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New strategies for the synthesis of porphyrinoids

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NEW STRATEGIES FOR THE SYNTHESIS OF PORPHYRINOIDS

A Dissertation

Submitted to the Graduate Faculty of the
Louisiana State University and
Agricultural and Mechanical College
in partial fulfilment of the
requirements for the degree of
Doctor of Philosophy

in

The Department of Chemistry

by
Moses Inyanje Ihachi
B.Sc., Moi University, 2005
December 2013

I dedicate this work to my dear lovely wife (Jackline Mukenya), my daughter (Gloria Ihachi) and my parents (Elizabeth Ihaji and James Mwanga). You were there with me in prayers, guidance and advice. Thank you so much!

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LIST OF ABBREVIATIONS

Abbreviation	Name
σ	Chemical shift
λ_{\max}	Wave length
Boc	<i>tert</i> -Butyl carbamate
br	Broad
Calcd.	Calculated
CAN	Ceric ammonium nitrate
CDCl_3	Deuterated chloroform
$^{\circ}\text{C}$	Degrees Celsius
CH_3OH	Methanol
CM	Cross metathesis
^{13}C NMR	Carbon 13 nuclear magnetic resonance
d	Doublet
DBU	1,8-Diazabicycloundec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
ESI	Electrospray ionization
FDA	United States Food and Drug Administration
GC	Gas Chromatography
h	Hours
HRMS	High resolution mass spectrometry
^1H NMR	Proton NMR
HZ	Hertz
MeOH	Methanol
MS	Mass spectrometry
Ms	Mesylate
m/z	Mass to charge ratio
NHC	N-heterocyclic carbenes
nm	Nanometer
NMR	Nuclear Magnetic resonance
OH	Hydroxyl
Pd/C	Palladium on activated carbon
PDT	Photodynamic therapy
pin	Pinacol
PPh_3	Triphenyl phosphine
ppm	Parts per million
PS	Photosensitizer
RCM	Ring closing metathesis
ROM	Ring opening metathesis
ROMP	Ring opening metathesis polymerization
ROS	Reactive oxygen species
RT	Room temperature
s	Singlet
Sphos	2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl

t	Triplet
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPSCI	Triisopropylsilyl chloride
TLC	Thin layer chromatography
TOF	Time of flight
μL	Microliter
UV-Vis	Ultraviolet visible

ABSTRACT

Chapter 1 describes the most stable isomer of porphyrin called porphycene. In this chapter photodynamic therapy (PDT) is explained, and the application of porphycenes in PDT is also described. Other biological applications and its uses in catalysis are also summarized here. The general chemical reactions of porphycenes are also explained.

Chapter 2 involves the synthesis of pyrroles and bipyrrroles. Functionalization of pyrrolic substituents is demonstrated using organometallic coupling reactions like Stille coupling and Grubbs olefin metathesis. The synthesis of divinyl bipyrrroles is intended to provide an important precursor to porphycene synthesis via ring closing metathesis using Grubbs catalyst.

Chapter 3 describes the synthesis of new 5,5'-dimethyl-2,2'-bipyrrrole. The methyls at the *alpha*-position of the pyrroles are reactive and are shown to be susceptible to halogenation, acetylation and oxidation reactions, giving new useful products for the synthesis of various porphyrinoids.

Chapter 4 explains the new approach towards porphycene synthesis via the synthesis of benzo-bridged 1,2-di(2-pyrrolyl)ethenes. Named coupling reactions like Ullmann, Suzuki, and Sonogashira, were performed on pyrrole derivatives. The synthesis of other possible porphyrinoids was also attempted.

CHAPTER 1: INTRODUCTION

1.1. Overview of Porphycenes

Porphycenes are tetrapyrrolic molecular systems whose parent molecule is porphyrin.¹ It is the first known isomer of porphyrins to be synthesized. The structure of porphycene **1.1** resembles closely that of the porphyrin macrocycle **1.2**, containing four monopyrrole rings **1.3** but with rearrangement of the methine bridges.² Its conjugation is likened to that of acenes **1.4**. It was first prepared in 1986 by Vogel and coworkers.¹ The macrocycle of porphycenes contains two bipyrrrole subunits in the northern and southern parts of the molecule connected by two bridging carbons in the east and west (Figure 1.1).¹

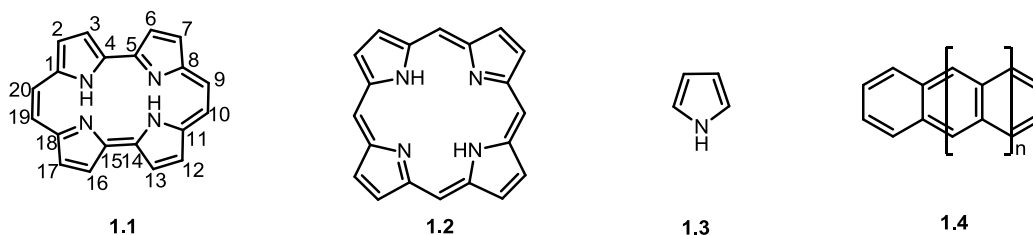


Figure 1.1: General structures of porphycene, porphyrin, pyrrole and acenes.

The subject molecule derives its name 'porphycene' from 'porphyrin' **1.2** and 'acene' **1.4** due to its resemblance to porphyrins and very high conjugation that is comparable with acenes. It is nearly planar in conformation with four nitrogen atoms in its core that can complex metals such as Zn, Cu, Co and Ni,¹ a property that makes it a strong ligand. The porphycene macrocycle is aromatic with an 18π conjugation system that displays spectroscopic features that are similar to its parent porphyrin.³ Hückel's $4n+2$ rule applies to this tetrapyrrolic macrocycle which causes it to be formally known as [18]porphyrin-(2.0.2.0).² The aromatic nature of porphycenes is evidenced by the upfield shift of internal NH protons to $\delta=3.15$ as compared to the NH of simple pyrrole that is found at $\delta=7.70$. The molecule is also planar. The UV/Vis spectral analysis in benzene of the macrocycle also helped in understanding the compound's conjugation as it shows a double Soret band at $\lambda=358/370$ nm ($\epsilon=139200$ and 106900) and also

three longer wavelength bands, so-called Q-bands at $\lambda=558$ (34200), 596 (30400), and 630 nm (51900). The Q-bands in the absorption spectra of porphycenes are stronger than those of porphyrin because, among other reasons, of its low D_{2h} symmetry, in contrast to the D_{4h} symmetry in porphyrin.¹

1.2. Photodynamic Therapy (PDT)

Photodynamic Therapy (PDT), is a binary medical treatment method that employs the use of light and a drug (photosensitizer) in presence of molecular oxygen to kill or destroy cancerous cells.⁴

Ultraviolet light has routinely been used to treat psoriasis when used together with psolarens (PUVA- psolarens and UVA, 320-400nm).⁵ Hematoporphyrin **1.6** (Figure 1.2) was the first porphyrin to be used for PDT. In the early 1960s, Lipson and his colleagues synthesized hematoporphyrin derivative (HPD) and showed its application as a diagnostic tool in implanted tumors of mice and rats.⁶ HPD is a mixture of hematoporphyrin **1.6**, protoporphyrin-IX **1.7**, hydroxyethylvinylporphyrin, and other compounds containing dimeric and oligomeric derivatives of hematoporphyrin.⁶ Twenty years later, Dougherty *et al.* prepared a more purified form of HPD by ultrafiltration; they called it Photofrin® **1.5**.⁷⁻⁹ Photofrin is a first generation cancer drug suffering several limitations as a photosensitizer including, its impure form because it contains a mixture of dimers and oligomers.¹⁰ It is composed of about 60 compounds, which makes it hard to determine its pharmacological activity, and it is also retained up to six weeks¹¹ in the patient's body after the therapy process, rendering the patient photosensitive to strong sunlight. However, Photofrin is still being used as a drug for PDT.

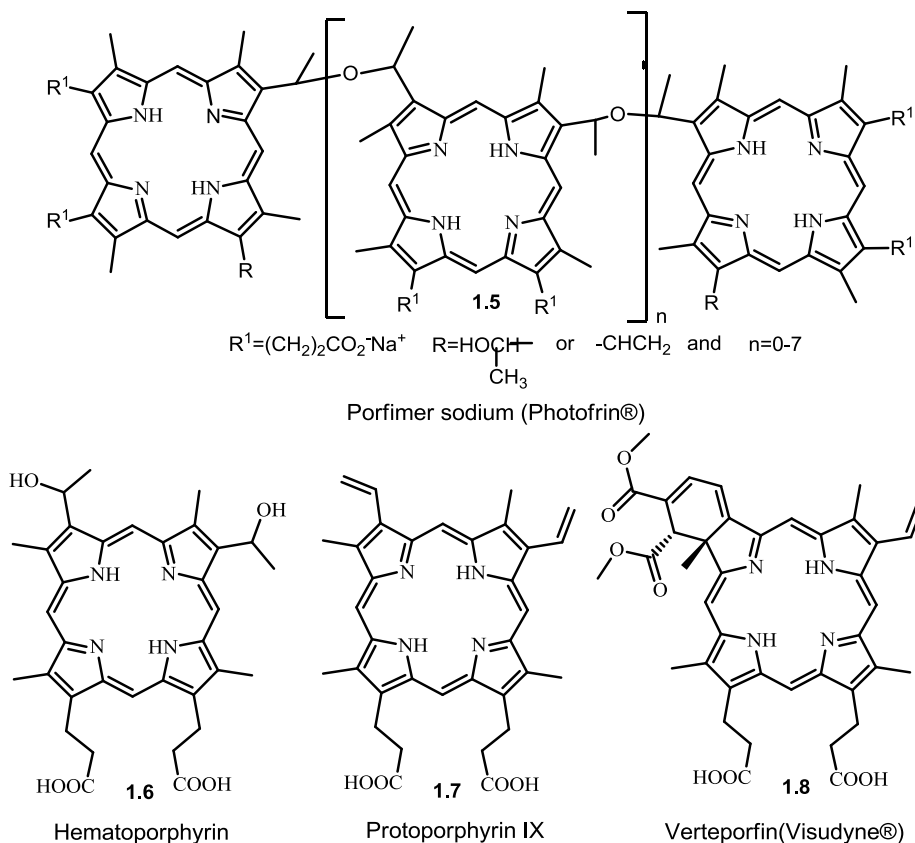


Figure 1.2: Chemical structures of sensitizers approved for PDT: - Photofrin®, hematoporphyrin, protoporphyrin IX, and verteporfin.

5-Aminolevulinic acid (ALA), also known by its trade name Levulan®, or its methyl ester, Metvix®, are prodrugs that transform into protoporphyrin IX in the body. Clinical studies have shown that protoporphyrin IX can induce tissue photosensitization; it however suffers from spectral property drawbacks similar to those of Photofrin.¹²

Verteporfin (Visudyne®) **1.8** is a chlorin-type photosensitizer used in the treatment of the wet form of age-related macular degeneration (ARMD), which involves damage of the macula (visual field) of the eye. This results in age-related loss of vision.¹³

Other methods for treating and diagnosis of cancer include chemotherapy, radiotherapy and surgery. PDT is better than these cancer therapy methods in the following ways ¹⁴⁻¹⁵ :-

- i. it is a non-invasive method; - hence tissue damage is limited or absent when compared to radiotherapy and surgery..

- ii. it can be controlled, and treatment is localized because of visual imaging of the tumor tissue.
- iii. side effects such as nausea and vomiting, as seen in chemotherapy, are avoided.
- iv. it can be used on elderly patients who are vulnerable to surgery, chemotherapy and radiotherapy.
- v. doses can be administered repeatedly without the eventual total dose limitations seen in the chemotherapy and radiotherapy methods of treatment
- vi. it can be performed in an out-patient setting.

1.2.1. Photosensitizers

A photosensitizer is a substance that sensitizes an organism, cell, or tissue, to light, eventually causing its death. Most porphyrin isomers and derivatives are good photosensitizers because they meet most of the required properties of a good photosensitizer.^{16,17} The attractive absorption, emission and UV-Vis spectral properties of porphycenes, among others, qualifies them to be classified as photosensitizers.

A good photosensitizer among other things, should:

- i. not be toxic to living cells,
- ii. be easily eliminated after therapeutic action,
- iii. be selective for malignant tissue over living tissue,
- iv. display low dark toxicity,
- v. have a high quantum yield of the triplet state,
- vi. efficiently generate cytotoxic oxygen species,
- vii. have an increased absorbance in the red region of the optical spectrum where light penetration is greatest,¹⁸ and

- viii. display strong absorption in the therapeutic window (between 650-750 nm) to ensure deep penetration of light through tissue and with minimal light scattering.⁴

The photosensitizer (for example a porphycene derivative), is injected into the patient's bloodstream intravenously and localizes at, or near, the tumor site (see Figure 1.3). This process takes a few hours depending on the photosensitizer and tumor type, (2-48 hours), and the patient is usually kept in the dark with minimal light exposure. Once localized, the tumor bed will fluoresce as well as other parts on the body containing malignant cells.¹⁸ Light of a specific wavelength and flux is shone around the located tumor for a specific time duration. The source of light can be laser light delivered using optic fiber to the surface of the lesion, or endoscopically to the tumor parenchyma using a catheter-like array of light emitting diodes (LED).¹⁹ Light activates the drug (photosensitizer), initiating toxic action. The cancerous cells die by apoptosis, necrosis, ischemia, inflammation and immune responses.^{4,18,20} Lasers are usually used as light sources. Investigations are still underway to provide more reasons as to why the photosensitizer localizes selectively at rapidly dividing cells. However, it is known that the photosensitizing dye localizes at the site of tumor cells in a patient possibly because tumor tissue has a large number of low-density lipoprotein (LDL) acceptors, and porphyrin drugs have an affinity for LDLs receptors.²⁰⁻²⁵ Other studies have shown that peripheral substituents,²⁶ axial ligands, and coordinating metal ions promote accumulation and retention of porphyrinoid photosensitizers.^{27,28} Poor lymphatic drainage, decreased pH value, and hypervascular cancerous tissue also accounts for the photosensitizer accumulation in the cancerous tissue.^{14,20} Irradiation of the dye with light of specific wavelength excites it to a short lived first excited singlet state ($^1P^*$) that could decay radiatively to ground state losing energy by fluorescence that plays a role in identification (detection) of tumor cells.

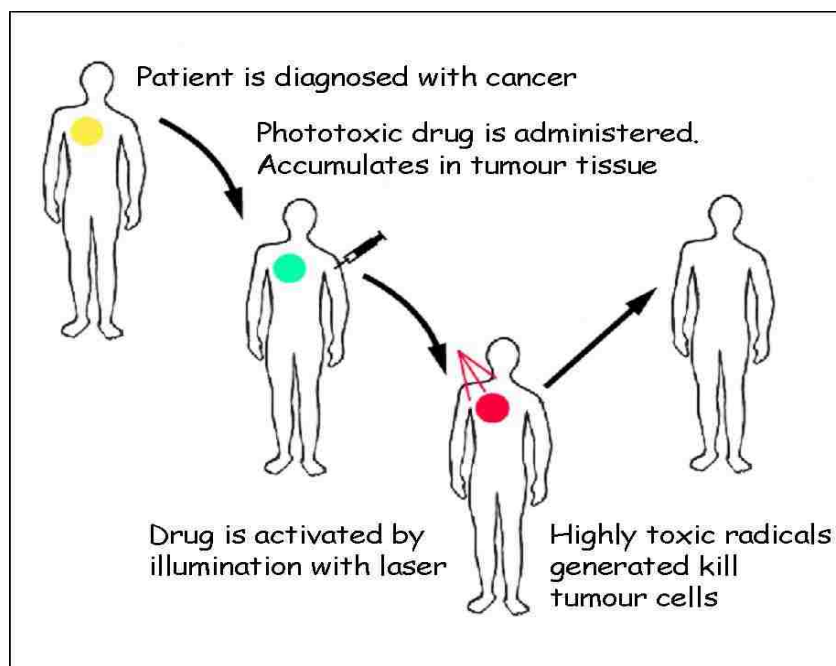


Figure 1.3: Photodynamic Therapy Process. Copy from website (2013)
<http://www.utar.edu.my/fes/index.jsp?fccatid=39&fcontentid=195&f2ndcontentid=177>

If photophysical properties are favorable, the first excited singlet state ($^1P^*$) of the photosensitizer can also undergo intersystem crossing (ISC) to form its triplet excited state ($^3P^*$) that could then relax to ground state non-radiatively by phosphorescence. The triplet state can also transfer energy to a stable triplet state of ground state dioxygen converting it to its cytotoxic singlet form (1O_2), that plays a critical role in cell death in PDT. The 1O_2 interacts with biomolecules in different compartments of the blood plasma, the endothelium cells of the tumor, and organelles of the rapidly dividing cancerous cells killing and destroying them by various processes (see Figure 1.4).^{4,19,29-30} The photosensitizer therefore is never active until light is introduced which activates it to generate highly cytotoxic species, including singlet oxygen, superoxide anion and hydroxyl radicals, which can cause irreversible damage to the tumor cells.

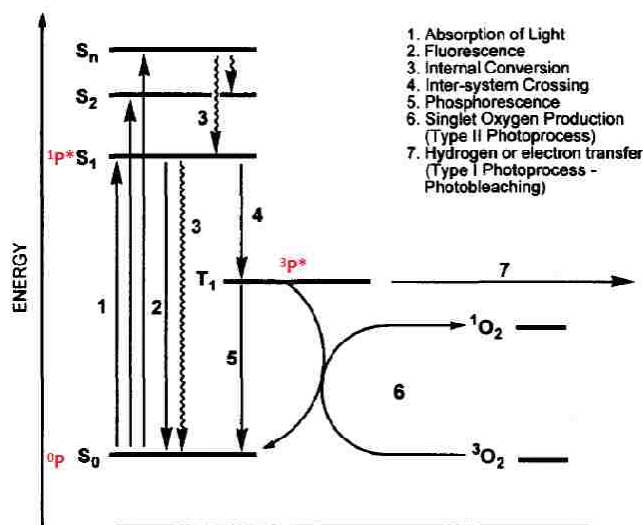


Figure 1.4: Generation of porphycene photosensitizer (**P**) excited states and cytotoxic singlet oxygen. (Modified Jablonski diagram).^{4, 29, 30}

1.3. Applications of Porphycenes

1.3.1. Biological Applications

As a photosensitizer, porphycene possesses superior UV-Vis spectral properties when compared to other porphyrin isomers, showing intense absorption in the phototherapeutic window for PDT (between 600 and 800 nm) which allows deep penetration of light through tissue with minimal light scattering. Such a spectral profile is red-shifted compared to other porphyrin systems.^{1,31} The higher absorption intensity of the porphycene Q-bands makes it even more applicable in PDT, a property that favors it over other porphyrinoids. 9-Acetoxy-2,7,12,17-tetrakis-(2-methoxyethyl)-porphycene (ATMPn) **1.9**, (Figure 1.5), has been used in treatment of psoriasis, a skin disorder. It shows a fluorescence maximum at 650 nm. A phase II clinical trial for topical PDT using 9-acetoxy-2,7,12,17-tetrakis-(2-methoxyethyl)-porphycene (ATMPn), for chronic plaque-stage psoriasis, has been pursued in the University of Regensburg.³² The acetoxy functional group at position 9 of the ring increases hydrophilicity and solubility of the porphycene by an order of two. This makes it more attractive for use in PDT than the routinely

used Photofrin®. ²⁶ In fact, the porphycene ATMPn and its analogues showed 17 to 220 times more biological activity than did Photofrin®. ²⁶

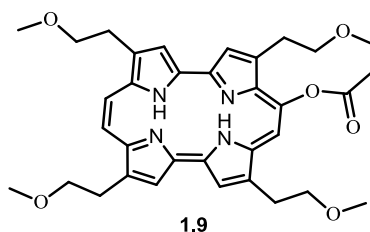


Figure 1.5: 9-Acetoxy-2,7,12,17-tetrakis-(2-methoxyethyl)-porphycene (ATMPn). ^{26,32}

Tetra-n-propyl-porphycene (TPP) **1.10** (Figure 1.6) was tested in mice implanted with the MS-2 fibrosarcoma, a neoplasia. Liposome-bound TPP was injected intravenously and was selectively delivered to the tumor site with good efficacy within 24 hours. The mitochondria were the earliest organelles to be affected. Supported by its absorbance in the 630-640 nm region, tetra-n-propyl-porphycene was found to be a good candidate as a photosensitizer for PDT. ^{25,33}

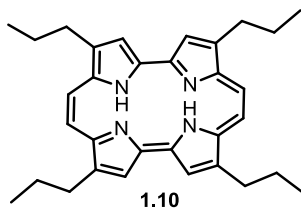


Figure 1.6: Tetra-n-propyl-porphycene (TPP).

Mak *et al.* reported the activity of sulfonated porphycenes against nasopharyngeal carcinoma cells (NPC). ³⁴ Nasopharyngeal carcinoma is the third leading type of cancer in Hong Kong. Sulfonated porphycenes PS6A and PS6 (Figure 1.7) were found to be effective mitochondria localizers, which after photoactivation destroyed the mitochondria, thereby killing the cancerous cells and tissues. The UV/Vis spectra of PS6A shows a Soret band at 375 nm and Q-bands at 574, 620 and 654 nm. PS6A porphycene is cationic while PS6 is neutral. The LC₅₀ value (the drug concentration enough to kill 50% of the population of living cells) of PS6 and PS6A were 11.6µM and 1.9µM, respectively; therefore PS6A was 5-fold more phototoxic than PS6. ³⁴

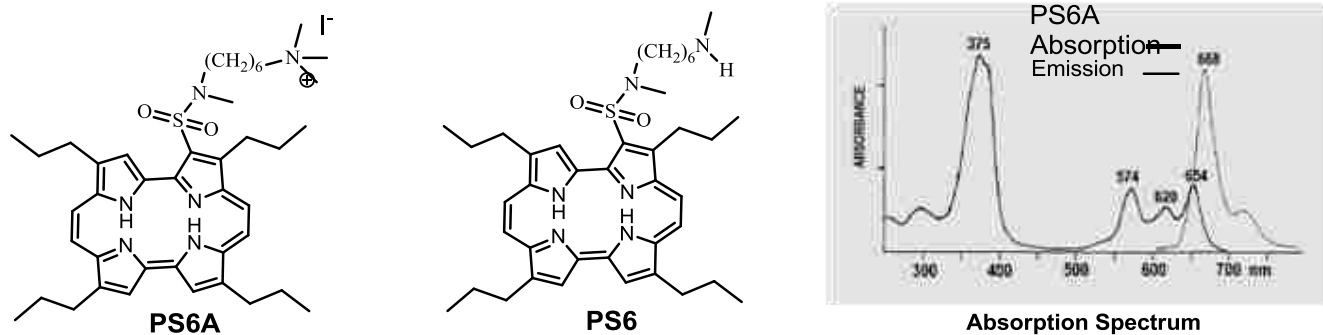


Figure 1.7: Structures of tetra-n-propylporphyrin-3-sulfonamides PS6A and PS6 and the UV-Vis absorption/ emission spectrum of PS6A (in CH_2Cl_2) at room temperature. Emission excitation at 574 nm.³⁴

Mak *et al.* added in their report that PS6A inhibited angiogenesis (formation of new blood vessels from pre-existing vessels) of human umbilical vein endothelial cells (HUVEC). *In vitro* cord formation in HUVEC was disrupted when the PS6A treated cell-culture was irradiated at 4 J/cm^2 (Figure 1.8).³⁴ Disruption of angiogenesis was thought to be useful in preventing metastasis of tumor cells in nasopharyngeal carcinoma patients and also minimizes the density of intratumoral microvessels.

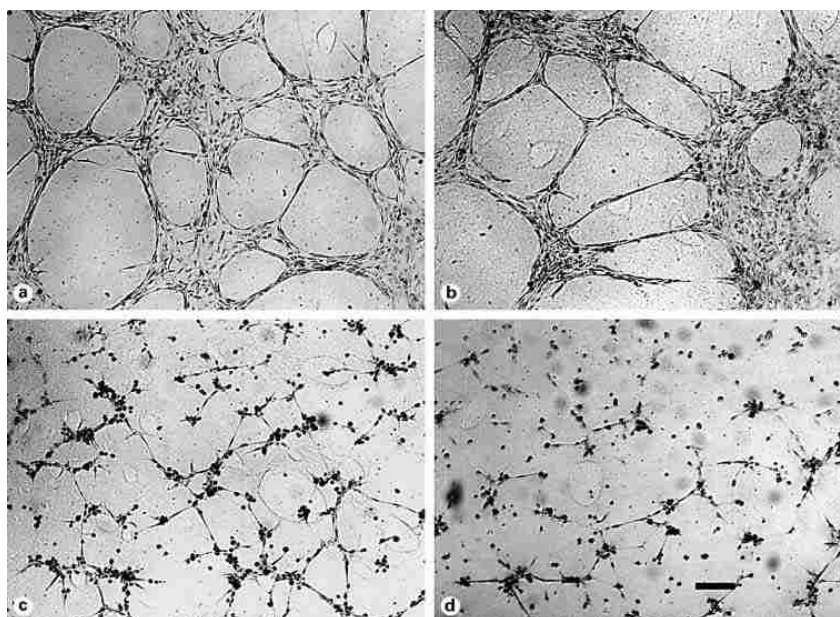


Figure 1.8: Inhibition of cord formation. **a** Untreated HUVECs form cords in Matrigel 6h after incubation. **b** PS6A (1.4 μM)-sensitized HUVECs without irradiation. **c, d** PS6A-sensitized HUVECs irradiated with 4 (**c**) and 8 J/cm^2 (**d**). The scale bar in **d** represents 100 μm .
Reproduced from reference 34.³⁴

Another second generation photosensitizer of importance is *m*-tetrahydroxyphenyl chlorin (*m*-THPC), also called *temoporfin* or Foscan® **1.12** (Figure 1.9). Foscan is approved for neck and head cancer photodynamic therapy.^{35, 36} However, Foscan® had several drawbacks as it showed prolonged skin sensitivity and high potency.³⁷ In 2011, Nonell *et al.* synthesized a porphycene macrocycle similar to it, called *temocene* **1.11** (*m*-THPPo, Figure 1.9).³⁸ Temocene on the other hand showed lower dark toxicity and was more photo-stable than temoporfin. Although temocene was less active as a photosensitizer when compared to temoporfin, its liposome-based analogue would eliminate this disadvantage as the liposome would act as a delivery vehicle.^{38,39}

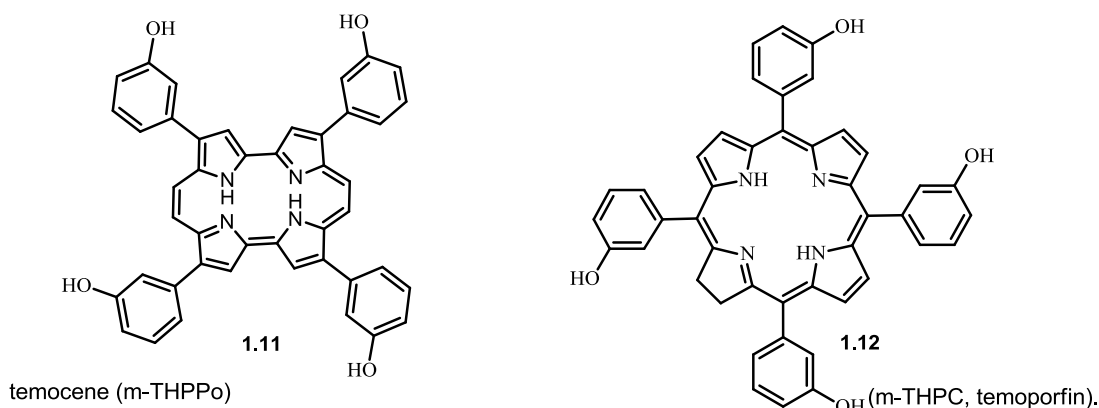
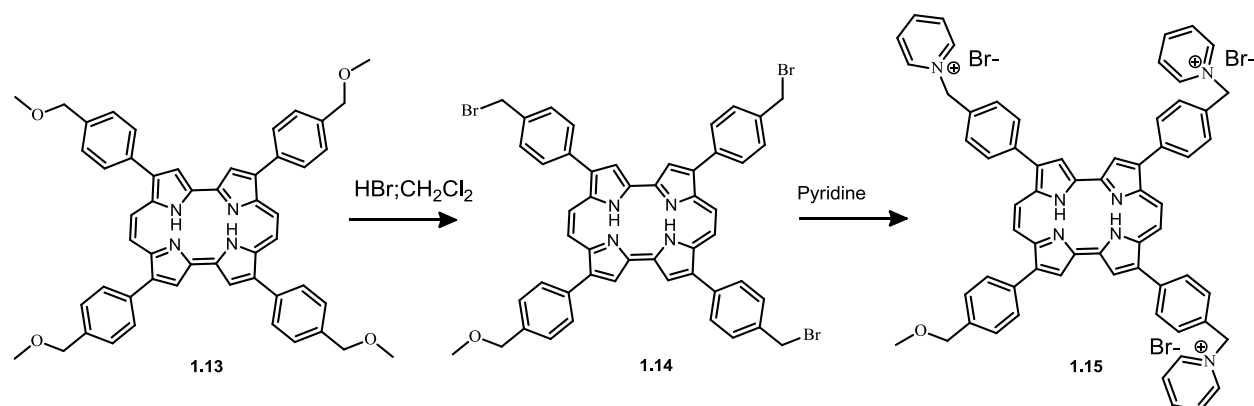


Figure 1.9: Chemical structures of temocene and temoporfin.³⁸

Aryl cationic porphycene derivatives have been tested for antimicrobial activity. In 2010, Nonell *et al.* synthesized the first tricationic water soluble porphycene **1.15**. Antimicrobial photodynamic therapy (APDT)⁴⁰ is currently actively being studied as an alternative to antibiotic treatment of localized infections. The tricationic water soluble porphycene was successfully shown to cause photoinactivation of Gram positive and Gram negative bacteria as well as the fungus *Candida* (Scheme 1.1).⁴¹



Scheme 1.1: Synthesis of cationic porphycenes.⁴¹

1.3.2 Porphycenes as Catalysts

A porphycene containing an imidazolium cation tag was synthesized by Hisaeda's group in 2011.⁴² This compound was effectively used as a catalyst in the photo-oxygenation of 1,5-dihydroxynaphthalene **1.16** to form 5-hydroxy-1,4-naphthoquinone **1.17** (Scheme 1.1) with a rate constant of $k = 2.33 \times 10^{-2} \text{ s}^{-1}$ in acetonitrile and $k = 1.47 \times 10^{-2} \text{ s}^{-1}$ in the ionic liquid *N,N,N*-trimethyl *N*-propylammonium bis(trifluoromethanesulfonyl)amide [TMPA][TFSA].

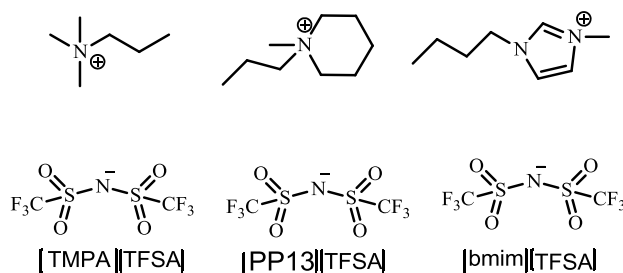
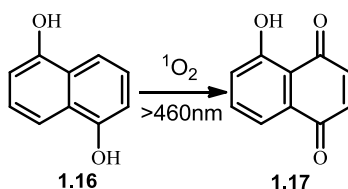
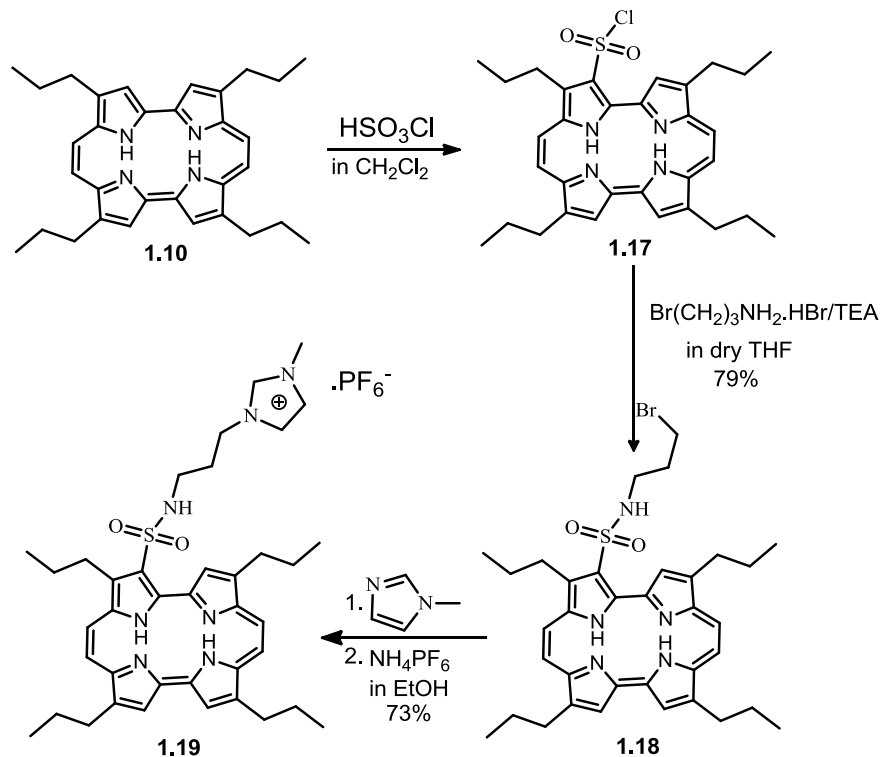


Figure 1.10: Ionic liquids used in the photooxidation reaction.⁴²



Scheme 1.2: Photo-oxygenation of 1,5-dihydroxynaphthalene.

The reaction involved a porphycene **1.10** containing an imidazolium cation tag that acted as a photosensitizer, which generated singlet oxygen upon irradiation with visible light at a wavelength of ≥ 460 nm (Scheme 1.3).



Scheme 1.3: Synthesis of a porphycene containing an imidazolium cation tag (**1.19**)

Ionic liquids were used as the solvents in their study. These liquids were preferred for easy work up, since the porphycene was soluble only in it, and not in organic solvent; - hence the two were recyclable. The ionic liquids of choice were *N,N,N*-trimethyl-*N*-propylammonium bis(trifluoromethanesulfonyl)amide [TPMA][TFSA] and *N,N,N*-trimethyl-*N*-propylpiperidinium bis(trifluoromethanesulfonyl)amide ([PP13][TFSA]). The photooxidized product was then easily recovered from the mixture by an organic solvent extraction. The turnover number of the porphycene was 3500.⁴²

In 2008, Hisaeda's group synthesized highly photostable sulfonated porphycenes *Cis*- 1 and *Trans*-2 (Figure 1.11), photosensitizers that were used in photodegradation of 2,4,6 trichlorophenol (TCP), a major environmental pollutant.⁴³⁻⁴⁵

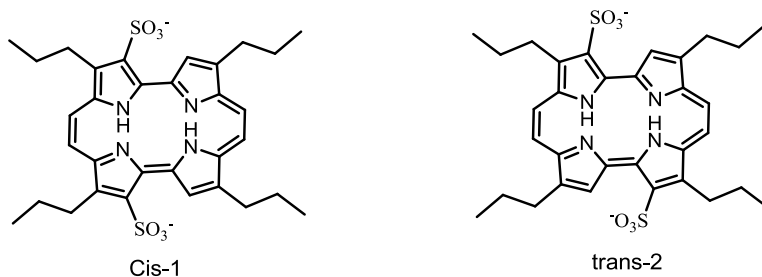
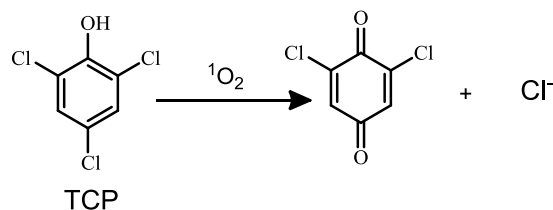


Figure 1.11: Sulfonated *Cis*-1 and *Trans*-2 porphycenes.



Scheme 1.4: Degradation of TCP by singlet oxygen.

Irradiation of the photosensitizer with light ($\lambda \geq 460$ nm) in water generates singlet oxygen ($^1\text{O}_2$), that degrades TCP to form 2,6-dichlorobenzoquinone (Scheme 1.4). A decrease in the TCP absorption peak at 312 nm and formation of 2,6-dichlorobenzoquinone at 273 nm demonstrates the catalytic activity with a turn over number of 185.⁴⁵

1.3.3 Porphycenes as Ligands (Metalloporphycenes)

Metal complexes of porphycenes are synthesized easily because of the N4 core in the macrocycle; also neutral porphycene can be regarded as a doubly protonated dianionic ligand. However, because the tendency to complex with metals is not as easy as in porphyrins due to the small and rectangular N4 core¹ -harsh conditions may need to be applied to effect the coordination.³¹ Divalent metal cations, for example zinc, copper, nickel, and cobalt,^{31,46} are mostly applied, although examples of monovalent cations⁴⁷ and those with higher valencies,⁴⁸ such as Fe(III), Sn(IV), and Al(III), are available in the literature. Vogel's group synthesized the first porphycene nickel complex³¹ using the acetate method, which involves reacting the free ligand with the metal acetate of choice (Figure 1.12).

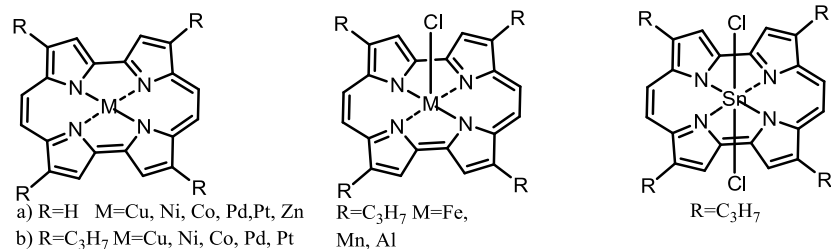


Figure 1.12: Examples of porphycene metal complexes.⁴⁸

Myoglobin (Mb), is a well known hemoprotein that has protoporphyrin IX iron (II) complex, heme **1.20** as its prosthetic group. It plays a major role in mammals in dioxygen (O₂) storage. Modification of the heme is known to change the biological and spectral properties of the hemoprotein. Reconstituted myoglobins (rMbs) with iron porphycene as the prosthetic group in place of the protoporphyrin IX iron complex, have recently been designed and studied.⁴⁹⁻⁵¹ In their initial findings, Takayashi *et al.* reported that myoglobin reconstituted with iron porphycene, 2,7-diethyl-3,6,12,17-tetramethyl-13,16-bis-carboxyethylporphycenatoiron **1.21**, showed better dioxygen binding affinity and a lower auto-oxidation rate than did the native myoglobin. This porphycene heme **1.21** had two propionate side chains at the 13 and 16 β -pyrrolic positions, which improved the physiological function of the myoglobin.⁵¹

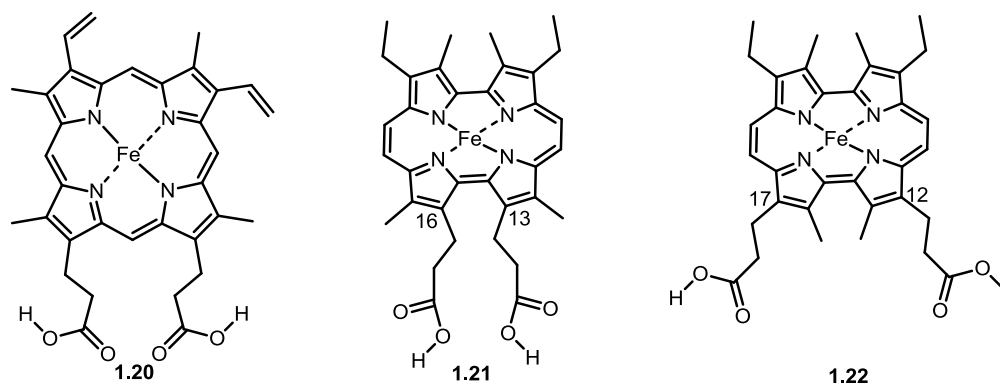


Figure 1.13: Hemes (prosthetic groups).

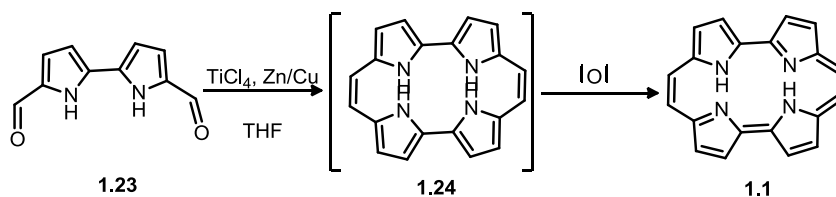
However, the authors later compared the isomeric iron porphycene heme derivative **1.22** substituted with the two propionate side chains at the 12 and 17 β -pyrrolic positions, with that having the substituents at position 13 and 16, and found similar oxygen binding affinity for the

reconstituted myoglobins. Unfortunately, the former was found to have a faster oxygen dissociation.⁵⁰

1.4. Porphycene Syntheses

1.4.1. Synthesis of Symmetrical Porphycenes

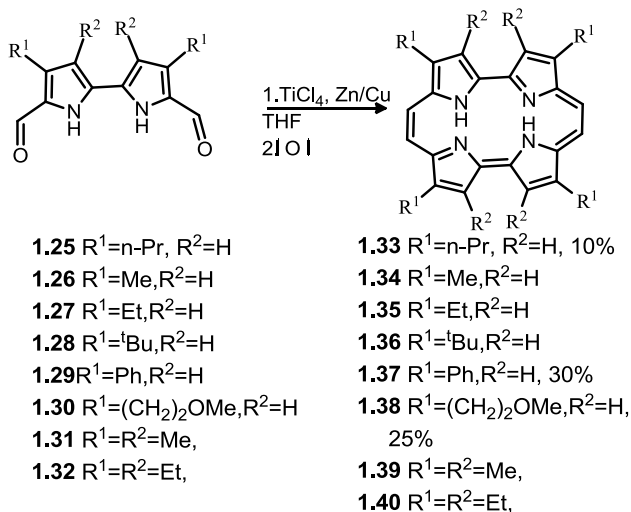
The first porphycene **1.1**, was synthesized by Vogel and coworkers in 1986 in pure form in 2-3% yield by condensing two 5,5'-diformyl-2,2'-bipyrrole **1.23** subunits employing titanium assisted reductive McMurry-type coupling (Scheme 1.5). Two coupling reactions, Ullmann and McMurry are used taking advantage of the symmetry of the expected porphycene adduct. Ullmann coupling provides the requisite 2,2'-bipyrrole moiety **5**.⁵²⁻⁵⁴ However, the dialdehyde synthesis preceding McMurry coupling requires some experimental precautions; thus, pure reagents and anhydrous conditions are essential.⁵⁵ The starting pyrrole substrates can be obtained from classical Knorr pyrrole synthesis^{56,57} or from the Barton-Zard protocol,^{58,59} among other methods that will be discussed in this Dissertation.



Scheme 1.5: First porphycene synthesis.¹

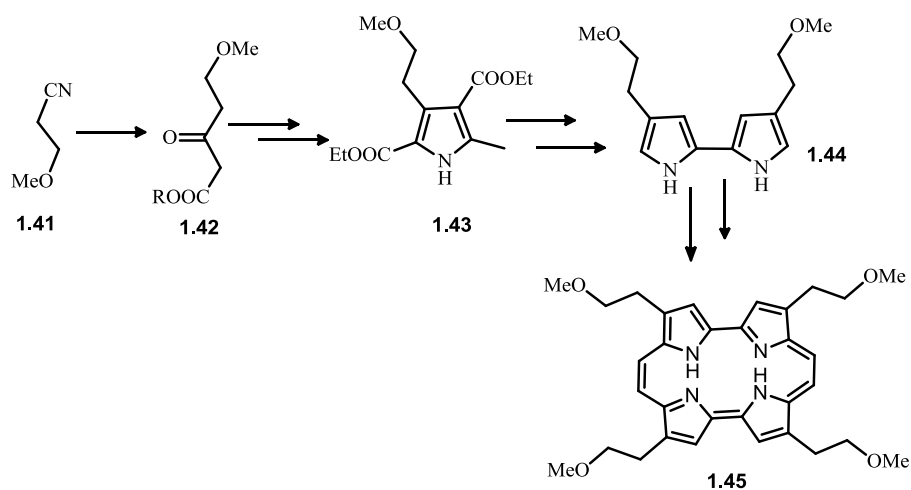
The condensation of the diformylbipyrrole **1.23** is presumed to go through the [20]annulene **1.24** which easily undergoes two-electron oxidation under the given reaction conditions to give an 18π conjugated system, porphycene **1.1**. To date, different porphycene analogues have been synthesized with varied substituents on the β -pyrrolic positions. The choice of the substituent may either be for solubility enhancement³¹ e.g **1.36**, increased conjugation **1.37**, improved synthetic yields⁶⁰ or for tuning the porphycene's chemical properties; for example, fluorescence and rate of metal complexation.⁶¹ Such substituents are usually

incorporated early in the synthesis of pyrrole starting materials^{58,59} and rarely in the late synthetic steps.



Scheme 1.6: Examples of porphycene analogues.⁵⁵

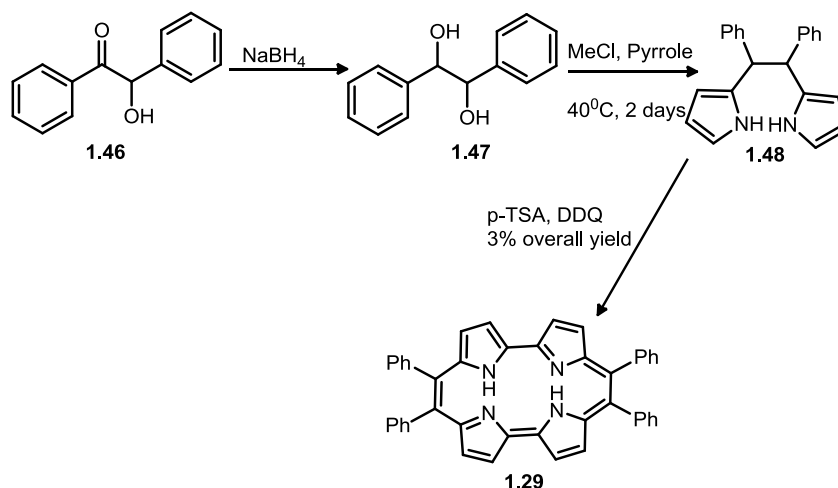
The synthesis of (methoxyethyl)-porphycene **1.38** was accomplished by Richert *et al.* in nine synthetic steps²⁶ starting from the methoxy-nitrile **1.41** which was transformed into a pyrrole by Knorr condensation. Further transformations accessed the tetra-ester bipyrrole **1.44**, a precursor of the (methoxyethyl)-porphycene **1.45** (Scheme 1.7).



Scheme 1.7: Synthesis of (methoxyethyl)-porphycene.²⁶

Srinivasan *et al.* in 2008 synthesized the *meso*-tetraarylporphycene **1.29** isomer with an overall yield of 3% by using an acid-catalyzed oxidative coupling reaction⁶²⁻⁶⁵ of 1,2-dibenzyl-diol

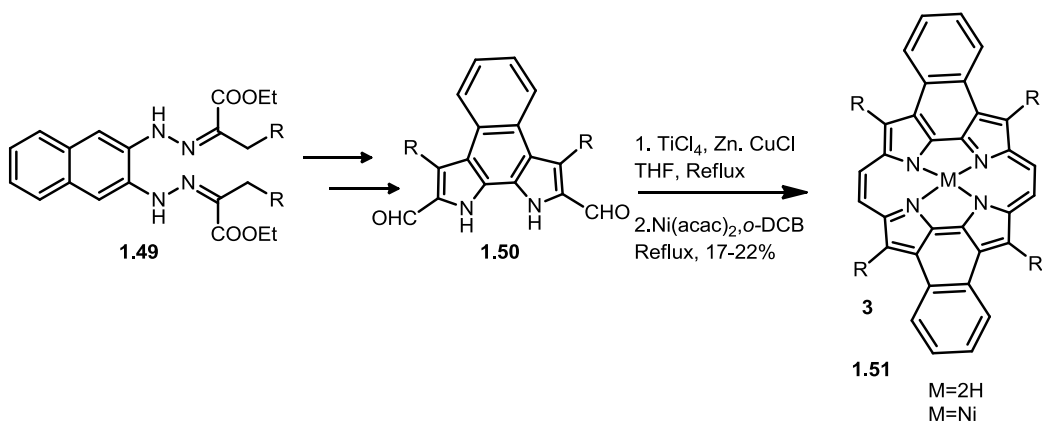
1.47 that was easily synthesized from the benzoin derivative **1.46**.⁶⁶ This is the only recent alternative synthetic methodology to the traditional McMurry coupling reaction developed by Vogel and coworkers, (Scheme 1.7). This synthetic route afforded different porphycene analogues in 3-5% overall yield. The compound has an absorption spectrum with a Soret band at 382 nm and Q-bands between 584 and 653 nm. The placement of the four phenyls at the *meso*-positions led to red shifts of the Soret band of 24 and 9 nm when compared with the first porphycene¹ and *meso*-tetra-*n*-propylporphycene, respectively.



Scheme 1.8: Synthesis of meso-tetraarylporphycene.⁶⁶

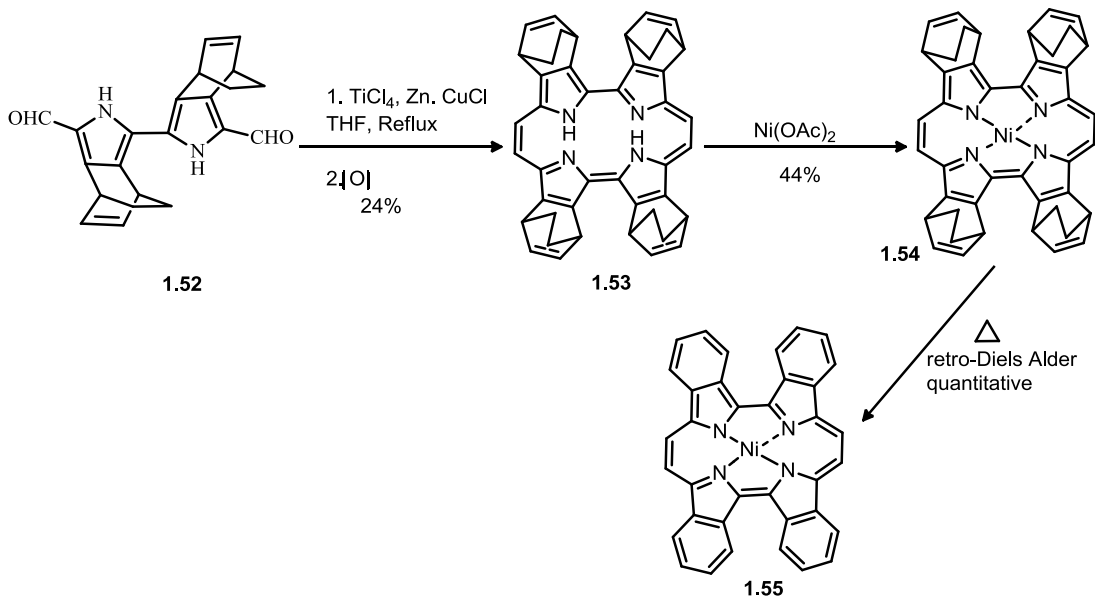
In the same year, 2008, Panda and coworkers described the synthesis of naphthobipyrrole-derived porphycenes **1.51**, from β -alkylated 2,9-diformylnaphthobipyrrole derivatives such as **1.50**, which were prepared easily from bishydrazone **1.49** (Scheme 1.9).⁶⁷ The Panda group complexed their macrocycles with metals such as Zn(II), Cu(II), Ni(II), and Pd(II) and found out that only Ni(II) could be inserted successfully by refluxing the free bases with nickel(II) acetate in the presence of *o*-dichlorobenzene and pyridine. The dinaphthoporphycene absorption spectrum showed bands at 265 nm, attributed to the naphthalene moiety, a porphycene Soret band at 400 nm, and Q-bands at around 715 nm. The

Ni(II) complex showed a general trend of red-shifted Soret bands and blue-shifted Q-bands when compared to the free base uncomplexed porphycene macrocycle.



Scheme 1.9: Synthesis of dinaphthoporphycenes.⁶⁷

In 2009, Yamada *et al.* reported the synthesis, structures, and optical and electrochemical properties of benzoporphycenes **1.53**⁶⁸ (Scheme 1.10). Diformylbipyrrole **1.52** was condensed using activated titanium to give the tetrasubstituted macrocycle **1.53** in 24% yield. Complexation with Ni(II) yielded metalloporphycene **1.54** which afforded β -substituted tetraphenyl nickel porphycene **1.55** after a heat-assisted retro-Diels Alder reaction.

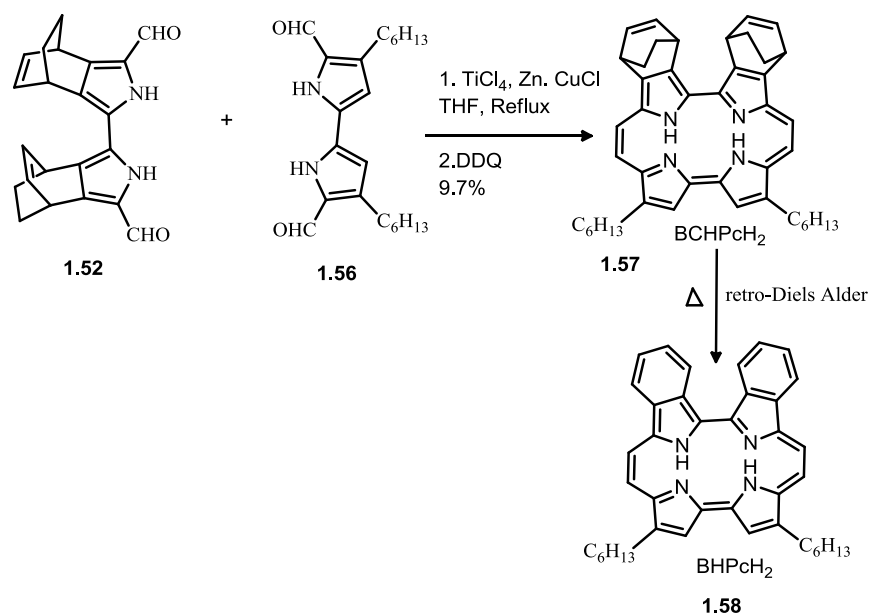


Scheme 1.10: Synthesis of benzoporphycenes.⁶⁸

Different porphycene metal analogues⁶⁹⁻⁷¹ and conjugated derivatives have been made. The basis for their synthesis is to enable their applications in the biological field.

1.4.2. Synthesis of Asymmetric Porphycenes

Bicyclo-[2.2.2]octadiene (BCOD)-fused porphycene was prepared by Kobayashi and co-workers (Scheme 1.11). The asymmetrical macrocycle, BHPcH₂ **1.57**, was obtained in 9.7% yield by a McMurry condensation reaction between two different β -substituted diformyl-bipyrroles **1.52** and **1.56**.⁶⁸ The reaction afforded dibenzoporphycene (BHPcH₂) **1.58** quantitatively after a retro-Diels-Alder reaction of the BCOD-fused BHPcH₂ porphycene **1.57**.⁶⁸



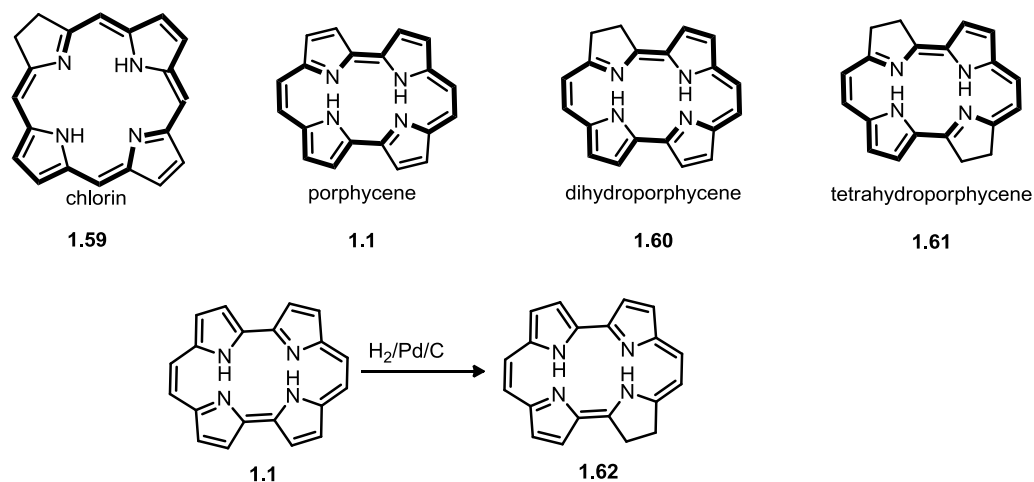
Scheme 1.11: Synthesis of asymmetric dibenzoporphycene **1.58**.⁶⁸

1.4.3. Reactions of Porphycenes

1.4.3.1. Hydrogenation of Porphycenes^{55,72}

The conjugation pathway of chlorin **1.59** has 18 π electrons that enables its aromatic character. The porphycene macrocycle and its derivatives also have the 18 π electron pathway which is similar to chlorin. Catalytic hydrogenation with hydrogen gas selectively reduces pyrrolic double bonds to give sigma bonds. This leads to formation of either 2,3-dihydroporphycene **1.60** or 2,3,12,13-tetrahydroporphycene **1.61**.⁷² This is a proof for the 18 π

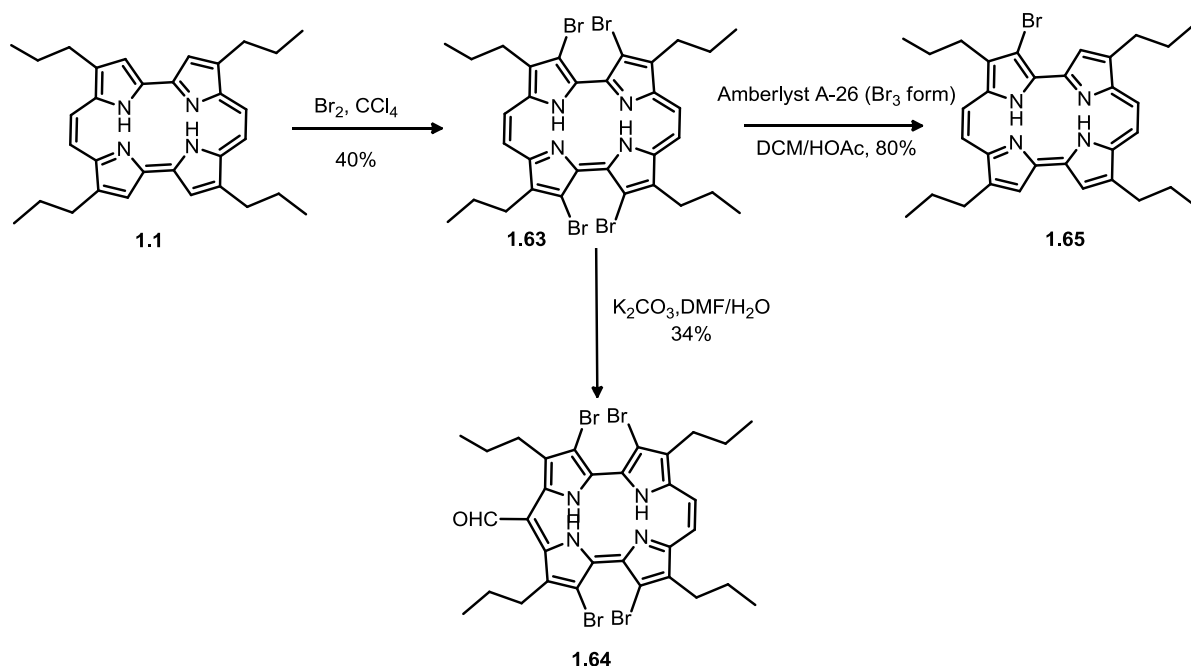
electron pathway, whose conjugated double bonds are not affected by the hydrogenation reaction.



Scheme 1.12: Chlorin and hydrogenated molecular structures of porphycene derivatives.

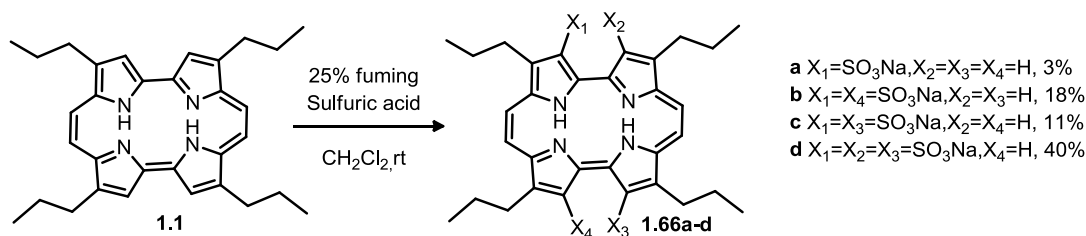
1.4.3.2. Electrophilic Aromatic Substitution in Porphycenes

Porphyrins are aromatic. Electrophilic substitution has been used to understand the pathway of π -electrons delocalization in porphyrins. Generally, electrophilic substitution occurs at the *meso*- rather than the *beta*- positions of the porphyrin macrocycle.⁷³ In contrast, porphycenes undergo electrophilic substitution at the *beta*- positions before the *meso*-positions. 2,7,12,17-Tetra-*n*-propylporphycene **1.1** can be tetra-brominated with bromine in carbon tetrachloride. Electrophilic substitution occurs at the β -pyrrolic positions to afford 3,6,13,16-tetrabromo-2,7,12,17-tetrapropylporphycene **1.63**. When the tetrabromo- adduct was heated in a basic DMF/water (7:1) solvent mixture, at 120 °C, it contracted to give isocorrole aldehyde **1.64**. Such a porphycene-isocorrole contraction has not been demonstrated in porphyrins.⁷⁴ 3-Bromo-2,7,12,17-tetra-*n*-propylporphycene **1.65** can also be synthesized by reacting 2,7,12,17-tetra-*n*-propylporphycene with bromine supported on a polymer such as Amberlyst A-26 (Br₃ form)⁷⁵ in acidic media (Scheme 1.13).⁷⁴



Scheme 1.13: Electrophilic substitution on porphycenes and ring contraction.⁷⁴

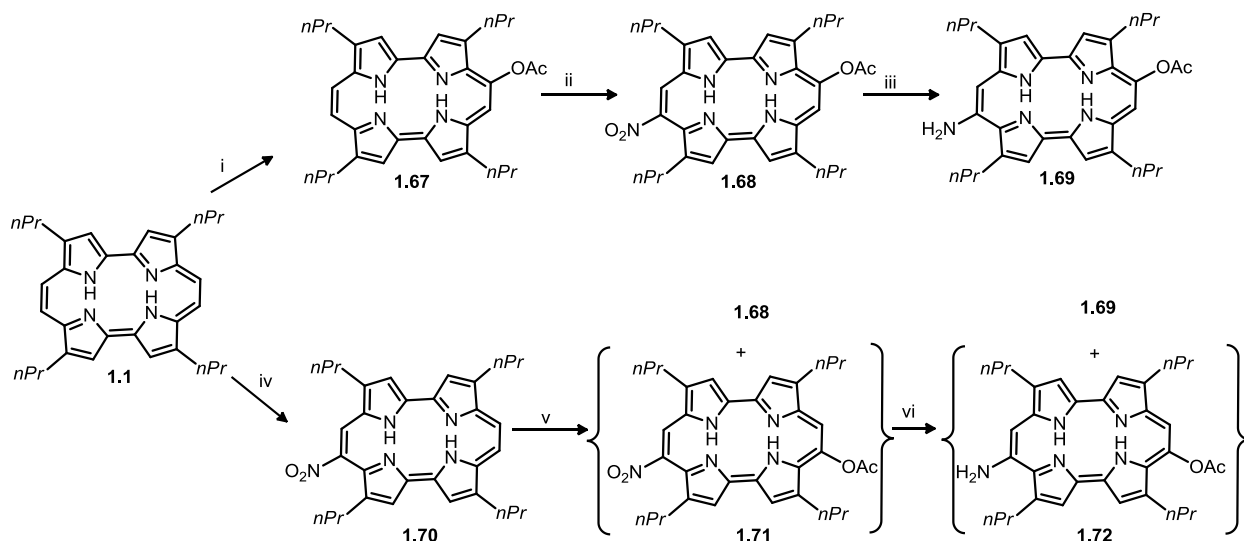
Mono-, di, and tri- sulfonated porphycenes **1.66** can also be prepared by electrophilic substitution. This is achieved by reacting a CH_2Cl_2 solution of 2,7,12,17-tetra-n-propylporphycene **1.1** with 25% fuming sulfuric acid.⁷⁶



Scheme 1.14: Sulfonation of porphycene **1.1**.

Just very recently, Taneda *et al.* reported the synthesis of *meso*-disubstituted asymmetric porphycenes. They demonstrated the electrophilic substitution reactions of a typical porphycene **1.1** by nitration and acetylation reactions. Nitration was accomplished using silver nitrate, and occurred regio-selectively at carbon-19. Acetylation with lead(IV) tetra-acetate occurred either at carbon-19 or -20 of porphycene **1.70** providing a 1:1 product mixture of **1.68** and **1.71**. These results were explained using DFT calculations of **1.70** which showed the

presence of an equal population of vacant orbitals at carbon-19 and -20 in the LUMO. However, when the acetylated porphycene **1.67** was nitrated, only the *trans* isomer was obtained. DFT computational analysis of **1.67** using UB3LYP/6-31G(d,p) level revealed that the HOMO largely occupies the carbon-19 site. The nitro-group was then reduced to an amine, using tin(II) chloride dihydrate, in acceptable yields.⁶⁶



Scheme 1.15: Electrophilic substitution of porphycene **1.1**: Reagents and conditions: i) $\text{Pb}(\text{CH}_2\text{COO})_4$, THF- CH_2Cl_2 , reflux, 30%; ii) AgNO_3 , $\text{CH}_3\text{COOH}-\text{CH}_2\text{Cl}_2$, 80% iii) $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$, pyridine, 90 °C, 59% iv) AgNO_3 , $\text{CH}_3\text{COOH}-\text{CH}_2\text{Cl}_2$, 60 °C, 85% v) $\text{Pb}(\text{CH}_2\text{COO})_4$ THF- CH_2Cl_2 , reflux, 48% vi) $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$, pyridine, 90 °C

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CHAPTER 2: SYNTHESIS OF 5,5'-DIVINYLBIPYRROLES, TOWARDS PORPHYCENE SYNTHESIS BY OLEFIN METATHESIS

2.1. Introduction

2.1.1. Background of Olefin Metathesis Catalysts:

Olefin metathesis is the exchange, or transposition, of olefinic carbenes to form new alkenes. Grubbs catalysts have been widely used in ring opening (ROM), ring opening polymerization (ROMP), cross metathesis (CM), and ring-closure (RCM) metathesis reactions. Ring-closure olefin metathesis has been applied in the synthesis of medium and large sized rings from acyclic diene precursors. Macrocyclization by use of Grubbs metathesis is highly efficient with substrates with or without conformational constraints.^{2,3}

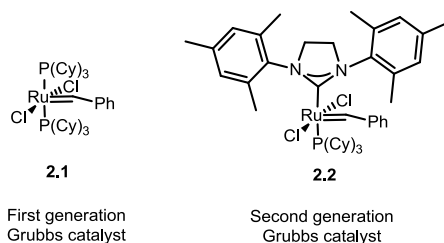


Figure 2.1: First and second generation Grubbs catalysts.

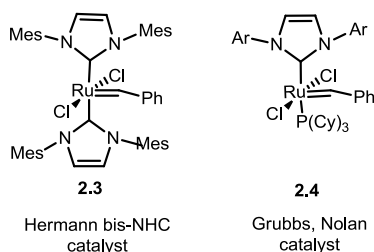


Figure 2.2: Initial N-heterocyclic carbenes (NHC) based metathesis catalysts.

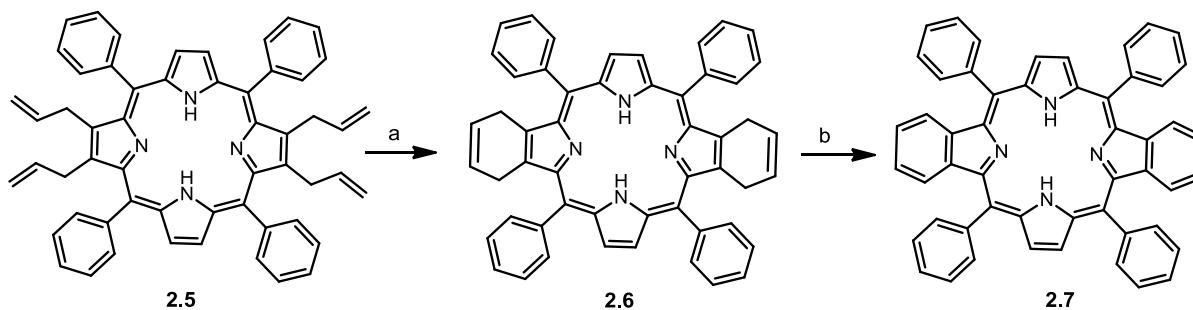
First generation Grubbs catalyst **2.1** was synthesized in 1995.⁴ The first generation catalysts are known not to be effective in ring closing metathesis and cross metathesis of some electron deficient alkenes. In 1998, Hermann *et al.* replaced both phosphine ligands of the first generation catalyst with unsaturated alkyl substituted N-heterocyclic carbenes (NHCs).⁵ This modification led to improved catalytic activity (Figure 2.2).

Shortly afterwards, Grubbs⁶ and Nolan^{7,8} independently modified the Herrmann catalyst by including aryl substituents on the N-heterocycles carbenes in place of the alkyl substituents. The improved turn-over catalytic activity prompted them to try mesityl-groups as substituents on saturated NHC. This led to the discovery of Grubbs second-generation catalyst **2.2** which was found to be very active even on sterically crowded alkenes, yet easy to handle and tolerant to other many functional groups like amides, esters, aldehydes, ketones and water.⁹ However the second generation catalysts suffered low reaction initiation during catalysis (Figure 2.1).

This problem was solved by replacing the phosphine ligand in the second generation catalyst with an electron donating group, like pyridine.¹⁰ With these improved catalyst properties, we were motivated to use it on 5,5'-divinyl-bipyrrole **2.8** for olefin metathesis ring closure to hopefully obtain a porphycene macrocycle **2.10** after oxidation.

2.1.2. Recent application of RCM.

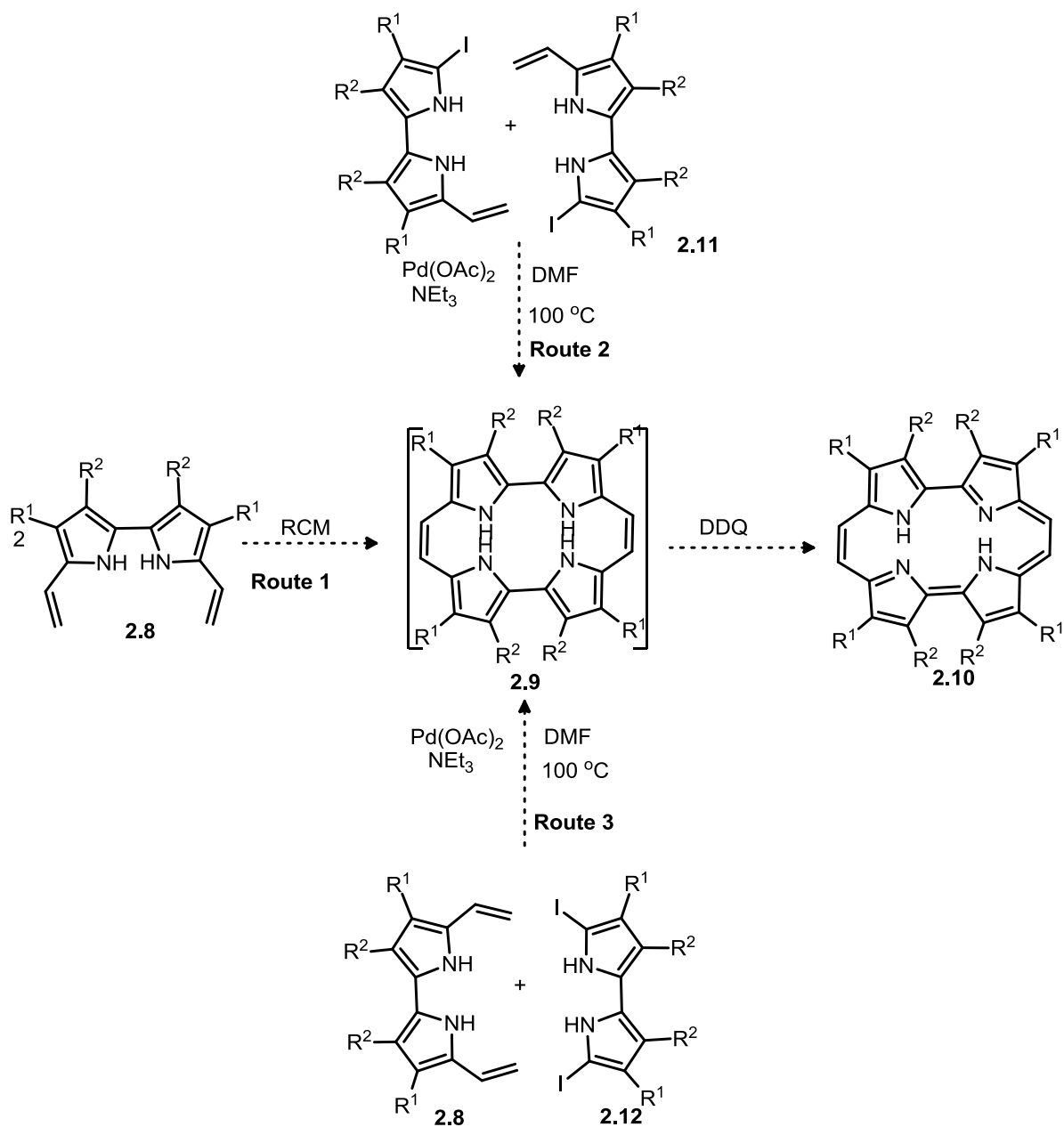
Scheme 2.1 shows recently synthesized benzoporphyrin **2.7** by ring-closure olefin metathesis as reported by Jiao *et al.*¹¹



Scheme 2.1: Metathesis followed by oxidation to generate dibenzoporphyrin **2.7**. Reaction conditions: a) 10% Grubbs' 2nd generation catalyst, dry DCM, 40 °C; b) DDQ, THF.

2.2. Syntheses

The planned route for the synthesis of the porphycene macrocycle from 5,5'-divinylbipyrroles is as shown below (Scheme 2.2).



Scheme 2.2: Proposed porphycene synthesis plan.

The synthesis of porphycene macrocycle could be attempted by the cross-metathesis of 5,5'-divinylbipyrrole **2.8** followed by ring-closure metathesis, and air or DDQ oxidation. Compound **2.8** can also be coupled to the 5,5'-diiodobipyrrole derivative **2.12** under Heck conditions; in this way symmetrical porphycenes could be accessed. Alternatively, unsymmetrical bipyrrole **2.11** could be coupled to itself under the same Heck coupling

conditions.¹² In the schematic plan above, 5,5'-divinylbipyrrole **2.8** was to be obtained from Wittig reactions performed on 5,5'-diformylbipyrrole **2.13**.



Scheme 2.3: Proposed synthesis of 5,5' divinylbipyrrole **2.8**.

It was found important to test our hypothesis by subjecting 5-formylpyrrole **2.19** to a Wittig reaction. The synthesis of 5-formylpyrrole **2.19** was effected starting from t-butyl 3,4,5-trimethylpyrrole-2-carboxylate **2.17**. Tetra-substituted pyrrole **2.17** was synthesized according to standard Johnson conditions.^{13,14} t-Butyl oximinoacetate **2.15**, was obtained by the nitrosation reaction of t-butyl acetoacetate **2.14** with sodium nitrite in acetic acid. t-Butyl oximinoacetate **2.15** was then subjected to a condensation reaction with 3-methyl-2,4-pentanedione **2.16** in the presence of zinc powder and acetic acid at 70 °C to provide t-butyl 3,4,5-trimethylpyrrole-2-carboxylate **2.17** in 37% yield. Pyrrole **2.17** was then decarboxylated in TFA to provide α -free pyrrole **2.18** as a brown unstable oil which easily decomposed in air. For this reason, the pyrrole product was taken directly to the formylation step. After Vilsmeier-Haack formylation¹⁵ of pyrrole **2.18**, 5-formylpyrrole **2.19** was isolated in 20% yield over two steps from the decarboxylation reaction on **2.17** (Scheme 1). Figure 2.3 shows the X-Ray structures of pyrrole carboxylate **2.17** and 5-formylpyrrole **2.19**.

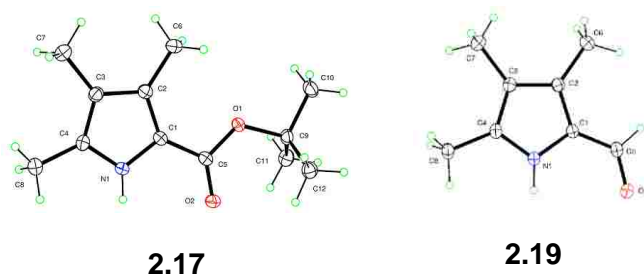
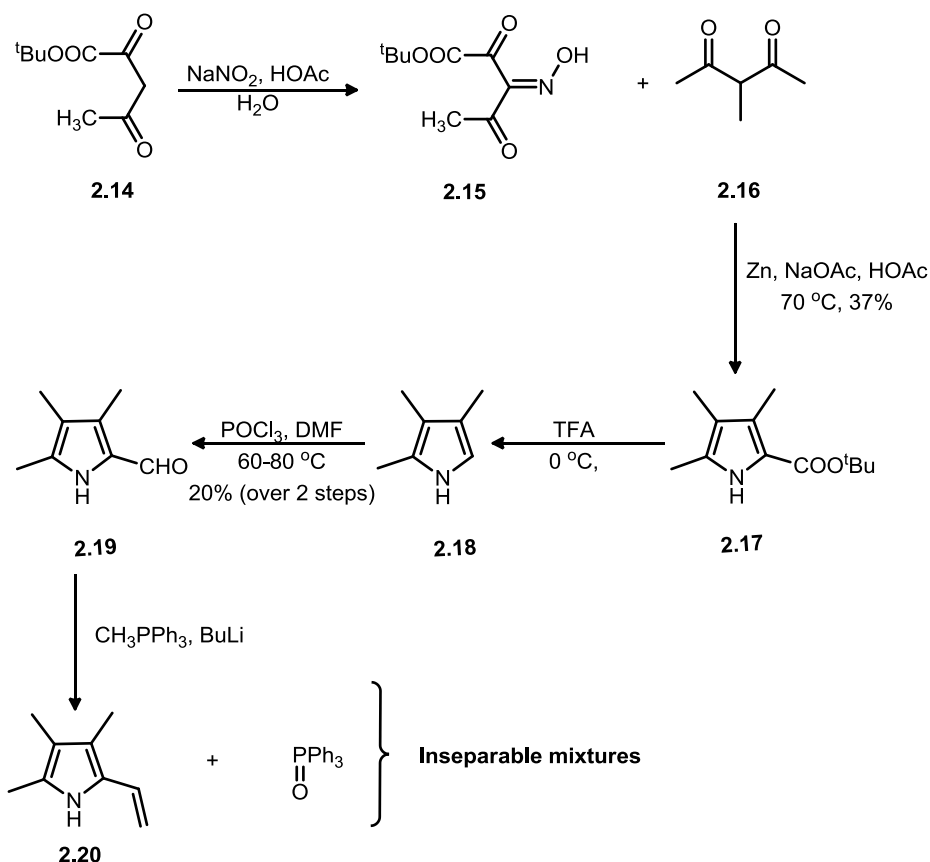


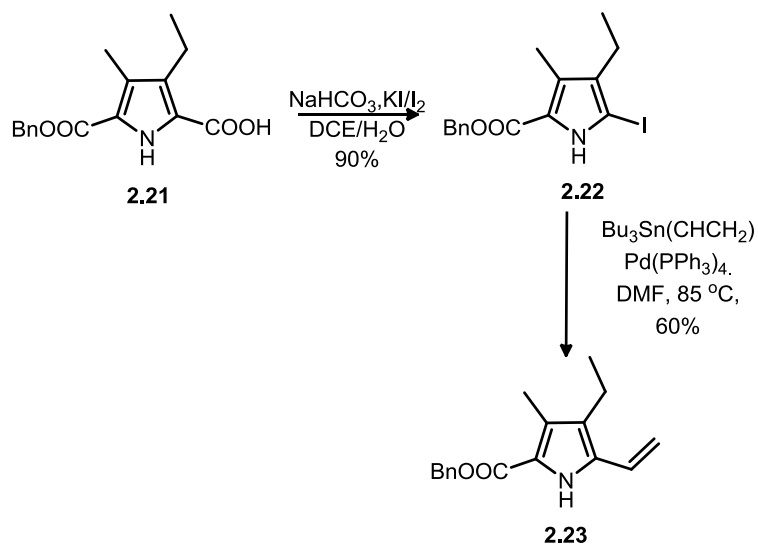
Figure 2.3: X-Ray structures of t-butyl ester pyrrole **2.17** and formyl pyrrole **2.19** with 50% ellipsoids.



Scheme 2.4: Synthesis of 5-vinylpyrrole **2.20**.

A Wittig reaction on 5-formylpyrrole **2.19** gave 5-vinylpyrrole **2.20** which was inseparable from the triphenylphosphine oxide by product. All adjustments of eluting solvent mixtures on the column did not help in the separation of the crude material. With this outcome, a different reaction to install the vinyl- substituent was necessary, before olefin metathesis could be tried with the vinylpyrrole.

Iodopyrrole starting material was therefore targeted for Stille coupling to make the 5-vinylpyrrole. The available acid pyrrole **2.21** was subjected to decarboxylative iodination to afford 5-iodopyrrole derivative **2.22** in 90% yield. Iodopyrrole **2.22** was then subjected to Stille coupling conditions using tributyl(vinyl)tin, and Pd(0) to provide 5-vinylpyrrole **2.23** in 60% yield. The vinylpyrrole was crystallized easily in dichloromethane/n-hexane solvent mixture and its X-Ray structure was determined (Figure 2.4).



Scheme 2.5: Synthesis of 5-vinylpyrrole **2.23**.

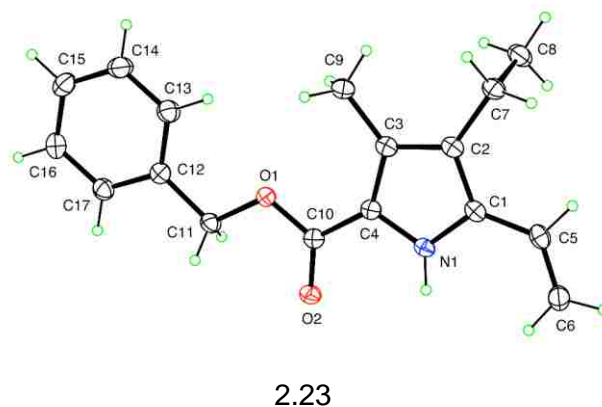
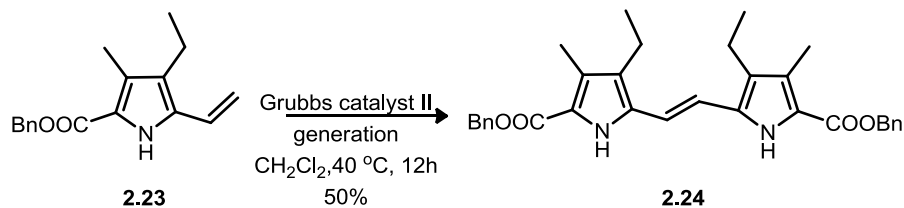
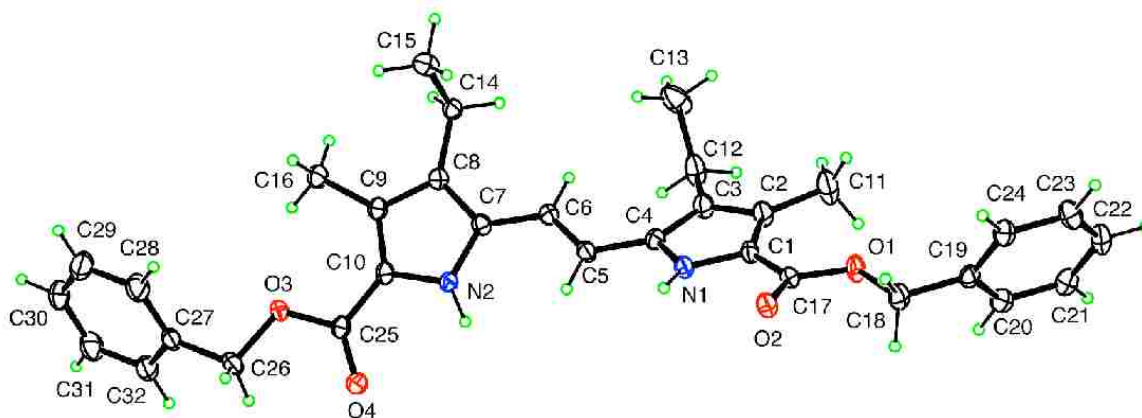


Figure 2.4: X-Ray crystal structure of 5-vinylpyrrole **2.10** with 50% ellipsoids.

To test for olefin metathesis, 5-vinylpyrrole **2.23** was exposed to olefin metathesis reaction conditions. In this case, Grubbs second generation catalyst was used. The metathesis reaction was conducted overnight in dichloromethane at room temperature to yield *trans*-1,2-bis(dipyrrolyl)ethene **2.24** in 50% yield. The X-Ray structure is shown below (Figure 2.5).



Scheme 2.5: Synthesis of *trans*-1,2-bis(dipyrrolyl)ethene **2.24**.

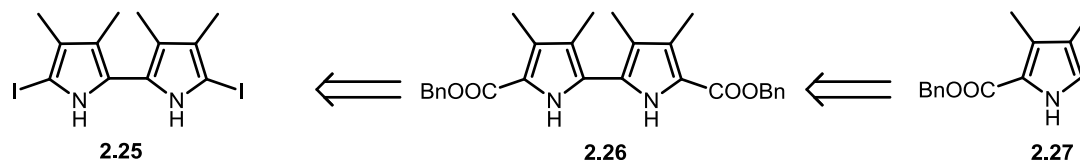


2.24

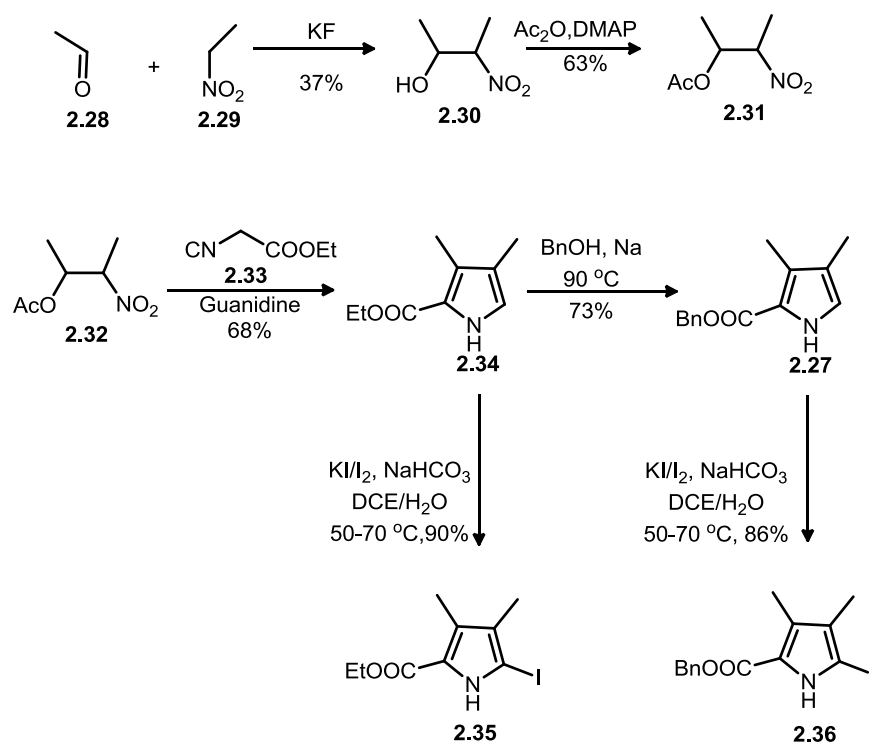
Figure 2.5: X-Ray crystal structure of *trans*-1,2-bis(dipyrrolyl)ethene **2.24** with 50% ellipsoids.

After confirming that the vinyl-group can be introduced on the pyrrole, and also olefin metathesis can be effected, the synthesis of 5,5'-di-iodobipyrrole **2.25** was started. The retrosynthetic plan below was followed (Scheme 2.6). Bipyrrole **2.25** could be obtained from bipyrrole 5,5'-diester **2.26** which is made from the Ullmann coupling of the iodo-derivative of pyrrole **2.27**.

The synthesis began by making benzyl 3,4-dimethylpyrrole-5-carboxylate **2.27**, whereby, the Barton-Zard protocol¹⁶ was followed. This involves an initial Aldol-Henry reaction between acetaldehyde **2.28** and nitroethane **2.29** to afford 2-nitro butan-3-ol **2.30**. The alcohol obtained was then acetylated with acetic anhydride and subjected to a Michael cyclization reaction with ethyl isocyanoacetate **2.33** under basic conditions to give the expected α -free pyrrole carboxylate **2.34** in 63% yield. Ethyl ester pyrrole **2.34** was then trans-esterified by refluxing with sodium in benzyl alcohol¹⁷ to afford benzyl ester pyrrole **2.27** in 73% yield.

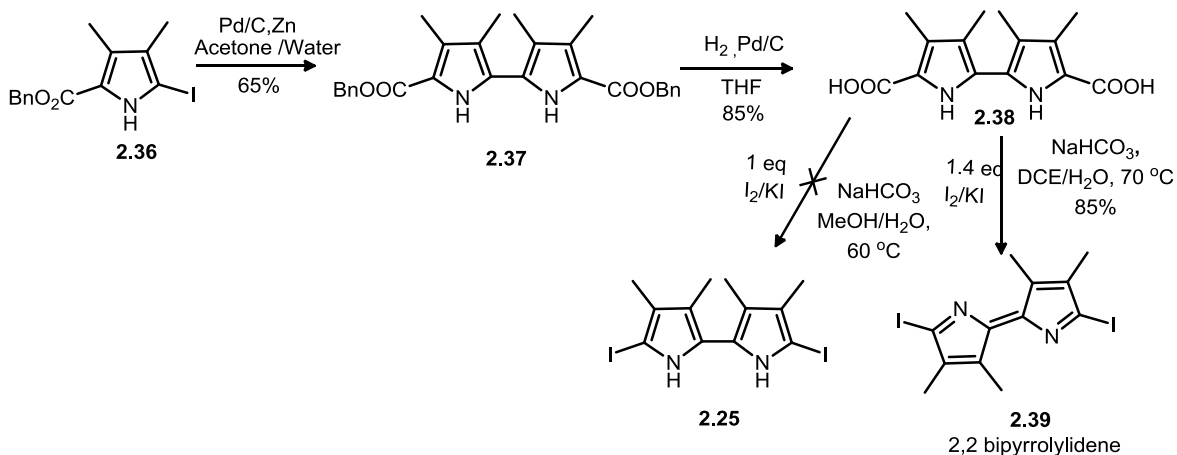


Scheme 2.6: Retrosynthesis of 5,5'-di-iodobipyrrole **2.25**.

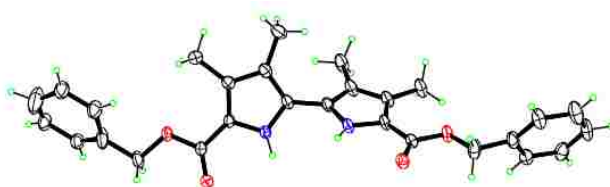


Scheme 2.7: Synthesis of 5-iodopyrroles **2.35** and **2.36**.

The two α -free ester pyrrole carboxylates were then iodinated quantitatively using an iodine/potassium iodide mixture by refluxing in methanol or dichloromethane and quenching with saturated sodium thiosulfate. This afforded 5-iodopyrroles **2.35** and **2.36** in 90 and 86% yields, respectively. (Scheme 2.7). 5-Iodopyrrole **2.36** was then coupled to itself using zinc and a palladium/carbon catalyst mixture in a 1:1 biphasic solvent mixture of acetone and water to afford the 5,5'-bis(benzyloxycarbonyl)-3,3',4,4'-tetramethyl-2,2'-bipyrrole **2.37** in 65% yield.¹⁸ The bipyrrole benzyl esters were then quantitatively debenzylated by catalytic hydrogenolysis using Pd/C to afford the diacid bypyrrole **2.38** which was then decarboxylatively iodinated with an iodine/potassium iodide mixture, by refluxing in 1,2-dichloroethane to give 2,2'-bipyrrolylidene **2.39**.



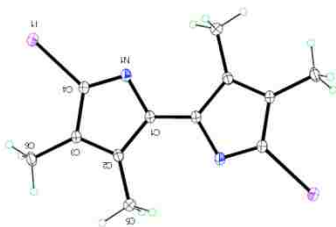
Scheme 2.8: Attempted synthesis of 5,5'-di-iodobipyrrole **2.25**.



2.37

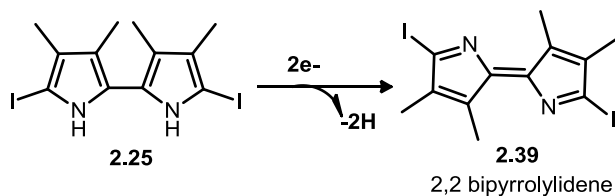
Figure 2.6: X-Ray crystal structure of 5,5'-bis(benzyloxycarbonyl)-bipyrrole **2.37** with 50% ellipsoids.

This reaction always failed, and only twice did the byproduct 2,2'-bipyrrolylidene **2.39** form, once in 85% yield (Scheme 2.8). The byproduct **2.39** was probably formed from the over-oxidation of the expected 5,5'-di-iodopyrrole product **2.25** by iodine. The scheme below suggests a possible oxidation reaction pathway.



2.39

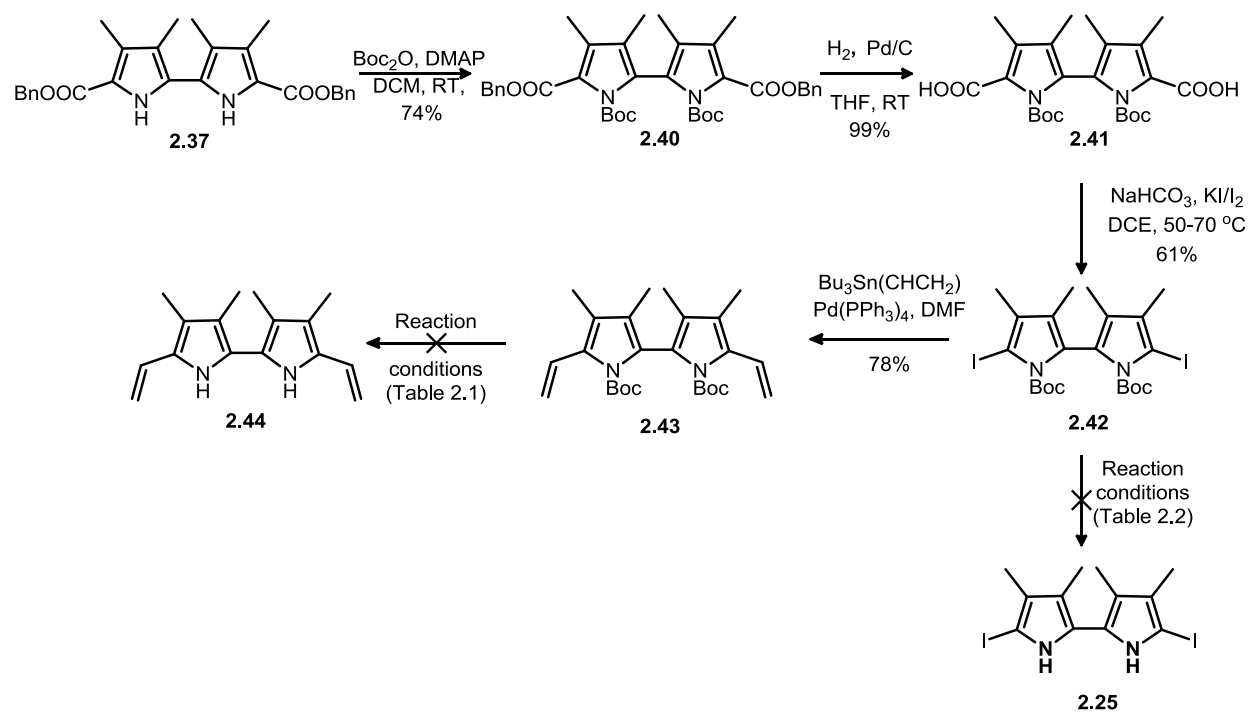
Figure 2.7: X-Ray crystal structure of 2,2'-bipyrrolylidene **2.39** with 50% ellipsoids.



Scheme 2.9: Oxidation of 5,5'-di-iodobipyrrole **2.25**.

From Scheme 2.9, one can deduce that protection of the pyrrolic-NH would be necessary to avoid oxidation of our intended di-iodobipyrrole **2.25**. The NH- of bipyrrole **2.37** were therefore protected with t-butyl esters before the next steps were performed. This was accomplished by reacting **2.37** with di-tert-butyl dicarbonate in the presence of DMAP, at room temperature in dichloromethane. The N-protected dibenzyl ester bipyrrole **2.40** was isolated in 74% yield.

Catalytic debenzylation of the protected bipyrrole **2.40** in the presence of Pd/C and hydrogen gas provided diacid **2.41** in quantitative yield. Decarboxylative iodination of **2.41** afforded 5,5'-di-iodo-N-boc-bipyrrole **2.42** in 61% yield. Bipyrrole **2.42** was then subjected to double Stille coupling conditions in DMF, Pd(PPh₃)₄, and tributyl(vinyl)tin as the vinyl source.¹⁹ 5,5'-Di-vinyl-N-boc-bipyrrole **2.43** was obtained in 78% yield (Scheme 2.10). N-Boc deprotection of the divinylbipyrrole **2.43** with TFA was unsuccessful as it only gave decomposed insoluble products (red sticky oil) that could not be characterized by NMR. Neither did ESI analysis show the expected mass. The acidic deprotection parameters with TFA were varied including reaction time duration, or temperature but the same undesired insoluble unknown products were obtained (Table 2.1 entry 1-3). Deprotection with phosphoric acid was not successful as only the starting material was isolated (entry 6). Bipyrrole **2.43** in ethanolic hydrochloric acid was also heated at 40 °C for 10 minutes but no starting material or product was isolated.



Scheme 2.10: Synthesis of 5,5'-vinyl-N,N'-diboc-bipyrrole **2.43**

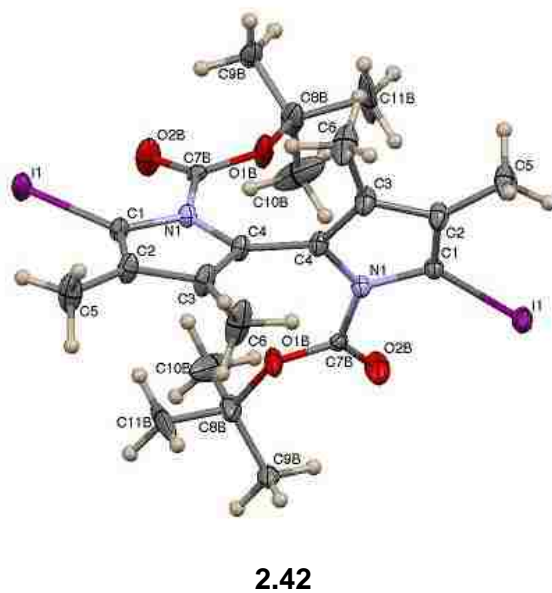
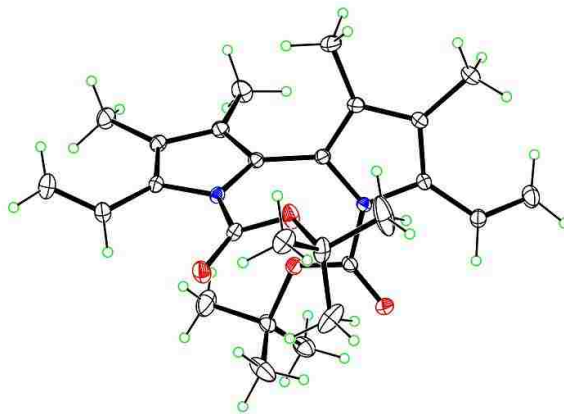


Figure 2.8: X-Ray crystal structure of 5,5'-di-iodo-N-boc-bipyrrole **2.42** with 50% ellipsoids.



2.43

Figure 2.9: X-Ray crystal structure of 5,5'-vinyl-N-boc-bipyrrole **2.43** with 50% ellipsoids.

The above deprotection conditions were harshly acidic. Mild and basic N-Boc deprotection conditions were therefore tried next. No deprotection was effected when mild acidic conditions using K-10 clay were applied (entry 7). Under basic conditions (entry 8-11), the starting material was recovered in almost quantitative yields. Decarboxylative N-Boc deprotection in ethylene glycol and potassium hydroxide did not yield any product, other than decomposed insoluble material (entry 11). Heating of bipyrrole **2.43** under vacuum with increasing temperature to 150 °C also failed. Only blackened insoluble products were obtained after heating (Table 2.1, entry 14).

Table 2.1: Reaction conditions for the attempted N-Boc deprotection of 5,5'-divinyl-N-Boc bipyrrole **2.43**.

Deprotection reagents		Reaction Temperature (°C)	Time	Product
1.	TFA	25 °C	2 min	insoluble product
2.	TFA	0 °C	2 min	insoluble product
3.	TFA/DCM (1:1)	0 °C	2 min	insoluble product
4.	85% H ₃ PO ₄ ,	25 °C, RT	2 h	Unknown products
5.	K ₃ PO ₄ ·H ₂ O(20mol%)	65 °C (reflux- MeOH)	15 min	Starting material
6.	Ethanol, HCl	40 °C	10 min	Unknown products

(Table 2.1 continued)

	Deprotection reagents	Reaction Temperature (°C)	Time	Product
7.	Montmorillonite K10 Clay ²⁰	85 °C (reflux DCE)	4 h	Starting material
8.	TBAF ²¹	80 °C	12 h	Starting material
9.	Na ₂ CO ₃ / DME ²²	85 °C	24 h	Starting material
10.	Cs ₂ CO ₃ , Imidazole	70 °C	24 h	Starting material
11.	NaOMe/MeOH ²³	60 °C	2 h	Starting material
12.	Ethylene glycol, KOH	Ramp-150 °C	1 h	decomposition
13.	CAN/MeCN ²⁴ oxidizer	80 °C	2 h	Unknown products
14.	No reagent ²⁵	Ramp-150 °C	25 min	decomposition

Since the vinyl group on bipyrrrole **2.43** seemed to be acid sensitive, deprotection of 5,5'-di-iodo-N-Boc bipyrrrole **2.42** was subjected to some of the deprotection conditions (Table 2.2) that were tried on 5,5'-divinyl-N-Boc bipyrrrole **2.43**.

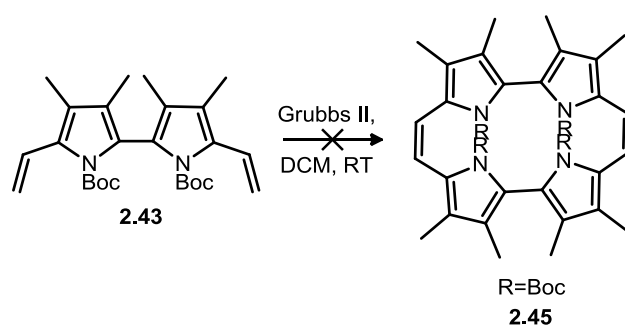
Table 2.2: Reaction conditions for the attempted N-Boc deprotection of 5,5'-di-iodo-N-Boc bipyrrrole **2.42**.

	Deprotection reagents	Reaction Temperature (°C)	Time	Product
1.	Br ₂ , H ₂ O ²⁶	0 °C	5 min	No starting material, Unknown brown solid
2.	K ₂ CO ₃ (5 eq), MeOH ²⁷	50 °C	2 h	Starting material
3.	K ₃ PO ₄ .H ₂ O (20mol %)	Microwave (120 °C)	2 min	Starting material

Attempted deprotection of **2.42** in the presence of liquid bromine was unsuccessful, no products could be identified (Table 2.2 entry 1). Refluxing a methanol solution of **2.42** in the presence of potassium carbonate failed as only the starting material was recovered (Table 2.2 entry 2). All of the deprotection acidic conditions tried led to decomposed material, while the

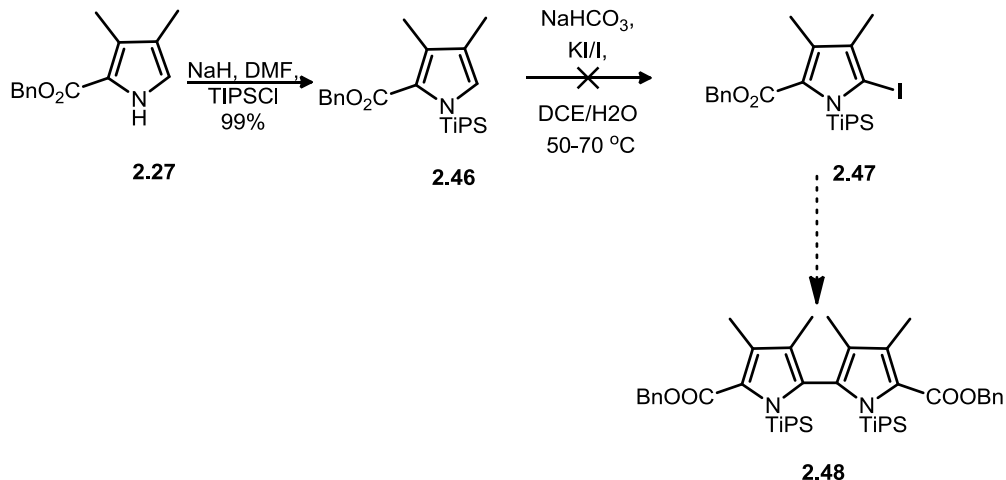
basic conditions were not effective as they only allowed the recovery of the starting material. 5,5'-Divinyl-N-Boc bipyrrrole **2.43** therefore seemed to be stable under basic conditions but unstable under acidic conditions. Polymerization of the terminal vinyl groups in acidic conditions might have led to insoluble products. The same side reaction could have taken place when the sample was heated at elevated temperatures.

Nevertheless, olefin metathesis of 5,5'-divinyl-N-Boc bipyrrrole **2.43** was attempted using Grubbs 2nd generation catalyst since it is known to be effective in ring closing metathesis when compared to the first generation catalysts.²⁸ After a daylong reaction time of the mixture in CH₂Cl₂, no change on TLC analysis was observed. The reaction was therefore stopped and the starting material recovered. The probable hindrance to the reaction would be steric hindrance between the bulky NBoc protecting group and the catalyst (Scheme 2.11).



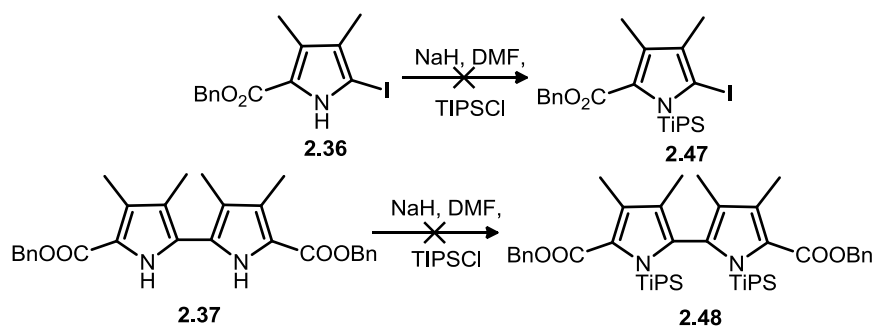
Scheme 2.11: Attempted RCM on 2.43.

The deprotection of the NBoc protecting group was therefore an insurmountable challenge. A different protecting group was therefore sought. The protection of pyrrolic NH was attempted with the tri-isopropyl silyl group because of its ability to be deprotected under basic conditions which would not affect the vinyl groups to cause sample decomposition. This strategy involves deprotonation of pyrrolic NH- using sodium hydride followed by subsequent protection of the nitrogen using triisopropyl chloride to afford NTiPS- protected pyrrole **2** in 99% yield (Scheme 2.12).²⁹



Scheme 2.12: Attempted synthesis of bipyrrrole **2.48**.

Iodination was then attempted on the protected pyrrole **2.46**, but this was not successful. The protecting group might have deactivated the nucleophilic nature of the pyrrole towards electrophilic reaction with iodine. Attempted NH-protection of 2-iodopyrrole **2.36** and 5,5'-bis(benzyloxycarbonyl)-bipyrrrole **2.37** with TIPS also failed. This might be because of the bulkiness of the protecting group (Scheme 2.13).



Scheme 2.13: Attempted TIPS- NH-protection of 2-iodopyrrole **2.36** and bipyrrrole **2.37**.

2.3. Future Work.

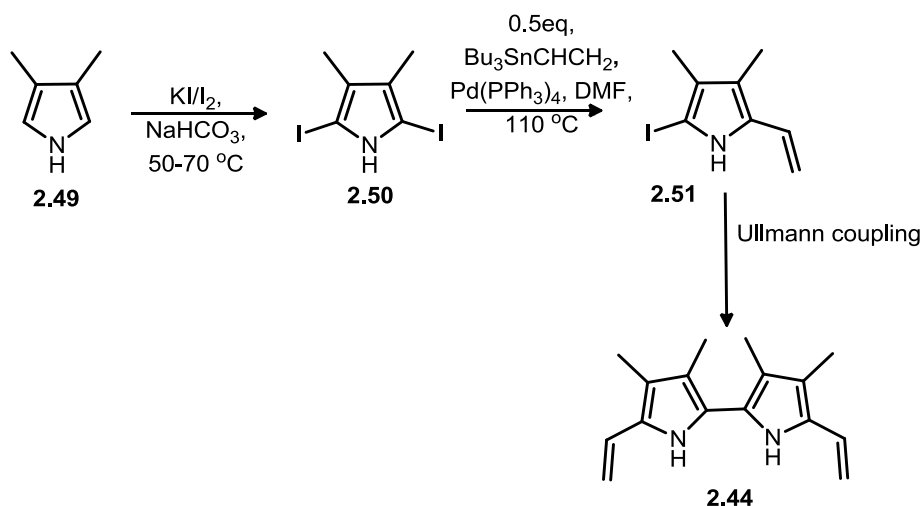
a) Proposed syntheses of 5,5'-divinylbipyrrrole **2.44**.

The synthesis of 5,5'-divinyl-bipyrrrole **2.44** is to be synthesized starting from 3,4-dimethylpyrrole **2.49**. 3,4-Dimethylpyrrole could be di-iodinated to provide di-iodopyrrole **2.50**

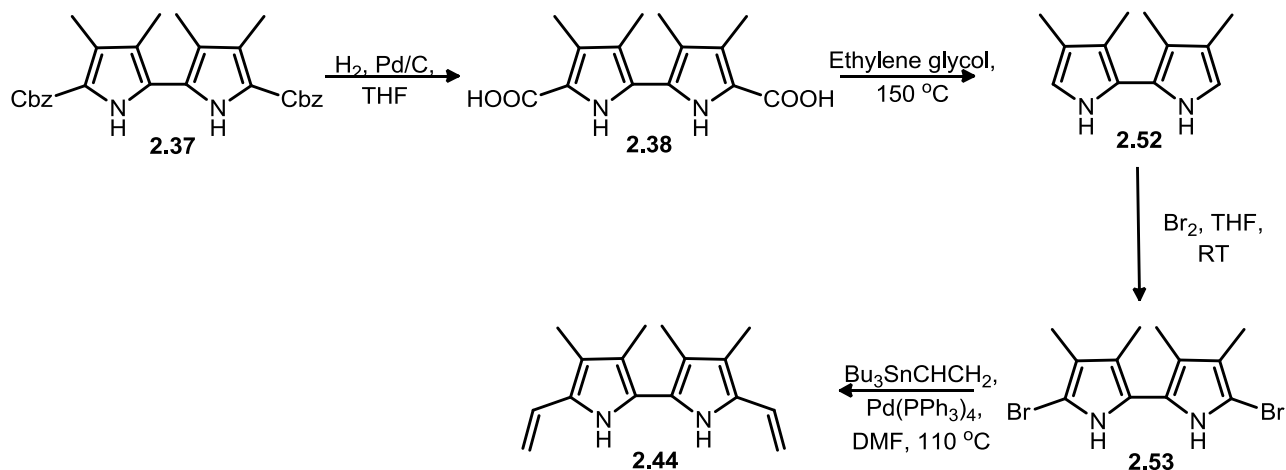
which could be mono-vinylated under Stille coupling conditions, followed by Ullmann coupling (Scheme 2.14).

b) Optimization of the synthesis of 2,2'-bipyrrrolylidine **2.39** is required as it is a new compound. The reaction reproducibility is not assured and so iodination conditions, change of solvent, and work-up procedures are to be modified to achieve reproducible results.

More chemical reactions are to be studied on 2,2'-bipyrrrolylidine **2.39**.



Scheme 2.14: Suggested synthesis of 5,5'-divinylbipyrrole **2.44**.



Scheme 2.15: Suggested synthesis of 5,5'-divinylbipyrrole **2.44**.

2.4. Experimental procedures

2.4.1. t-Butyl oximinoacetate (2.15)

t-Butyl acetoacetate **2.14** (26.0g, 0.164 mol) was dissolved in acetic acid (54 ml). The mixture was then treated with a solution of sodium nitrite (11.5 g, 0.166 mol) in water (40 ml). This was done in a dropwise manner while stirring at a rate that allowed the temperature to be maintained well below 10 °C by using an ice bath. The solution was stirred for 1.5 h, and a yellow solution (t-butyl oximinoacetate) resulted, which was then stored overnight in a refrigerator.

2.4.2. t-Butyl 3,4,5-trimethylpyrrole-2-carboxylate (2.17)

t-Butyl oximinoacetate **2.15**, which was prepared by addition of t-butyl acetoacetate (25.0 g, 0.164 mol), acetic acid (54.0 ml), sodium nitrite (11.5 g, 0.166 mol) and water, was added dropwise to a solution of 3-methyl-2,4-pentanedione **2.16** (25.0 g, 0.22 mol) in acetic acid (85.0ml) during portion-wise addition of an intimate mixture of zinc dust (25.0 g, 0.45 mol) and sodium acetate (25.0 g, 0.32 mol). The rate of addition was controlled so that the temperature of the mixture was maintained at 65 °C. After addition was complete, the mixture was heated under reflux for 1.5 h after which TLC showed the presence of the product. The solution was poured into ice water (200 ml), filtered, washed with water (100 ml), dissolved in CH₂Cl₂ (50 ml), dried over anhydrous Na₂SO₄, filtered, and then evaporated to dryness. The solid was recrystallized from CH₂Cl₂/hexanes (5:1) and put in the freezer for further crystallization, to yield colorless crystals (17.0 g, 37.0 %). mp 114-116 °C (lit. mp³⁰ 138.5 °C); ¹H NMR (CDCl₃, 400 MHz): δ 8.79 (s, br, 1H), 2.23 (s, 3H), 2.19 (s, 3H), 1.91 (s, 3H), 1.57 (s, 9H). HRMS (ESI-TOF) *m/z* 210.1477 [M+H]⁺, calcd. for C₁₂H₂₀NO₂ 210.1488.

2.4.3. 2-Formyl-3,4,5-trimethylpyrrole (2.19)

t-Butyl 3,4,5-trimethylpyrrole-2-carboxylate (**2.17**) (1.00 g, 0.00478 mol) was dissolved in TFA (5 ml) in a 100 ml round bottomed flask and stirred for 5 min; it was then warmed to 40 °C.

Stirring was continued for another 30 min. TFA was then removed using a rotary evaporator. The remaining mixture was diluted with water (20 ml) and neutralized with aqueous sodium carbonate (5 g, in 100 ml of water). The mixture was transferred into a 500 ml separatory funnel and water (2 x 50 ml) was added. The organics were separated from the aqueous phase by extraction with dichloromethane (2 x 50 ml), dried over anhydrous Na₂SO₄, filtered and concentrated on a rotary evaporator at 35 °C to yield a brown oil. The oil was immediately taken to the next step before it polymerized, without further purification or characterization.

The formylation reaction involved use of dry DMF as solvent; thus it was in excess amount. Firstly, phosphorus oxychloride (1.83 ml, 0.02 mol) was added to DMF (1.60 ml, 0.02 mol) under argon at 0 °C, and the mixture was stirred at this temperature for a period of 15 min before adding a DMF solution (20 ml) of the decarboxylated product (0.75g, 0.007 mol). The temperature was then raised to 60 °C and the mixture was refluxed for 1 h. Aqueous sodium acetate solution (20 ml) was then added to the mixture, which was stirred at 85 °C for another 1 h. Sodium carbonate (1.5 g) was added portion-wise to the hydrolyzed mixture during 20 min with stirring. The mixture was then transferred to a separatory funnel and washed with water (2 x 50 ml); the organics were taken into dichloromethane (2 x 50 ml) and dried over anhydrous Na₂SO₄, filtered, and the solvent was removed under vacuum. The crude product was then purified by column chromatography (silica gel) eluting with MeOH/CH₂Cl₂ (1:49) to obtain the title compound in (0.53 g, 56% yield). Recrystallization of the product from MeOH/ CH₂Cl₂ (1:49) yielded colorless crystals. mp 140 °C (lit. mp³¹ 147 °C); ¹H NMR (CDCl₃, 400 MHz) δ 9.48 (s, 1H), 8.82 (s, br, 1H), 2.25 (s, 3H), 2.22 (s, 3H), 1.93 (s, 3H).

2.4.4. 2-Acetoxy-3-nitrobutane (2.31)

In a three-necked round-bottomed flask equipped with a magnetic stirrer and chilled in an ice-salt bath, acetaldehyde (**2.28**, 13.0 ml, 0.465 mol), 2-propanol (8.5 ml) and potassium fluoride (0.67 g, 0.023 mol, 0.05 mol equiv.) were added. To the mixture, nitroethane (**2.29**, 16.5 ml, 0.46 mol) was added dropwise at 0 °C over a period of 1h. The mixture was slowly warmed

up to room temperature and kept for 10 h under argon with continuous stirring before removing all solvent under vacuum. The resulting oily crude product was filtered to remove solid inorganic waste and washed with CH_2Cl_2 (100 ml). After removing all solvent under vacuum, a yellow oily product, 2-nitro-3-butanol **2.30**, was obtained (20.11 g, 37%) which was immediately used for the next step in the synthesis.

2-Nitro-3-butanol (7.5 g, 0.063 mol) was added dropwise over a 10 min period to a solution of CH_2Cl_2 (5 ml), acetic anhydride (9.60 g, 94 mmol, 1.5 equiv.), and 4-dimethylaminopyridine (DMAP, 0.1 g). The reaction was exothermic. The mixture was allowed to stir for 4 h at room temperature under argon. Methanol (30 ml) was added to destroy excess acetic anhydride and the mixture was allowed to stir further for 30 min. The mixture was then poured into dilute sodium bicarbonate (9 g in 50 ml of water) and extracted with CH_2Cl_2 (3 x 20 ml). The organic layer was dried over anhydrous Na_2SO_4 and filtered through a short column of silica gel. Evaporation of the solvent gave the desired product **2.31** as a green liquid (11.86 g, 58%).

2.4.5. Ethyl 3,4-dimethyl-1*H*-pyrrole-2-carboxylate (**2.34**)

In a dry multi-neck round-bottomed flask, equipped with a magnetic stirrer, ethyl isocyanoacetate **2.33** (5.80 g, 0.051 mol, 1.05 equiv.), tetramethylguanidine (11.66 g, 0.100 mol, 2.05 equiv.) and a mixture of dry THF (6 ml) and 2-propanol (6 ml) were added and the flask was cooled in an ice water bath. To the mixture, at 0 °C, a solution of 2-acetoxy-3-nitrobutane **2.31** (7.88 g, 0.049 mol, 1 equiv.) in the remaining mixture of dry THF (18 ml) and 2-propanol (18ml) was added dropwise over a period of 30 min. The mixture was allowed to stir at room temperature for 20 h under argon after the addition was complete. The resulting mixture was concentrated under vacuum to dryness. The oily residue was taken up in CH_2Cl_2 (30 ml) and washed successively with water (3 x 6 ml), 5% aqueous HCl (6 x 3 ml), water (10 x 3 ml), aqueous saturated sodium bicarbonate (18 ml) and finally brine (18 ml). After drying over anhydrous Na_2SO_4 , the solvent was removed under vacuum to yield the product **2.34** (5.51 g,

68%). mp 87-90 °C (lit. mp³² 105-108 °C) ¹H NMR (CDCl₃, 400 MHz): δ ppm 8.85 (s, br, 1H), 6.67 (d, *J* = 2.3 Hz, 1H), 4.32 (q, *J*=7.1 Hz, 2H), 2.28 (s, 3H), 2.02 (s, 3H), 1.36 (t, *J*=7.1 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ, ppm 10.09, 10.43, 14.71, 59.98, 119.43, 120.29, 120.70, 126.75, 162.00. HRMS (ESI-TOF) *m/z* 168.1026 [M+H]⁺, calcd. for C₉H₁₄NO₂ 168.1019.

2.4.6. Ethyl 3,4-dimethyl-5-iodo-1*H*-pyrrole-2-carboxylate (2.35)

NaHCO₃ (1.32g, 0.016 moles, 2.5 equiv.) was dissolved in water (6.0 ml) and heated to 50 °C while stirring. To this basic solution, pyrrole carboxylate **2.34** was added (1.05g, 0.006 moles, 1 equiv.) in several portions. When most of it was completely dissolved, methanol (10 ml) was added and the temperature was quickly raised to 71 °C. A saturated solution of I₂/KI (1.47/1.92 g in 4 ml water) was then added into the mixture over several minutes while stirring. The reaction mixture was refluxed for an additional 40 min. Saturated Na₂S₂O₃ solution was added to the mixture in portions to remove excess iodine until the solution decolorized. The aqueous layer was extracted using CH₂Cl₂ (100 ml). The organic layer was dried over anhydrous Na₂SO₄, concentrated under reduced pressure, and purified on a silica gel column (eluted with CH₂Cl₂) to yield a yellow solid (1.70 g, 92%). mp 126 °C (lit. mp³³ 150 °C) ¹H NMR (CDCl₃, 400 MHz): δ 9.08 (s, br, 1H), 4.34 (q, *J*=7.1 Hz, 2H), 2.30 (s, 3H), 1.97 (s, 3H), 1.37 (t, *J*=7.1 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ, ppm 11.27, 12.05, 14.72, 60.39, 123.89, 126.49, 127.10, 160.99. HRMS (ESI-TOF) *m/z* 293.9988 [M+H]⁺, calcd. for C₉H₁₃I NO₂ 293.9985.

2.4.7. Benzyl 3,4 –dimethyl-1*H*- pyrrole-2-carboxylate (2.27)

Sodium (0.168 g, 0.0073 mol) was added to benzyl alcohol (60 ml) in an 100 ml round-bottomed flask mmol while stirring. Once all the sodium had reacted, ethyl ester pyrrole (**2.34**, 2.32 g, 14 mmol) was added and the resulting mixture was heated in an oil bath for 6 h at 100 °C. The mixture was allowed to stand at room temperature overnight and acetic acid (0.438 g, 7.3 mmol) was added to neutralize excess sodium benzyloxide. Benzyl alcohol was evaporated off under reduced pressure to dryness and the residue which solidified on standing was dissolved in CH₂Cl₂ (20 ml), washed with water (100 ml), and treated with decolorizing carbon.

After filtration through a Celite plug, the solution was dried over anhydrous Na_2SO_4 and the solvent was evaporated under vacuum to yield a brown liquid, which was further distilled under high vacuum to give a thick brown liquid. The residue was dried under vacuum to give a brown solid of **2.27** (2.80 g, 87%). mp 72-75 °C (lit. mp³⁴ 73-74 °C) ^1H NMR (CDCl_3 , 400 MHz): δ 9.07 (s, br, 1H), 7.55-7.31 (m, 5H), 6.67 (d, $J=3.1$ Hz, 1H), 5.36 (s, 2H), 2.36 (s, 3H), 2.06 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ , ppm 161.67, 136.63, 128.65, 128.29, 128.16, 127.22, 120.81, 120.72, 120.67, 118.95, 65.70, 10.53, 10.02.

2.4.8. Benzyl 3-ethyl-4-methyl-5-iodo-1*H*-pyrrole-2-carboxylate (2.22)

NaHCO_3 (0.84 g, 0.01 mol) was dissolved in water (5 ml) and heated to 50 °C. To this basic solution was added pyrrole carboxylate **2.21** (1.15 g, 0.004 mol) in one portion. The mixture was then stirred for 5 min at 50 °C to dissolve most of the pyrrole. 1,2-Dichloroethane (15 ml) was then added and the temperature was then raised to 70 °C. A saturated solution of KI/I_2 (1.92 g/ 1.47 g, 2:1 molar ratio) in water (10 ml) was then added into the refluxing reaction mixture over 5 min. The mixture was then refluxed for an additional 40 min. After cooling the flask to room temperature, saturated $\text{Na}_2\text{S}_2\text{O}_3$ (5 ml) was added to the mixture with stirring until the purple color of the solution disappeared. The crude organic product was then extracted using a separatory funnel with CH_2Cl_2 (50 ml), dried over dry Na_2SO_4 , filtered and the volatiles were removed under reduced pressure to afford the titled product **2.22** in 1.33 g, 0.0036 mol, 90% yield. mp 112 °C (lit. mp³⁵ 112.5-113 °C) ^1H NMR (400 MHz, CDCl_3): δ 8.91 (s, 1H), 7.50-7.29 (m, 5H), 5.32 (s, 2H), 2.40 (q, $J=7.5$ Hz, 2H), 2.34 (s, 3H), 1.06 (t, $J=7.6$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ , ppm 136.38, 132.60, 128.48, 127.11, 123.67, 66.11, 20.19, 14.94, 11.05. HRMS (ESI-TOF) m/z 392.0124 $[\text{M}+\text{Na}]^+$, calcd. for $\text{C}_{15}\text{H}_{16}\text{INNaO}_2$ 392.0118.

2.4.9. Benzyl 4-ethyl-3-methyl-5-vinylpyrrole-2-carboxylate (2.23)

$\text{Pd}(\text{PPh}_3)_4$ (0.054 g, 0.000047 mol, 0.05 equiv.) was added to a nitrogen purged, stirred solution of **2.22** (0.340 g, 0.00093 mol) and $\text{Bu}_3\text{SnCHCH}_2$ (0.34 cm^3 , 0.00113 mol) in DMF (9.5 ml). The solution was degassed for 30 min and stirred under nitrogen at reflux temperature (90

°C) for 16 h. The solvent was evaporated and the residue was taken into CH₂Cl₂ (10 ml) and stirred with a saturated aqueous Na₂S₂O₃ solution (5 ml) for 30 min. The mixture was then filtered through a Celite plug. The Celite was washed with CH₂Cl₂ (2 x 20 ml) and the combined organic filtrate was washed with water (2 x 15 ml). The organic fraction was separated and dried over anhydrous Na₂SO₄. The solvent was evaporated and the residue was purified by using silica gel column chromatography, eluting with CH₂Cl₂ /hexanes (5:1), to afford the titled vinylpyrrole **2.23** (150 mg, 60%). mp 83-85 °C ¹H NMR (400 MHz, CDCl₃): δ 8.84 (s, 1H), 7.76-7.70 (m, 5H), 6.60 (dd, *J*=17.8, 11.4 Hz, 1H), 5.43 (d, *J*= 11.4 Hz, 1H), 5.33 (s, 2H), 5.18 (d, *J*= 17.8 Hz, 1H), 2.48 (q, *J*=7.5 Hz 2H), 2.30 (s, 3H), 1.08 (t, *J*=7.6 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ, ppm 161.62, 132.51, 132.40, 131.74, 131.71, 130.57, 128.76, 128.75, 128.63, 128.30, 126.95, 125.03, 111.75, 77.54, 77.22, 76.90, 65.94, 17.23, 15.85, 10.50. HRMS (ESI-TOF) *m/z* 270.1473 [M+H]⁺, calcd. for C₁₇H₂₀NO₂ 270.1489.

2.4.10. Dibenzyl (3,3'-diethyl-4,4'-dimethyl-2,2'-dipyrrolyl)-1,2-ethene-5,5'-dicarboxylate (2.24)

5-Vinylpyrrole **2.23** (0.070 g, 0.00026 mol, 1 equiv.) was dissolved in anhydrous CH₂Cl₂ (1.5 ml). Grubbs 2nd generation catalyst (22 mg, 0.000026 mol, 10%) was dissolved in CH₂Cl₂ (1.5 ml) and added in a dropwise manner to the vinylpyrrole solution under a nitrogen atmosphere while stirring. The mixture was then refluxed for 12 h at 40 °C. The reaction was monitored by TLC until a strongly luminescent polar spot was observed. The solvent was then evaporated at reduced pressure. The crude residue was then purified by column chromatography (silica gel) eluting with CH₂Cl₂/hexanes (v/v=5:1) to afford the titled product **2.24** as a colorless solid (52.5 mg, 50% yield). mp 309 °C (decomp.) ¹H NMR (CDCl₃, 400 MHz) ppm: δ 8.85 (s, br, 2H), 7.45-7.32 (m, 10H), 6.61 (s, 2H), 5.34 (s, 4H), 2.52 (s, 4H), 2.30 (s, 6H), 1.62 (s, 4H) 1.10 (s, 6H). ¹³C NMR (100 MHz, CDCl₃): δ, ppm 161.73, 136.60, 130.55, 128.79, 128.42, 128.37, 128.34, 128.03, 127.80, 119.38, 114.16, 66.09, 17.46, 16.00, 10.60. HRMS (ESI-TOF) *m/z* 511.2591 [M+H]⁺, calcd. for C₃₂H₃₅N₂O₄ 511.2591.

2.4.11. Benzyl 3,4-dimethyl-5-iodo-1*H*-pyrrole-2-carboxylate (2.36)

NaHCO₃ (2.29 g, 0.026 moles, 2.5 equiv.) was dissolved in water (10 ml) and heated to 50 °C while stirring. To this basic solution, was added (2.35 g, 0.01 moles, 1 equiv.) of pyrrole carboxylate **2.27** in several portions. When most of it was completely dissolved, 1,2-dichloroethane (15 ml) was added and the temperature was quickly raised to 70 °C. A saturated solution of I₂/KI (3.80/4.93 g in 5.0 ml water) was then added into the mixture over several minutes while stirring. The reaction mixture was refluxed for an additional 40 min. Saturated Na₂S₂O₃ solution (10 ml) was then added to the mixture in portions to remove excess iodine. The aqueous layer was separated and extracted using CH₂Cl₂ (20.0 ml). The organic layer was dried over anhydrous Na₂SO₄, concentrated under reduced pressure, and purified by column (silica gel) chromatography eluting with 100% CH₂Cl₂ to yield a yellow solid of **2.36** (3.06g, 86%). mp 127 °C (lit. mp³³ 127-129 °C) ¹H NMR (CDCl₃, 400 MHz) ppm: δ 9.16 (s, br, 1H), 7.44-7.35 (m, 5H), 5.35 (s, 2H), 2.33 (s, 3H), 1.98 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ, ppm 11.39, 12.04, 66.13, 74.07, 123.49, 126.62, 127.63, 128.38, 128.78, 136.39, 160.65. HRMS (ESI) *m/z* 356.0121 [M+H]⁺, calcd. for C₁₄H₁₅INO₂ 356.0142.

2.4.12. 5,5'-Bis (benzyloxycarbonyl)-3,3',4,4'-tetramethyl-2,2'-bipyrrole (2.37)

Activated zinc was obtained by washing zinc dust with 3M HCl and then filtering through filter paper, after which it was washed successively with water, ethanol, and diethyl ether, and then dried under vacuum. A mixture of Pd-C (732 mg) and activated zinc powder (732 mg, 11.26mmol) were placed in a dry 100 ml round-bottom flask. After removing air under vacuum, the flask was filled with argon. After that, 5 ml of acetone was added to the reaction mixture which was stirred at ambient temperature under argon for 15 min to activate the catalyst before adding 2-iodopyrrole **2.36** (1.0 g, 0.028 mol) dissolved in 20 ml of acetone. Then 25 ml of distilled water was added through a syringe into the reaction flask. The reaction mixture was stirred vigorously at room temperature for 24 h under argon. TLC was used to follow the reaction; the 5,5'-diester-2,2'-bipyrroles display a characteristic blue fluorescence under UV

irradiation (around 366 nm) on silica gel TLC plates. CH₂Cl₂ (40 ml) was added into the resulting mixture and it was sonicated to form two layers. After removing the water layer with a separatory funnel, the organic solvents were collected and dried over anhydrous Na₂SO₄, before evaporation under vacuum. The pure target compounds were obtained by using silica gel column chromatography using CH₂Cl₂ /hexanes (5:1) solvent mixture as eluent. Further purification could be performed by recrystallization from 1:5 CH₂Cl₂ /hexane, or from ethanol. Yield of isolated product was 834 mg, 65% yield. mp 211-212.6 °C (lit. mp¹⁸ 220 °C) ¹H NMR (400 MHz, CDCl₃): δ 8.86 (s, 2H), 7.41-7.27 (m, 10 H), 5.29 (s, 4H), 2.31 (s, 6H), 2.02 (s, 6H). ¹³C NMR (100 MHz, CDCl₃): δ, ppm 161.51, 136.50, 128.77, 128.34, 128.30, 128.21, 124.96, 120.08, 119.24, 66.03, 10.87, 10.11. HRMS (ESI-TOF) *m/z* 457.2135 [M+H]⁺, calcd. for C₂₈H₂₉N₂O₄ 457.2122.

2.4.13. 5,5'-bis (benzyloxycarbonyl)-3,3',4,4'-tetramethyl-2,2'-N,N'-Boc-bipyrrole (2.40)

A mixture of dibenzyl ester bipyrrole **2.37** (1.097 g, 0.0024 mol), 4-dimethylaminopyridine (0.147 g, 0.0012 mol), and di-tert-butyl- dicarbonate (2.095 g, 0.0096 mol) were dissolved in dry CH₂Cl₂ (30 ml). Dry THF (5 ml) was also added to dissolve all the starting material. The reaction was left to stir overnight. The reaction was monitored by TLC. On completion, the solvent was removed under reduced pressure and the crude was purified with a silica gel column eluting with two solvent systems, 100% CH₂Cl₂, followed by 1% MeOH: 99% CH₂Cl₂. Concentration of desired fractions afforded the titled product as an oil: 1.165 g, 0.001776 mol, 74% yield. ¹H NMR (400 MHz, CDCl₃): δ 7.34-7.32 (m, 10H), 5.30 (s, 2H), 5.28 (s, 2H), 2.18 (s, 6H), 1.74 (s, 6H), 1.21 (s, 9H).

2.4.14. 5,5'-di-Iodo-3,3',4,4'-tetramethyl-2,2'-N,N'-Boc-bipyrrole (2.42)

Pd/C (0.900 g) catalyst was activated by stirring in dry THF (15 ml) under a hydrogen atmosphere for 20 min. Di-benzyl ester bipyrrole (1.57 g, 0.0024 mol) in dry THF (15 ml) was then added into the activated catalyst suspended in THF via syringe. The reaction mixture was stirred under hydrogen gas overnight when no more starting material was observed. The

inorganics were then filtered off on a Celite cake and the Celite cake washed with THF (25 ml). The filtrate fractions were collected and concentrated under reduced pressure to give a white solid of the diacid **2.41** which was taken to the next step without further characterization. The diacid bipyrrrole **2.41** collected was then taken into water (20 ml). NaHCO₃ (1.21 g, 0.0144 mol) was added into the suspension and the mixture was heated at 50 °C for 10 min to dissolve most of the starting material. When most of the diacid had dissolved, 1,2-dichloroethane (30 ml) was added. The mixture was then refluxed at 70 °C for 5 min. KI/I₂ (2.0 g/1.52 g, 0.012 mol/0.006 mol) mixture in water (10 ml) was added in a dropwise manner over 5 min. The mixture was additionally refluxed for an hour at 70 °C. The reaction mixture was then cooled to room temperature and saturated sodium thiosulfate (10 ml) was added to discharge excess unreacted iodine. Organics were then extracted with CH₂Cl₂ (2 x 30 ml) and separated using a separatory funnel, dried over anhydrous Na₂SO₄, filtered and the filtrate collected was concentrated *in vacuo*. The crude product obtained was purified using a silica gel column eluting with CH₂Cl₂/n-hexanes (1:1). After concentration of the fractions, the titled product **2.42** was obtained as a brown solid. Yield 0.930 g, 0.00146 mol, 61%. mp 120 °C. ¹H NMR (400 MHz, CDCl₃): δ 2.04 (s, 6H), 1.78 (s, 6H), 1.27 (s, 9H). HRMS (ESI-TOF) *m/z* 641.0520 [M+H]⁺, calcd. for C₂₂H₃₁I₂N₂O₄ 641.0368.

2.4.15. 5,5'-di-Vinyl-3,3',4,4'-tetramethyl-2,2'-N,N'-Boc-bipyrrrole (2.43)

A DMF solution (10 ml) of Pd(PPh₃)₄ (0.104 g, 0.00009 mol, 10%), di-iodobipyrrrole **2.42** (0.578 g, 0.0009 mol), and Bu₃SnCHCH₂ (1.3 ml, 0.0045 mol) was degassed with dry nitrogen for 30 min. The solution was then stirred under an argon atmosphere at 110 °C for 16 h. The solvent was then evaporated off under reduced pressure. The crude product was then taken into CH₂Cl₂ (50 ml) and then filtered through a Celite cake to remove the catalyst residues. The cake was then washed with CH₂Cl₂ (2 x 20 ml). The filtrate was then washed with saturated sodium thiosulfate (10 ml) to discharge displaced iodine. Organics were then extracted with CH₂Cl₂ (2 x 30 ml) and separated using a separatory funnel, dried over anhydrous Na₂SO₄,

filtered and the filtrate collected was concentrated *in vacuo*. The crude product was further purified by silica gel column chromatography eluting with CH₂Cl₂/n-hexanes (1:1). Yield 0.30g, 0.68mmol, 76%. mp 140 °C ¹H NMR (400 MHz, CDCl₃): δ 6.98 (dd, *J*=17.7, 11.4Hz, 1H), 5.33 (s, *J*=11.5, 2.0Hz, 1H), 5.24 (s, *J*=17.8, 2.0Hz, 1H), 2.09 (s, 6H), 1.76 (s, 6H) 1.25 (s, 9H). ¹³C NMR (100 MHz, CDCl₃): δ, ppm 9.90, 11.10, 27.80, 82.64, 114.95, 121.09, 122.57, 123.74, 129.06, 130.45, 150.15. HRMS (ESI-TOF) *m/z* 441.2740 [M+H]⁺.

2.4.16. Benzyl 3,4 –dimethyl-NTIPS- pyrrole-2-carboxylate (2.46)

Sodium hydride (60% dispersion in mineral oil, 0.210g, 0.00524 mol) was weighed into a dry 50 ml round-bottomed flask. The flask was evacuated and nitrogen purged three times. Pentanes (dry) (10 ml) was used to dissolve the mineral oil and expose the active protected sodium hydride. The white suspension was then cooled to 0 °C (salt-ice bath), and flask evacuated. An Argon balloon was then installed. Pyrrole **2.27** (1.00 g, 0.00437 mol) in dry DMF (20 ml) was added in a dropwise manner to the chilled suspension over 10 min at 0 °C. When hydrogen gas evolution had ceased (4 h), triisopropyl chloride (0.96 ml, 0.00437 mol) was added drop wise at 0 °C and stirring was continued at 0 °C for 2 h. The reaction was then quenched by adding wet ethyl ether (10 ml) at 0 °C. Volatiles were then removed under reduced pressure. The crude product was re-dissolved in ethyl acetate (25 ml) and washed with water (200 ml). The organic fractions were separated, dried over anhydrous Na₂SO₄, filtered and concentrated. The crude product was then purified over silica column chromatography eluting with CH₂Cl₂ to yield the titled product **2.46** in 1.67g, 0.00432 mol, 99% yield.

2.5. References

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CHAPTER 3: SYNTHESIS AND REACTIVITY STUDIES OF A NOVEL 5,5'-DIMETHYL-2,2'-BIPYRROLE

3.1. Introduction

3.1.1. General Structure

Bipyrroles are generally composed of two pyrroles joined by a single bond. They can be symmetrical or unsymmetrical. Bipyrroles **3.1** are constituents of some of the porphyrinoid isomers. Therefore improved synthesis of bipyrroles and studies on reactivity potentials around the molecule is deemed important (Figure 3.1).

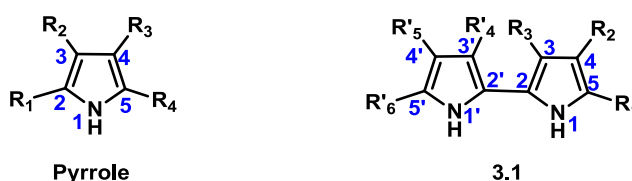


Figure 3.1: Pyrrole and bipyrrole general structure.

Bipyrrolic molecular structures (highlighted in blue, Figure 3.2) are found in porphycenes **3.2**¹ and its derivatives such as corrrhycenes **3.3**,² isocorroles **3.4**,³ and hemiporphycenes **3.5**.⁴ They show a characteristic blue color under longer wavelength of the UV-lamp because of the extended conjugation in their aromatic pathway.

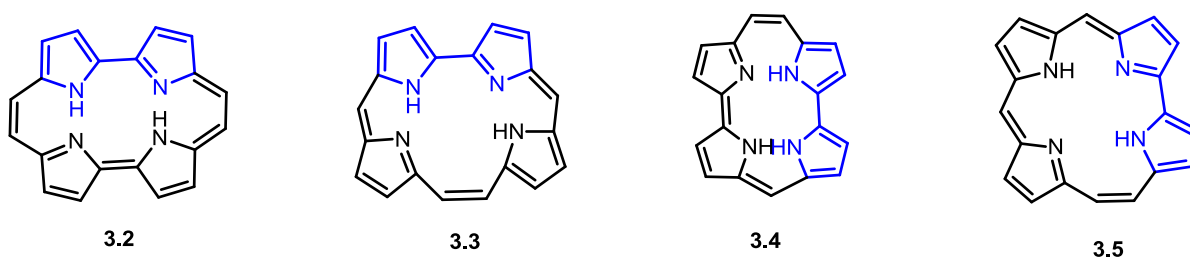
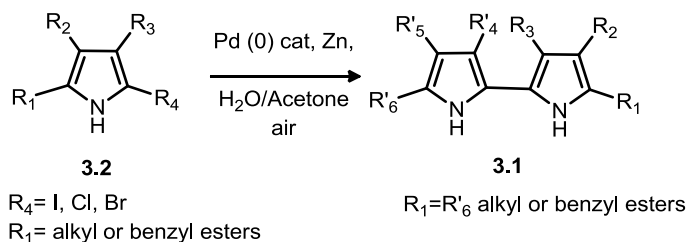


Figure 3.2: Macrocycles containing bipyrroles (in blue color).

3.1.2. Background on Syntheses of Bipyrroles

Oxidative and reductive coupling have been used in the synthesis of bipyrroles from their pyrrole precursors. The low yielding oxidative coupling protocols^{5,6} are uncommon when compared to the common reductive coupling protocols.⁷⁻¹⁰ The Ullmann coupling reaction of iodopyrroles is conventionally used in such syntheses. Early application of Ullmann coupling on

pyrroles was performed by Vogel *et al.* during the synthesis of the first porphyrin isomer, porphycene.¹ Copper metal is commonly used in the dimerization of halopyrroles, although under high temperature conditions. Mild conditions for Ullmann reductive coupling have recently been reported, using palladium and zinc (Scheme 3.1).¹¹



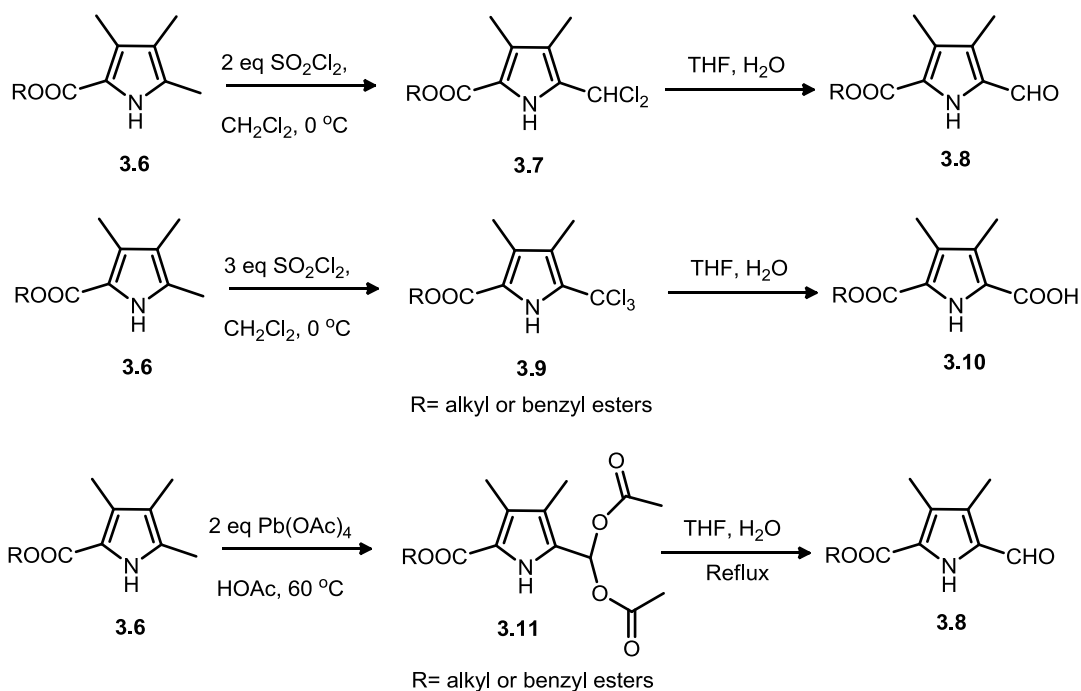
Scheme 3.1: Reductive Ullmann coupling of halopyrroles.

Itahara reported that Ullmann coupling of pyrroles requires aryl groups at the opposite alpha-positions for higher yields.¹² It is also common to synthesize the bipyrroles bearing alkyl esters at R'₆ and R₁. This limits the scope of reaction transformations that would be attempted if methyl groups are used instead of esters. For this reason, the synthesis, and reactions of the rare 5,5'-dimethyl-2,2'-bipyrrole will be reported in this chapter. Alpha methyl groups on pyrroles possess benzylic character.

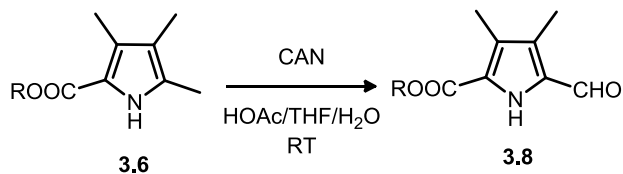
3.1.3. Reactions of Pyrrolic 5-methyls

Methyl substituents on position 5 of pyrroles undergo several reactions. Such reactions are envisioned to also take place on bipyrroles. The methyl group can be halogenated, by chlorine or bromine followed by aqueous work-up to give alcohols, aldehyde **3.8** or carboxylic acid **3.10** after hydrolysis (Scheme 3.2).¹³

The α-methyl on pyrrole **3.6** can also be oxidized by ceric ammonium nitrate, in acidic conditions, to give the aldehyde pyrrole **3.8**¹⁴ in 82% yield (Scheme 3.3). The α-methyl can also take part in the Knoevenagel reaction with aryl aldehydes to give *trans*-alkenes. This results in an extended conjugation and increased absorption properties.



Scheme 3.2: Halogenations and hydrolysis of α -methylpyrroles.¹³

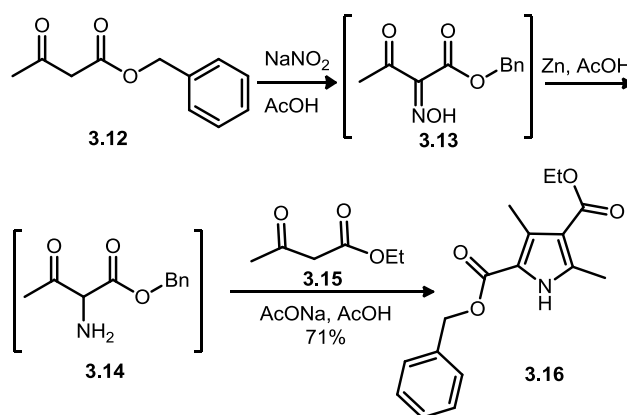


Scheme 3.3: Oxidation of α -methyl to aldehyde.¹⁴

3.2. Synthesis

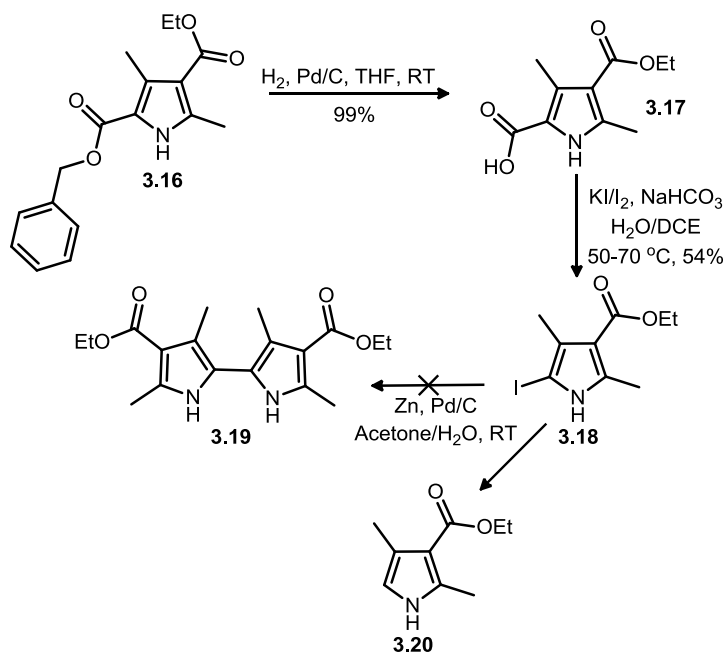
The synthesis of 5,5'-dimethyl-2,2'-bipyrrole began by synthesizing a tetra substituted mixed ester Knorr pyrrole **3.16**.¹⁵⁻¹⁶

Benzyl acetoacetate **3.12** was subjected to a nitrosation reaction to afford oxime **3.13**. Oxime **3.13** was then reduced by zinc in acetic acid to afford amine **3.14**, that was then condensed with ethyl acetoacetate to give the mixed ester Knorr pyrrole **3.16** in 71% yield.



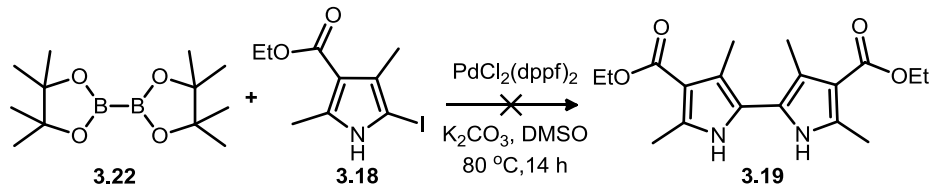
Scheme 3.4: Synthesis of mixed ester pyrrole **3.16**.

The mixed ester Knorr pyrrole **3.16** was then catalytically debenzylated using Pd/C to give the acid **3.17** in 99% yield. Decarboxylative iodination afforded iodopyrrole **3.18** in an acceptable yield of 54% (Scheme 3.5). Ullmann coupling was then attempted with the iodopyrrole at room temperature, but this failed, giving dehalogenated pyrrole **3.20** instead, a common byproduct of Ullmann coupling. Iodopyrrole **3.18** was then subjected to modified reductive Ullmann coupling as described by Jiao *et al.*,¹¹ however, the reaction mixture was refluxed. Unfortunately no desired product was obtained (Scheme 3.5).



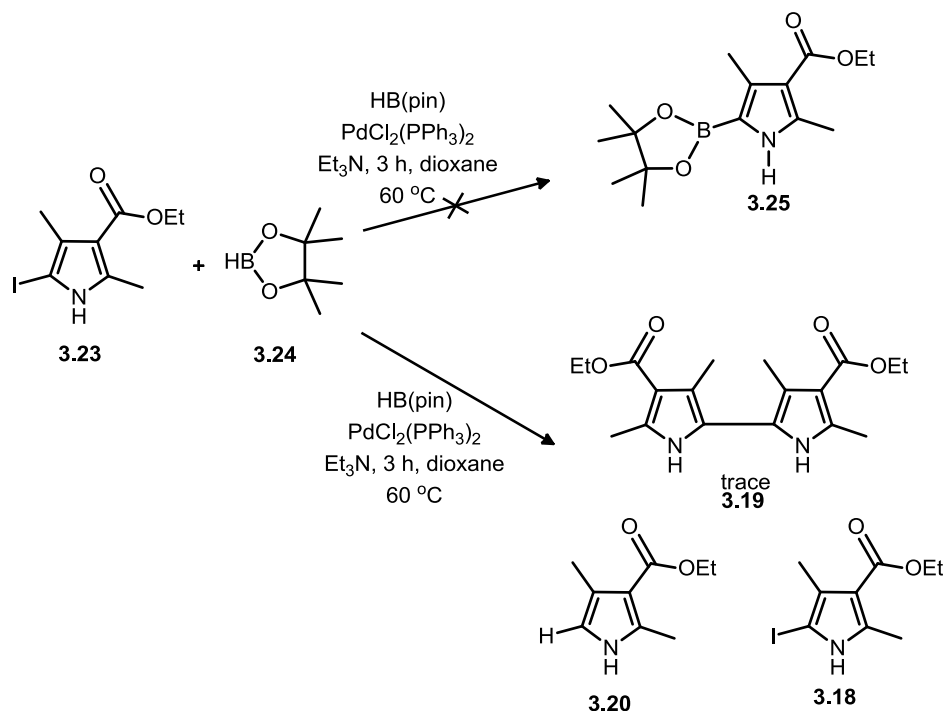
Scheme 3.5: Attempted synthesis of bipyrrole **3.19**.

Due to the failed reactions, an alternate route was sought to couple iodopyrrole **3.18** to itself. One pot boronation of iodopyrrole **3.18** followed by Suzuki type of coupling did not yield the expected bipyrrole product **3.19** (Scheme 3.6).¹⁷



Scheme 3.6: Attempted synthesis of bipyrrole **3.19** by *in-situ* Suzuki coupling.

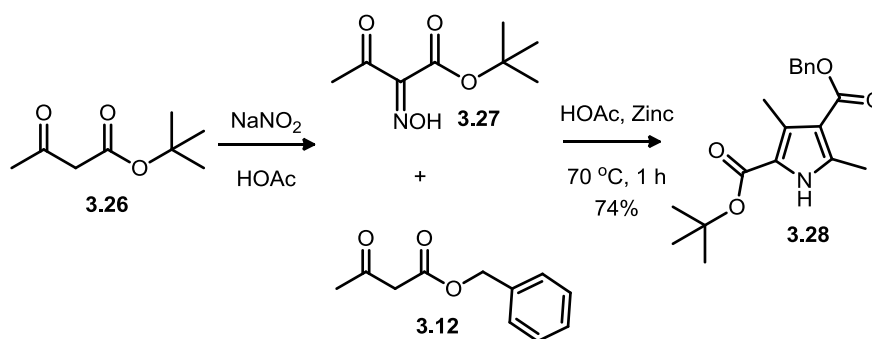
It was therefore found necessary to do stepwise boronation and Suzuki coupling reactions. A different catalyst was tried. $\text{PdCl}_2(\text{dppf})_2$ was substituted with $\text{PdCl}_2(\text{PPh}_3)_2$.¹⁸ This reaction did not yield the desired pyrrole borate **3.25** that is needed for synthesis of the targeted bipyrrole, but the starting material was recovered along with the dehalogenated pyrrole **3.20**. It is worth mentioning that traces of our target bipyrrole **3.19** were observed (Scheme 3.7).



Scheme 3.7: Attempted synthesis of bipyrrole **3.19**.

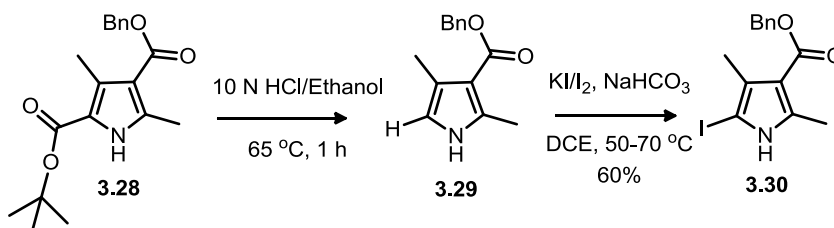
Previous studies on bipyrrrole synthesis¹¹ concluded that the presence of a benzyl ester substituent on an iodopyrrole is important for the bipyrrrole synthesis. It was therefore decided to synthesize such a pyrrole (Scheme 3.8) following a mixed ester Knorr pyrrole synthesis protocol.¹⁵

t-Butyl acetoacetate **3.26** was subjected to a nitrosation reaction with sodium nitrite to give oxime **3.27**. This was then reduced *in-situ* with zinc to make an amine that was then condensed with benzyl acetoacetate **3.12** to provide the mixed ester Knorr pyrrole **3.28** in 74% yield (Scheme 3.8).¹⁶

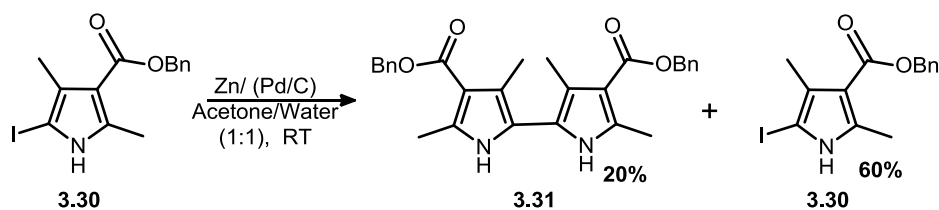


Scheme 3.8: Synthesis of tetra-substituted mixed ester pyrrole **3.28**.

The decarboxylation of the pyrrole **3.28** under acidic conditions (hydrochloric acid/ethanol) quantitatively yielded α -free pyrrole **3.29**,¹⁹ which underwent iodination in the presence of iodine/potassium mixture in refluxing 1,2-dichloroethane to give the key intermediate pyrrole **3.30** in 60% yield (Scheme 3.9).

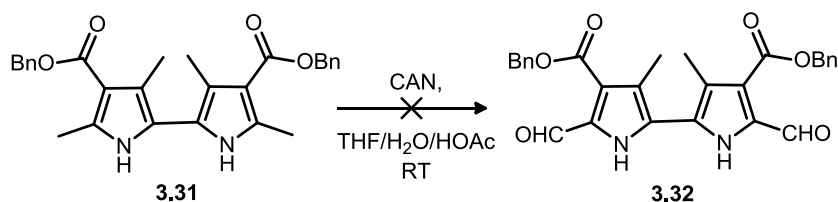


Scheme 3.9: Synthesis of iodopyrrole **3.30**.



Scheme 3.10: Synthesis of bipyrrole **3.31**.

Reductive Ullmann coupling of iodopyrrole **3.30** with a combination of zinc and palladium/carbon finally afforded 5,5'-dimethyl-2,2'-bipyrrole **3.31** in 20% yield.¹¹ Iodopyrrole starting material **3.30** was recovered in 60% yield.



Scheme 3.11: Attempted synthesis of bipyrrole **3.32**.

With the 5,5'-dimethyl bipyrrole in hand, oxidation reaction of the methyls were attempted using ceric ammonium nitrate.¹⁴ The bipyrrole was dissolved in a solvent mixture of THF/HOAc/H₂O and reacted with ceric ammonium nitrate. The reaction failed to provide the expected dialdehyde product **3.32** although no starting material was recovered. The crude product was not the alcohol intermediate of the reaction either. Therefore the product might have decomposed due to the presence of strongly electron withdrawing groups, i.e. aldehydes and two benzyl esters. More studies on the reactivity of such a bipyrrole species is therefore required.

3.3. Conclusions

5,5'-Dimethylbipyrrole was successfully synthesized. However, it was noted and confirmed that benzyl esters at the fourth positions are necessary to effect Ullmann coupling. Oxidation reactions of the α -methyls on the bipyrrole seems to be a challenge with the mild CAN

conditions. More reactions on the α -methyl substituents need to be explored, for example chlorination using sulfuryl chloride⁹ and acetylation using lead(IV) tetraacetate (LTA).

3.4. Experimental Section

3.4.1. Benzyl 4-ethoxycarbonyl-3,5-dimethylpyrrole-2-carboxylate (3.16)

A solution of benzyl acetoacetate (38.4 g, 0.200 mol) in acetic acid (40 ml) was cooled on ice bath to 5 °C and a solution of NaNO₂ (14.0 g, 0.2 mol, 1 eq) in water (20 ml) was injected slowly under the level of the reaction mixture with cooling and vigorous stirring over a 20 min period so that the internal temperature did not exceed +15 °C. The syringe was then washed with water (2 x 3 ml) and the washings were also added to the mixture. The reaction mixture was stirred on a melting ice bath for 16 h overnight, to give the oxime.

To a 3-necked 1 litre round bottom flask loaded with a large egg-shaped stir-bar, internal thermometer, and addition funnel, was added anhydrous sodium acetate (20 g, 4.1 mol), and ethyl acetoacetate (29.0 g, 0.220 mol, 1.1 eq) dissolved in acetic acid (100 ml). With vigorous stirring, Zn dust (10 g, 0.152 mol, Aldrich <10 micrometer) was then added followed by dropwise addition of the oxime (44 g, 0.200 mol). This addition was carried out over a 45 min period, while additional Zn dust (40 g, 0.611 mol) was simultaneously added to the mixture in approximately 5 g portions a few minutes apart. Each Zn addition was accompanied by a temperature spike, but the internal temperature in the flask was kept below +85 °C. The bath temperature was 60 °C and the internal temperature in the flask was controlled by the rate of addition of Zn dust and the oxime. The total quantity of Zn dust used was 50 g. At the end, the addition funnel was washed with additional acetic acid (3 x 10 ml) and this was added to the mixture and stirring was continued for 1 h at 60 °C. The resulting foamy reaction mixture was diluted by addition of water (100 ml) and the mixture was stirred for 1 h at 60 °C. The reaction mixture was then poured into a large beaker, diluted with water (0.5 L), some crushed ice was added (total mixture volume was 1.5 L), and the slurry was placed on an ice bath and stirred for 1 h. The precipitate was collected by filtration, washed thoroughly with water, and dried by

suction. The crude product obtained was dissolved in CH_2Cl_2 (100 ml), washed with water and then, dried over anhydrous Na_2SO_4 , filtered, and then the volatiles (CH_2Cl_2) were removed under reduced pressure to give solid product. Yield: (43.0 g, 0.143 mol, 71.4 % yield over 2 steps). mp 113-116 °C (lit. mp²⁰ 122-123 °C) ^1H NMR (400 MHz, CDCl_3): 1.36 (t, J = 7.10 Hz, 3H, CH_2CH_3), 2.50 (s, 3H, CH_3), 2.59 (s, 3H, CH_3), 4.29 (q, J = 7.12 Hz, 2H, CH_2CH_3), 5.33 (s, 2H, CH_2Ar), 7.38 (m, 5H, Ar), 9.13 (s, 1H, N-H). ^{13}C NMR (100 MHz, CDCl_3): 12.30, 14.59, 59.74, 66.23, 113.97, 117.77, 128.48, 131.77, 136.25, 139.40, 161.50, 165.60. HRMS (ESI+): calculated for $\text{C}_{17}\text{H}_{19}\text{NO}_4$ 301.1387; found 301.1382.

3.4.2. 4-(Ethoxycarbonyl)-3,5-dimethylpyrrole-2-carboxylic acid (3.18)

Pd/C catalyst (0.6 g, 40%) was transferred to a 100 ml round bottom flask containing a dry magnetic stirrer. The flask was corked and evacuated for 15 min. THF (10 ml) was added via syringe and the catalyst suspension was stirred for 20 min under H_2 gas for activation. The benzyl ester pyrrole (1.5 g, 0.005 mol, 1 eq) was dissolved in 20 ml of THF and the pyrrole solution was then transferred to the catalyst suspension via syringe, all at once. The mixture was allowed to stir overnight at room temperature under hydrogen gas. The reaction was judged to be complete by TLC, evidenced by the more polar spot formed. The inorganics were then filtered out over a Celite cake and washed with THF (50 ml). Organics were then collected, evaporated and the resulting white solid product was collected and taken to the next step without further purification.

NaHCO_3 (1.05 g, 0.0125 mol, 2.5 eq) was dissolved in water (30 ml) and heated to 50 °C while stirring. To this basic solution, the starting material pyrrole was added (1.06 g, 0.005 mol, 1 eq) while stirring. 1,2-Dichloroethane (40 ml) was added to the mixture. The temperature was quickly raised to 70 °C. KI/I_2 (2.4 g, 0.0145 mol, 2.9 eq/ 1.840 g, 0.00725 mol, 1.45 eq) was dissolved in water (10 ml) and added in a dropwise manner over several min. The reaction mixture was refluxed for an additional 40 min; then saturated $\text{Na}_2\text{S}_2\text{O}_3$ was added to the mixture to remove excess iodine. The reaction was cooled down and the mixture was transferred to a

separatory funnel. The organic products were extracted with CH_2Cl_2 (50 ml), which was dried over anhydrous Na_2SO_4 and filtered by suction. The solvent was removed with a rotor-evaporator. Yield 0.792 g, 0.0027 mol, 54%. mp 143-145 °C (lit. mp²¹ 146-148 °C) ^1H NMR (400 MHz, CDCl_3): 1.35 (t, $J=7.11\text{Hz}$, 3H, CH_2CH_3), 2.21 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 4.28 (q, $J=7.08\text{Hz}$, 2H, CH_2CH_3), 8.33 (s, 1H, N-H). ^{13}C NMR (100 MHz, CDCl_3): 14.51, 29.70, 59.69, 64.35, 112.36, 127.01, 139.73, 165.24. HRMS (ESI+): calculated for $\text{C}_9\text{H}_{12}\text{INO}_4$ 292.9985; found 292.9978.

3.4.3. t-Butyl 4-benzyloxycarbonyl-3,5-dimethylpyrrole-2-carboxylate (3.28)

Into a chilled mixture of tert-butyl acetoacetate (15.8 g, 0.100 mol) and glacial acetic acid (20 ml) was slowly added a 50% weight by volume aqueous solution of NaNO_2 (6.9 g, 0.100 mol, 14 ml water). The temperature of the mixture was maintained between 2 and 5 °C (for 1 h) throughout the addition. The resulting solution was warmed to 23 °C (room temperature) and allowed to stir for 3.5 h to give a crude solution of tert-butyl 2-hydroximino-3-oxobutyrate which was used in the next step without further purification.

A solution of benzyl acetoacetate (19.22 g, 0.100 mol) in glacial acetic acid (40 ml) was added in one portion to the mixture and the resulting solution was warmed to 65 °C in an oil bath. To the warm solution was added zinc dust (6.54 g, 0.100 mol) in small portions. Another portion of zinc dust was added after the initial effervescence subsided (2 g, 0.030 mol). The mixture was maintained at 65-70 °C for 1 h and then poured into 600 ml of cold water. The resulting precipitate was isolated via filtration and dried under vacuum to afford a pale yellow solid. The wet (moistened) solid was then taken into CH_2Cl_2 (200 ml) and separated using a separatory funnel. Organic fractions were collected, dried over anhydrous Na_2SO_4 , filtered and then the volatiles were removed under reduced pressure to give the product as a yellow solid powder. Further purification was done in a small amount of cold methanol (100 ml) in the refrigerator. Further purification was done on a silica gel column (15 X 12 cm) eluting with ethanol/hexanes (1:1). Yield (24.70 g, 0.075 mol, 75%). mp 107-109 °C ^1H NMR (400 MHz,

CDCl₃): δ, ppm 9.37 (s, 1H), 7.44-7.32 (m, 5H), 5.31 (s, 1H), 2.56 (s, 3H), 2.51 (s, 3H), 1.58 (s, 9H). ¹³C NMR (100 MHz, CDCl₃): δ, ppm 165.49, 161.53, 138.98, 136.83, 130.27, 128.68, 128.20, 128.10, 119.48, 113.19, 81.44, 77.54, 77.23, 76.91, 65.58, 28.64, 14.64, 12.34. HRMS (ESI-TOF) *m/z* 330.1693 [M+H]⁺. calcd. for C₁₉H₂₄NO₄ 329.1627.

3.4.4. Benzyl 3,5-dimethylpyrrole-4-carboxylate (3.29)

A solution (yellow suspension) of pyrrole **3.28** (3.25 g, 0.00987 mol) dissolved in ethanol (10 ml) was stirred vigorously as hydrochloric acid (10 M, 3.7 ml) was slowly added at 20 °C. Then the reaction mixture was heated to 67 °C for 1 h, cooled to 5 °C and poured into ice cold water. The solid was collected by filtration and washed with water to yield the desired product. The wet product was transferred into CH₂CH₂ (100 ml). The solution was placed into a separatory funnel and organics separated over a water (50 ml) washing. The organic layer was then dried over anhydrous Na₂SO₄, filtered, and the volatiles were removed under reduced pressure to yield a brownish oil that crystallized on standing. The yield was 2.12 g, 0.00925 mol, 94%. mp 72-74 °C ¹H NMR (400 MHz, CDCl₃): δ, ppm 8.08 (s, 1H), 7.32-7.18 (m, 5H), 6.22 (s, 1H), 5.18 (s, 2H), 2.36 (s, 3H), 2.14 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ, ppm 166.26, 137.18, 136.53, 128.62, 128.07, 127.94, 121.84, 114.55, 110.55, 65.25, 14.40, 12.95.

3.4.5. Benzyl 2-iodo-3,5-dimethylpyrrole-4-carboxylate (3.30)

Pyrrole **3.29** (2.1g, 0.00916 mol) was dissolved in 30 ml of 1,2-dichloroethane (DCE). Sodium bicarbonate (1.92 g, 0.0229 mol) was added into the solution followed by water (20 ml). The suspension was heated at 50 °C for 10 min. I₂/KI solution (10 ml water, 0.0133 mol / 0.0266 mol, 3.37 / 4.41 g) was added dropwise to the above suspension at 70 °C. After complete addition, the mixture was left to stir at reflux (70 °C) for an extra 1 h. Saturated sodium thiosulfate was added to the cooled mixture dropwise to discharge excess iodine. The solution was then diluted with CH₂Cl₂ (30 ml) and transferred into a separatory funnel. The organics were separated, dried over anhydrous Na₂SO₄, filtered and the volatiles were removed under reduced pressure. Silica gel column chromatography was carried out, eluting with CH₂CH₂ (4 X

9)cm to afford the desired product. (1.96 g, 0.0055 mol, 60%). mp 127 °C ¹H NMR (400 MHz, CDCl₃): δ, ppm 8.04 (s, 1H), 7.57-7.27 (m, 5H), 5.30 (s, 2H), 2.50 (s, 3H), 2.22 (s, 3H). ¹³C NMR (400 MHz, CDCl₃): δ, 164.75, 139.98, 136.92, 128.70, 128.19, 128.10, 127.25, 112.13, 77.55, 77.23, 76.91, 65.59, 64.41, 14.80, 14.56. HRMS (ESI) *m/z* 356.0121 [M+H]⁺, calcd. for C₁₄H₁₅INO₂ 356.0142.

3.4.6. Dibenzyl 2,2',5,5'-tetramethylbipyrrole-4,4'-dicarboxylate (3.31)

Activated zinc was obtained by washing zinc dust with 3M HCl and then filtering through filter paper, after which it was washed successively with water, ethanol, and diethyl ether, and then dried under vacuum. A mixture of Pd/C (1.0 g) and activated zinc powder (1.08 g, 0.0166 mol, 3 eq) were placed in a dry 100 ml round bottom flask. After removing air under vacuum, the flask was filled with argon. Acetone (10 ml) was added to the reaction mixture and it was stirred at ambient temperature under argon for 15 min to activate the catalyst before adding the 2-iodopyrrole **3.30** (2.10 g, 0.00916 mol) dissolved in 25 ml of acetone. Distilled water (35 ml) was added through a syringe to the reaction flask. The reaction mixture was stirred vigorously at room temperature for 24 h under argon. It was filtered through a Celite cake. CH₂Cl₂ (40 ml) was added into the resulting mixture which was sonicated to form two layers. After removing the water layer with a separatory funnel, the organic solvents were collected and dried over anhydrous Na₂SO₄ before evaporation under vacuum. Purification was done using a silica gel column eluting with EtOAc/n-hexanes (1:2). Yield (0.50 g, 0.0011 mol, 20%). mp 197-200 °C (lit. mp²² 205.5-206.5 °C) ¹H NMR (400 MHz, CDCl₃): δ, ppm 8.09 (s, 2H), 7.44-7.29 (m, 10H), 5.28 (s, 4H), 2.46 (s, 6H), 2.12 (s, 6H). ¹³C NMR (100 MHz, CDCl₃) δ, ppm 164.74, 139.97, 136.92, 128.69, 128.18, 128.10, 127.25, 112.12, 65.59, 64.40, 14.79, 14.55. HRMS (ESI) *m/z* 457.2130 [M+H]⁺.

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CHAPTER 4: SYNTHESIS OF BENZO-BRIDGED 1,2-DI(2-PYRROLYL)ETHENES AND THEIR CONSTITUENT MACROCYCLES

4.1. Background

1,2-Di(2-pyrrolyl)ethenes **4.1** (Figure 4.1) are molecules composed of two pyrroles joined or bridged, typically by an alkene moiety (highlighted in blue color in Figure 4.2). Such a structure is found in several porphyrinoid macrocyclic structures such as porphycenes¹ **4.2**, corphycene **4.3** (porphycerin),^{2,3} hemiporphycenes **4.4**,² stretched porphycenes **4.5**, and isocorroles **4.6**⁴ (Figure 4.2).⁵

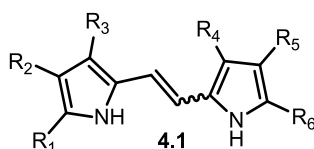


Figure 4.1: Generalized structure of 1,2-di(2-pyrrolyl)ethenes.

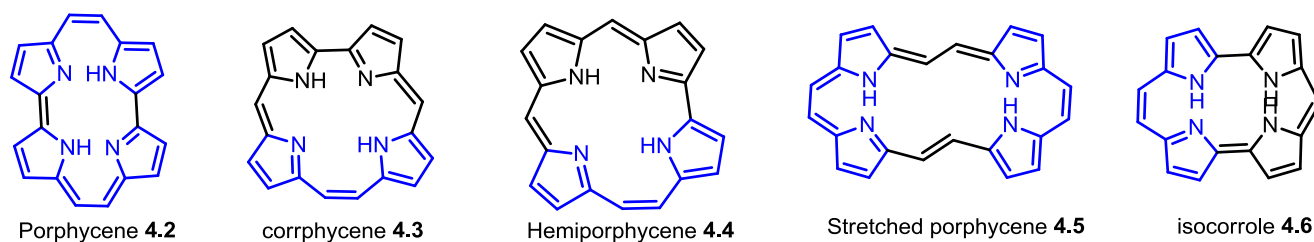
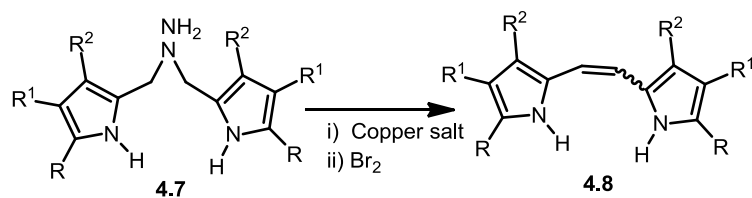


Figure 4.2: Generalized structure of some of the porphyrin isomers.

Therefore, 1,2-di(2-pyrrolyl)ethenes are building blocks of interest in our research for targeted potential photosensitizing agents and dyes such as porphycenes. Figure 4.1 shows a generalized structure of 1,2-di(2-pyrrolyl)ethenes. Dipyrrolylethenes typically have a long-wavelength absorption peak at 387 nm with violet fluorescence due to extended conjugation which is absent in pyrroles.⁶ Substitution of the structure with ethene linkages or aryl- groups increases the conjugation; hence the absorption is red-shifted.

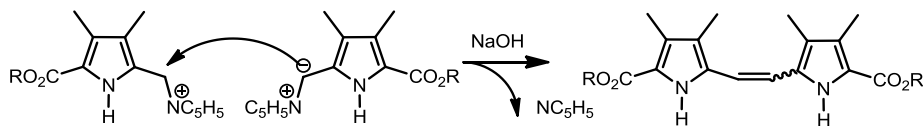
4.1.1. Synthesis

Fischer and Scheyer⁷ synthesized 1,2-di(2-pyrrolyl)ethene by oxidation of *N,N*-di(2-pyrrolylmethyl)hydrazine **4.7** using cuprammonium salts, to give 1,2-di(2-pyrrolyl)ethene **4.8** followed by a bromine assisted re-oxidation to give 1,2-di(2-pyrrolyl)ethenes (Scheme 4.1).



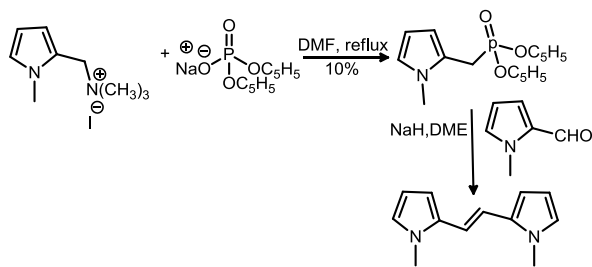
Scheme 4.1 Fischer synthesis of 1,2-di(pyrrolyl)ethenes.⁷

In 1965, Hayes *et al.* prepared 1,2-di(2-pyrrolyl)ethenes in low yield by a base-catalysed reaction of 1-(2-pyrrolylmethyl)pyridinium salt, (Scheme 4.2).⁶



Scheme 4.2: Base-catalysed synthesis of 1,2-di(2-pyrrolyl)ethenes.

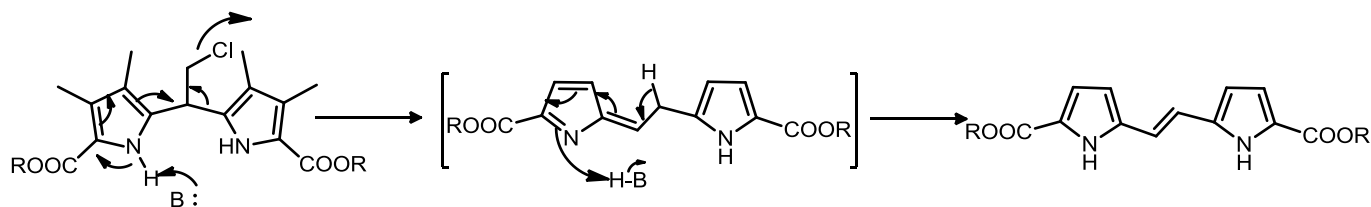
Werner *et al.* followed a Horner–Wadsworth–Emmons reaction approach to synthesize the di(pyrrolyl)ethene starting from trimethyl-(2-pyrrolylmethyl)ammonium iodide and 2-formylpyrrole. In this way, unsymmetrical di(pyrrolyl)ethenes were accessed in the *E*-configuration, but in low yields except when the pyrrolic NH was methyl protected (Scheme 4.3).⁸



Scheme 4.3: Horner–Wadsworth–Emmons 1,2 di(pyrrolyl)ethene synthesis.⁸

In 1994, Smith *et al.* isolated 1,2-di(2-pyrrolyl)ethene⁹ as a minor product as they attempted to synthesize 1,1-di(2-pyrrolyl)ethene. An acid catalyzed condensation of 2-unsubstituted pyrrole with chloroacetaldehyde diethyl acetal and an excess of Montmorillonite K-10 clay and TFA in dichloromethane gave 5-(chloromethyl)-dipyrromethane. Base treatment

(DBU) of 5-(chloromethyl)-dipyrromethane in dichloromethane provided 1,1-di(2-pyrrolyl)ethene and the *trans*- and *cis*- configurations of 1,2-di(2-pyrrolyl)ethene (Scheme 4.4).



Scheme 4.4: Proposed mechanism for the formation of 1,2-di(2-pyrrolyl)ethene during base catalysed elimination from 5-(chloromethyl)-dipyrromethane.⁹

4.2. Syntheses

4.2.1. Syntheses of 1,2 Di(pyrrolyl)ethene Derivatives

It is obvious that all the methods discussed above afford *E*-configurations of 1,2-di(2-pyrrolyl)ethene, but the *cis*-configuration is needed for our cyclization to produce a macrocycle. There was need for locking the configuration as *cis*- in order to close the porphycene. Therefore, a different route for the synthesis of 1,2-di(pyrrolyl)ethene that would give the *cis*-configuration was sought (Figure 4.3).

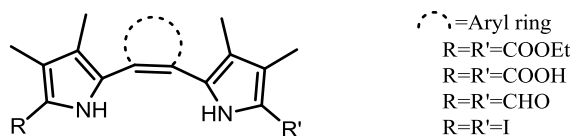
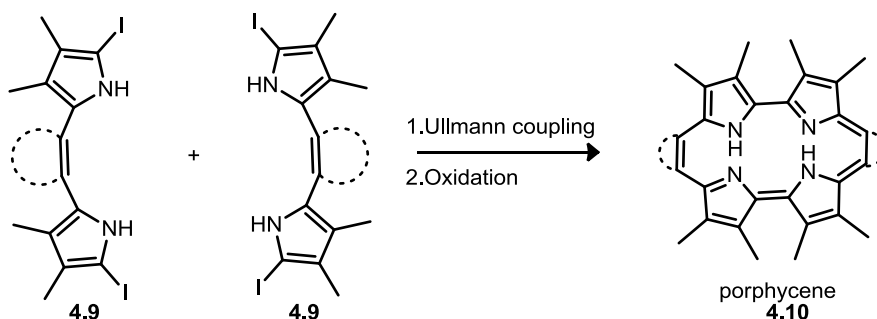


Figure 4.3 Generalized structure of targeted 1,2-di(2-pyrrolyl)ethenes.

Scheme 4.5 shows our approach to porphycene synthesis from diido-di(2-pyrrolyl)ethene through the modified Ullmann coupling designed by our group in 2007,¹⁰ followed by oxidation in air, or by using DDQ. In this chapter, the synthetic journey to it and other porphyrin isomers previously described is reported.

To investigate and understand the overall structure of 1,2-di(2-pyrrolyl)ethene, it was decided to synthesize 1,2-di(2-pyrrolyl)ethene from 1,2-di(2-pyrrolyl)ethyne **4.25**. This synthesis began by preparation of the ethyl ester pyrrole carboxylate **4.17** following the Barton-Zard protocol¹¹ which involves an initial Aldol-Henry reaction between acetaldehyde **4.11** and nitroethane **4.12** to afford 2-nitrobutan-3-ol **4.13**.

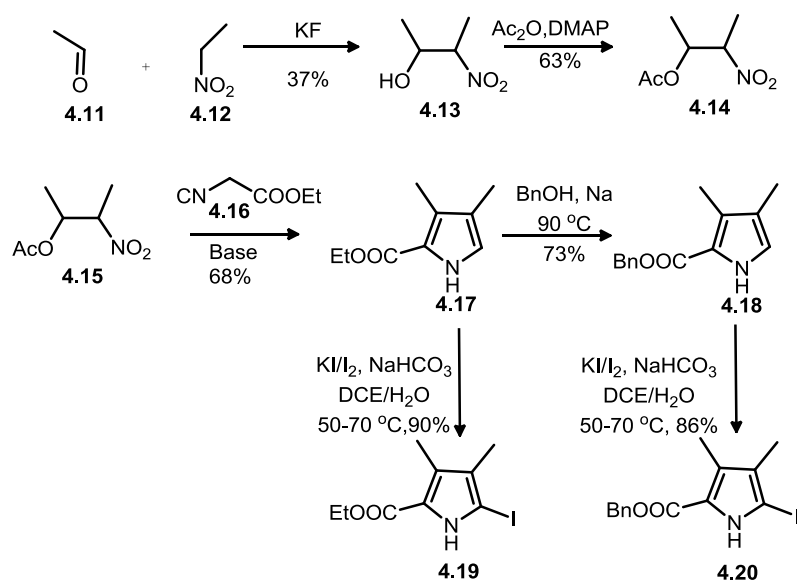


Scheme 4.5: General approach to synthesis of porphycenes **4.10** from targeted 1,2-di(2-pyrrolyl)ethene **4.9**.

The alcohol obtained was then acetylated by acetic anhydride and subjected to a Michael cyclization reaction with ethyl isocyanoacetate **4.16** under basic conditions to give the expected α -free pyrrole carboxylate **4.17** in 63% yield. Ethyl ester pyrrole **4.17** was then transesterified in refluxing benzyl alcohol¹² to afford benzyl ester pyrrole in 73% yield. The two α -free ester pyrrole carboxylates were then iodinated quantitatively using an iodine/potassium iodide mix by refluxing in methanol or dichloromethane and quenching with saturated sodium thiosulfate (Scheme 4.6).

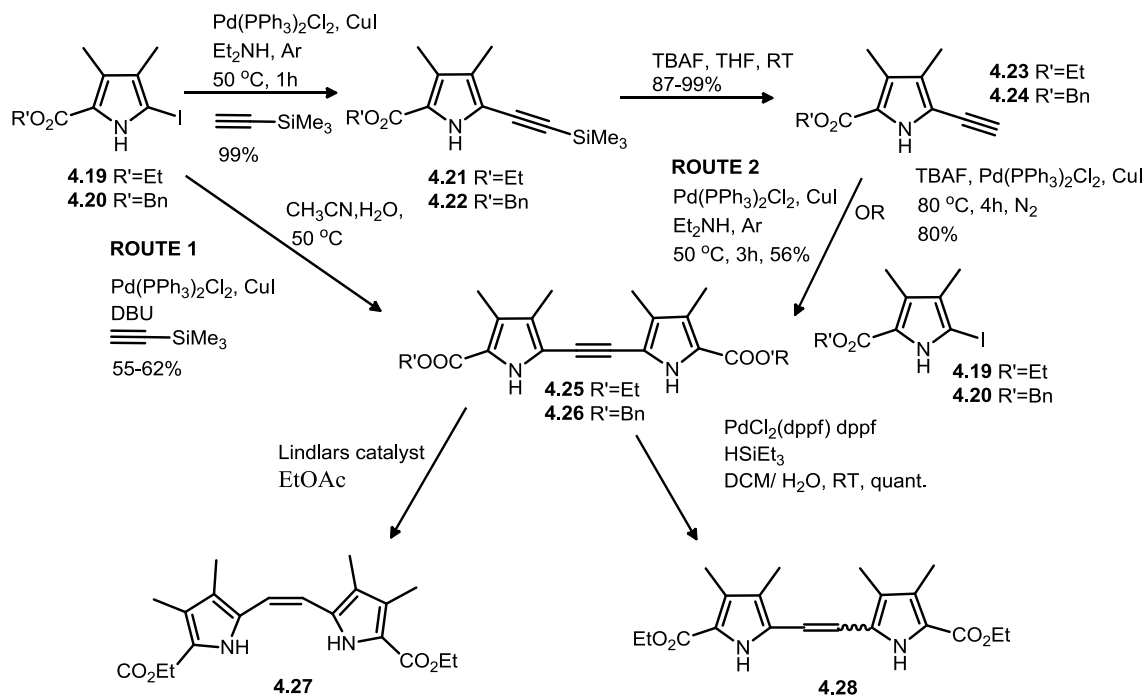
Sonogashira coupling¹³ of two equivalents of the iodopyrroles **4.19** and **4.20** with (trimethylsilyl)acetylene was approached in two ways;

Route 1: 2-Iodopyrroles **4.19** and **4.20** were coupled with (trimethylsilyl)acetylene as a source of the two carbon atom alkynyl bridge moiety in a one pot reaction following Grieco's method.^{14,15} This method is restricted to symmetrical 1,2-di(2-pyrrolyl)ethynes. The method takes advantage of the in-situ deprotection of (trimethylsilyl)acetylene by DBU eliminating an extra step of deprotection, work-up and column purification, hence saving time.



Scheme 4.6: Synthesis of 2-iodopyrroles **4.19** and **4.20**.

The internal alkynes **4.25** and **4.26** were obtained in 55 and 62% yield, respectively (Scheme 4.7). X-Ray crystal structures of internal alkynes **4.25** and **4.26** are shown in Figure 4.4 below. The two compounds adopt an almost planar conformation. The crystals were grown by slow evaporation of their dichloromethane/hexanes (5:1) solutions.



Scheme 4.7: Attempted synthesis of *cis*-1,2-di(2-pyrrolyl)ethene **4.27**.³⁰

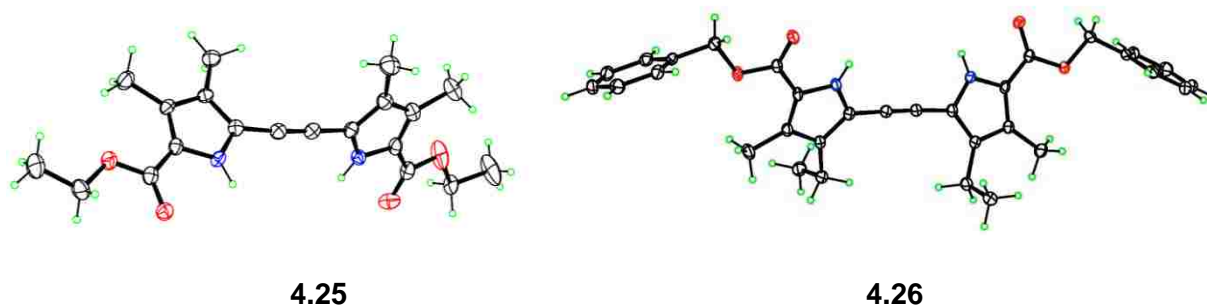


Figure 4.4: X-Ray structures of 1,2-di(2-pyrrolyl)ethynes **4.25** and **4.26** with 50% ellipsoids.

Route 2: 1,2-Di(2-pyrrolyl)ethynes **4.25** and **4.26** were synthesized in three steps according to the literature.^{16,17} The procedure involved acetylation of the 2-iodopyrroles **4.19** and **4.20** with (trimethylsilyl)acetylene followed by base-catalyzed desilylation (TBAF) before a second Pd(II) Sonogashira coupling was effected.

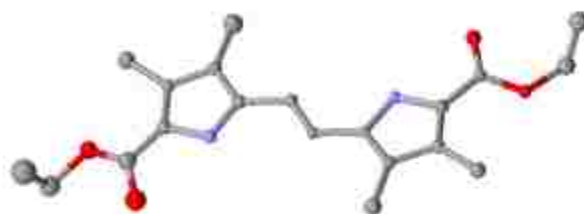


Figure 4.5: X-Ray structure of *trans*-1,2-di(2-pyrrolyl)ethene.

In this case, 2-iodopyrrole carboxylate was first coupled to (trimethylsilyl)acetylene employing a catalytic amount of bis(triphenylphosphine)palladium(II) dichloride and copper(I) iodide in freshly dried diethylamine at 50 °C to afford silyl-terminated pyrrole acetylenes **4.21** and **4.22** in 99% yields. The silyl-terminated acetylene pyrrole was then quantitatively desilylated using *n*-Bu₄NF in THF to afford deprotected acetylene pyrroles **4.23** and **4.24** in 87-99% yield. With the acetylene pyrrole at hand, a second Sonogashira coupling was performed using 2-iodopyrrole as a counterpart to give the internal alkyne dipyrrole in 56% yield. This route can also be used to synthesize unsymmetrical internal alkynes. Similarly, 1,2-di(2-pyrrolyl)ethyne **4.25** was

accessed in higher yields (80%), using the Li *et al.* protocol; these authors used copper, amine and solvent-free conditions for the Sonogashira coupling.¹⁸

To reduce the alkyne to alkene, catalytic hydrogenation using Lindlars' poisoned catalyst was first attempted. After an overnight reaction under a hydrogen balloon and work-up, an oily product was isolated which was proven to be the *cis*-1,2-di(pyrrolyl)ethene **4.27** by using NMR data. The ¹H NMR showed a symmetrical molecule after integration with no *trans*-coupling of alkenylic protons. The oily product was hard to crystallize even after many attempts.

A recent alternative stereoselective procedure to reduce the internal alkyne to the *cis*-1,2-di(pyrrolyl)ethene using triethylsilane was then attempted. Interestingly, in our hands this method yielded the *trans*-isomer.¹⁹ With the help of Dr. Fronczek, the X-ray structure was obtained and it was shown to be the *trans*- isomer (Figure 4.5). It is also worth mentioning that two different types of crystals were observed with this method; prismatic crystals (*trans*-isomer) and very thin irresolvable needles that we assume are the *cis*-isomer. Next steps could not be accomplished with the *cis*-isomer of the di(pyrrolyl)ethene since the alkene would be lost if subjected to the reaction conditions (hydrolysis, acid work-up, and decarboxylative iodination). The solution to this problem, as earlier mentioned, is to lock the internal alkene into a *cis*-conformation using a substituent. This can be done in three ways:

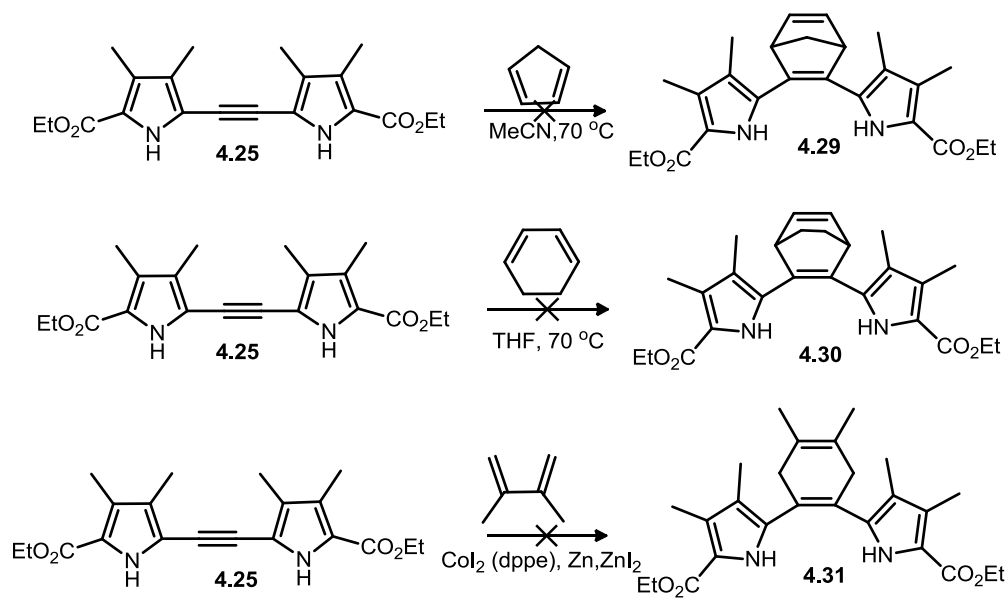
- i. Diels Alder reaction of the internal alkyne (as the dienophile);
- ii. Larock indole synthesis on the internal alkyne,²⁰
- iii. Synthesis of benzene or *o*-xylene bridged 1,2-di(2-pyrrolyl)ethene via Suzuki²¹ or Stille coupling,²²

Route 1: Diels Alder reaction on the internal alkyne.

The Diels-Alder reaction of internal alkenes has been demonstrated. Although the reaction requires harsh conditions,²³⁻²⁶ the use of a catalyst,²⁷ or long reaction times, it was attempted. Internal alkyne **4.25** in acetonitrile was refluxed with cyclopentadiene or

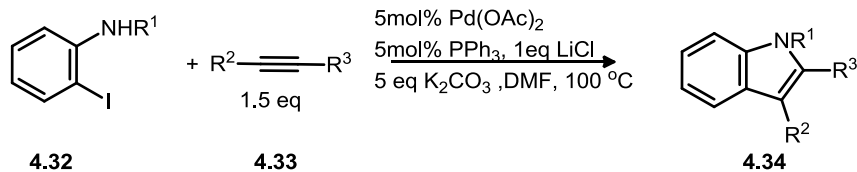
cyclohexadiene in an attempt to form 1,2-di(2-pyrrolyl)ethene derivatives **4.29** and **4.30**, respectively. The reaction yielded no product, and all the alkyne starting material was recovered. The use of a cobalt(II) complex as a catalyst also failed to furnish 1,2-di(2-pyrrolyl)ethene derivative **4.31** during the Diels-Alder reaction of the internal alkyne and 2,3-dimethyl-but-1,3-diene (Scheme 4.8).

All these reactions most likely failed due to the electron richness of the pyrrolic system. The reaction probably requires an inverse electron-demand Diels-Alder (DA_{inv}) transformation using an electron poor diene such as 2,4-cyclopentadien-1-one.



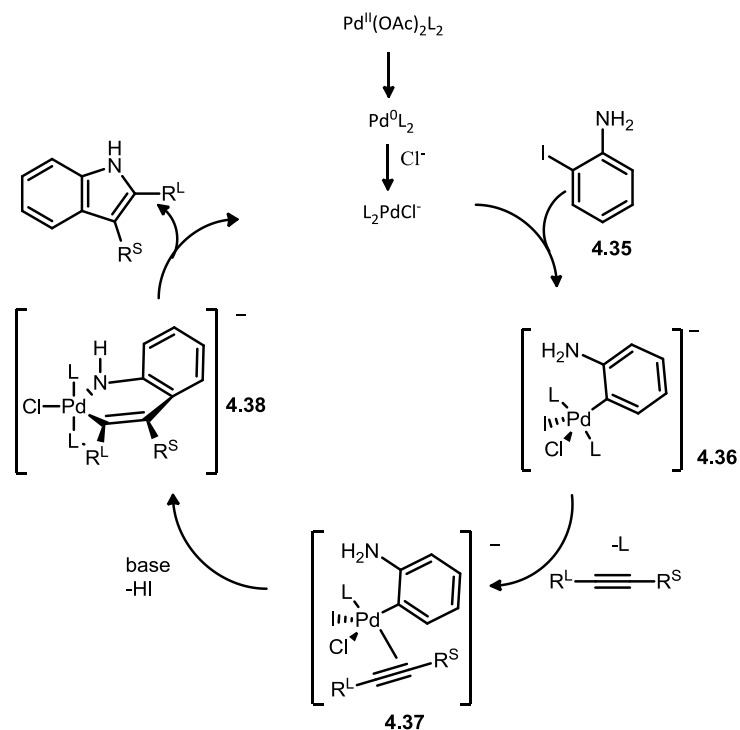
Scheme 4.8: Attempted Diels-Alder reactions of 1,2-di(2-pyrrolyl)ethyne **4.25**.
Route 2: Larock indole synthesis on the internal alkyne.

The Larock indole synthesis is generally a Pd(II) base-catalyzed heteroannulation reaction between 2-iodoaniline derivatives **4.32**, and internal or terminal alkynes such as **4.33**.^{20,28} *o*-Bromoanilines are usually unreactive, so the reaction is traditionally done using *o*-iodoanilines. The reaction is also very regioselective, giving products with the nitrogen atom of the indole formed facing the most sterically bulky group in the case of unsymmetrical alkynes.²⁰ Interestingly, internal alkynes terminated with sterically bulky groups like tertiary alkyl groups gave high yields (Scheme 4.9).



Scheme 4.9: General reaction scheme of Larock indole synthesis.

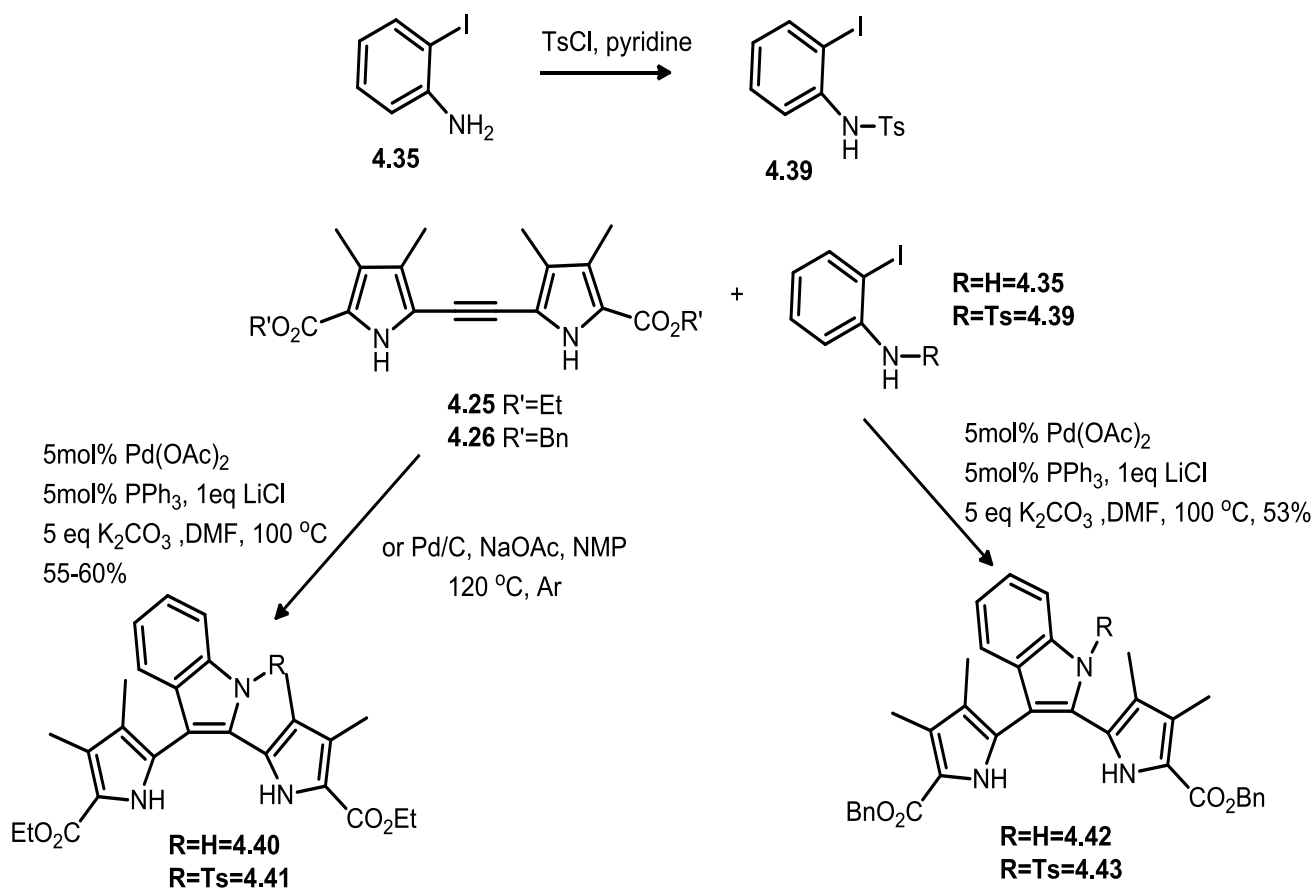
Larock *et al.* presumed that the reaction takes place in six main steps. (1) Pd(OAc)_2 is reduced to Pd(0) , (2) formation of a chloride-ligated zerovalent palladium species by coordination of a chloride,²⁹ (3) oxidative addition of the aryl iodide to Pd(0) to form species **4.36**, (4) coordination of the alkyne to the palladium atom of **4.36** to form complex **4.37**, followed by *syn*-insertion of the alkyne into the aryl-palladium bond, (5) halide displacement by the nitrogen atom of the vinylic palladium intermediate to form a six-membered palladacycle **4.38**, and (6) reductive elimination to afford the target indole and to recycle Pd(0) (Scheme 4.10).



Scheme 4.10: Catalytic cycle of Indole synthesis.^{28,29}

Motivated by the development of the above reaction by Larock *et al.*, our research group had reported the synthesis of indolyldipyrroles. The reaction was effected using 1,2-di(2-

pyrrolyl)ethynes **4.25** and **4.26** and 2-iodoaniline (Scheme 4.11).³⁰ The two starting materials were heated at 100 °C in *N,N*-dimethylformamide in the presence of LiCl, and palladium acetate (with or without using a triphenylphosphine ligand) to yield the indolyldipyrroles in acceptable yields. The reaction was best when the aniline –NH₂ was protected with a tosyl- group to furnish *N*-tosyl-2-iodoaniline **4.39**.³¹ Since our internal alkynes were symmetrical, the regioselectivity of our products was not a concern (Figure 4.6).



Scheme 4.11: Synthesis of indolyldipyrroles.³⁰⁻³²

Indolyldipyrroles are structurally half-porphycenes. With the two compounds at hand, we decided to derivatize them into 5,5'-di-iodo-indolyldipyrroles. The two ethyl- and benzyl esters

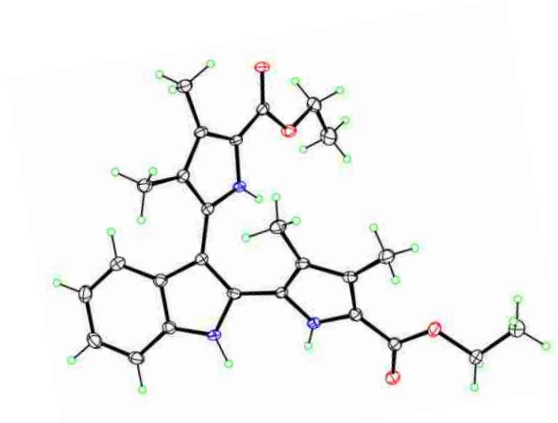
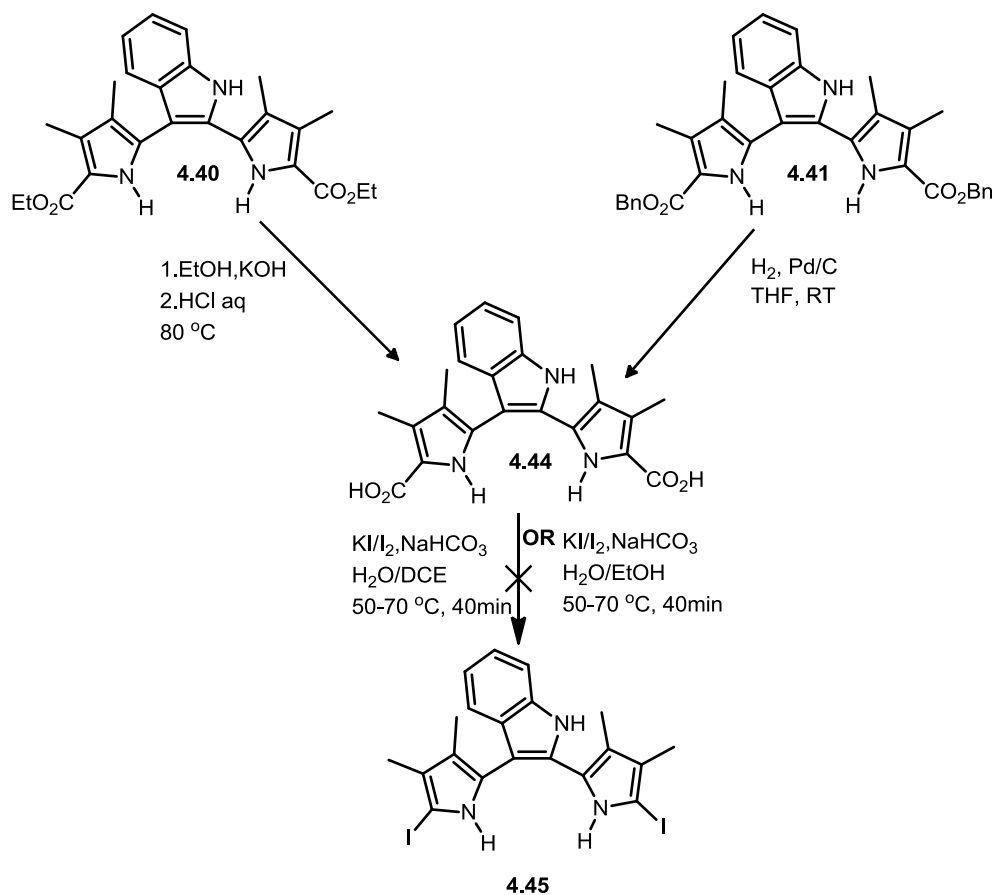


Figure 4.6: X-Ray structure of indolyldipyrroles **4.40** with 50% ellipsoids.

on the α,α' positions of the pyrroles in the indolyldipyrrole were then to be converted into iodides in the following ways: **1)** Indolyldipyrrole carboxylate **4.40** was base hydrolyzed in refluxing ethanolic potassium hydroxide solution to yield the salt, that gave the diacid **4.44**, after acidic work-up (Scheme 4.12). The reaction was followed by TLC, and was judged to be over only when a more polar spot was seen. **2)** Indolyldipyrrole carboxylate **4.42** was subjected to catalytic hydrogenolysis using Pd/C hydrogen gas (balloon) to afford the diacid **4.44**. The reaction was followed by TLC, and was judged to be over only when a more polar spot was seen. The synthesis of α,α' -diido-indolyldipyrrole **4.45** was then attempted by following a decarboxylative iodination protocol in basic media. Unfortunately, no desired product was detected or isolated. A possible reason for the failed reaction is that the indole moiety could be causing a competing side reaction that stops iodination on the pyrrolic rings.

Route 3: Synthesis of benzene- or *o*-xylene-bridged di(pyrrolyl)ethene via Stille and Suzuki coupling was attempted. The plan was to modify 2-iodopyrrole **4.19** by substituting the iodine with a stannyl or borate that could then be used for Stille^{22,33} or Suzuki coupling²¹ with 0.5 equivalents of 1,2-diodo-benzene derivative **4.47** or **4.48** to provide bis(pyrrol-2-yl)arene **4.49**.

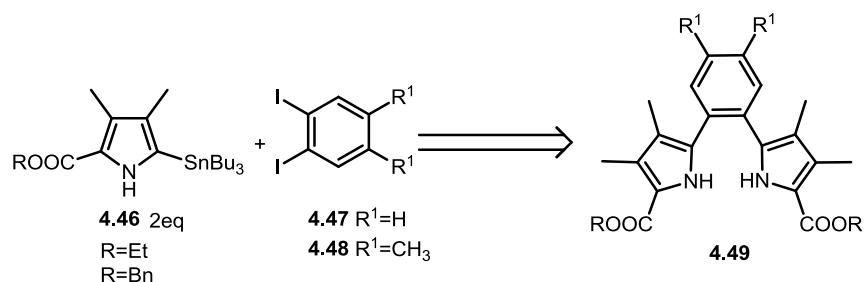


Scheme 4.12: Attempted synthesis of α,α' -diido-indolyldipyrrole **4.45**.

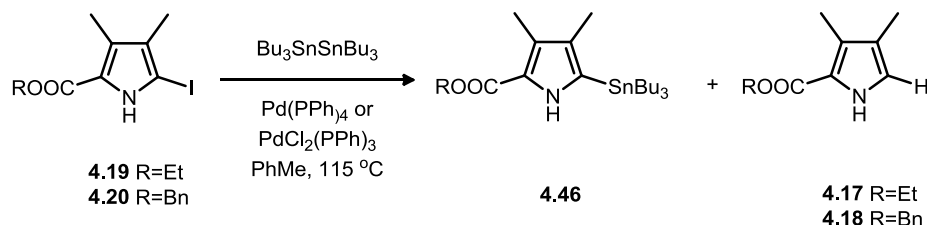
The pyrroles of choice were still 3,4-dimethyl-2-ethoxycarbonylpyrrole **4.17** and 3,4-dimethyl-2-benzyloxycarbonylpyrrole **4.18** as the ester on the pyrrole is known to stabilize the pyrrole nucleus towards degradation.

Bis(pyrrol-2-yl)arene **4.49** was first to be synthesized by a Stille coupling reaction between the stannyl pyrrole **4.46** and 1,2-di-iodobenzene derivative **4.47** and **4.48** (Scheme 4.13). For the synthesis of the Stille coupling substrate, a mixture of iodopyrrole **4.19**, bis(tributyltin), and a catalytic amount of Pd(0), was refluxed in toluene following a procedure developed by Pidcock *et al.*³⁴

Unfortunately, no desired product was obtained; instead, dehalogenated α -free pyrrole **4.17** was isolated. Possibly steric hindrance between the β -methyl of the 2-iodopyrrole, and the three n-butyl- groups of the bis(tributyltin) reagent, is the reason (Scheme 4.14).

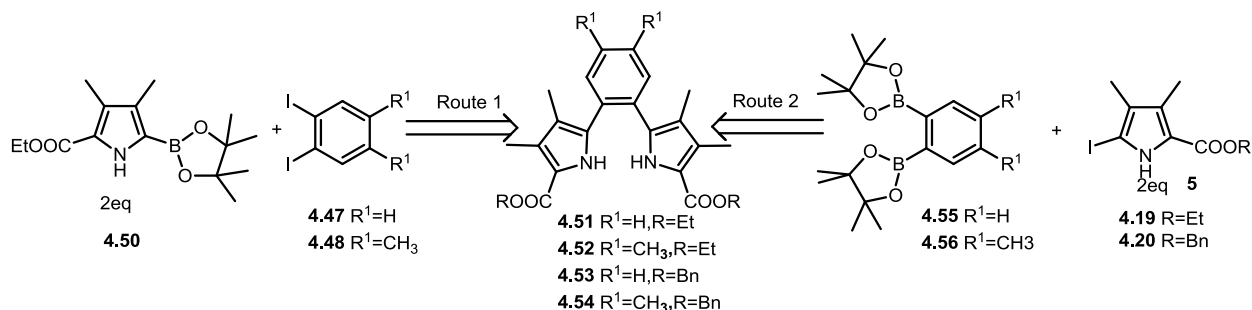


Scheme 4.13: Synthetic plan for the synthesis of bis(pyrrol-2-yl)arene **4.49** by Stille Coupling



Scheme 4.14: Attempted synthesis of 2-(tributyltin)pyrrole-5-carboxylate.

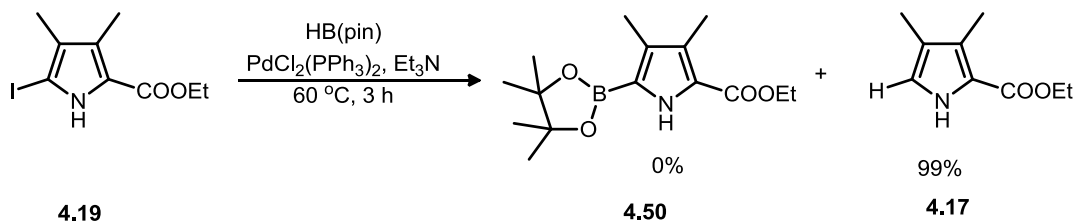
Alternatively, two mole equivalents of the 2-iodopyrrole derivatives could be reacted with one mole of 1,2-benzenediboronic acid bis(pinacol ester) moiety **4.55** or **4.56** to afford bis(pyrrol-2-yl)arenes **4.51-4.54** (Scheme 4.15).



Scheme 4.15: Synthetic plan for the synthesis of bis(pyrrol-2-yl)arene **4.51-4.54** by Suzuki coupling.

Route 1: In this synthetic plan, the synthesis of the 2-borylpyrrole was attempted by following a procedure developed recently by Setsune *et al.*³⁵ This group reported that their method is superior to previous methods^{36,37} as there was no need to protect the pyrrolic nitrogen, hence eliminating one synthetic step. In addition to that, this protocol avoids oxidative self-coupling side-reactions that occur during Suzuki coupling of the 1,2-diiodobenzene and the

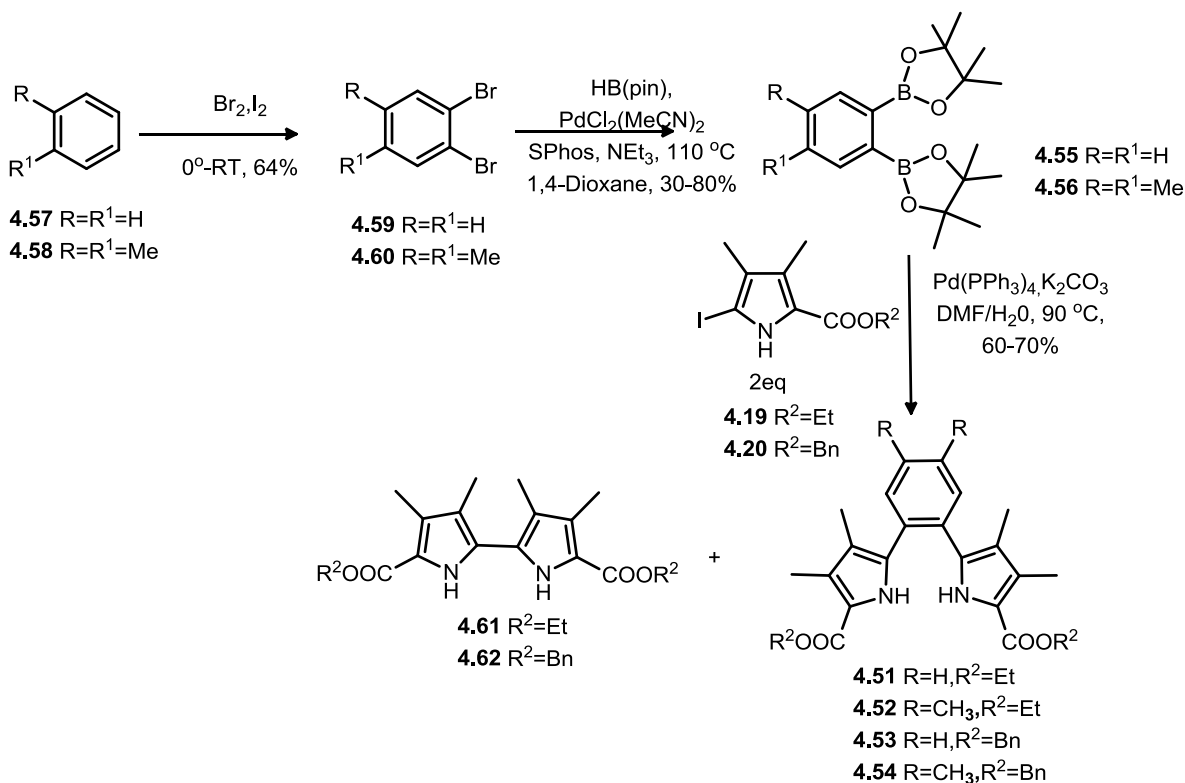
2-borylpyrrole. Only one other earlier literature report by Miyaura *et al.* had this advantage, although it only worked with sterically unhindered pyrroles.³⁸ 2-Iodopyrrole **4.19** was therefore subjected to the borylation conditions using pinacolborane in the presence of a Pd(II) catalyst and base. Unfortunately, we were unable to reproduce their results. Only the dehalogenated product **4.17** was isolated, which is the substrate in the synthesis of the 2-iodopyrrole (Scheme 4.16).



Scheme 4.16: Attempted synthesis of 2-borylpyrrole **4.50**.³⁵

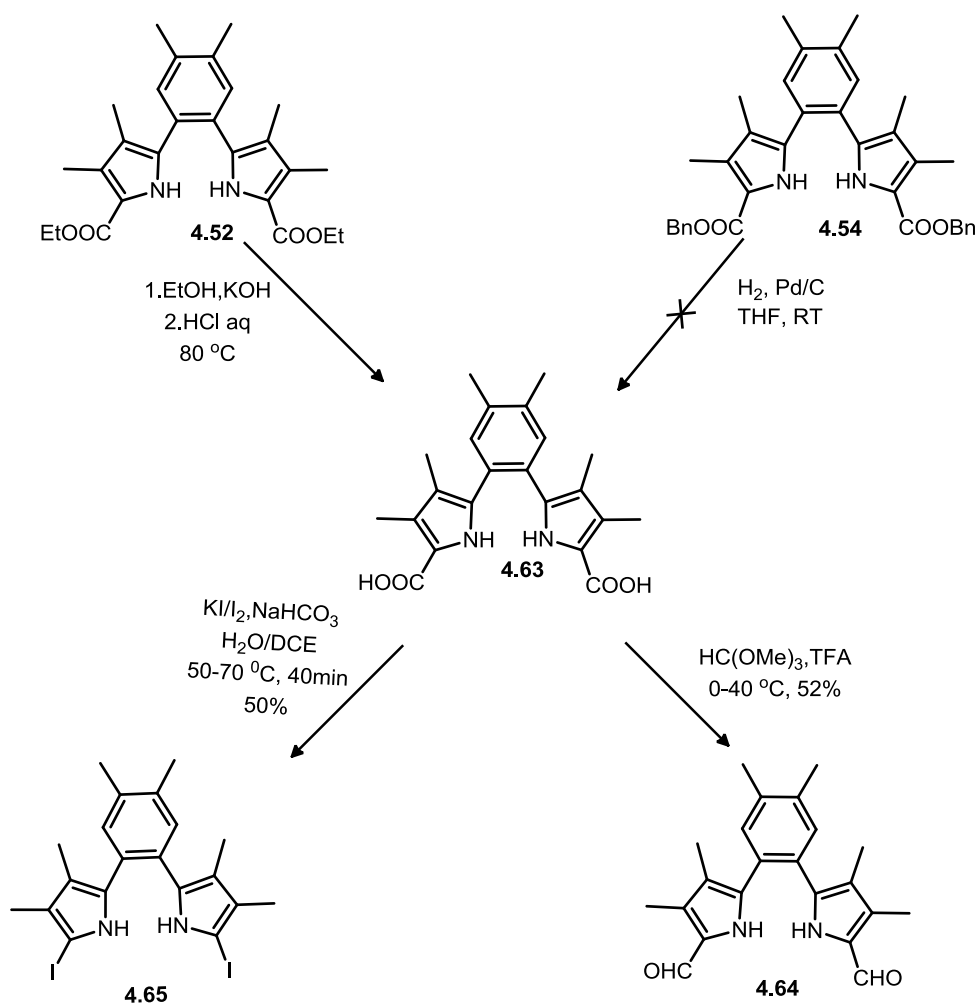
Route 2: Following the failure of route 1, route 2 of the planned retro-synthesis (Scheme 4.15) was adopted. In this route, the diboron pinacol esters is installed first on the *o*-xylene or benzene substrates, then it is used in a Suzuki coupling with the 2-iodopyrroles. Benzene **4.57** and *o*-xylenes **4.58** were dibrominated using liquid bromine at 0 °C to give 1,2 dibromo- adducts such as **4.59** and **4.60** in about 64% yield.³⁹ Using the method developed by Buchwald and Billingsley, the 1,2-dibromoaryls were then subjected to borylation reaction conditions by heating in 1,4-dioxane at 110 °C in the presence of a Pd(II) catalyst, SPhos, and triethylamine to afford the 1,2-bis(pinacolatoboryl)benzenes **4.55** and **4.56** in 30-80% yields (Scheme 4.17).⁴⁰⁻⁴¹ Two equivalents of the 2-iodopyrrole were then coupled to the 1,2-bis(pinacolatoboryl)benzenes **4.55** and **4.56** in a typical Suzuki coupling reaction to afford the benzene bridged dipyrrole compounds **4.51-4.54** in 60-70% yields. The Ullmann coupled bipyrrole **4.61** by-product (Figure 4.7) was also isolated and characterized as shown by X-Ray crystallography (Figure 4.7). Bis(pyrrol-2-yl)benzene diesters **4.52** and **4.54** were then quantitatively hydrolyzed to the diacid **4.63** under basic conditions in refluxing ethanol. Catalytic debenzoylation of **4.54** was

unsuccessful, so basic hydrolysis was selected. Decarboxylative iodination of the diacid **4.63** provided 5,5'-diiodo-bis(pyrrol-2-yl)benzene **4.65** in 50% yield.



Scheme 4.17: Synthesis of bis(pyrrol-2-yl)benzenes.

With the diacid **4.63** at hand, acid catalyzed diformylation was performed. This reaction is a one-pot decarboxylation and formylation transformation. The diacid was decarboxylated in a limited amount of cold trifluoroacetic acid at 0 °C and formylated according to the Clezy formylation⁴² protocol, using trimethylorthoformate, to yield 5,5'-diformyl-bis(pyrrol-2-yl) *o*-xylene **4.64** in 52% yield (Figure 4.9). An alternate route (Scheme 4.19) to 5,5'-diformyl-bis(pyrrol-2-yl) *o*-xylene **4.64** was also followed, whereby 2-formyl-5-iodo pyrrole **4.67** was coupled to the 1,2-bis(pinacolatoboryl)-*o*-xylene **4.56** by a typical Suzuki coupling reaction to afford the bridged dipyrrole compound **4.64** in lower overall yield. The deficit is accounted for by the low yielding synthesis of 2-formyl-5-iodopyrrole from the acid pyrrole starting material **4.66** that leads to competing substitution reaction of the aldehyde with iodine to give 2,5-diiodopyrrole **4.68** (Scheme 4.19).⁴³



Scheme 4.18: Synthesis of 5,5'-diformyl bis(pyrrol-2-yl) *o*-xylene **4.64** and 5,5'-diiodo bis(pyrrol-2-yl)-*o*-xylene **4.65**.

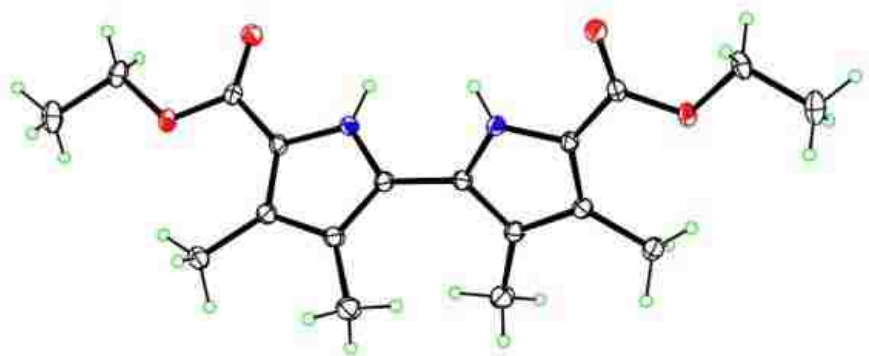
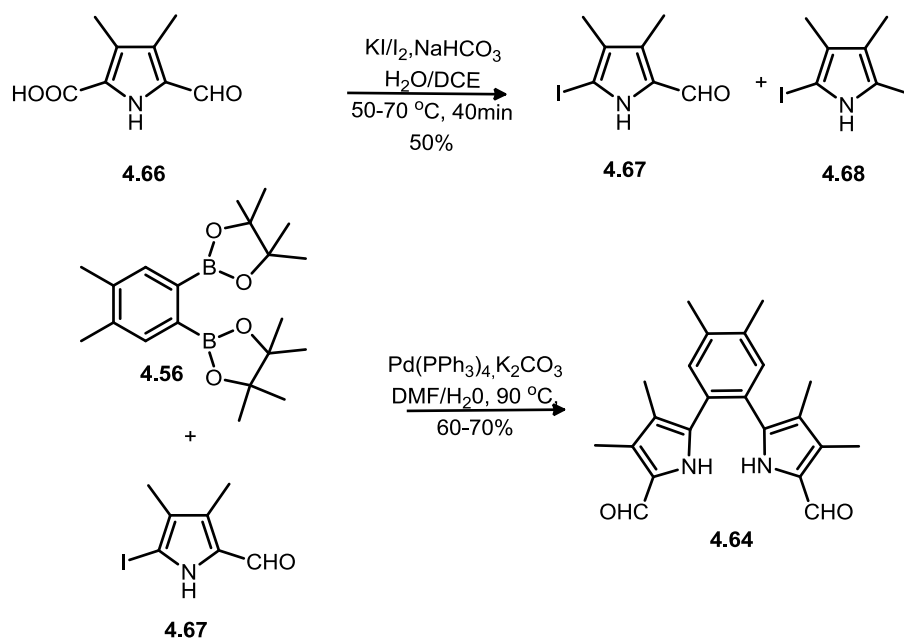


Figure 4.7: X-Ray structure of bipyrrole **4.61** with 50% ellipsoids



Scheme 4.19: Alternate synthetic route for the synthesis of 5,5'-diformyl-bis(pyrrol-2-yl)-*o*-xylene **4.64**.

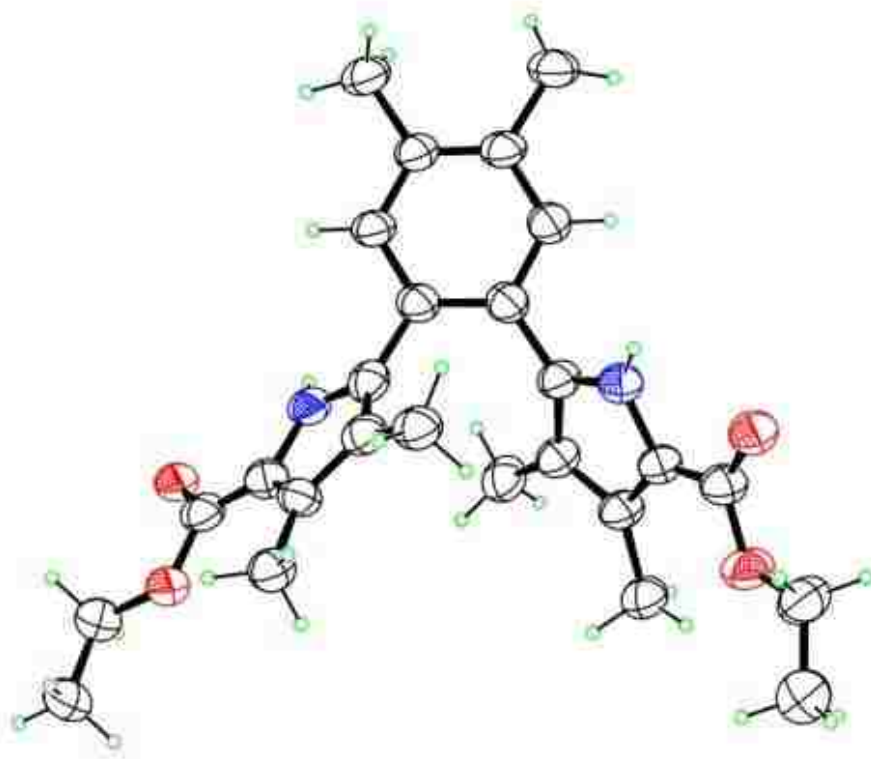


Figure 4.8: X-Ray structure of 5,5'-diester-bis(pyrrol-2-yl)-*o*-xylene **4.52** with 50% ellipsoids.

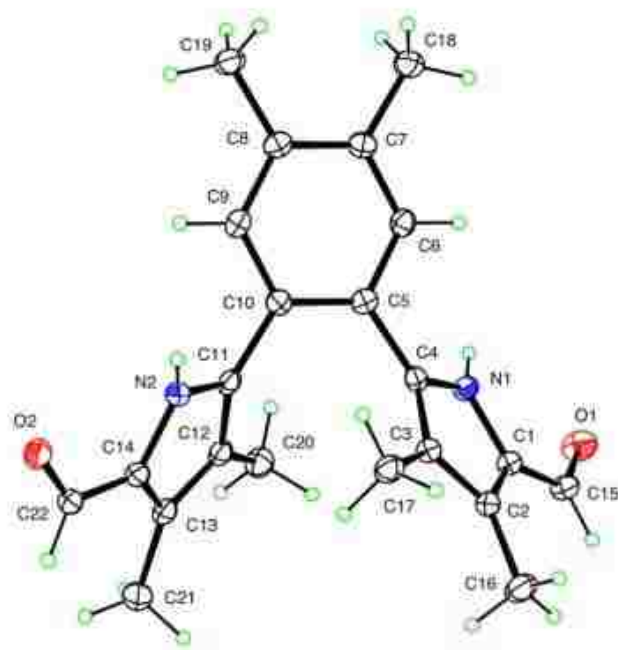


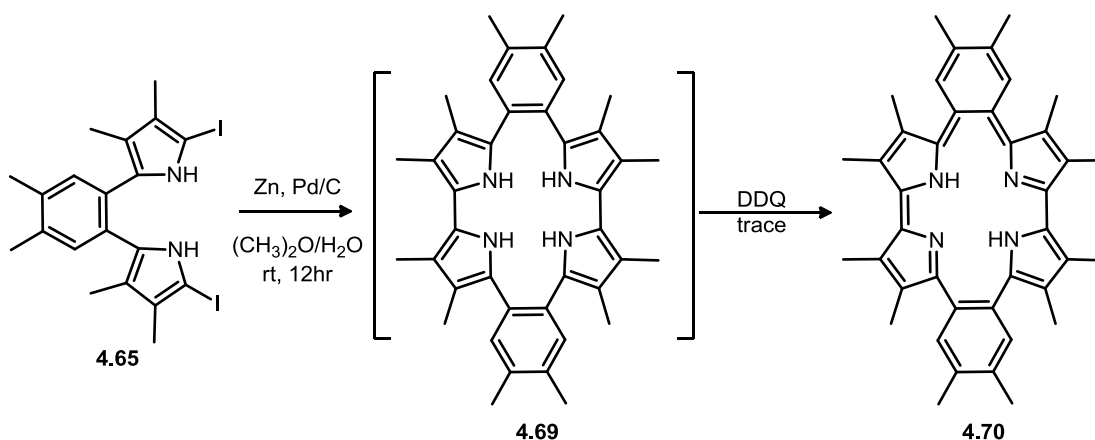
Figure 4.9: X-Ray structure of 5,5'-diformyl-bis(pyrrol-2-yl)-*o*-xylene **4.64** with 50% ellipsoids.

4.2.2. Syntheses of Macrocycles from 1,2-Di(pyrrolyl)ethene

After successful syntheses of the 1,2-di(pyrrolyl)ethene analogues the scene was set to attempt cyclization reactions. It was envisioned that the cyclization reactions would afford porphycenes (2.0.2.0) **4.2**, corphycenes (2.1.0.1) **4.3**, hemiporphycenes (2.2.2.2) **4.4**, and 2.1.2.1.

4.2.2.1. Ullmann Coupling

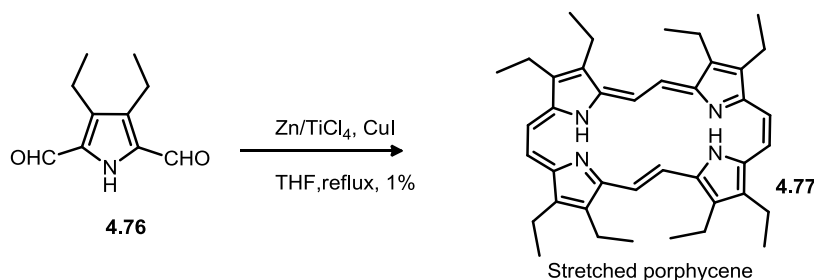
Porphycenes are traditionally made by a McMurry condensation reaction between two diformylbipyrroles.¹ Instead, it was decided to close the ring using reductive Ullmann coupling of 5,5'-diiodo-bis(pyrrol-2-yl)-*o*-xylene **4.65** following a modified Ullmann coupling procedure designed earlier in our research group.¹⁰ 5,5'-Diiodo-bis(pyrrol-2-yl)-*o*-xylene was coupled to itself using activated zinc and palladium/carbon in an acetone/water solvent mixture by stirring in an inert atmosphere overnight (Scheme 4.20). Although the reaction was successful, it only afforded the porphycene **4.70** in trace amounts after purification.



Scheme 4.20: Synthesis of porphycene by Ullmann coupling.

4.2.2.2. McMurry Coupling

22 π -Acetylene-cumulene porphycenes **4.73** were first reported by Vogel and coworkers.^{5,14} This group synthesized the stretched porphycenes in 18% yield by reductive coupling of acetylenic dipyrroledialdehyde **4.71** using low valent titanium.^{44,45} The product showed a large bathochromic shift of the Soret and Q-bands when compared to the porphycene analogue. Catalytic hydrogenation of acetylene-cumulene porphycene **4.73** with poisoned palladium provided tetrahydro-stretched porphycene **4.75**. Under the same conditions, 2,5-pyrroledicarbaldehyde **4.76** was condensed to afford the stretched porphycene **4.77** in 1% yield (Scheme 4.21).



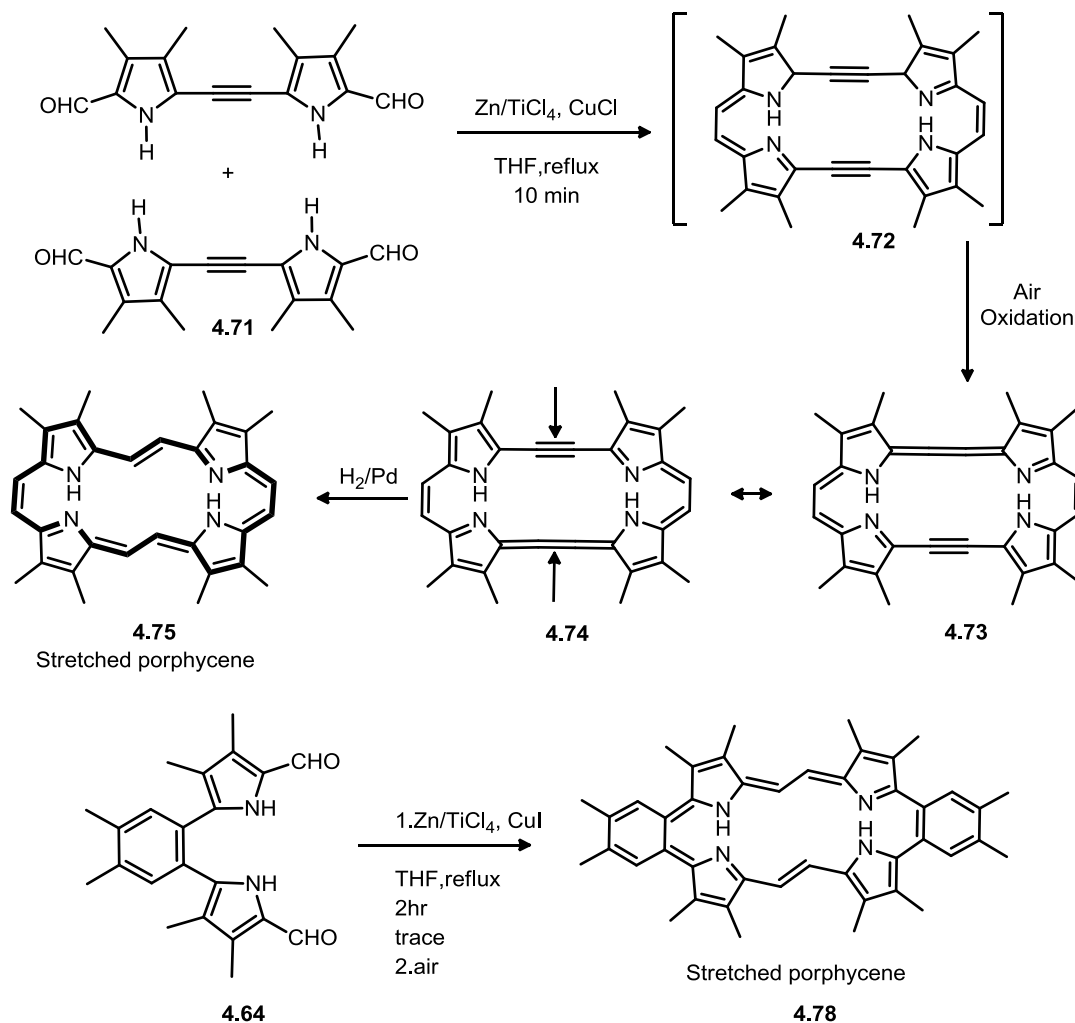
Scheme 4.21: Previous synthesis of stretched porphycenes.

We also synthesized stretched porphycenes **4.5** (2.2.2.2) through reductive coupling of 5,5'-diformyl-bis(pyrrol-2-yl)-*o*-xylene **4.64** with low-valent titanium (Scheme 4.22).⁴⁴ This reaction led to the formation of a pair of two bridging *meso*-sp² carbons in the macrocycle. After

oxidation in air, the expected non-polymeric product **4.78** was obtained in low yield, and was only detected and characterized by mass spectrometry. Complete characterization therefore requires further experimentation and larger samples.

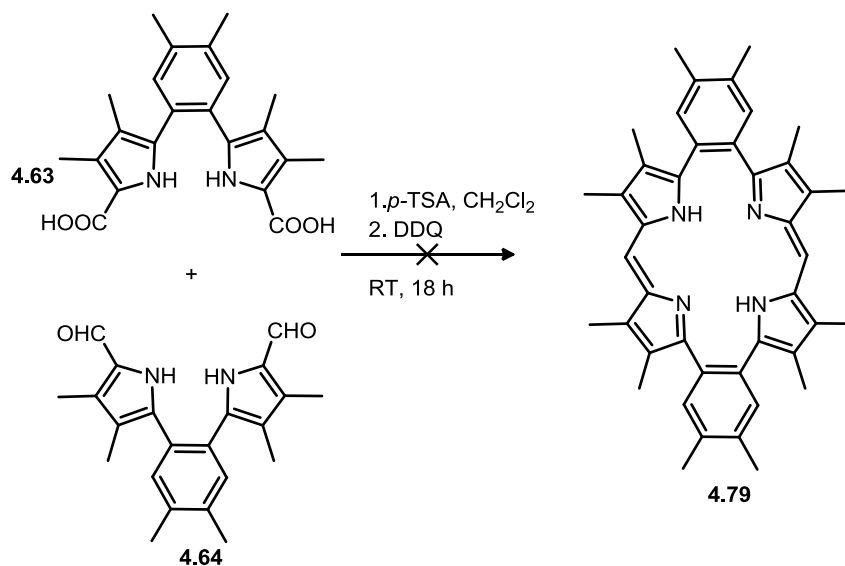
4.2.2.3. MacDonald condensations

2 + 2 MacDonald condensation⁴⁶ was also explored to incorporate bis(pyrrol-2-yl)-*o*-xylene into other isomeric porphyrin macrocycles, e.g the 2.1.2.1 system. This cyclization was attempted as a room temperature condensation reaction between the diacid- **4.63** and diformyldipyrrolylethene **4.64** in the presence of *para*-toluene sulfonic acid before oxidation of the crude mixture with oxygen or DDQ.



Scheme 4.22: Synthesis of stretched porphycene **4.78**.

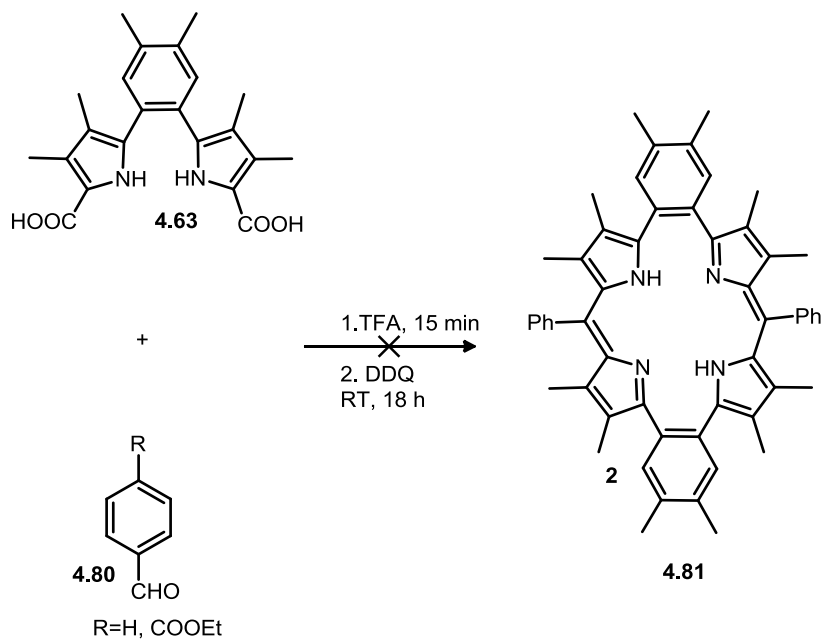
Unfortunately, only the dialdehyde starting material was isolated and no desired product **4.79** was obtained (Scheme 4.23). The failure of this reaction is attributed to the inability of *para*-toluene sulfonic acid to decarboxylate the diacid before the condensation reaction could occur. Trifluoroacetic acid was therefore used in a similar reaction but this time using benzaldehyde derivatives



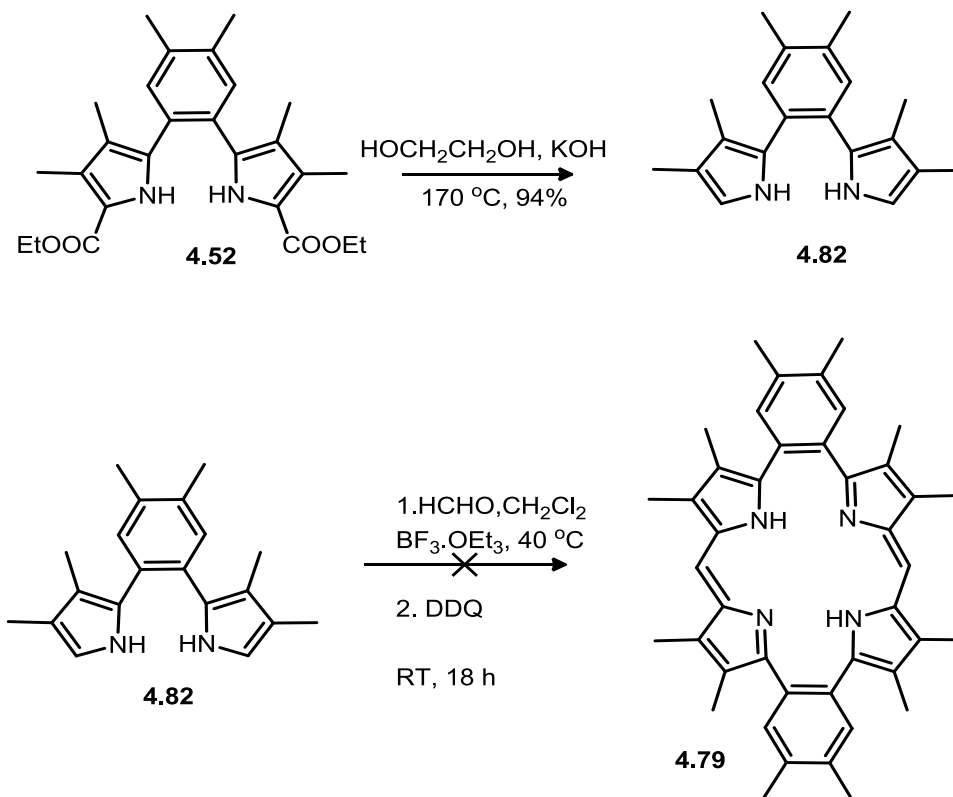
Scheme 4.23: Attempted Synthesis of macrocycle **4.79**.

. The diacid was first decarboxylated *in-situ* in presence of trifluoroacetic acid, before the benzaldehyde was added as a dichloromethane solution. The very dilute (2.84×10^{-3} M) reaction mixture was stirred overnight at room temperature and monitored by UV/Vis and thin layer chromatography. This reaction also failed, with no desired product being isolated, and instead the benzaldehyde **75** was recovered (Scheme 4.24).

A third MacDonald condensation attempt was performed using boron trifluoride diethyl etherate as the Lewis acid catalyst. The participating aldehyde of choice was formaldehyde and the decarboxylated α,α' -free dipyrroethene **4.82** was used. Compound **4.82** was obtained in 94% yield by a one-pot basic hydrolysis and thermal decarboxylation of the dicarboxylate **4.52** in ethylene glycol at 170 °C under inert conditions. This condensation reaction also failed with no starting material being recovered (Scheme 4.25).

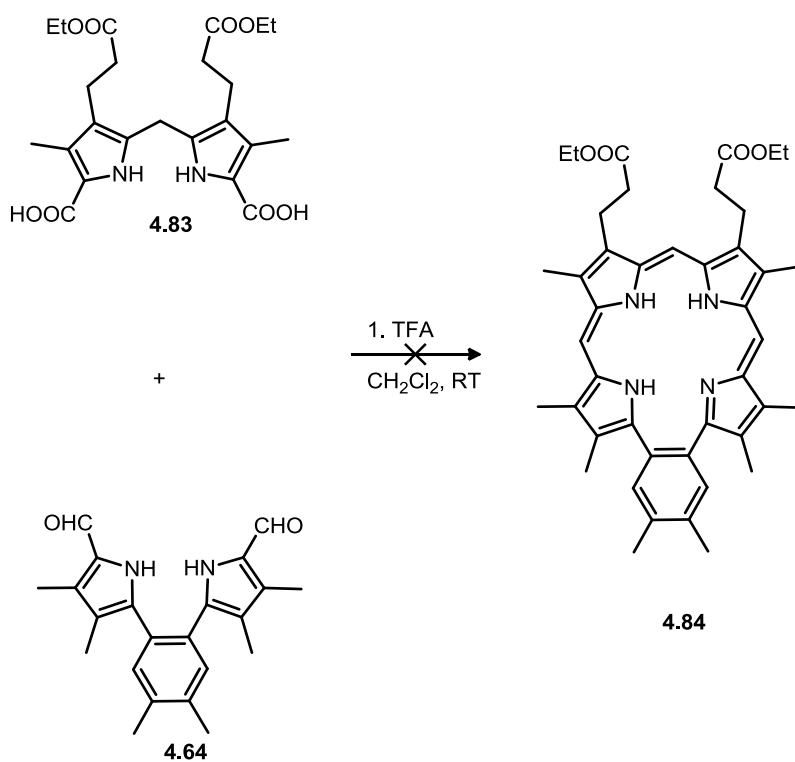


Scheme 4.24: Alternate attempted synthesis of 2.1.2.1 macrocycle by MacDonald condensation.

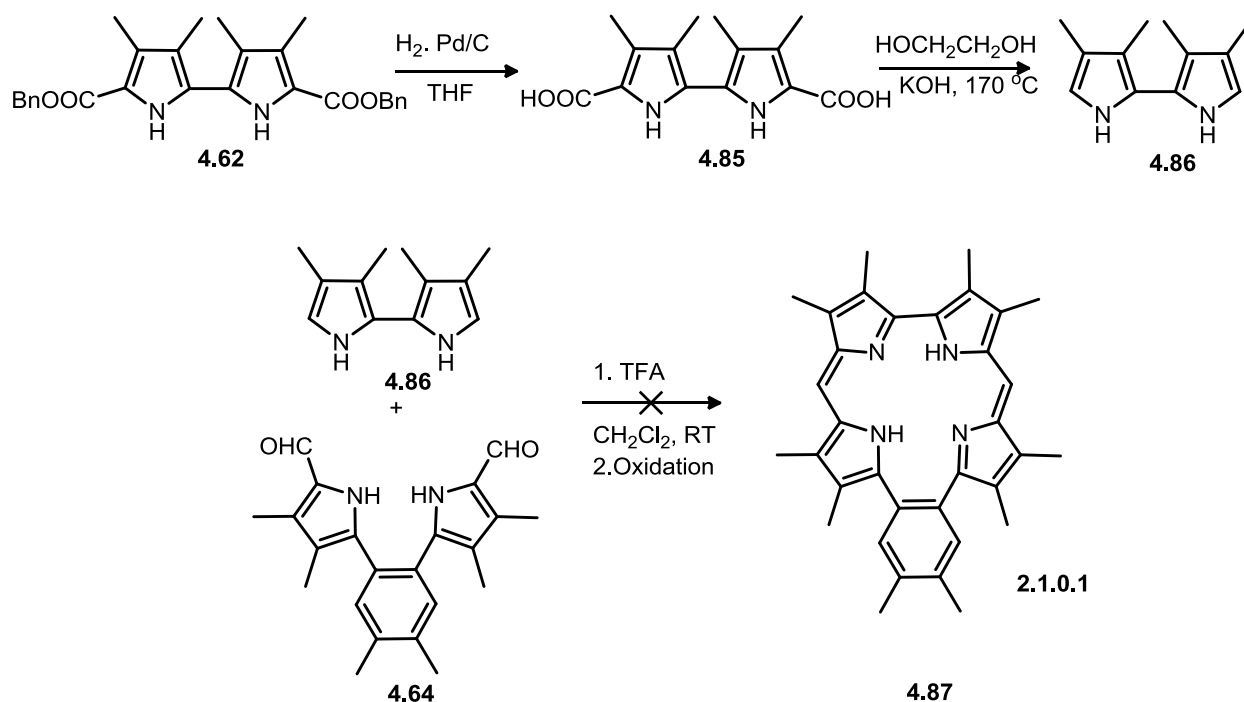


Scheme 4.25: Alternate attempted synthesis of 2.1.2.1 macrocycle **4.79** by MacDonald condensation.

An attempt to synthesize the 2.1.1.1 system **4.84** following a MacDonald condensation in the presence of TFA, employing dipyrromethane and diformyl dipyrrolyethene was also unsuccessful (Scheme 4.26). Next, the synthesis of corrphycenes (2.1.0.1) **4.87** was attempted, by condensing α,α' -unsubstituted bipyrrole **4.86** and diformyl-dipyrrolylethene **4.64** (Scheme 4.27). This reaction did not yield the expected macrocycle. Obviously, all the above strategies posed a great challenge in our syntheses. There was therefore need for a new approach. It was decided to avoid the 2+2 condensations during cyclization by first synthesizing the open tetrapyrrolic system and closing the ring later by Ullmann or McMurry coupling. The tetrapyrrolic system would be accessed by standard dipyrromethane approaches (Scheme 4.28).



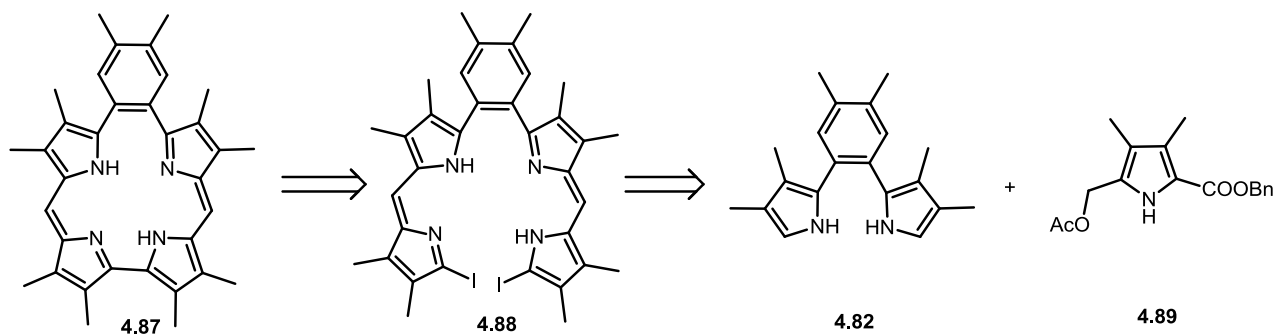
Scheme 4.26: Attempted synthesis of 2.1.1.1 macrocycle **4.84**.



Scheme 4.27: Attempted synthesis of corrphycene **4.87** macrocycle by MacDonald condensation.

Two routes were followed;-

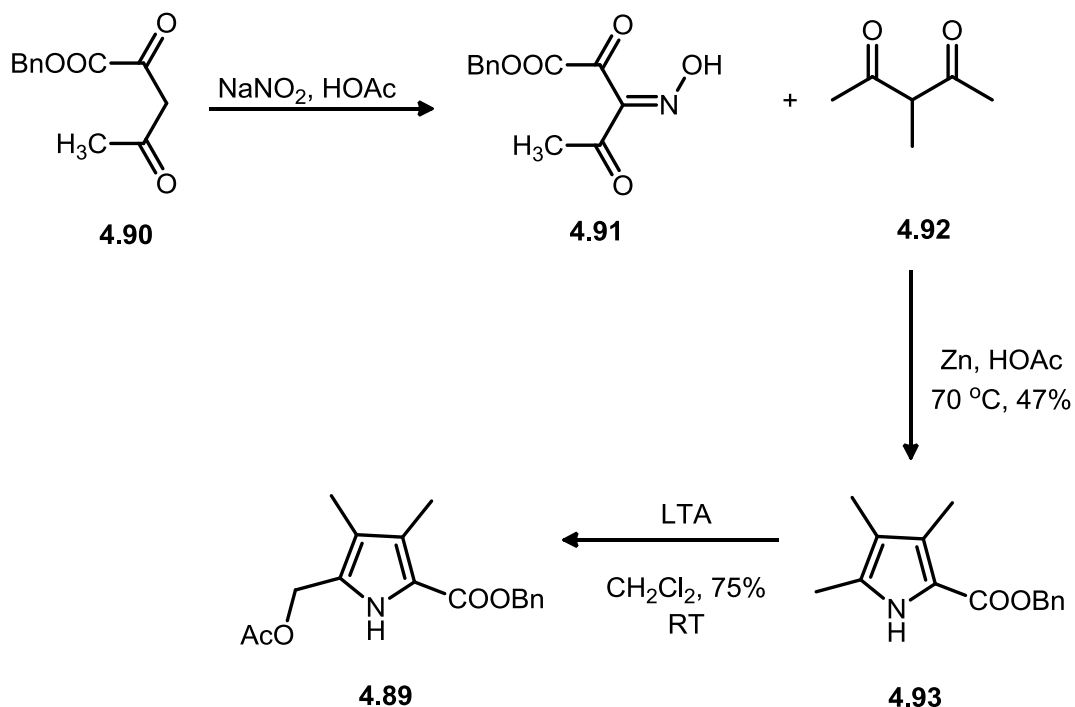
Route 1: The initial strategy for the synthesis of corrphycene **4.87** involved Ullmann coupling of the iodine terminated tetrapyrrolic system **4.88**, which was to be obtained by a condensation reaction between α,α' -free dipyrrolylene **4.82** and 2-acetoxymethylpyrrole **4.89** (Scheme 4.28).



Scheme 4.28: Retrosynthesis of corrphycene **4.87**.

The required tetrasubstituted pyrrole **4.89**, was synthesized by following Johnson's procedure.⁴⁷ Benzyl oximinoacetate **4.91**, was made by the nitrosation reaction of benzyl

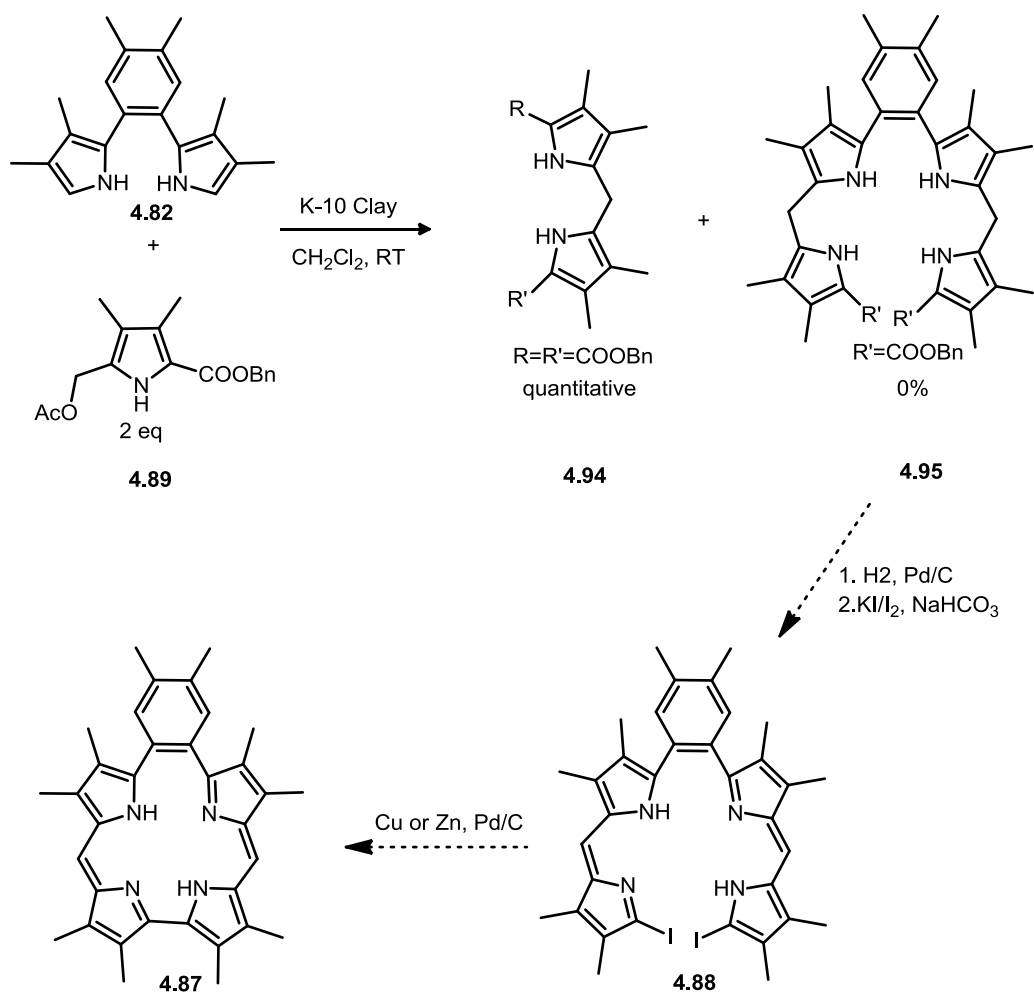
acetoacetate **4.90** with sodium nitrite in acetic acid. Compound **4.91** was then subjected to a condensation reaction with 3-methyl-2,4-pentanedione **4.92** in the presence of zinc powder and acetic acid at 70 °C to provide benzyl 3,4,5-trimethylpyrrole-2-carboxylate **4.93** in 47% yield (Scheme 4.29).



Scheme 4.29: Synthesis of 2-acetoxymethylpyrrole **4.89**⁴⁸

With this pyrrole **4.93** in our hand, it was subjected to a radical α -methyl acetylation employing lead tetraacetate (LTA)⁴⁸ that yielded 2-acetoxymethylpyrrole **4.89** in 75% yield (Scheme 4.30).

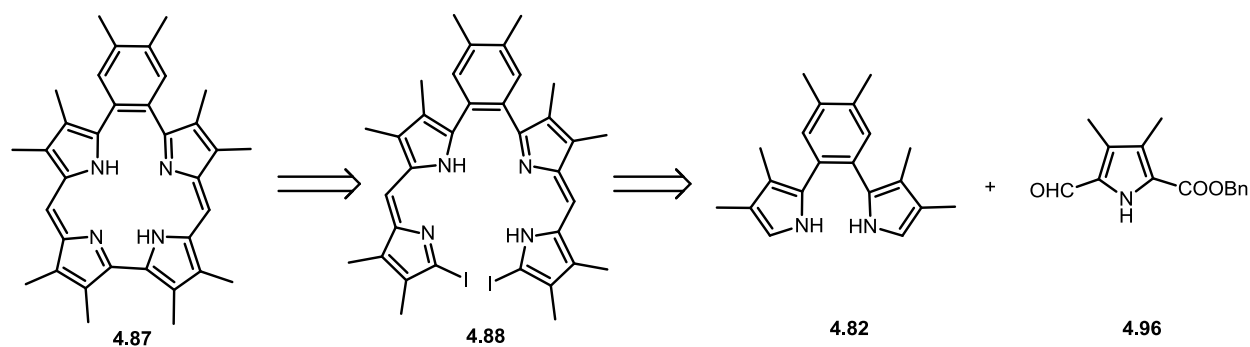
It was hoped to condense dipyrrole **4.82** and 2-acetoxymethylpyrrole **4.89** in presence of K-10 clay to give the unsymmetrical tetrapyrrolic structure **4.95** that would thereafter be transformed to the precursor **4.88** for Ullmann coupling ring closure. The condensation method of Jackson *et al.*⁴⁸ was reported not to result in self-condensation of the 2-acetoxymethylpyrrole.



Scheme 4.30: Attempted synthesis of tetrapyrrole **4.95**.

It was followed, but surprisingly, the 2-acetoxymethylpyrrole substrate self-condensed when stirred in dichloromethane in the presence of the α, α' -dipyrrrolylene **4.82** and Montmorillonite K-10 clay at room temperature, to give the symmetrical dipyrromethane side reaction product **4.94** in quantitative amounts.

Route 2: After several unsuccessful attempts to follow route 1 above, condensation reactions using an aldehyde pyrrole in place of the 2-acetoxymethane on the pyrrole precursors were attempted. In this alternate route, the formylpyrrole was to be condensed with α, α' -dipyrrrolylene **4.82** in TFA and dichloromethane (Scheme 4.31).

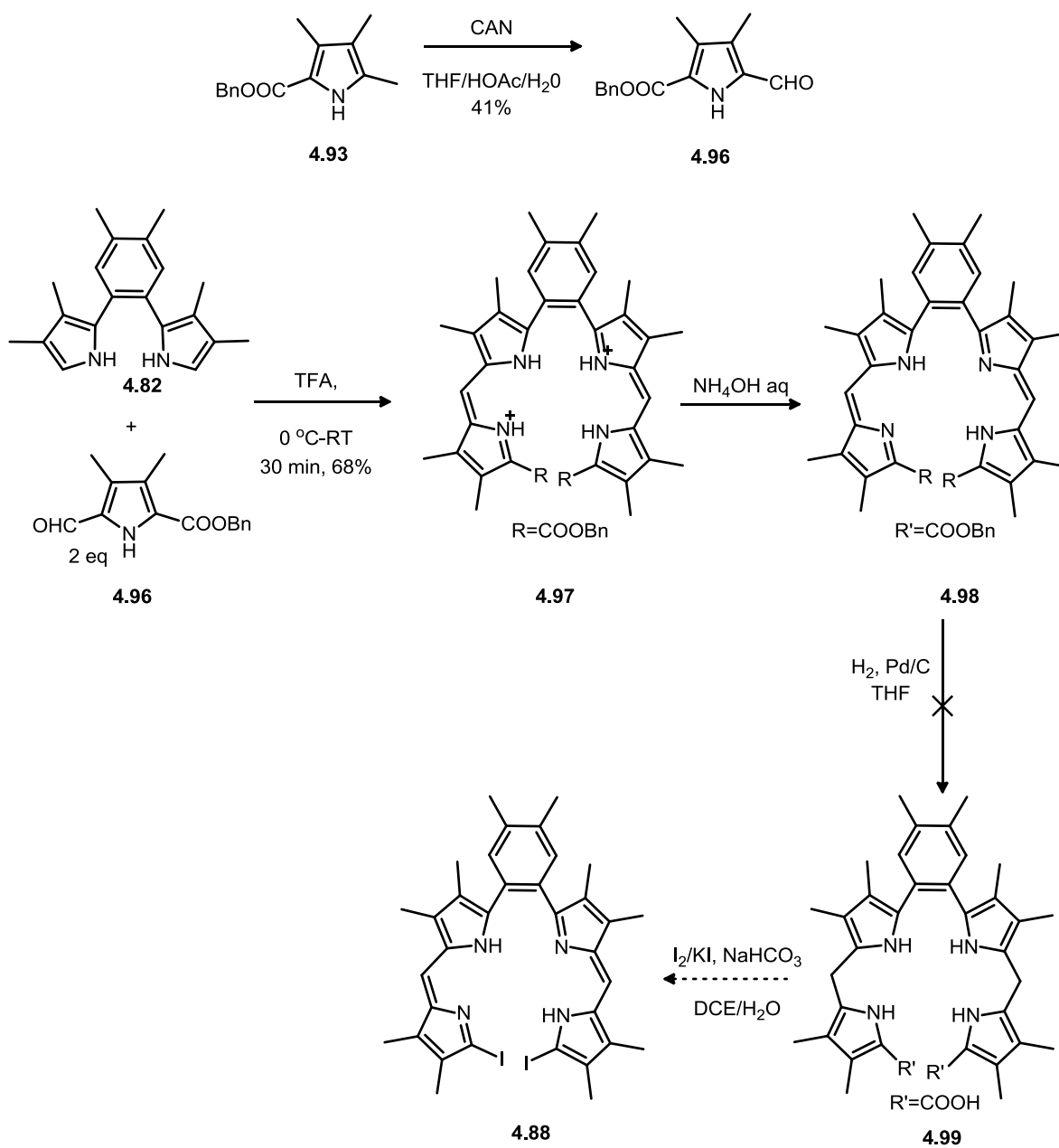


Scheme 4.31: Alternate retro-synthetic scheme for the synthesis of macrocycle **4.87**.

The α -methyl group of the tetrasubstituted pyrrole **4.93** was oxidized by using ceric ammonium nitrate to give the aldehyde group and afford benzyl 2-formyl-3,4-dimethylpyrrole-2-carboxylate **4.96**. The formylpyrrole was then condensed with the decarboxylated α,α' -free dipyrrolylene **4.82** in the presence of trifluoroacetic acid to yield a salt **4.97** which was then neutralized by washing with ammonium hydroxide solution to afford the tetrapyrrolic system **4.98** in 68% yield (Scheme 4.32). This reaction was monitored primarily by UV/Visible spectroscopy (Figure 4.10 and 4.11).

Dibenzyl ester tetrapyrrole **4.98** was then subjected to a one-pot catalytic hydrogenation of the *meso*-sp² carbon and ester debenzylation using palladium-carbon and hydrogen gas at one atmosphere. Compound **4.98** did not debenzylate successfully under catalytic hydrogenolysis. An easier approach to di-iodotetrapyrrole **4.88** was therefore attempted using 2-formyl-5-iodopyrrole **4.67** as a starting material in the condensation reaction with dipyrrole **4.82** (Scheme 4.33). The iodopyrrole was obtained from iodination of the acid pyrrole **4.66** using iodine monochloride and sodium acetate in acetic acid medium.

Compound **4.67** was then condensed with **4.82** in trifluoroacetic acid to afford a,c-biladiene **4.100**, which was neutralized in ammonium hydroxide solution to furnish the desired tetrapyrrole **4.88**. This reaction was followed by UV/Vis spectroscopy (Figure 4.12 and 4.13).



Scheme 4.32: Attempted synthesis of tetrapyrrolic system **4.88**.

From the experiments attempted so far, cyclization reactions were challenging. Only two macrocycles were observed as traces in their mass spectra (ESI); these were **4.70** and **4.78**.

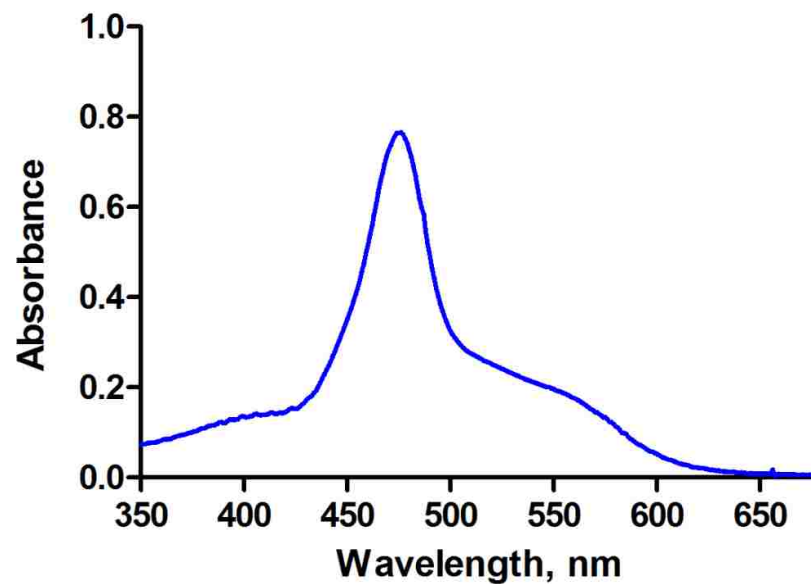


Figure 4.10: UV-Visible spectrum, in CH₂Cl₂, of a,c-biladiene **4.97**.

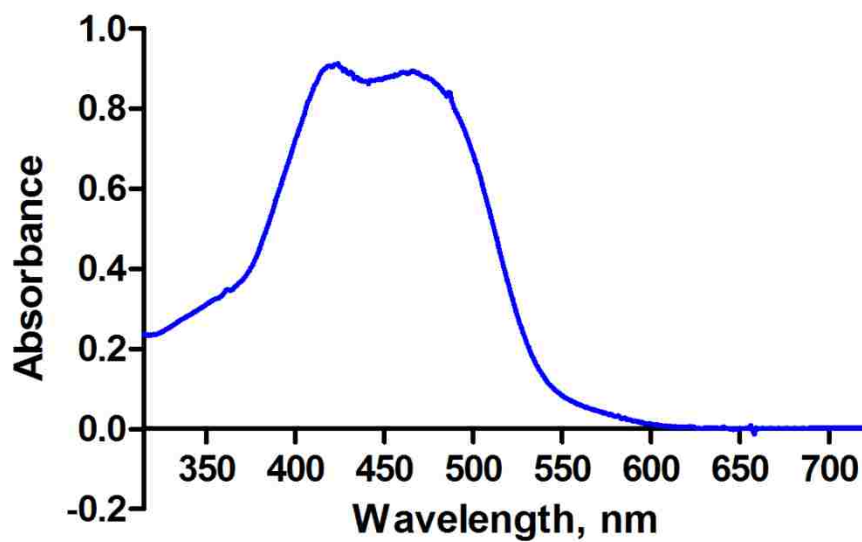


Figure 4.11: UV-Visible spectrum, in CH₂Cl₂, of tetrapyrrole **4.98**.

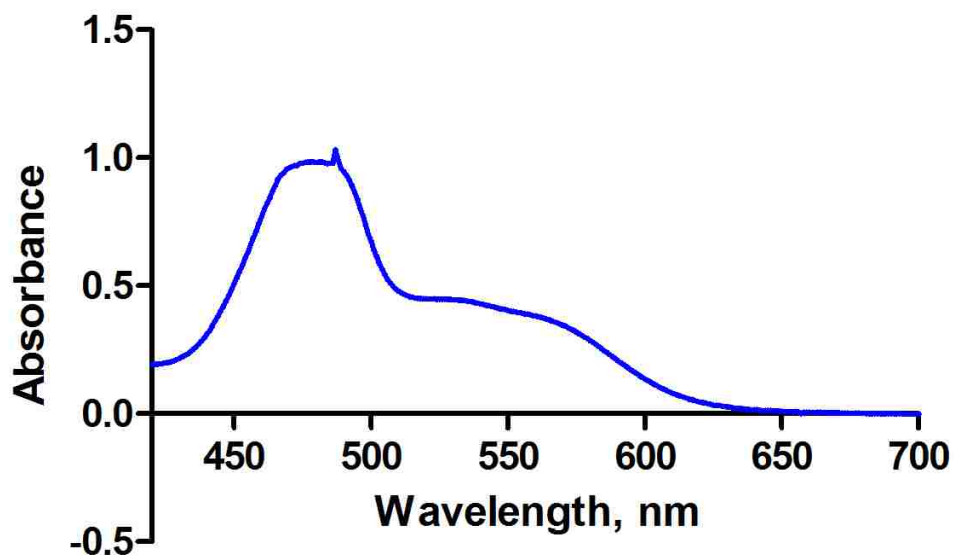


Figure 4.12: UV-Visible spectrum, in CH₂Cl₂, of a,c-biladiene **4.100**.

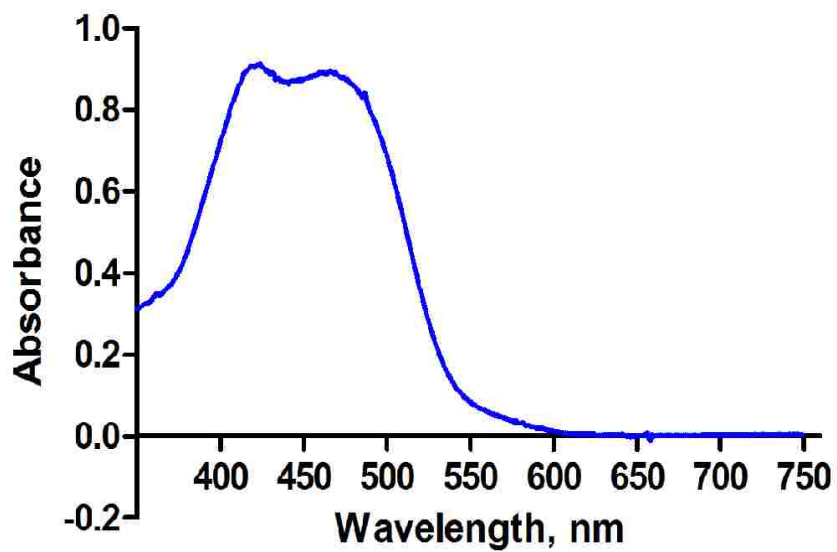
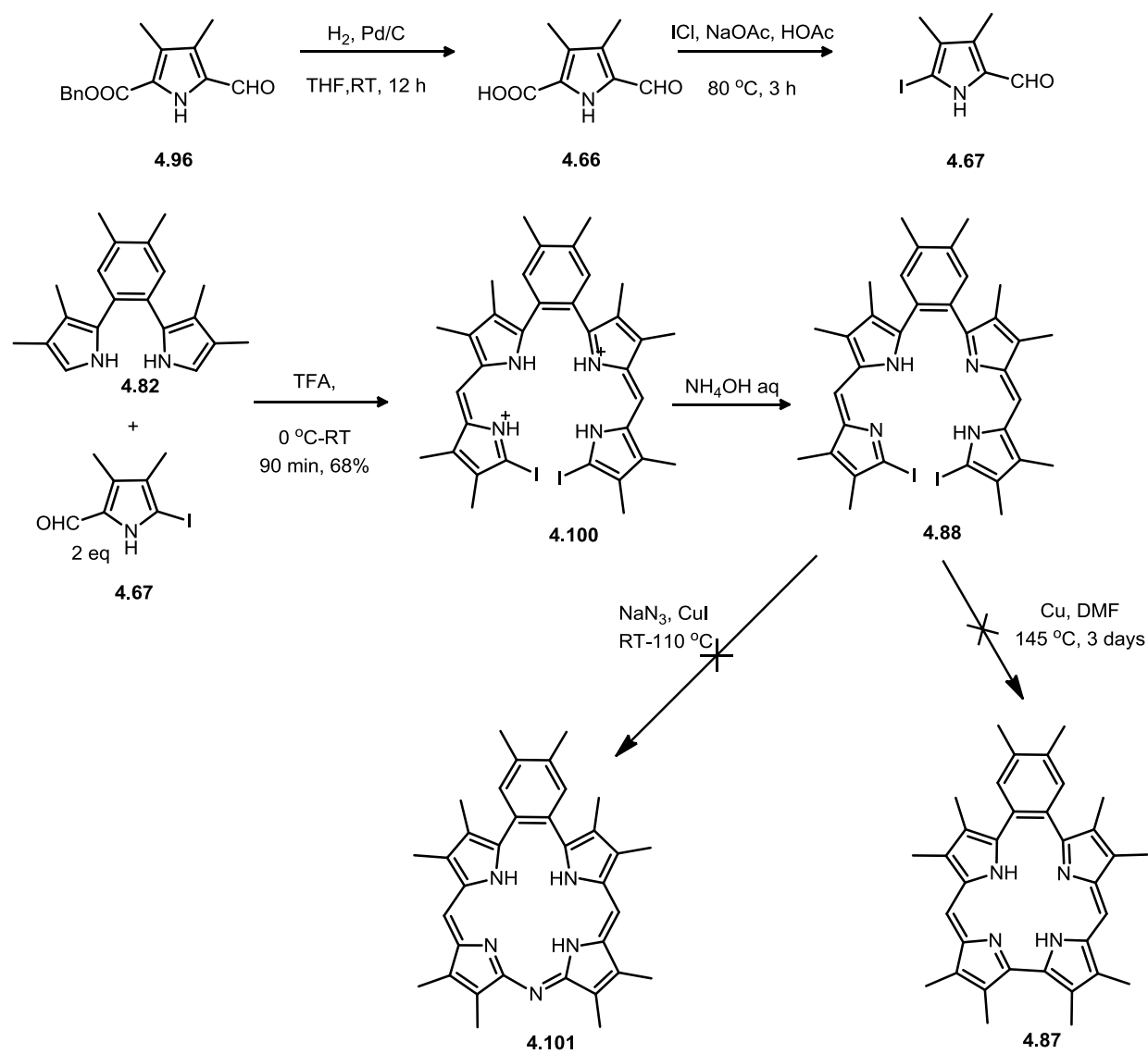


Figure 4.13: UV-Visible spectrum, in CH₂Cl₂, of tetrapyrrole **4.88**.



Scheme 4.33: Synthesis of macrocycles **4.87** and **4.101**.

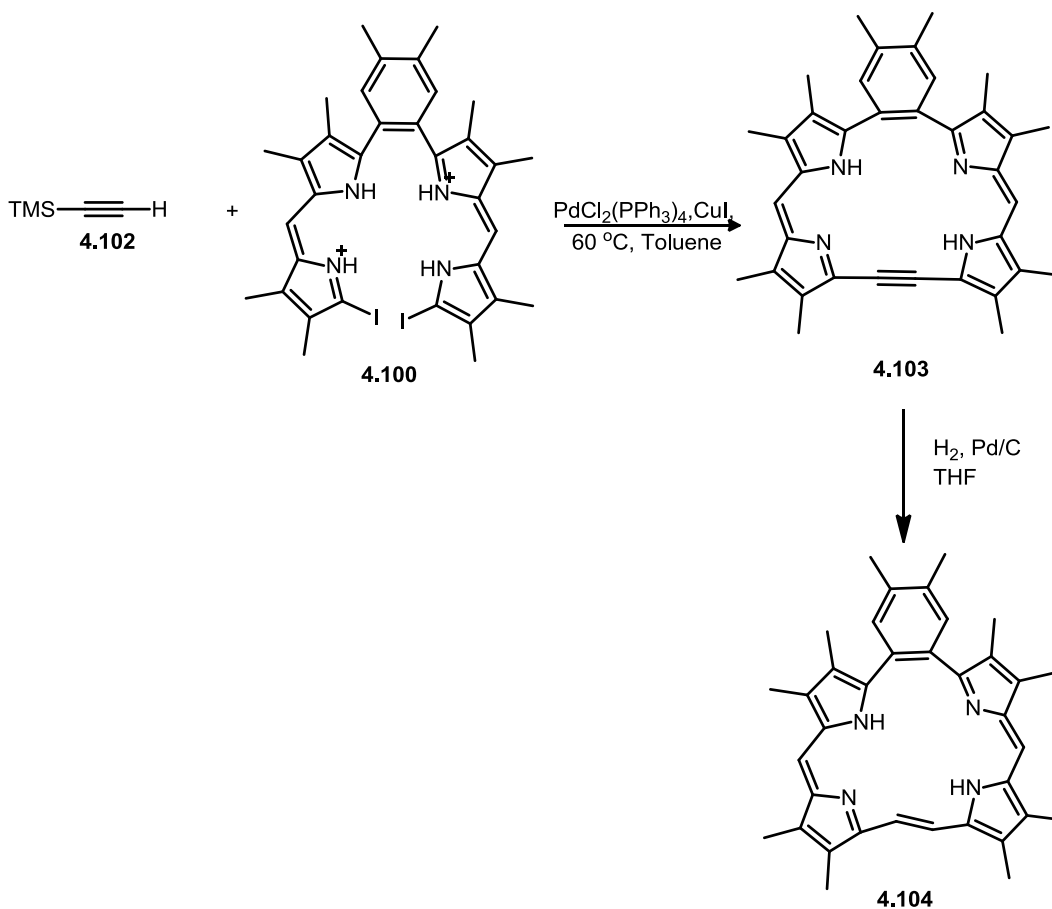
4.3. Future Work

Possible reactions that could be also attempted on these new compounds are as suggested below.

4.3.1. Ring closure by Sonogashira coupling of terminal iodo-pyrroles.

Di-iodo tetrapyrrole **4.100** could be subjected to a one-pot Sonogashira coupling using trimethylsilylethyne (0.5 equivalents of **4.100**) as the alkyne source to generate macrocycle **4.103**. Grieco's method could be followed, where DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) is

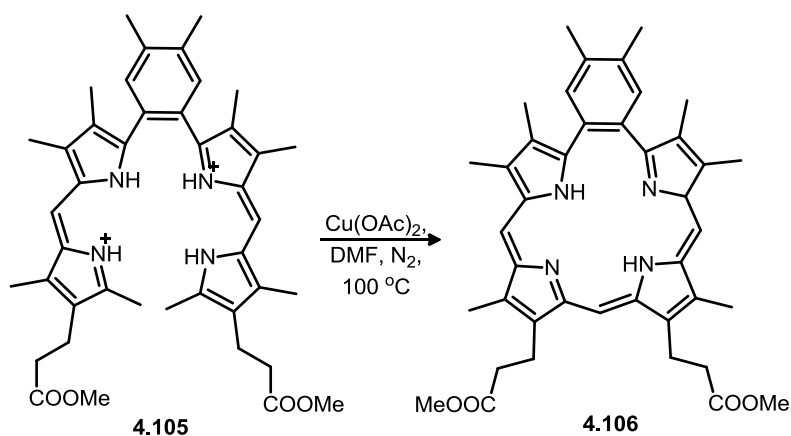
employed as the amidine base that participates in the *in-situ* deprotection of trimethylsilylethynylene as well as the actual Sonogashira coupling process. Macrocycle **4.103** could then be exposed to catalytic hydrogenation to reduce the internal alkyne to a *trans*-alkene affording macrocycle **4.104** (Scheme 4.34).



Scheme 4.34: Ring closure by Sonogashira coupling of terminal iodo-pyrroles.

4.3.2. Ring closure by copper-induced cyclization.

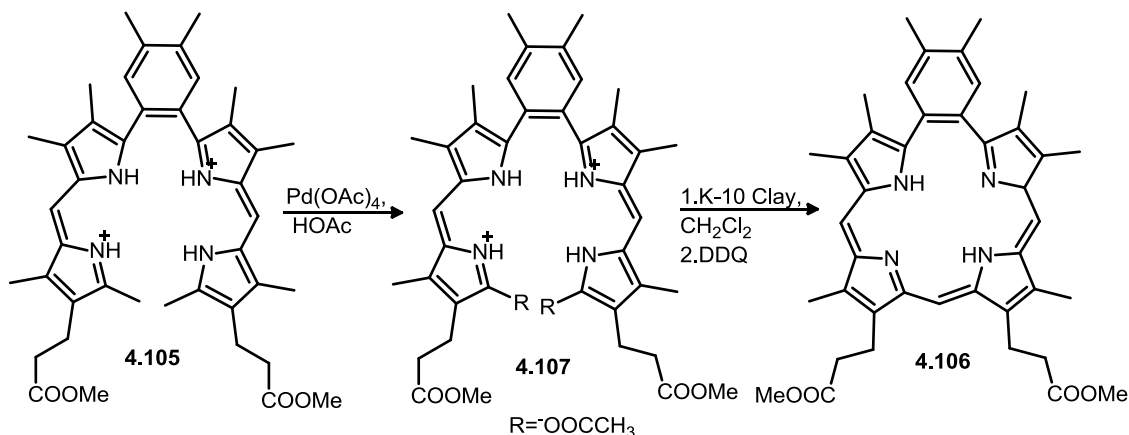
Oxidative copper-induced cyclization reaction could be attempted on the tetrapyrrole **4.105**. Such a reaction was performed recently in our group as the key step in the synthesis of protoporphyrin-IX derivatives⁴⁹⁻⁵⁰ and so product **4.106** may be accessed (Scheme 4.35).



Scheme 4.35: Ring closure by copper-induced cyclization.

4.3.3: Ring closure by condensation of terminal acetyl-pyrroles.

An alternate route to macrocycle **4.106** is the possible condensation ring closure reaction of **4.107** using K-10 clay. Compound **4.107** could be easily obtained from a radical reaction of lead(IV) tetra-acetate on **4.105**. Oxidation of the condensed product with DDQ could then give macrocycle **4.106** (Scheme 4.36).



Scheme 4.36: Ring closure by condensation of terminal acetyl-pyrroles.

4.4. Experimental procedures

4.4.1. 2-Acetoxy-3-nitrobutane (4.14)

In a three-necked round-bottomed flask equipped with a magnetic stirrer and chilled in an ice-salt bath, acetaldehyde (**4.11**, 13.0 ml, 0.465 mol), 2-propanol (8.5 ml) and potassium fluoride (0.67 g, 0.023 mol, 0.05 mol equiv.) were added. To the mixture, nitroethane (**4.11**, 16.5

ml, 0.46 mol) was added dropwise at 0 °C over a period of 1 h. The mixture was slowly warmed up to room temperature and kept for 10 h under argon with continuous stirring before removing all solvent under vacuum. The resulting oily crude product was filtered to remove solid inorganic waste and washed with CH₂Cl₂. After removing all solvent under vacuum, a yellow oily product, 2-nitro-3-butanol (**4.13**), was obtained (20.11 g, 37%) which was immediately used for the next step in the synthesis.

2-Nitro-3-butanol (7.5 g, 0.063 mol) was added dropwise over a 10 min period to a solution of CH₂Cl₂ (5 ml), acetic anhydride (9.60 g, 0.094 mol, 1.5 equiv.), and 4-dimethylaminopyridine (DMAP, 0.1 g). The reaction was exothermic. The mixture was allowed to stir for 4 h at room temperature under argon. Methanol (30 ml) was added to destroy excess acetic anhydride and the mixture was allowed to stir further for 30 min. The mixture was then poured into dilute sodium bicarbonate (9 g in 50 ml of water) and extracted with CH₂Cl₂ (3 x 20 ml). The organic layer was dried over anhydrous Na₂SO₄ and filtered through a short column of silica gel. Evaporation of the solvent gave the desired product **4.14** as a green liquid (11.86 g, 58%).

4.4.2. Ethyl 3,4-dimethyl-1*H*-pyrrole-2-carboxylate (**4.17**)

In a dry multi-neck round-bottomed flask, equipped with a magnetic stirrer, ethyl isocyanoacetate (**4.16**; 5.80 g, 0.0513 mol, 1.05 equiv.), tetramethylguanidine (11.66 g, 0.100 mol, 2.05 equiv.) and a mixture of dry THF (6 ml) and 2-propanol (6 ml) were added and the flask was cooled in an ice water bath. To the mixture, at 0 °C, a solution of 2-acetoxy-3-nitrobutane (**4.14**; 7.88 g, 0.049 mol, 1 equiv.) in the remaining mixture of dry THF and 2-propanol (36 ml, 1:1) was added dropwise over a period of 30 min. The mixture was allowed to stir at room temperature for another 20 h under argon after the addition was complete. The resulting mixture was concentrated under vacuum to dryness. The oily residue was taken up in CH₂Cl₂ (30 ml) and washed successively with water (3 x 6 ml), 5% aqueous HCl (6 x 3 ml), water (3 x 10 ml), aqueous saturated sodium bicarbonate (18 ml) and finally brine (18 ml). After

drying over anhydrous Na_2SO_4 , the solvent was removed under vacuum to yield the product **4.17** (5.51 g, 68%). mp 87-90 °C (lit. mp⁵¹ 105-108 °C) ^1H NMR (CDCl_3 , 400 MHz): δ ppm 8.85 (s, br, 1H), 6.67 (d, $J = 2.3$ Hz, 1H), 4.32 (q, $J=7.1$ Hz, 2H), 2.28 (s, 3H), 2.02 (s, 3H), 1.36 (t, $J=7.1$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ , ppm 10.09, 10.43, 14.71, 59.98, 119.43, 120.29, 120.70, 126.75, 162.00. HRMS (ESI-TOF) m/z 168.1026 $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_9\text{H}_{14}\text{NO}_2$ 168.1019.

4.4.3. Ethyl 3,4-dimethyl-5-iodo-1*H*-pyrrole-2-carboxylate (4.19)

NaHCO_3 (1.32g, 0.016 moles, 2.5 equiv.) was dissolved in water (6.0 ml) and heated to 50 °C while stirring. To this basic solution, pyrrole carboxylate (**4.17**) was added rapidly (1.05 g, 0.006 moles, 1 equiv.) in several portions. When most of it was completely dissolved, methanol (10 ml) was added and the temperature was quickly raised to 71 °C. A saturated solution of I_2/KI (1.47/1.92g in 4 ml water) was then added into the mixture over several min while stirring. The reaction mixture was refluxed for an additional 40 min. Saturated $\text{Na}_2\text{S}_2\text{O}_3$ solution was added to the mixture in portions to remove excess iodine until the solution decolorized. The aqueous layer was extracted using CH_2Cl_2 . The organic layer was dried over anhydrous Na_2SO_4 , concentrated under reduced pressure, and purified on a silica gel column (eluted with CH_2Cl_2) to yield a yellow solid (1.70g, 92%). mp 126 °C (lit. mp⁵² 150 °C) ^1H NMR (CDCl_3 , 400 MHz): δ 9.08 (s, br, 1H), 4.34 (q, $J=7.1$ Hz, 2H), 2.30 (s, 3H), 1.97 (s, 3H), 1.37 (t, $J=7.1$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ , ppm 11.27, 12.05, 14.72, 60.39, 123.89, 126.49, 127.10, 160.99. HRMS (ESI-TOF) m/z 293.9988 $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_9\text{H}_{13}\text{INO}_2$ 293.9985.

4.4.4. Benzyl 3,4 -dimethyl-1*H*- pyrrole-2-carboxylate (4.18)

Sodium (0.168 g, 0.0073 mol) was added to benzyl alcohol (60 ml) in a 100 ml round-bottomed flask while stirring. Once all the sodium had reacted, ethyl ester pyrrole (**4.17**, 2.32 g, 14 mmol) was added and the resulting mixture was heated in an oil bath for 6 h at 100 °C. The mixture was allowed to stand at room temperature overnight and acetic acid (0.438 g, 0.0073 mol) was added to neutralize sodium benzyloxyde. Benzyl alcohol was evaporated off under reduced pressure to dryness and the residue which solidified on standing was dissolved in

CH₂Cl₂ (20 ml), washed with water (100 ml), and treated with decolorizing carbon. After filtration through a Celite plug, the solution was dried over anhydrous Na₂SO₄ and the solvent was evaporated under vacuum to yield a brown liquid, which was further distilled under high vacuum to give a thick brown liquid. The residue was dried under vacuum to give a brown solid of **4.18** (2.80 g, 87%). mp 72-75 °C (lit. mp⁵³ 73-74 °C) ¹H NMR (CDCl₃, 400 MHz): δ 9.07 (s, br, 1H), 7.55-7.31 (m, 5H), 6.67 (d, J=3.1 Hz, 1H), 5.36 (s, 2H), 2.36 (s, 3H), 2.06 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ, ppm HRMS (ESI-TOF) *m/z* 293.9988 [M+H]⁺, calcd. for C₉H₁₃INO₂ 293.9985.

4.4.5. Benzyl 3,4-dimethyl-5-iodo-1*H*-pyrrole-2-carboxylate (4.20)

NaHCO₃ (2.29 g, 0.026 moles, 2.5 equiv.) was dissolved in water (10 ml) and heated to 50 °C while stirring. To this basic solution, was added (2.35g, 0.01 moles, 1 equiv.) of pyrrole carboxylate **4.18** rapidly in several portions. When most of it was completely dissolved, 1,2-dichloroethane (15 ml) was added and the temperature was quickly raised to 70 °C. A saturated solution of I₂/KI (3.80/4.93 g in 5.0 ml water) was then added into the mixture over several minutes while stirring. The reaction mixture was refluxed for an additional 40 min. Saturated Na₂S₂O₃ solution (10 ml) was then added to the mixture in portions to remove excess iodine. The aqueous layer was separated and extracted using CH₂Cl₂ (20 ml). The organic layer was dried over anhydrous Na₂SO₄, concentrated under reduced pressure and purified by column (silica gel) chromatography eluting with CH₂Cl₂ to yield a yellow solid of **4.20** (3.06 g, 86%). mp 127 °C (lit. mp⁵² 127-129 °C) ¹H NMR (CDCl₃, 400 MHz) ppm: δ 9.16 (s, br, 1H), 7.44-7.35 (m, 5H), 5.35 (s, 2H), 2.33 (s, 3H), 1.98 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ, ppm 11.39, 12.04, 66.13, 74.07, 123.49, 126.62, 127.63, 128.38, 128.78, 136.39, 160.65. HRMS (ESI) *m/z* 356.0121 [M+H]⁺, calcd. for C₁₄H₁₅INO₂ 356.0142.

4.4.6. Ethyl 3,4-dimethyl-5-(trimethylsilyl)ethynyl-1*H*-pyrrole-2-carboxylate (4.21)

To a solution of **4.19** (0.450 g, 0.0015 mol) in dry triethylamine (10 ml) were added under argon atmosphere (trimethylsilyl)acetylene (0.333 ml, 0.0023 mol) dichlorobis(triphenylphosphine)palladium(II) (0.018 g, 0.000026 mol), and copper(I) iodide (10

mg, 0.000053 mol). The homogeneous mixture was stirred at 50 °C for 1h. The reaction was easily monitored by TLC. After evaporation of the solvent *in vacuo*, the residue was subjected to silica gel column chromatography eluting with n-hexane/CH₂Cl₂/EtOAc (5:1:1) to afford the titled product **4.21** in 99% (0.39 g) yield as a brown solid. ¹H NMR (CDCl₃, 400 MHz): δ, ppm 8.76 (1H, s), 4.31 (2H, *J*=7.1Hz, q), 2.24 (3H, s), 2.05 (3H, s), 1.34 (3H, *J*=7.1Hz, t), 0.25 (9H, s). ¹³C NMR (100 MHz, CDCl₃): δ, ppm 0.14, 9.94, 10.62, 14.69, 60.33, 95.91, 100.10, 114.93, 119.57, 126.84, 161.05. HRMS (ESI-TOF) *m/z* 264.1396 [M+H]⁺.

4.4.7. Benzyl 3,4-dimethyl-5-(trimethylsilyl)ethynyl-1*H*-pyrrole-2-carboxylate (4.22)

This compound was prepared according to the general procedure used to prepare ethynyl pyrrole **4.21** above in 99% yield. ¹H NMR (CDCl₃, 400MHz): δ, ppm 8.76 (1H, s), 7.43-7.35 (5H, m), 5.30 (2H, s), 2.26 (3H, s), 2.05 (3H, s), 0.25 (9H, s). ¹³C NMR (100 MHz, CDCl₃): δ, ppm 0.13, 9.93, 10.71, 66.11, 95.77, 100.31, 115.29, 119.16, 126.89, 127.11, 128.45, 128.82, 136.35, 160.66. HRMS (ESI-TOF) *m/z* 326.1552 [M+H]⁺ calcd. for C₁₉H₂₄NO₂Si 326.1571.

4.4.8. Ethyl 3,4-dimethyl-5-ethynyl-1*H*-pyrrole-2-carboxylate (4.23)

To a solution of **4.21** (0.39 g, 0.0015 mol), in dry THF (5.0 ml) was added tetrabutylammonium fluoride (1.0 M, THF solution, 1.5 ml) in a dropwise manner over 2 min. After stirring for 90 min at room temperature, the resulting crude mixture of the product was concentrated under reduced pressure. The crude residue was then purified further through a silica gel column (3 x 12 cm) eluting with CH₂Cl₂. The expected product was obtained in 87% (0.25 g) yield as a white solid. ¹H NMR (CDCl₃, 400 MHz): δ, ppm 8.84 (1H, s), 4.32 (2H, *J*=7.1 Hz, s), 3.36 (1H, s), 2.25 (3H, s), 2.07 (3H, s), 1.37 (3H, *J*=7.1 Hz, t). ¹³C NMR (100 MHz, CDCl₃): δ, ppm 9.82, 10.59, 14.68, 60.42, 75.24, 82.42, 113.81, 119.85, 126.45, 127.05, 161.08. HRMS (ESI-TOF) *m/z* 192.0995 [M+H]⁺ calcd. for C₁₁H₁₄NO₂ 192.1019.

4.4.9. Benzyl 3,4-dimethyl-5-ethynyl-1*H*-pyrrole-2-carboxylate (4.24)

This compound was prepared according to the general procedure used to prepare ethynylpyrrole **4.23** above in 97% yield as a white solid. HRMS (ESI-TOF) *m/z* 254.1060 [M+H]

4.4.10. 1,2-Bis[2-(5-ethyloxycarbonyl-3,4-dimethylpyrrolyl)] ethyne (4.25)

Method A: Into a solution of iodopyrrole **4.19** (0.368 g, 0.00126 mol) and terminal alkyne **4.23** (0.240 g, 0.00126 mol) in dry diethylamine (7 ml), was added dichloro bis(triphenylphosphine) palladium(II) (0.015 g, 0.000021 mol) and copper(I) iodide (0.008 g, 0.000042 mol). The resulting homogeneous mixture was stirred at 50 °C under argon for 3 h. After evaporation of the solvent *in vacuo*, the crude product was subjected to silica gel column chromatography eluting with n-hexanes/CH₂Cl₂/EtOAc 5:1:1 to give the titled product as a brown solid in 56% (0.250 g) yield. Crystallization was performed using a n-hexanes/CH₂Cl₂ mixture. mp 220 °C. ¹H NMR (CDCl₃, 400 MHz): δ, ppm 8.88 (2H, s), 4.34 (4H, *J*=7.1 Hz, q), 2.28 (6H, s), 2.10 (6H, s), 1.37 (6H, *J*=7.1 Hz, t). ¹³C NMR (100 MHz, CDCl₃): δ, ppm 10.06, 10.68, 14.69, 60.45, 85.35, 114.62, 120.14, 126.64, 126.75, 161.17. HRMS (ESI-TOF) *m/z* 357.1793 [M+H]⁺ calcd. for C₂₀H₂₅N₂O₄ 357.1809.

Method B:¹⁸ A mixture of **4.19** (0.527 g, 0.0018 mol, 1.2 eq), alkyne **4.23** (0.287 g, 0.0015 mol), dichloro bis(triphenylphosphine) palladium(II) (3 mol %, 32 mg), and TBAF (1.0 M, 0.0075 mol, 7.5 ml, 5 eq.) was stirred under nitrogen at 80 °C for the desired time (4 h) when most of the starting material was consumed as monitored by TLC. The crude was washed with water (2 x 50 ml) and extracted with THF (3 x 20 ml). The organics were collected, dried over anhydrous Na₂SO₄, filtered and solvent removed under reduced pressure. The crude product was purified by using silica gel column chromatography using n-hexanes/CH₂Cl₂/EtOAc 5:1:1 as the elutant. The targeted compound was obtained in 0.430 g, 0.0012 mol, 80 %, yield.

4.4.11. 1,2-bis[2-(5-Benzoyloxycarbonyl-3,4-dimethylpyrrolyl)] ethyne (4.26)

Was synthesized according to Li *et al.* modified Sonogashira coupling procedure (Method B) in 28% yield. ¹H NMR (250 MHz, CDCl₃): δ, ppm 11.99 (2H, s), 7.47–7.32 (10H, m), 5.29 (4H, s), 2.2 (6H, s), 2.0 (6H, s). *m/z* 480.129 [M+H].

4.4.12. *Cis*-1,2-[2-(5-ethoxycarbonyl-4-ethyl-3-methylpyrrolyl)] ethane (4.27)

Commercially available Lindlar's catalyst (5 % wt. Pd on CaCO₃, poisoned with lead; 150 mg, 100 % wt.) was added to a solution of alkyne **4.25** (150 mg, 0.00042 mol) in dry ethyl acetate (15 ml). The flask was evacuated and flushed with hydrogen gas (two freeze/thaw cycles) and the mixture was stirred under hydrogen gas for 12 h. The resulting mixture was then filtered over a Celite cake and washed with ethylacetate (2 × 30 ml). The solvent was removed under reduced pressure and the crude residue was purified by silica gel column chromatography eluting with ethyl acetate/dichloromethane/hexanes (1:1:5) to yield the titled product as a yellow oil that solidified to a yellow powder (47 mg, 0.13 mmol, 31% yield). mp 220 °C ¹H NMR (400 MHz, CDCl₃): δ, ppm 8.79 (2H, s,), 6.63 (2H, s, CHCH), 4.35 (4H, *J*=7.1 Hz, q,), 2.27 (6H, s), 2.09 (6H, s), 1.38 (6H, t). ¹³C NMR (100 MHz, CDCl₃): δ, ppm 9.39.10.66, 14.78, 60.33, 114.31,119.55, 121.03, 127.99, 130.73, 161.97. HRMS (ESI-TOF): *m/z* 359.1965 [M + H], calcd. for C₂₀H₂₆N₂O₄ 359.1971.

4.4.13. *Trans and Cis*-1,2-[2-(5-ethoxycarbonyl-4-ethyl-3-methylpyrrolyl)]ethene (4.28)¹⁹

Under air atmosphere, a 10 ml round bottomed flask was charged with the internal alkyne **4.25** (0.100 g, 0.00028 mol) ,triethylsilane (0.09 ml, 0.065 g, 0.00056 mol), [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.0031 g, 0.0000042 mol, 1.5%), dppe (0.0078 g, 0.000014 mol, 5%), and THF/H₂O (1.0/0.1 ml).The mixture was stirred for 24 h at room temperature when the solvent was removed under reduced pressure and the crude product obtained was purified further by silica column chromatography eluting with n-hexanes/CH₂Cl₂/EtOAc (5:1:1) to afford the product in 91% (0.093g, 0.00026 mol) yield. mp 222 °C ¹H NMR (400 MHz, CDCl₃): δ, ppm 8.79 (2H, s,), 6.63 (2H, s, CHCH), 4.35 (4H, *J*=7.1 Hz, q,), 2.27 (6H, s), 2.09 (6H, s), 1.38 (6H, t). ¹³C NMR (100 MHz, CDCl₃): δ, ppm 9.39.10.66, 14.78, 60.33, 114.31,119.55, 121.03, 127.99, 130.73, 161.97. HRMS (ESI-TOF): *m/z* 357.1821 [M-H], calcd. for C₂₀H₂₅N₂O₄ 359.182.

4.4.14. 2,3-bis[2-(5-benzyloxycarbonyl-3,4-dimethylpyrrolyl)]-indole (4.42)

Internal alkyne **4.26** (0.40g, 0.00084 mol) was transferred into a 50 ml round bottomed flask together with 2-iodoaniline (0.368 g, 0.00168 mol), palladium(II) acetate (0.019 g, 0.000084 mol, 10%) lithium chloride (0.036 g, 0.00084 mol), and potassium carbonate (1.16 g, 0.0084 mol), and dissolved in DMF (20 ml). The reaction mixture was evacuated and purged with nitrogen gas and heated at 80 °C for 48 h. The reaction was monitored by TLC. Ethyl acetate (100 ml) was added to the reaction mixture and the organic layer was washed with brine (3 x 50 ml). The organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified over a silica gel column (2 x 13) cm³, eluting with n-hexanes/ethyl acetate (7:1) followed by n-hexanes/CH₂Cl₂/EtOAc (5:1:1). Yield 0.254 g, 0.00045mol, 53%. ¹H NMR (400 MHz, CDCl₃): δ, ppm 8.87 (1H, s,), 8.82 (1H, s,), 8.40 (1H, s,), 7.53-7.32 (12H, m), 7.19-7.15(2H, m) 5.31 (2H, s), 5.22 (2H, s), 2.30 (3H, s), 2.30 (3H, s) 2.06 (3H, s), 1.75(3H, s). HRMS (ESI-TOF): *m/z* 572,253 [M + H], calcd. for C₃₆H₃₄N₃O₄ 572.2544

4.4.15. *N*-(2-Iodo-phenyl)-4-methyl-benzenesulfonamide (4.39)

To a solution of the aniline **4.35** (0.438 g, 0.002 mol) in pyridine (10 ml), was added *p*-toluene sulfonyl chloride (0.514 g, 0.0027 mol), and the mixture was stirred at reflux (100 °C), for 16 h. The solvent was then removed under reduced pressure and the crude product was diluted with dichloromethane (50 ml) and washed with 1N HCl, water (50 ml), and brine (50 ml). The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated. The crude product was then purified by silica column chromatography (7 x 2 ml) eluting with CH₂Cl₂ to yield the titled product as yellow oil which solidified on standing to form a yellow solid in 74% (0.549 g) yield. mp 91-92.5 °C(lit. mp⁵⁴ 90-92 °C) ¹H NMR (400 MHz, CDCl₃): δ, ppm 7.67-7.63 (4H, m), 7.32-7.29 (1H, m), 7.22-7.20 (2H, m) 6.85-6.81 (2H, m), 2.38 (3H, s). ¹³C NMR (100 MHz, CDCl₃): δ, ppm 21.77, 92.51, 122.66, 127.04, 127.64, 129.68, 129.83, 136.09, 137.69, 139.29, 144.42. HRMS (ESI-TOF): *m/z* 373.9681 [M + H], calcd. for C₁₃H₁₃INO₂S 373.9706.

4.4.16. 2,3-Bis[2-(5-benzyloxycarbonyl-3,4-dimethylpyrrolyl)]-N-Ts-indole 4.41³¹.

A mixture of *N*-Ts-2-iodoaniline (0.762 g, 0.002 mol), alkyne **4.25** (0.364 g, 0.001 mol), 10% Pd/C (0.033 g, 3 mol% of *N*-Ts-2-iodoaniline), and NaOAc (0.168 g, 0.002 mol) in *N*-methyl-2-pyrrolidone (NMP, 10 ml) contained in a 25 ml round bottomed flask was sealed with a septum and air was evacuated with argon purges thrice. The mixture was then heated at 120 °C for 24 h. The resulting suspension was stirred with additional ethyl acetate (2 x 40) ml and saturated ammonium chloride (20 ml), and filtered through a filter paper. Organics were then separated using a separatory funnel, dried over anhydrous Na₂SO₄, filtered and then removed under reduced pressure. The crude product was purified on a silica gel column (7 x 3 cm) eluting with *n*-hexanes/CH₂Cl₂/EtOAc (5:1:1). Yield 0.500 g, 0.00083 mol, 85%.

4.4.17. 4,5-Dibromo-*o*-xylenes (4.60)

Iodine (0.40 g, 0.00158 mol) was added to *o*-xylenes (11.73 ml, 0.094 mol). This was followed by the dropwise addition of liquid bromine (9.96 ml, 0.194 mol), over 2 h, maintaining the temperature at 0 °C throughout. The resultant solid (brown) cake was left to stand at room temperature overnight before being dissolved in Et₂O (100 ml), washed with 2N NaOH (2 x 50 ml), water (2 x 50 ml) dried over anhydrous MgSO₄, filtered and concentrated *in vacuo* to afford a faintly pink colored oil which crystallized on standing. Recrystallization from methanol gave a white crystalline solid (alternatively, the crystallized solid was washed with hexanes and filtered) in 64% (15.78 g, 0.060 mol) yield. mp 71 °C (lit. mp⁵⁵ 88 °C) ¹H NMR (CDCl₃, 400 MHz,): δ, ppm 7.38 (2H, s), 2.19 (6H, s). ¹³C NMR (100 MHz, CDCl₃): δ, ppm 19.28, 121.30, 134.40, 137.83. GC-MS 264.0 molecular weight for C₈H₈Br₂ 263.96.

4.4.18. Compound 4.56⁴⁰

To a dry 50 ml heavy walled round bottomed flask were added bis(acetonitrile)dichloropalladium(II) (52 mg, 0.0002 mol, 2 mol%), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (Sphos) (328 mg, 0.0008 mol), and 4,5-dibromo-*o*-xylene **4.60** (2.64 g, 0.010 mol). The flask was capped by a rubber septum and evacuated followed by dry nitrogen

gas purges, twice. Into the flask, was added dry 1, 4-dioxane (12 ml), triethylamine (11.2 ml, 0.080 mol), and pinacolborane (6 ml, 0.040 mol), dropwise in that order via syringes. The reaction mixture was then heated at 110 °C and monitored by TLC. After complete consumption of the dibromide, the reaction mixture was then cooled to room temperature and filtered through a short Celite cake with ethyl acetate washings (2 x 25 ml). The organic solvents were then removed under reduced pressure to afford the crude product that was further purified by silica gel column chromatography, eluting with CH₂Cl₂/n-hexanes (5:1) solvent system to give an oil. Yield 80 %, 2.874 g, 0.008 mol. ¹H NMR (CDCl₃, 400 MHz): δ, ppm 7.44 (2H, s), 2.26 (6H, s), 1.37 (24H, s). ¹³C NMR (100 MHz, CDCl₃): δ, ppm 19.76, 25.06, 76.91, 77.23, 77.55, 83.80, 135.18, 137.76 HRMS (ESI-TOF) *m/z* 359.2571 [M+H]⁺, calcd. for C₂₀H₃₂B₂O₄ 358.25.

4.4.19. Compound 4.55

Compound **4.55** was obtained in 30% yield from 1,2-dibromo benzene **4.59** using the same procedure for synthesizing dipinacol **4.56** above. ¹H NMR (CDCl₃, 400 MHz): δ, ppm 7.67-7.65 (2H, m), 7.39-7.37 (2H, m), 1.38 (24H, s). ¹³C NMR (100 MHz, CDCl₃): δ, ppm 25.09, 76.91, 77.23, 77.55, 84.03, 129.32, 133.65. HRMS (ESI-TOF) *m/z* 331.2257 [M+H]⁺, calcd. for C₁₈H₂₉B₂O₄ 330.2284.

4.4.20. Compound 4.52

To a 100 ml round bottomed flask loaded with a magnetic stirrer were added Pd(PPh₃)₄ (1.016 g, 0.00088 mol), dipinacol **4.56** (2.10 g, 0.0059 mol), potassium carbonate (4.863 g, 0.035 mol), and 2-iodopyrrole **4.19** (4.125 g, 0.0141 mol). The flask was covered with a septum, evacuated and purged with nitrogen gas (two sequences). Water (5.28 ml, 0.293 mol) was added followed by DMF (30 ml). The resultant mixture was then degassed with nitrogen for 30 min and stirred for 20 min more at room temperature. The mixture was then heated on an oil bath at 90 °C for 20 h more under nitrogen gas. The reaction was tracked using TLC. When judged complete, the flask was cooled to room temperature and the solvent was removed under reduced pressure. The resulting semi-solid crude mixture was then taken into ethyl acetate (100

ml) and washed with water. Organics were separated with a separatory funnel, dried over anhydrous Na_2SO_4 , filtered and the solvents were removed under reduced pressure. The crude product was then further purified using a silica column eluting with n-hexanes/ethyl acetate (5:1). mp 189-190 °C ^1H NMR (CDCl_3 , 400 MHz,): δ , ppm 8.57 (2H, s), 7.21 (2H, s), 4.23 (4H, q), 2.33 (6H, s), 2.24 (6H, s), 1.68 (6H, s), 1.30 (6H, t). ^{13}C NMR (100 MHz, CDCl_3): δ , ppm 9.38, 10.76, 10.91, 14.63, 14.76, 19.71, 59.88, 118.58, 118.96, 127.50, 129.20, 131.92, 136.88, 161.81. HRMS (ESI-TOF) m/z 437.2432 $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{26}\text{H}_{32}\text{N}_2\text{O}_4$ 436.24.

4.4.21. Compound 4.53

This compound was synthesized following the method above for **4.52**, but 2-iodopyrrole derivative **4.20** was used instead of **4.19**, and 1,2-diboronpinacol ester **4.55**, instead of **4.56**. In addition, purification was done by eluting the crude product from a silica gel column with two solvent systems; CH_2Cl_2 /n-hexanes (2:1) followed by n-hexanes/ethyl acetate (5:1). Yield 34%. mp 195-198 °C. ^1H NMR (CDCl_3 , 400 MHz,): δ , ppm 8.47 (2H, s), 7.39 (14H, m), 5.24 (4H, s), 2.25 (6H, s), 1.73 (6H, s). ^{13}C NMR (100 MHz, CDCl_3): δ , ppm 9.43, 10.84, 65.78, 118.60, 119.37, 128.14, 128.24, 128.36, 128.76, 130.97, 131.58, 131.87. HRMS (ESI-TOF) m/z 555.2252 $[\text{M}+\text{Na}]^+$, calcd. for $\text{C}_{34}\text{H}_{31}\text{N}_2\text{NaO}_4$ 555.2254.

4.4.22. Compound 4.54

This compound was synthesized following the method above for **4.52**, but 2-iodopyrrole derivative **4.20** was used instead of **4.19**. In addition, purification was performed by eluting the crude product from a silica gel column with petroleum ether/ethyl acetate (7:1). Yield 54%. mp 199 °C. ^1H NMR (CDCl_3 , 400 MHz,): δ , ppm 8.63 (2H, s), 7.36 (10H, m), 7.20 (2H, s), 5.23 (4H, s), 2.31 (6H, s), 2.25 (6H, s), 1.68 (6H, s) ^{13}C NMR (100 MHz, CDCl_3): δ , ppm 9.35, 10.88, 19.70, 65.71, 76.91, 77.23, 77.54, 118.25, 119.10, 127.79, 128.11, 128.18, 128.32, 128.72, 129.12, 131.99, 132.36, 136.67, 137.01. HRMS (ESI-TOF) m/z 561.2745 $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{36}\text{H}_{36}\text{N}_2\text{O}_4$ 560.2675.

4.4.23. Compound 4.51

This compound was synthesized following the method above for **4.52**, but dipinacol derivative **4.55** was used instead of **4.56**. In addition, purification was done by eluting the crude product from a silica gel column eluting with n-hexanes/ethyl acetate (5:1). Yield 60 %. mp 187 °C. ¹H NMR (CDCl₃, 400MHz): δ ppm 8.41 (2H, s), 7.47-7.40 (4H, m), 4.26 (6H, q, *J* = 7.1 Hz), 2.26 (6H, s), 1.75 (6H, s), 1.32 (4H, t). ¹³C NMR (100 MHz, CDCl₃): δ, ppm: 9.45, 10.73, 14.65, 59.94, 118.97, 119.25, 127.57, 128.26, 130.92, 131.53, 131.72, 161.67. HRMS (ESI-TOF) *m/z* 409.2117 [M+H]⁺, calcd. for C₂₄H₂₈N₂O₄ 408.2049.

4.4.24. Dialdehyde Compound 4.64

Diester **4.52** (1.18 g, 0.0027 mol) was taken into absolute ethanol (30 ml) and warmed to 70 °C to dissolve it. Potassium hydroxide (1.82 g, 0.0324 mol) was added and the reflux set-up was evacuated and nitrogen purged. The resulting mixture was then refluxed at 75 °C for 6 h. On complete hydrolysis, the reaction mixture was cooled and the yellow suspension dissolved into distilled water (100 ml). The solution was then acidified to pH 5 using 1N HCl to precipitate out the crude diacid product. The precipitate was then re-dissolved into ethyl acetate, and the organics were separated with a separatory funnel, dried over anhydrous Na₂SO₄, filtered and solvents were removed under reduced pressure to give the diacid **4.63** which was taken directly to the next step (Clezy formylation). Compound **4.63** (0.677 g, 0.00178 mol) was dissolved in trifluoroacetic acid (10 ml) at 0 °C. The flask was evacuated and purged with nitrogen in three sequences. The resulting solution was then gradually warmed to room temperature with stirring for 30 min. Trimethyl orthoformate (0.0178 mol, 1.95ml, 10 eq) was added through a syringe while maintaining the temperature below 25 °C. Stirring was continued for 1 h. The reaction flask was then cooled to about 5 °C when aqueous ammonium hydroxide was added until pH 7 was achieved. The red-brown crude product was then extracted with ethyl acetate (2 x 50 ml), dried over anhydrous Na₂SO₄, filtered and the volatiles were removed. Further purification was performed over silica column eluting with ethyl acetate/n-hexanes (1:1) to afford the titled

dialdehyde product **4.64** in 0.322g, 0.00093 mol, 52% yield. mp 205 °C (decomp). ¹H NMR (CDCl₃, 400MHz,): δ ppm 10.26 (2H, s), 9.28 (2H, s), 7.01 (2H, s) 2.23 (6H, s), 2.17 (6H, s), 1.59 (6H, s). ¹³C NMR (100 MHz, CDCl₃): δ, ppm: 8.82, 9.17, 19.54, 29.85, 118.93, 128.20, 129.20, 132.21, 136.71, 137.71, 176.37. HRMS (ESI) *m/z* 349.1922 [M+H]⁺, calcd. for C₂₂H₂₄N₂O₂ 348.1848.

4.4.25. Compound 4.65

Into a flask containing diacid **4.63** (1.00 g, 0.0027 mol) as an unworked-up precipitate, in a mixture of ethanol (30 ml) and water (10 ml) pH 6, was added a solution of sodium bicarbonate (1.474 g, 0.0176 mol) in water (28 ml). The mixture was then stirred at room temperature for 5 min. Iodine (1.71 g, 0.00675 mol, 2.5 eq) was then added into the mixture as a methanol solution (10ml) all at once. The flask was then evacuated and nitrogen purged, and allowed to stir at room temperature for 11 h more in darkness (flask covered by aluminum foil). The reaction was then quenched by the addition of saturated sodium thiosulfate (2 ml) and the crude product was extracted using a separatory funnel with ethyl acetate (2 x 25 ml). The organic layer was then washed with water (30 ml), brine (30 ml), and extracted once more with ethyl acetate (25 ml). The organic layer collected was then dried over anhydrous Na₂SO₄, filtered and the volatiles were removed. Further purification was performed on a silica gel column eluting with two solvent systems: ethyl acetate/n-hexanes (1:7), followed by ethyl acetate/n-hexanes (1:5). Yield 50%, 0.730g. ¹H NMR (CDCl₃, 400 MHz,): δ ppm 7.97 (2H, s), 2.39 (6H, s), 2.13 (6H, s), 0.66 (6H, s). ¹³C NMR (100 MHz, CDCl₃): δ, ppm: 16.80, 17.51, 20.25, 67.00, 108.34, 126.17, 126.93, 141.98, 146.23, 181.95 HRMS (ESI-TOF) *m/z* 542.9799 [M+H]⁺, calcd. for C₂₀H₂₀I₂N₂O₄ 541.9716.

4.4.26. Porphycene 4.70

Activated zinc (0.065 g, 0.001 mol), and Pd/C (10%, 65 mg) were placed into a round bottomed flask containing a magnetic stirrer. The flask was evacuated and acetone, 10 ml was added via syringe to the inorganic mixture. The flask was nitrogen purged and the mixture was

then stirred for 20 min to activate the catalyst mixture. Di-iodo-1,2-(dipyrrolyl)ethene **4.65** (0.090 g, 0.000167 mol) was then added as a suspension in acetone (10 ml) via a syringe followed by water (10 ml). The mixture was then let to stir for 48 h. The inorganics were then removed by filtering through a Celite cake, followed by a ethyl acetate washing (25 ml). The organics were separated, dried over anhydrous Na_2SO_4 , filtered and the volatiles were removed. Further purification was accomplished on a silica gel column eluting with ethyl acetate/n-hexanes (1:5) to yield a trace amount of porphycene **4.70** detected by mass spectroscopy only.

4.4.27. Stretched porphycene (4.78)

TiCl_4 (2.76 ml, 0.025 mol) was added dropwise to a solution of zinc dust (3.27 g, 0.050 mol) and copper(I) chloride (0.198 g, 0.002 mol) in dry THF (100 ml) under a dry nitrogen gas atmosphere, at room temperature. The mixture was heated at reflux for 2 h. Dialdehyde **4.64** was added as a THF solution (100 ml) over 1 h into the boiling reaction mixture. The mixture was further refluxed for 1 h more. After cooling to 0 °C (ice-water bath), a 6% NH_3 solution (100 ml) was added in a dropwise manner over 30 min during stirring. The organic solvent was then removed under reduced pressure and the aqueous solution was diluted with CH_2Cl_2 (100 ml). The solids were removed by suction filtration followed by CH_2Cl_2 (2 x 10 ml) washings. The organics were separated using a separatory funnel and collected, dried over anhydrous Na_2SO_4 , filtered and the solvent was removed under reduced pressure. Purification of the crude was performed over a silica gel column eluting with CH_2Cl_2 . The expected product was only obtained in trace amounts, as detected by ESI.

4.4.28. Benzyl 3,4,5-trimethylpyrrole-2-carboxylate (4.93)

A solution of sodium nitrite (4.3 g, 0.0624 mol) in water (9 ml) was added with stirring into a glacial acetic acid solution (20 ml) of benzyl acetoacetate **4.90** (10 g, 0.052 mol) over 30 min, at about 10 °C. The cooled mixture was stirred for a further 4 h and then kept at room temperature. The oxime **4.91** solution was added to 3-methylpentane-2,4-dione **4.92** (7.1 ml, 5.9 g, 0.052 mol) in acetic acid (20 ml) in the presence of zinc dust (6.8 g, 0.104 mol). The addition

of zinc dust was done carefully during stirring, maintaining the reflux temperature at 70 °C. After complete addition of zinc dust, the reaction mixture was further refluxed at 70 °C for 15 min. The yellow precipitate was poured into ice-water to crush out more pyrrole product. The crude product was filtered off and dissolved in CH₂Cl₂ (200 ml). The organics were then separated using a separatory funnel, dried over anhydrous Na₂SO₄, filtered and volatiles removed to give the titled pyrrole in 47%, 0.025 mol, 6.00 g yield . mp 100-102 °C (lit. mp⁵⁶ 119-120 °C). ¹H NMR (CDCl₃, 400 MHz): δ ppm 8.69 (1H, s), 7.44-7.33 (5H, m), 5.31 (2H, s), 2.29 (3H, s), 2.19 (3H, s), 1.93 (3H, s). ¹³C NMR (100 MHz, CDCl₃): δ, ppm: 8.92, 10.95, 11.65, 65.55, 116.44, 117.50, 128.18, 128.21, 128.72, 130.07, 136.04. HRMS (ESI) *m/z* 266.1156 [M+H]⁺ calcd. for C₁₅H₁₇NNaO₂ 266.1151.

4.4.29. Benzyl 5-acetoxy 3,4-dimethyl-2-carboxylate (4.89)

Lead tetra-acetate (1.463 g, 0.0033 mol) was added in three portions over 30 min to a stirred solution of benzyl 3,4,5-trimethylpyrrole-2-carboxylate **4.93** (0.73 g, 0.003 mol) in glacial acetic acid (10 ml) and acetic anhydride (0.5 ml). The mixture was then stirred for 3-12 h and poured into ice water and stirred for 5 min. The yellowish solid was filtered off, taken into CH₂Cl₂ (50 ml), and water (50 ml) was added. The organic fraction was collected from the separatory funnel, dried over anhydrous Na₂SO₄, filtered and the volatiles were removed to give a white solid that was purified using a silica gel column eluting with CH₂Cl₂. Yield 75 %, 0.68 g, 0.0023 mol.

4.4.30. Benzyl 3,4 -dimethyl-5-formyl-2-carboxylate (4.96)

Tetrasubstituted pyrrole **4.93** (2.425 g, 0.010 mol) was dissolved in 320 ml of THF/H₂O/acetic acid (1:1:1.2) solvent mixture. The mixture was stirred at room temperature for 10 min. Ceric ammonium nitrate (22.48 g, 0.041 mol) was added in one portion and the resulting reaction mixture was stirred at room temperature for 90 min. The orange suspension formed was then taken into CH₂Cl₂ (100 ml) and separated using a separatory funnel. The organic layer was washed with saturated NaHCO₃ to pH 7, followed by the addition of water (100 ml) and

brine (100 ml). The organic layer was again separated, dried over anhydrous Na_2SO_4 , filtered and the volatiles were removed under reduced pressure to afford the titled product which was later purified using a silica gel column eluting with $\text{MeOH}/\text{CH}_2\text{Cl}_2$ (1:99). Yield 1,3 g, 0.005 mol, 50 %. mp 111-113 °C (lit. mp⁵⁷ 119-119.5 °C) ^1H NMR (CDCl_3 , 400 MHz,): δ ppm 9.77 (1H, s), 9.52 (1H, s), 7.44-7.36 (5H, m) 5.34 (4H, s), 2.29 (6H, s), 2.28 (6H, s). ^{13}C NMR (100 MHz, CDCl_3): δ , ppm: 1.22, 8.71, 9.98, 66.83, 124.30, 127.68, 128.63, 128.69, 128.87, 130.33, 135.65, 160.91, 179.41. HRMS (ESI-TOF) m/z 258.1172 $[\text{M}+\text{H}]^+$.

4.4.31. Bis-dipyrromethene 4.98

Diacid **4.63** (0.438 g, 0.00115 mol) in a 100 ml round bottomed flask was cooled to 0 °C and trifluoroacetic acid (15 ml) was added in a dropwise manner under a nitrogen gas atmosphere. The resulting green mixture was stirred for 30 min at room temperature. Formylpyrrole **4.96** (0.681 g, 0.00265 mol, 2.3 eq) dissolved in dry methanol (25 ml) was then added directly through a syringe to the mixture. The color of the solution changed from brown to red in 5 min. The reaction was monitored by UV/Vis until a single absorption peak was observed at 480 nm. The protonated product **4.97** formed was basified with NH_4OH solution to pH 8 and extracted with CH_2Cl_2 (2 x 50 ml). The organic layer was then concentrated *in vacuo* and the crude product was further purified using a silica gel column eluting with ethyl acetate/ CH_2Cl_2 (1:8). The titled product eluted first with the solvent ($R_f=0.8$) as an orangish band. The fractions were collected together to give a yellow solid of **4.98**. Yield 0.60 g, 0.00078 mol, 68 %. mp 200-203 °C. ^1H NMR (CDCl_3 , 400 MHz,): δ ppm 7.50 (2H, s), 7.37-7.19 (4H, m), 7.21-7.09 (3H, m) 7.09-7.01 (3H, m), 6.68 (2H, s), 5.19 (4H, s), 2.30 (6H, s), 2.25 (6H, s), 2.17 (6H, s), 2.02 (6H, s), 1.59 (6H, s). ^{13}C NMR (100 MHz, CDCl_3): δ , ppm: 9.30, 10.01, 10.39, 10.79, 19.75, 65.47, 115.20, 123.98, 127.05, 127.36, 127.70, 128.44, 131.38, 133.13, 134.29, 136.59, 138.06, 140.25, 152.52, 160.76, 174.02 HRMS (ESI) m/z 771.3887 $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{50}\text{H}_{51}\text{N}_4\text{O}_4$ 771.391.

4.4.32 3,4 -dimethyl-2-formyl-5-iodo-pyrrole (4.67)

Pd/C (0.300 g) was transferred into a dry 100 ml round bottomed flask. The flask was evacuated and THF (10 ml) was added via syringe. The vacuum was replaced by hydrogen gas balloon. The catalyst was activated for 15 min by stirring in hydrogen gas atmosphere. Benzyl 3,4-dimethyl-5-formyl-2-carboxylate **4.96** (0.77 g, 0.003 mol) in THF (20 ml) was then added through a syringe all at once and stirring was continued overnight at room temperature. The reaction was stopped when only a new more polar spot was observed on TLC. The mixture was then filtered through Celite, followed by an ethyl acetate (25 ml) rinse. The solvent was then removed under reduced pressure leaving behind a pale yellow solid of the acid **4.66**, which was immediately taken to the next step (iodination) without further characterization due to its unstable nature. Acid pyrrole **4.66** (0.500 g, 0.003 mol) was then taken into glacial acetic acid (15 ml). Into the mixture was then added sodium acetate (0.468 g, .0.0057 mol) and a reflux condenser was installed. The set-up was evacuated and purged with dry nitrogen three times. The mixture was then heated at 80 °C. Iodine monochloride (1 Molar, 0.584 g, 0.0036 mol) in CH₂Cl₂ (3.6 ml), was then added to the heated mixture as a steady stream of droplets over 20 min and heating was continued for 3 h more at 80 °C. The reaction flask was then cooled to room temperature and few ice cubes were added to cool it further. 10% of Sodium thiosulfate (5 ml) was then added and the mixture was stirred to quench the unreacted iodine in the crude mixture (until the purple color disappeared). More cold water (100 ml) was added to crash out the product as a brown solid. The solid was filtered off, and taken into CH₂Cl₂ (50 ml), washed with saturated sodium bicarbonate (50 ml), water (100 ml), and brine (100 ml). Organics were separated, dried over anhydrous Na₂SO₄, filtered and the volatiles were removed to give a white solid that was purified further using a silica gel column eluting with MeOH/CH₂Cl₂ (1:99). Yield 0.388 g, 0.00156 mol, 52 %. mp 170 °C (lit. mp¹⁶ 179-180 °C) ¹H NMR (CDCl₃, 400 MHz): δ ppm 9.59 (1H, s), 9.40 (1H, s), 2.30 (3H, s), 1.98 (3H, s). ¹³C NMR (100 MHz, CDCl₃):

δ , ppm: 9.30, 11.49, 126.74, 130.71, 133.71, 176.00 HRMS (ESI) m/z 249.9736 $[M+H]^+$ calcd. for C_7H_9INO 249.9729.

4.4.33. Bis-dipyrromethene 4.88

Diacid **4.63** (0.923 g, 0.00243 mol) in a 100 ml round bottomed flask was cooled to 0 °C and trifluoroacetic acid (15 ml) was added in a dropwise manner under a nitrogen gas atmosphere. The resulting green mixture was stirred for 30 min at room temperature. Formylpyrrole **4.67** (1.33 g, 0.00534 mol, 2.2 eq) dissolved in dry methanol (35 ml) was then added dropwise over 5 min through a syringe to the mixture. The color of the solution changed from brown to red in 5 min. The reaction was stirred for 1 h and monitored by UV/Vis until a single absorption peak was observed at around 470 nm. The protonated product **4.100** formed was basified with 15% NH_4OH solution to pH 8 and extracted with CH_2Cl_2 (2 x 50 ml). The organic layer was washed with water (50 ml), brine (50 ml) then concentrated *in-vacuo* and the crude product was further purified by use of silica gel column chromatography eluting with ethyl acetate/ CH_2Cl_2 (1:8). The titled product **4.88** eluted first with the solvent ($R_f=0.8$) as an orangish band. The fractions were collected together to give a yellow solid of **4.88**. Yield 1.95 mmol, 1.47 g, 80%. mp 220 °C (decomp.) 1H NMR ($CDCl_3$, 400 MHz): δ ppm 7.36 (2H, s), 6.59 (2H, s), 2.40 (6H, s), 2.12 (12H, s), 1.89 (6H, s), 1.84 (6H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ , ppm: 9.85, 10.06, 10.35, 12.66, 19.88, 117.14, 120.42, 127.83, 129.20, 129.34, 131.73, 131.90, 132.78, 137.35, 137.93, 139.31, 148.58 HRMS (ESI) m/z 755.1061 $[M+H]^+$ calcd. for $C_{34}H_{37}I_2N_4$ 755.1108.

4.5. References

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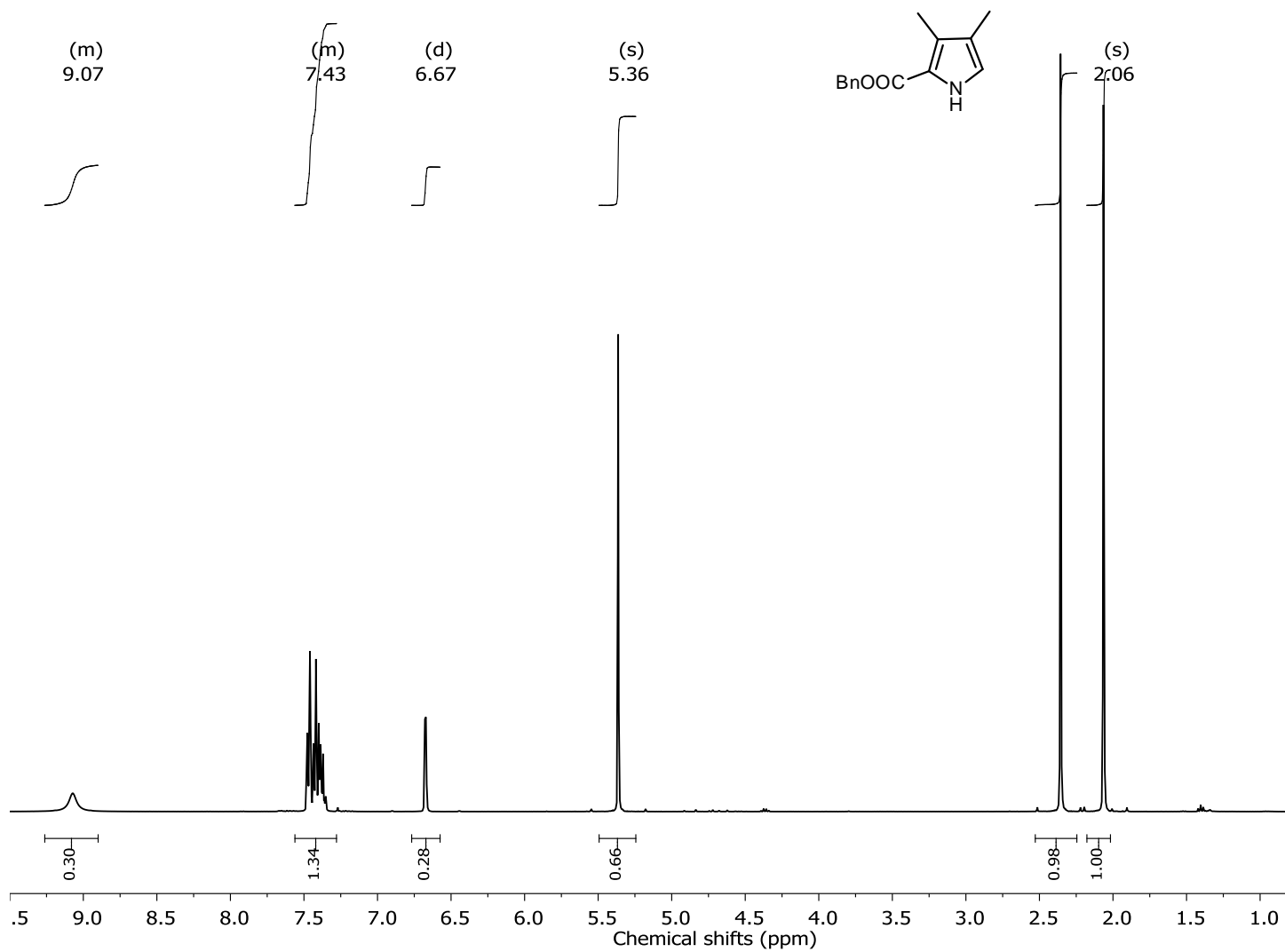
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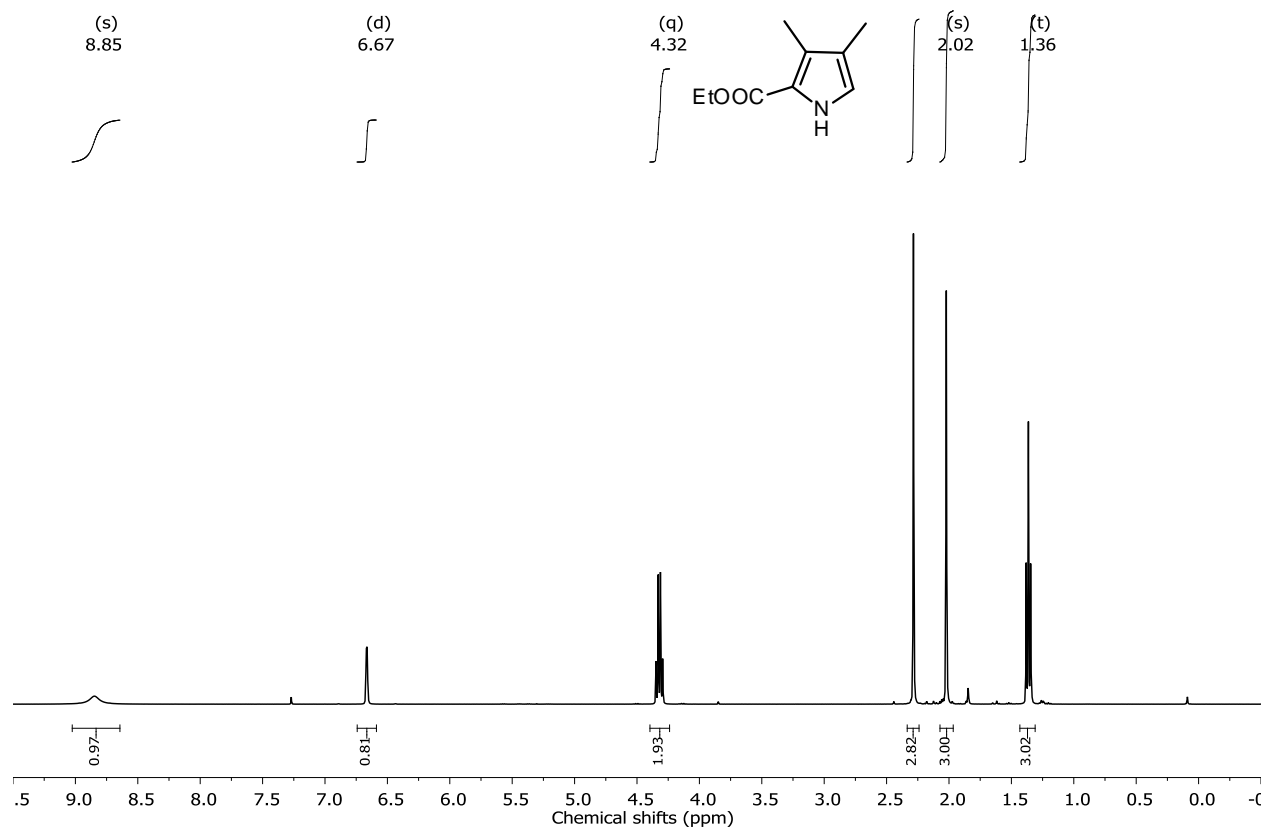
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APPENDIX A: CHAPTER 2 CHARACTERIZATION DATA

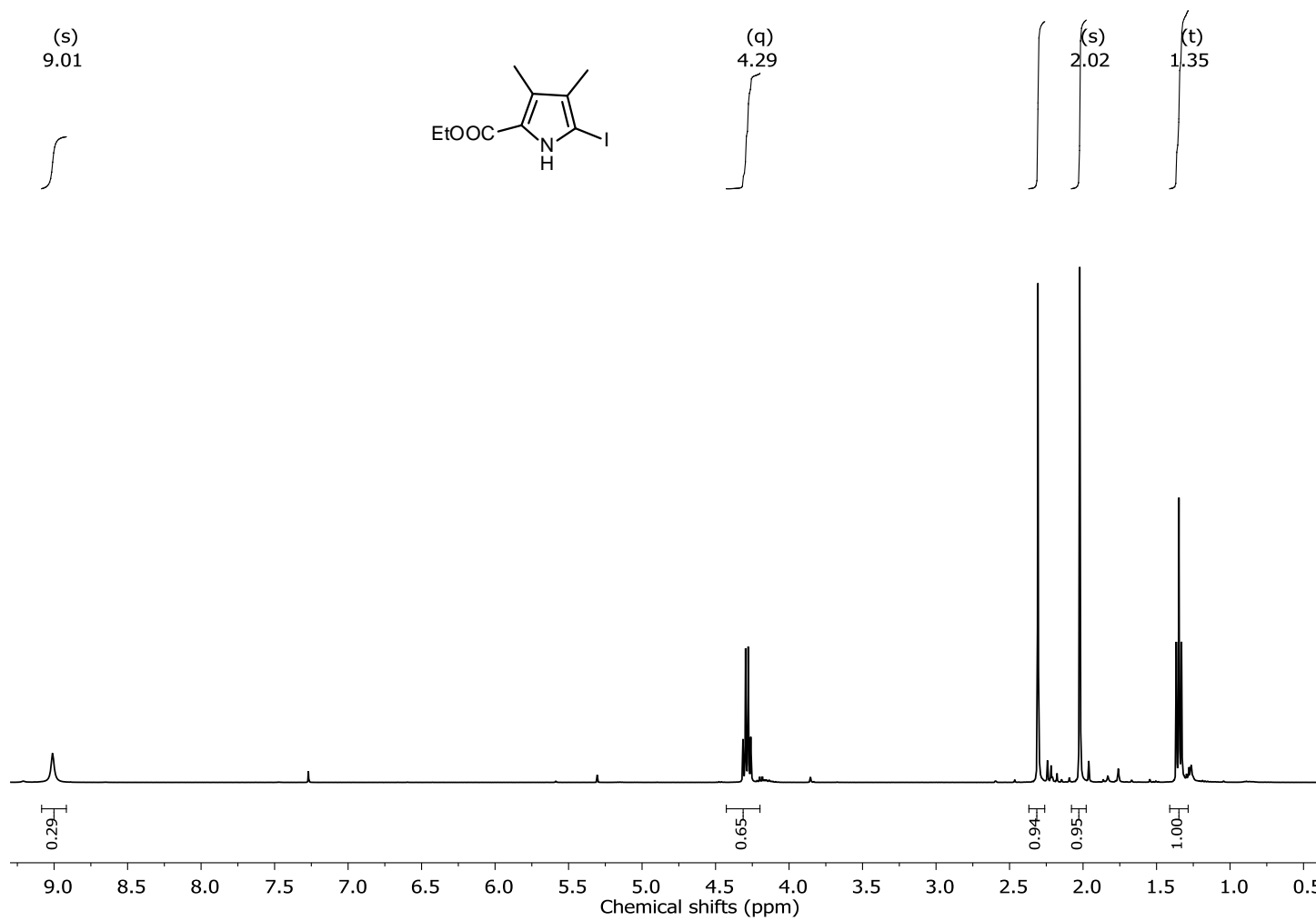
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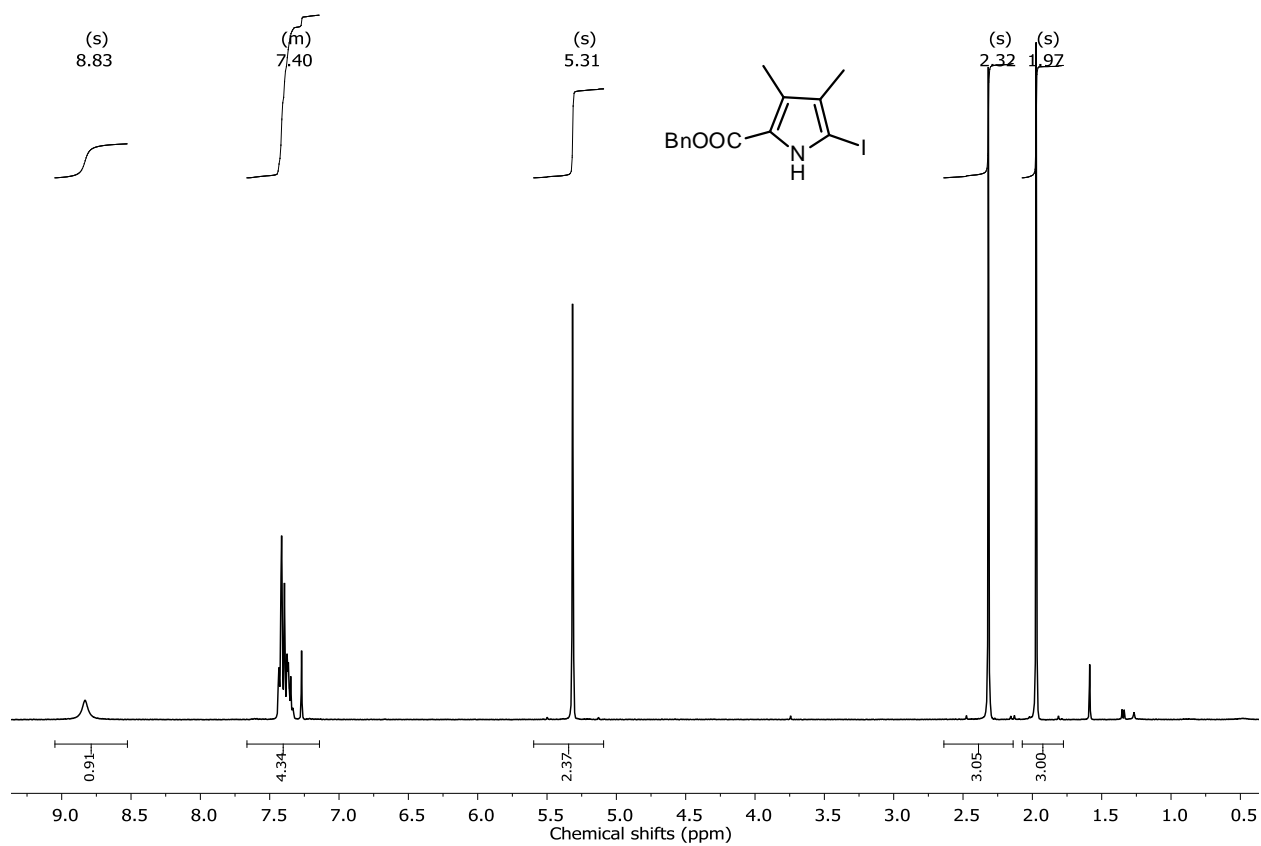
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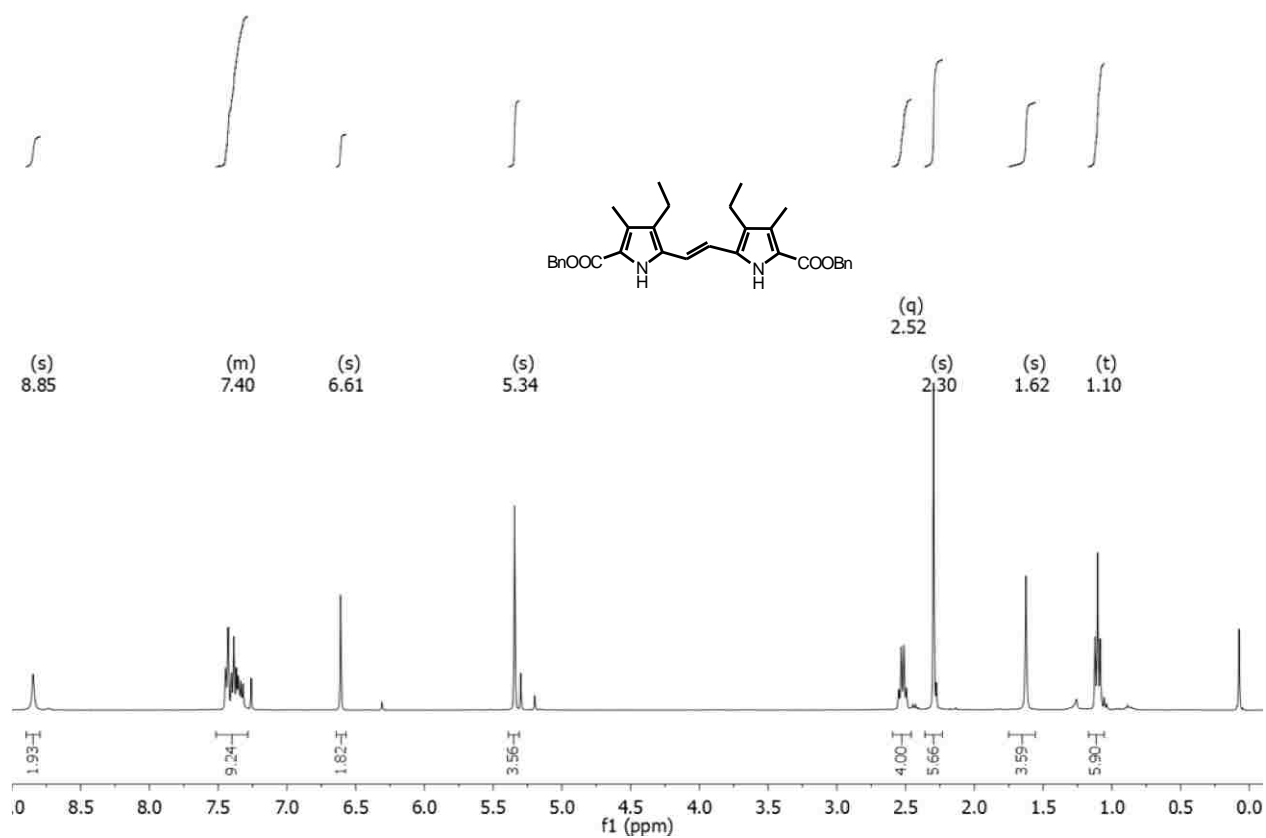
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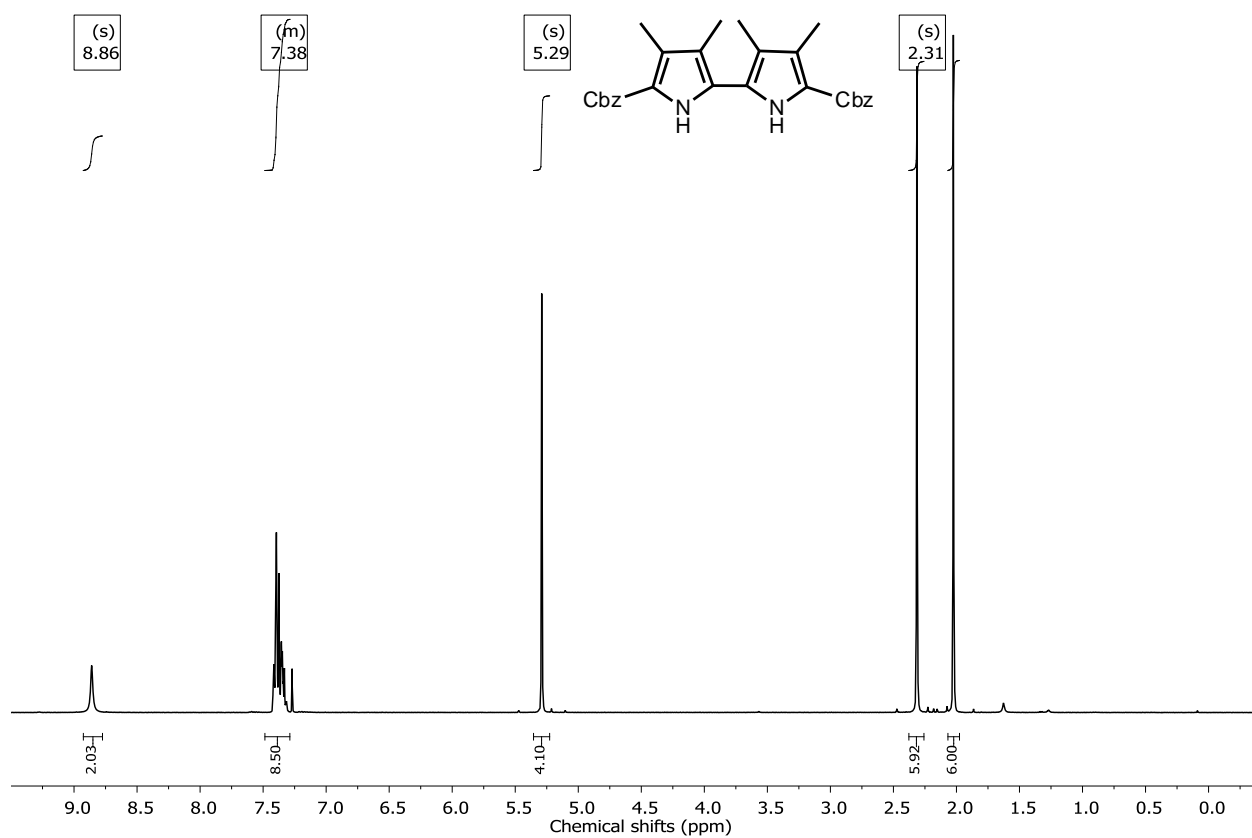
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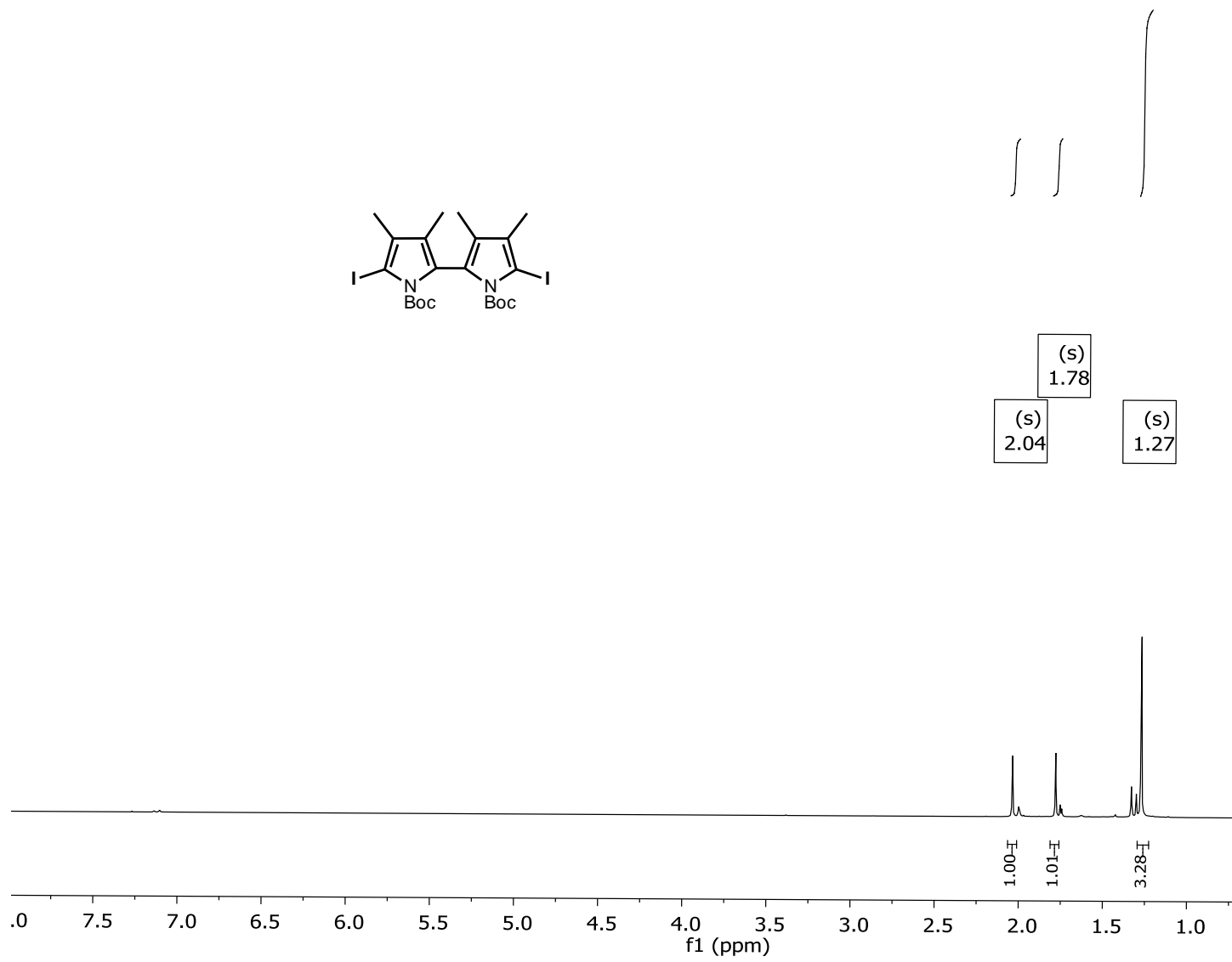
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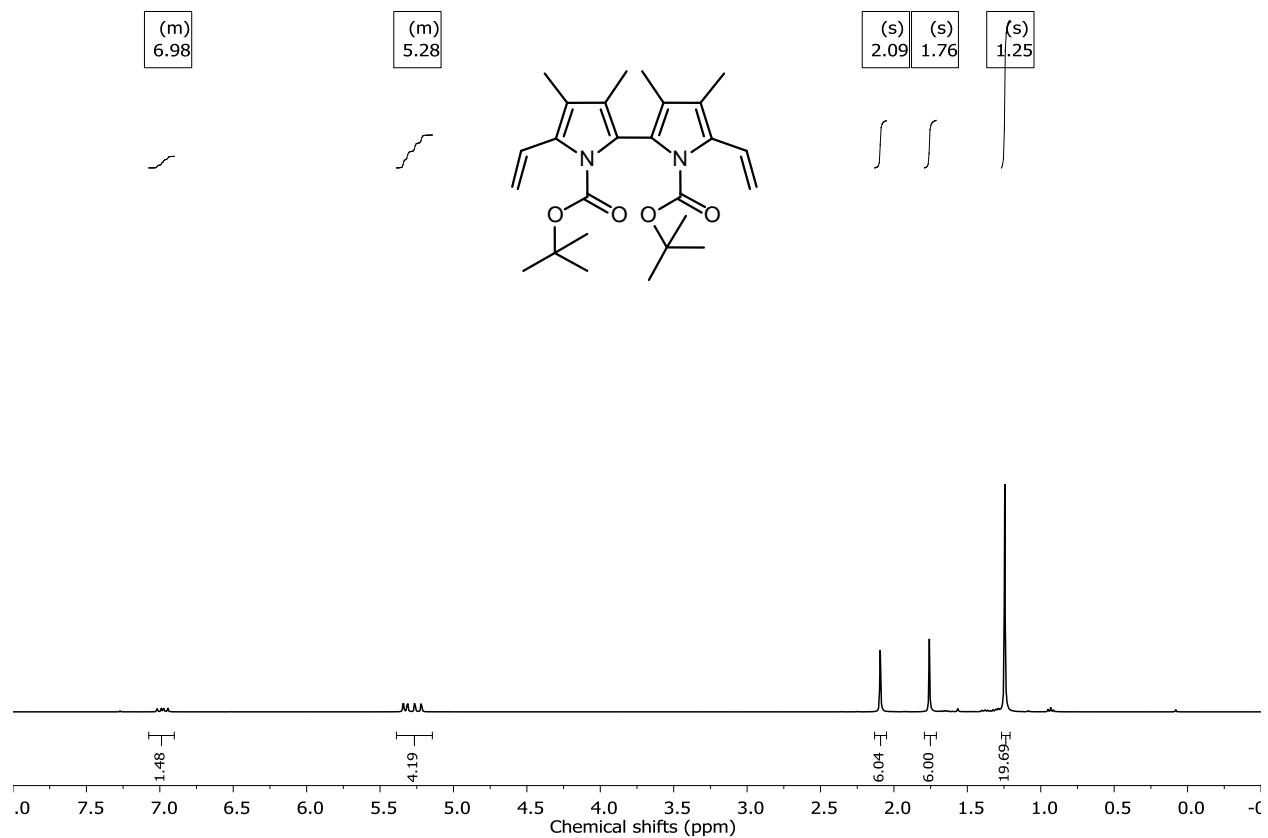
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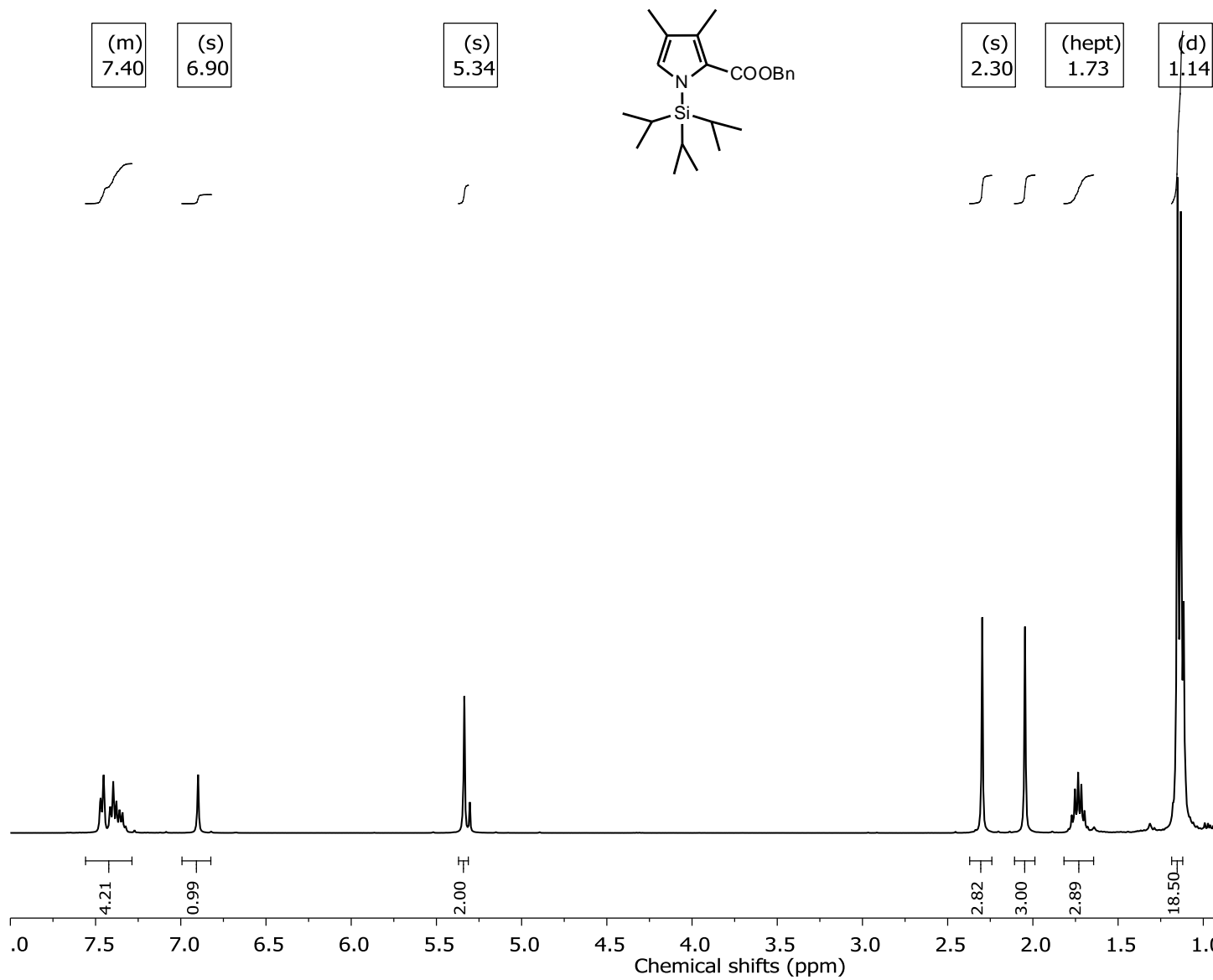
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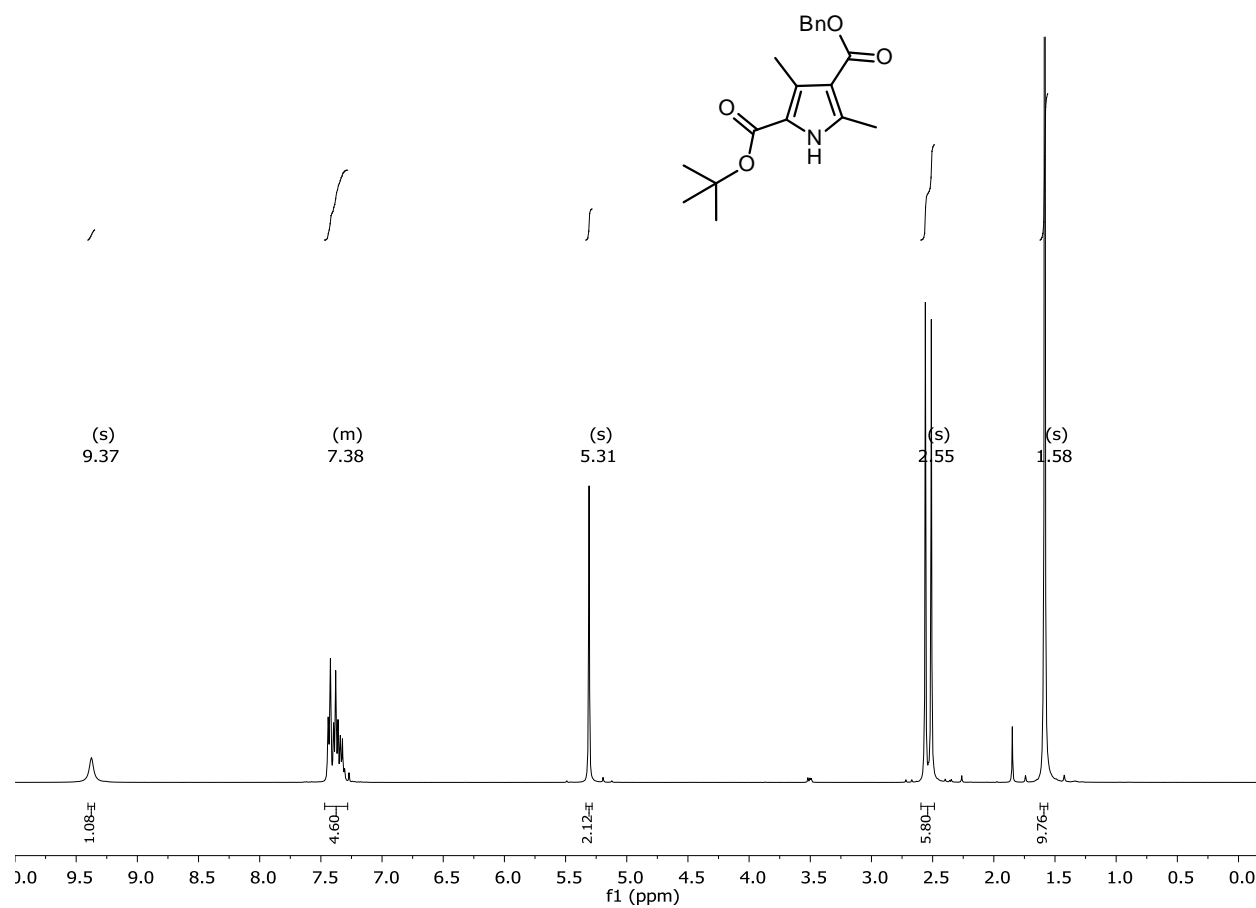


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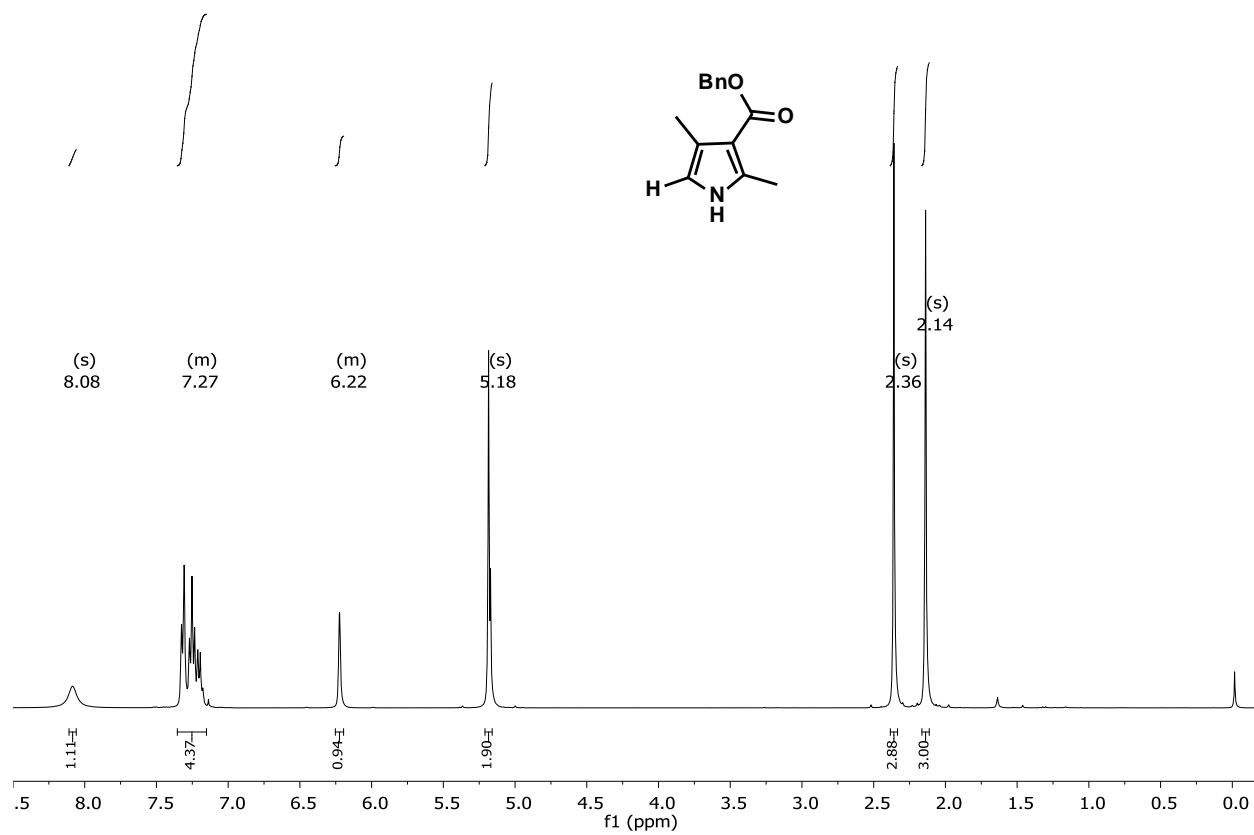


APPENDIX B: CHAPTER 3 CHARACTERIZATION DATA

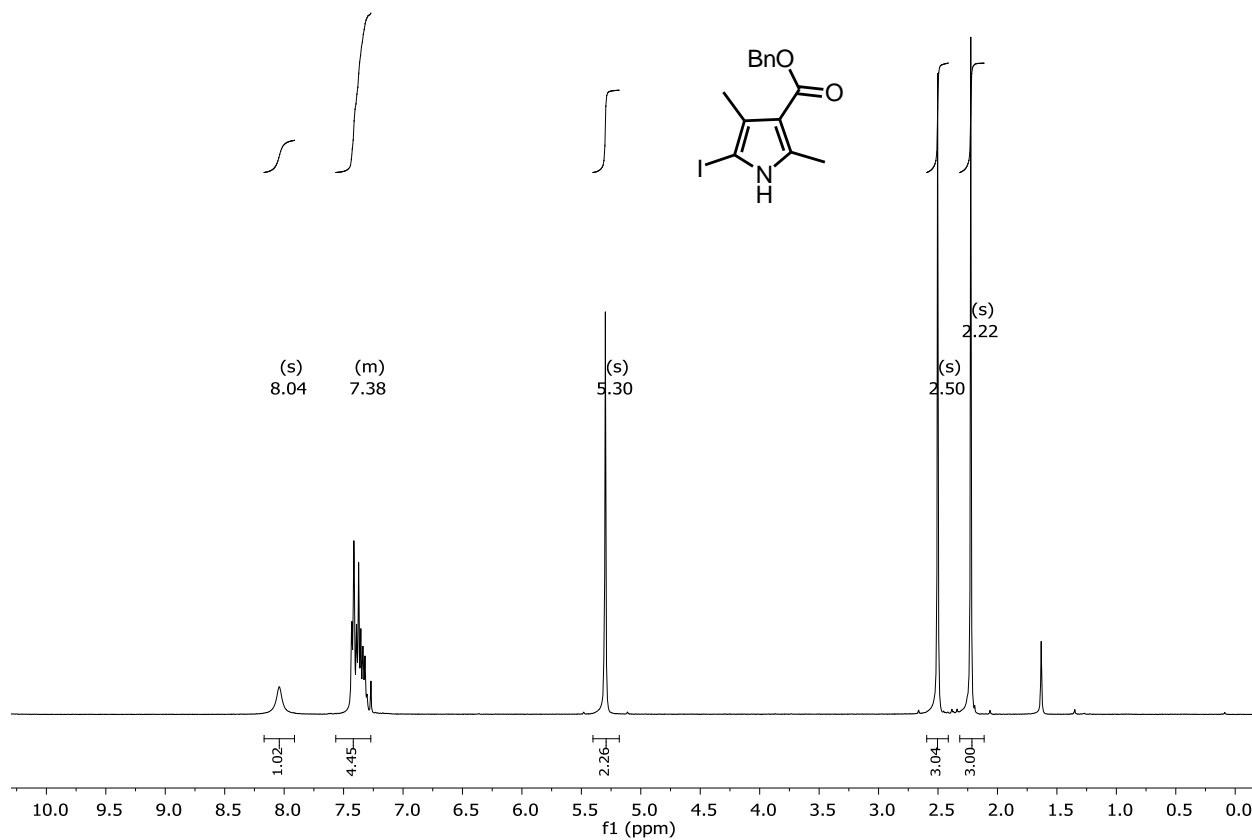
$^1\text{H-NMR}$ Spectrum of Compound **3.28** in CDCl_3 at 400 MHz



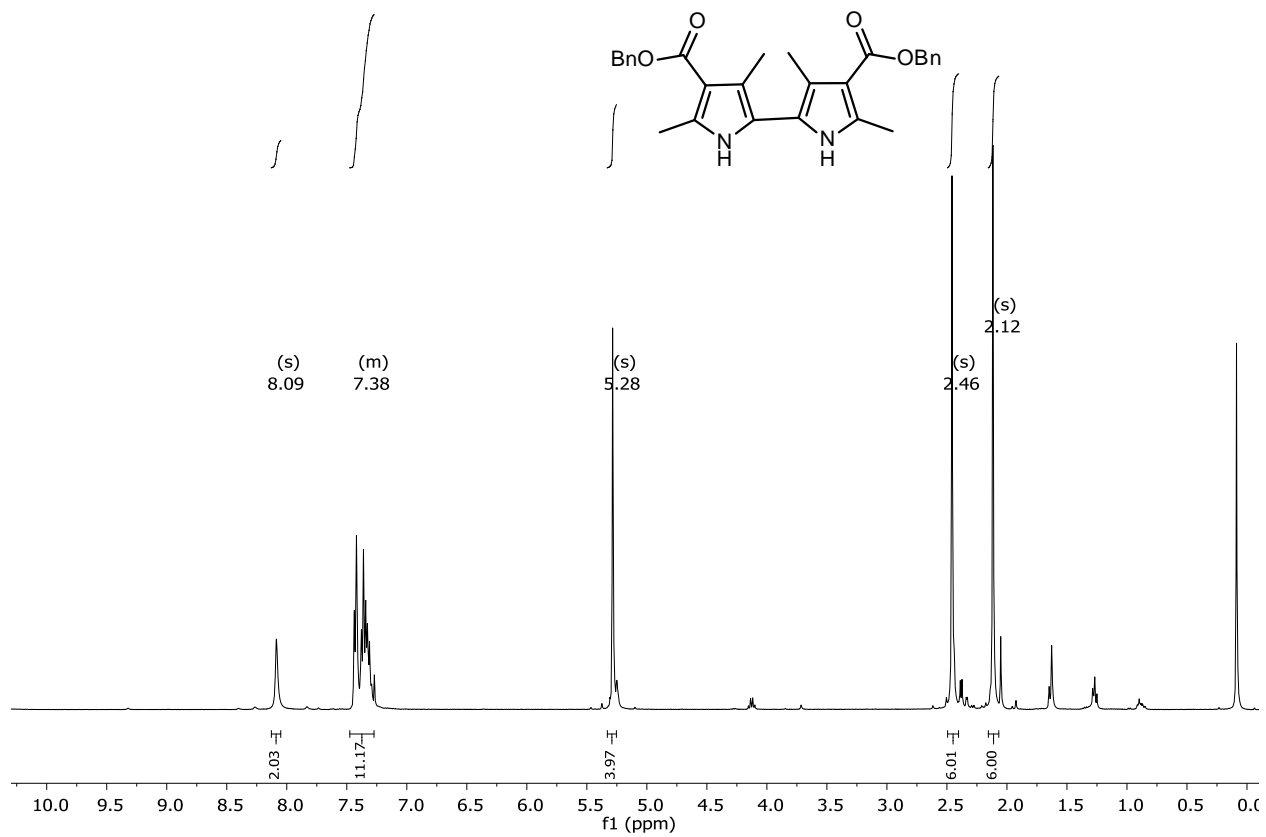
¹H-NMR Spectrum of Compound **3.29** in CDCl₃ at 400 MHz



¹H-NMR Spectrum of Compound **3.30** in CDCl₃ at 400 MHz

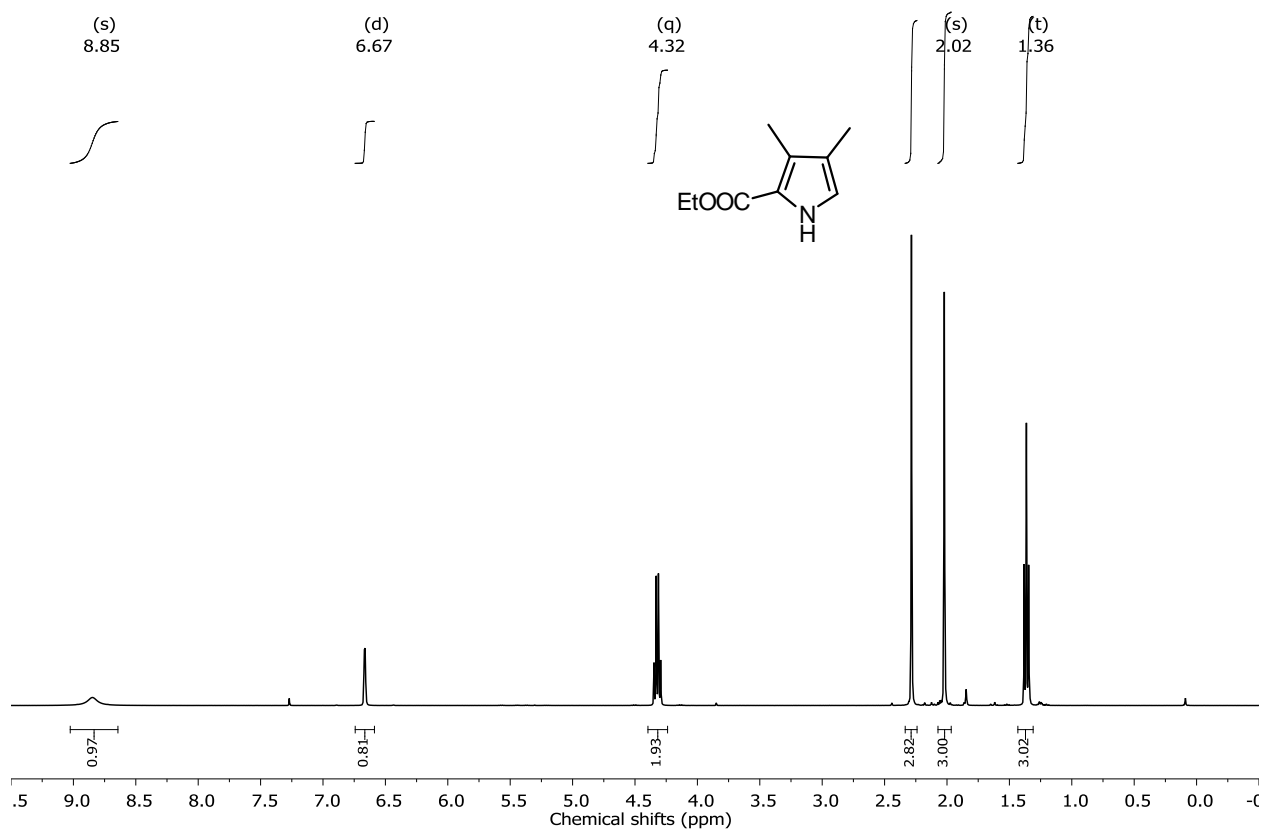


¹H-NMR Spectrum of Compound **3.31** in CDCl₃ at 400 MHz.

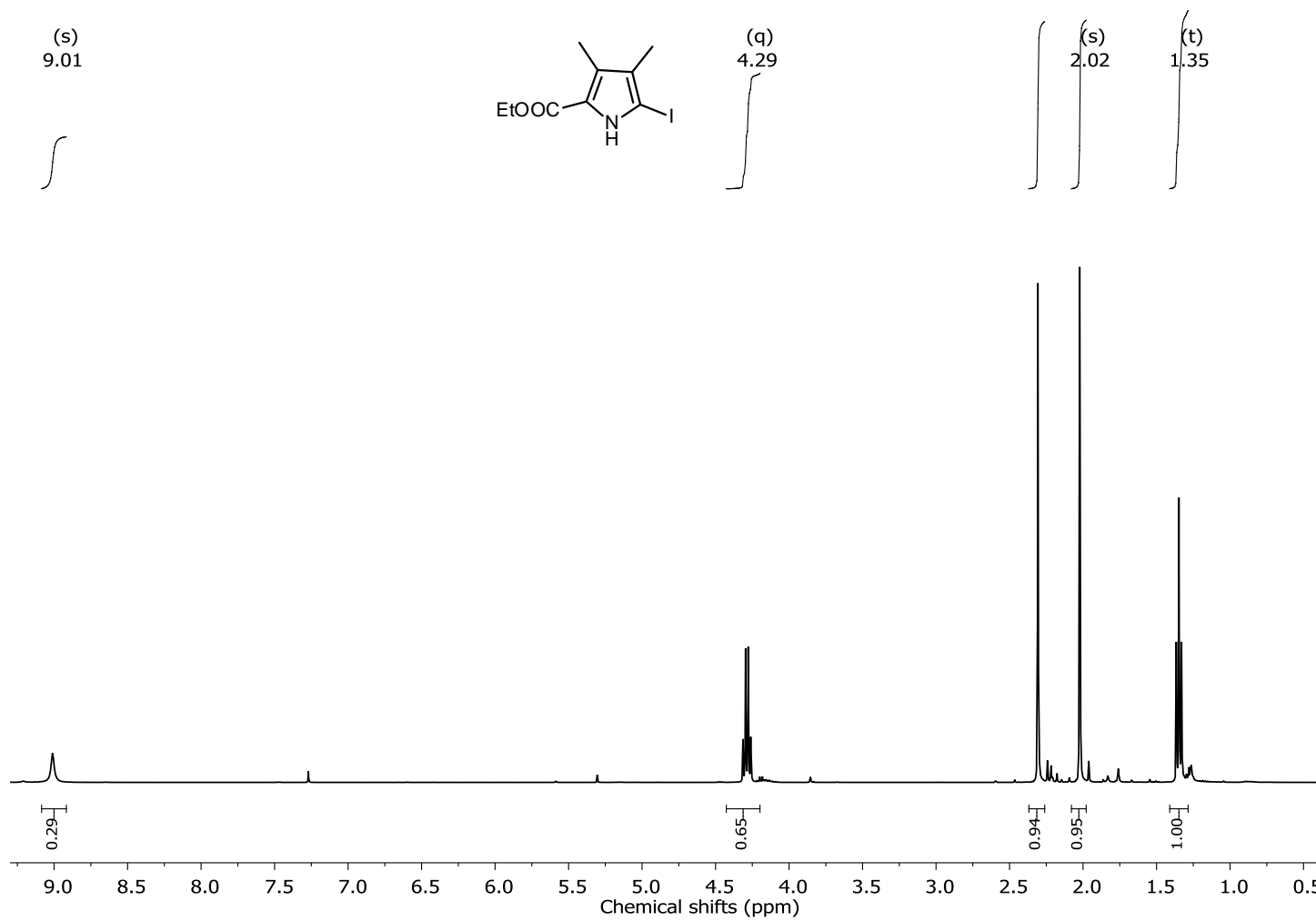


APPENDIX C: CHAPTER 4 CHARACTERIZATION DATA

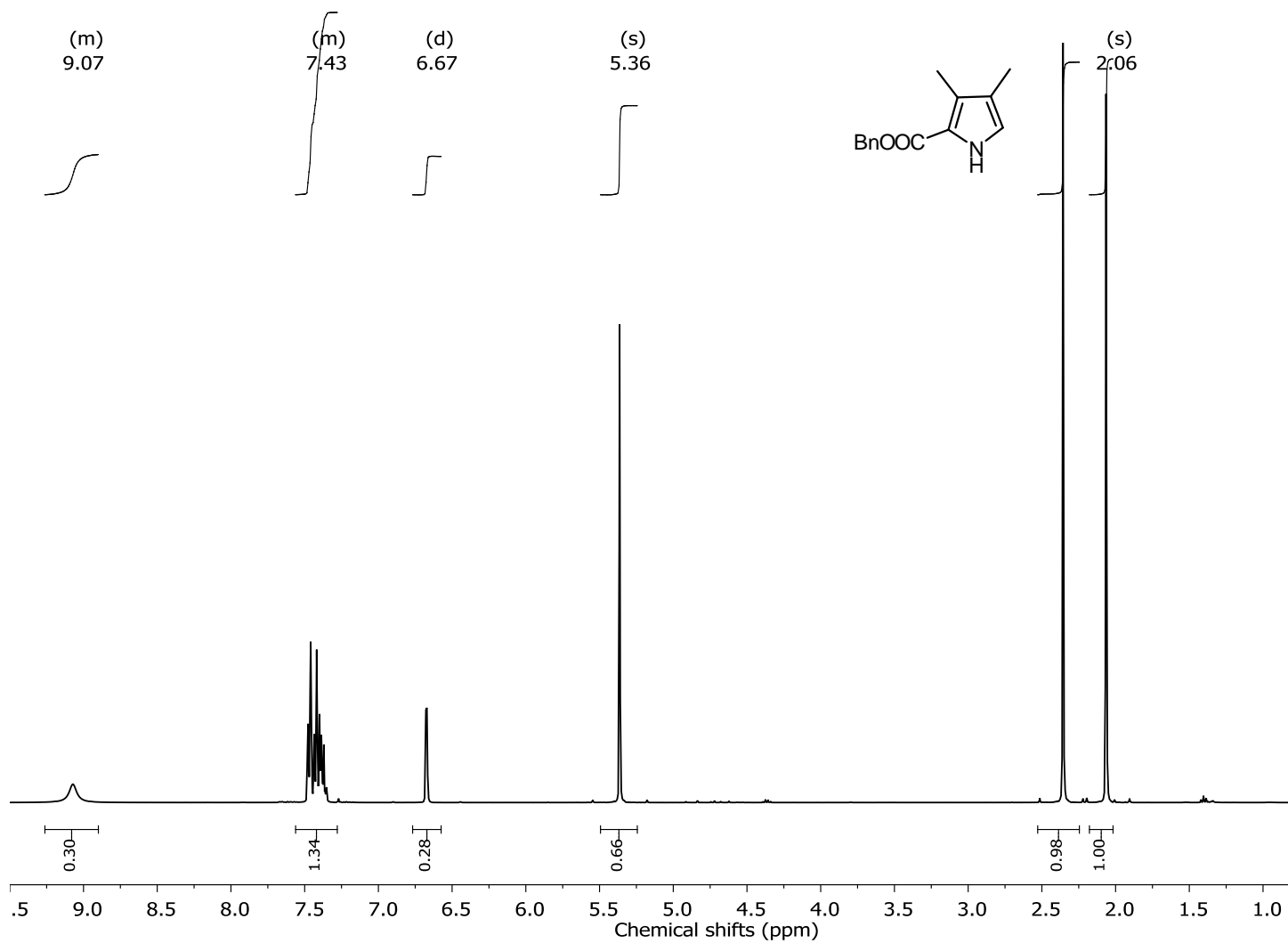
$^1\text{H-NMR}$ Spectrum of Compound **4.17** in CDCl_3 at 400 MHz.



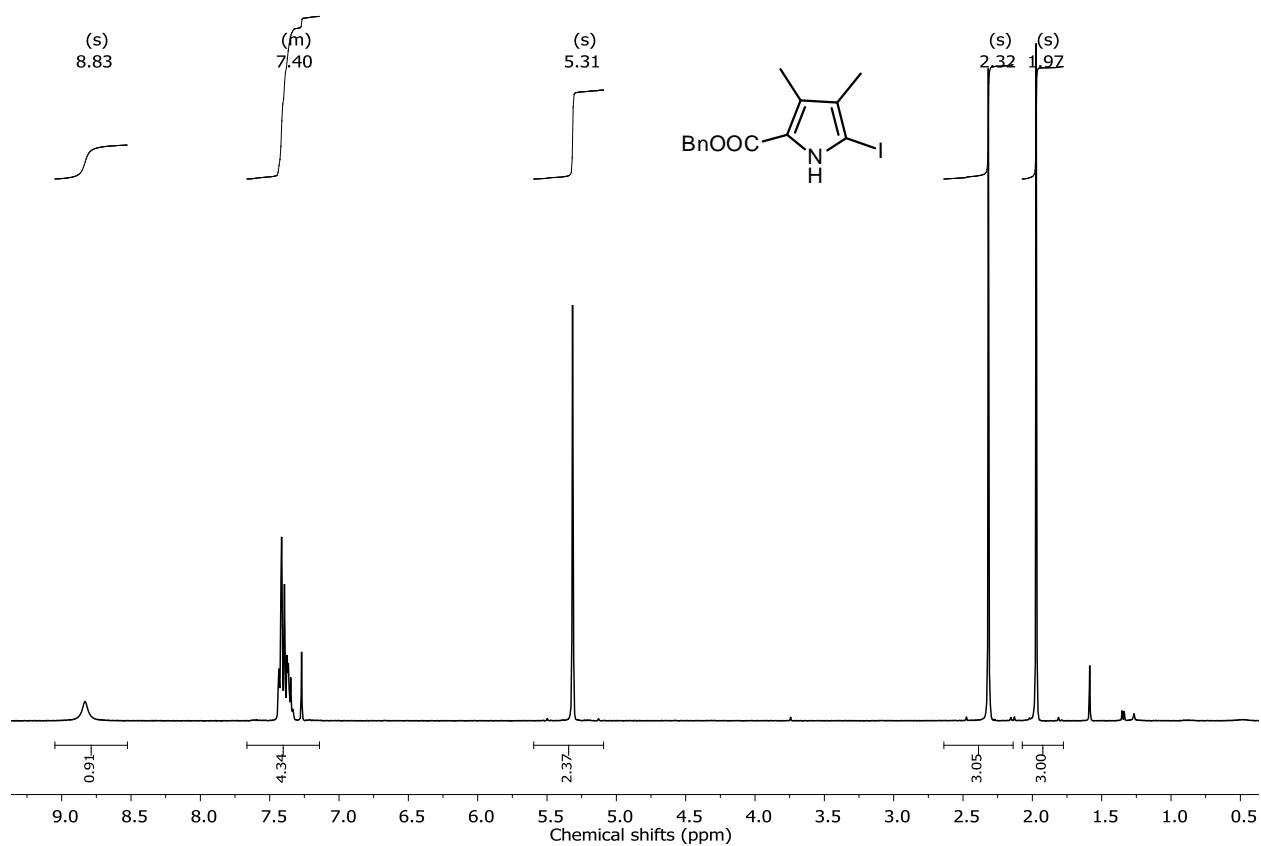
¹H-NMR Spectrum of Compound **4.19** in CDCl₃ at 400 MHz.



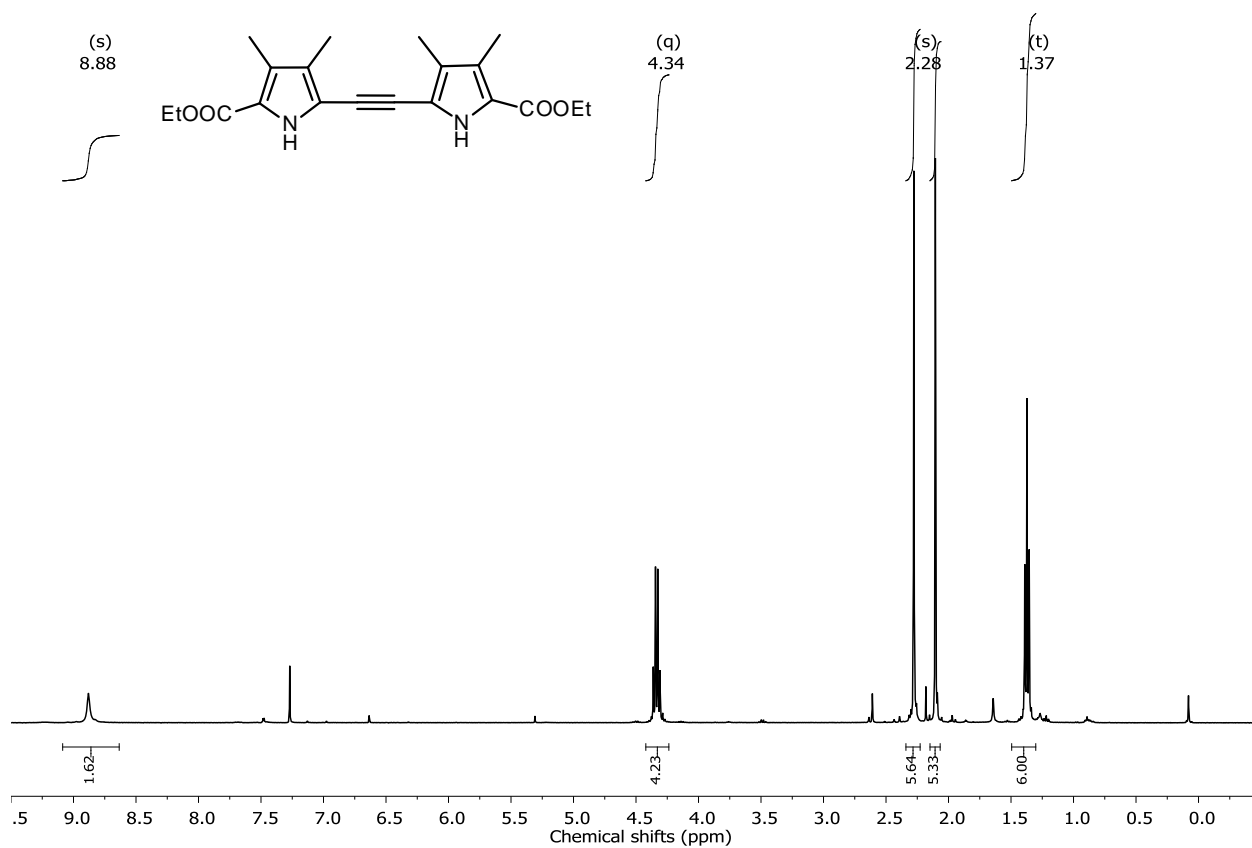
¹H-NMR Spectrum of Compound **4.18** in CDCl₃ at 400 MHz.



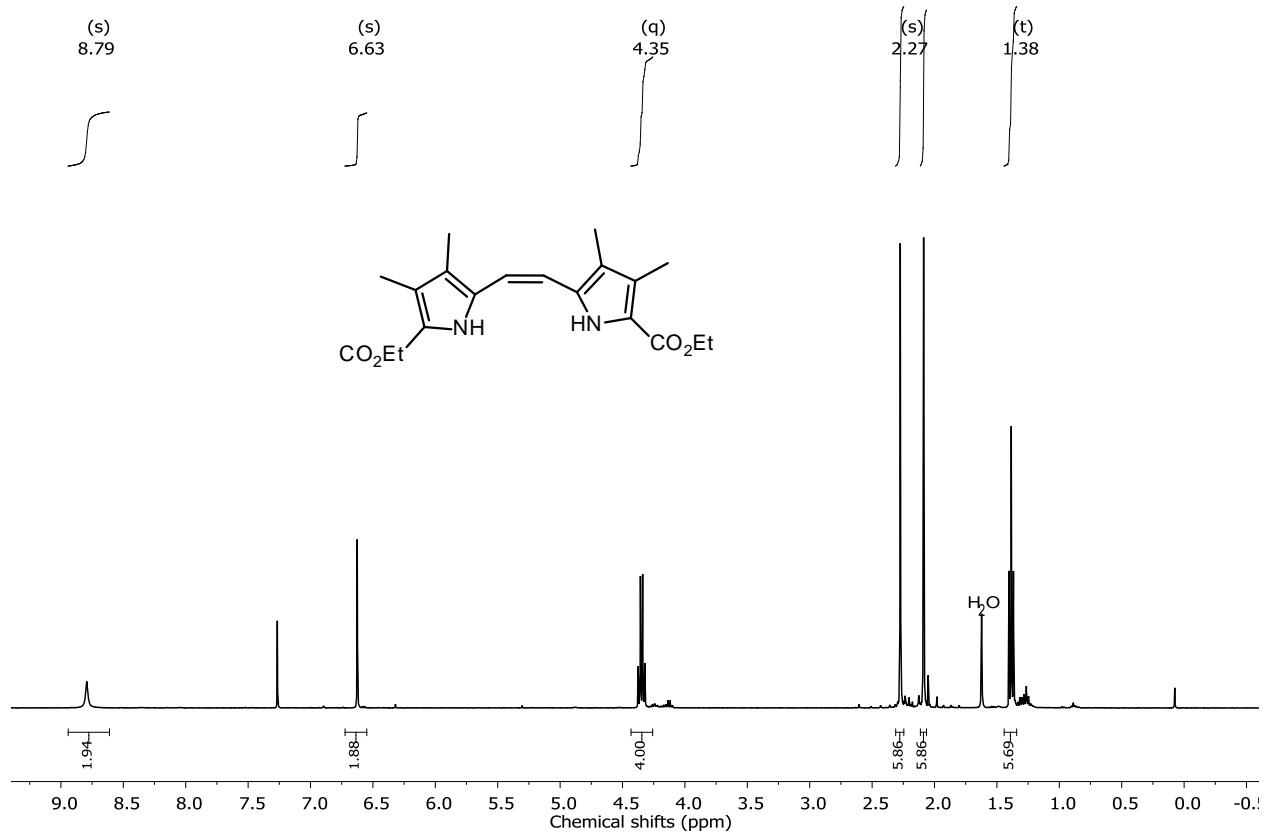
¹H-NMR Spectrum of Compound **4.20** in CDCl₃ at 400 MHz.



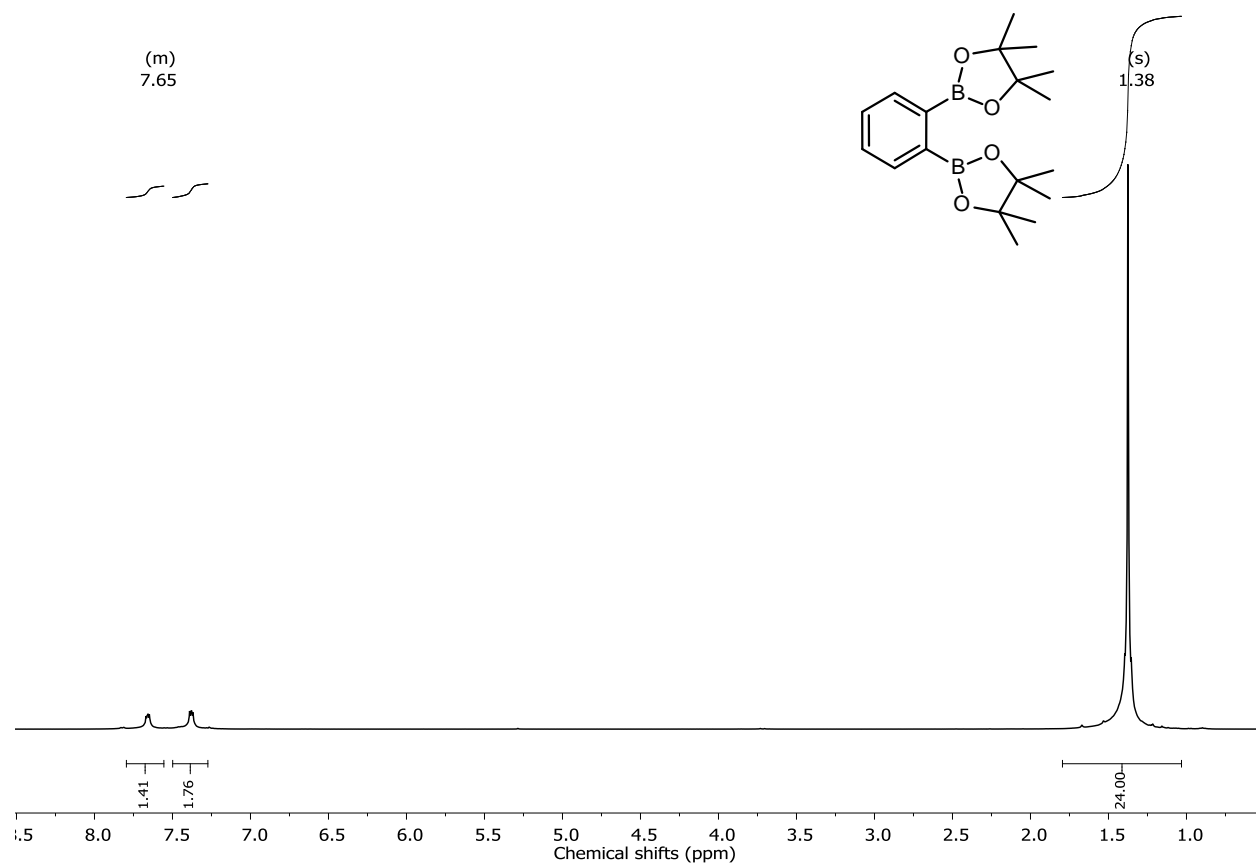
¹H-NMR Spectrum of Compound **4.25** in CDCl₃ at 400 MHz.



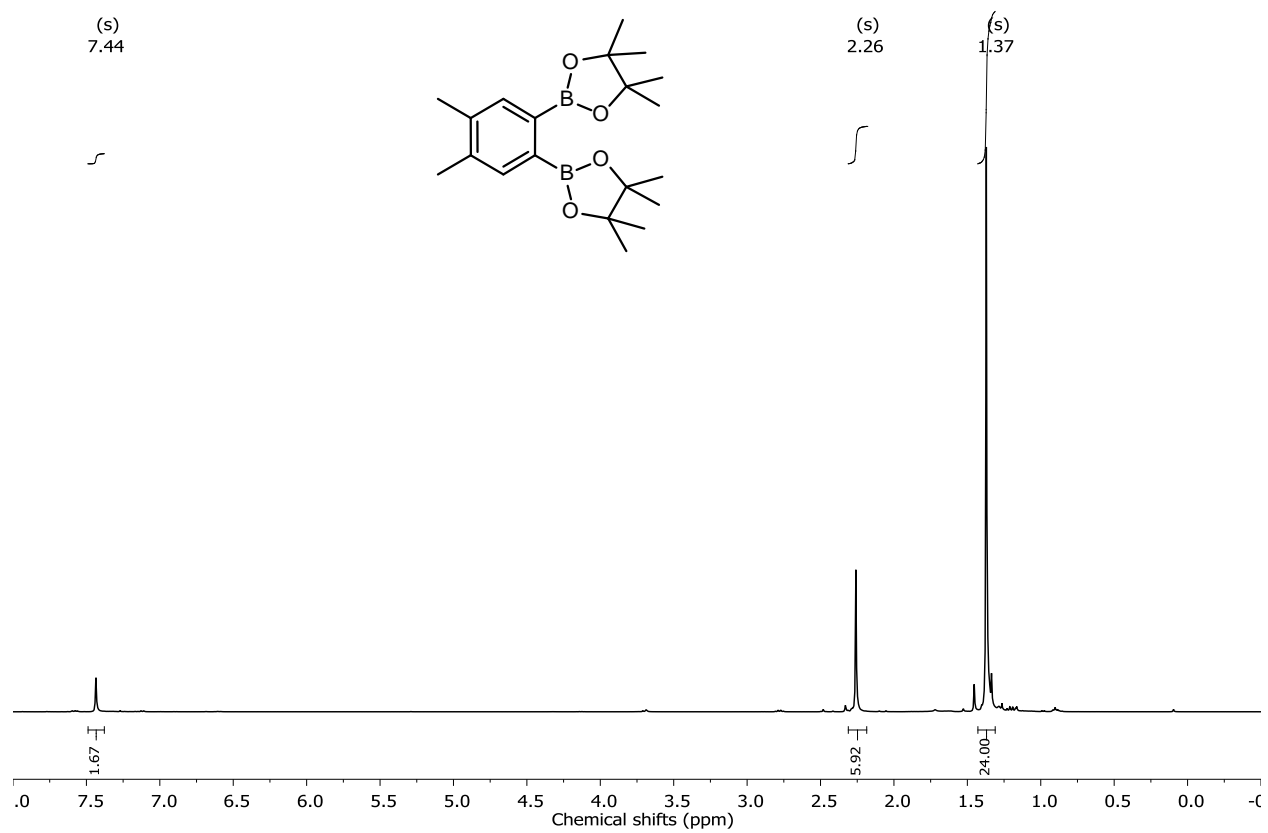
¹H-NMR Spectrum of Compound **4.27** in CDCl₃ at 400 MHz.



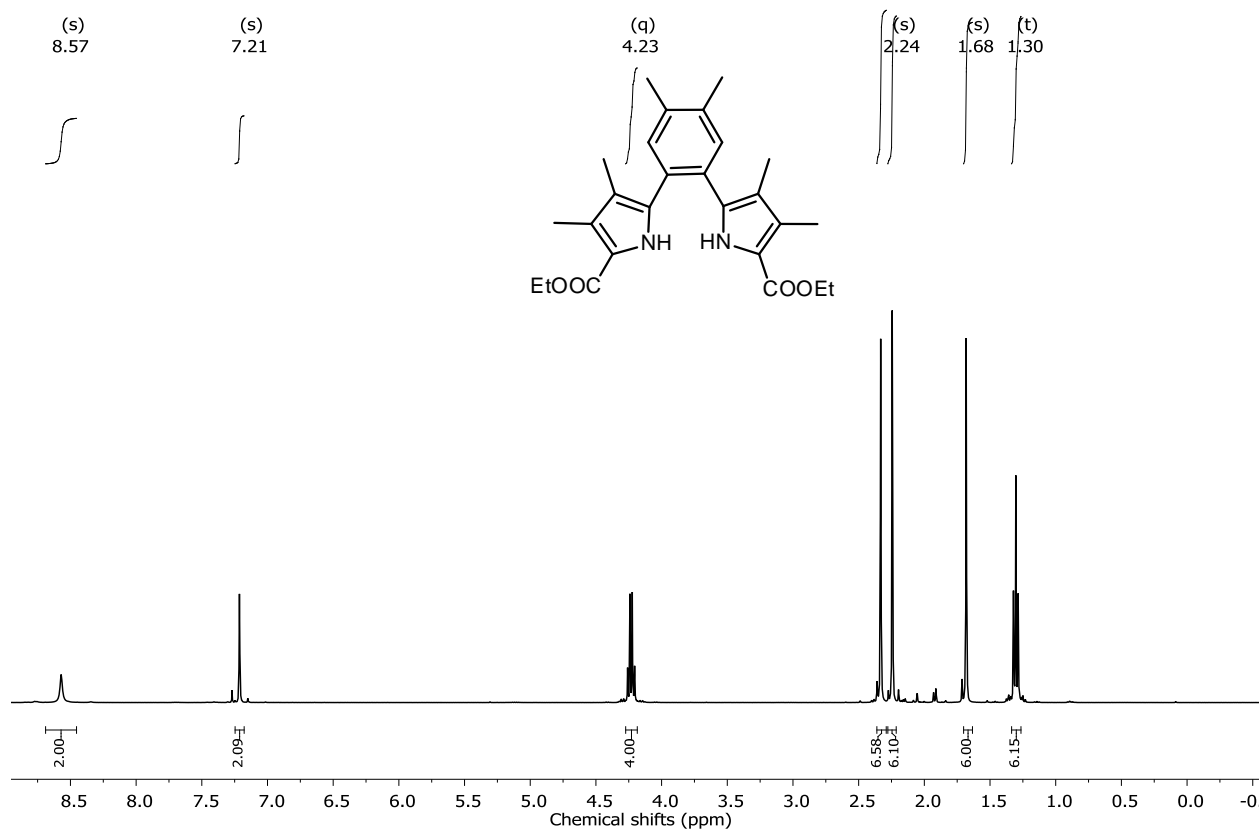
¹H-NMR Spectrum of Compound **4.55** in CDCl₃ at 400 MHz.



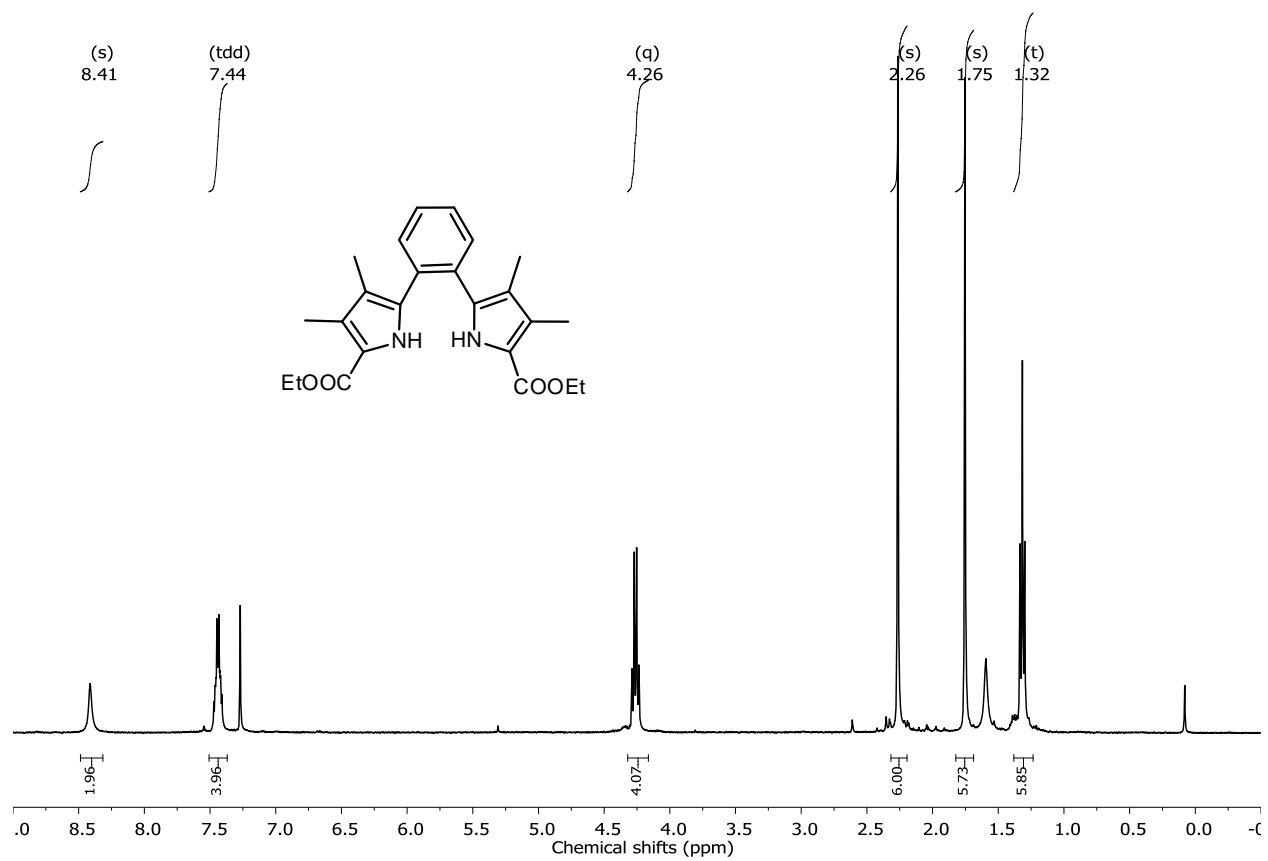
¹H-NMR Spectrum of Compound **4.56** in CDCl₃ at 400 MHz.



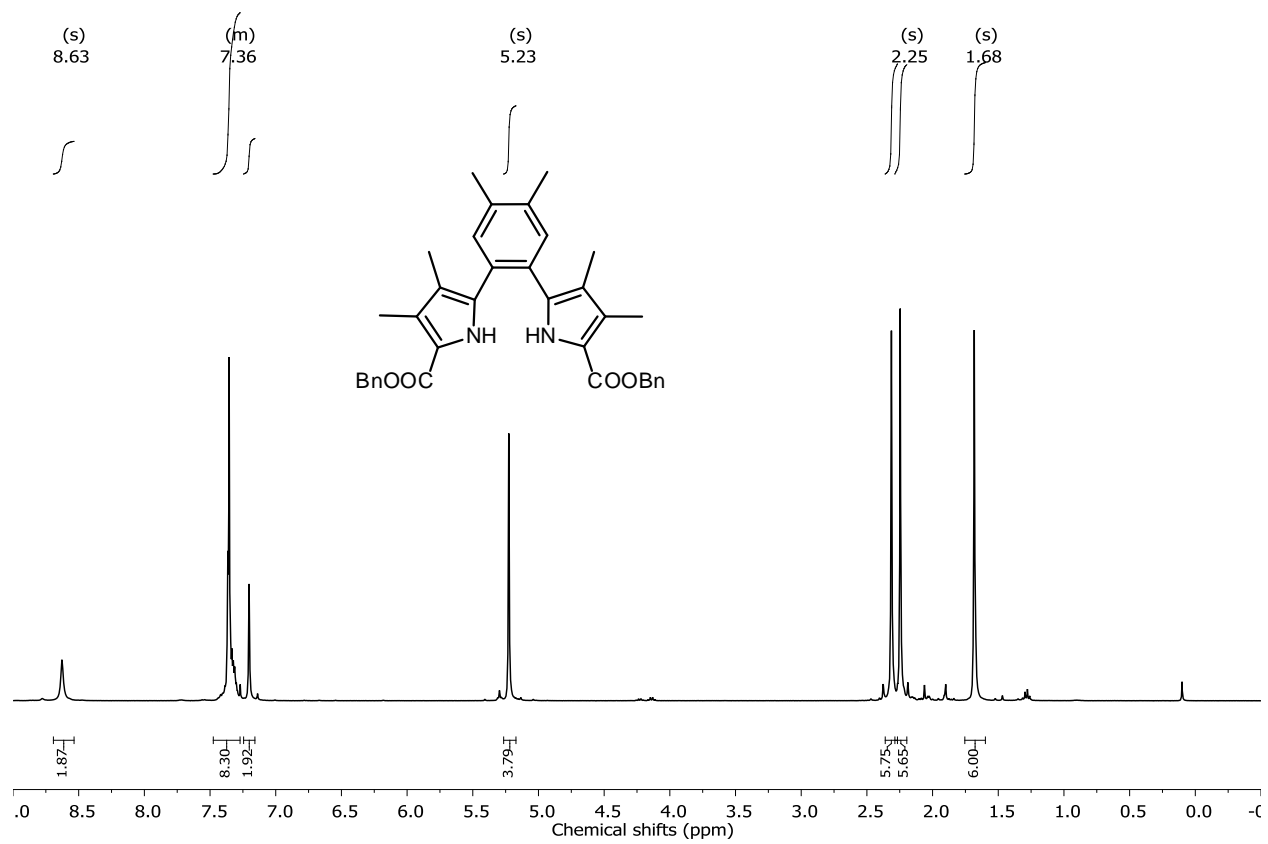
¹H-NMR Spectrum of Compound **4.52** in CDCl₃ at 400 MHz.



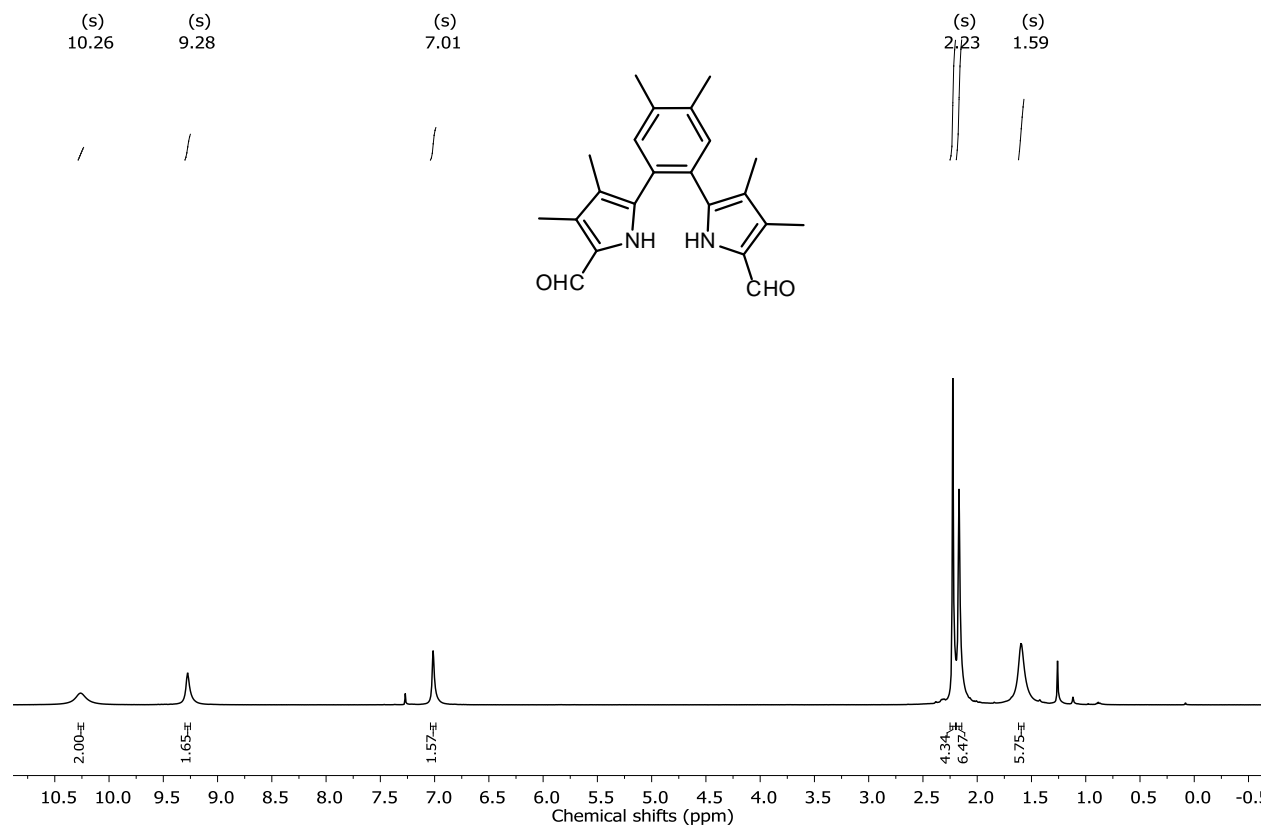
¹H-NMR Spectrum of Compound **4.51** in CDCl₃ at 400 MHz.



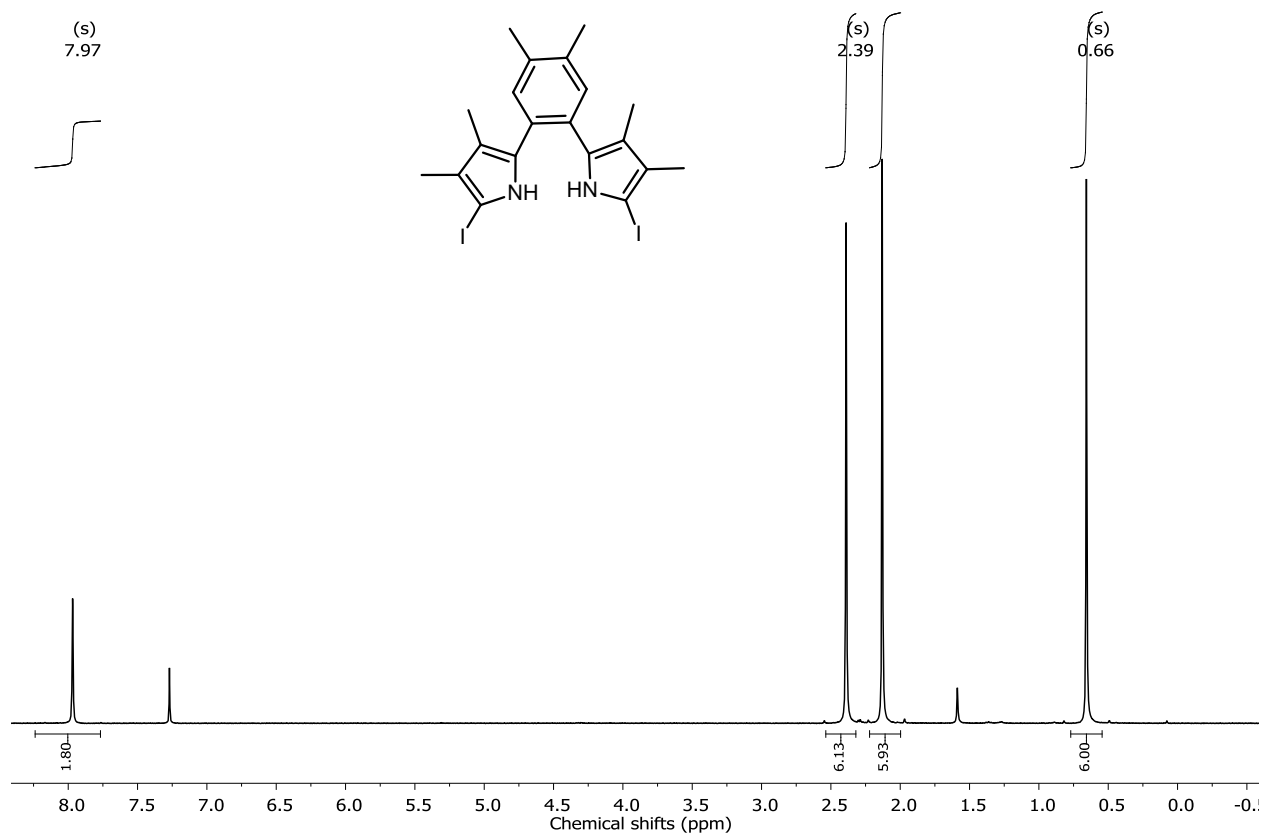
¹H-NMR Spectrum of Compound **4.54** in CDCl₃ at 400 MHz



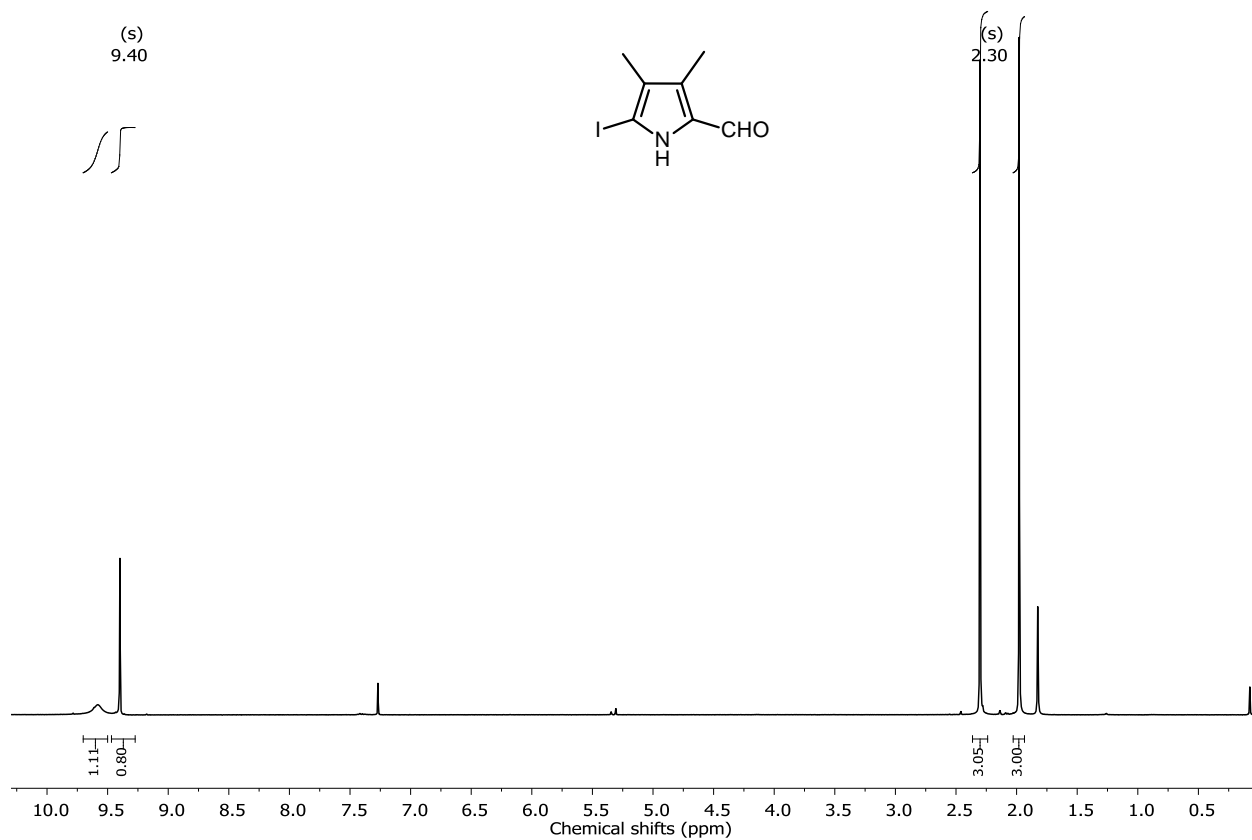
¹H-NMR Spectrum of Compound **4.64** in CDCl₃ at 400 MHz.



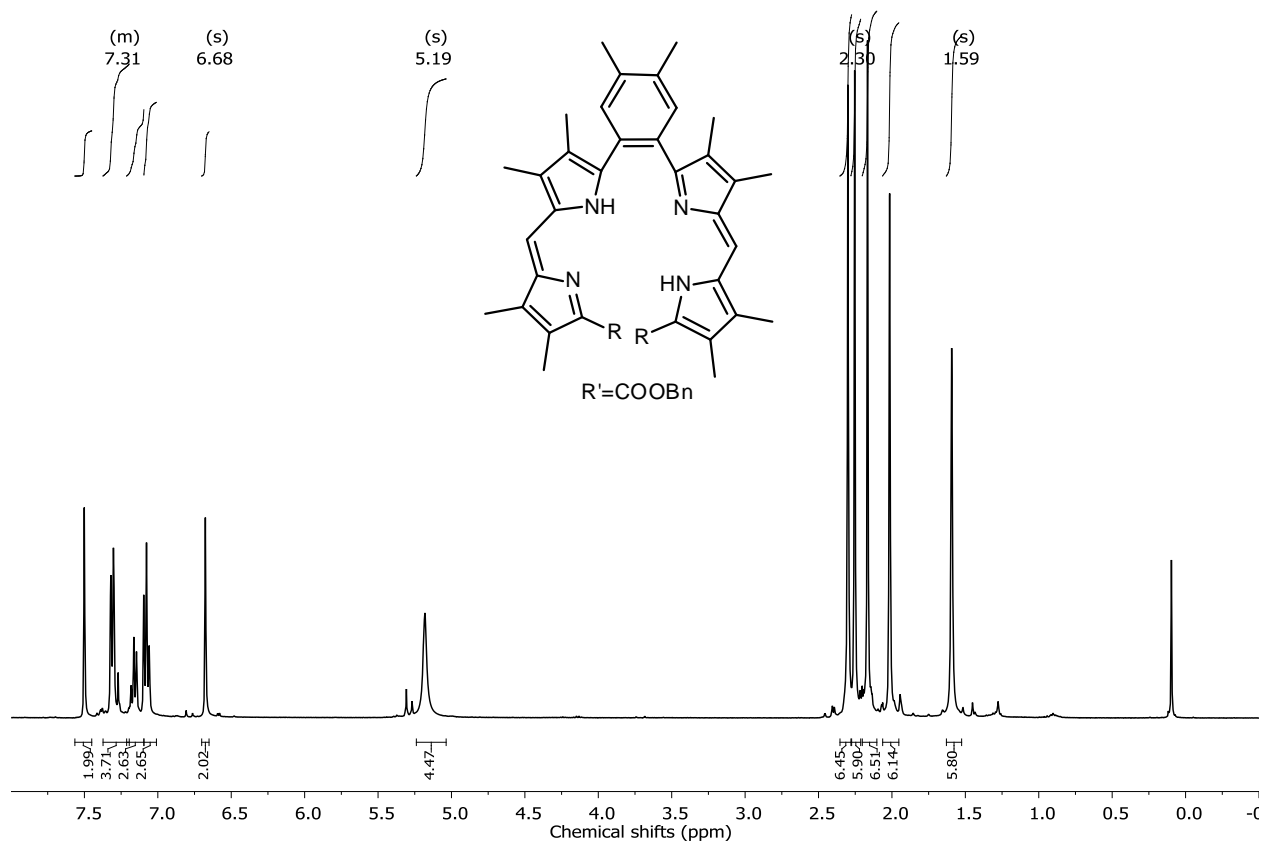
$^1\text{H-NMR}$ Spectrum of Compound **4.65** in CDCl_3 at 400 MHz.



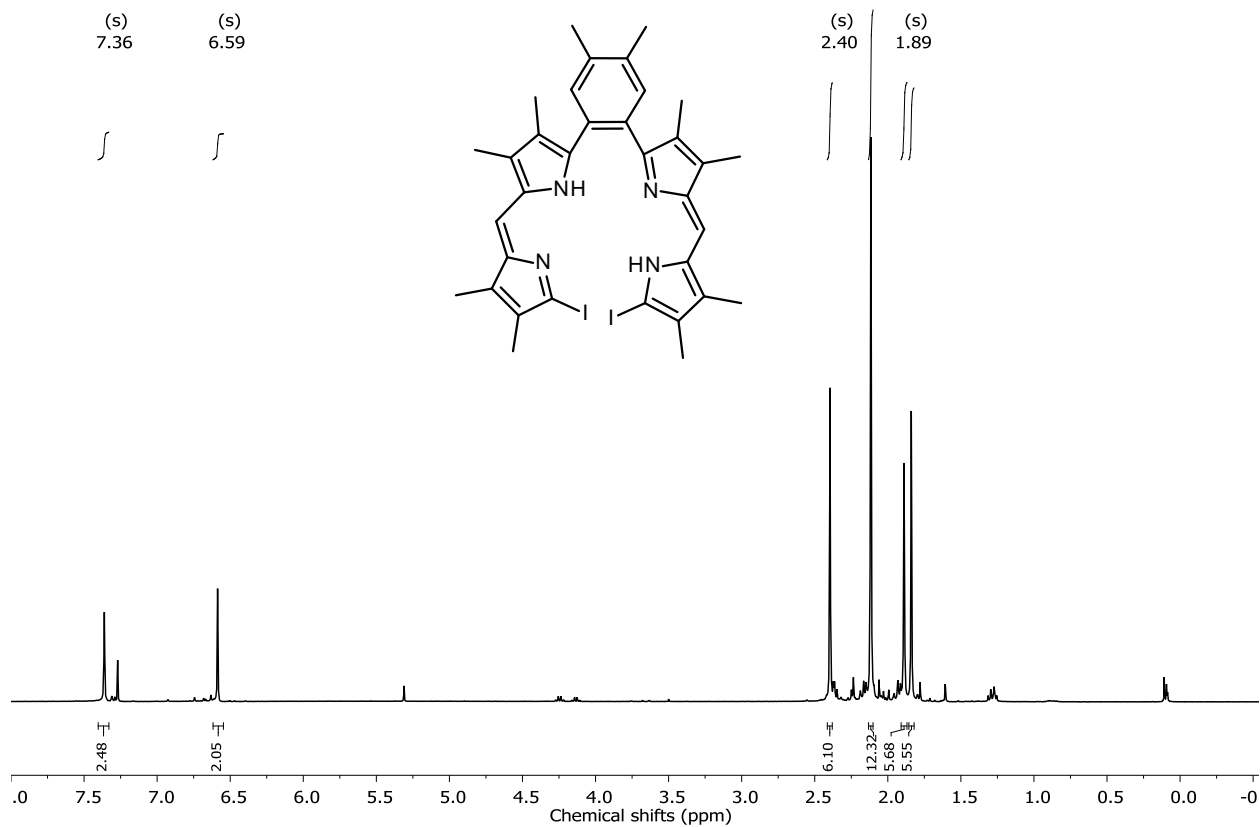
¹H-NMR Spectrum of Compound **4.67** in CDCl₃ at 400 MHz.



¹H-NMR Spectrum of Compound **4.98** in CDCl₃ at 400 MHz.



¹H-NMR Spectrum of Compound **4.88** in CDCl₃ at 400 MHz.



APPENDIX D: LETTER OF PERMISSION

SPRINGER ORDER DETAILS

Oct 11, 2013

Order Number:	500800219
Order date:	Oct 11, 2013
Licensed content publisher:	Springer
Licensed content publication:	Journal of Biomedical Science
Licensed content title:	Photodynamic activities of sulfonamide derivatives of porphycene on nasopharyngeal carcinoma cells
Licensed content author:	Nai-Ki Mak
Licensed content date:	Jan 1, 2003
Volume number:	10
Issue number:	4
Type of Use:	Thesis/Dissertation
Portion:	Figures
Author of this Springer article:	No
Order reference number:	
Title of your thesis / dissertation:	NEW STRATEGIES FOR THE SYNTHESIS OF PORPHYRINOIDS
Expected completion date:	Dec 2013

VITA

Moses Inyanje Ihachi was born in Nairobi, Kenya, to Mr. James Ihachi Mwanga and Mrs. Elizabeth Nabangala Ihachi. He attended his first school at Loresho Primary School from 1988-1995. He was then enrolled at Bukembe High school for his secondary education where he graduated in 1999. He attended Moi University, Kenya, from 2001-2005 where he earned his Bachelor's of Science degree, in chemistry in December 2005. From 2005-2006 he taught chemistry and biology at St. Charles Lwanga High School, Kakamega district, Kenya. He later moved to Teremi High school, in Chwele, Kenya, where he taught chemistry and physics from 2006-2008. In Fall 2008, he was accepted to Graduate School Doctoral program at Louisiana State University (LSU) in the Department of Chemistry. He joined Dr. Kevin M. Smith research group in the Spring of 2009. Moses has currently successfully defended his Ph.D dissertation in organic chemistry, and will be awarded the Doctor of Philosophy degree in organic chemistry during the December 2013 commencement at LSU, Baton Rouge, Louisiana.