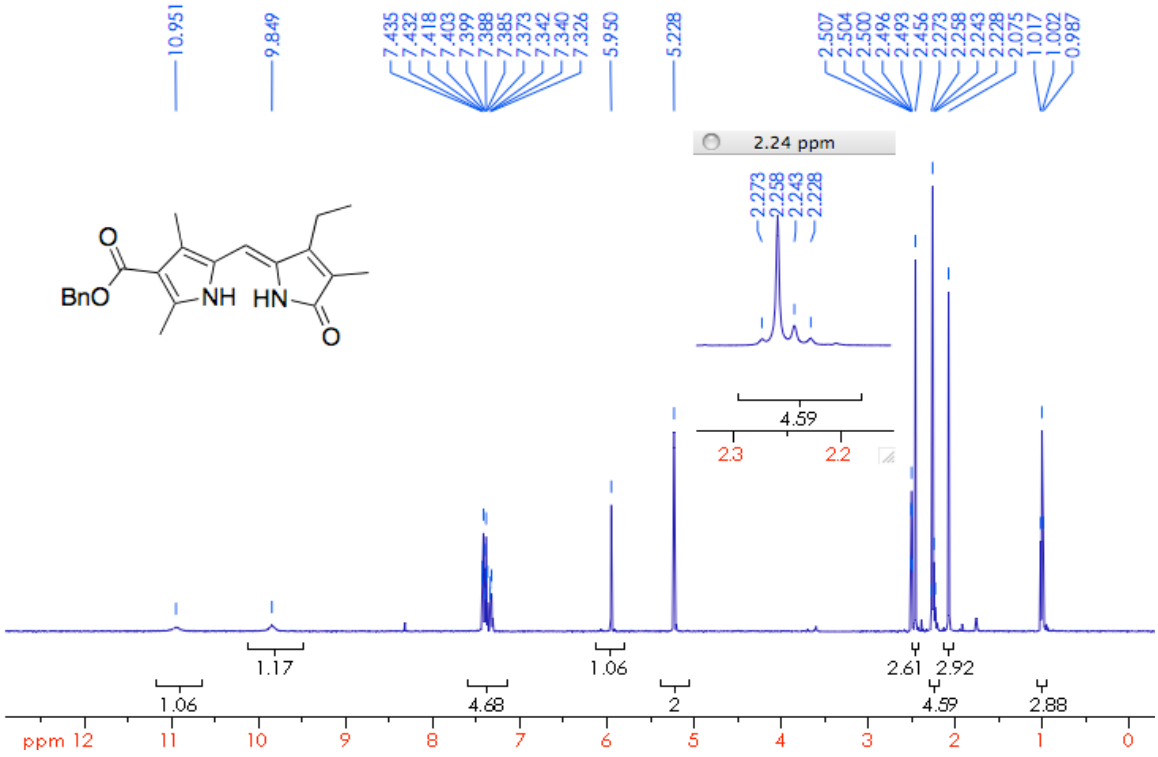


^{13}C NMR Spectrum in $CDCl_3$

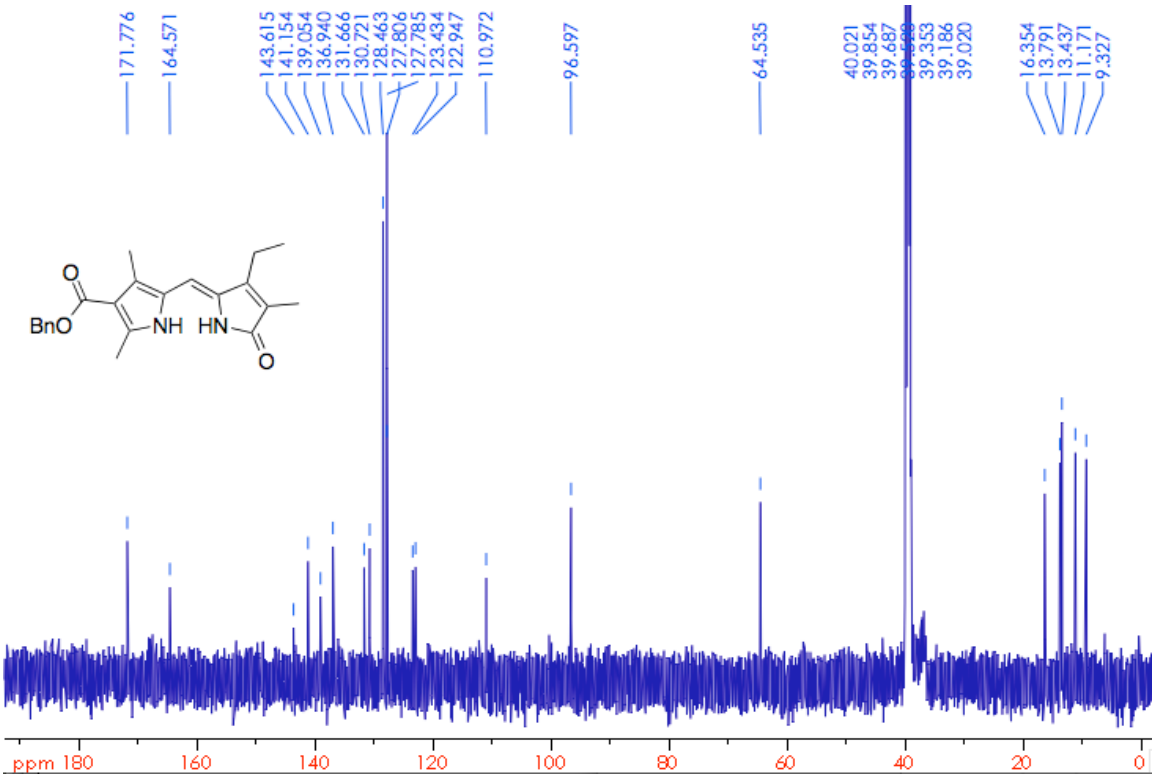


APPENDIX B.22 (*Z*)-Benzyl 5-((3-ethyl-4-methyl-5-oxo-1*H*-pyrrol-2(5*H*)-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrole-3-carboxylate (**56**)

^{1}H NMR Spectrum in DMSO-d_6

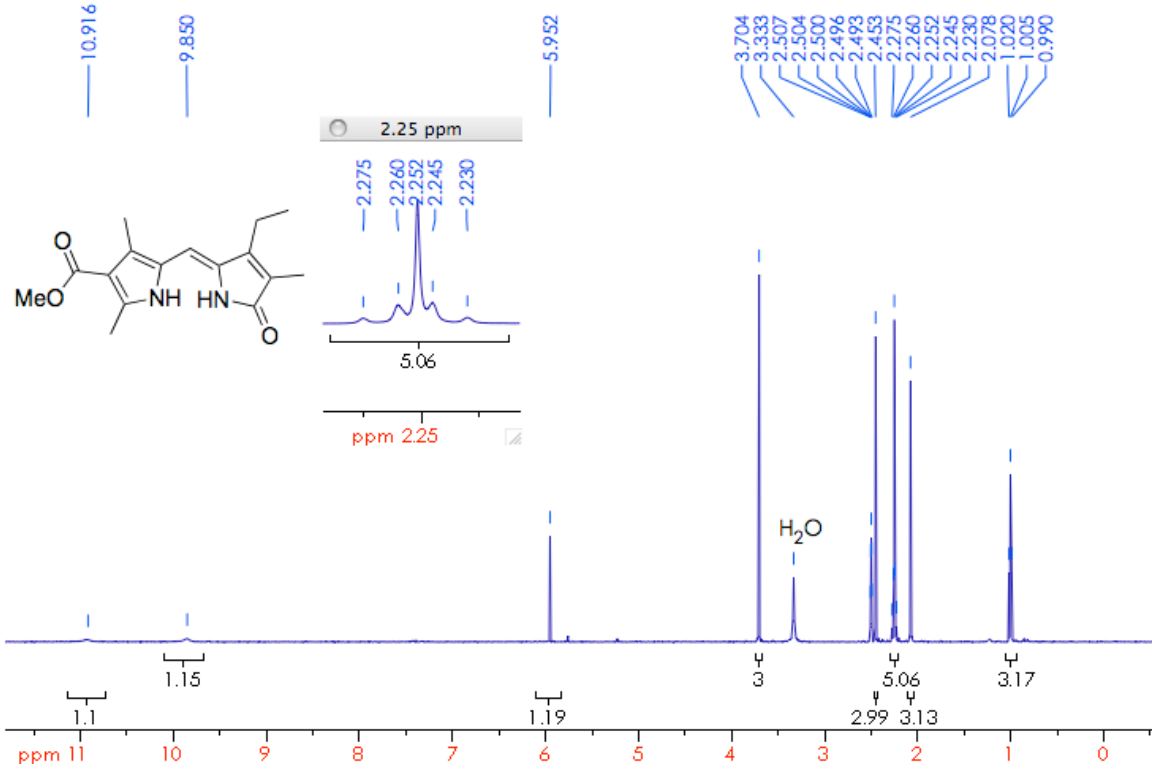


^{13}C NMR Spectrum in DMSO-d_6

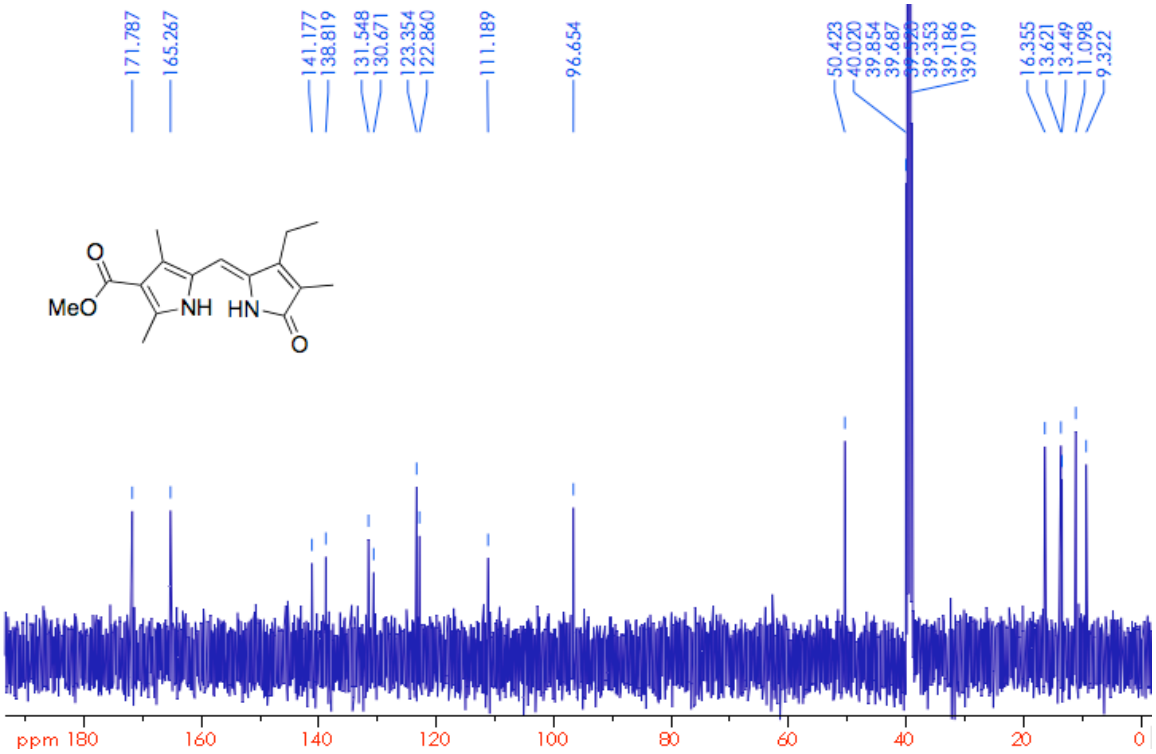


APPENDIX B.23 (*Z*)-Methyl 5-((3-ethyl-4-methyl-5-oxo-1*H*-pyrrol-2(5*H*)-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrole-3-carboxylate (**57**)

^{1}H NMR Spectrum in DMSO-d_6

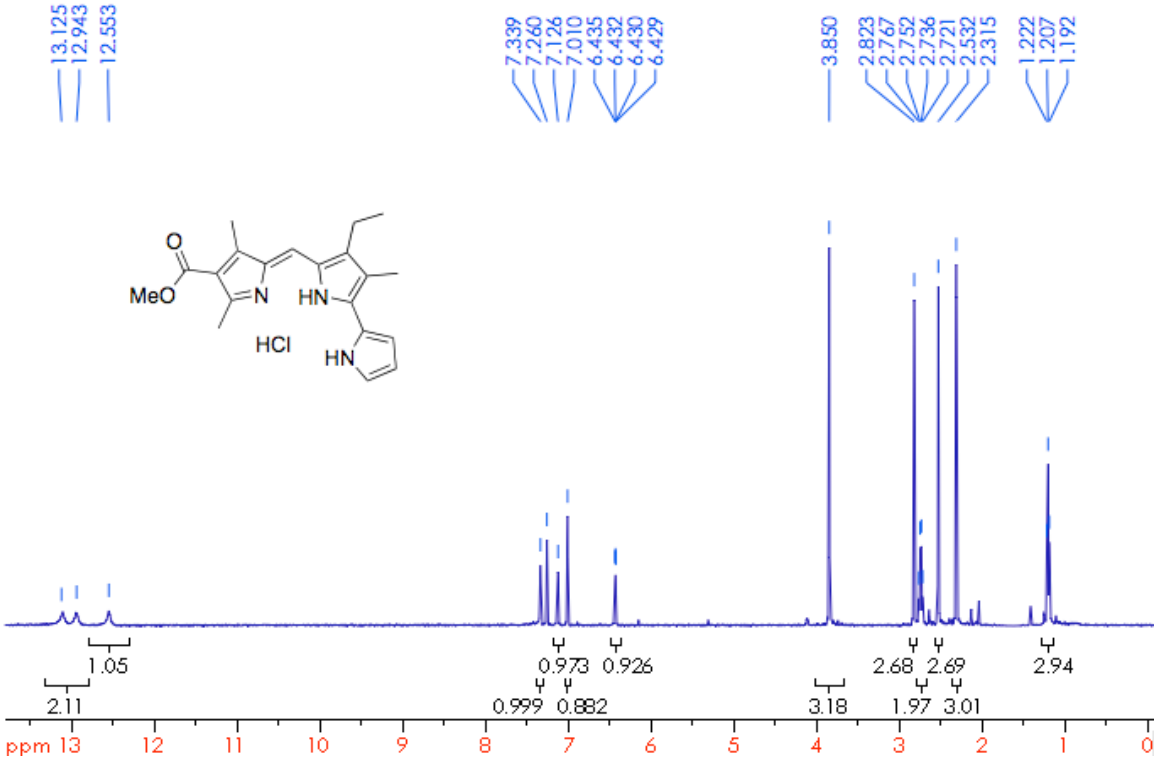


^{13}C NMR Spectrum in DMSO-d_6

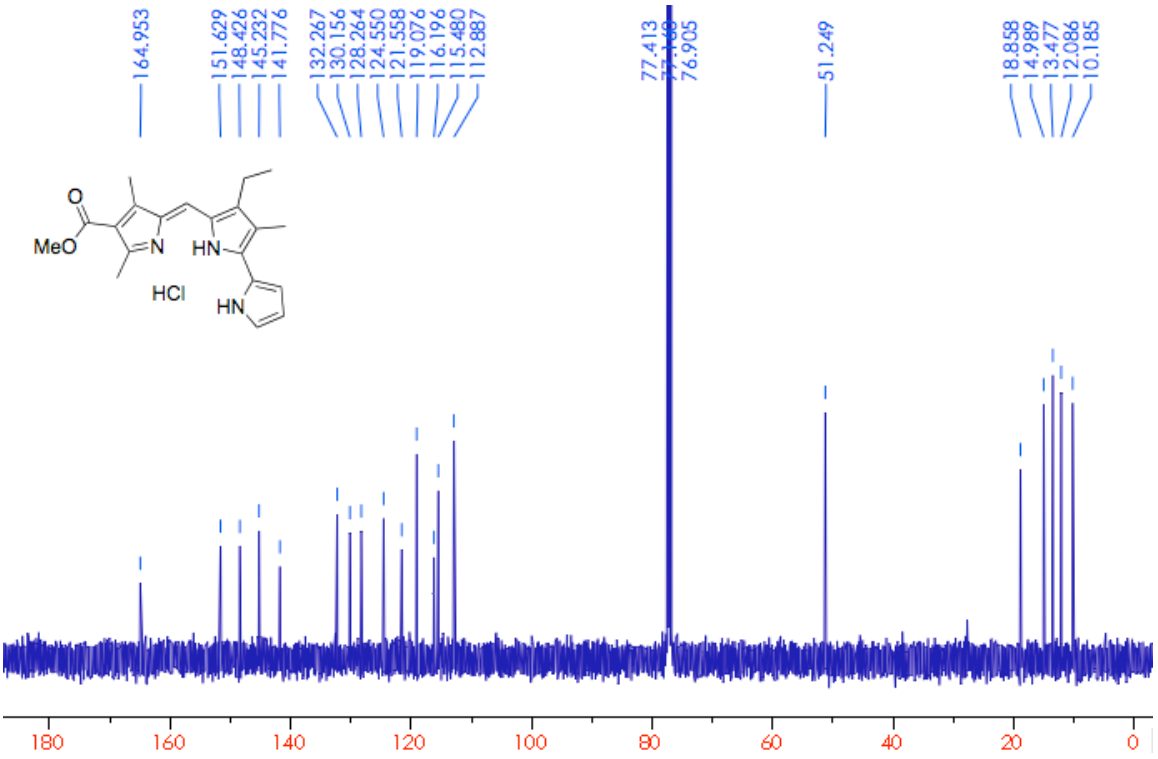


APPENDIX B.24 (*Z*)-Methyl 2-((4-ethyl-3-methyl-1*H*,1'*H*-2,2'-bipyrrol-5-yl)methylene)-3,5-dimethyl-2*H*-pyrrole-4-carboxylate (**58**)

^{1}H NMR Spectrum in $CDCl_3$

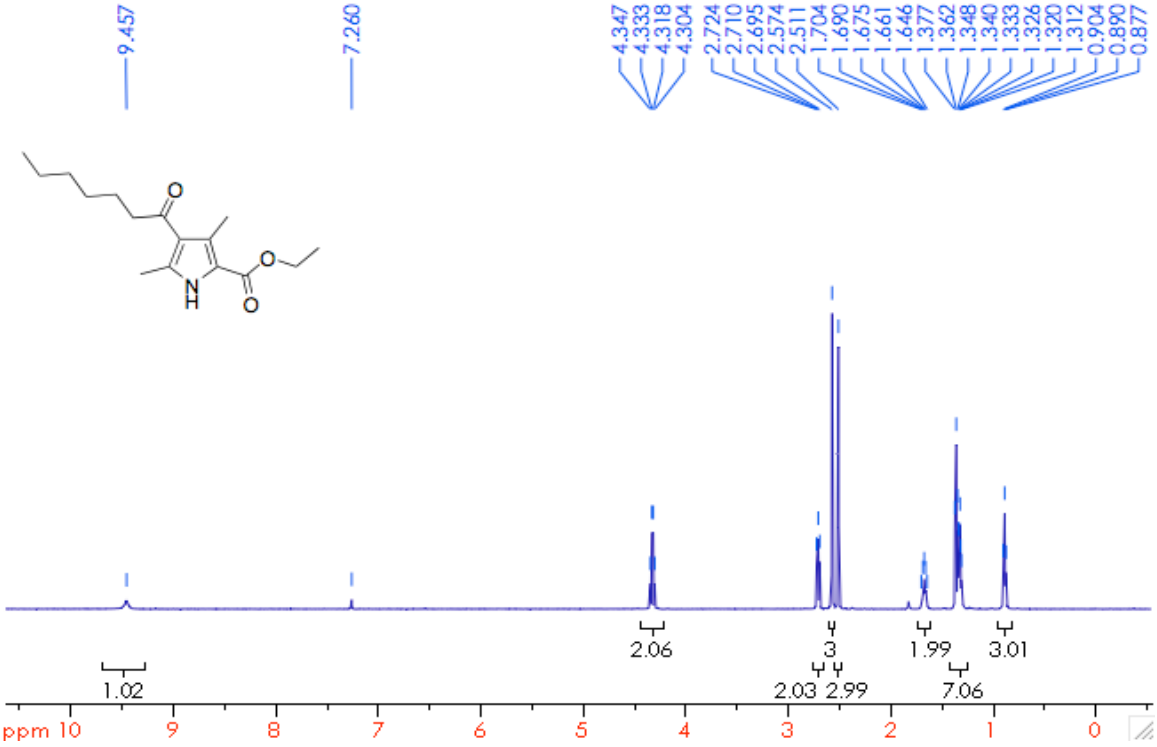


^{13}C NMR Spectrum in $CDCl_3$

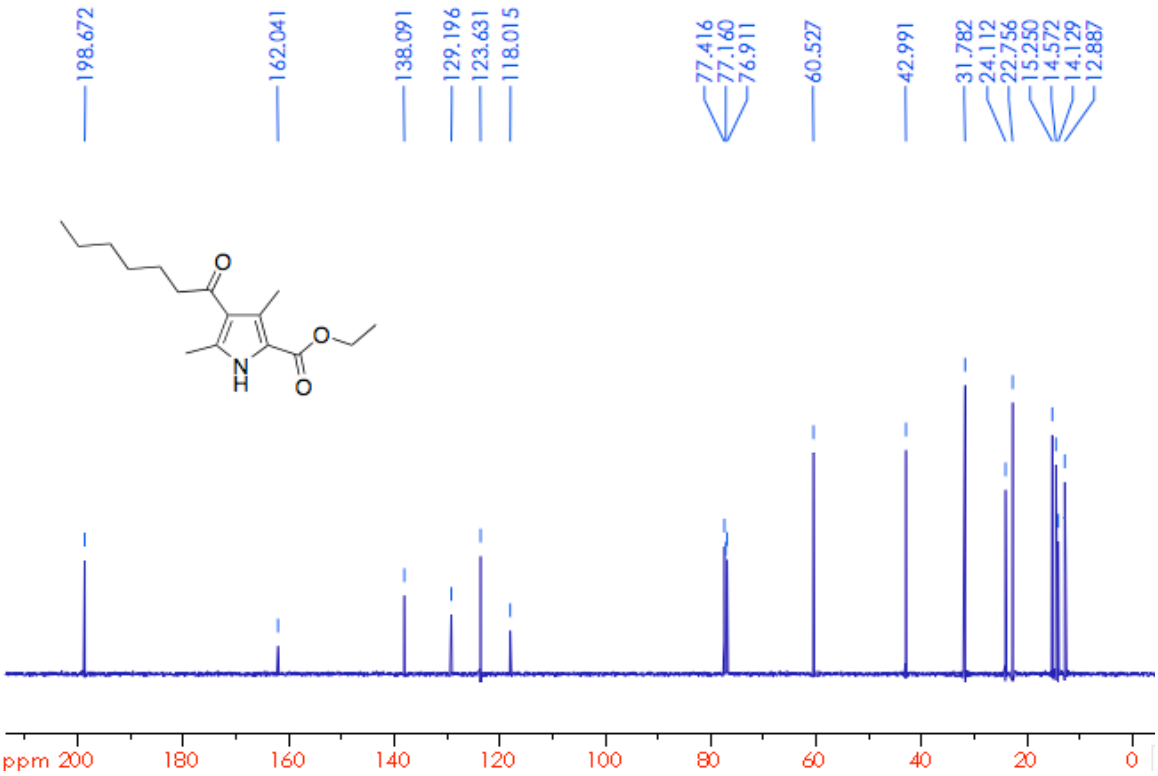


APPENDIX B.25 Ethyl 4-heptanoyl-3,5-dimethyl-1*H*-pyrrole-2-carboxylate (**60**)

^{1}H NMR Spectrum in $CDCl_3$

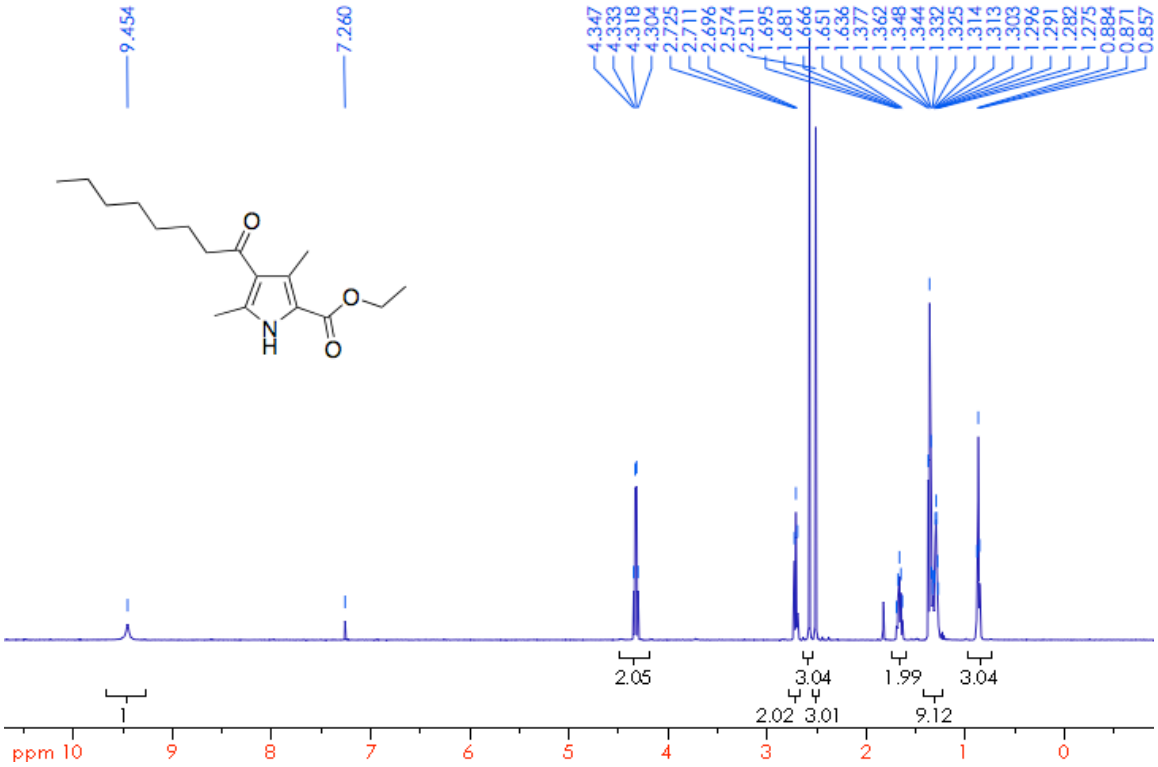


^{13}C NMR Spectrum in $CDCl_3$

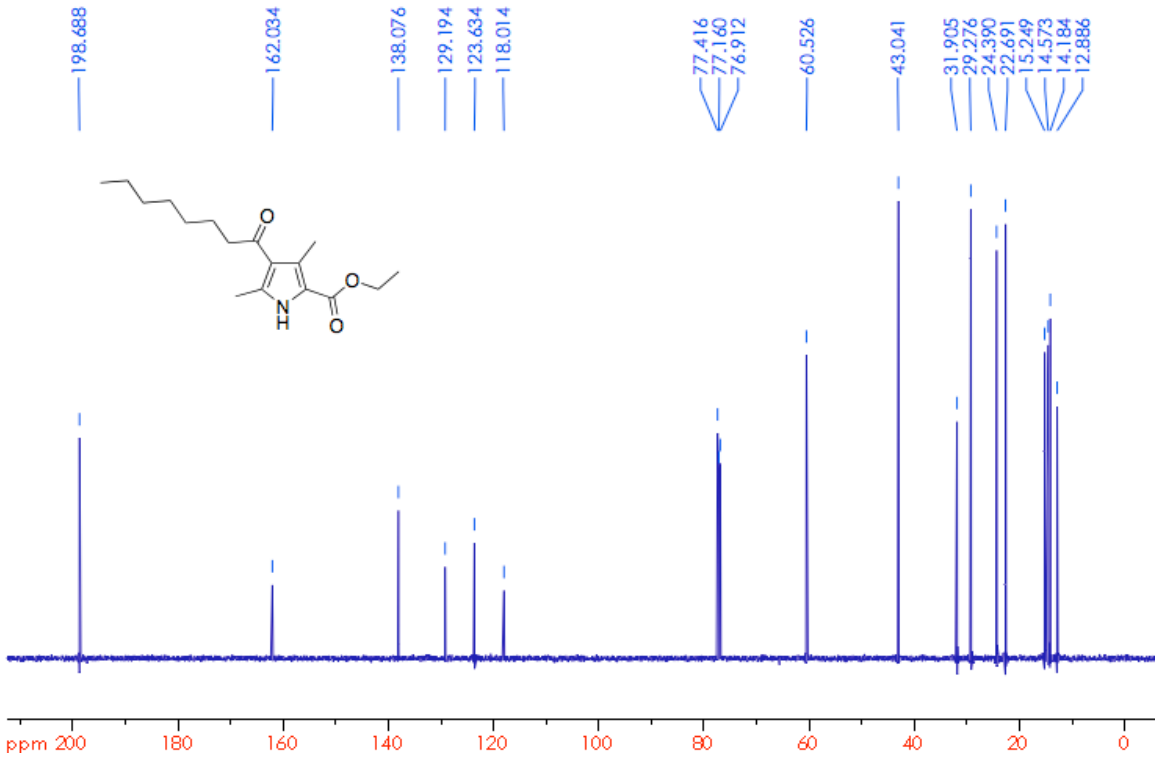


APPENDIX B.26 Ethyl 3,5-dimethyl-4-octanoyl-1*H*-pyrrole-2-carboxylate (**61**)[190]

^{1}H NMR Spectrum in $CDCl_3$

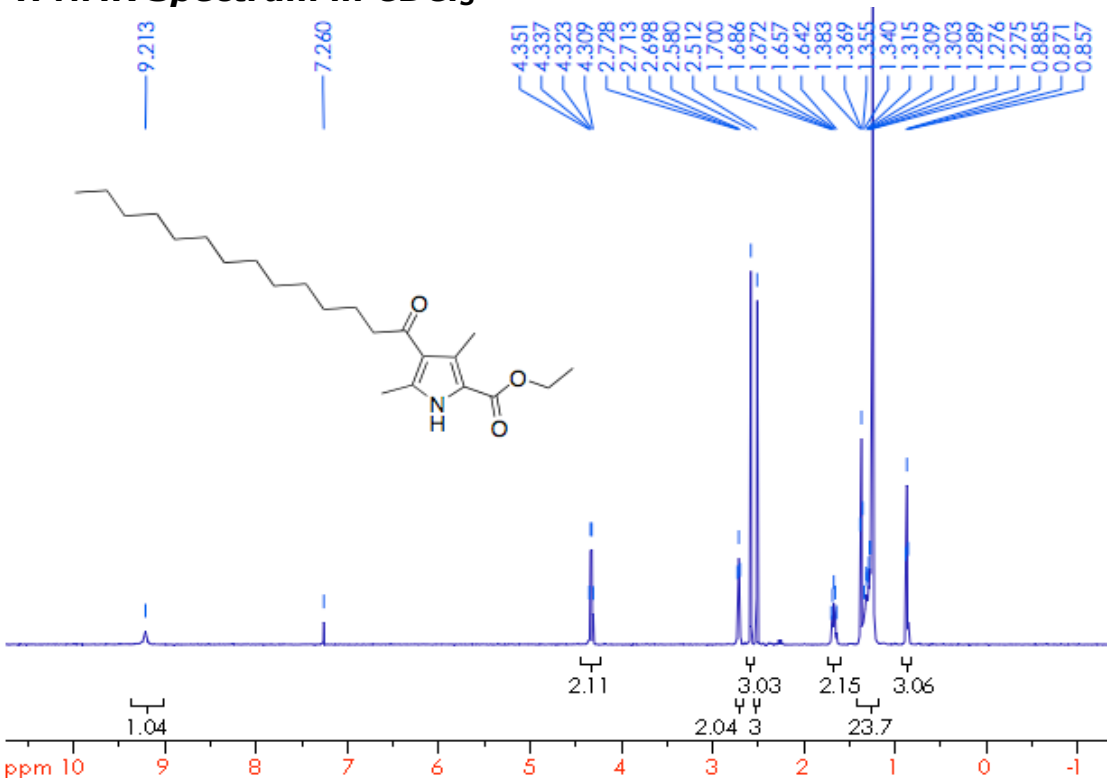


^{13}C NMR Spectrum in $CDCl_3$

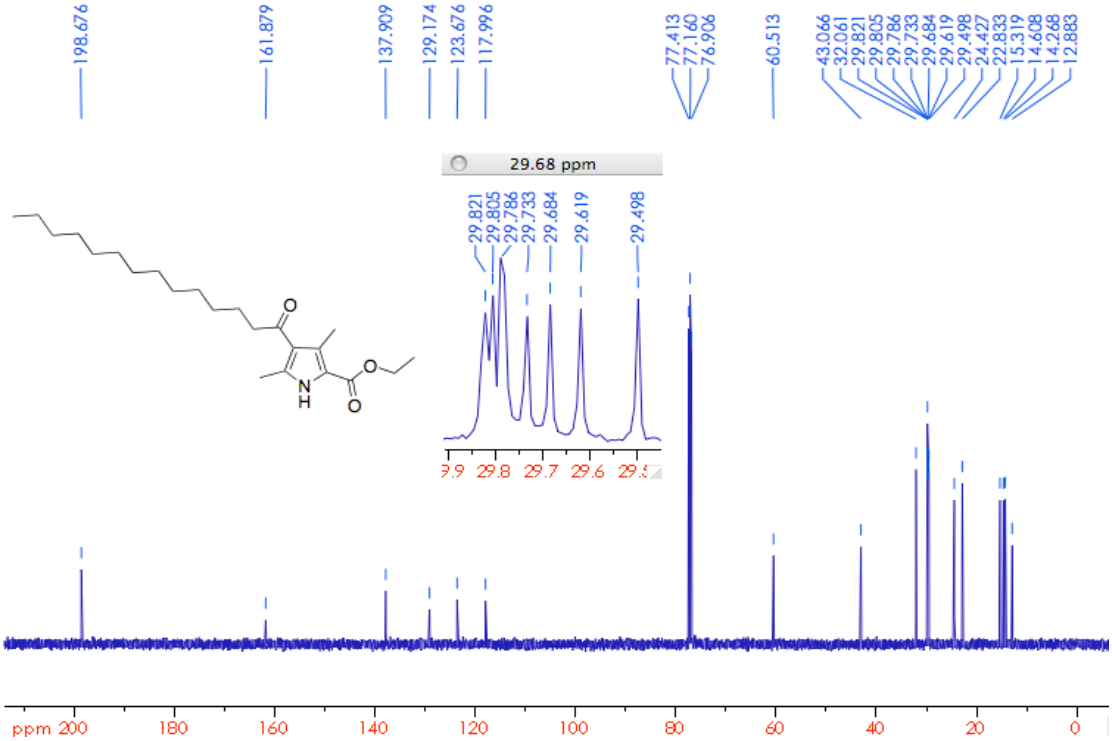


APPENDIX B.27 Ethyl 3,5-dimethyl-4-tetradecanoyl-1*H*-pyrrole-2-carboxylate (**62**)

^{1}H NMR Spectrum in $CDCl_3$

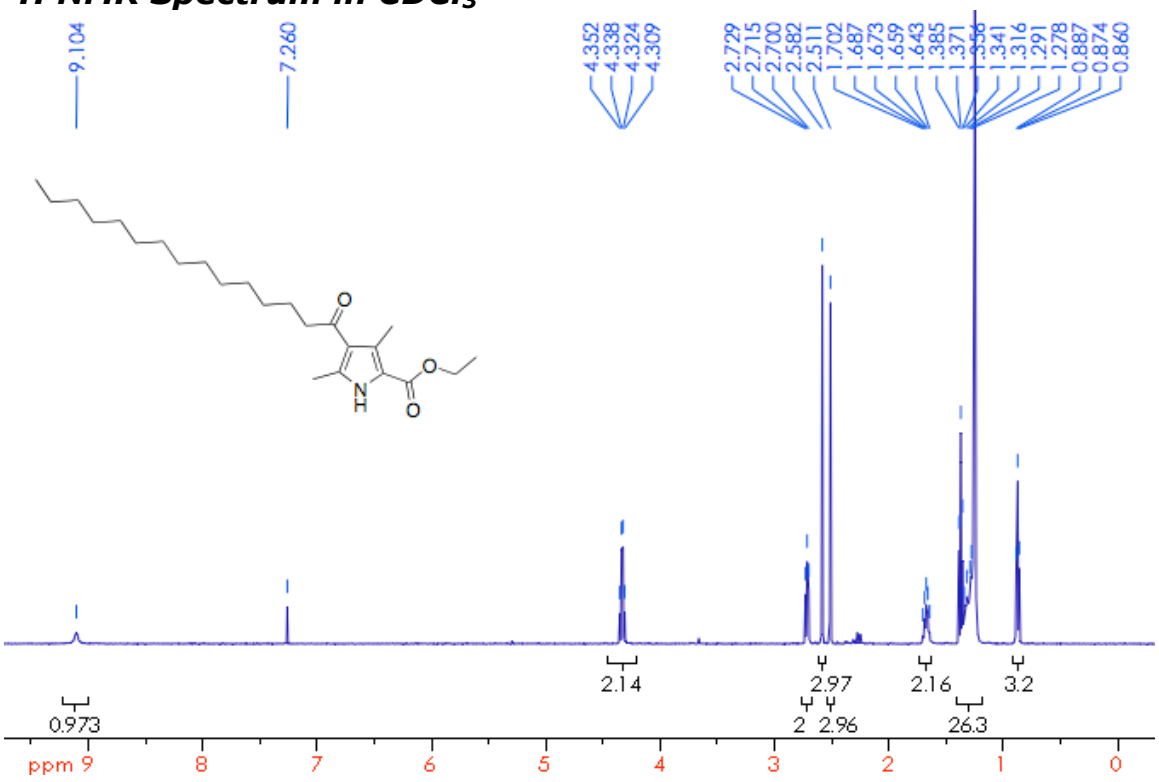


^{13}C NMR Spectrum in $CDCl_3$

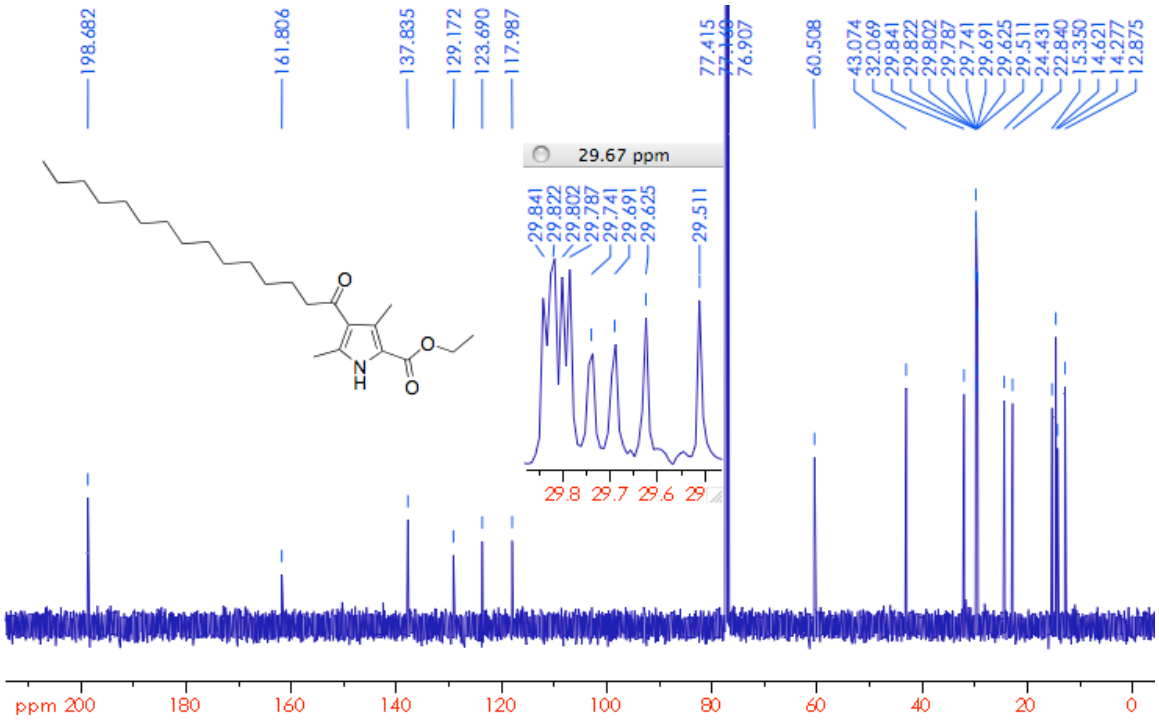


APPENDIX B.28 Ethyl 3,5-dimethyl-4-pentadecanoyl-1*H*-pyrrole-2-carboxylate (**63**)

^{1}H NMR Spectrum in $CDCl_3$

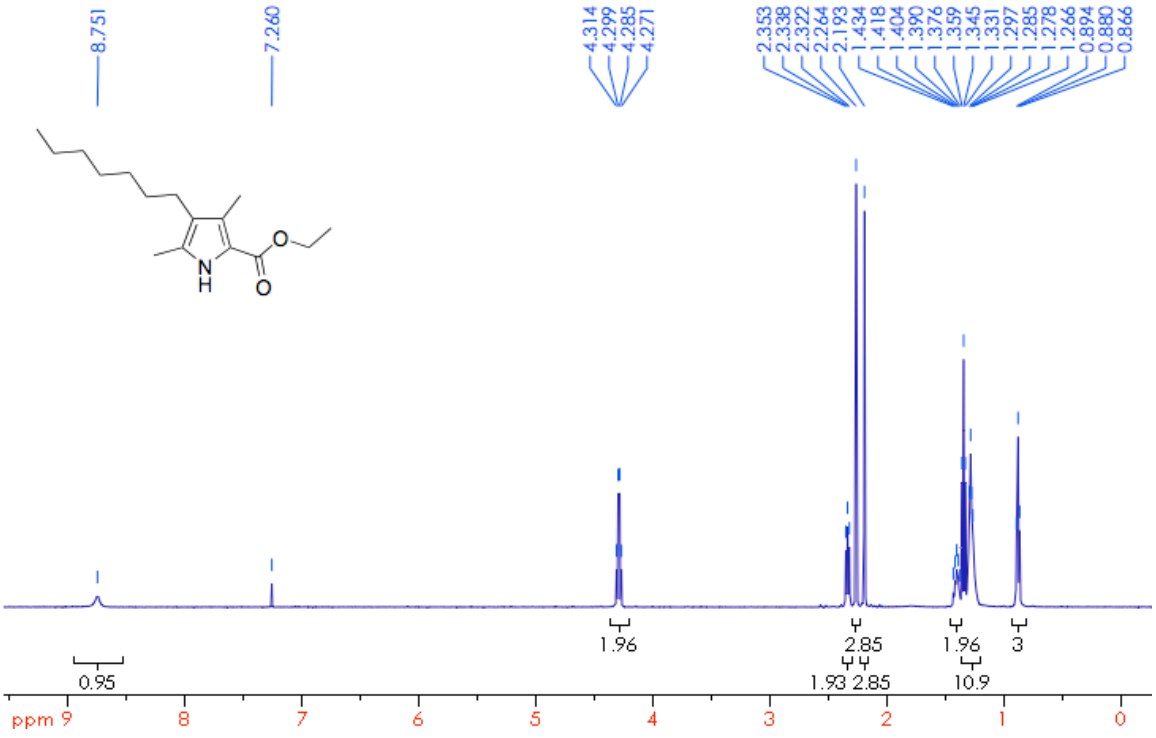


^{13}C NMR Spectrum in $CDCl_3$

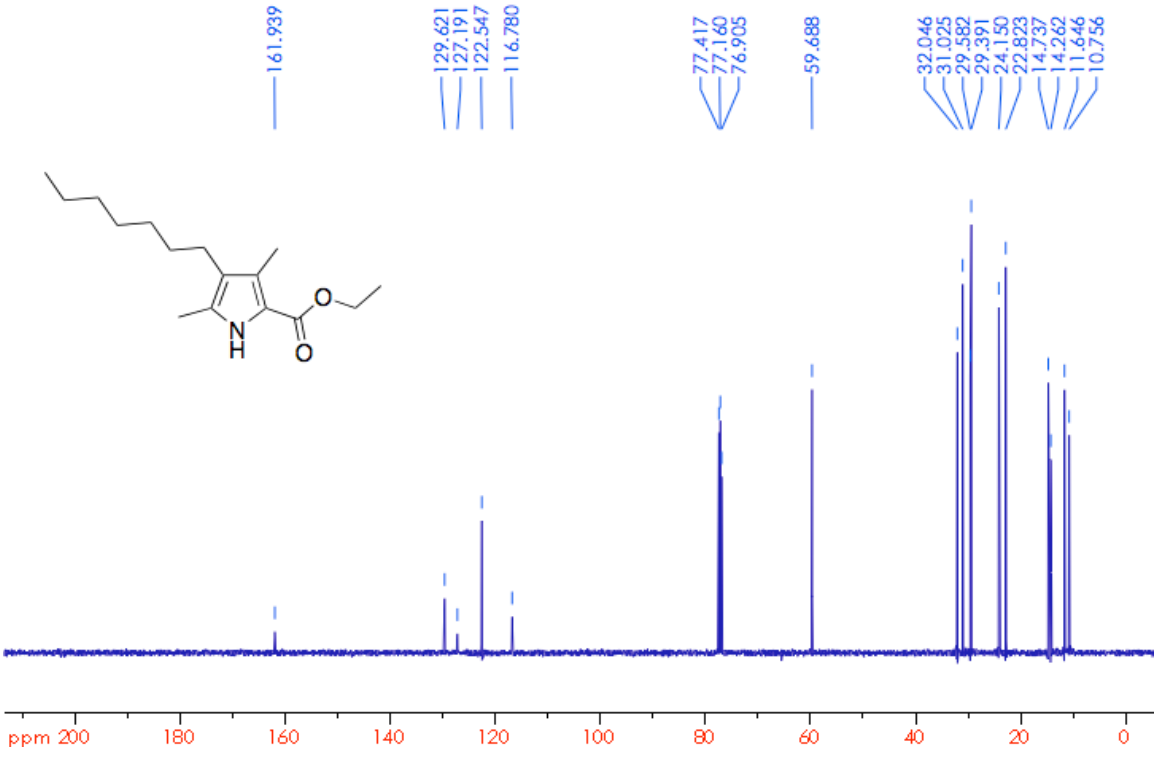


APPENDIX B.29 Ethyl 3,5-dimethyl-4-heptyl-1*H*-pyrrole-2-carboxylate (**64**)

^{1}H NMR Spectrum in $CDCl_3$

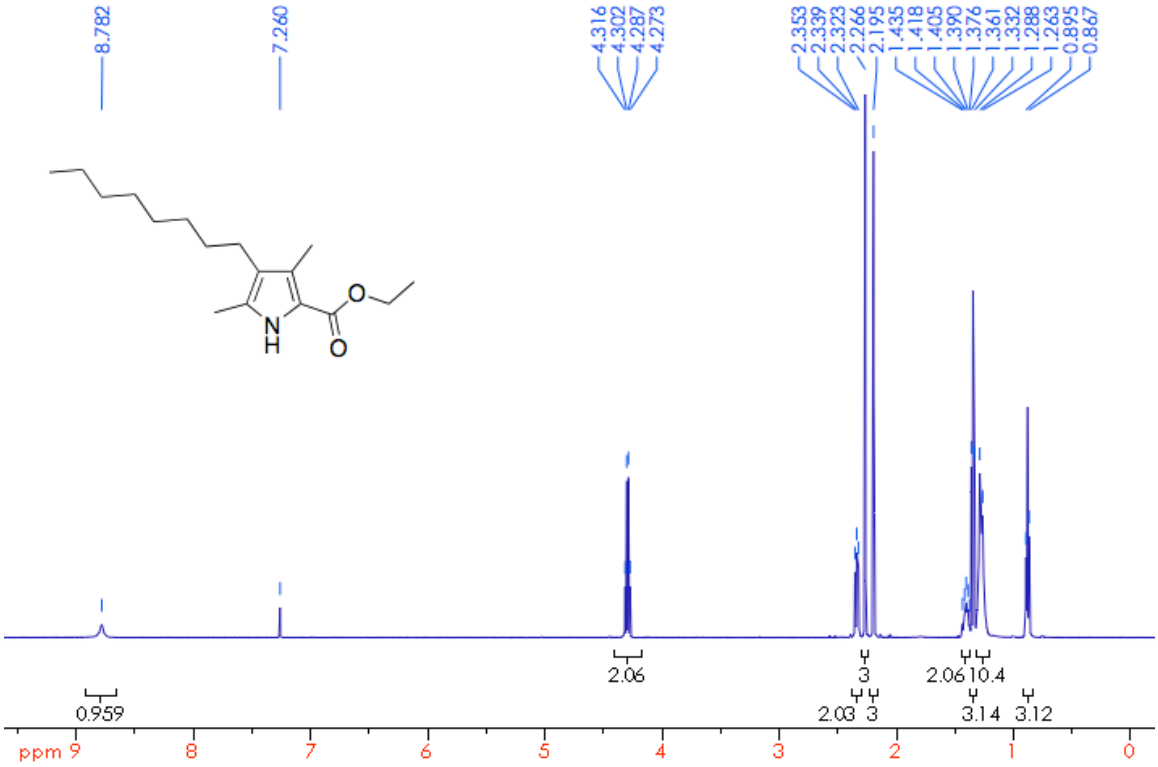


^{13}C NMR Spectrum in $CDCl_3$

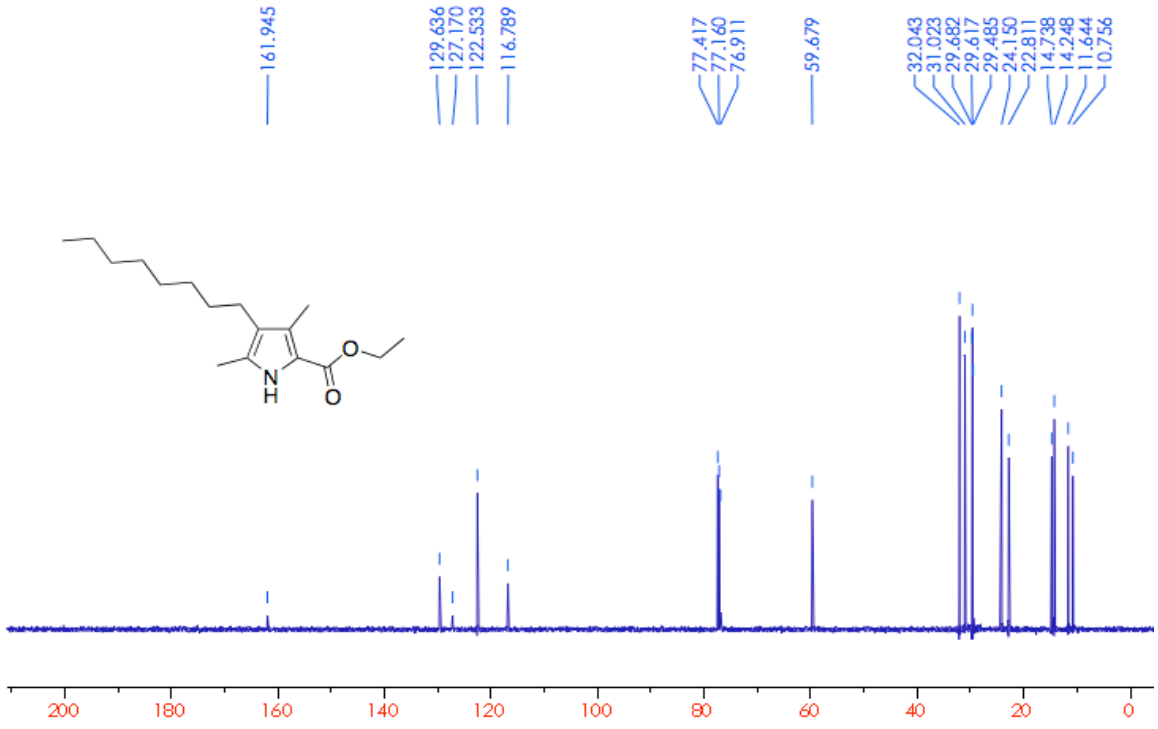


APPENDIX B.30 Ethyl 3,5-dimethyl-4-octyl-1*H*-pyrrole-2-carboxylate (**65**)[190]

^{1}H NMR Spectrum in $CDCl_3$

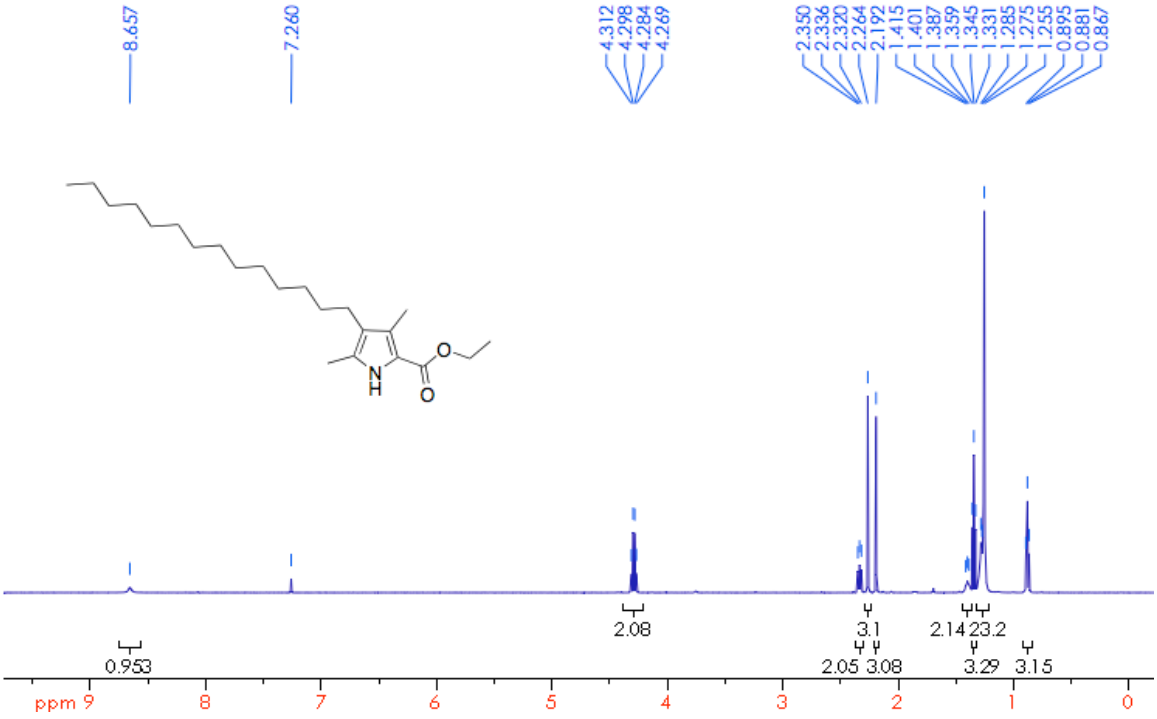


^{13}C NMR Spectrum in $CDCl_3$

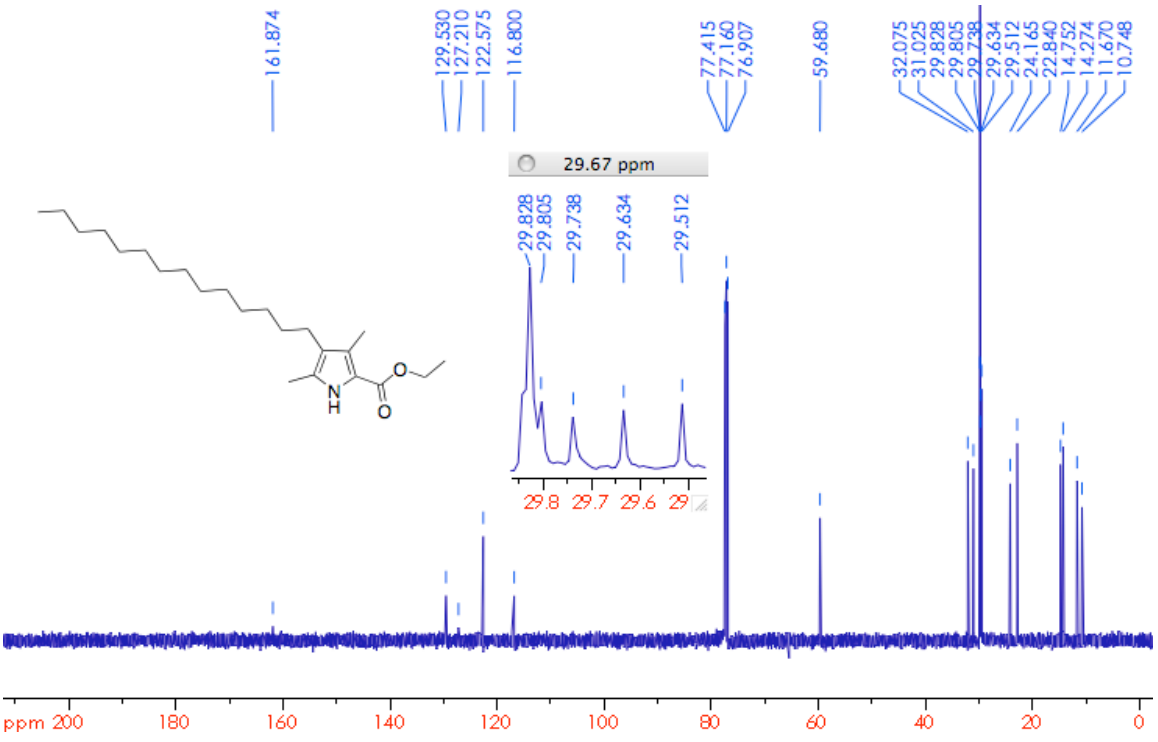


APPENDIX B.31 Ethyl 3,5-dimethyl-4-tetradecyl-1*H*-pyrrole-2-carboxylate (**66**)[191]

^{1}H NMR Spectrum in $CDCl_3$

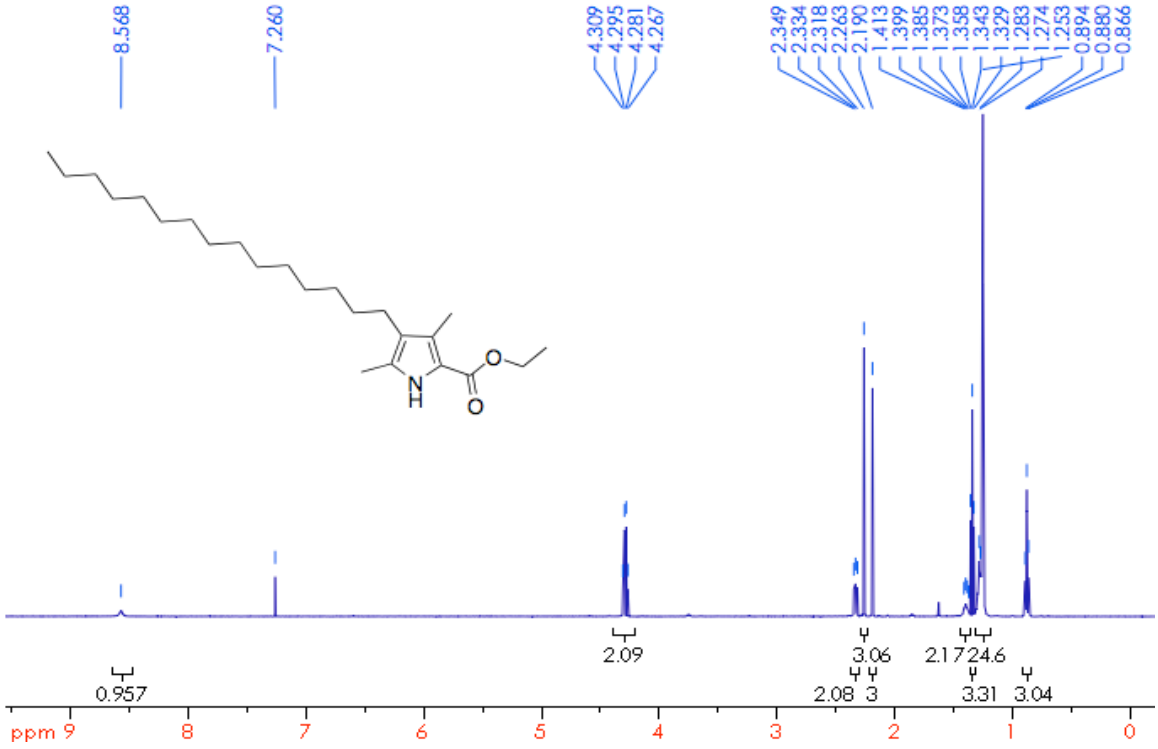


^{13}C NMR Spectrum in $CDCl_3$

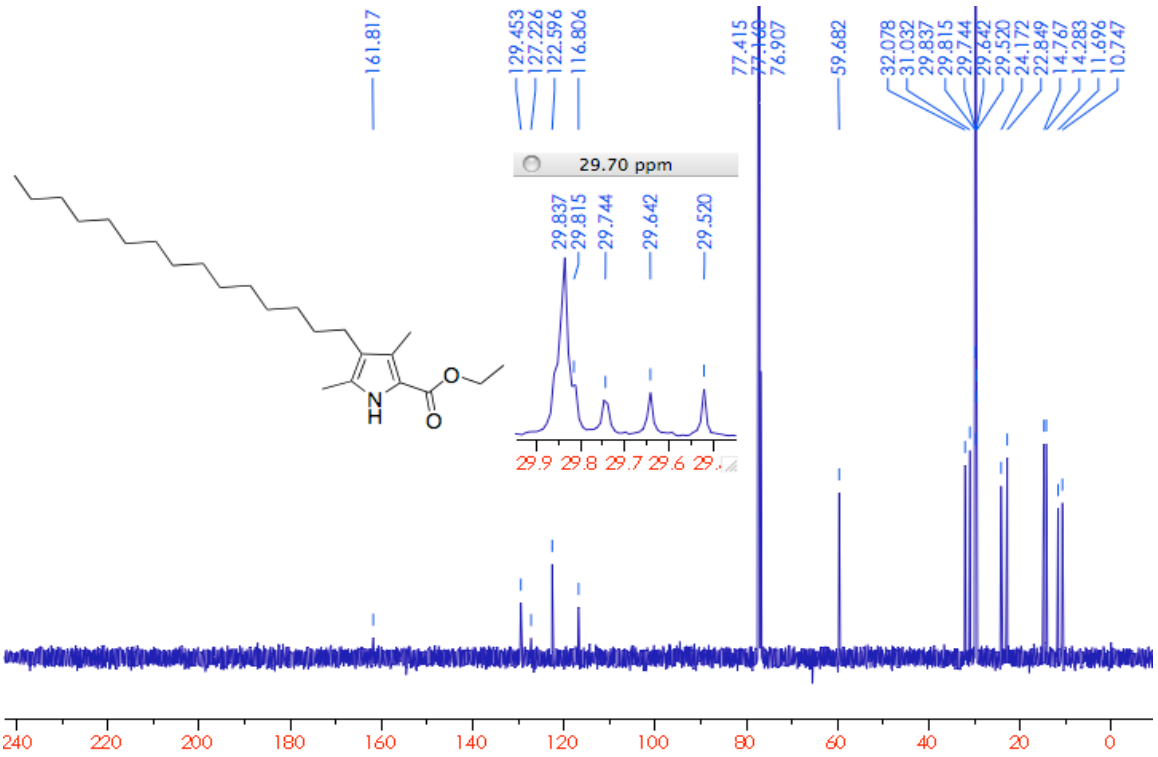


APPENDIX B.32 Ethyl 3,5-dimethyl-4-pentadecyl-1*H*-pyrrole-2-carboxylate (**67**)

^{1}H NMR Spectrum in $CDCl_3$

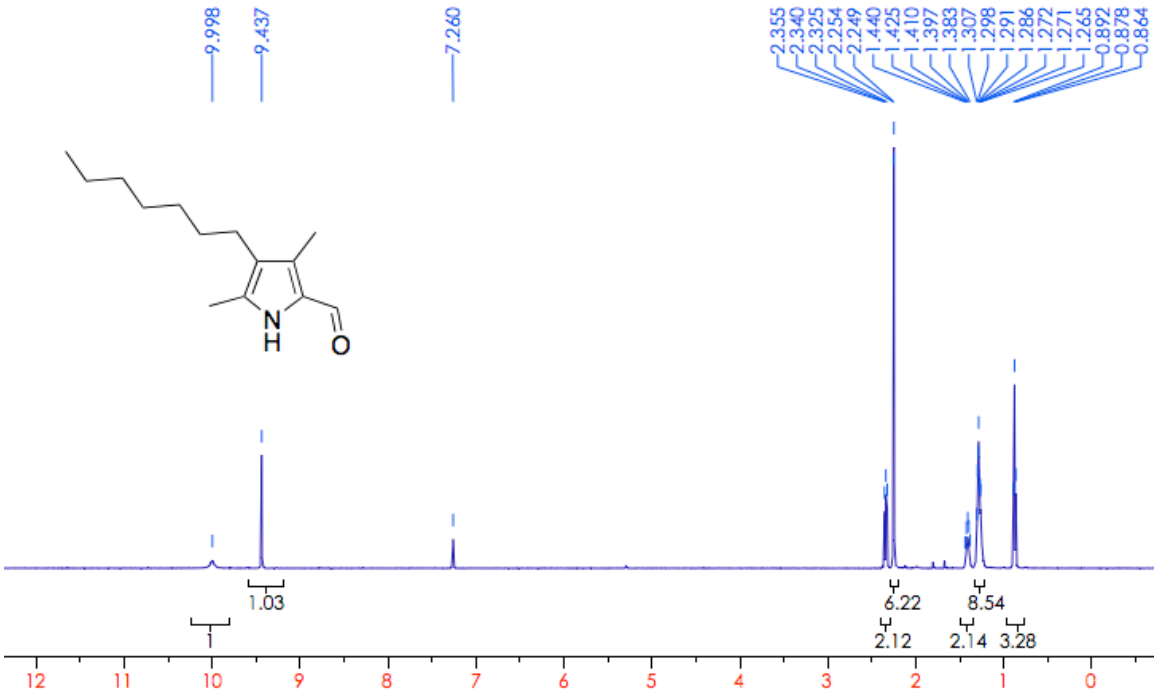


^{13}C NMR Spectrum in $CDCl_3$

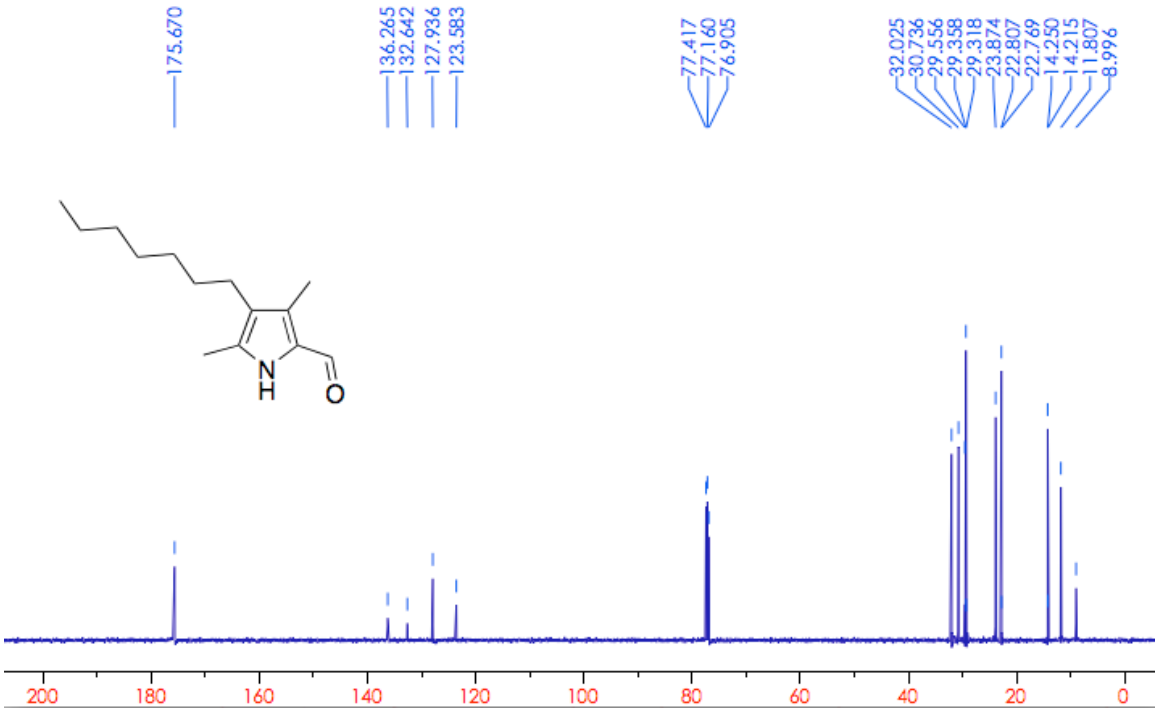


APPENDIX B.33 3,5-Dimethyl-4-heptyl-1*H*-pyrrole-2-carbaldehyde (**68**)

^{1}H NMR Spectrum in $CDCl_3$

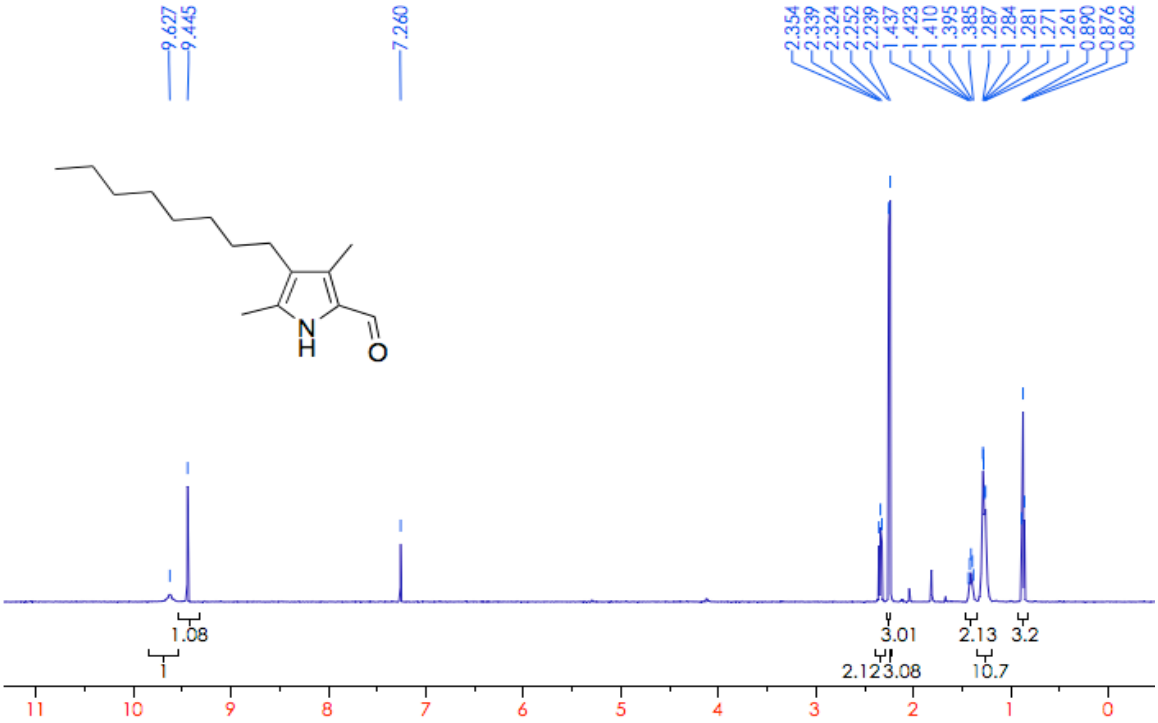


^{13}C NMR Spectrum in $CDCl_3$

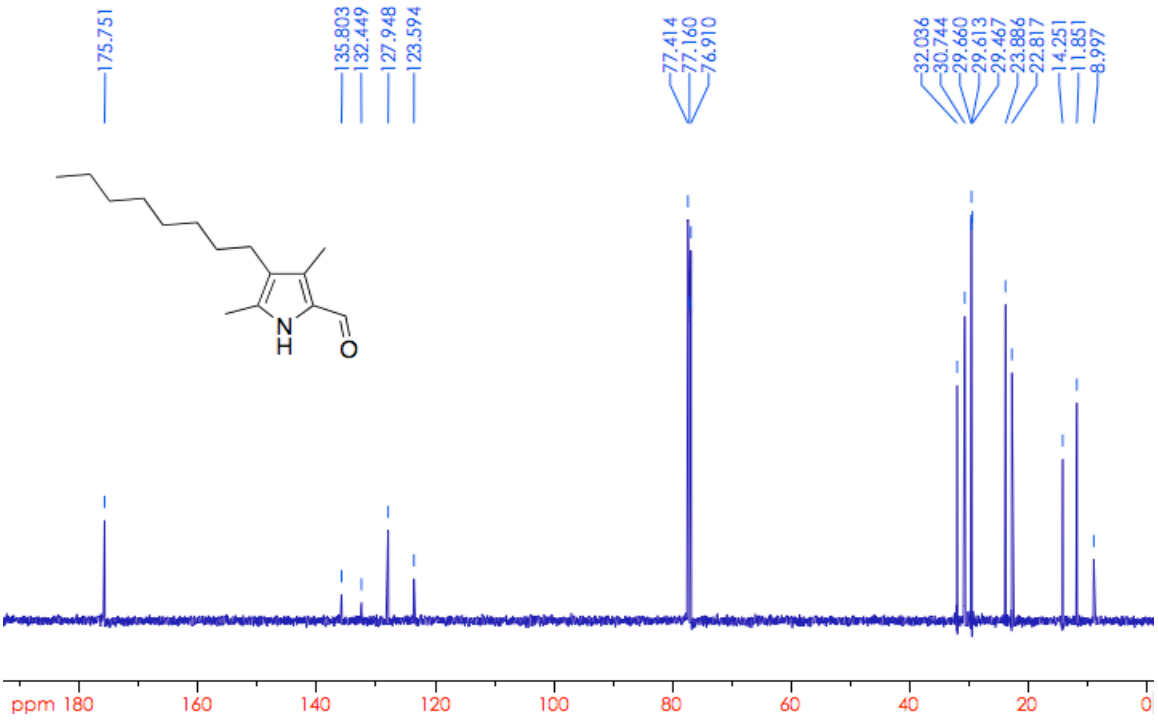


APPENDIX B.34 3,5-Dimethyl-4-octyl-1*H*-pyrrole-2-carbaldehyde (**69**)

^{1}H NMR Spectrum in $CDCl_3$

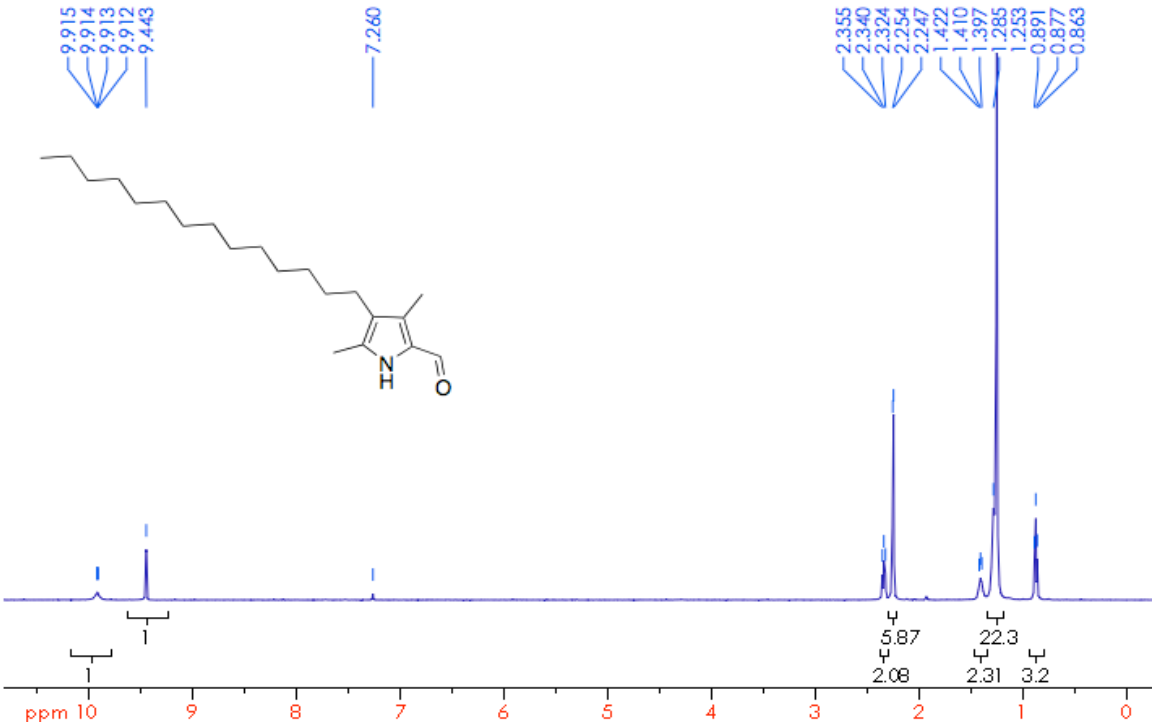


^{13}C NMR Spectrum in $CDCl_3$

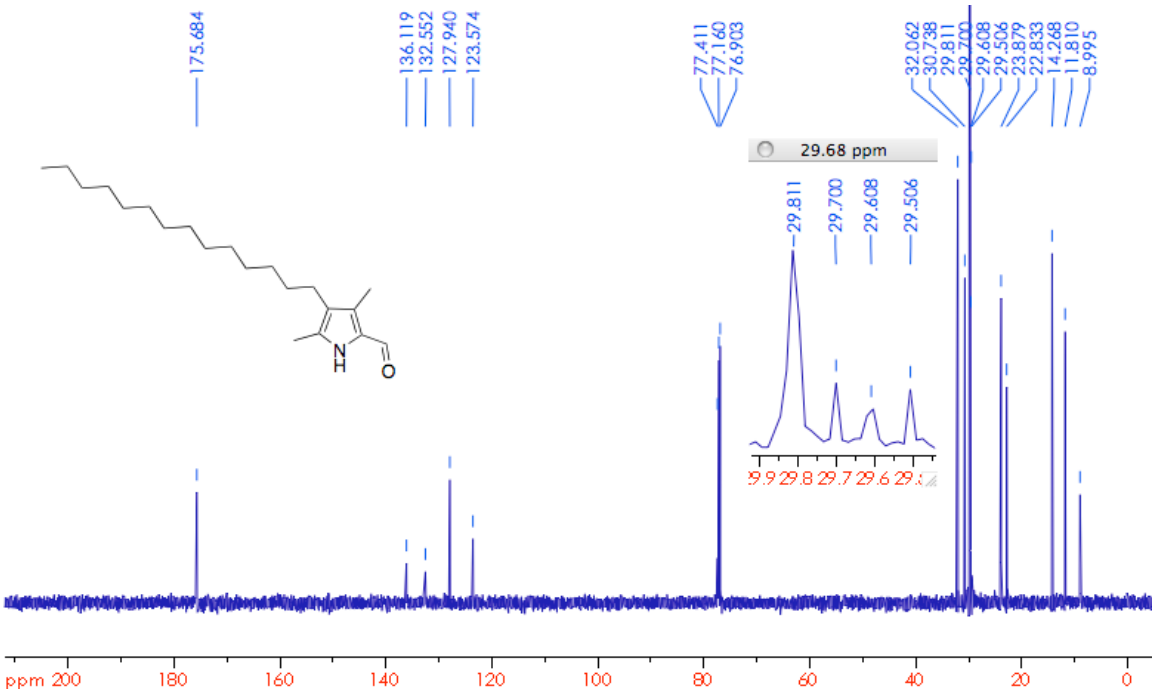


APPENDIX B.35 3,5-Dimethyl-4-tetradecyl-1*H*-pyrrole-2-carbaldehyde (**70**)

^{1}H NMR Spectrum in $CDCl_3$

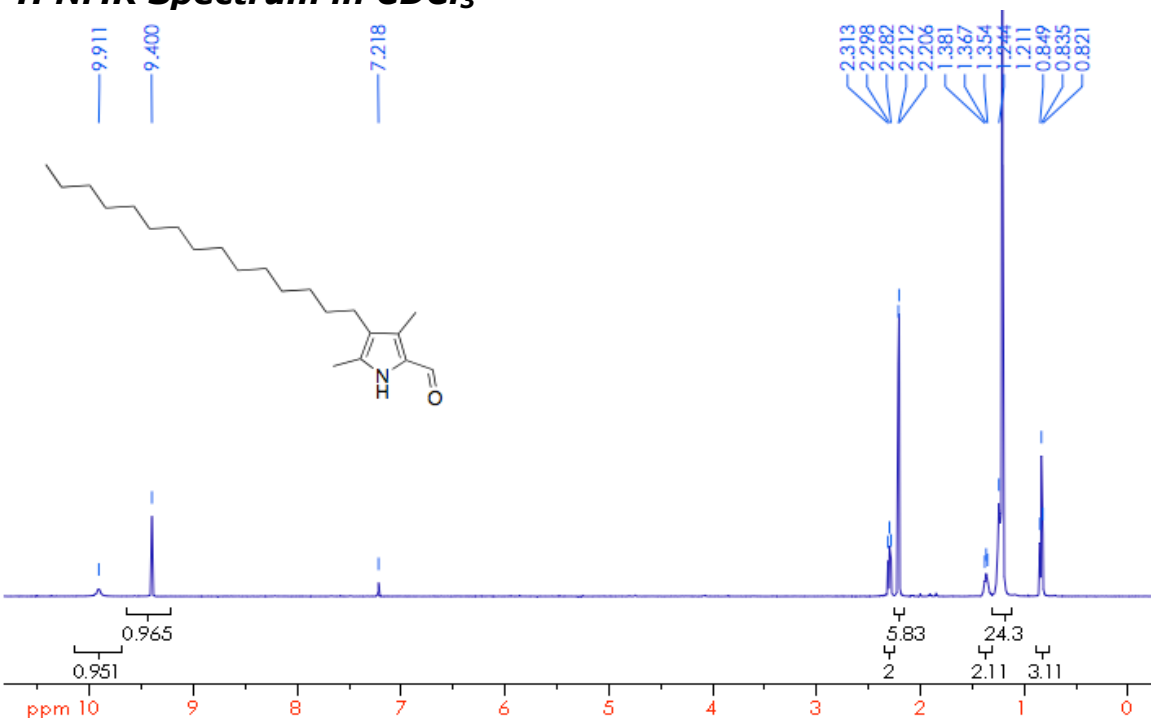


^{13}C NMR Spectrum in $CDCl_3$

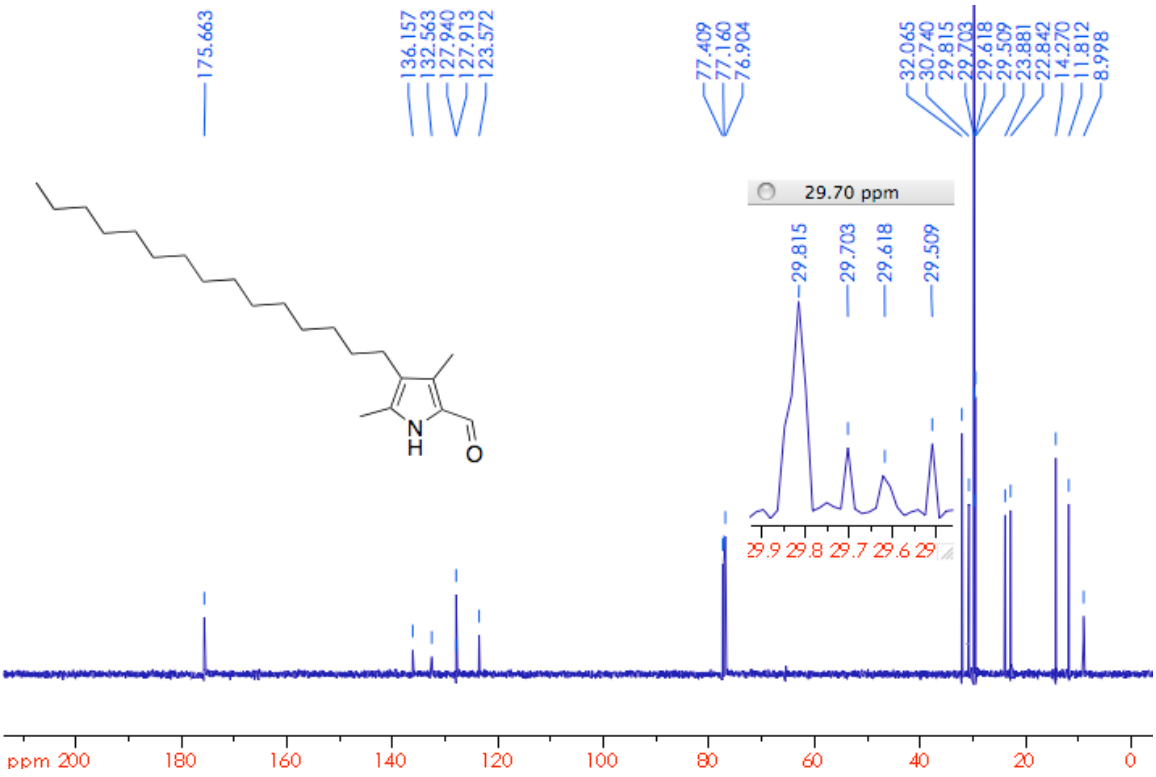


APPENDIX B.36 3,5-Dimethyl-4-pentadecyl-1*H*-pyrrole-2-carbaldehyde (**71**)

^{1}H NMR Spectrum in $CDCl_3$

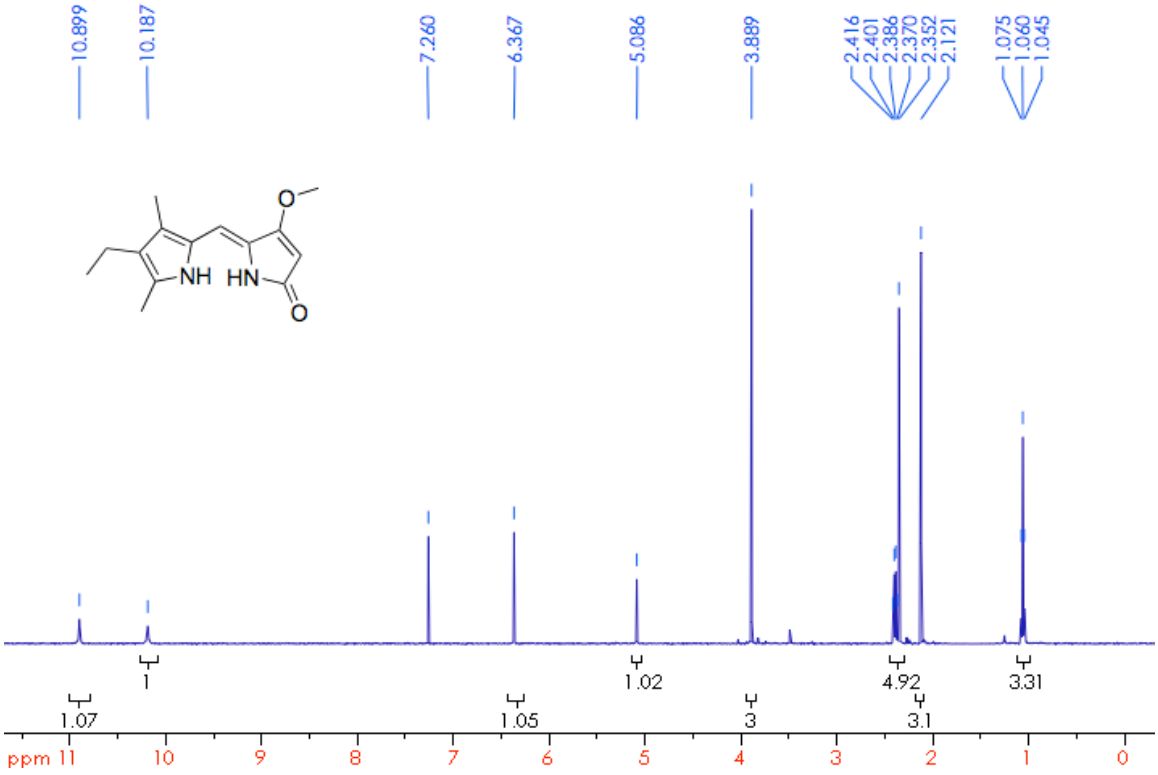


^{13}C NMR Spectrum in $CDCl_3$

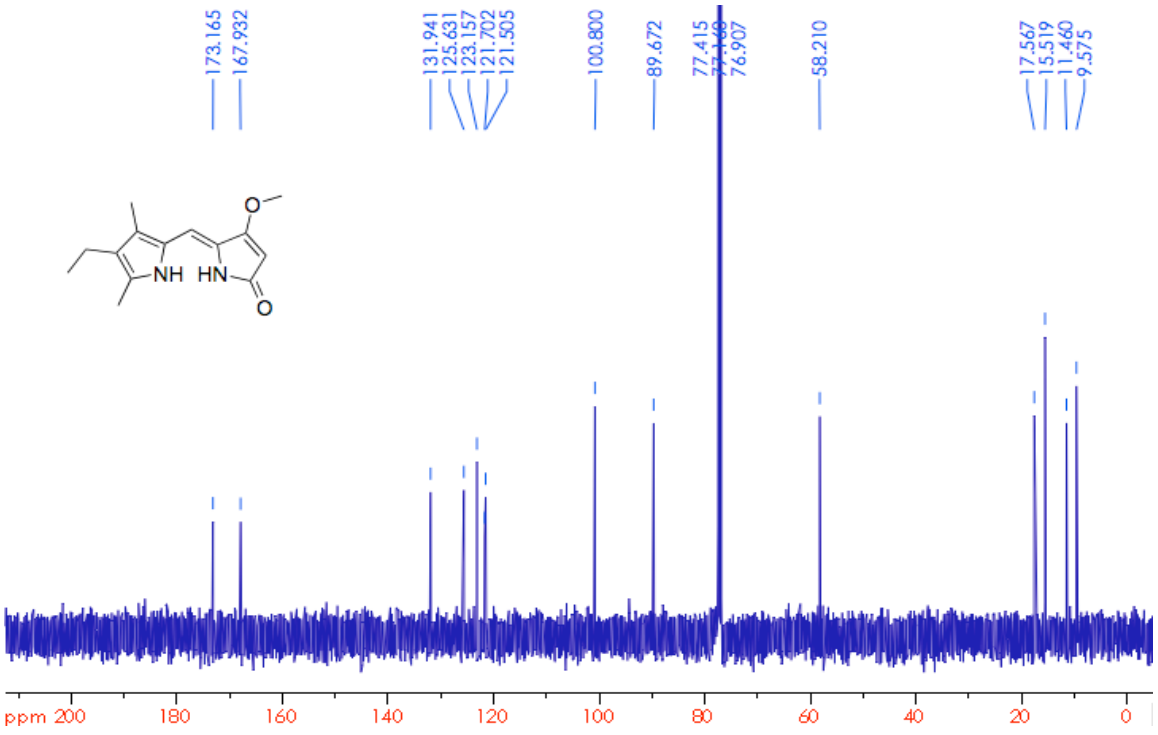


APPENDIX B.37 3(*Z*)-5-((3,5-Dimethyl-4-ethyl-1*H*-pyrrol-2-yl)methylene)-4-methoxy-1*H*-pyrrol-2(5*H*)-one (**73**)

^{1}H NMR Spectrum in $CDCl_3$

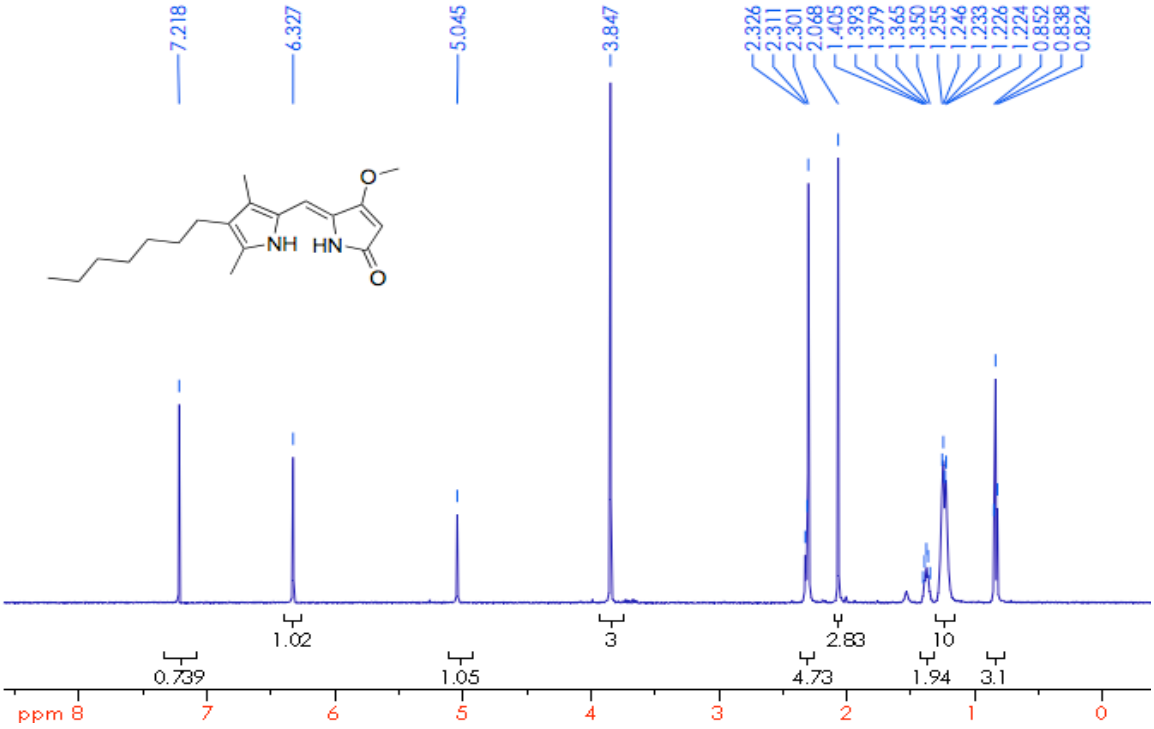


^{13}C NMR Spectrum in $CDCl_3$

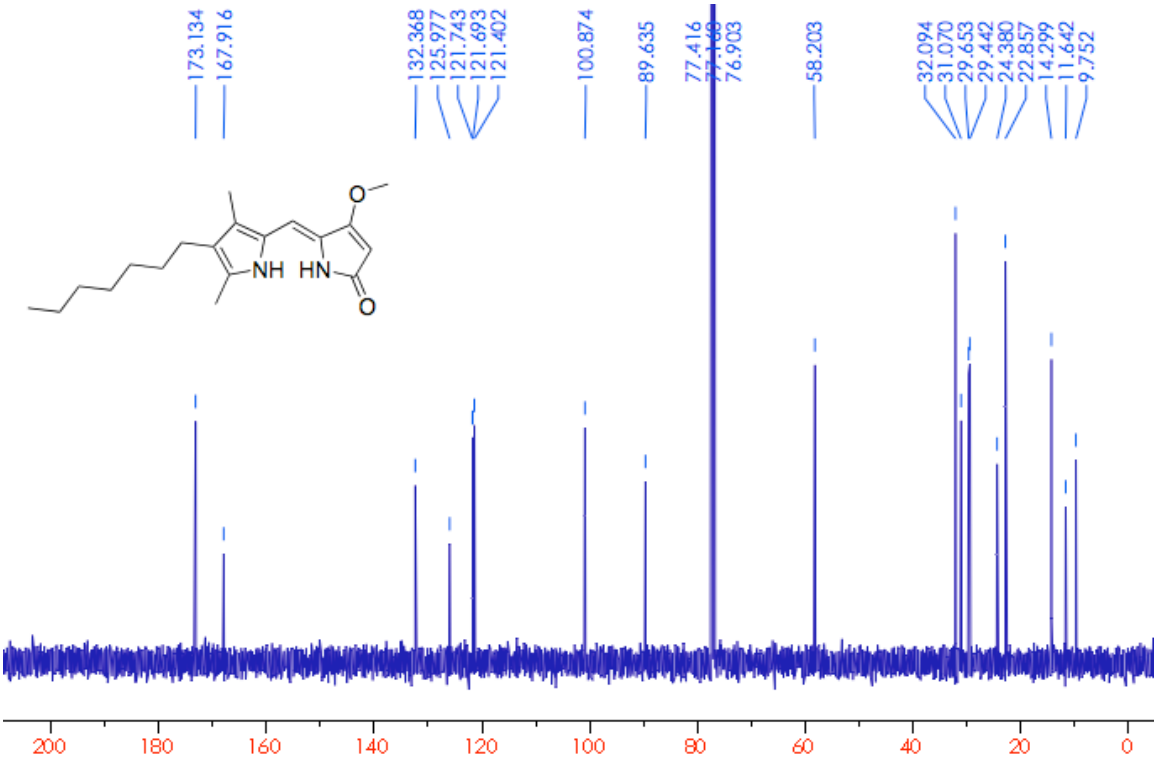


APPENDIX B.38 3(*Z*)-5-((3,5-dimethyl-4-heptyl-1*H*-pyrrol-2-yl)methylene)-4-methoxy-1*H*-pyrrol-2(5*H*)-one (**74**)

^{1}H NMR Spectrum in $CDCl_3$

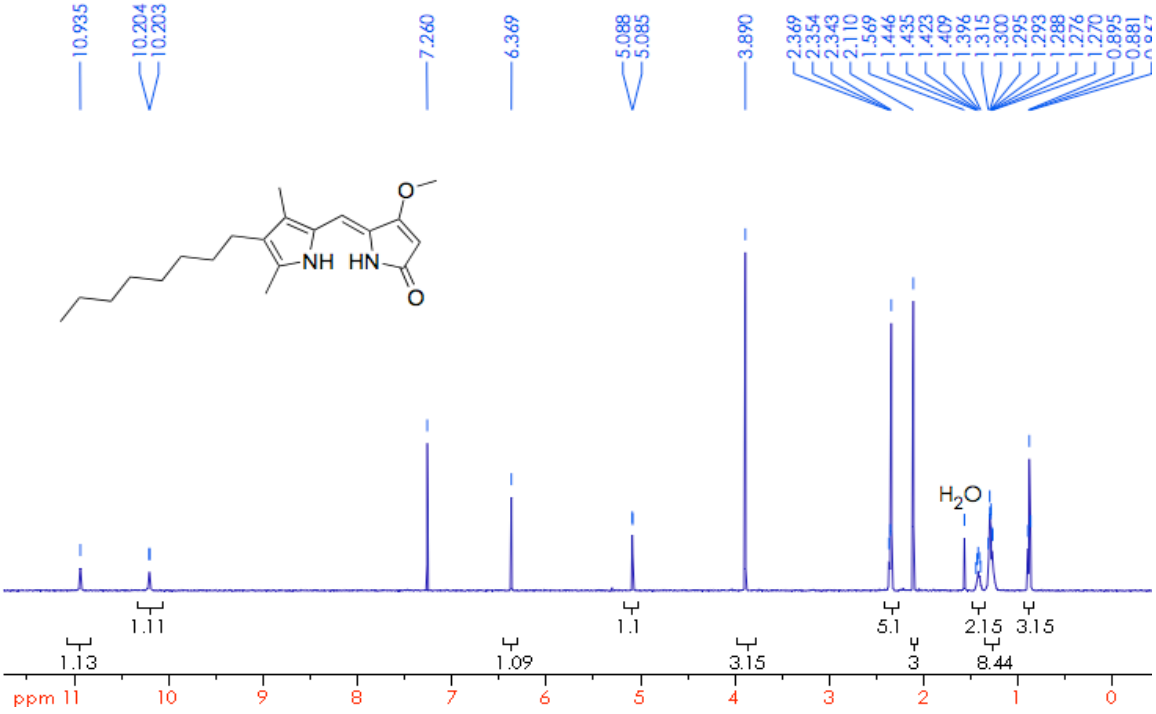


^{13}C NMR Spectrum in $CDCl_3$

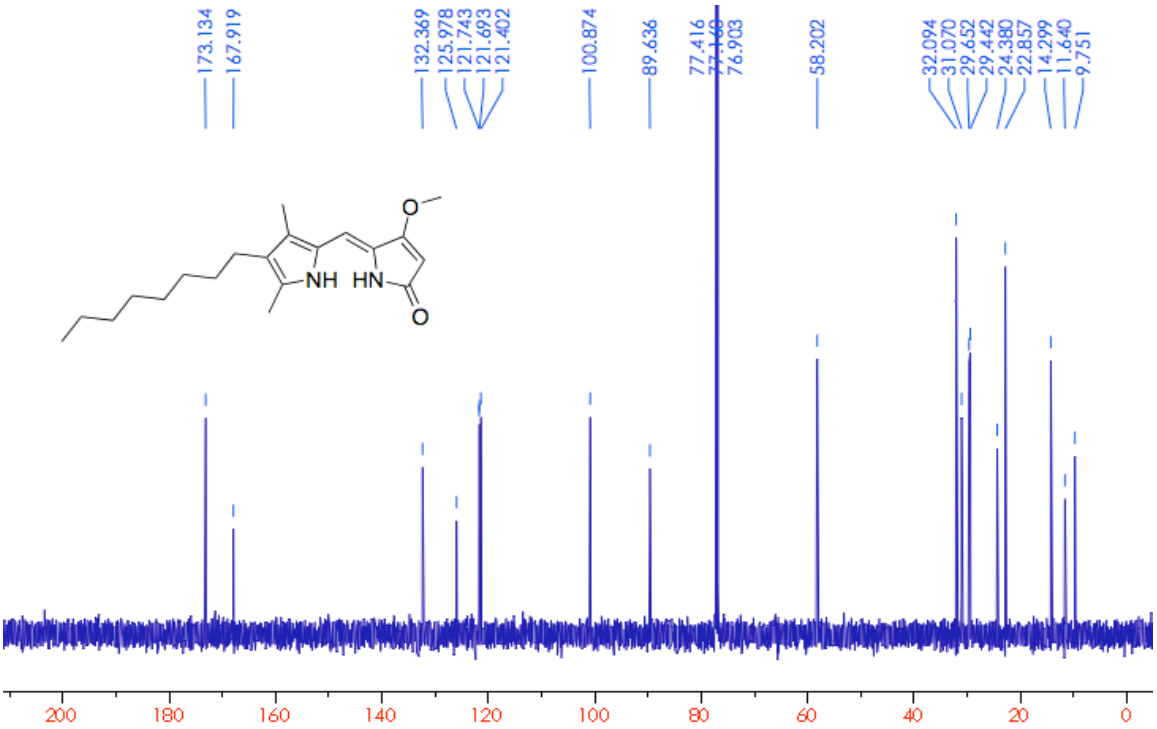


APPENDIX B.39 3(*Z*)-5-((3,5-dimethyl-4-octyl-1*H*-pyrrol-2-yl)methylene)-4-methoxy-1*H*-pyrrol-2(5*H*)-one (**75**)

^{1}H NMR Spectrum in $CDCl_3$

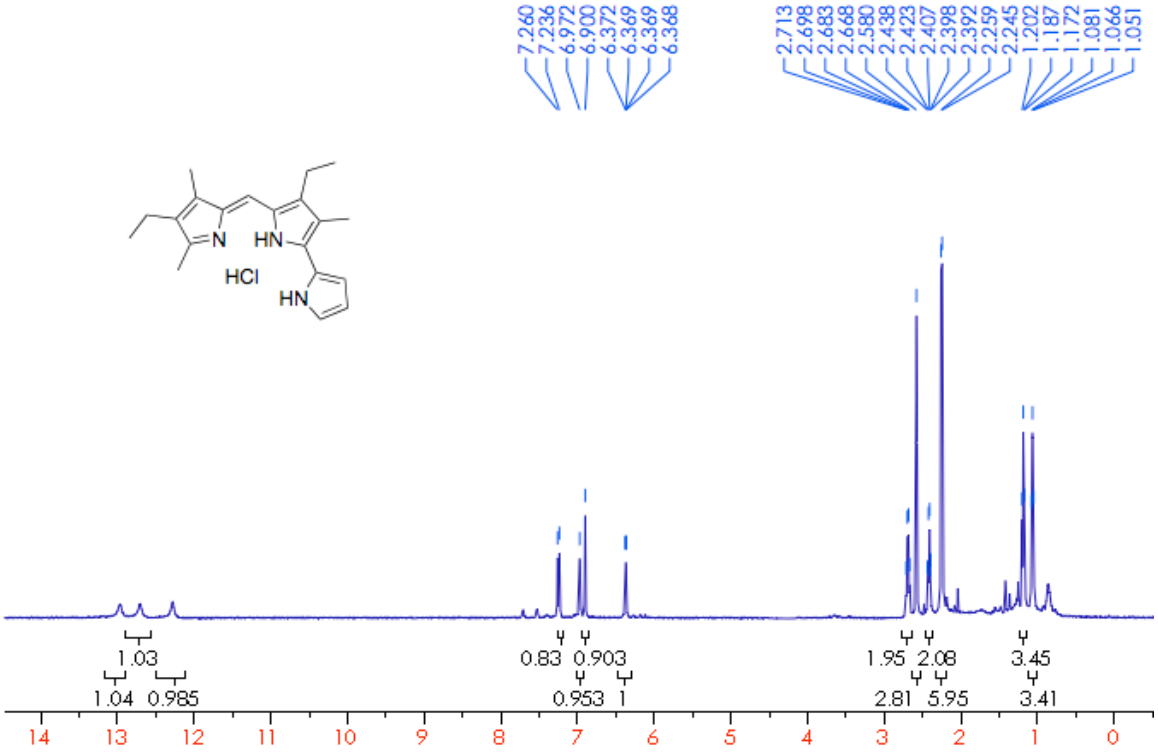


^{13}C NMR Spectrum in $CDCl_3$

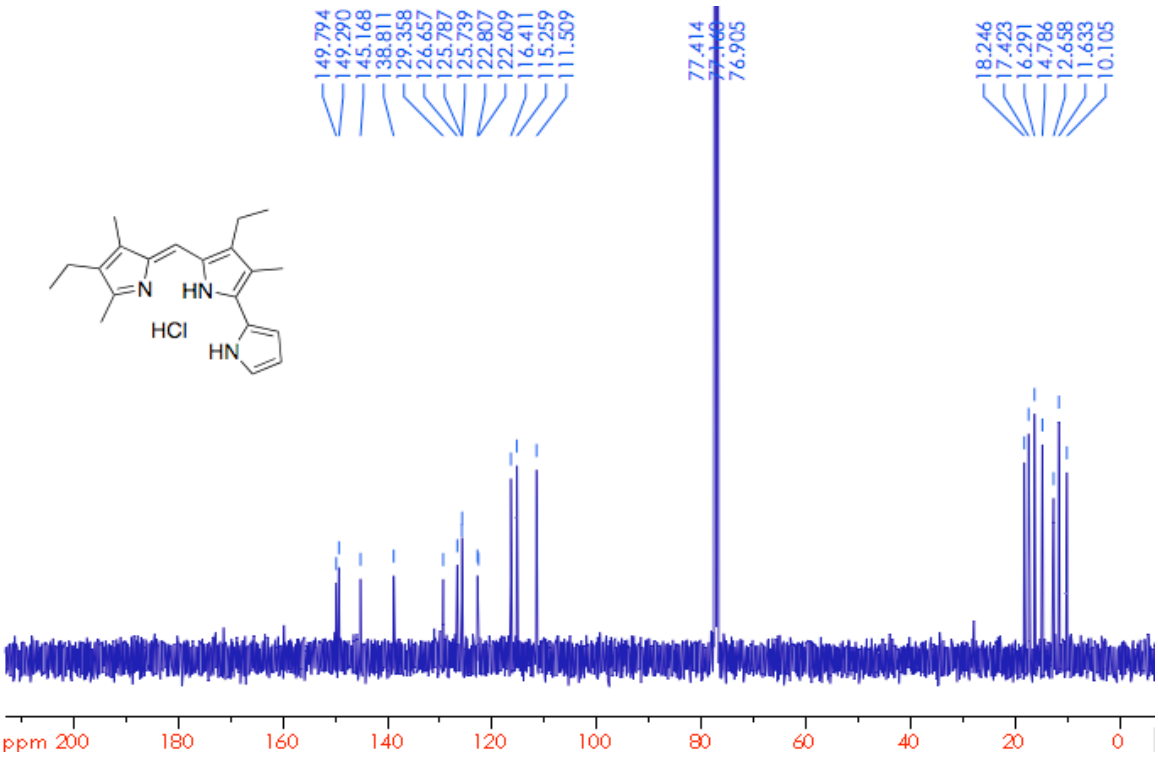


APPENDIX B.40 (*Z*)-4-Ethyl-5-((4-ethyl-3,5-dimethyl-2*H*-pyrrol-2-ylidene)methyl)-3-methyl-1*H*,1'*H*-2,2'-bipyrrole (**82**)

^{1}H NMR Spectrum in $CDCl_3$

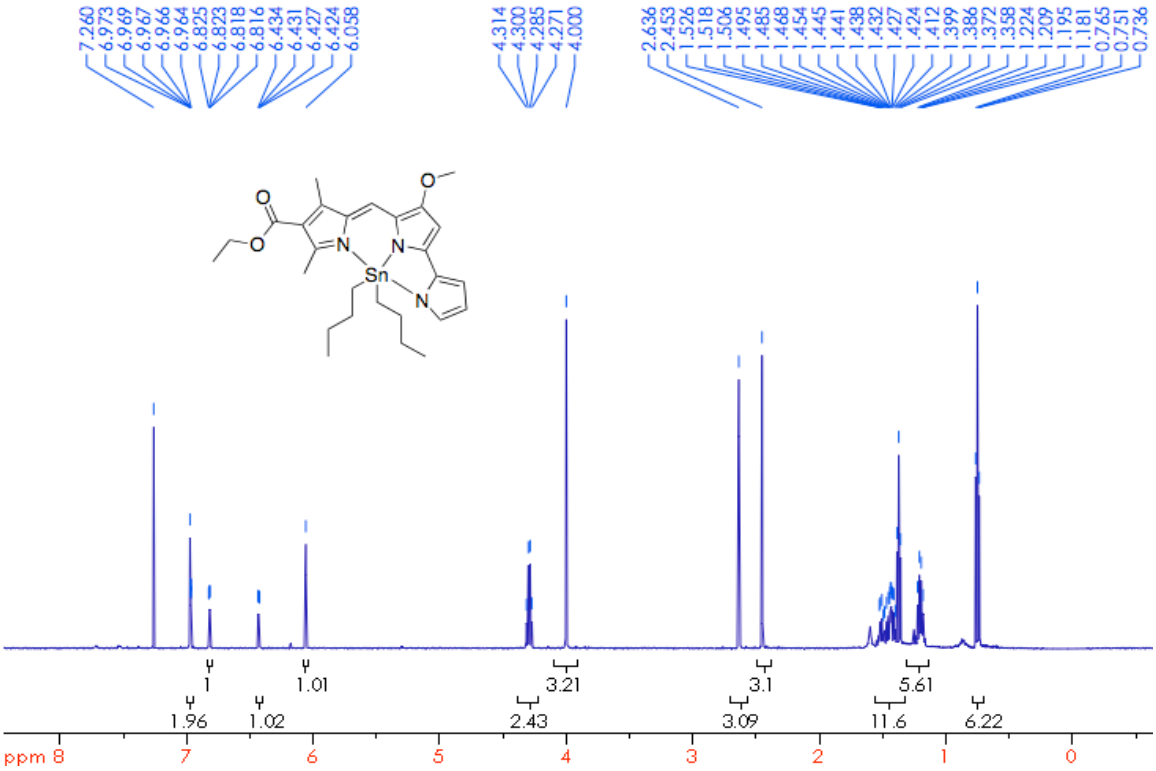


^{13}C NMR Spectrum in $CDCl_3$

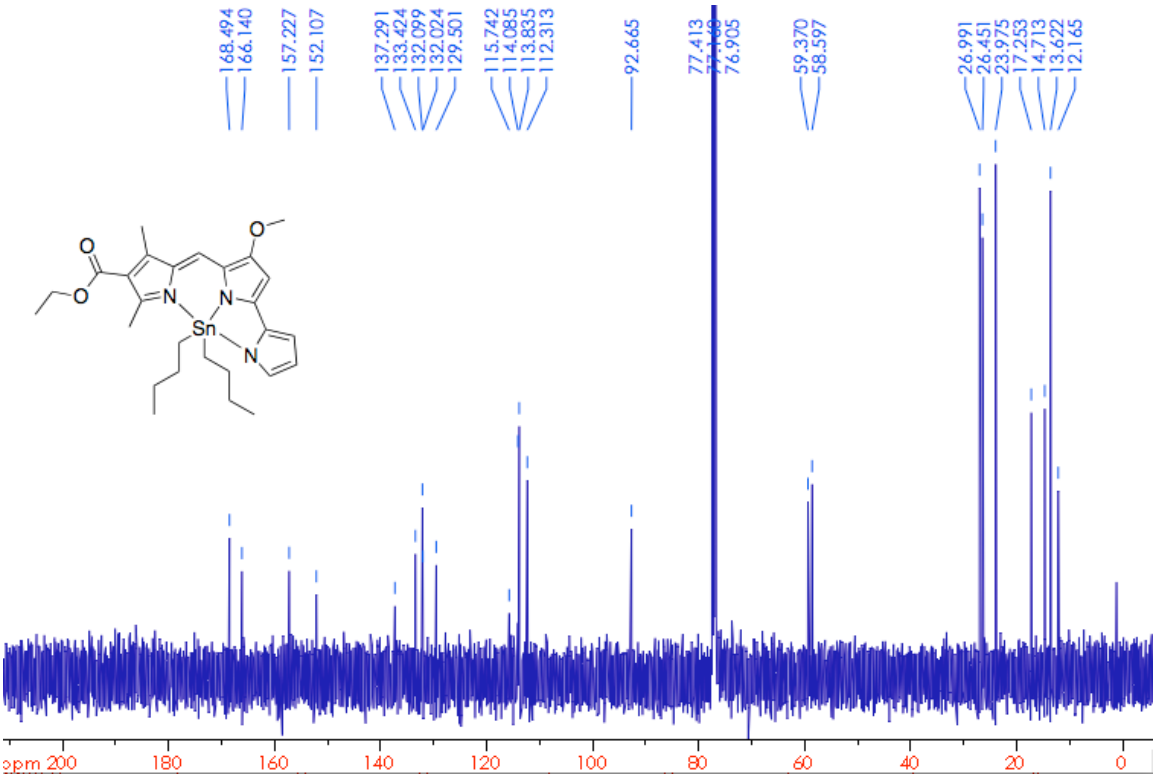


APPENDIX B.41 $(Bu)_2$(**1**)Sn(IV)(**83**)

^{1}H NMR Spectrum in $CDCl_3$

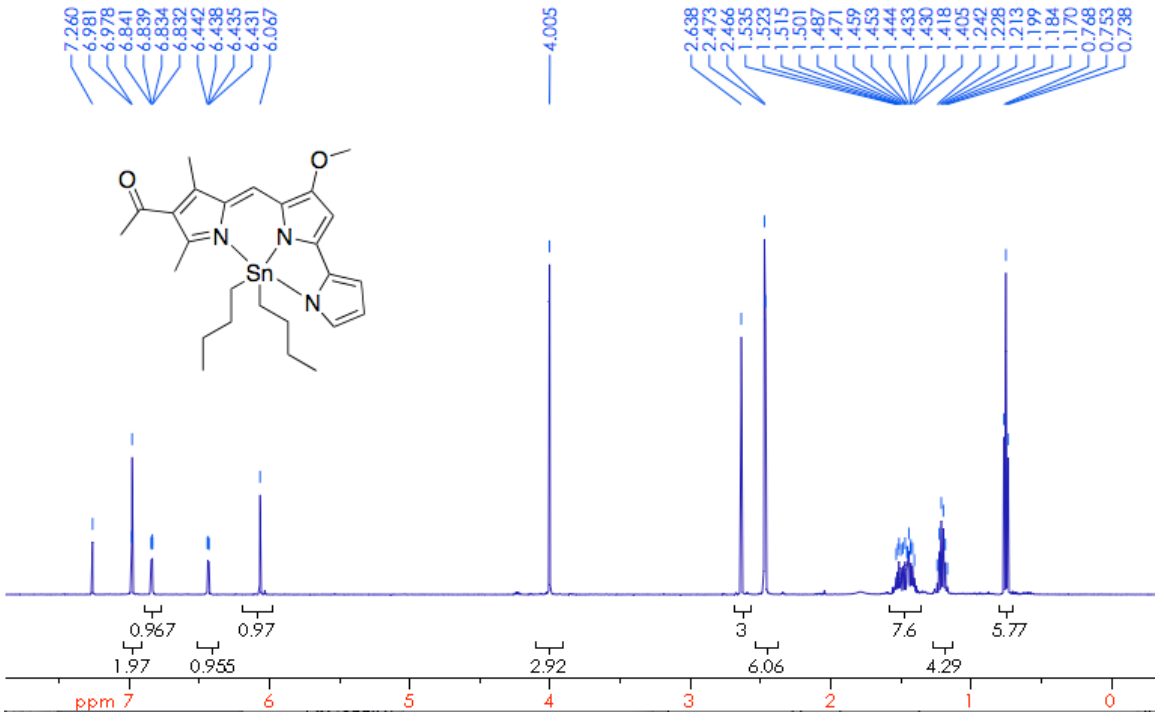


^{13}C NMR Spectrum in $CDCl_3$

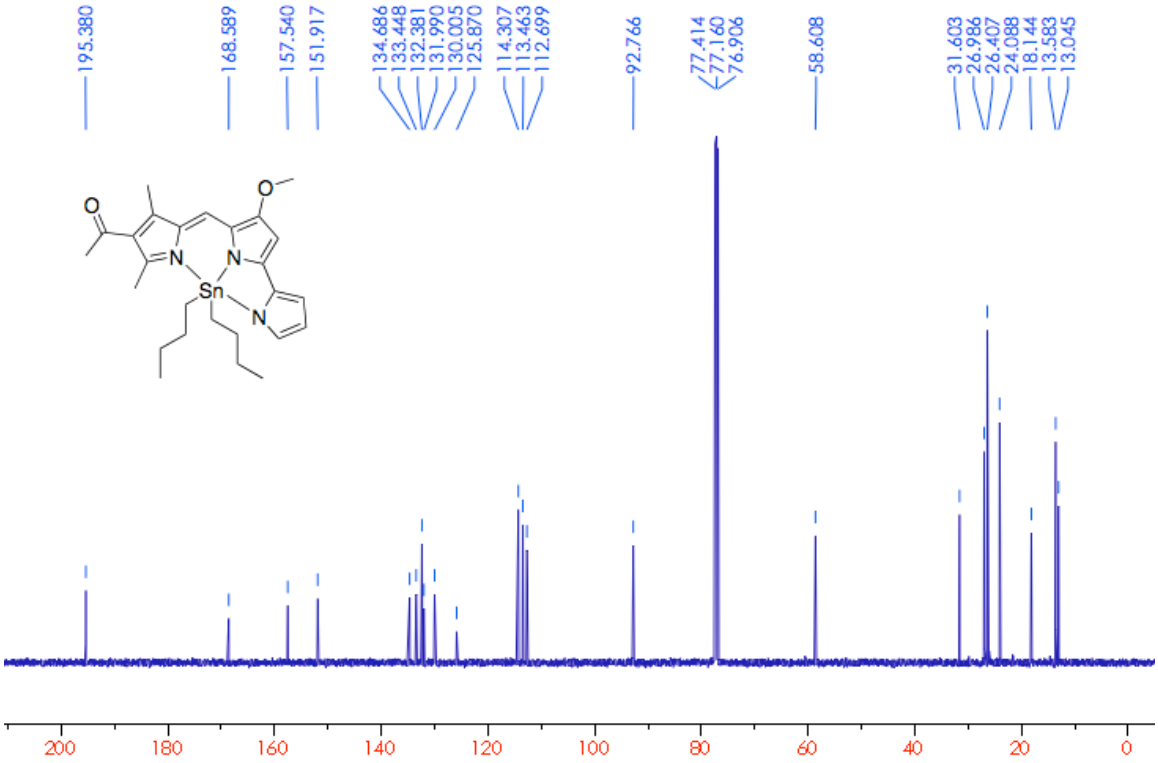


APPENDIX B.42 $(Bu)_2$(**84**)Sn(IV) (**85**)

^{1}H NMR Spectrum in $CDCl_3$

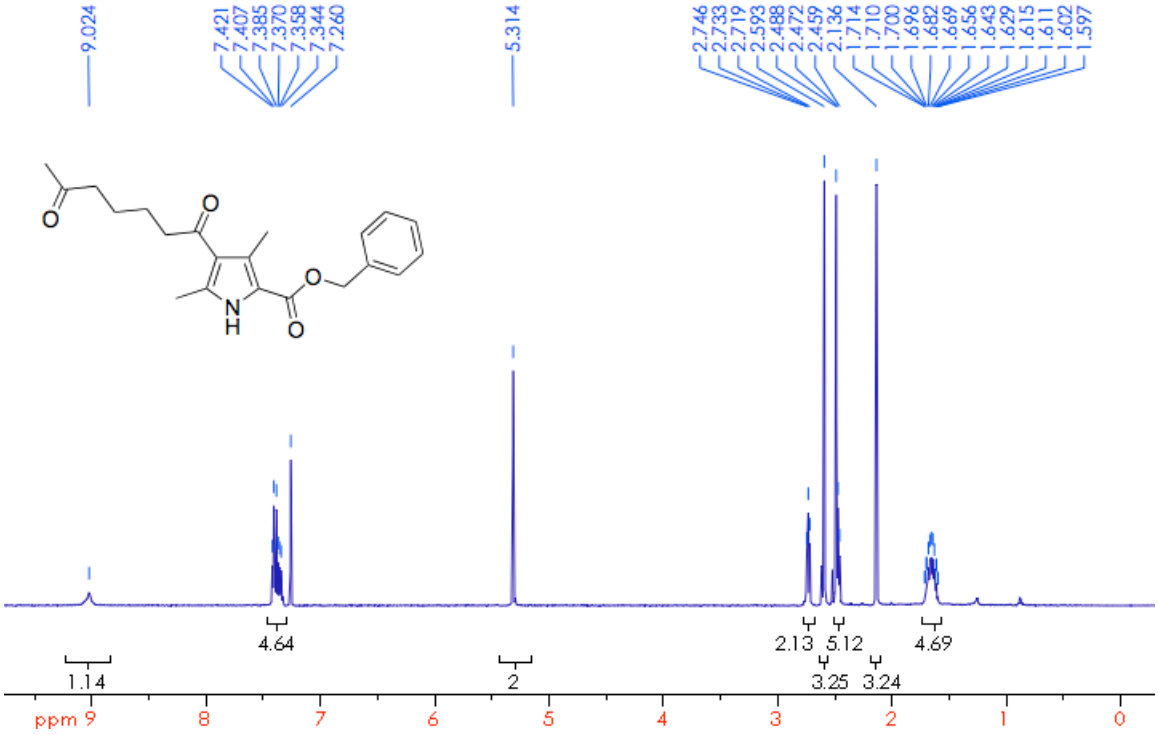


^{13}C NMR Spectrum in $CDCl_3$

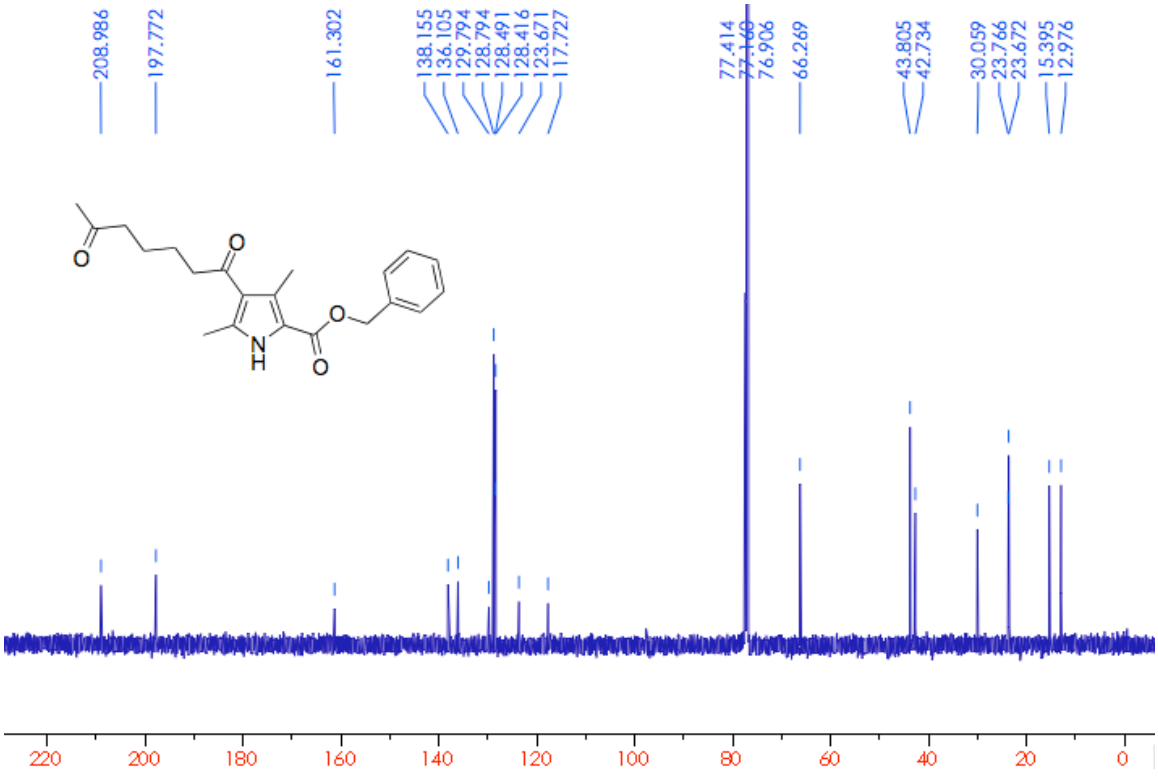


APPENDIX B.43 Benzyl 3,5-dimethyl-4-(6-oxoheptanoyl)-1*H*-pyrrole-2-carboxylate (**88**)

^{1}H NMR Spectrum in $CDCl_3$

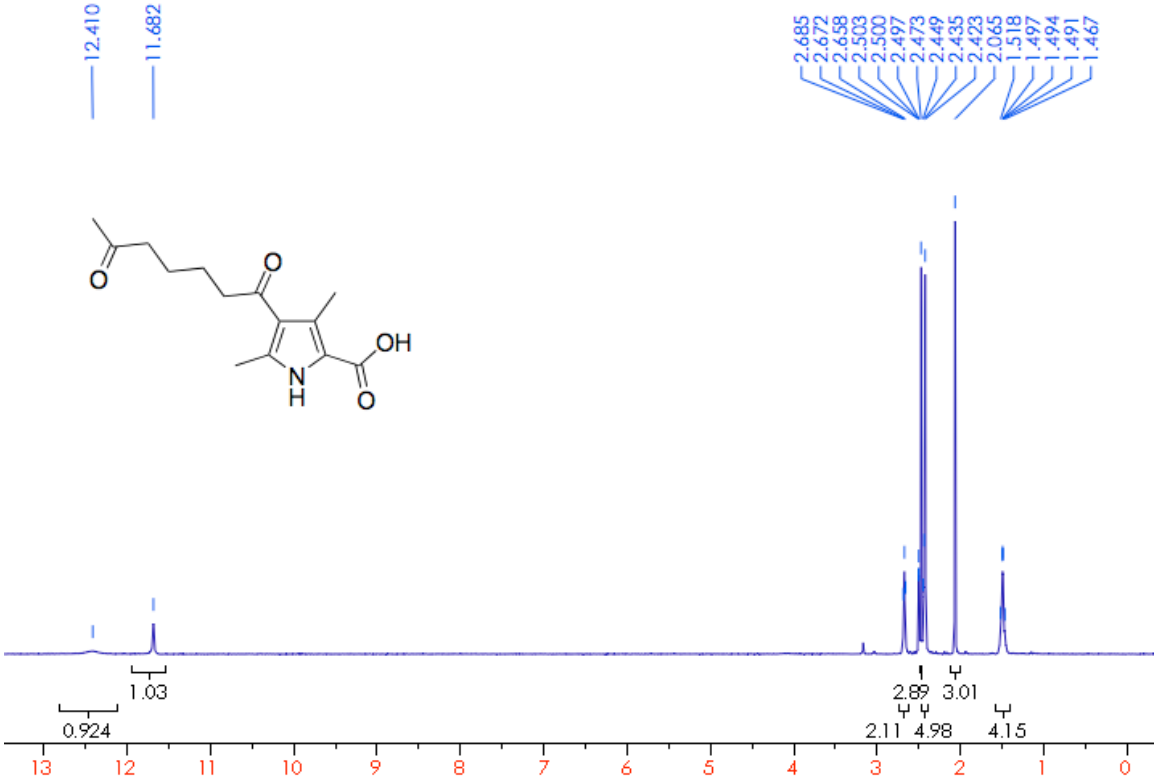


^{13}C NMR Spectrum in $CDCl_3$

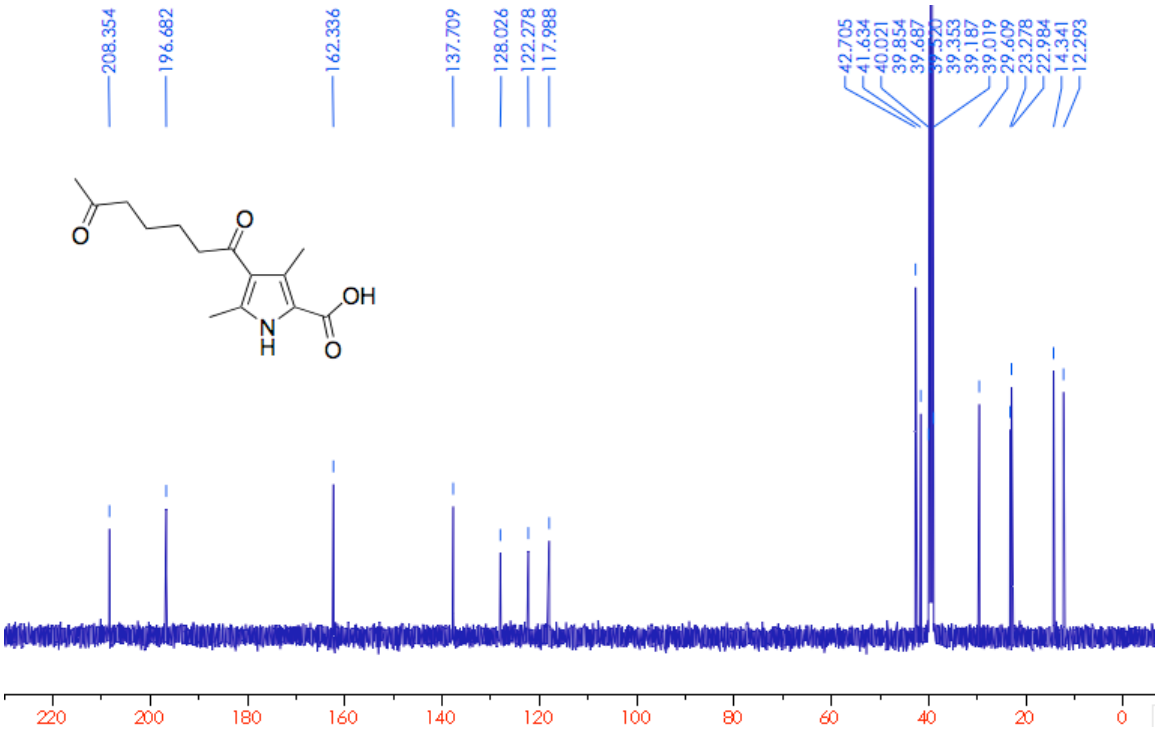


APPENDIX B.44 3,5-Dimethyl-4-(6-oxoheptanoyl)-1*H*-pyrrole-2-carboxylic acid (**89**)

^{1}H NMR Spectrum in DMSO-d_6

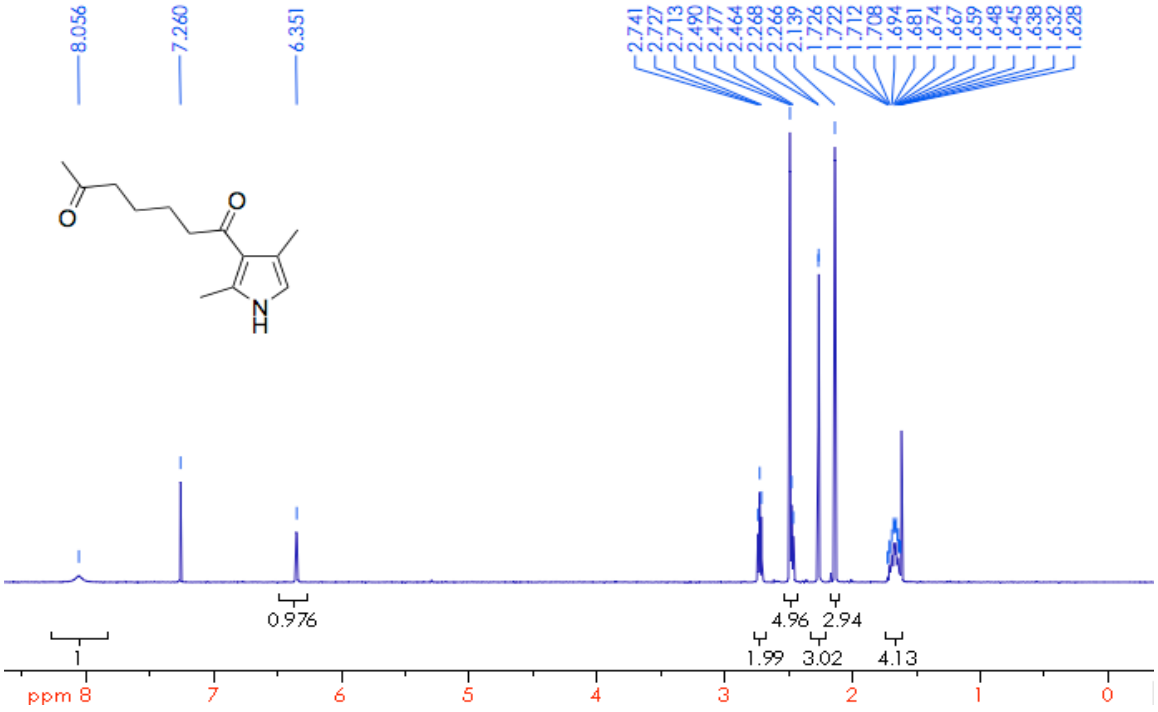


^{13}C NMR Spectrum in DMSO-d_6

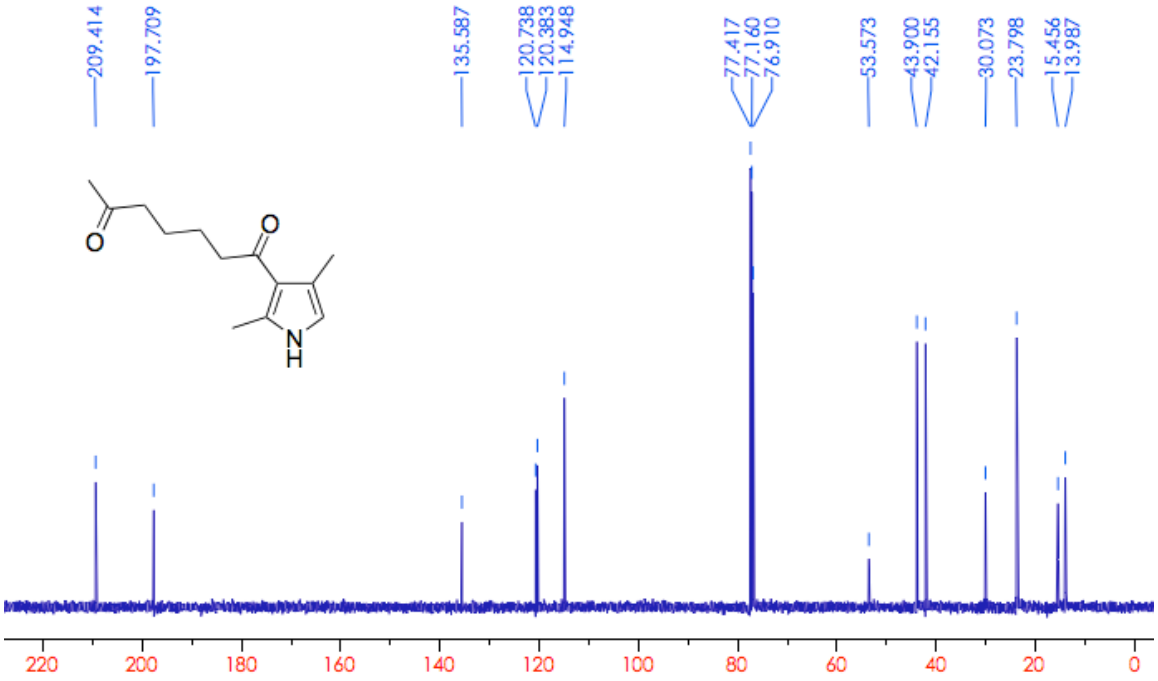


APPENDIX B.45 1-(2,4-Dimethyl-1*H*-pyrrol-3-yl)heptane-1,6-dione (**90**)

^{1}H NMR Spectrum in $CDCl_3$

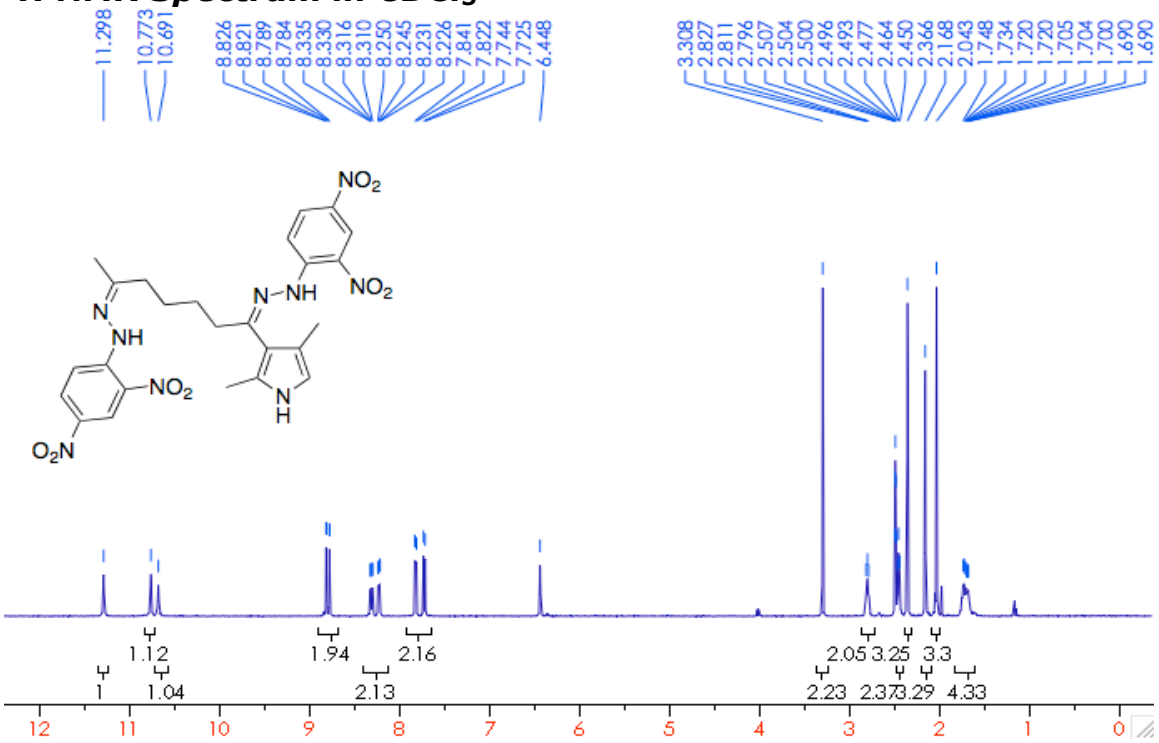


^{13}C NMR Spectrum in $CDCl_3$

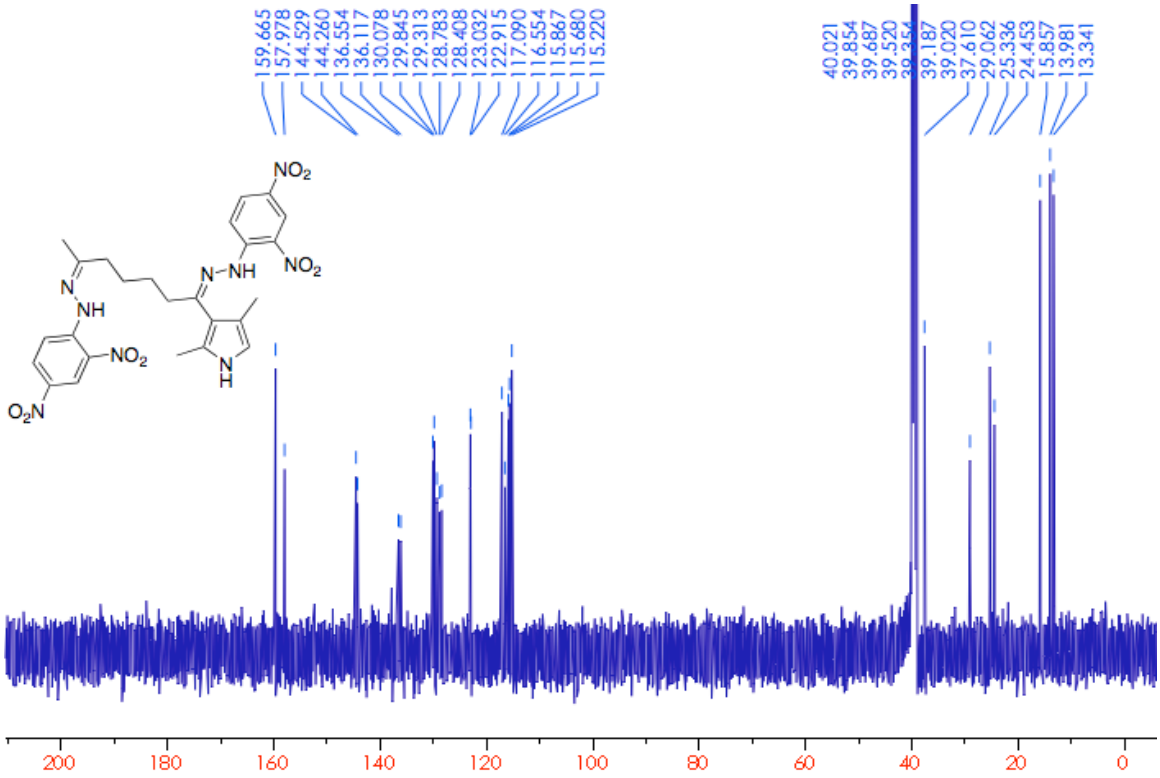


APPENDIX B.46 3-((1*Z*,6*Z*)-1,6-Bis(2-(2,4-dinitrophenyl)hydrazono)heptyl)-2,4-dimethyl-1*H*-pyrrole (**91**)

^{1}H NMR Spectrum in $CDCl_3$

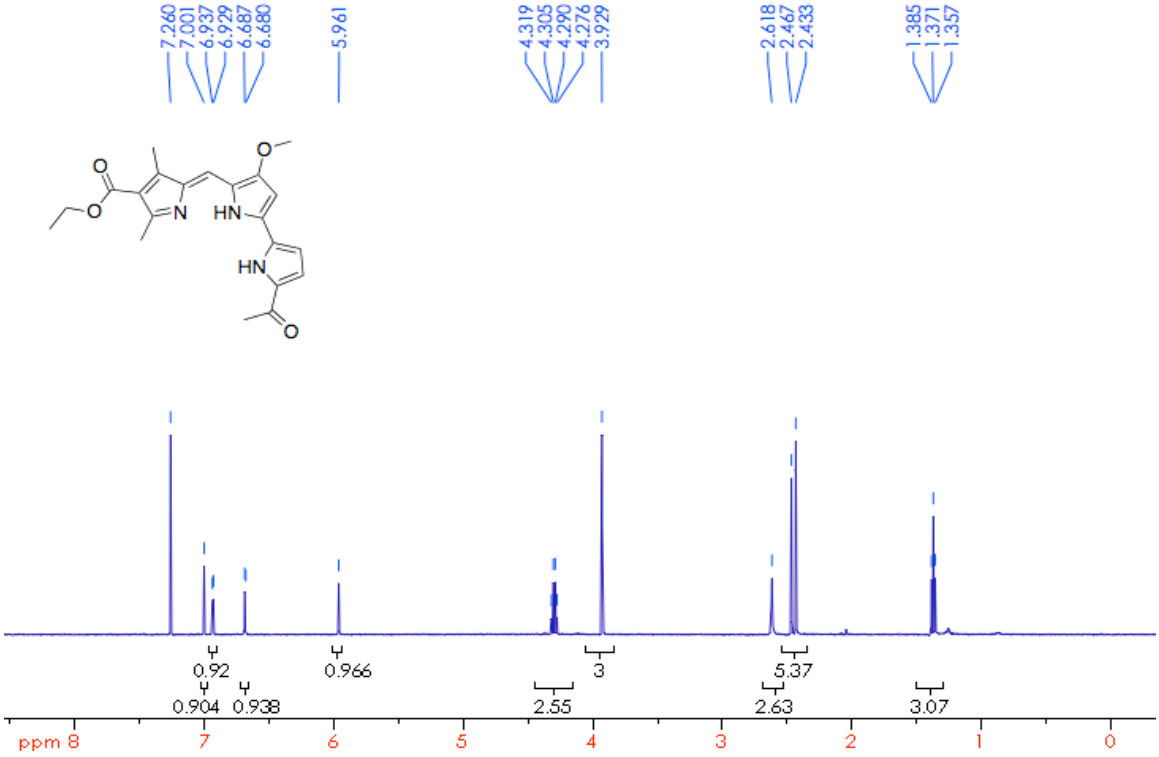


^{13}C NMR Spectrum in $CDCl_3$

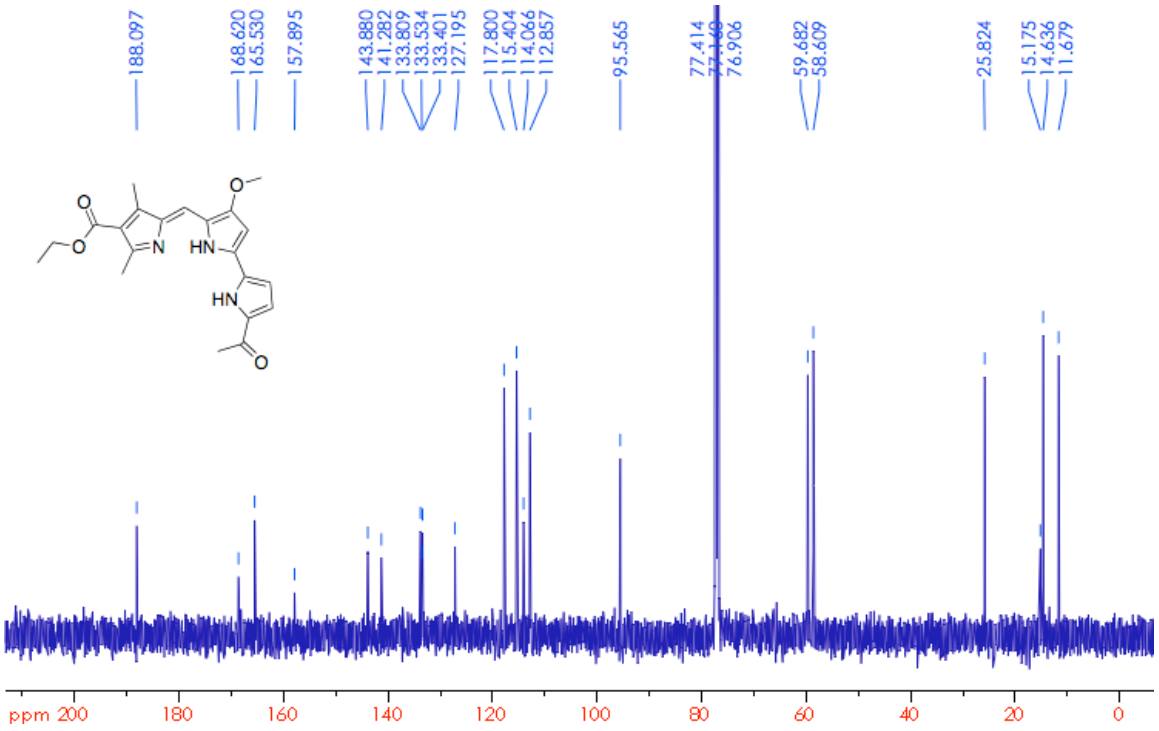


APPENDIX B.47 (*Z*)-Ethyl 2-((5'-acetyl-4-methoxy-1H,1'H-2,2'-bipyrrol-5-yl)methylene)-3,5-dimethyl-2H-pyrrole-4-carboxylate (**92**)

^{1}H NMR Spectrum in $CDCl_3$

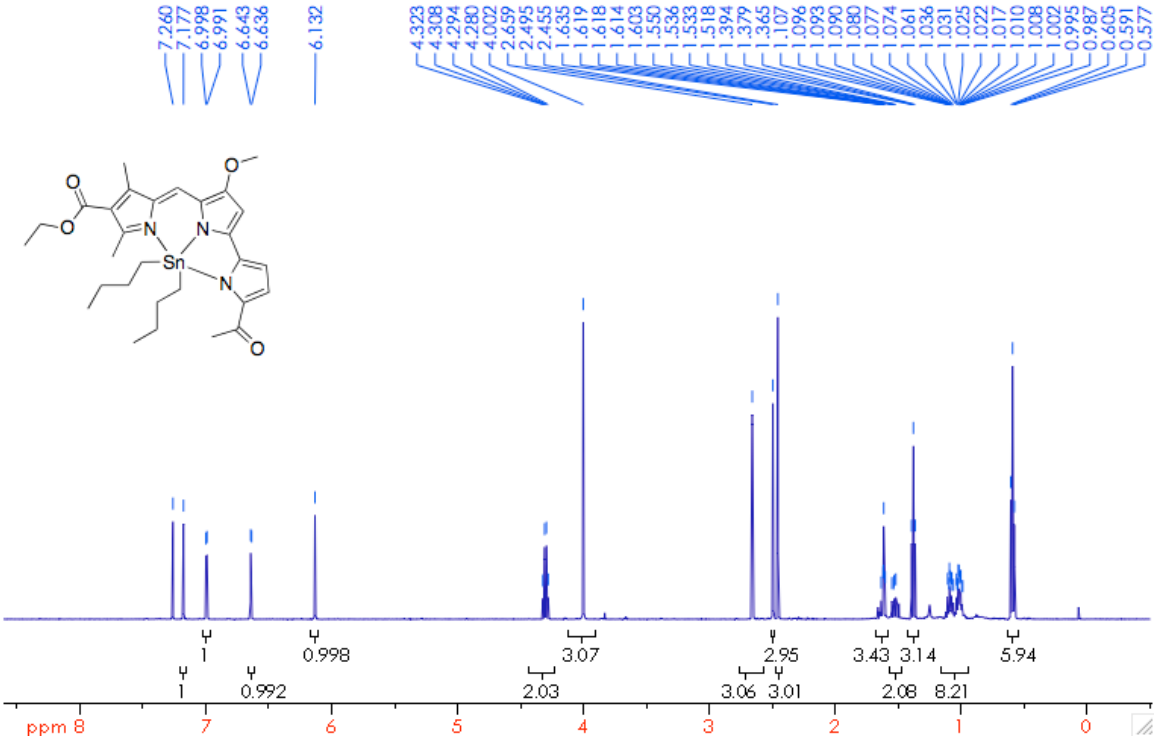


^{13}C NMR Spectrum in $CDCl_3$

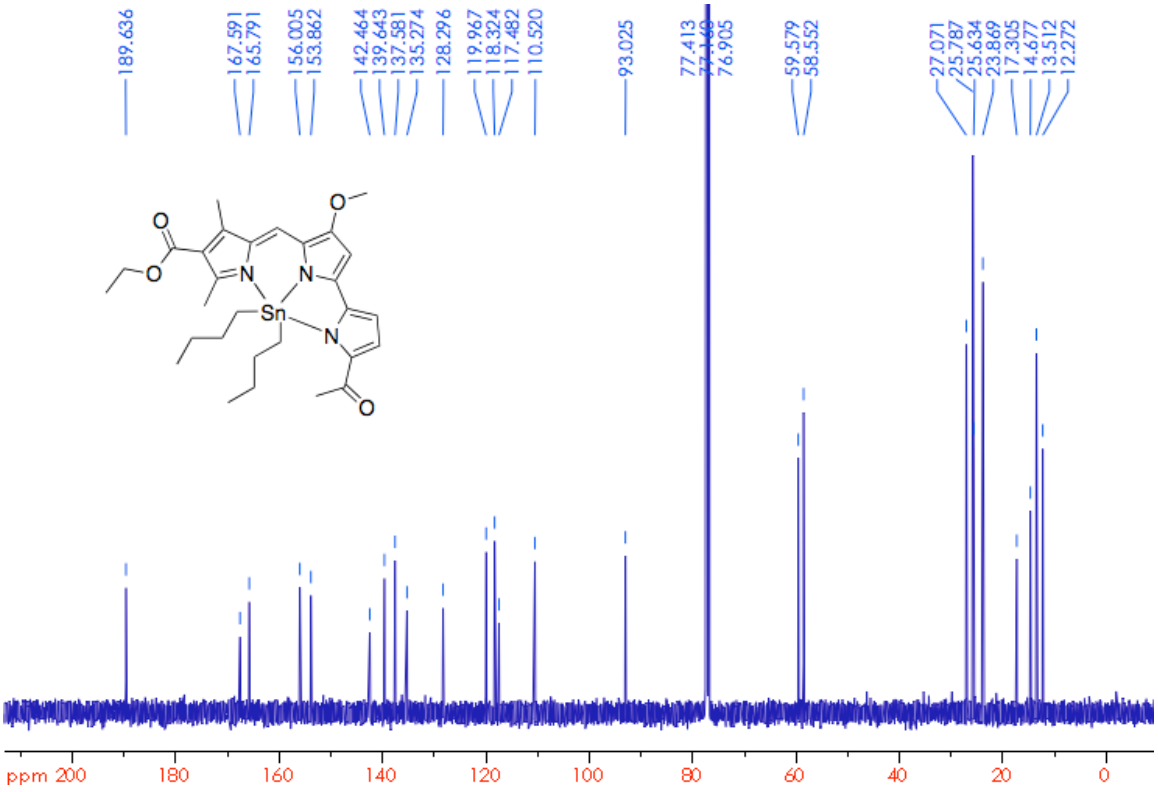


APPENDIX B.48 ((Bu)$_2$(**92**)Sn(IV) (**93**)

^{1}H NMR Spectrum in $CDCl_3$

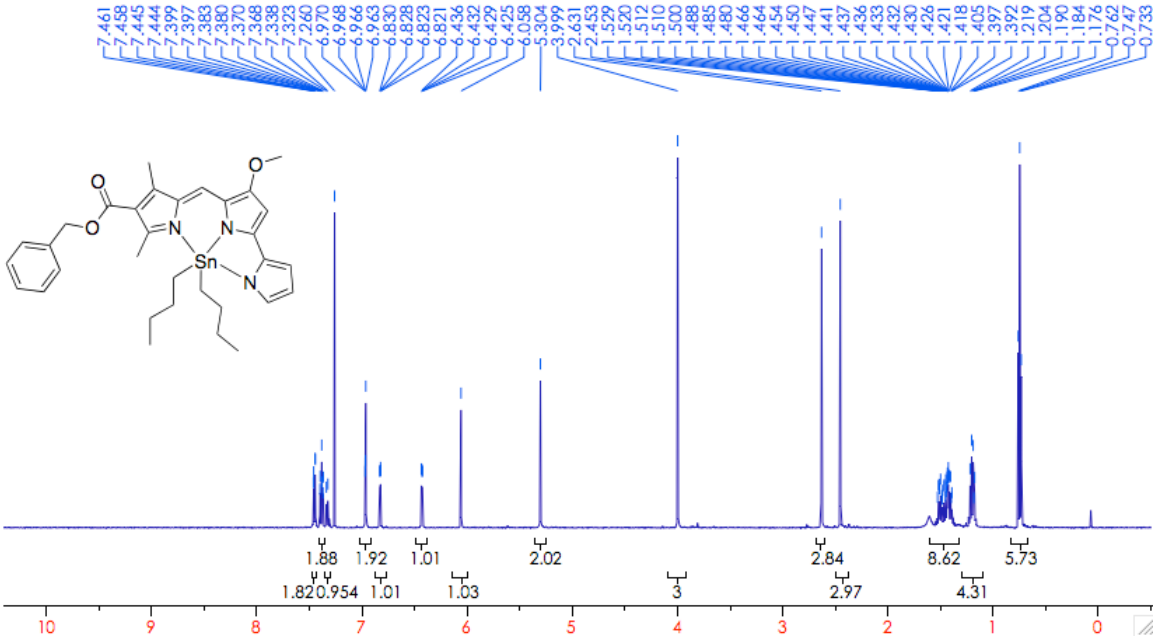


^{13}C NMR Spectrum in $CDCl_3$

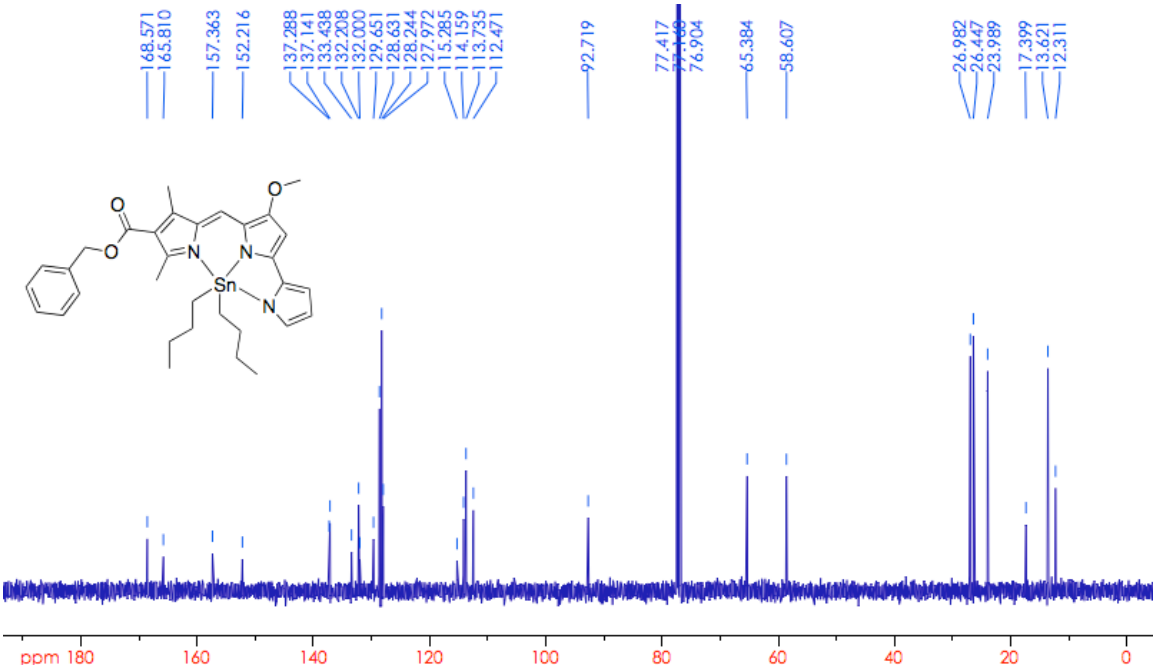


APPENDIX B.49 $(Bu)_2$(**94**)Sn(IV) (**95**)

^{1}H NMR Spectrum in $CDCl_3$

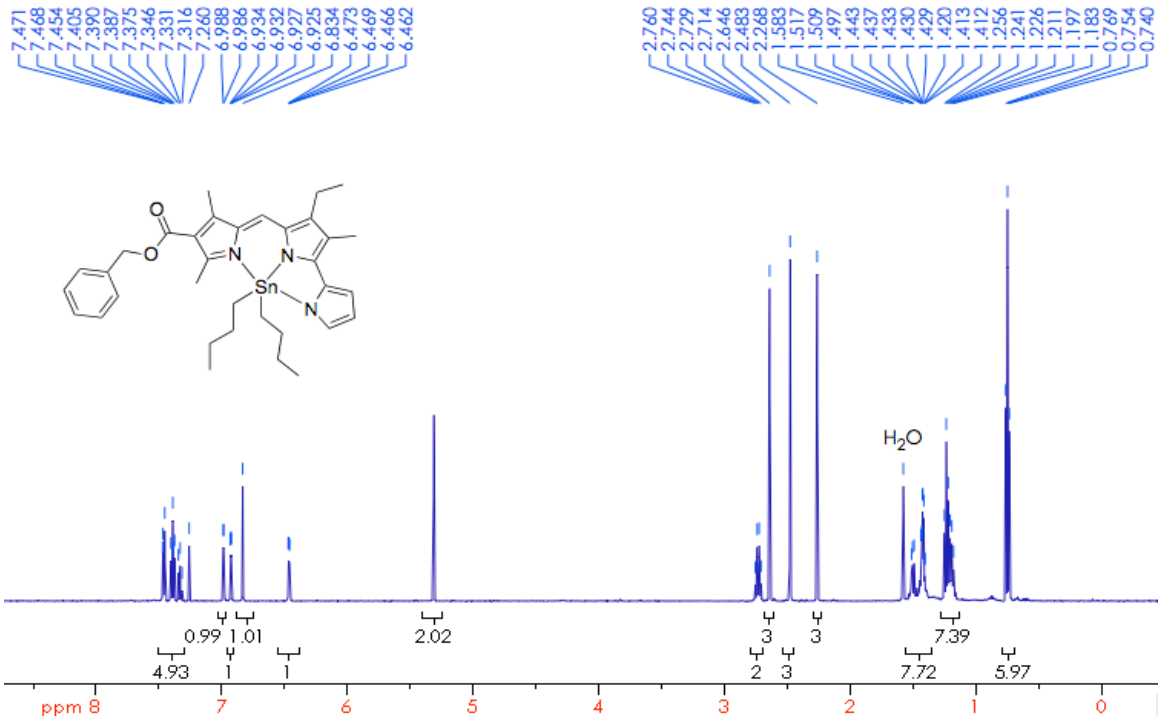


^{13}C NMR Spectrum in $CDCl_3$

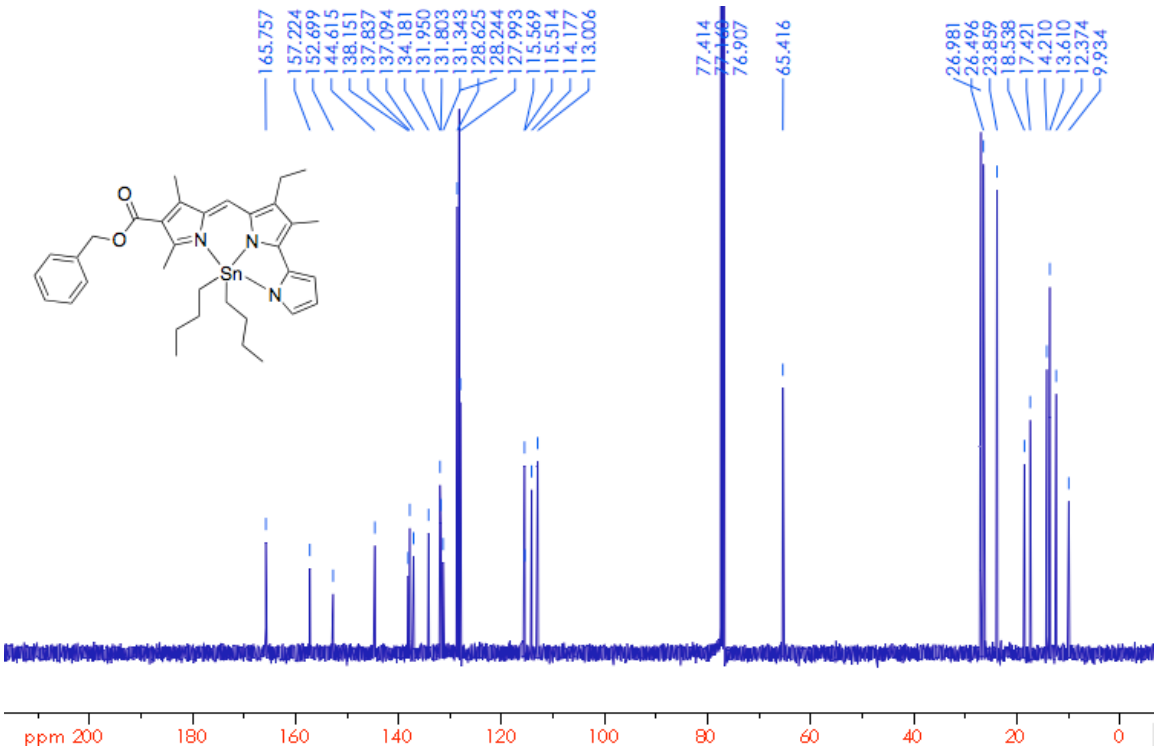


APPENDIX B.50 $(Bu)_2$((*Z*)-Methyl 2-((4-ethyl-3-methyl-1*H*,1'*H*-2,2'-bipyrrol-5-yl)methylene)-3,5-dimethyl-2*H*-pyrrole-4-carboxylate)Sn(IV) (**96**)

^{1}H NMR Spectrum in $CDCl_3$

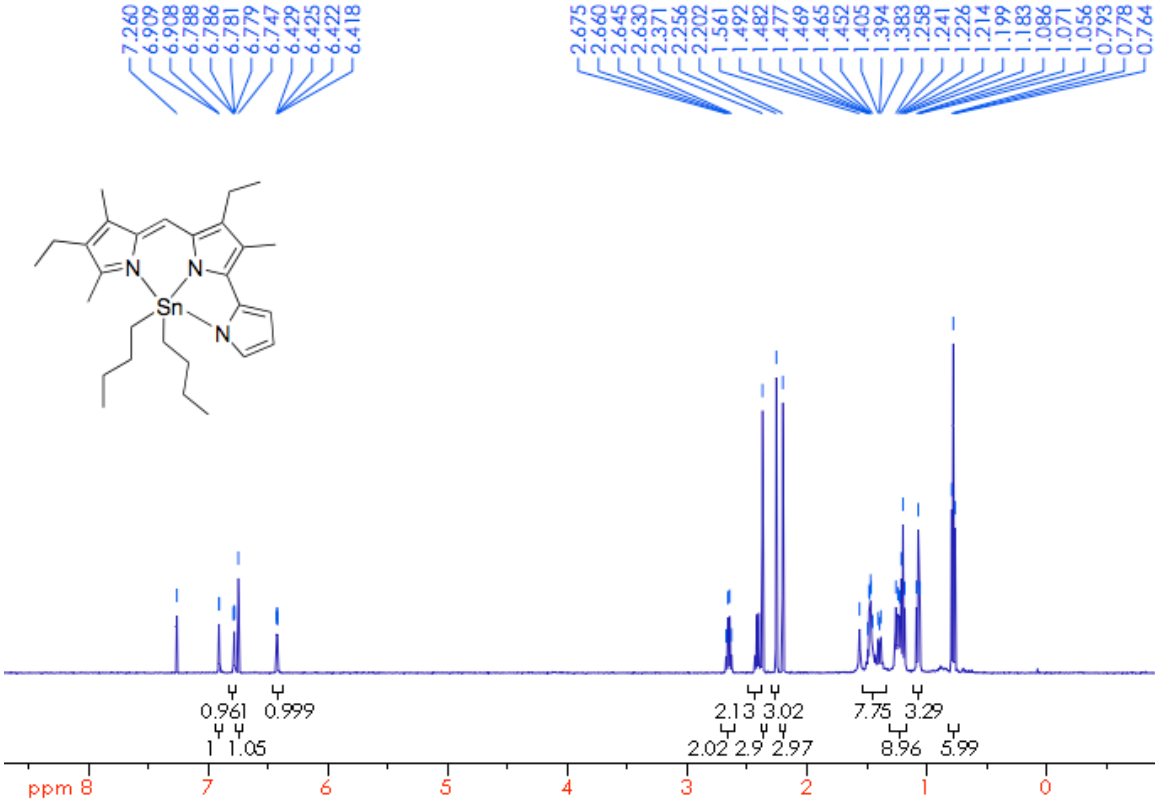


^{13}C NMR Spectrum in $CDCl_3$

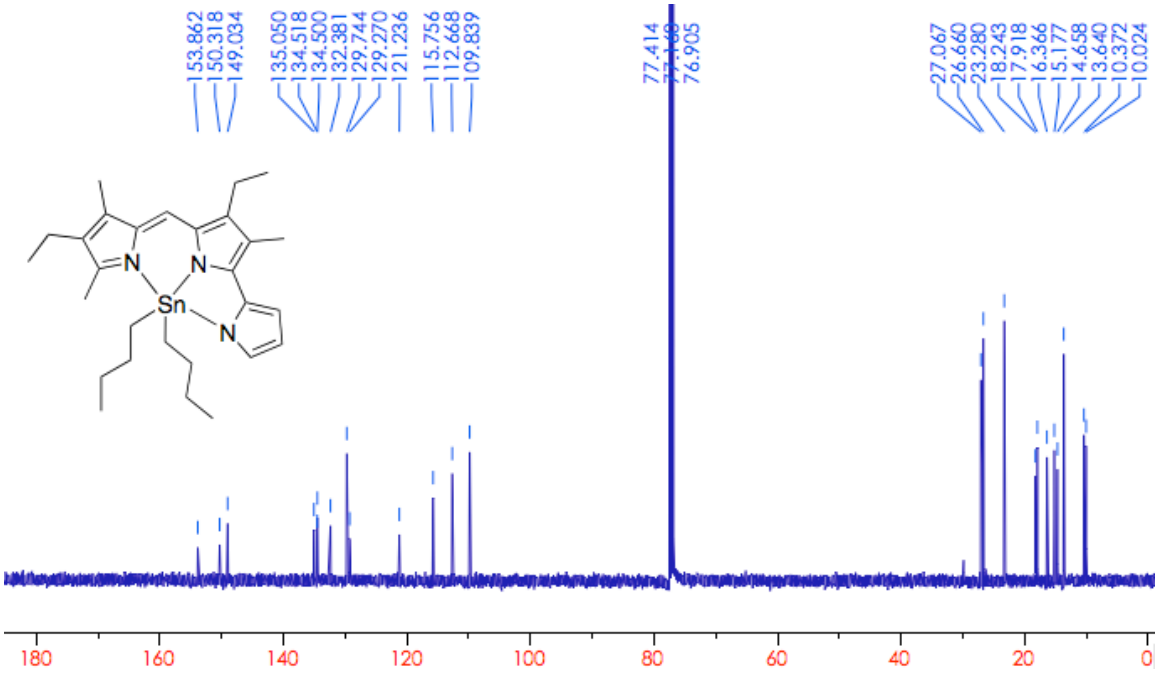


APPENDIX B.51 $(Bu)_2$(**82**)Sn(IV) (**97**)

^{1}H NMR Spectrum in $CDCl_3$

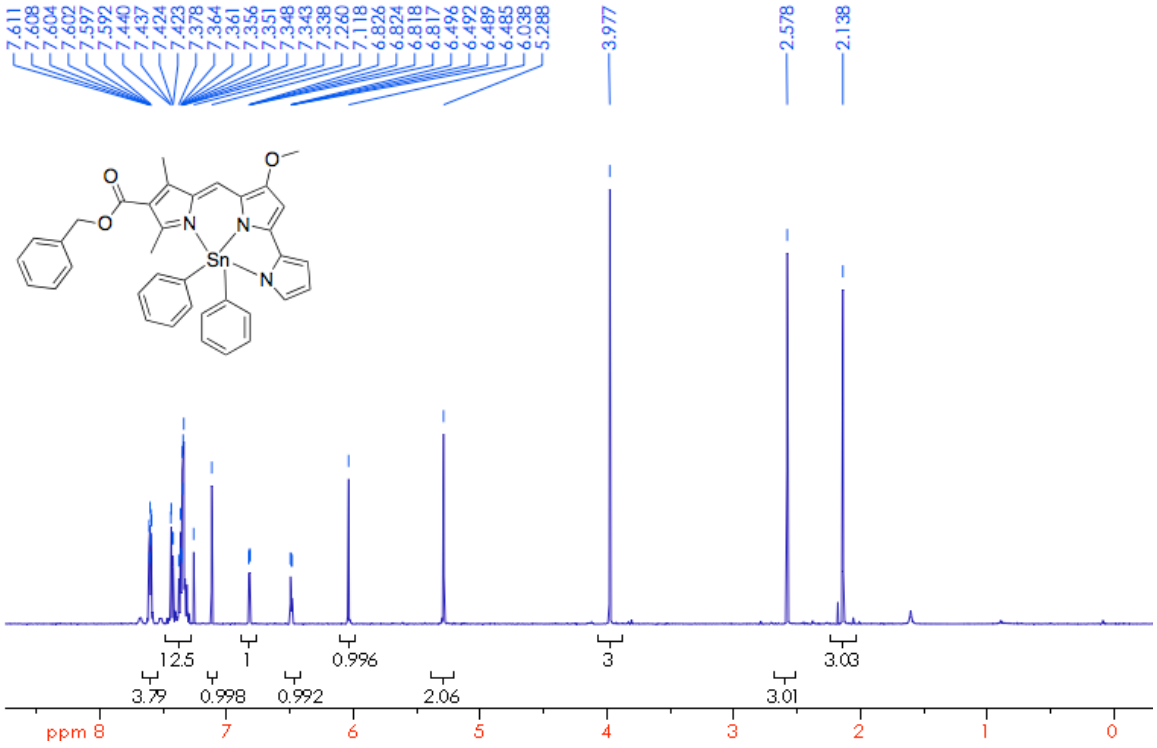


^{13}C NMR Spectrum in $CDCl_3$

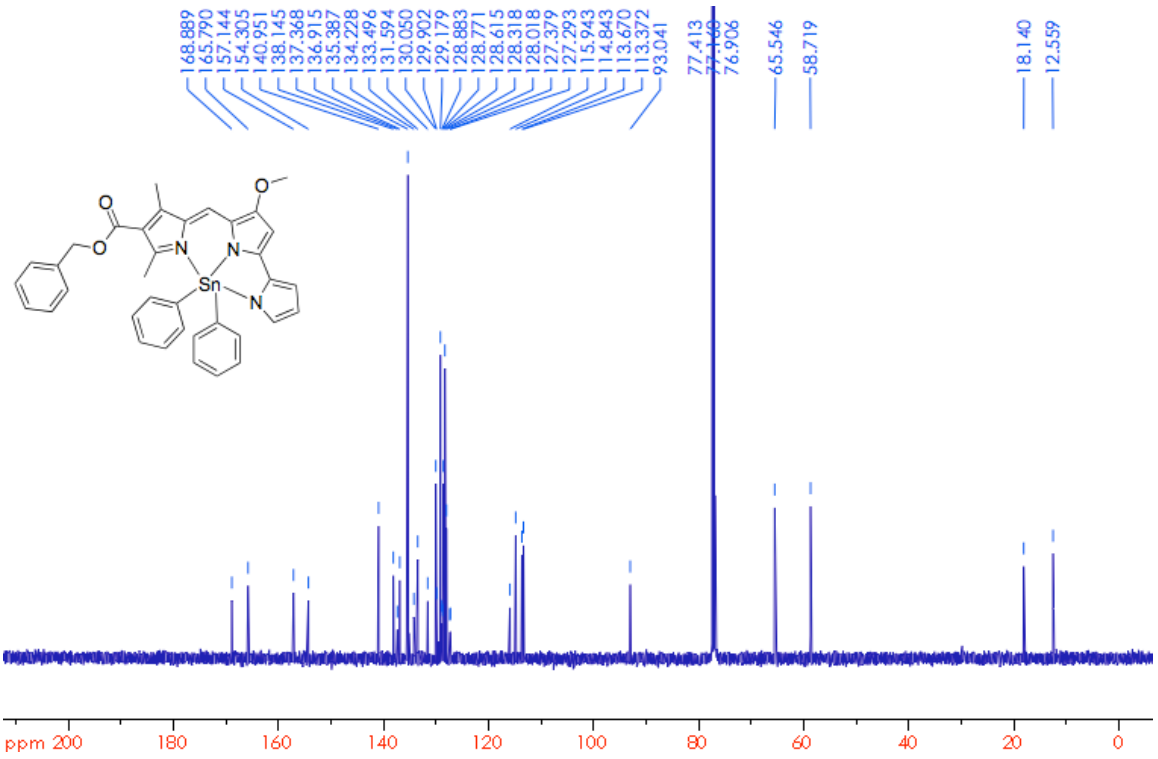


APPENDIX B.52 $(Ph)_2$(**94**)Sn(IV) (**98**)

^{1}H NMR Spectrum in $CDCl_3$

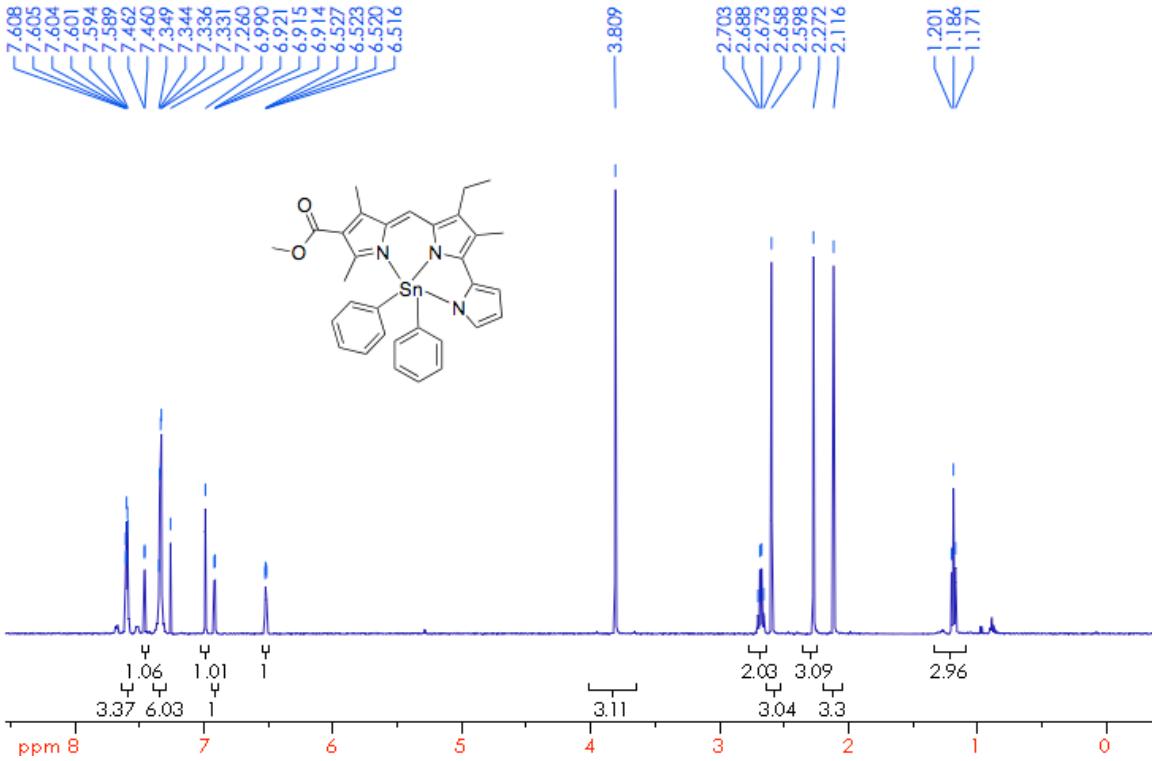


^{13}C NMR Spectrum in $CDCl_3$

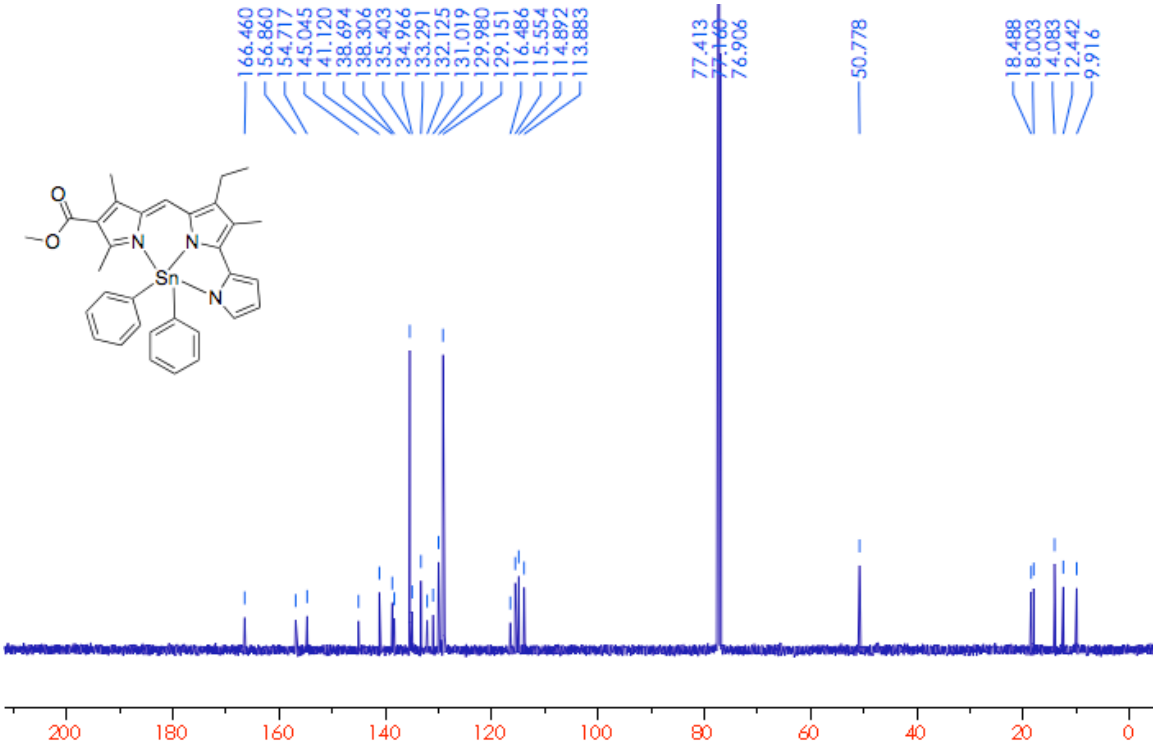


APPENDIX B.53 $(Ph)_2$(**58**)Sn(IV) (**99**)

^{1}H NMR Spectrum in $CDCl_3$

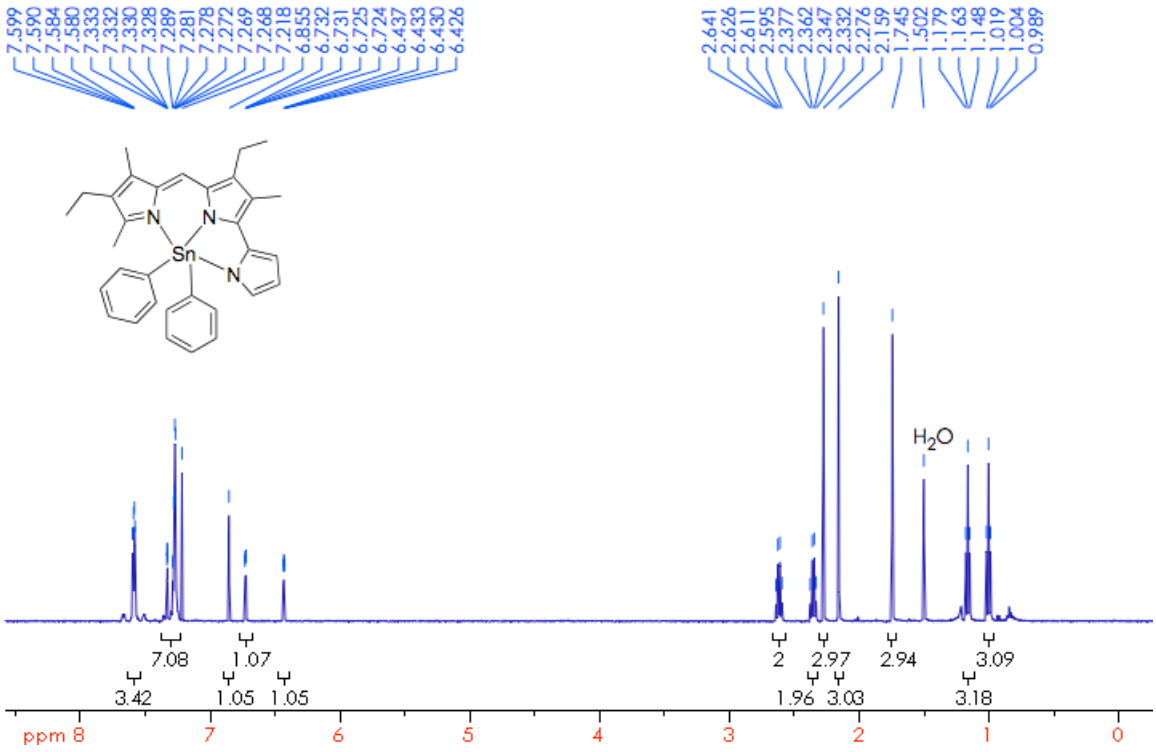


^{13}C NMR Spectrum in $CDCl_3$

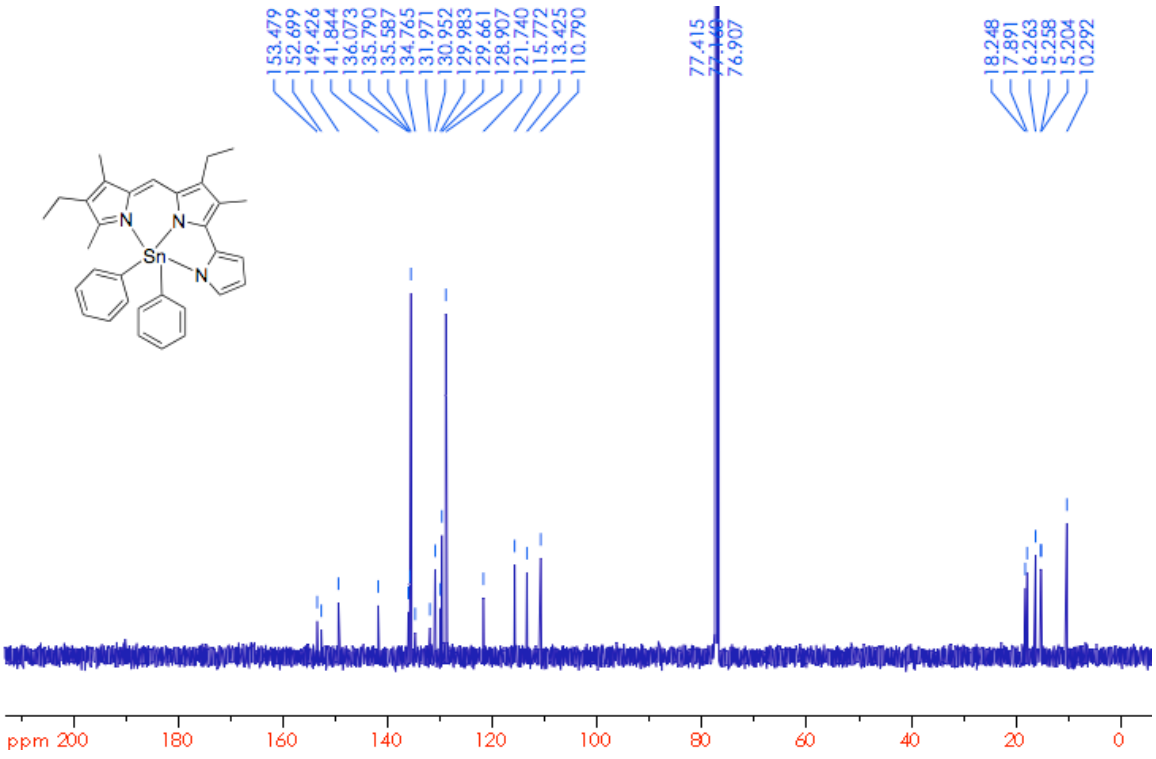


APPENDIX B.54 $(Ph)_2$(**82**)Sn(IV) (**100**)

^{1}H NMR Spectrum in $CDCl_3$

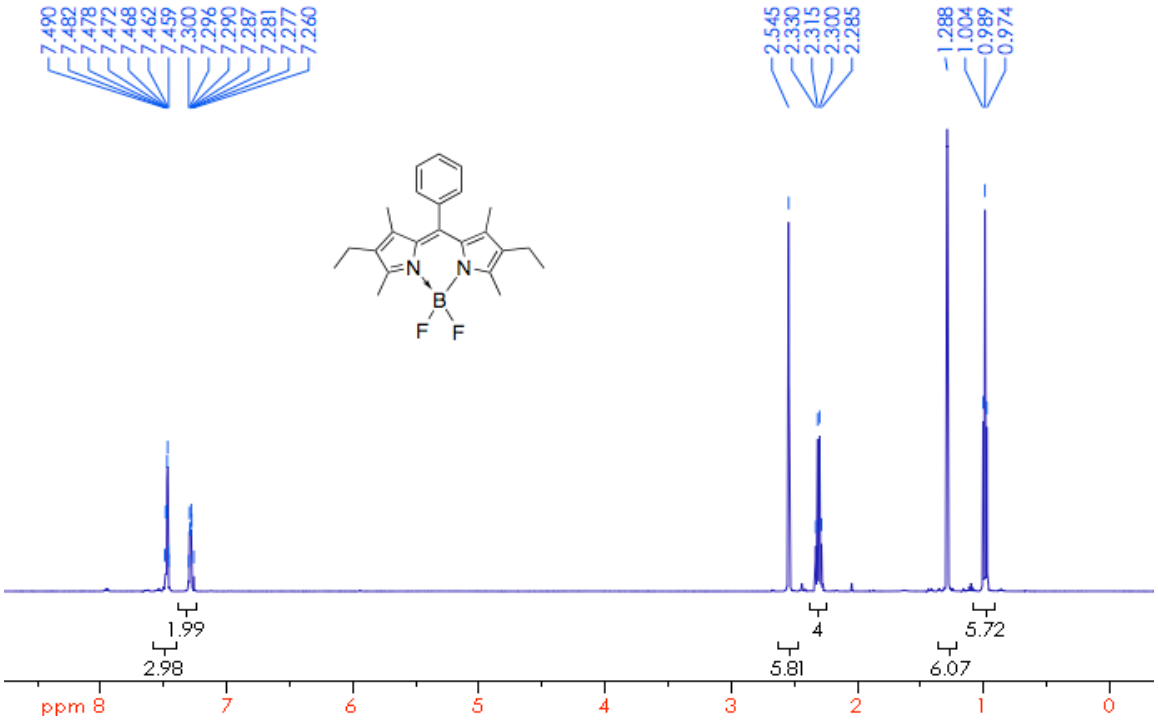


^{13}C NMR Spectrum in $CDCl_3$

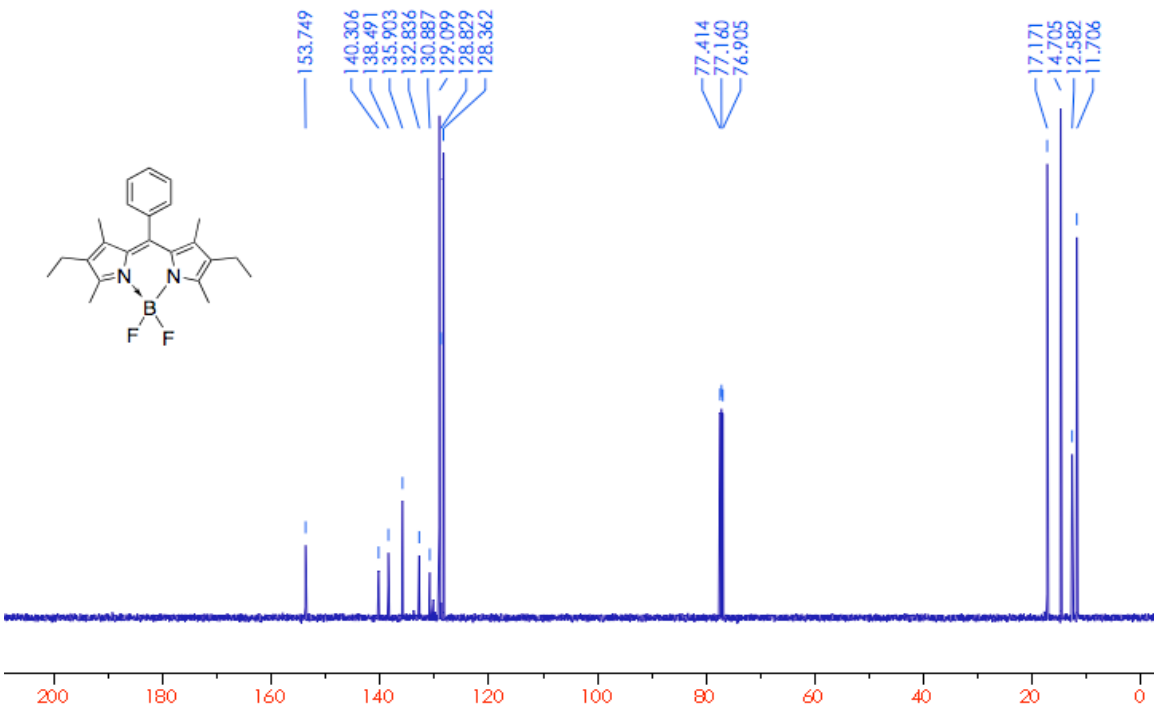


APPENDIX B.55 1,3,5,7-Tetramethyl-2,6-diethyl-8-phenyl-4-bora-3a,4a-diaza-*s*-indacene (**104**)[148]

^{1}H NMR Spectrum in $CDCl_3$

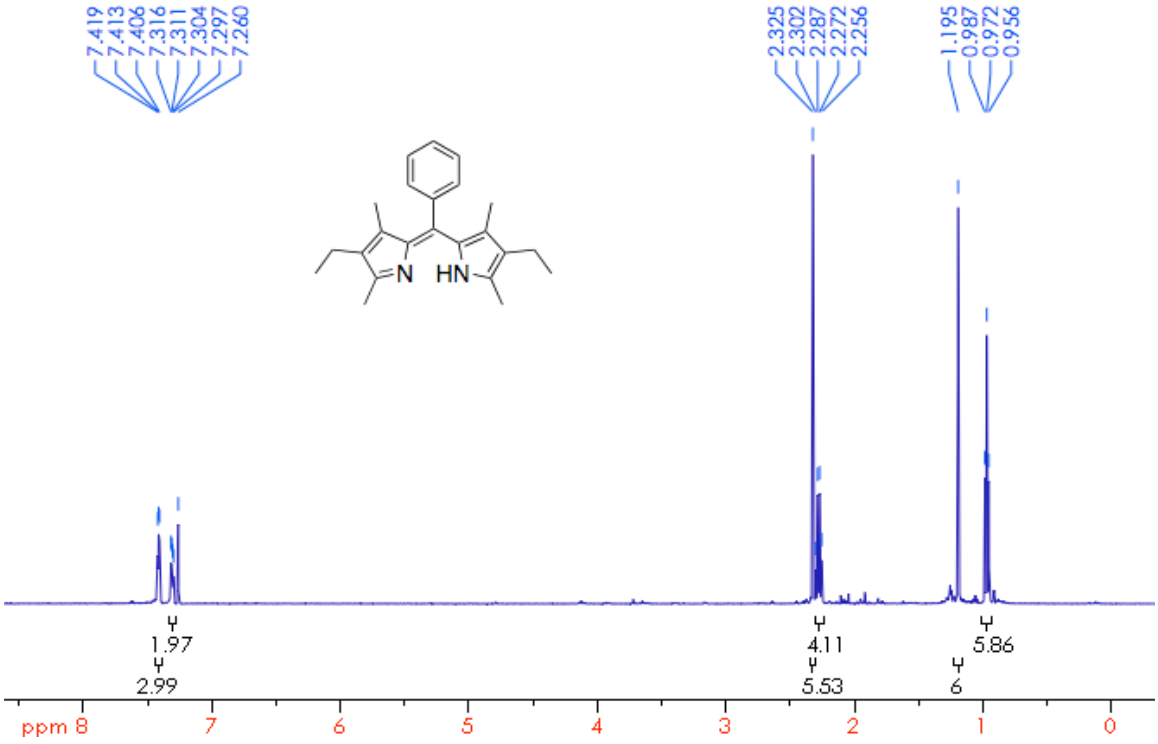


^{13}C NMR Spectrum in $CDCl_3$

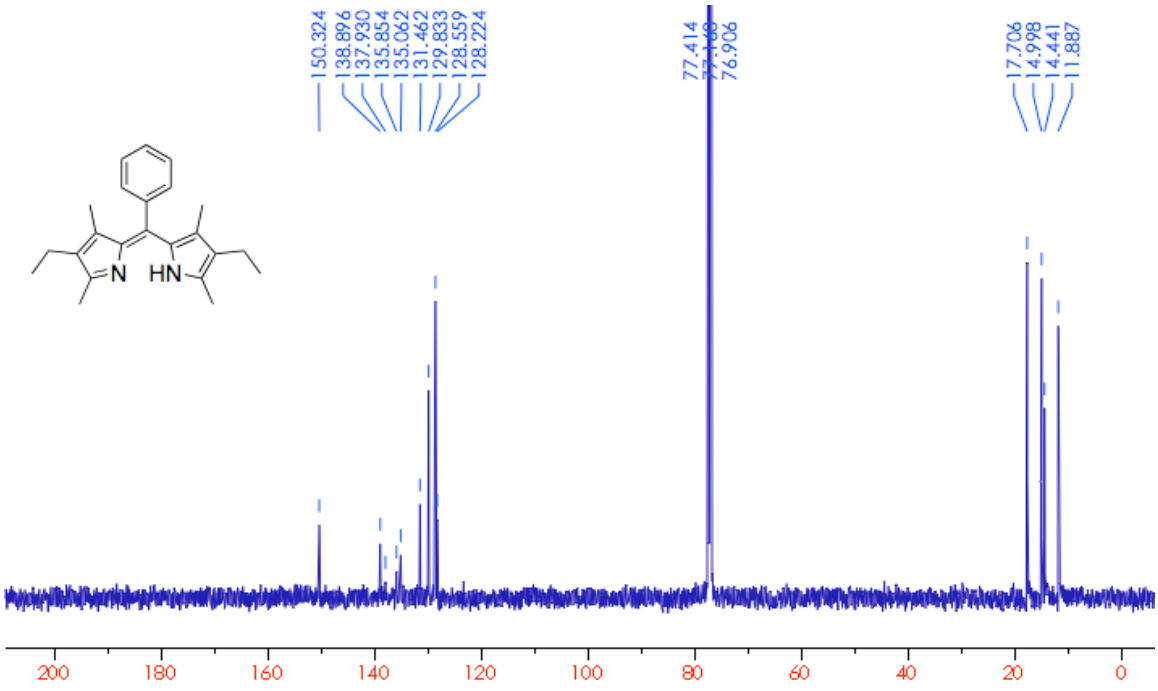


APPENDIX B.56 (*Z*)-3-ethyl-5-((4-ethyl-3,5-dimethyl-2H-pyrrol-2-ylidene)(phenyl)methyl)-2,4-dimethyl-1H-pyrrole (**105**)

^{1}H NMR Spectrum in $CDCl_3$

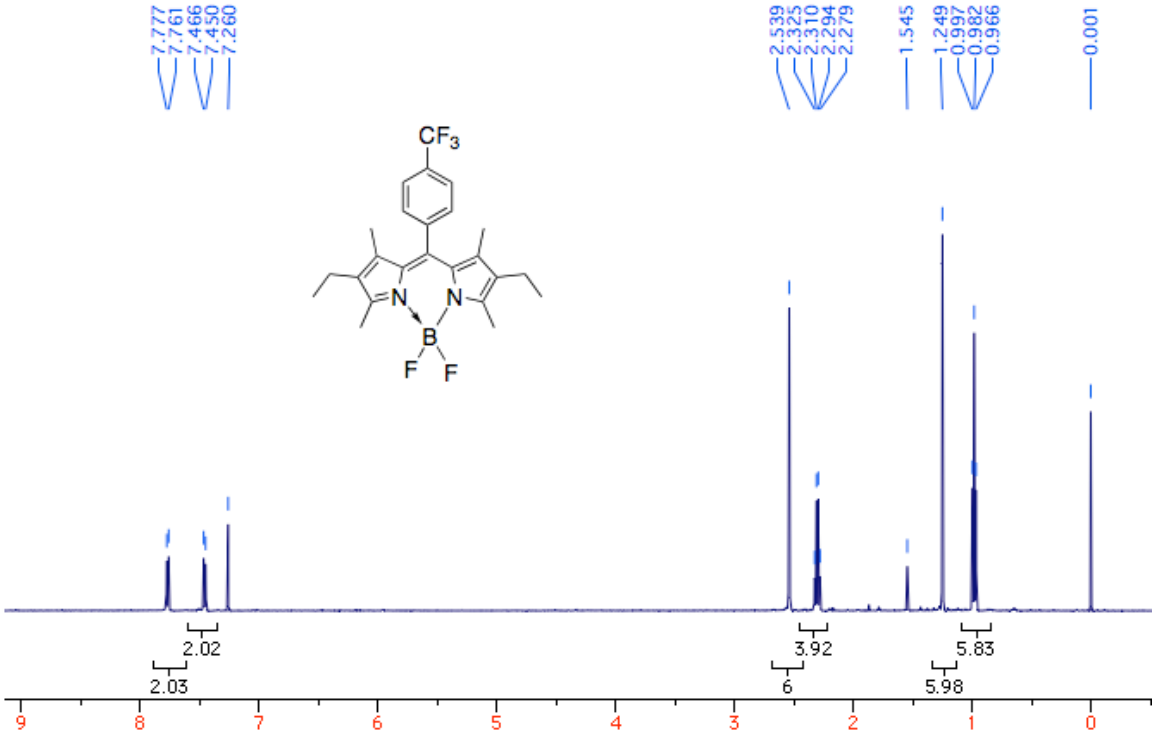


^{13}C NMR Spectrum in $CDCl_3$

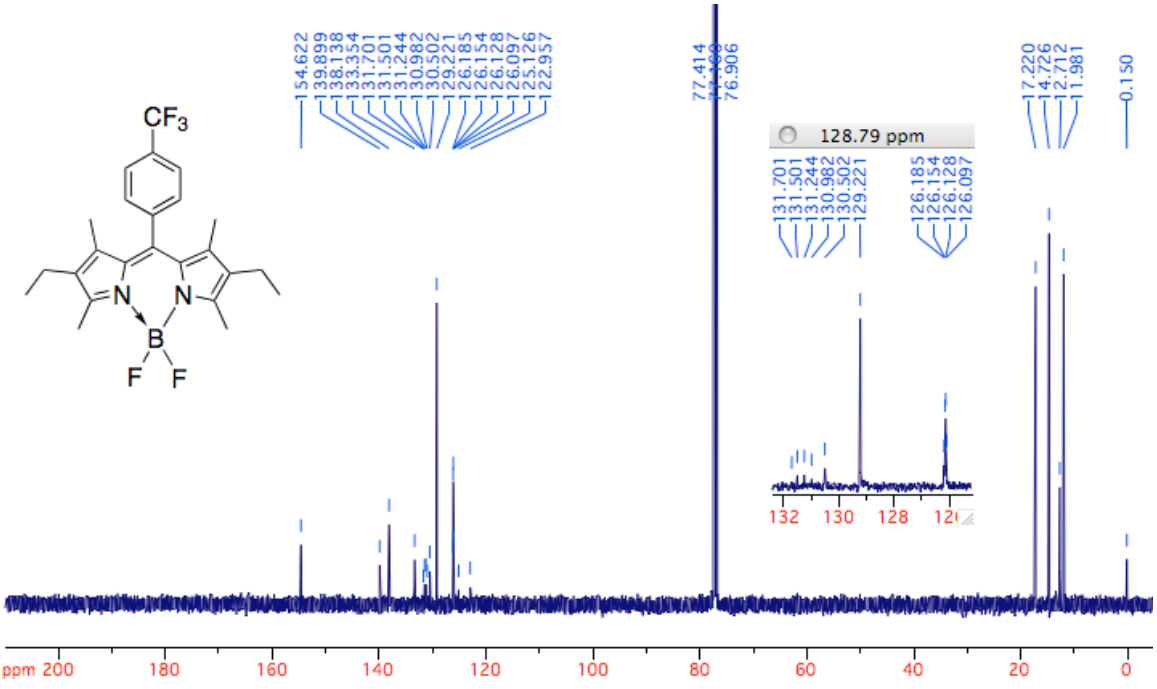


APPENDIX B.57 1,3,5,7-Tetramethyl-2,6-diethyl-8-(4-trifluoromethylphenyl)- 4-bora-3a,4a-diaza-*s*-indacene (**106**)

^{1}H NMR Spectrum in $CDCl_3$

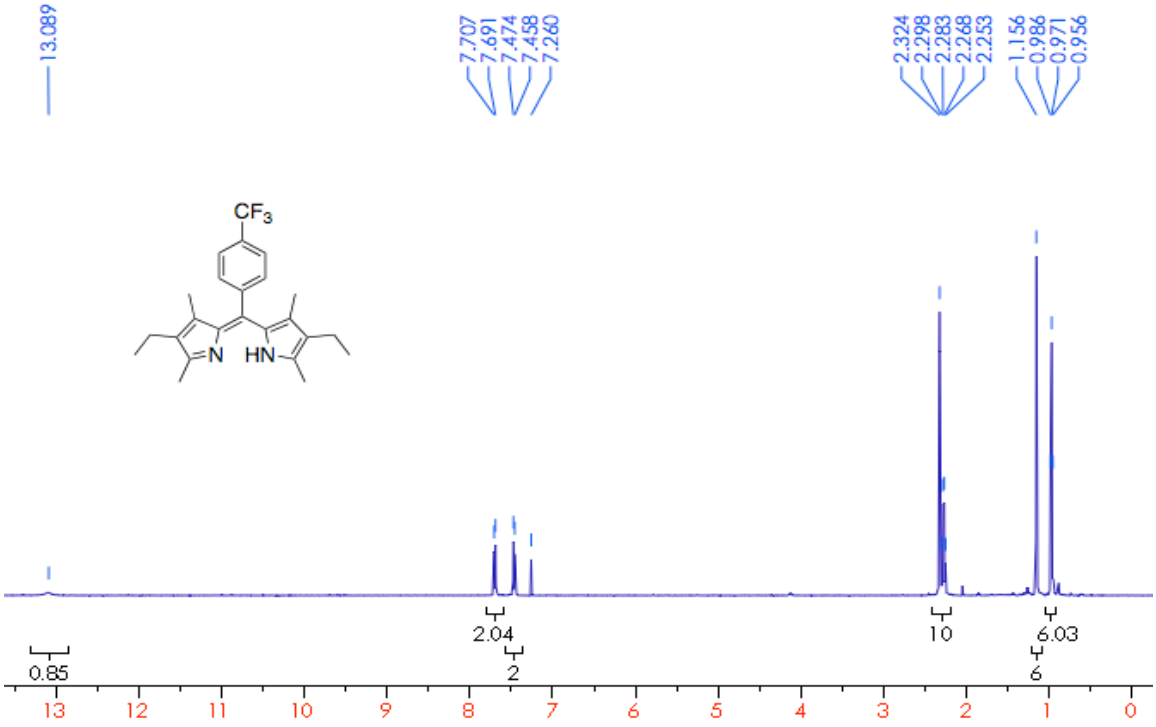


^{13}C NMR Spectrum in $CDCl_3$

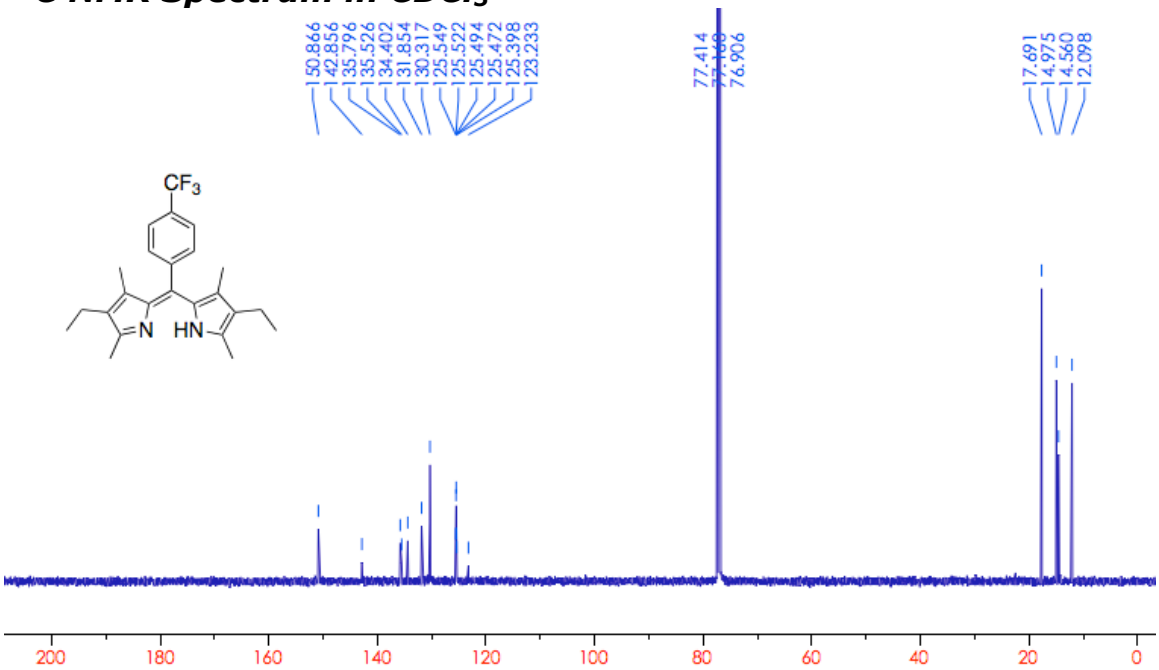


APPENDIX B.58 (*Z*)-3-Ethyl-5-((4-ethyl-3,5-dimethyl-2*H*-pyrrol-2-ylidene)(4-(trifluoromethyl)phenyl)methyl)-2,4-dimethyl-1*H*-pyrrole (**107**)

^{1}H NMR Spectrum in $CDCl_3$

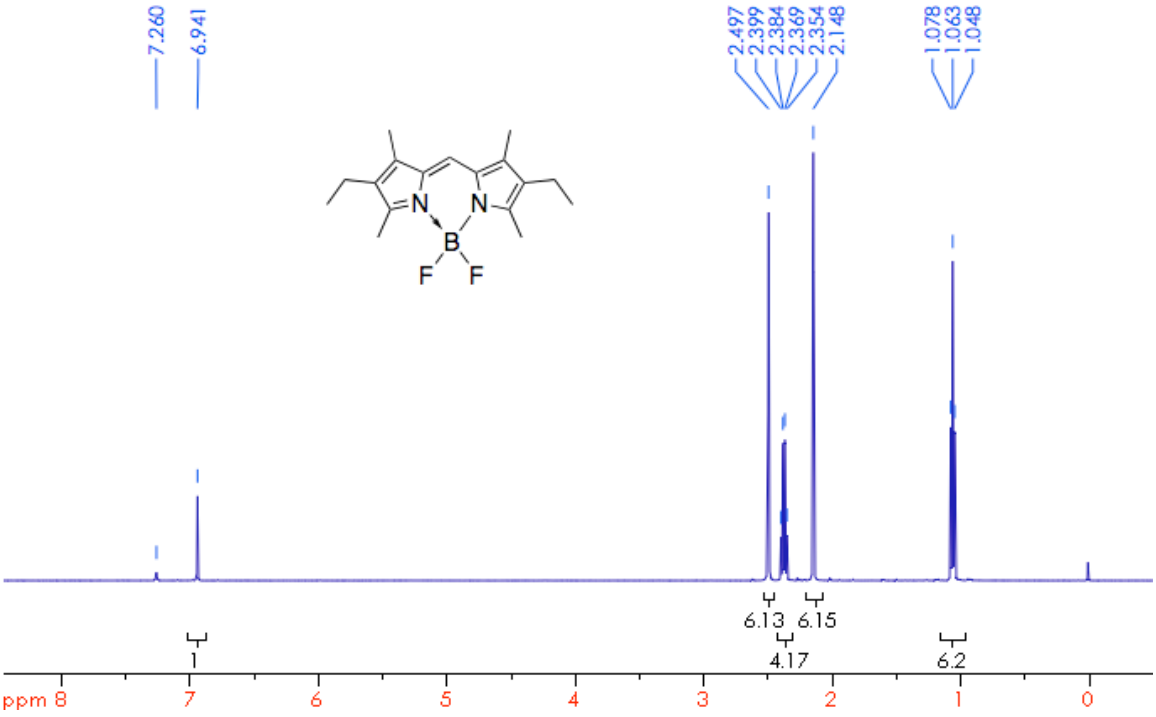


^{13}C NMR Spectrum in $CDCl_3$

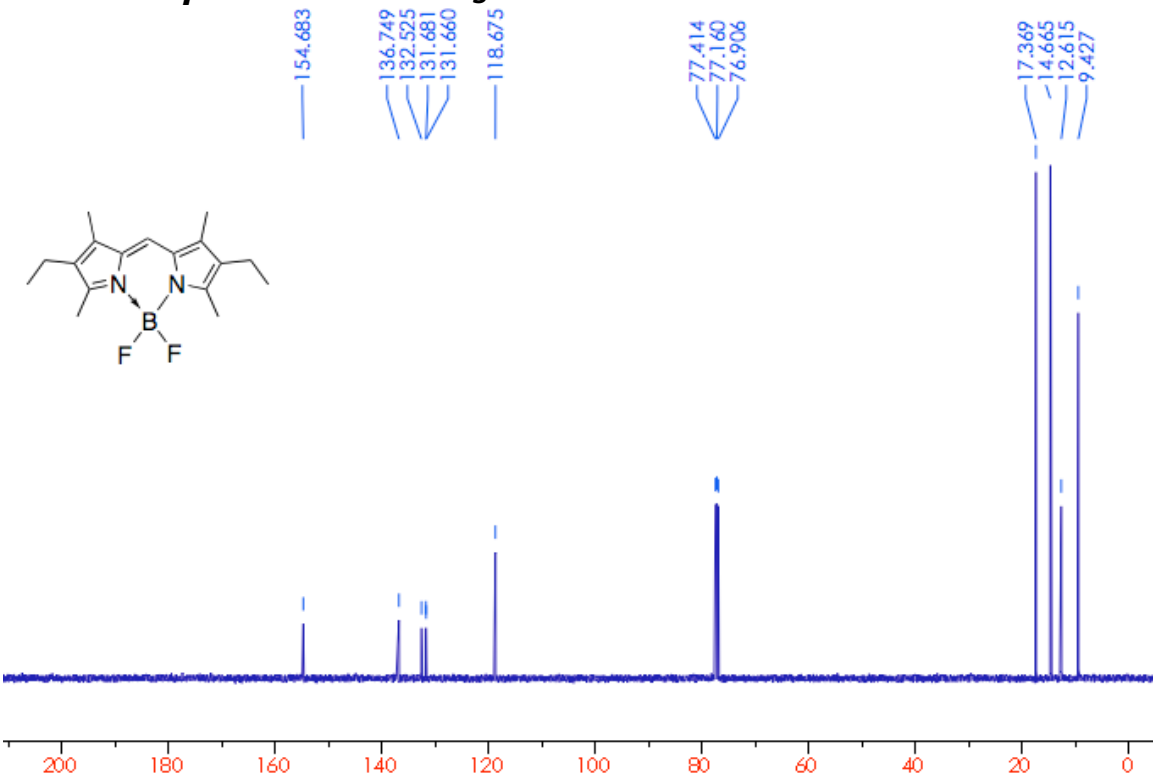


APPENDIX B.59 1,3,5,7-Tetramethyl-2,6-diethyl-8-H-4-bora-3a,4a-diaza-*s*-indacene (**108**)[116, 192]

^{1}H NMR Spectrum in $CDCl_3$

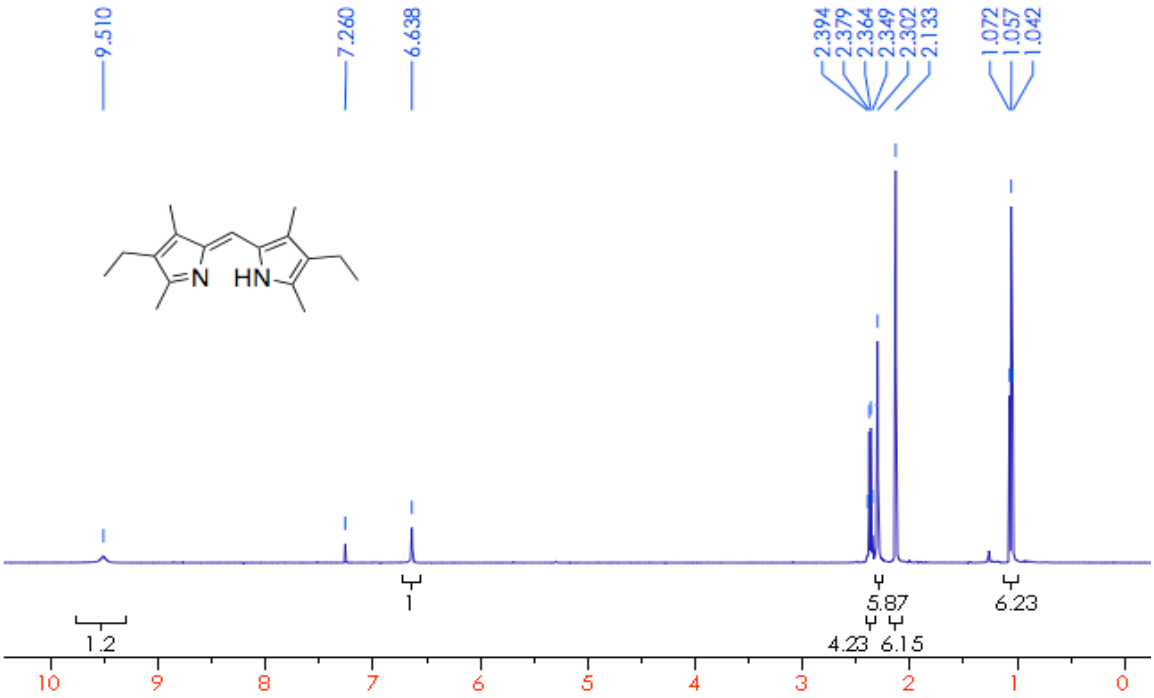


^{13}C NMR Spectrum in $CDCl_3$

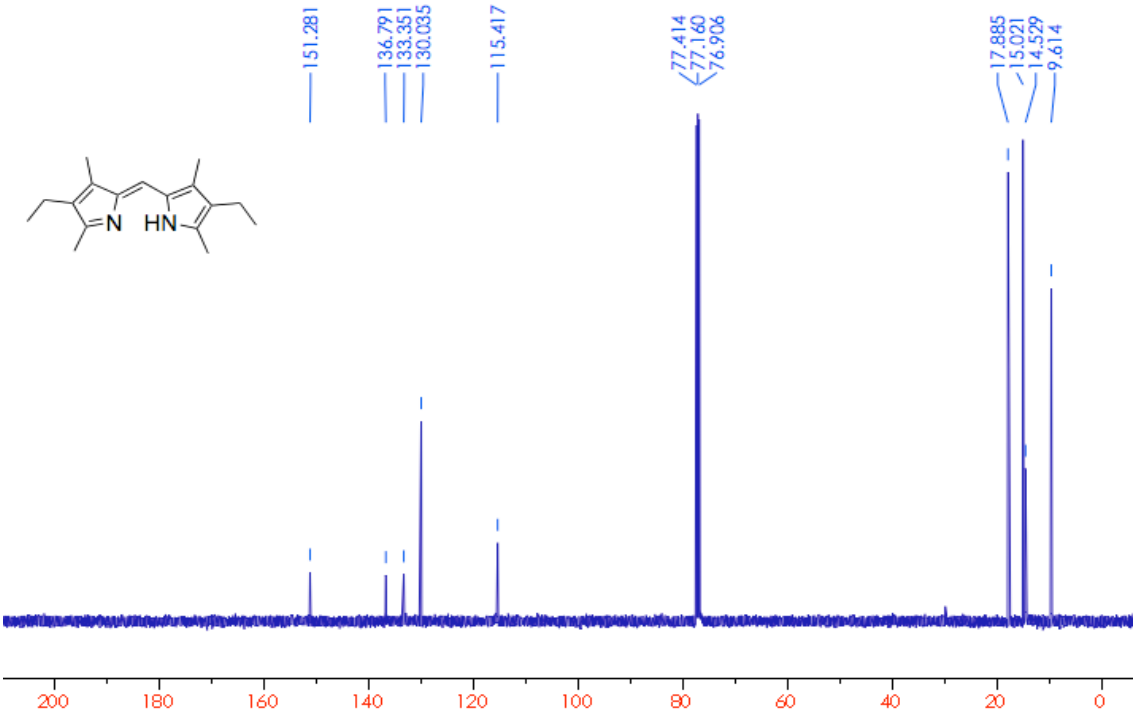


APPENDIX B.60 1,3,5,7-Tetramethyl-2,6-diethyl-8-H-4-bora-3a,4a-diaza-*s*-indacene (**109**)

^{1}H NMR Spectrum in $CDCl_3$

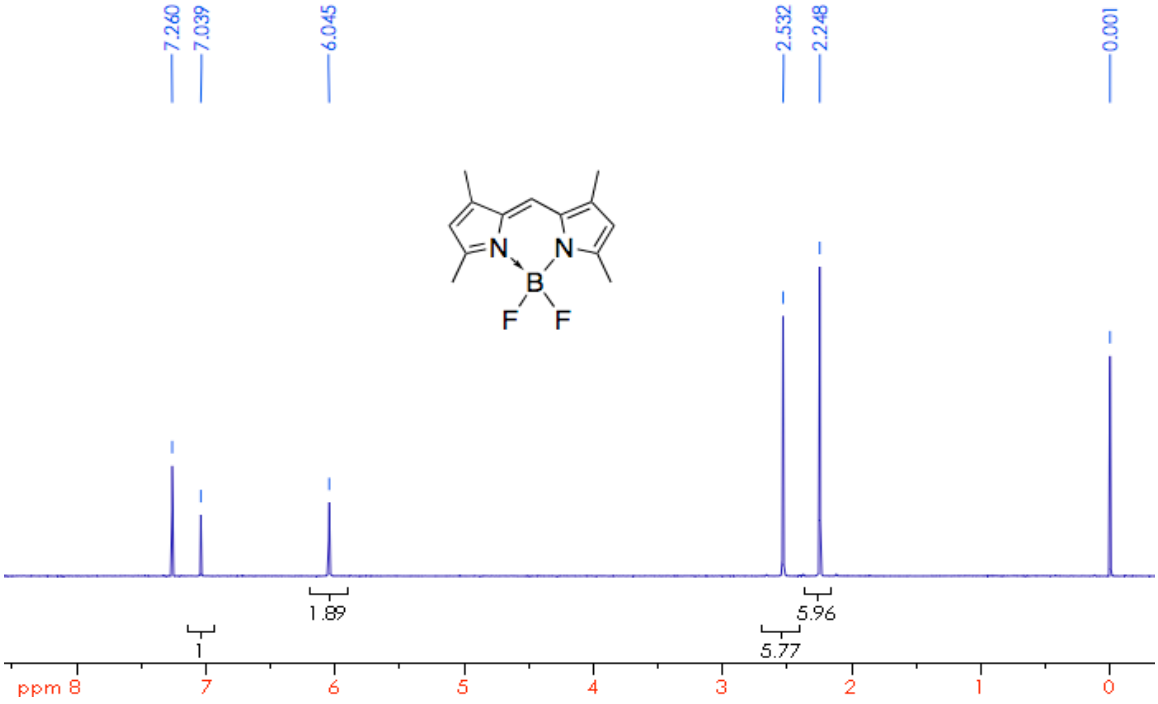


^{13}C NMR Spectrum in $CDCl_3$

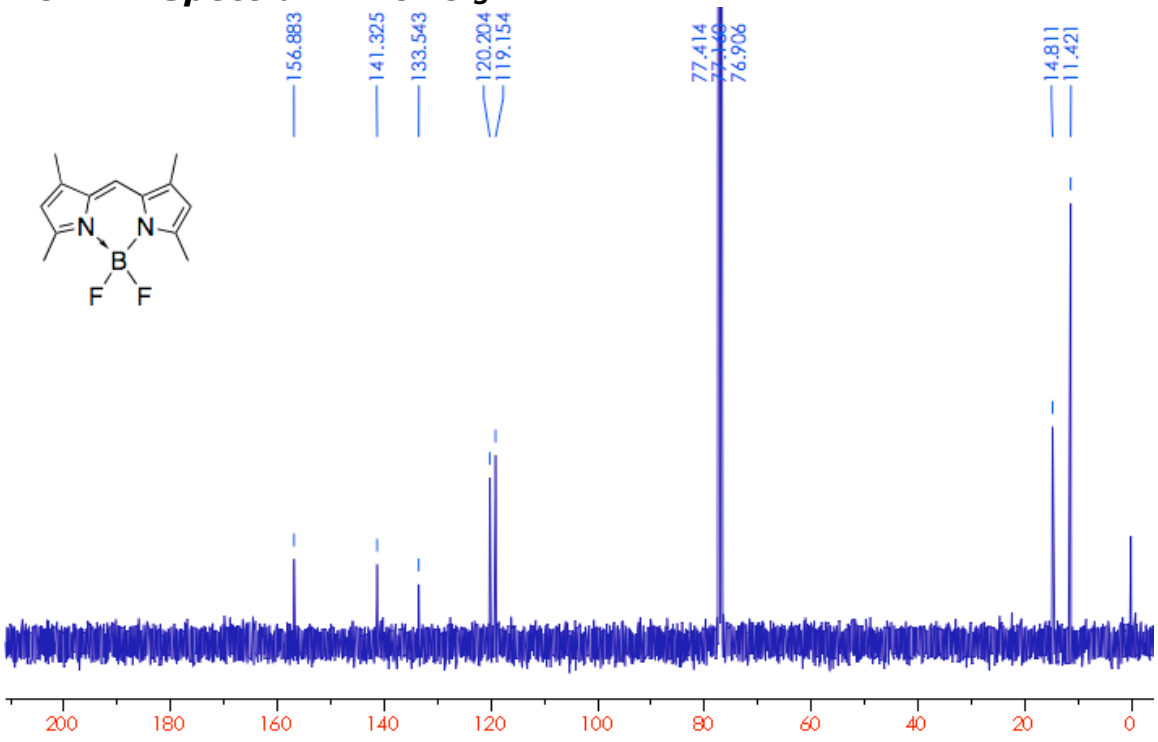


APPENDIX B.61 1,3,5,7-Tetramethyl-8-*H*-4-bora-3a,4a-diaza-*s*-indacene (**110**)[116]

^{1}H NMR Spectrum in $CDCl_3$

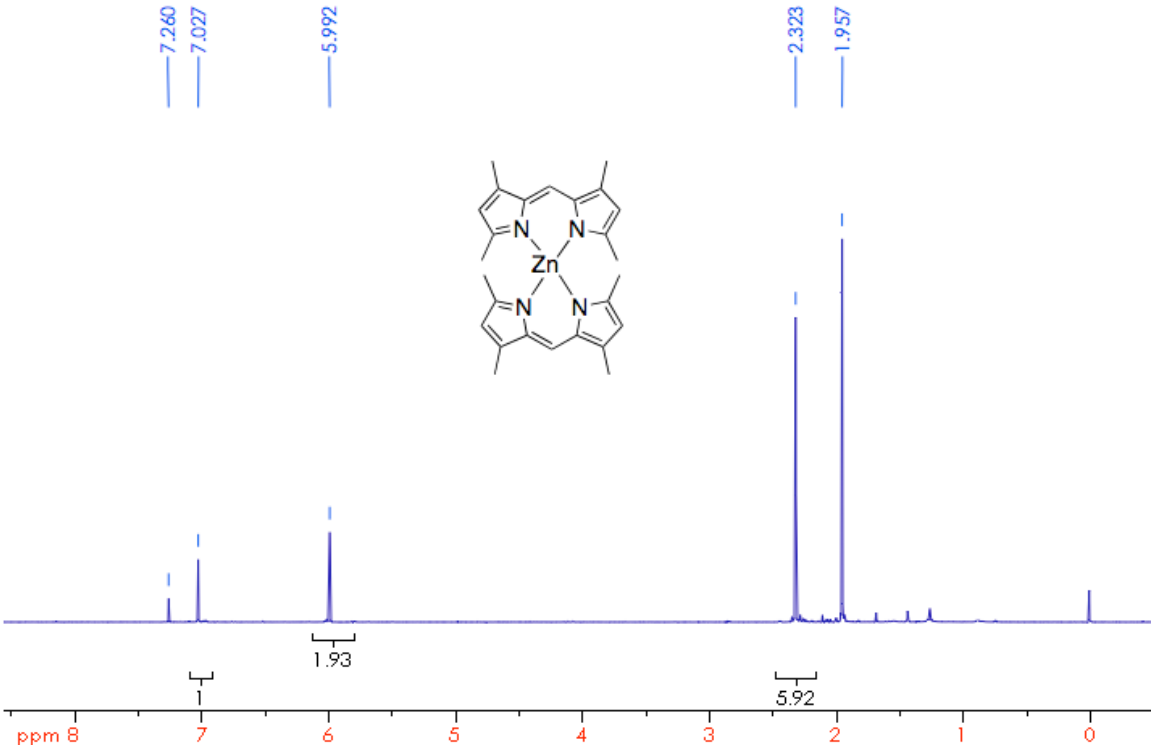


^{13}C NMR Spectrum in $CDCl_3$

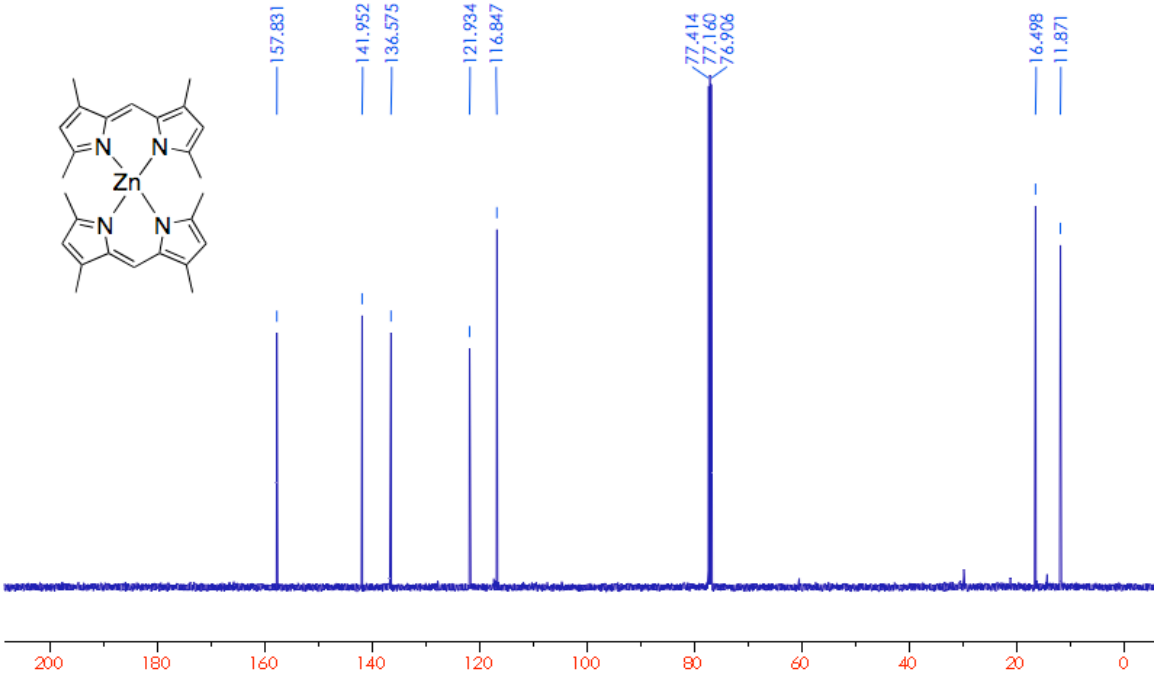


APPENDIX B.62 Zinc[k^2-(3,3′, 5,5′-tetramethyl-meso-*H*-dipyrrinato)] **(111Zn)**

^{1}H NMR Spectrum in $CDCl_3$

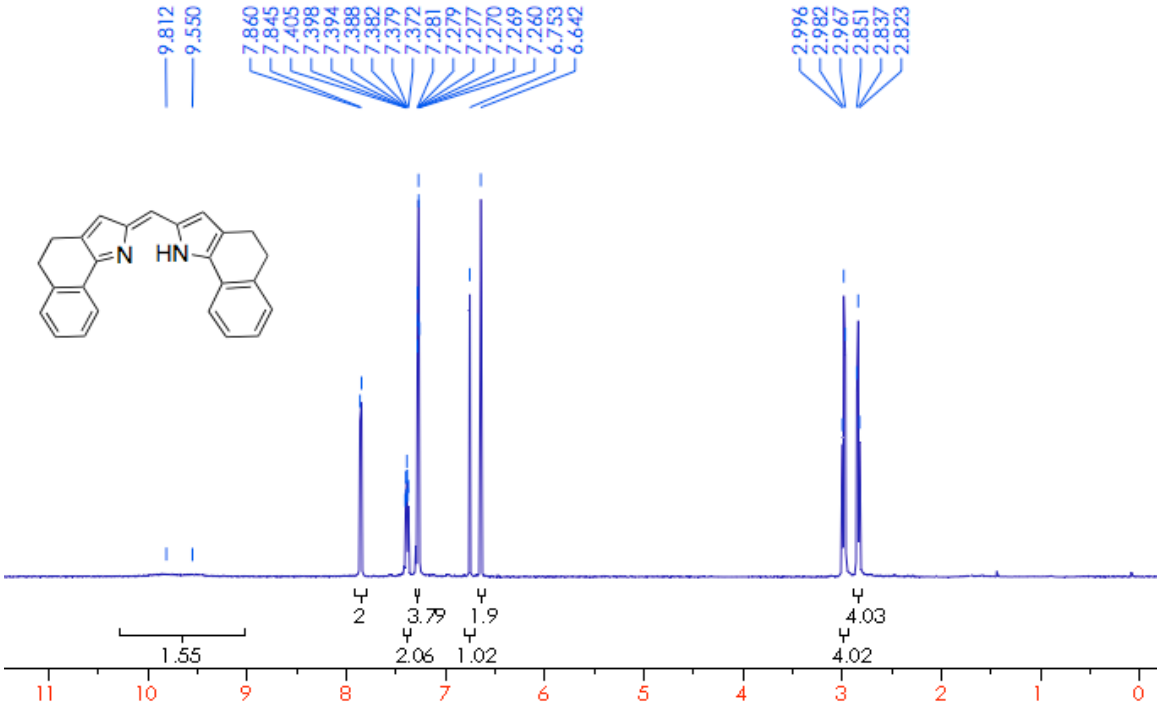


^{13}C NMR Spectrum in $CDCl_3$

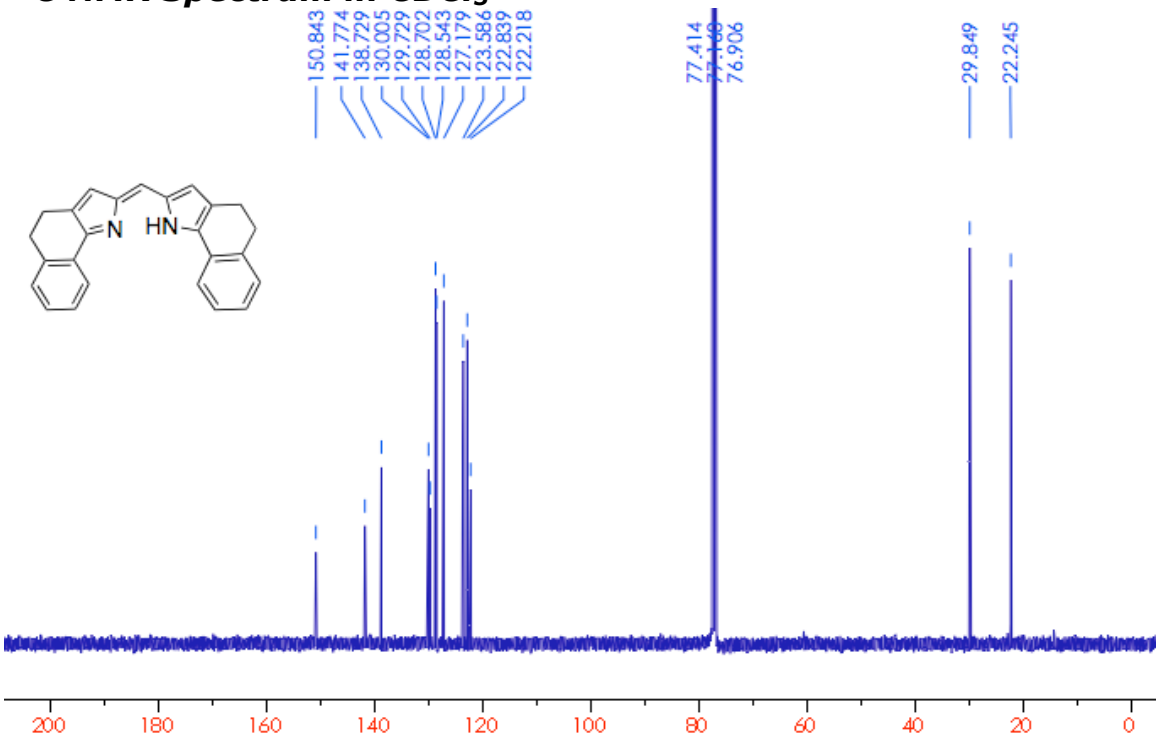


APPENDIX B.63 **(***Z*)-2-((4,5-dihydro-1*H*-benzo[*g*]indol-2-yl)methylene)-4,5-dihydro-2*H*-benzo[*g*] indole **(113)**

^{1}H NMR Spectrum in $CDCl_3$

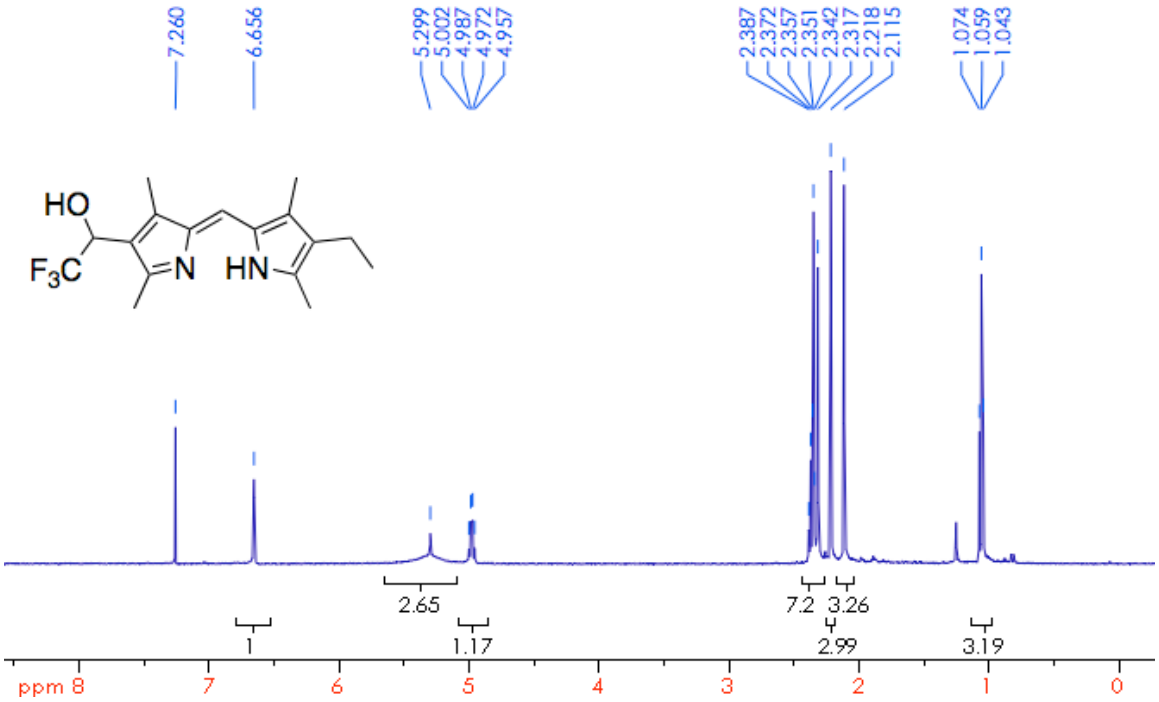


^{13}C NMR Spectrum in $CDCl_3$

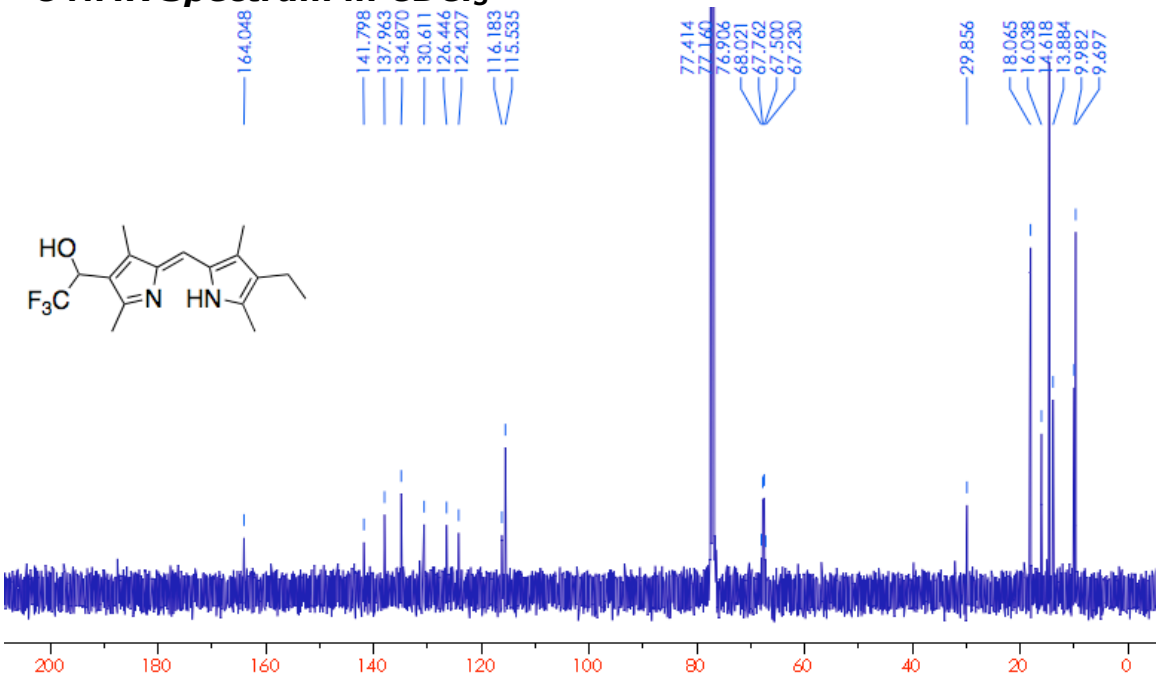


APPENDIX B.64 (*Z*)-1-(2-((4-Ethyl-3,5-dimethyl-1*H*-pyrrol-2-yl)methylene)-3,5-dimethyl-2*H*-pyrrol-4-yl)-2,2,2-trifluoroethanol (**115**)

^{1}H NMR Spectrum in $CDCl_3$

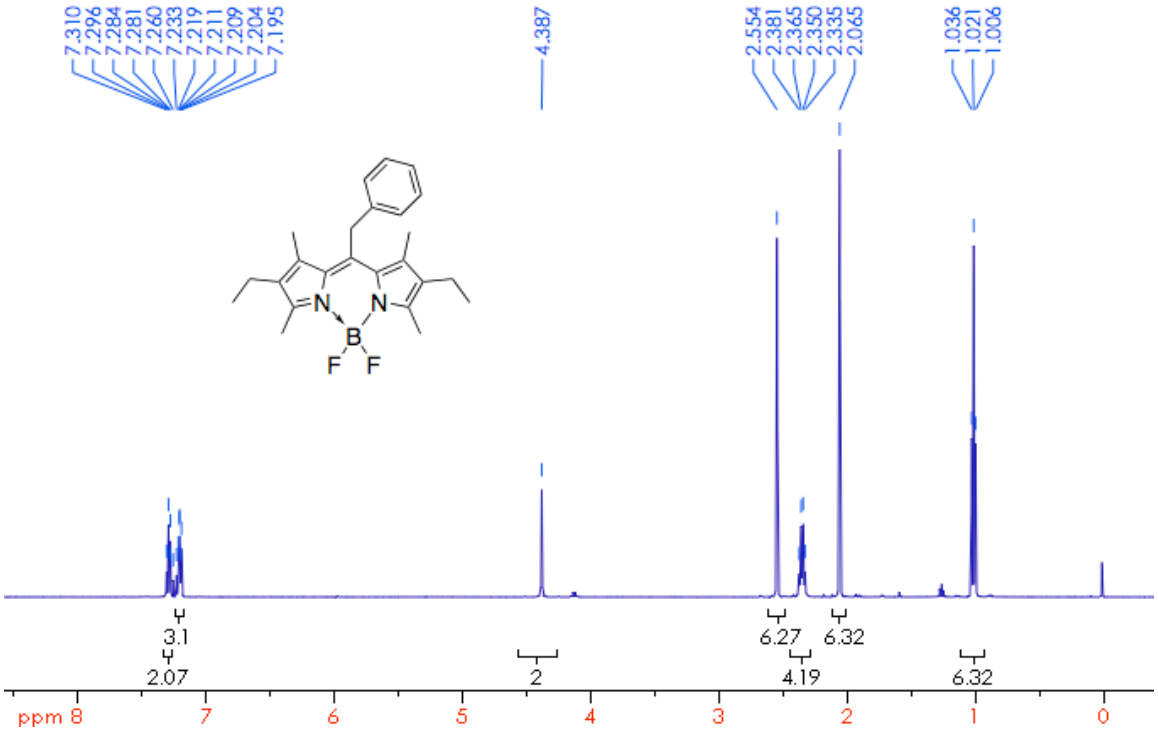


^{13}C NMR Spectrum in $CDCl_3$

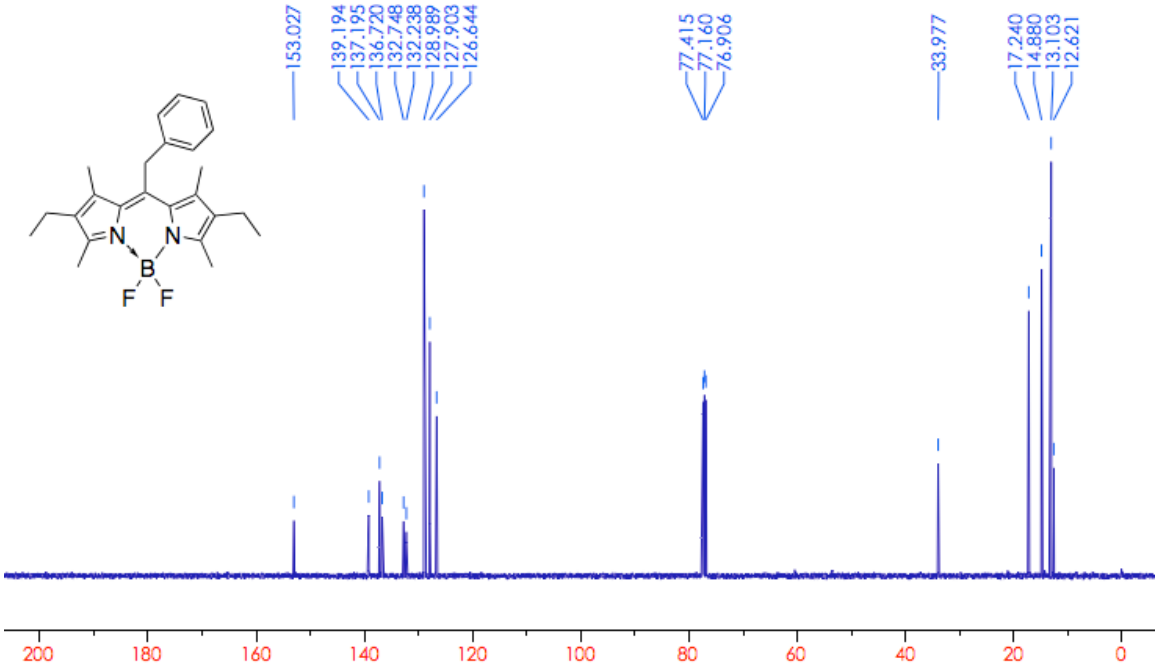


APPENDIX B.65 1,3,5,7-Tetramethyl-2,6-diethyl-8-benzyl-4-bora-3a,4a-diaza-*s*-indacene (**116**)

^{1}H NMR Spectrum in $CDCl_3$

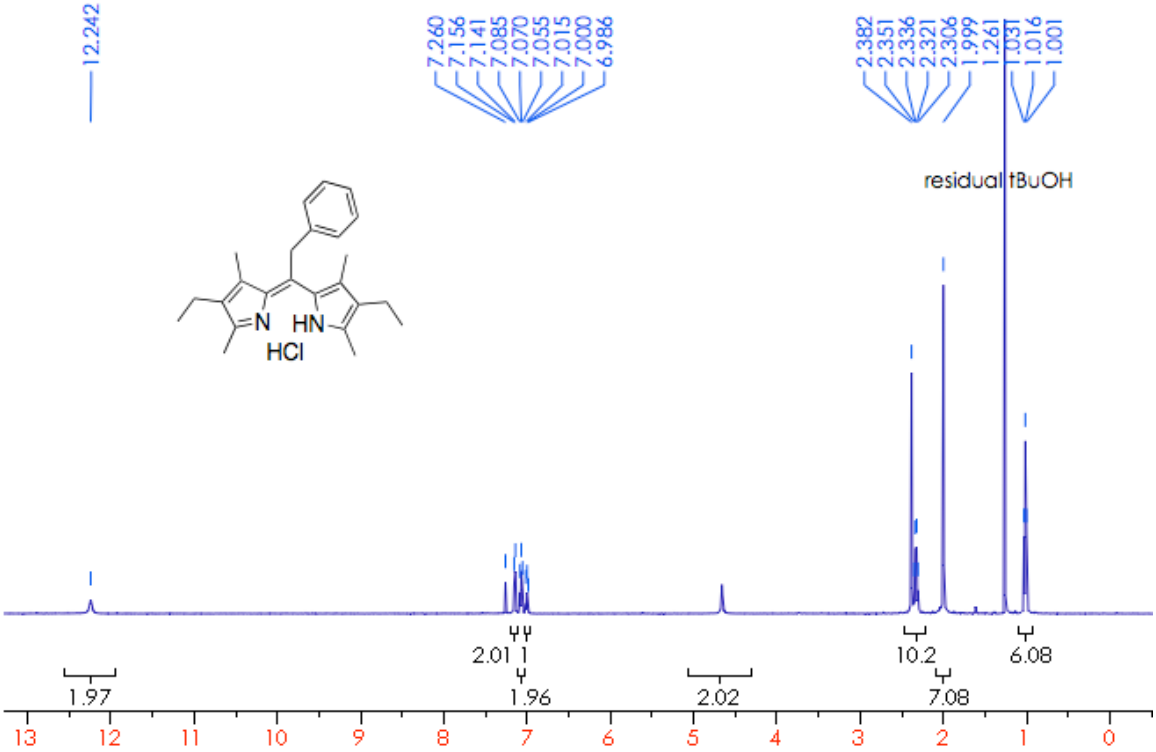


^{13}C NMR Spectrum in $CDCl_3$

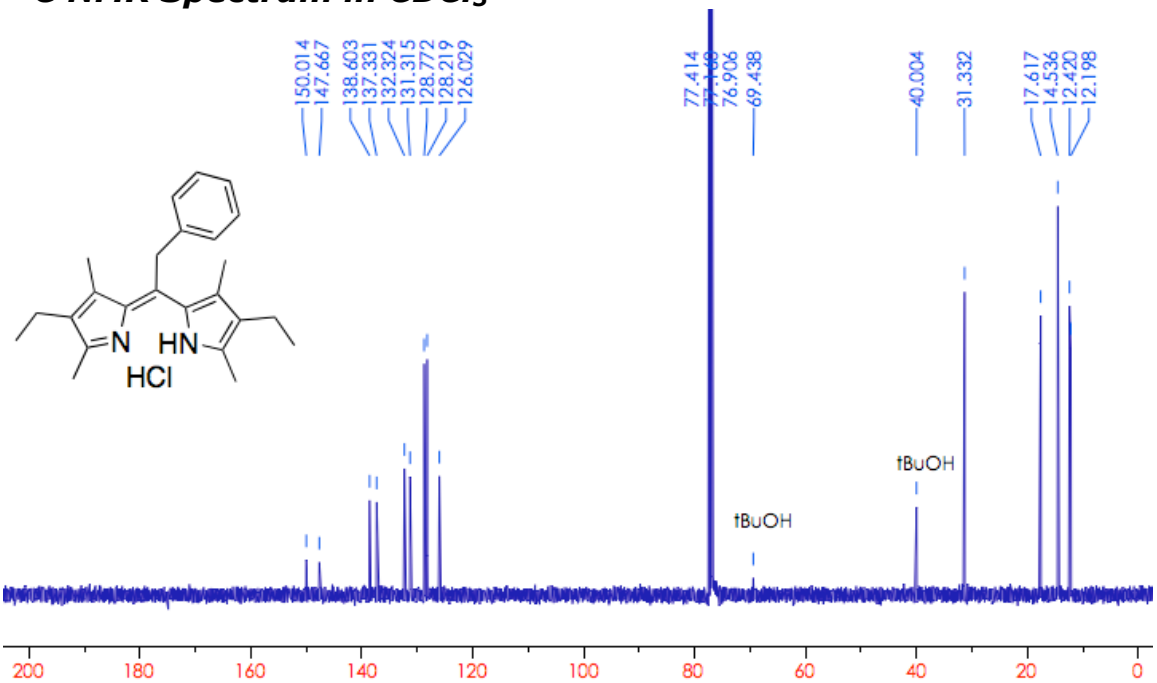


APPENDIX B.66 (*Z*)-3-Ethyl-5-(1-(4-ethyl-3,5-dimethyl-2*H*-pyrrol-2-ylidene)-2-phenylethyl)-2,4-dimethyl-1*H*-pyrrole hydrochloride (**117**)

^{1}H NMR Spectrum in $CDCl_3$

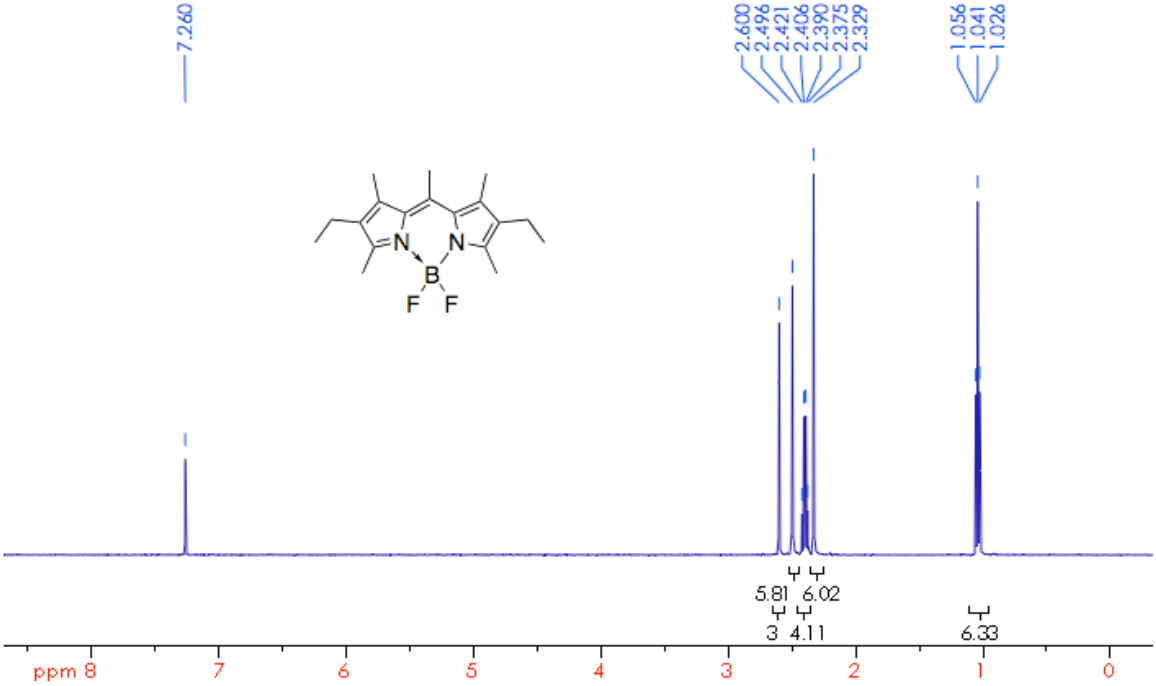


^{13}C NMR Spectrum in $CDCl_3$

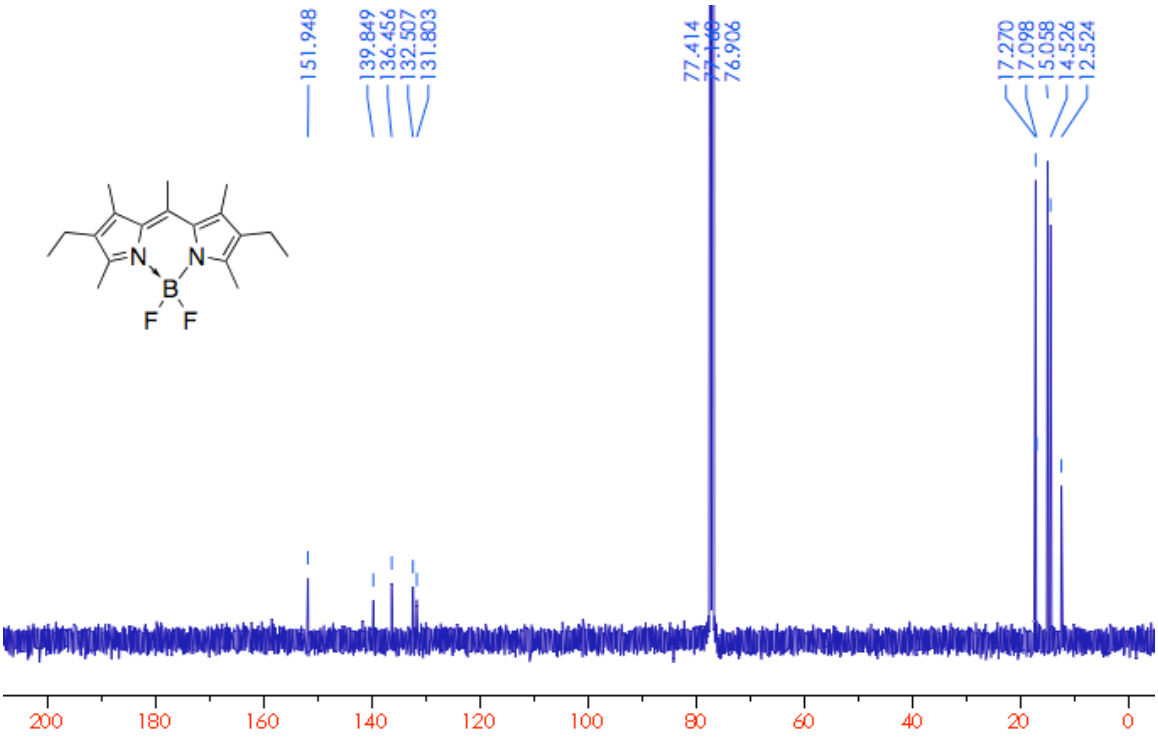


APPENDIX B.67 1,3,5,7-Tetramethyl-2,6-diethyl-8-methyl-4-bora-3a,4a-diaza-*s*-indacene (**118**)

^{1}H NMR Spectrum in $CDCl_3$

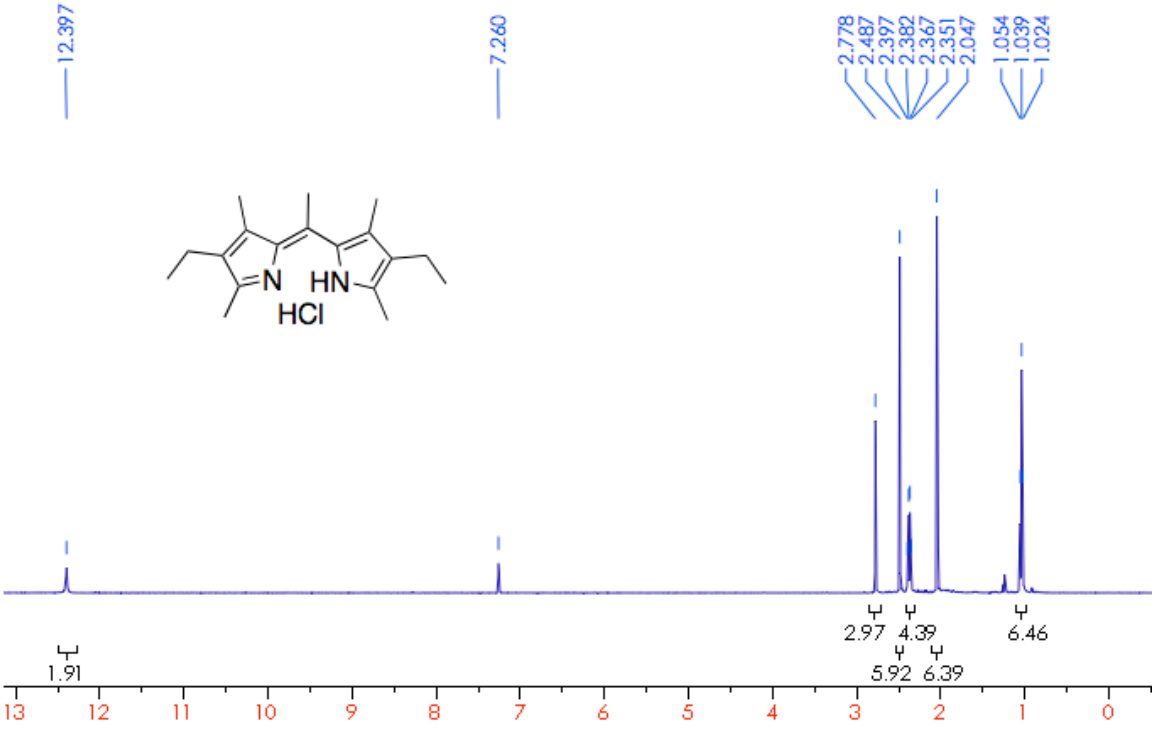


^{13}C NMR Spectrum in $CDCl_3$

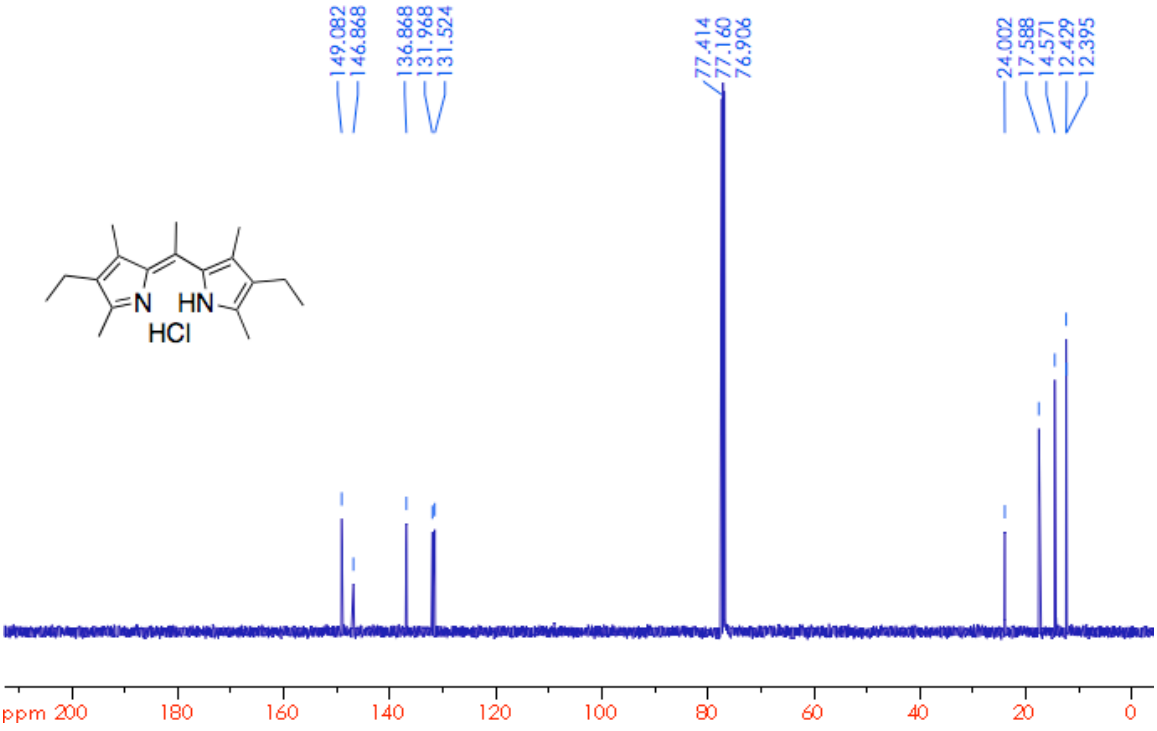


APPENDIX B.68 (*Z*)-3-Ethyl-5-(1-(4-ethyl-3,5-dimethyl-2*H*-pyrrol-2-ylidene)-2-methyl)-2,4-dimethyl-1*H*-pyrrole hydrochloride (**119**)

^{1}H NMR Spectrum in $CDCl_3$

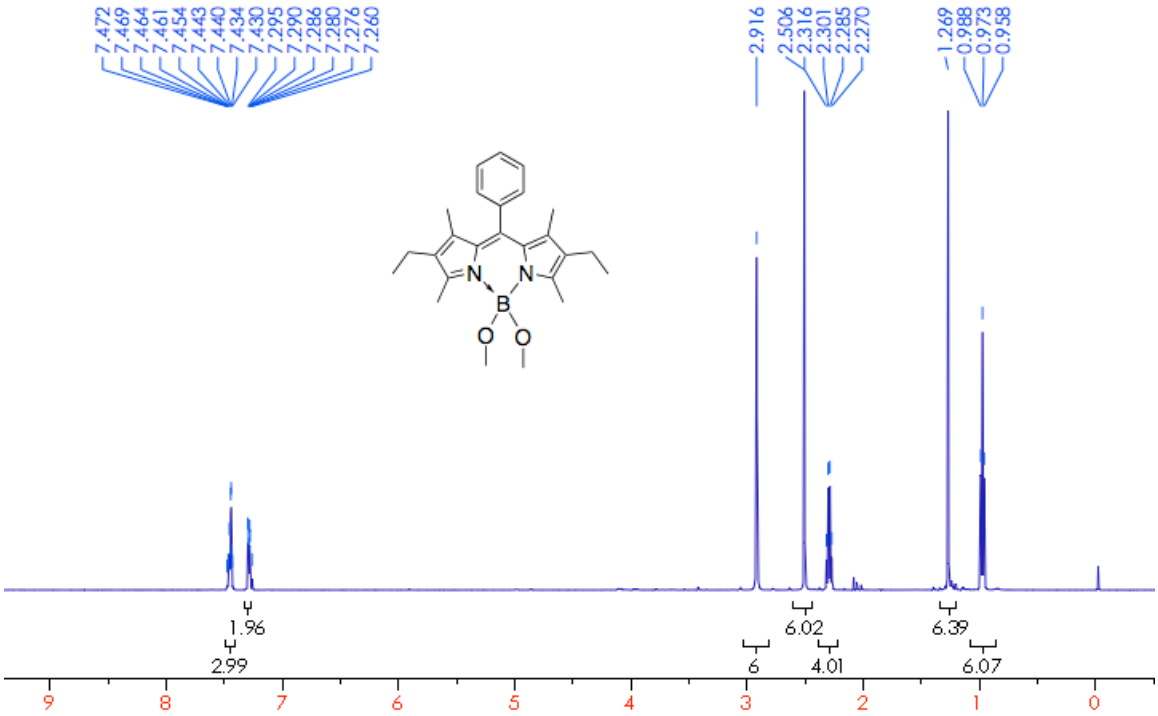


^{13}C NMR Spectrum in $CDCl_3$

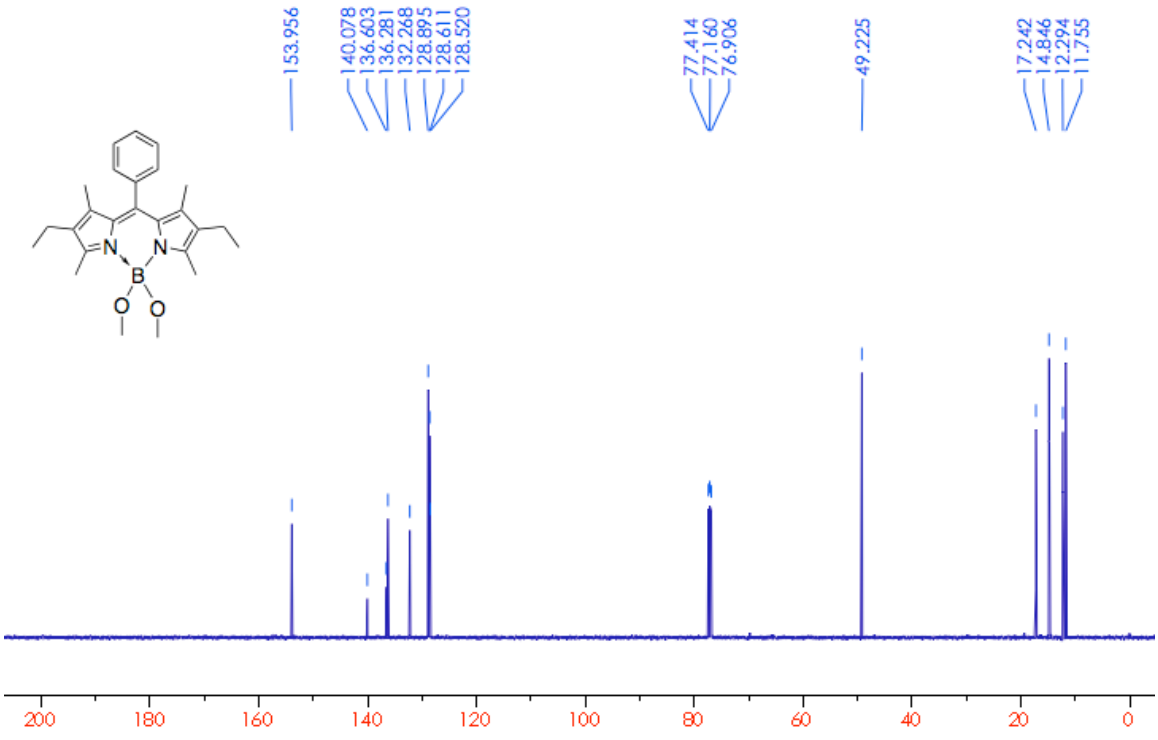


APPENDIX B.69 4,4-Dimethoxy-1,3,5,7-tetramethyl-2,6-diethyl-8-phenyl-4-bora-3a,4a-diaza-*s*-indacene (**121**)

^{1}H NMR Spectrum in $CDCl_3$

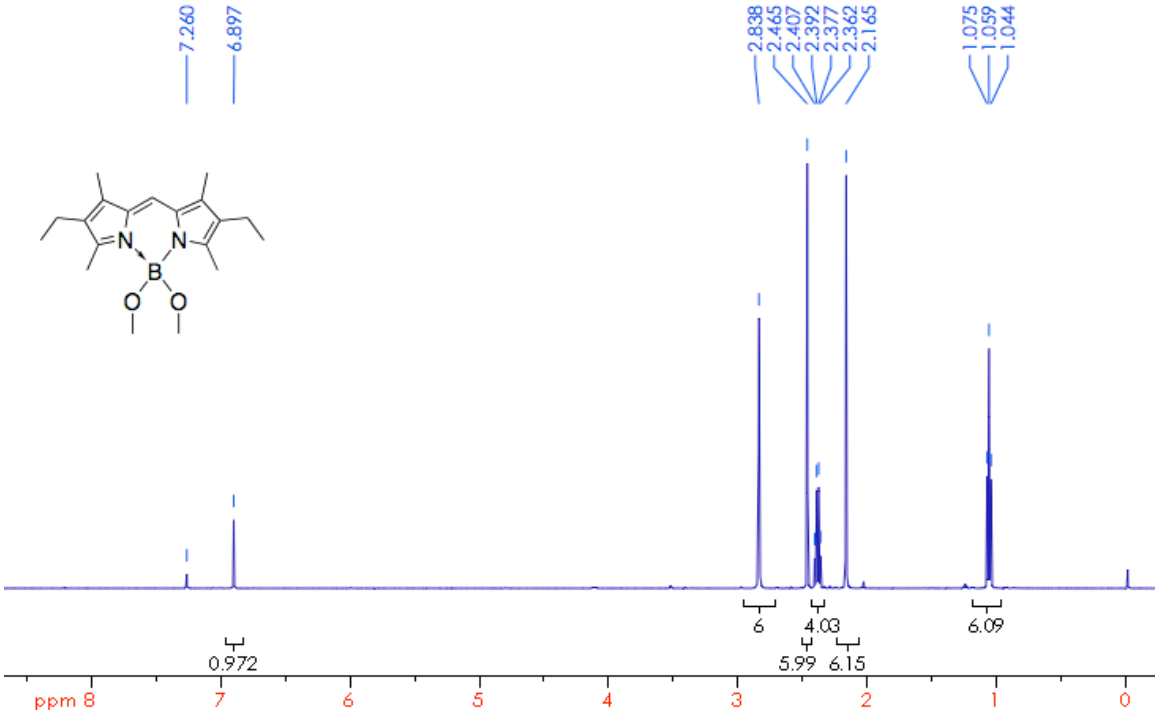


^{13}C NMR Spectrum in $CDCl_3$

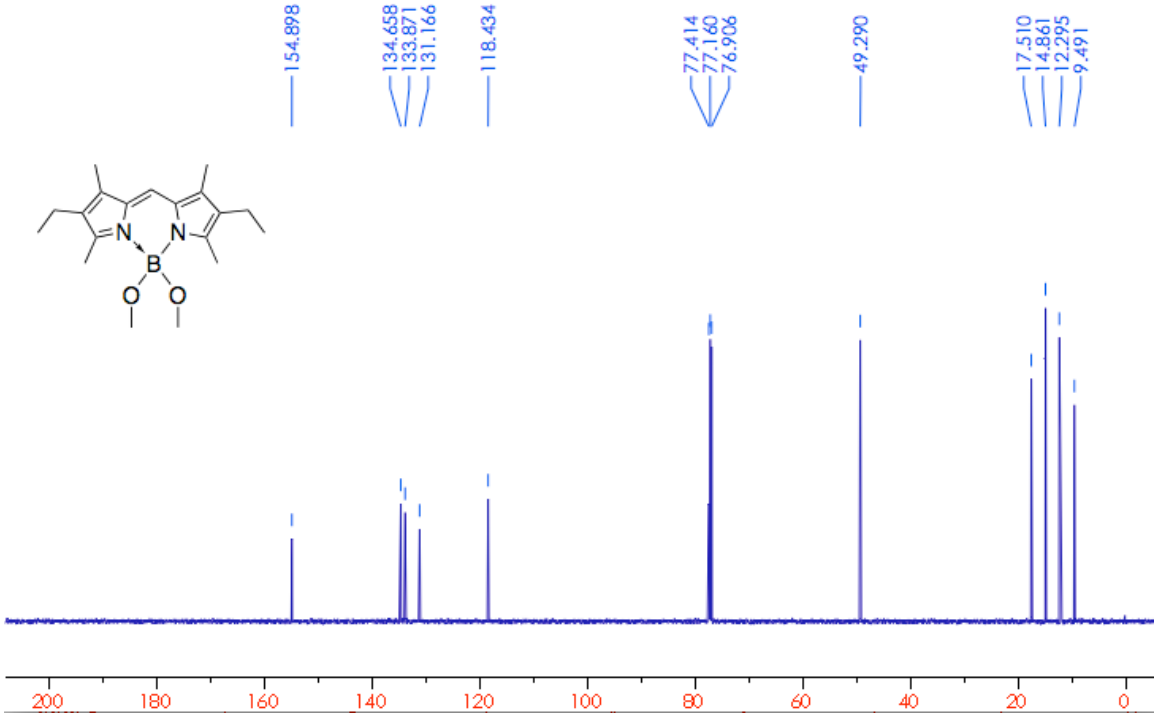


APPENDIX B.70 4,4-Dimethoxy-1,3,5,7-tetramethyl-2,6-diethyl-8-*H*-4-bora-3a,4a-diaza-*s*-indacene (**122**)

^{1}H NMR Spectrum in $CDCl_3$

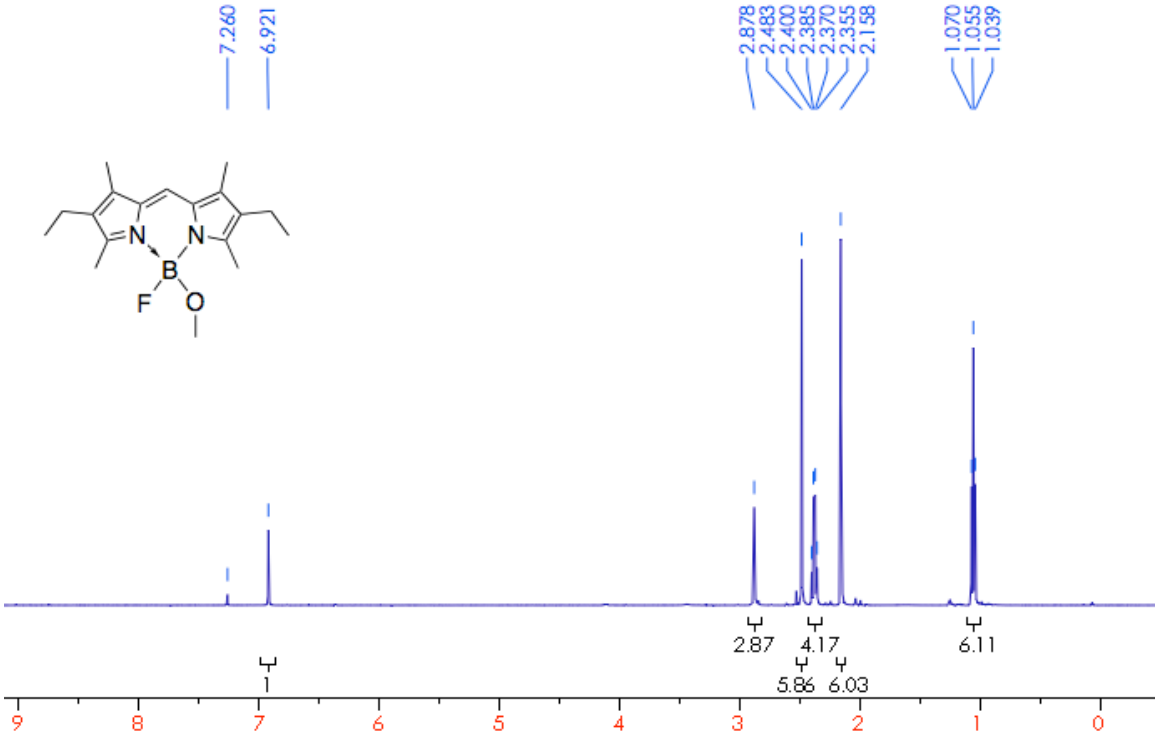


^{13}C NMR Spectrum in $CDCl_3$

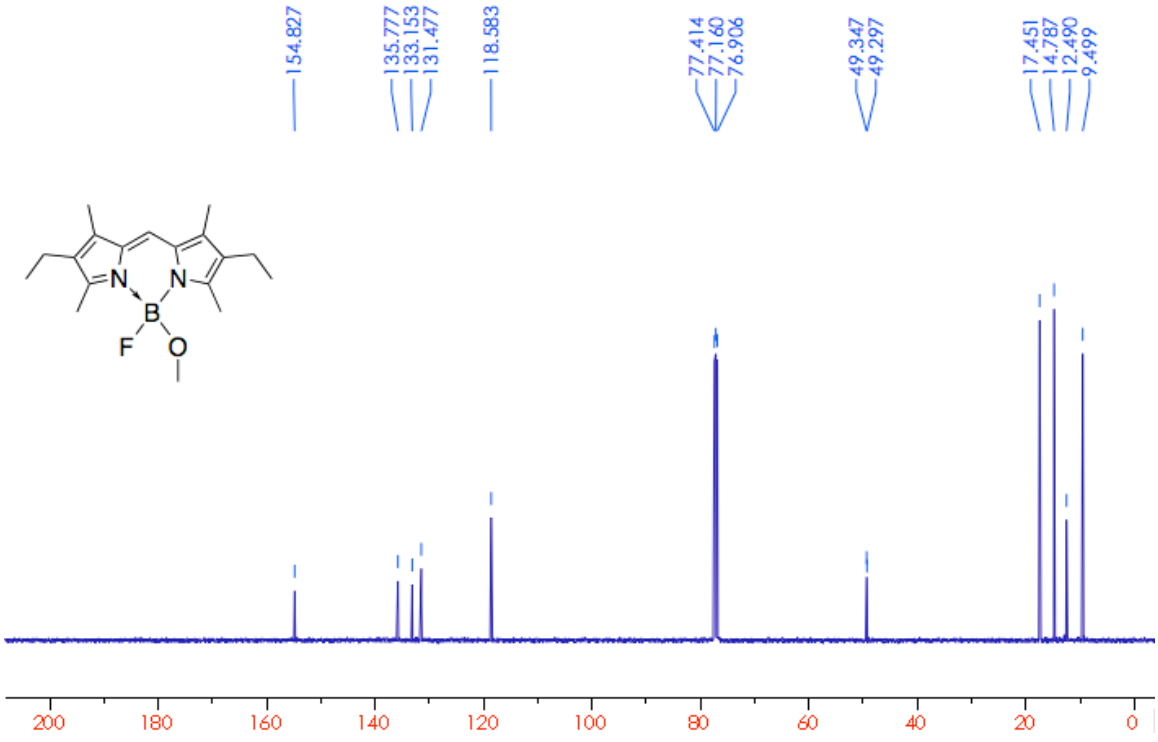


APPENDIX B.71 4-Fluoro-4-methoxy-1,3,5,7-tetramethyl-2,6-diethyl-8-*H*-4-bora-3a,4a-diaza-*s*-indacene (**123**)

^{1}H NMR Spectrum in $CDCl_3$

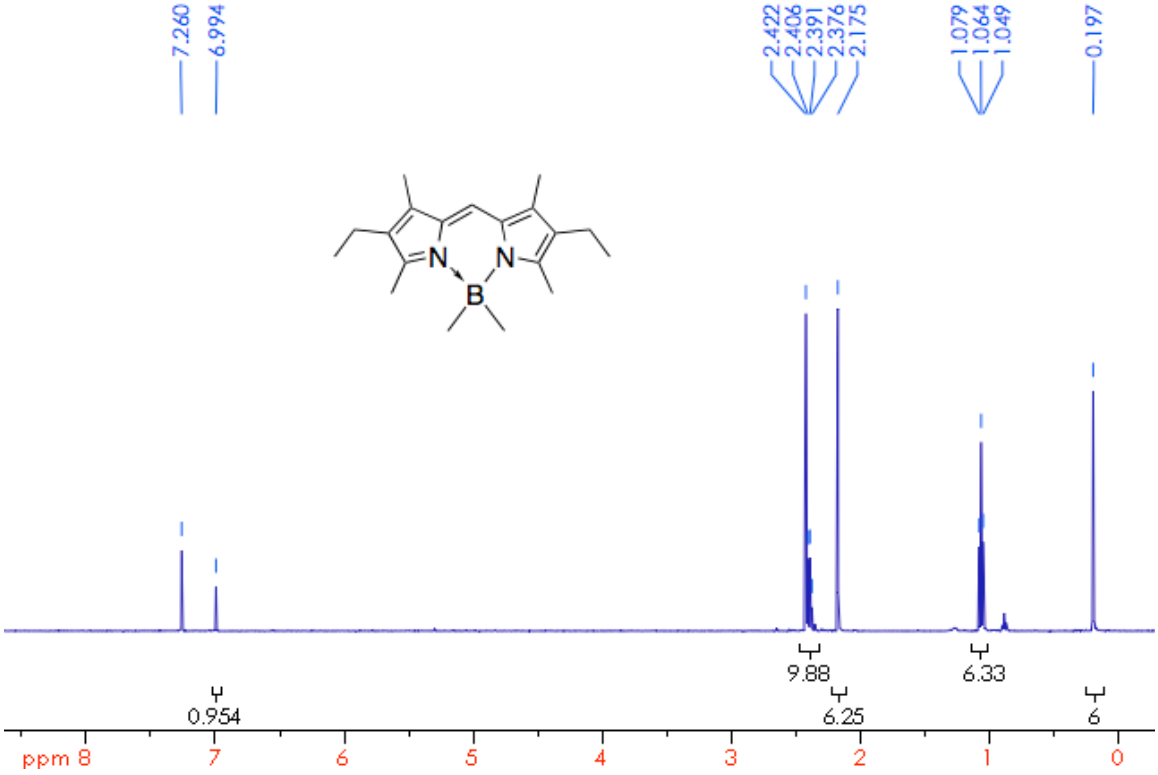


^{13}C NMR Spectrum in $CDCl_3$

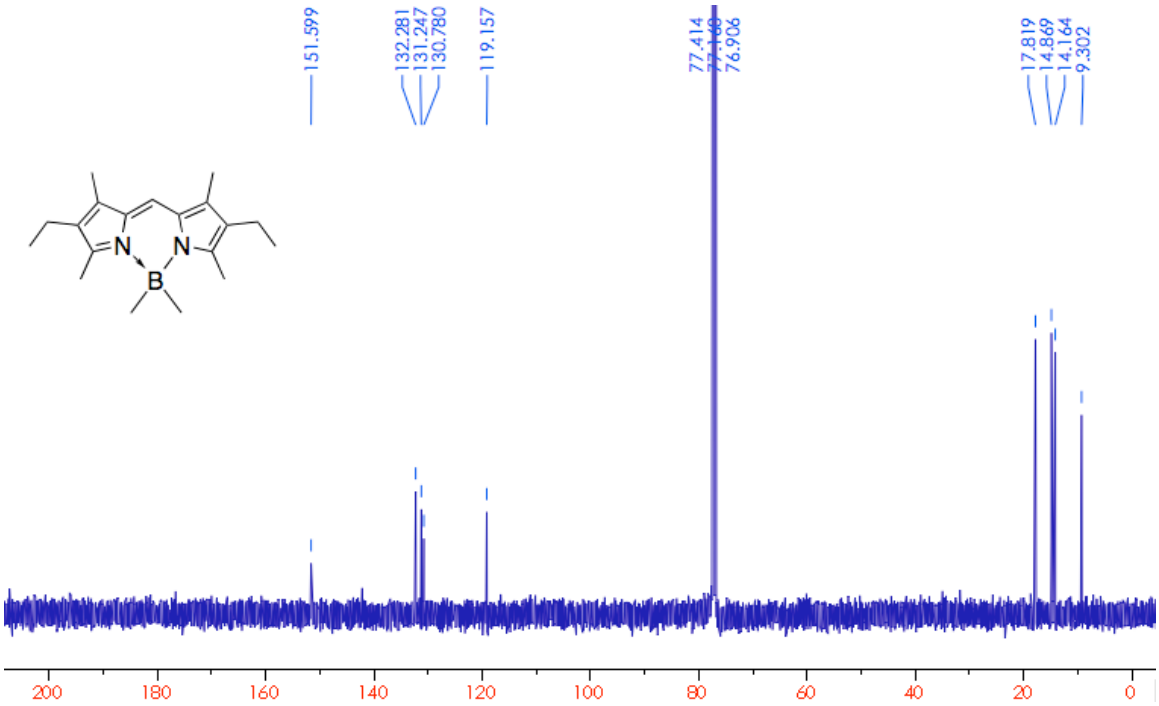


APPENDIX B.72 4,4′-Dimethyl-1,3,5,7-tetramethyl-2,6-diethyl-8-*H*-4-bora-3a,4a-diaza-*s*-indacene (**124**)

^{1}H NMR Spectrum in $CDCl_3$

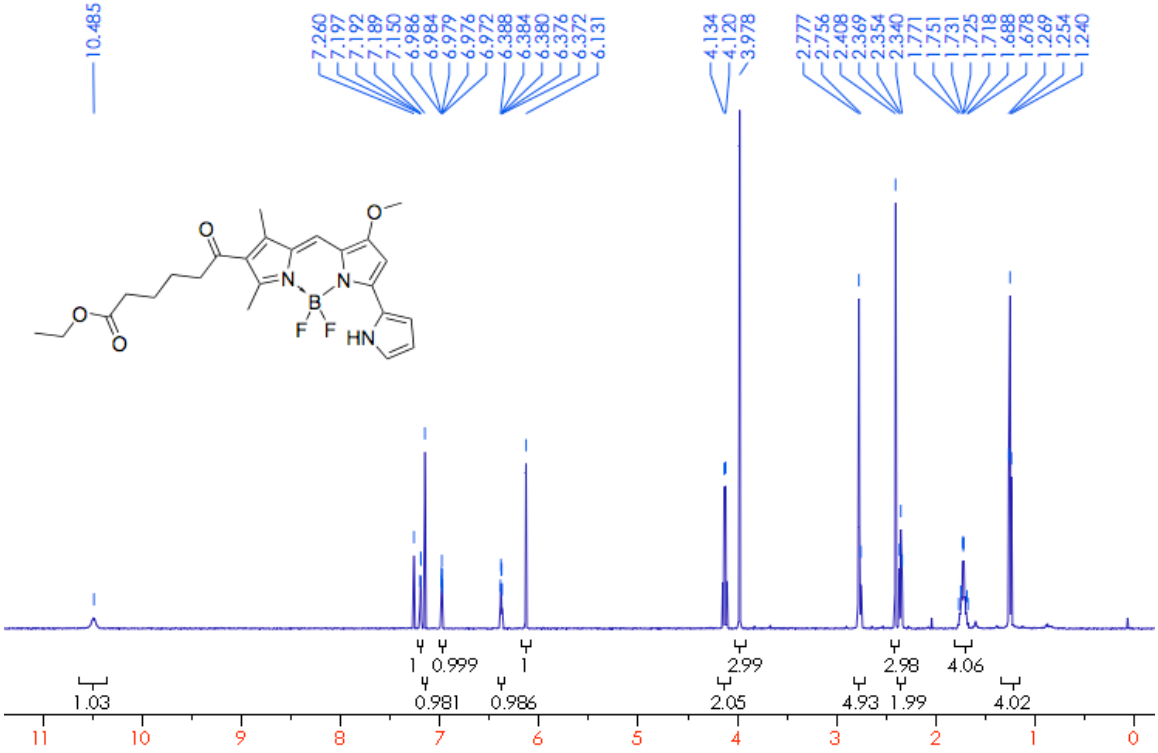


^{13}C NMR Spectrum in $CDCl_3$

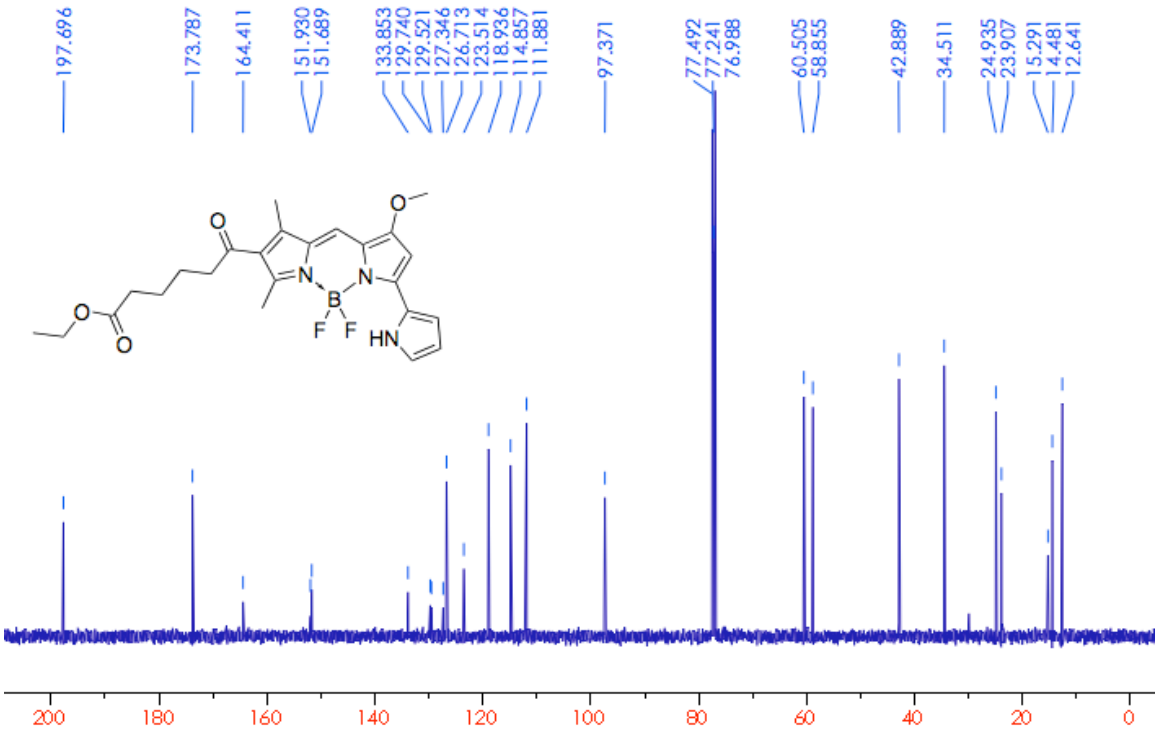


APPENDIX B.73 (**125**)BF_2 (**126**)

^{1}H NMR Spectrum in $CDCl_3$

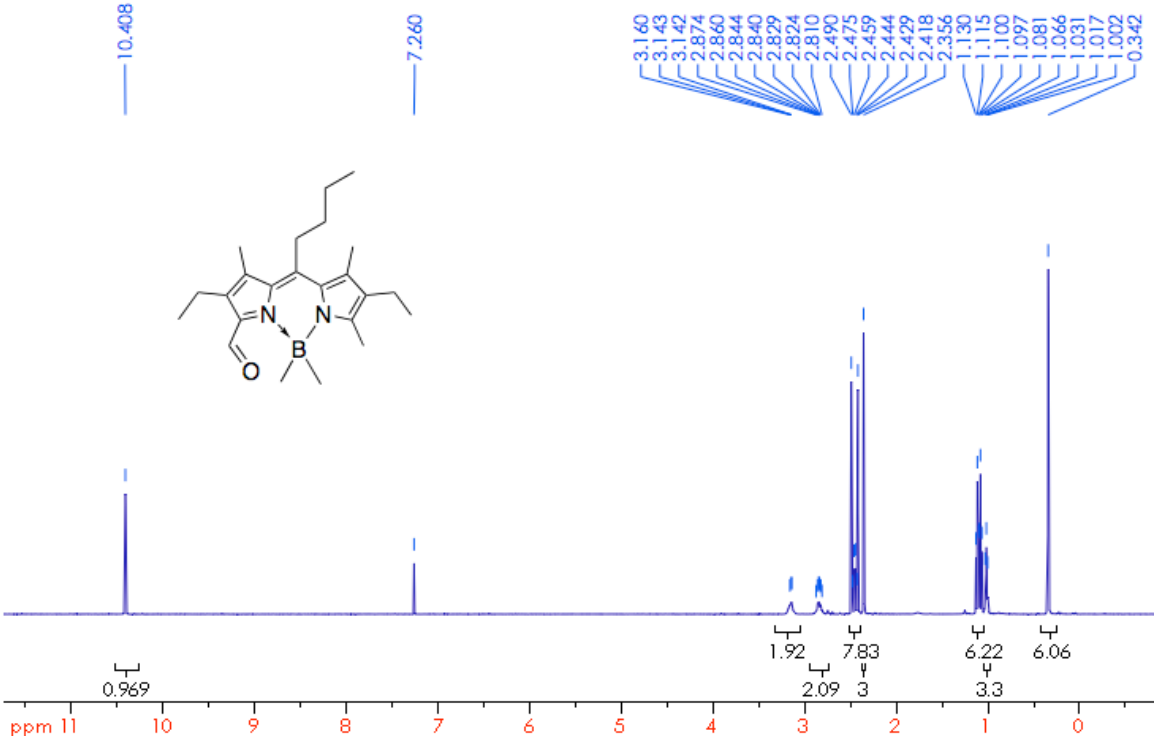


^{13}C NMR Spectrum in $CDCl_3$

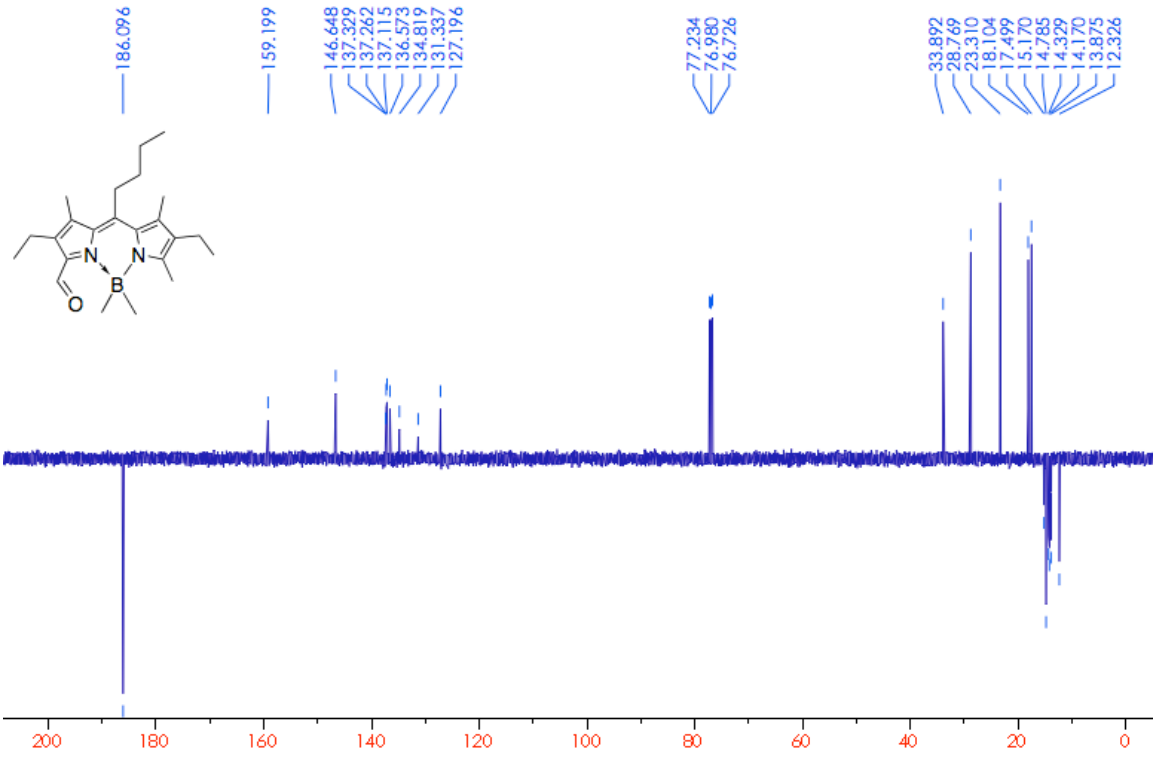


APPENDIX B.74 1,3,5,7-tetramethyl-2,6-diethyl-8-*H*-4-bora-3a,4a-diaza-*s*-indacene (**129**)

^{1}H NMR Spectrum in $CDCl_3$

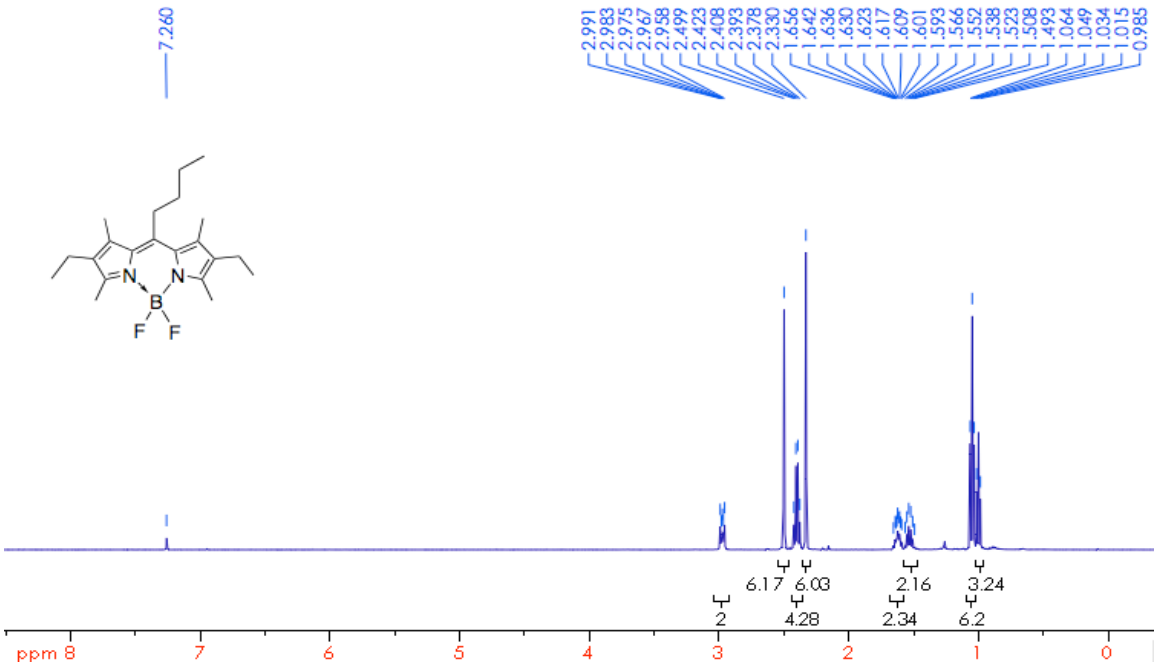


^{13}C NMR Spectrum in $CDCl_3$

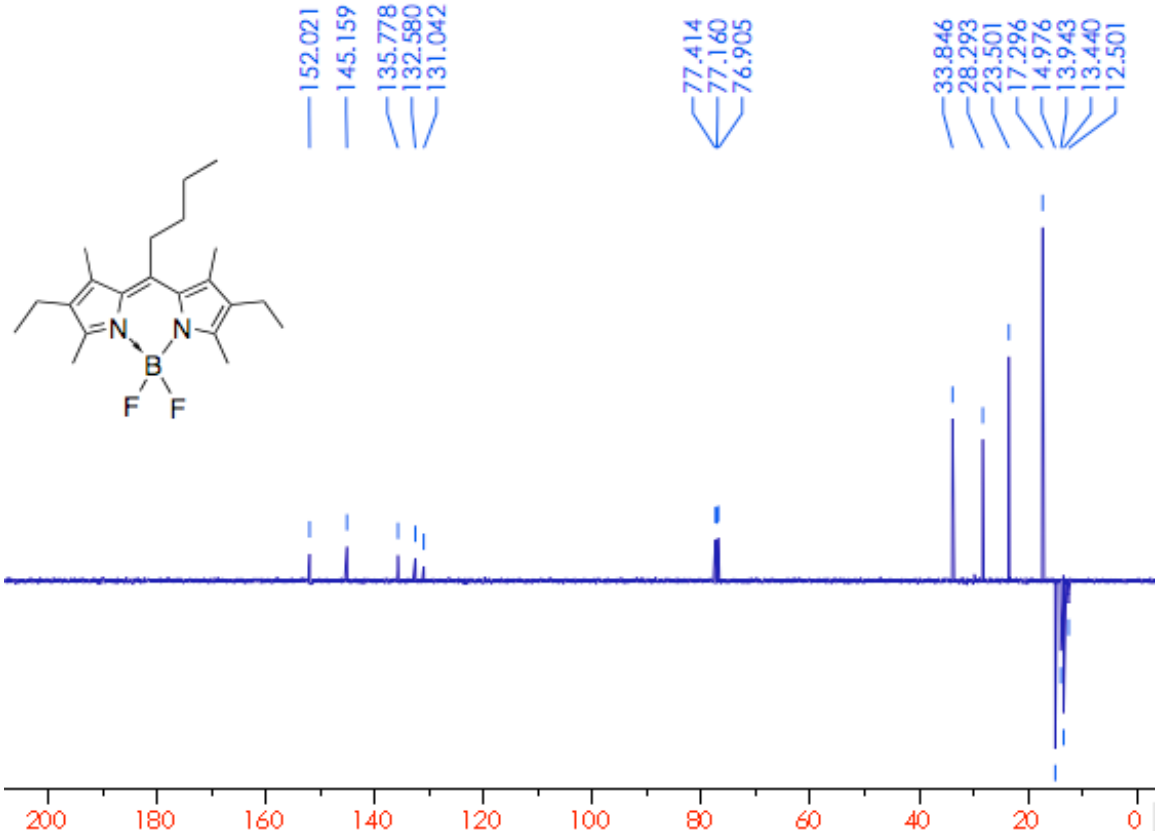


APPENDIX B.75 1,3,5,7-tetramethyl-2,6-diethyl-8-butyl-4-bora-3a,4a-diaza-*s*-indacene (**130**)

^{1}H NMR Spectrum in $CDCl_3$

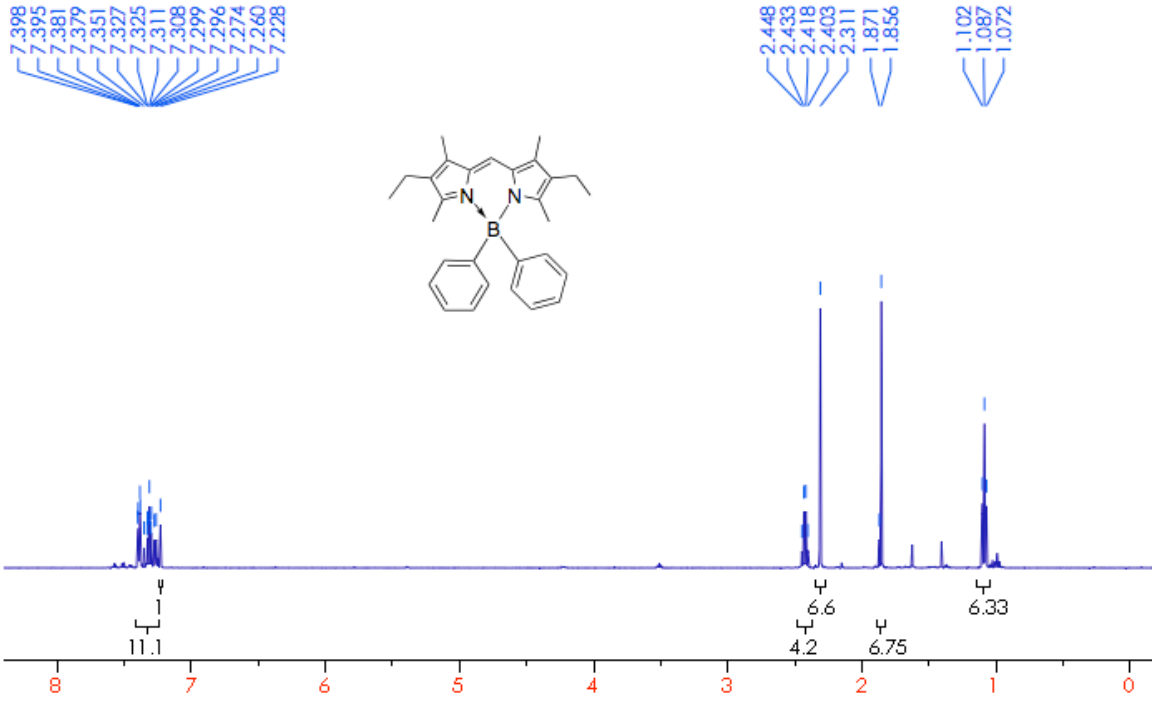


^{13}C NMR Spectrum in $CDCl_3$

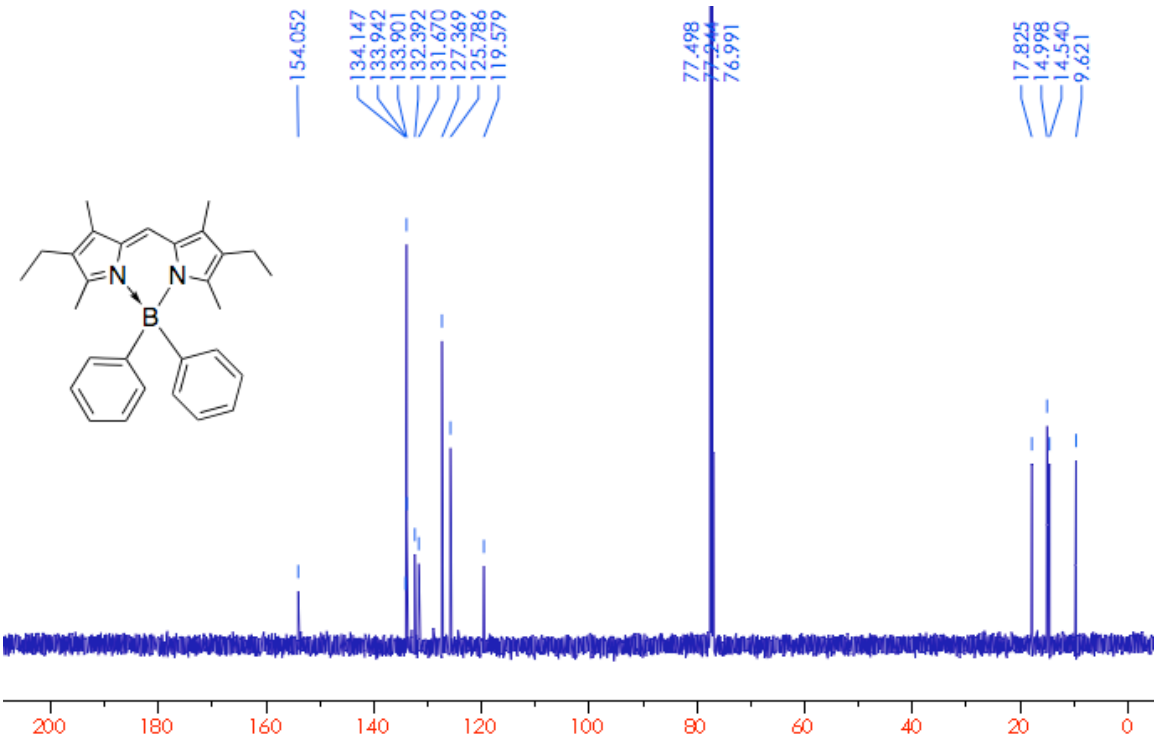


APPENDIX B.76 4,4-Diphenyl-1,3,5,7-tetramethyl-2,6-diethyl-8 *H*-4-bora-3a,4a-diaza-*s*-indacene (**131**)

^{1}H NMR Spectrum in $CDCl_3$

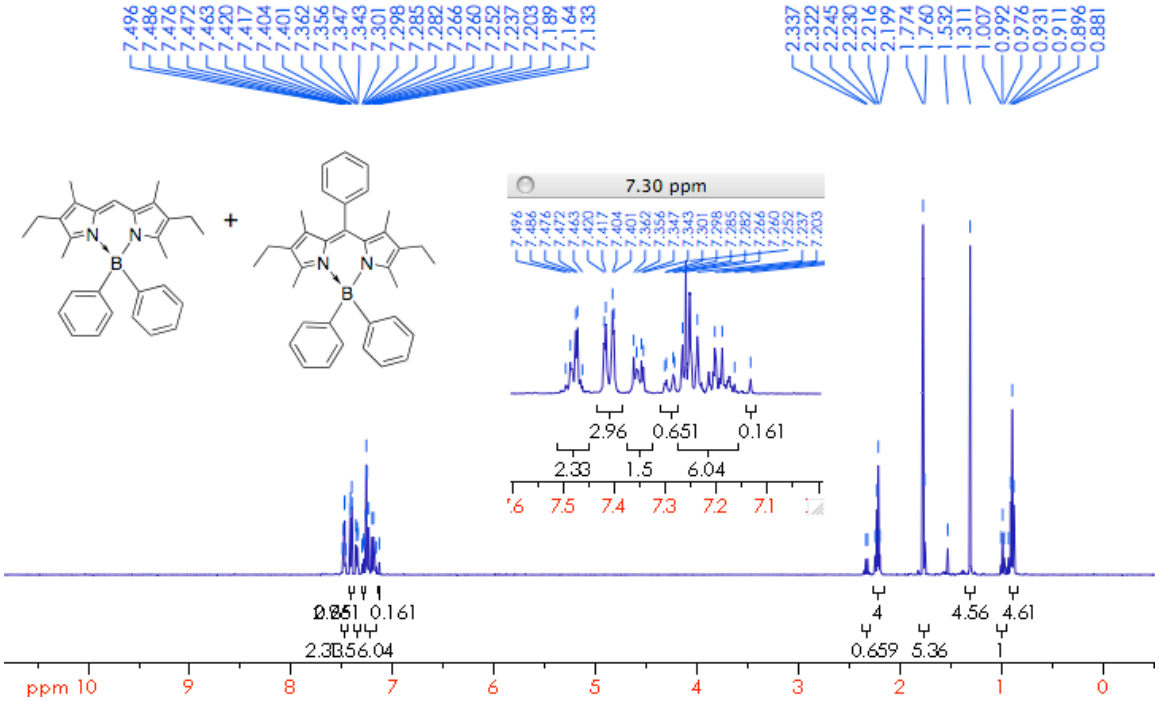


^{13}C NMR Spectrum in $CDCl_3$

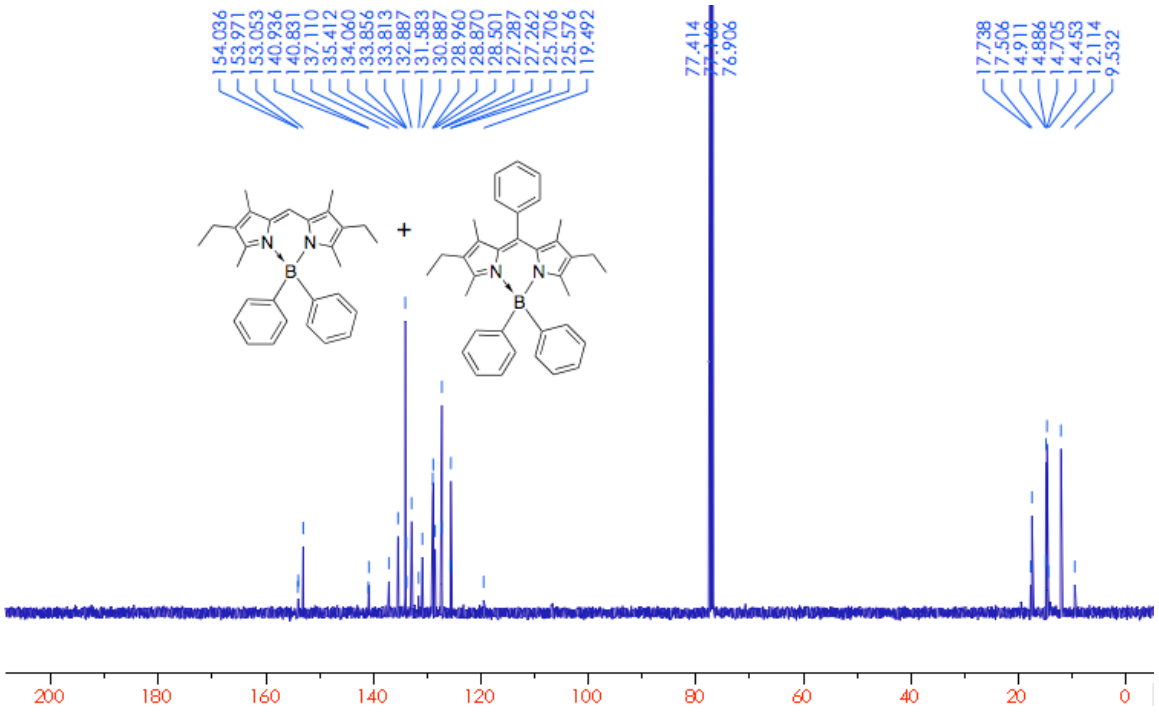


APPENDIX B.77 4,4-Diphenyl-1,3,5,7-tetramethyl-2,6-diethyl-8-*H*-4-bora-3a,4a-diaza-*s*-indacene (**131**) and 4,4-diphenyl-1,3,5,7-tetramethyl-2,6-diethyl-8-phenyl-4-bora-3a,4a-diaza-*s*-indacene (**132**)

^{1}H NMR Spectrum in $CDCl_3$

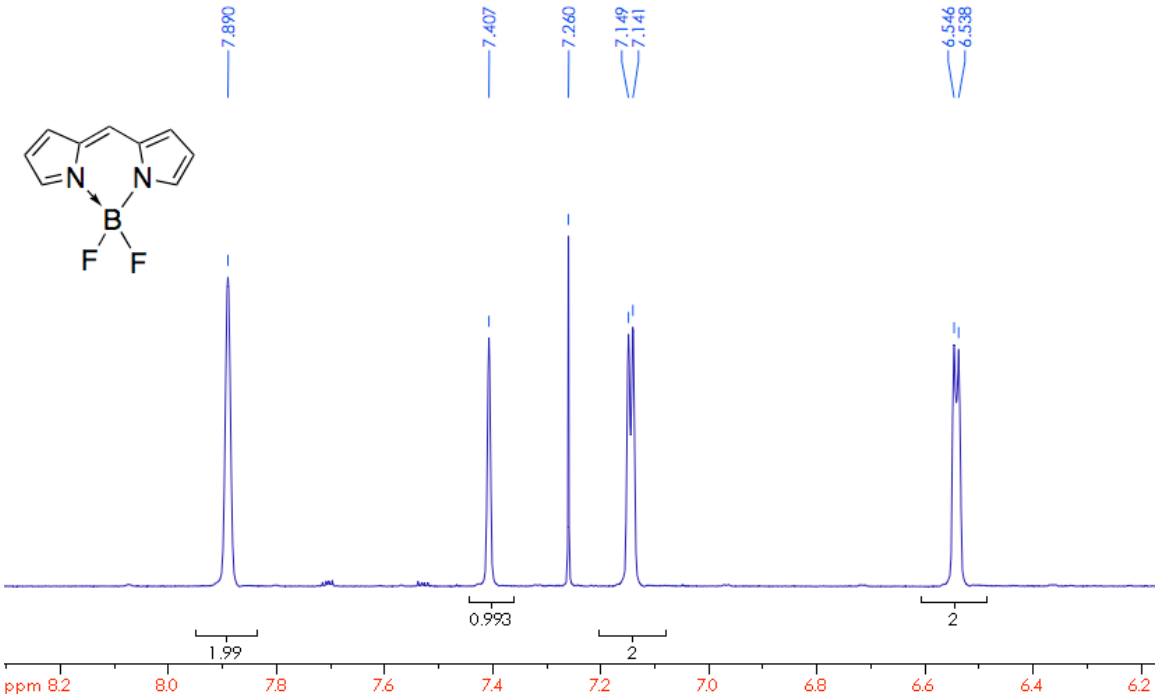


^{13}C NMR Spectrum in $CDCl_3$

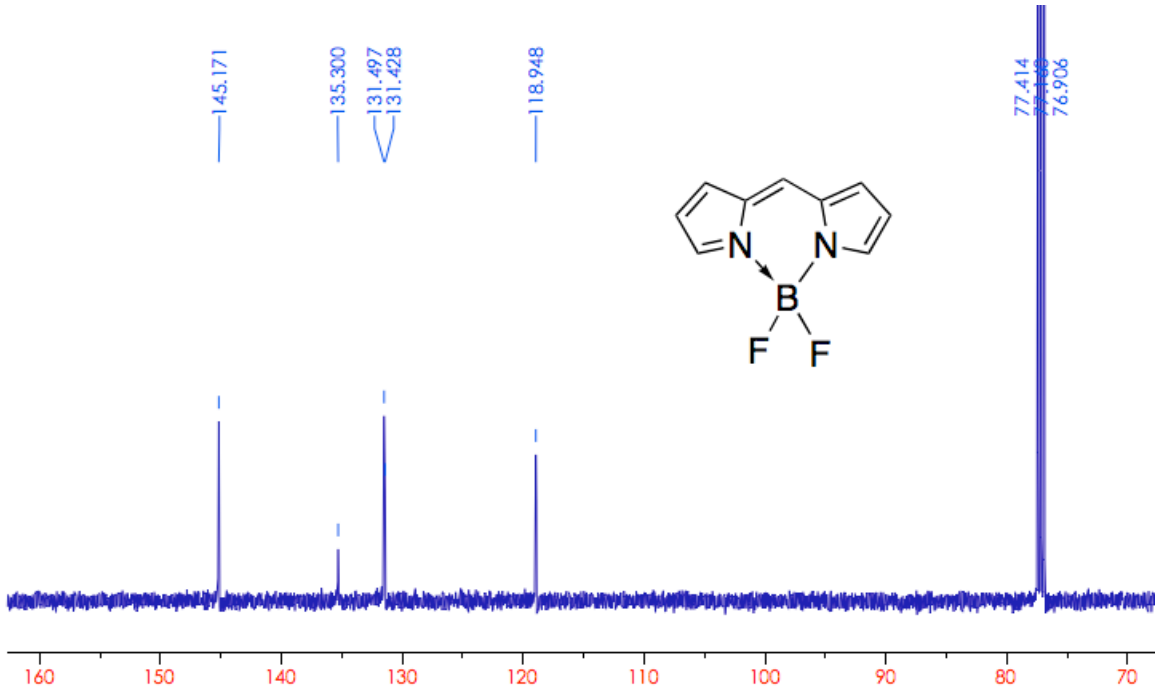


APPENDIX B.78 4-Bora-3a,4a-diaza-*s*-indacene (**133**)[159-161]

^{1}H NMR Spectrum in $CDCl_3$

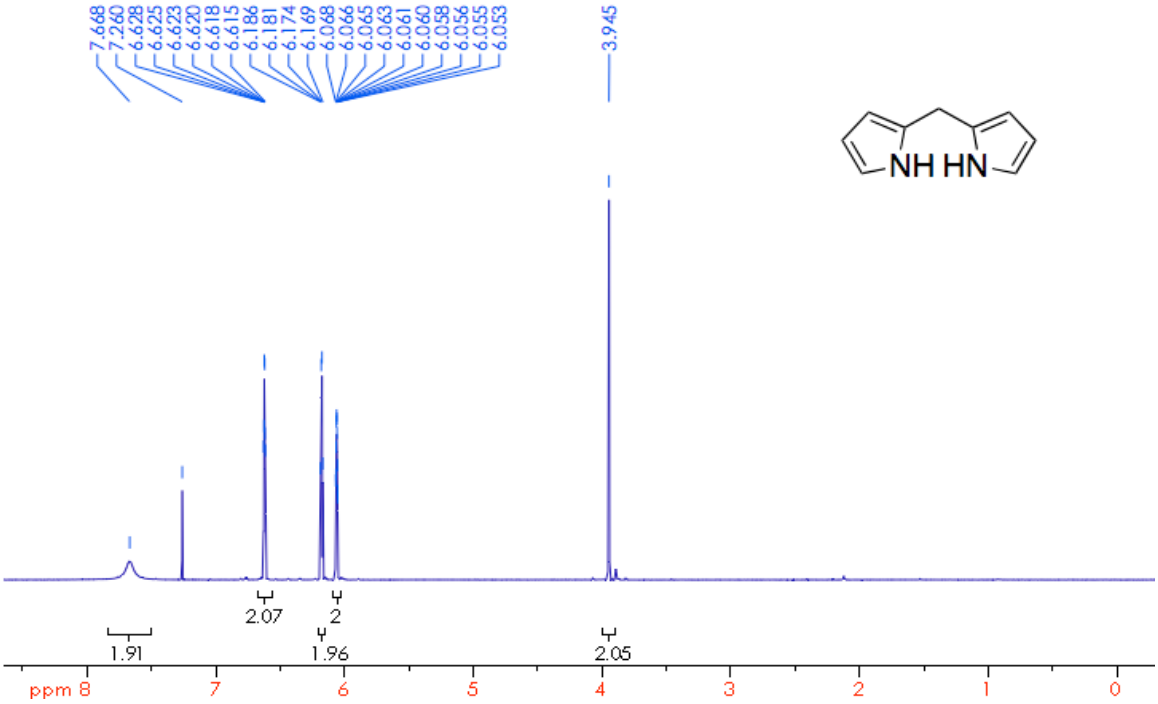


^{13}C NMR Spectrum in $CDCl_3$

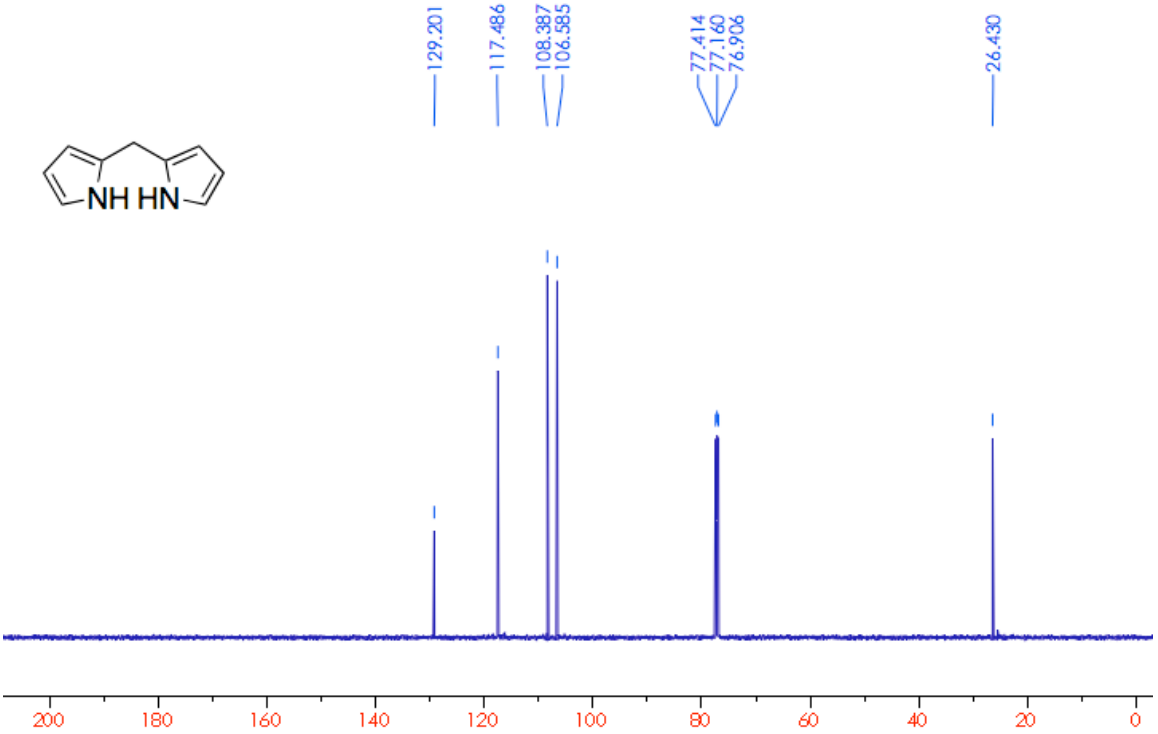


APPENDIX B.79 Di(1*H*-pyrrol-2-yl)methane (**134**)[162]

^{1}H NMR Spectrum in $CDCl_3$

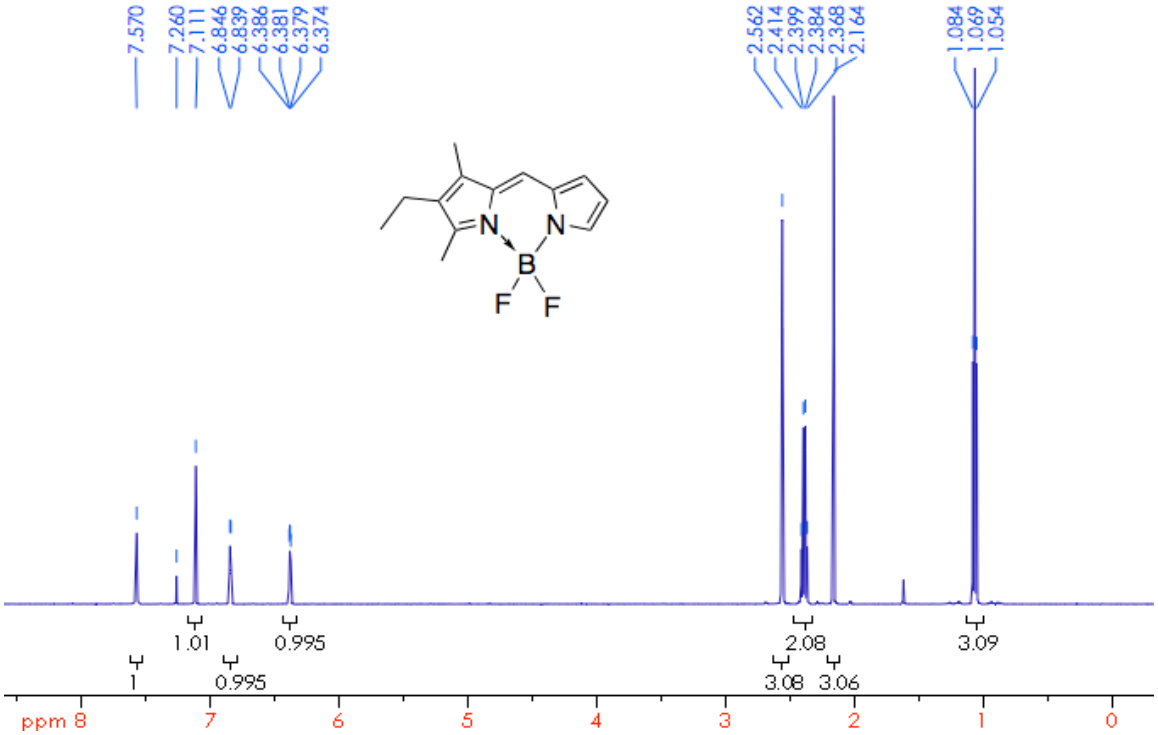


^{13}C NMR Spectrum in $CDCl_3$

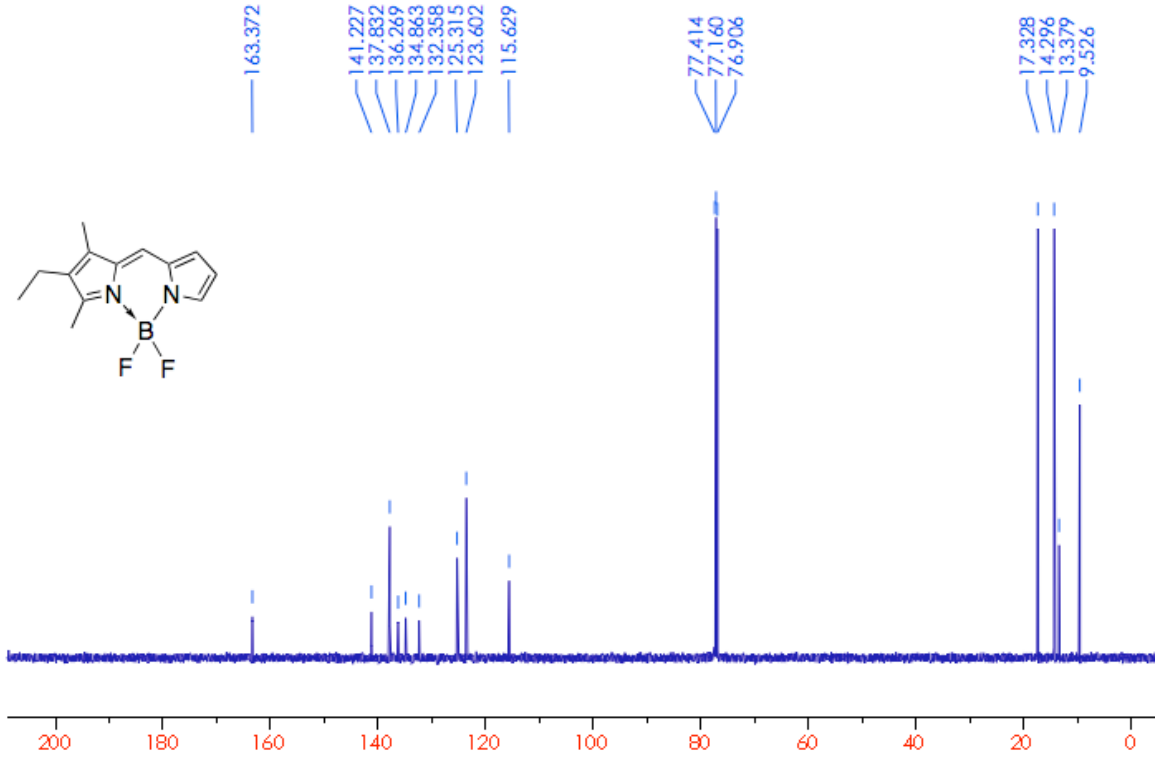


APPENDIX B.80 1,3-Dimethyl-2-ethyl-8 *H*-4-bora-3a,4a-diaza-*s*-indacene (**135**)

^{1}H NMR Spectrum in $CDCl_3$

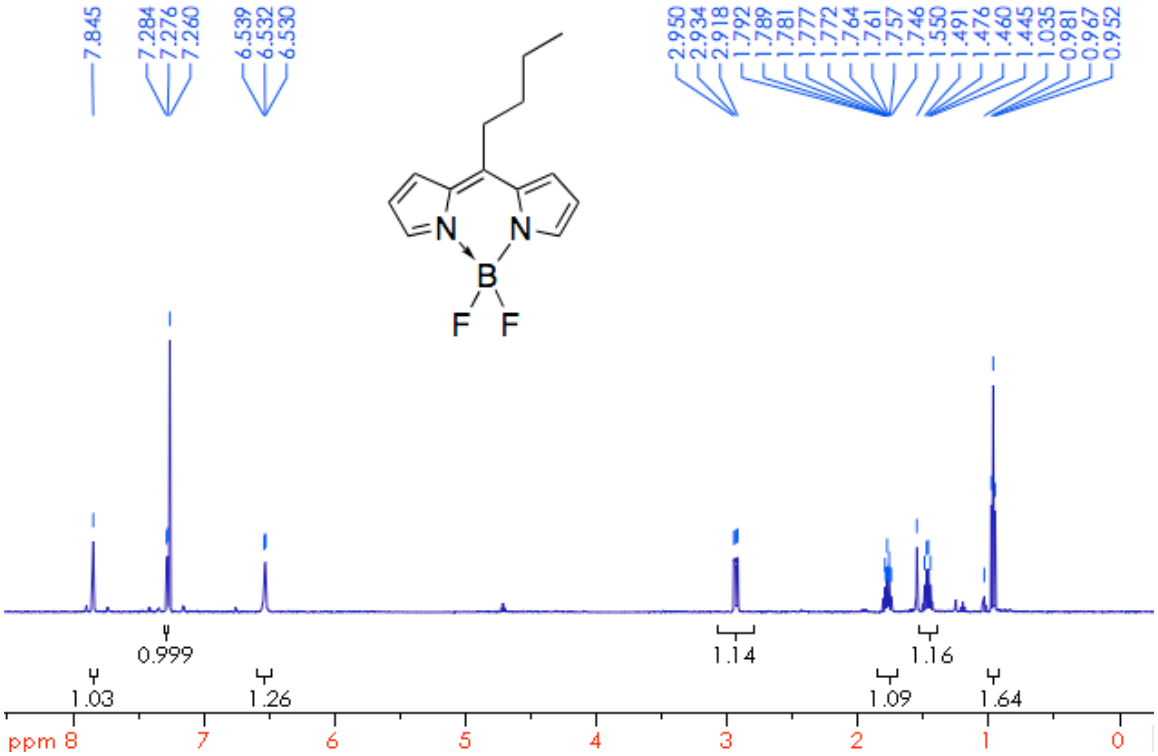


^{13}C NMR Spectrum in $CDCl_3$

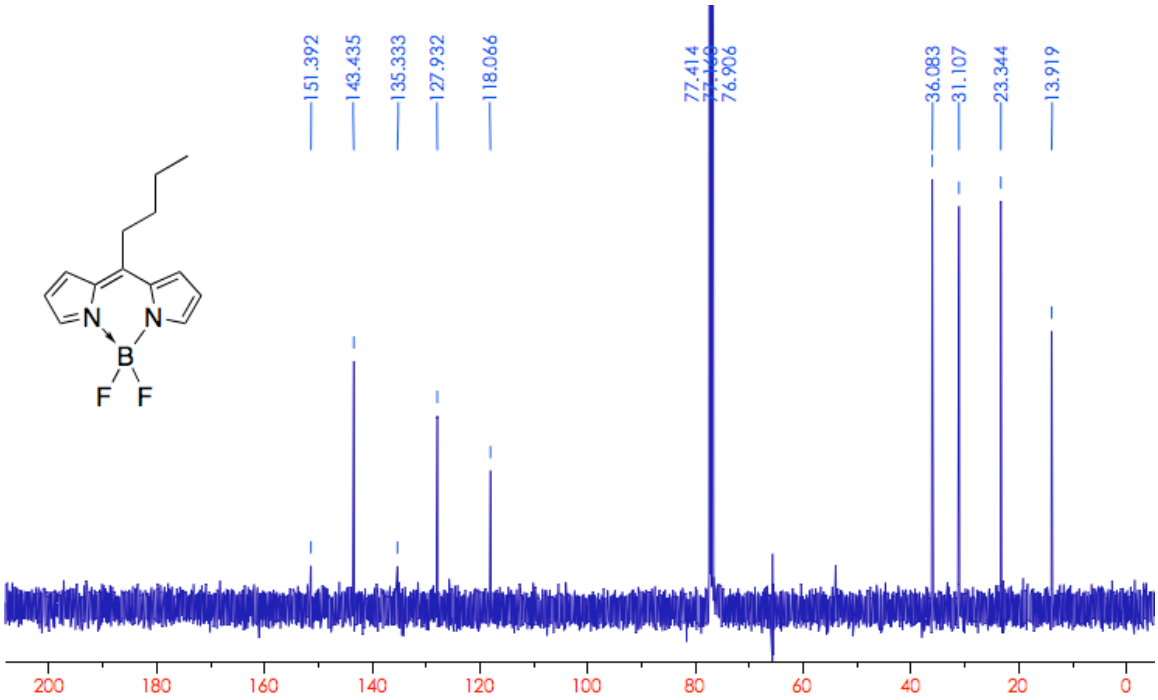


APPENDIX B.81 8-Butyl-4-bora-3a,4a-diaza-*s*-indacene (**136**)

^{1}H NMR Spectrum in $CDCl_3$

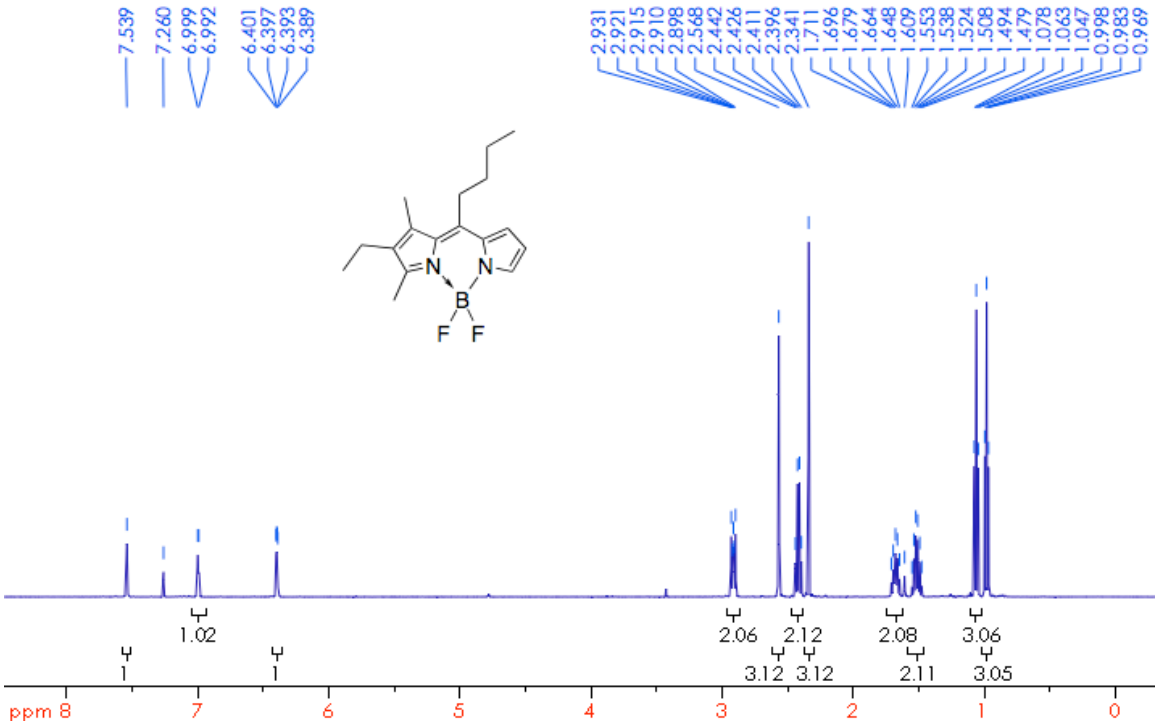


^{13}C NMR Spectrum in $CDCl_3$

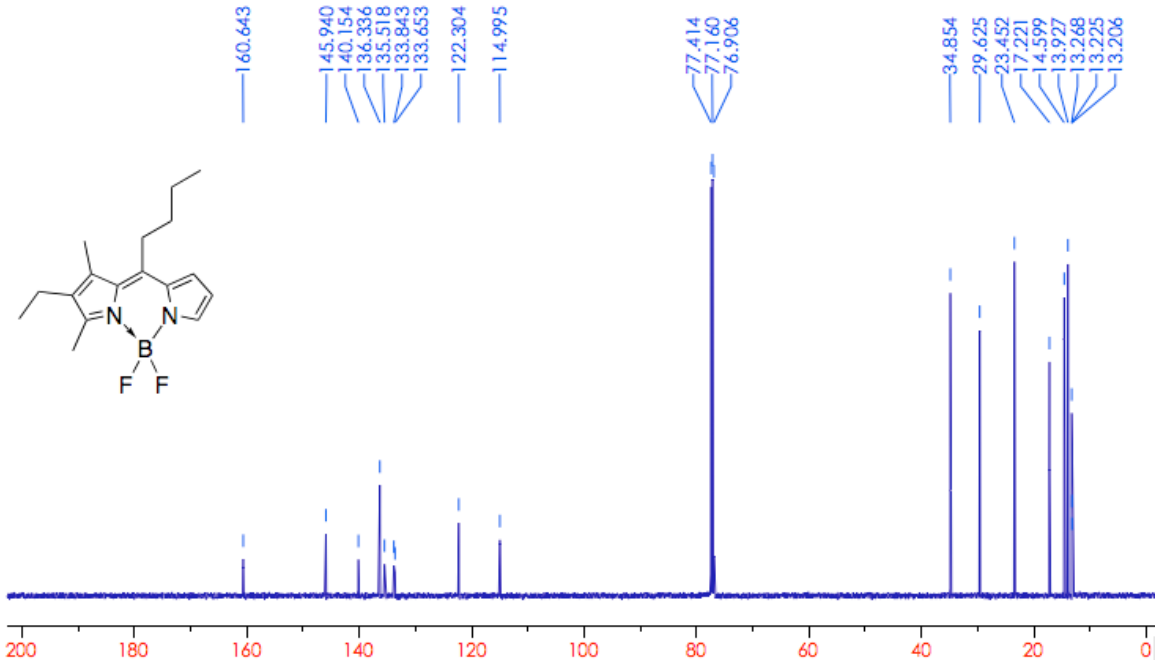


APPENDIX B.82 1,3-Dimethyl-2-ethyl-8-butyl-4-bora-3a,4a-diaza-*s*-indacene (**137**)

^{1}H NMR Spectrum in $CDCl_3$

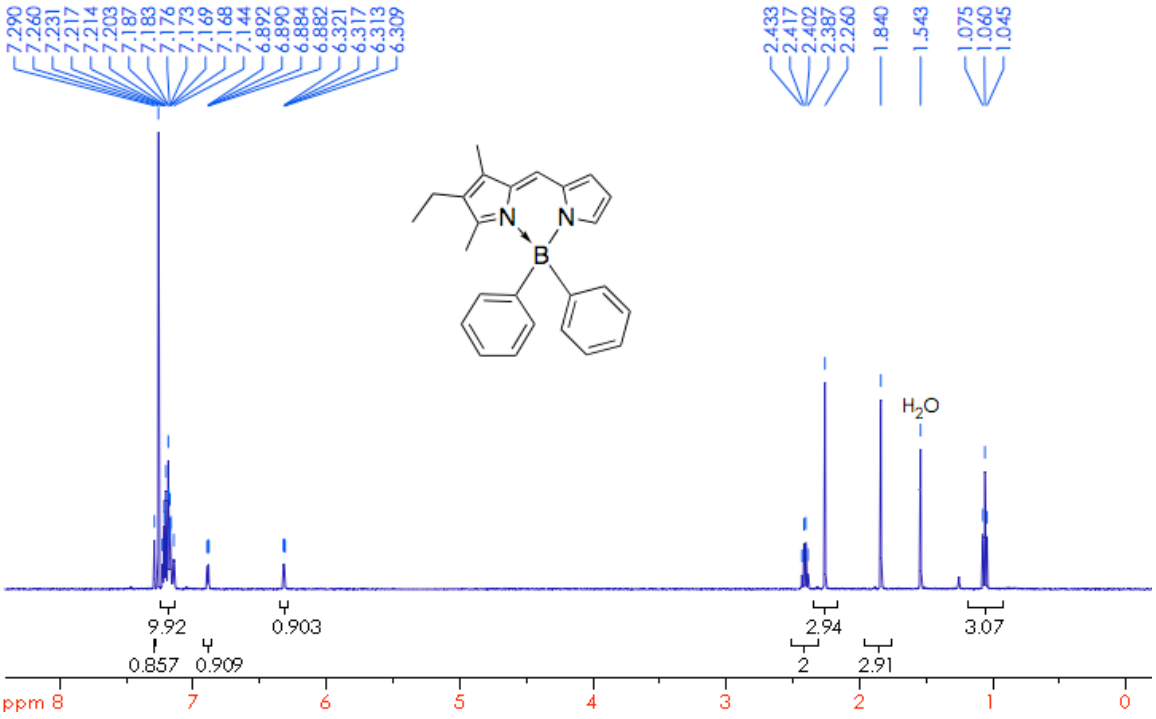


^{13}C NMR Spectrum in $CDCl_3$

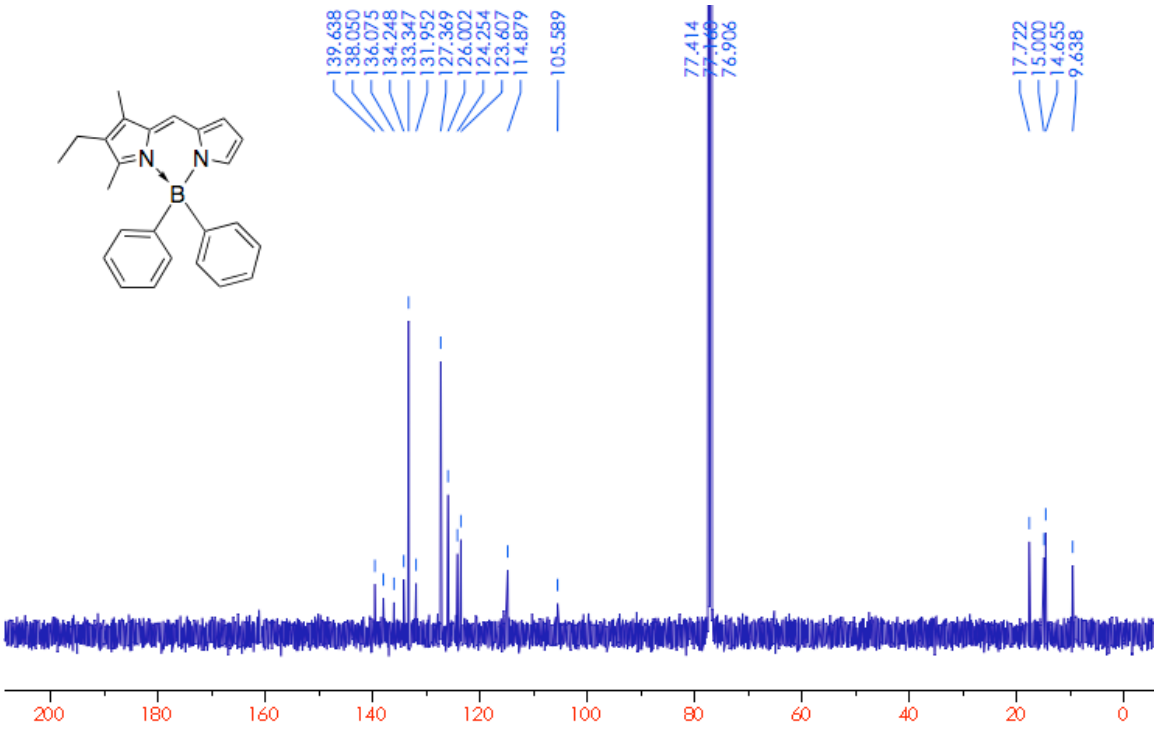


APPENDIX B.83 4,4-Diphenyl-1,3-dimethyl-2-ethyl-8*H*-4-bora-3a,4a-diaza-*s*-indacene (**138**)

^{1}H NMR Spectrum in $CDCl_3$

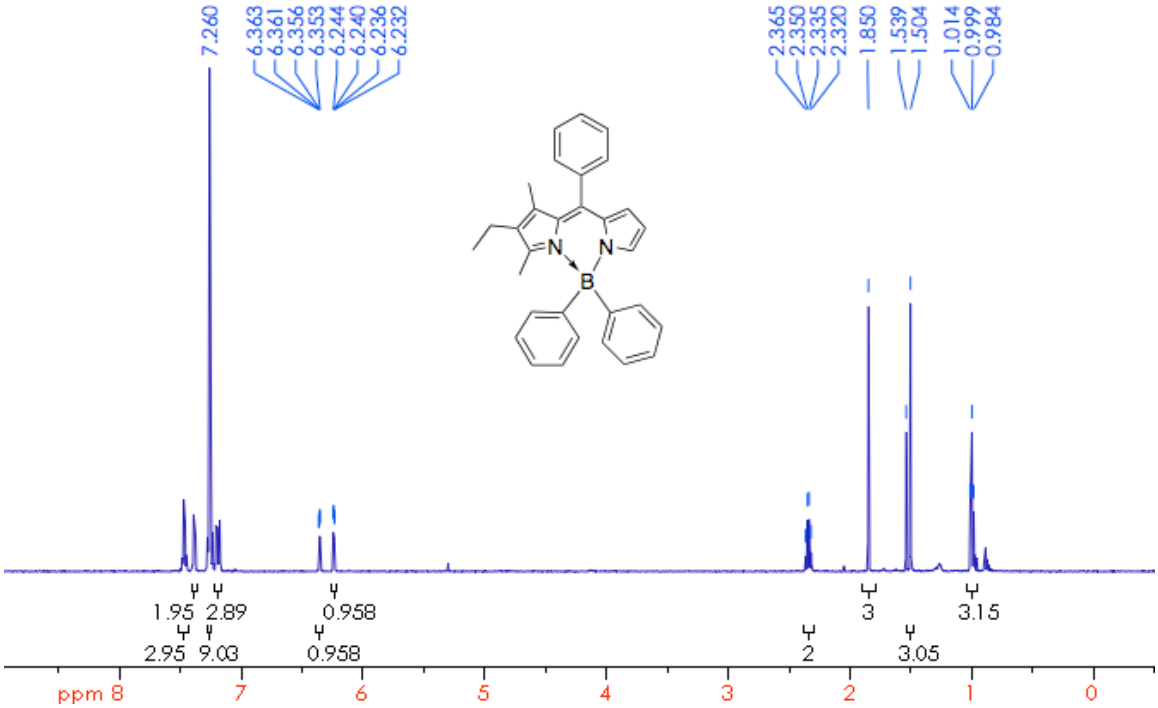


^{13}C NMR Spectrum in $CDCl_3$

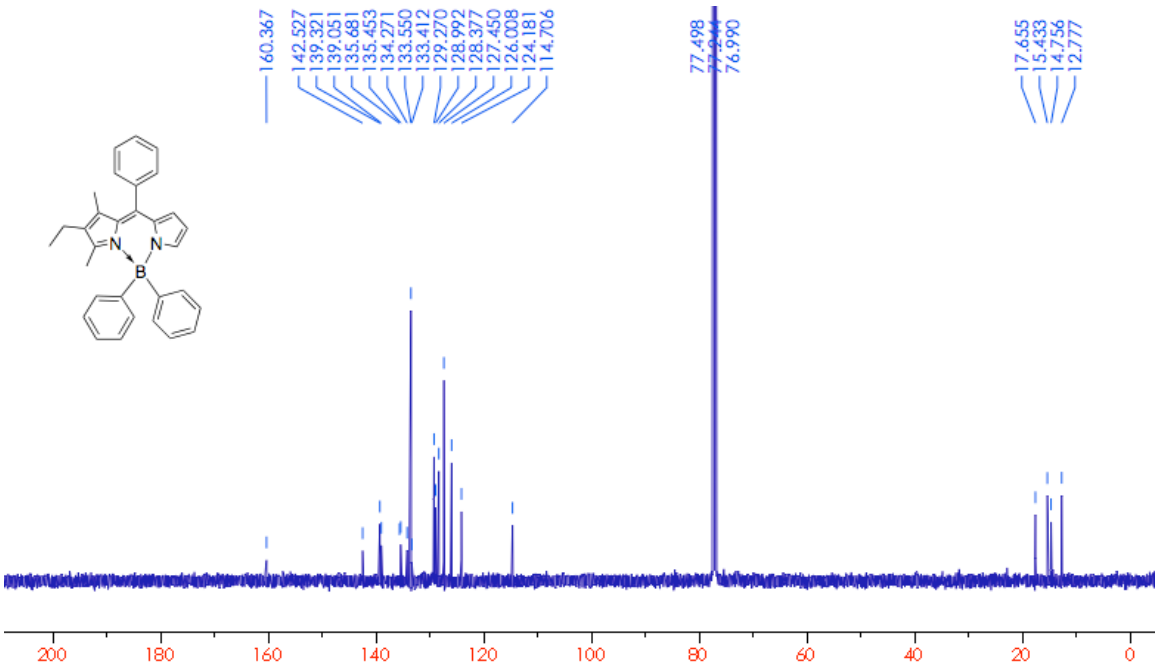


APPENDIX B.84 4,4-Diphenyl-1,3-dimethyl-2-ethyl-8-phenyl-4-bora3a,4a-diaza-*s*-indacene (**139**)

^{1}H NMR Spectrum in $CDCl_3$

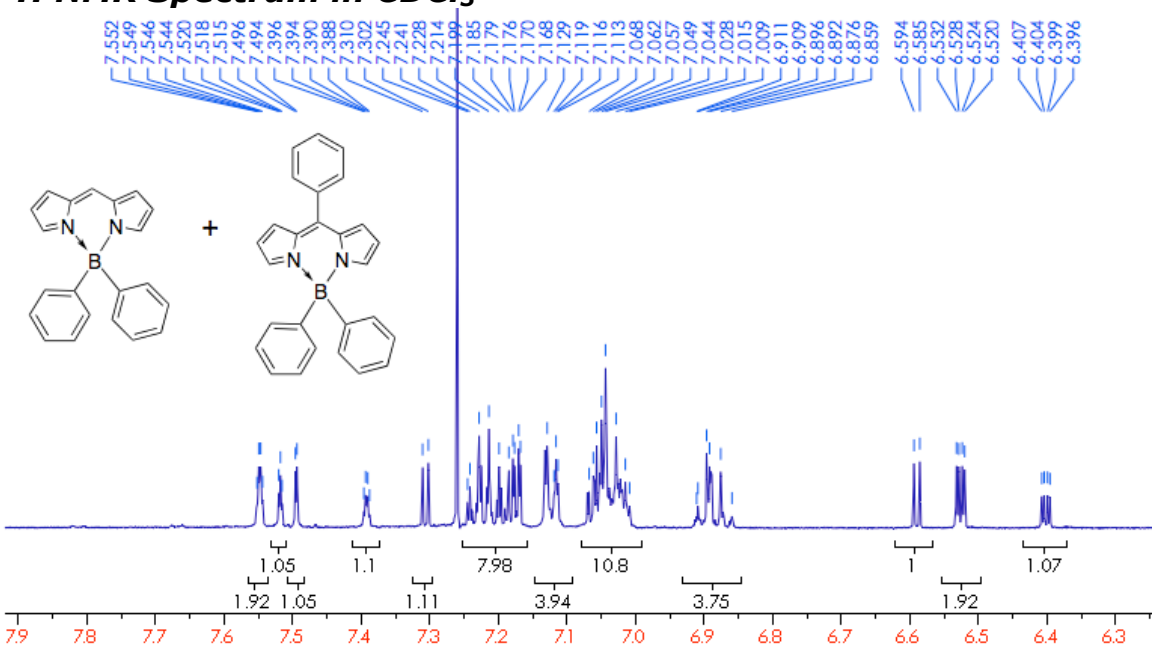


^{13}C NMR Spectrum in $CDCl_3$

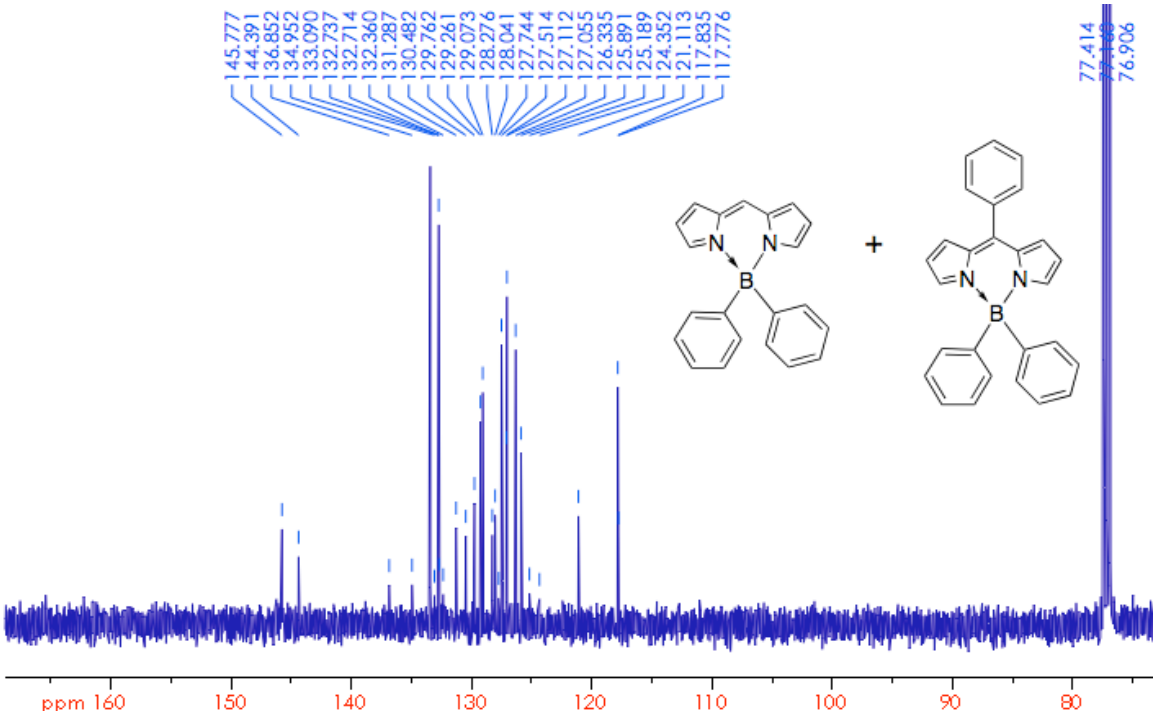


APPENDIX B.85 4,4-Diphenyl-8*H*-4-bora-3a,4a-diaza-*s*-indacene (**140**) and 4,4-diphenyl-8-phenyl-4-bora-3a,4a-diaza-*s*-indacene (**141**)

^{1}H NMR Spectrum in $CDCl_3$

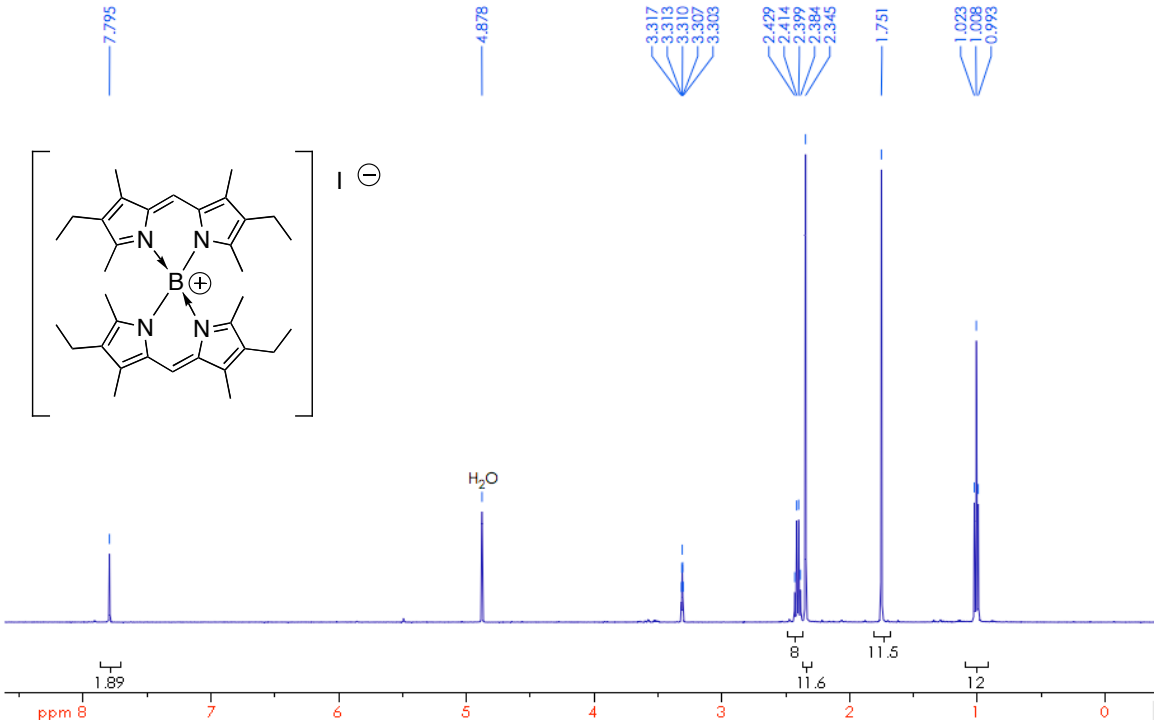


^{13}C NMR Spectrum in $CDCl_3$

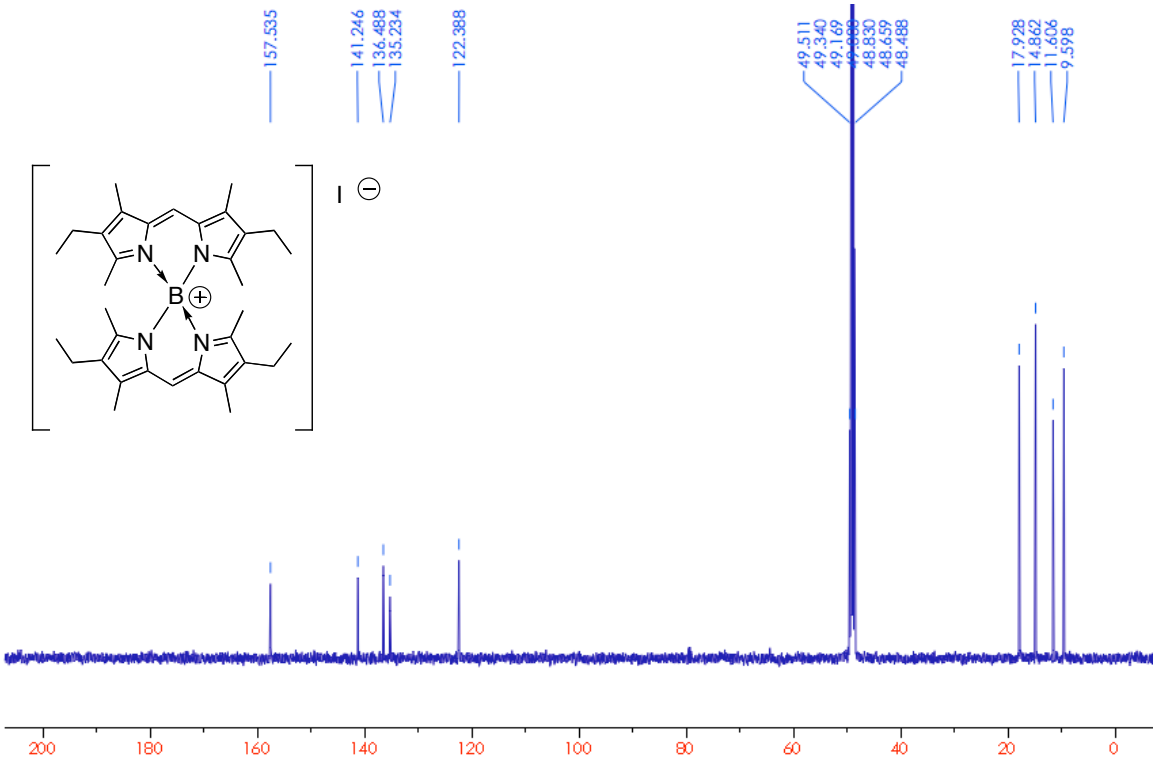


APPENDIX B.86 κ^2-(4,4′-Diethyl-3,3′,5,5′-tetramethyldipyrrinato) boronium iodide (**142I**)

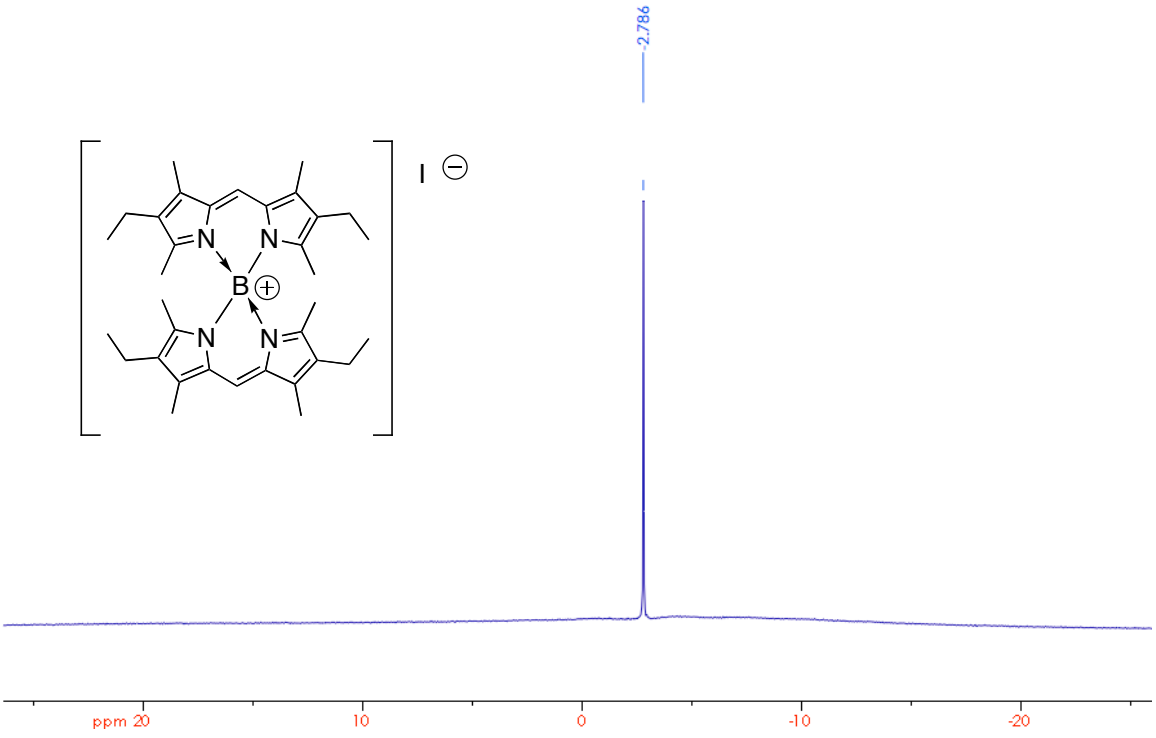
^{1}H Spectrum in Methanol-d_4



^{13}C Spectrum in Methanol-d_4

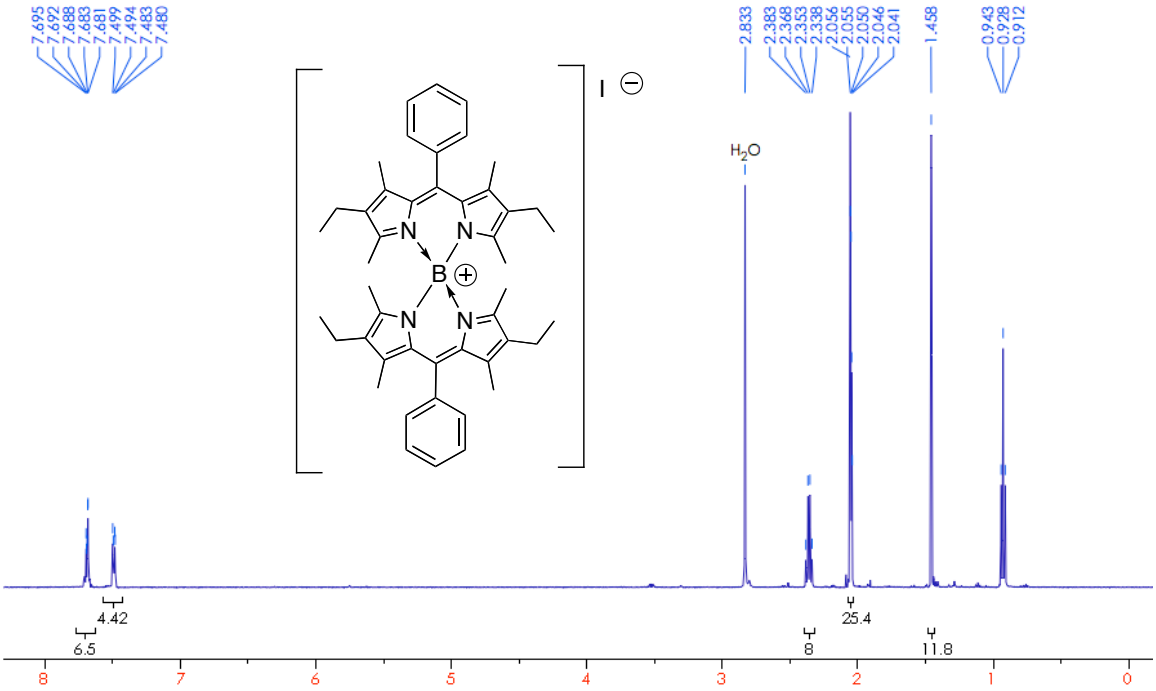


^{11}B Spectrum in Methanol-d_4

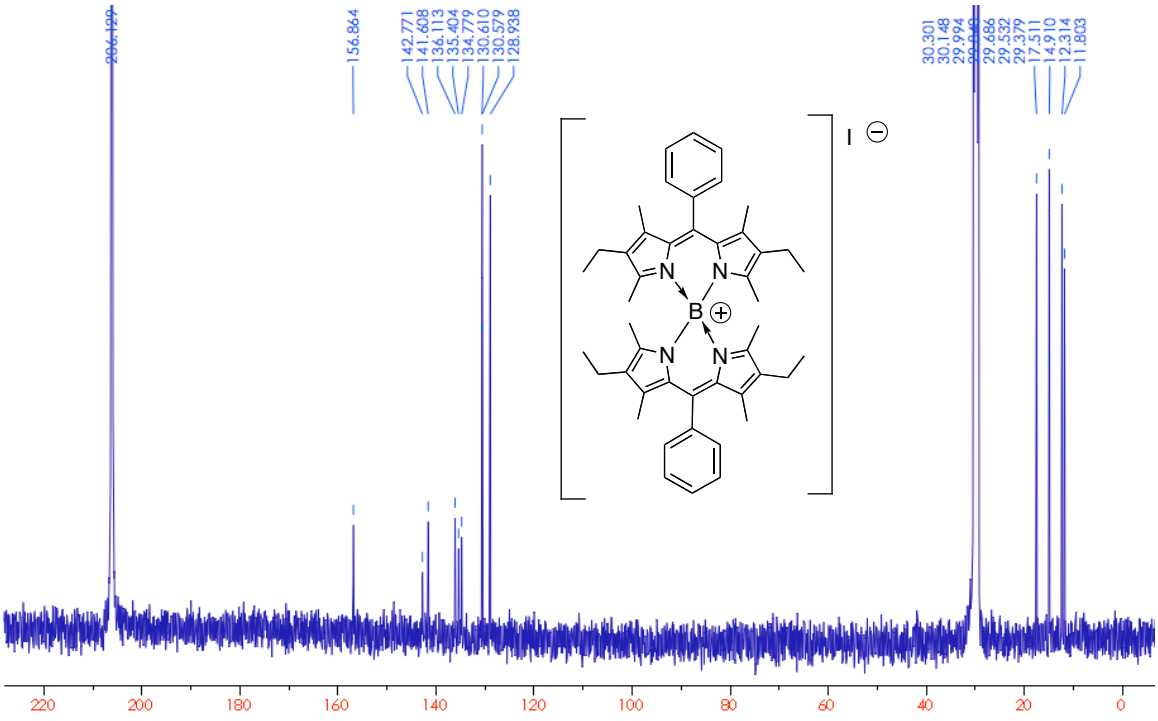


APPENDIX B.87 κ^2-(4,4′-Diethyl-3,3′,5,5′-tetramethyl-*meso*-phenyl-dipyrrinato) boronium iodide (**143I**)

^{1}H Spectrum in Acetone-d_6



^{13}C Spectrum in Acetone-d_6



^{11}B Spectrum in Acetone-d_6