

ABSTRACT

BHAUMIK, JAYEETA. RATIONAL SYNTHESIS OF IMIDAZOLYL PORPHYRINIC MOLECULES FOR SELF-ASSEMBLY AND WATER-SOLUBILITY. (Under the Direction of Dr. Jonathan S. Lindsey.)

The objective of this work is to develop synthetic methodology for self-assembling and water-soluble imidazole-containing porphyrinic molecules. The synthesis of the following types of compounds is described: (1) Imidazole-containing porphyrinic compounds; (2) Derivatization of the imidazolyl porphyrins to obtain water-soluble imidazolium porphyrins, and (3) Improved synthesis of tetrahydrodipyrins - a precursor of hydroporphyrins. The self-assembly of imidazolyl metalloporphyrins was examined by UV-VIS spectroscopic analysis. Each imidazoyl metalloporphyrin was found to aggregate in non-polar solvents such as CH₂Cl₂. The test of water solubility was also based on absorption spectroscopy. A refined synthesis of a tetrahydrodipyrin is described for medium-scale synthesis (>10 g of the product), which facilitates access to diverse hydroporphyrins. Water-soluble porphyrinic molecules are useful for life sciences applications, and the tetrahydrodipyrin precursors are important for the synthesis of a variety of hydroporphyrins. Taken together, this work advances the methodology for preparing a variety of synthetic porphyrins.

**Rational Synthesis of Imidazolyl Porphyrinic Molecules
for Self-Assembly and Water-Solubility**

By

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DEDICATION

*This work is dedicated to the loving memory of
My Favorite Grandma 'Beu'*

BIOGRAPHY

Jayeeta Bhaumik was born in August 1977. Her parents are Khagaraj and Gitika Bhaumik. She grew up with her elder sister, Ranjana, and younger brother, Debraj, in India. Her father, an engineer, had to relocate with his family to different cities of West Bengal quite often. This gave Jayeeta a chance to study in different institutions and get to know many people. She obtained her high school degree from Kamala Girls' School in Calcutta. During this time, she developed her strong interest in physical sciences, especially in chemistry. That led her to obtain a Bachelor's degree in Chemistry from the University of Calcutta in 1999. In order to obtain a Master's degree in Physical Chemistry, she later moved to Kalyani University and completed her M. Sc. (Master of Science) degree in 2001. Because Jayeeta wanted to obtain her Ph.D. degree in the USA, she prepared for the GRE exam. After successfully completing the exam and obtaining offers from several US universities, she chose NC State University as the best place to pursue her Ph.D. in the fall of 2002. She has enjoyed working under the supervision of her mentor, Prof. J. S. Lindsey, for the last three years and has learned a lot from him. Her future goal after successfully obtaining her M.S. degree is to continue work for her Ph.D. degree at NCSU. Afterwards, she wants to devote herself to teaching and research. She finds this pursuit to be the best way to learn and expand the knowledge of chemistry and apply them to serve mankind.

ACKNOWLEDGEMENTS

I would not be where I am if my parents, relatives and friends were not with me in my happy and sad days. My beloved grandma, who passed away from colon cancer in December 2003, had always inspired me to obtain higher education. My husband (Dr. Joydev K. Laha), whom I met and married after arriving at NCSU, has always been with me in my good and bad days. I would not have explored studying in the U.S. if my cousin, Dr. Manasi G. Saha, and her family were not there to inspire me. So I thank all of you for being with me until now and everafter.

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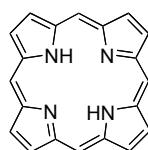
Chapter I: General Introduction

I.A. General Information on Porphyrinic Molecules

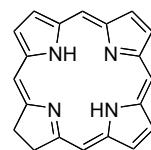
1. Structure: Porphyrinic molecules have long been of interest to chemists because these macrocycles are involved in several essential biological processes. Porphyrins are aromatic, fully conjugated, planar macrocycles (Chart I.1). Chlorins, members of the porphyrin family, are aromatic, but one of the pyrrole rings is saturated. Bacteriochlorins are the more reduced derivatives of chlorins with two saturated pyrrole rings at the opposite side of the tetrapyrrolic macrocycle, whereas isobacteriochlorins are isomers of bacteriochlorins with two saturated pyrrole rings at the same side of the macrocycle. The examples of ring-contracted macrocycles are corrins. On the contrary to the above-discussed macrocycles, corrins are not conjugated, hence corrins are non-aromatic.

Chart I.1

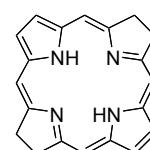
Structure of Porphyrinic Molecules



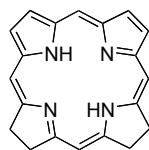
Porphyrin



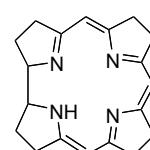
Chlorin



Bacteriochlorin



Isobacteriochlorin



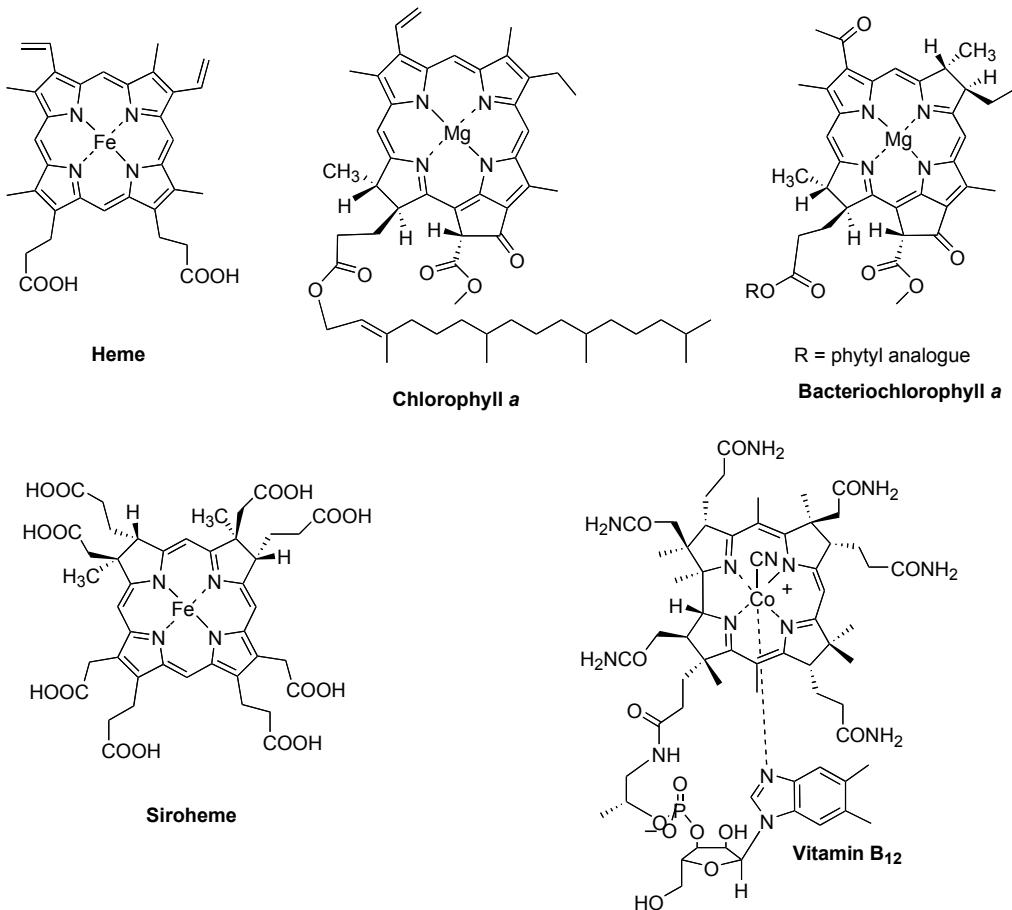
Corrin

2. Natural Pigments: Porphyrinic macrocycles are present in numerous biological systems. For instance, heme is present in animal blood. Heme is a pigment with an iron-

porphyrin core, which is involved in the transport of oxygen to cells (Chart I.2). Another class of hydroporphyrin-based natural pigments includes chlorophylls (Chl) and bacteriochlorophylls (BChl). These macrocycles are involved in photosynthesis. Different varieties of the natural pigments carrying out photosynthesis (Chl *a-d*, and BChl *a-g*) are known.¹¹ Photosynthetic pigments are porphyrinic compounds (chlorins or bacteriochlorins) which differ from each other (1) by the degree of unsaturation, (2) at the side chains and (3) by the functional groups. These pigments form antenna complexes, commonly called light-harvesting arrays, in order to perform photosynthesis. These light-harvesting arrays¹⁵ consist of a large number of molecules (500 or more) that can bind to each other, either through a binder molecule (in most cases a protein molecule) or by hydrogen or coordinate bonding, commonly called self-assembly.^{12a} Siroheme, an isobacteriochlorin-based pigment, plays important roles in sulfur and nitrogen metabolism of numerous organisms. Vitamin B₁₂, which consists of a corrin framework, is a cofactor important enzymatic reactions.¹³²

Chart I.2

Naturally Occuring Porphyrinic Molecules



3. UV-VIS Absorption Properties: The structure of a given porphyrinic compound greatly affects the UV-VIS absorption properties, but they show a common feature of a B band (or Soret band) and Q bands in the absorption spectrum (Figure I.1). The intensity of the bands differs to a greater extent depending on the structure of the porphyrinic molecule. Porphyrins absorb visible light and show a very sharp and strong B band in the blue region (399–420 nm) and very weak Q bands in the red region (500–600 nm). In the case of aggregates of porphyrinic molecules, the absorption spectrum typically becomes broader. Chlorins and isobacteriochlorins show enhanced absorption as a strong B band along with a red shifted and more intense Q_y band (Figure I.1). The absorption spectrum of bacteriochlorins is different

in the sense that these macrocycles have a much stronger Q_y band. This makes bacteriochlorins special candidates for PDT (photodynamic therapy), an emerging method for treating cancer.

Figure I.1

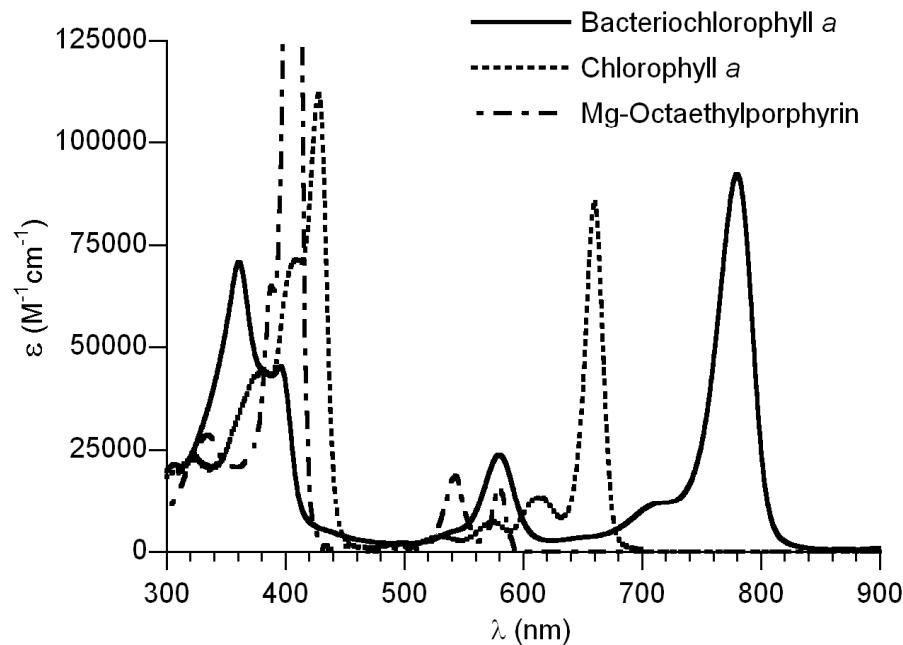


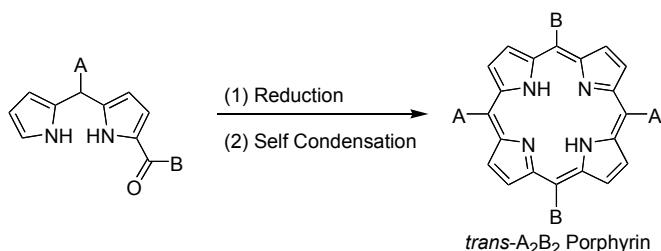
Figure I.1: UV-VIS absorption spectra of Bacteriochlorophyll a, Chlorophyll a and Mg-Octaethylporphyrin.

4. Syntheses: Due to the presence of tetrapyrrolic macrocycles in various pigments and the utility of porphyrins, different synthetic routes have been explored for the synthesis of porphyrinic molecules. Some of those routes are statistical, resulting in more than one porphyrin, whereas others are rational routes afford a single porphyrinic product. Here are some examples of rational syntheses of porphyrinic molecules. The rational synthesis of *trans*-A₂B₂ porphyrins entails the reduction of a 1-acyldipyrromethane followed by self-condensation of the resulting dipyrromethane-1-carbinol in the presence of an acid (Chart

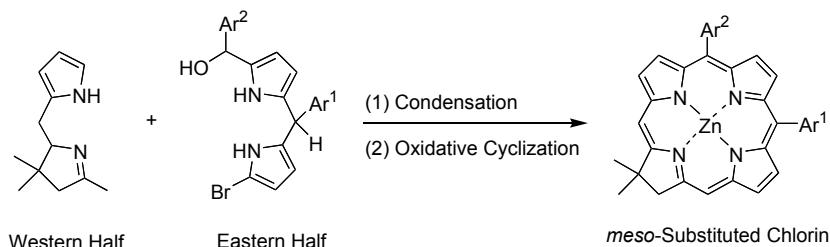
I.3).¹²⁶ Chlorins are synthesized by the condensation of a bromodipyrrromethane-9-carbinol (Eastern half) and a tetrahydropyrrin (Western half) in the presence of an acid followed by metal-mediated oxidative cyclization under reflux conditions in acetonitrile.^{14,127} Bacteriochlorins are synthesized by the Lewis acid catalyzed self-condensation of a dihydronaphthalene-acetal at room temperature.¹²⁸

Chart I.3

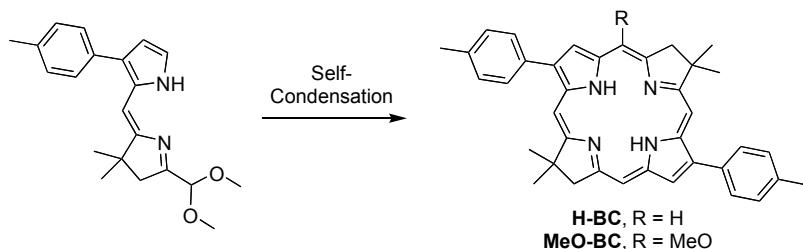
Synthesis of a *Trans-A₂B₂* Porphyrin



Synthesis of a *Meso* Substituted Chlorin



Synthesis of a Bacteriochlorin



5. Applications: Porphyrins are important in artificial photosynthesis because of their structural resemblance to the photosynthetic pigments chlorophylls and bacteriochlorophylls.

Synthetic tetrapyrrolic macrocycles are useful in various applications such as solar cells, bioconjugation and PDT. Porphyrins are useful in information storage because of their high stability and redox activity. Because of their physicochemical properties, porphyrins could be used in manufacturing solar cells. Synthetic porphyrins with structural similarity to the self-assembling bacteriochlorophyll *c* pigments could be useful in molecular-based solar cells. Compact water-soluble porphyrins (*trans*-A₂ or *trans*-AB) could be useful for bioconjugative studies. Synthetic chlorins are good candidates in the preparation of the molecular photonic wires. Bacteriochlorins are valuable for PDT due to their strong absorption in the red/near-IR region. Synthetic as well as natural bacteriochlorins find utility in PDT applications. In PDT the tetrapyrrolic macrocycles are used as tumor localizing photosensitizers to destroy cancerous tissue. The order of effectiveness is porphyrins < chlorins < bacteriochlorins reflecting increasing capacity of the molecules to absorb near-IR light.^{12b}

I.B. Imidazole-Containing Porphyrins

Porphyrins bearing imidazole and other *N*-heterocyclic groups are important because of their usefulness in medicine, molecular electronics and in the treatment of cancer using PDT. Several metalloporphyrins with pyridine substituents in the presence of a sugar unit are known to be useful as PDT.¹¹¹ Quinoline porphyrins have been utilized for cell photosensitization and for molecular recognition of carbohydrates.¹¹² Another example of porphyrins with heterocyclic substituents takes the advantage of Watson-Crick-type nucleic acid base (“nucleobase”) pairing interactions between purine and pyrimidine.^{113a} Nuclease activity is exhibited by benzimidazole-metalloporphyrin dye conjugates.^{113b} Porphyrin-

acridine conjugates are valuable bifunctional antitumor agents.¹¹⁴ Also, photoconductive copolyimides have been synthesized containing porphyrin and carbazole moieties.¹¹⁵ Finally, examples of porphyrins with thiazole,¹¹⁶ pteridine,¹¹⁷ and pyrazole¹¹⁸ substituents are also found in the literature.

Imidazole is important in both biology and laboratory chemistry. This heterocycle is present in histidine, hemoglobin and other biomolecules and has significant medicinal properties¹⁶ (antifungal agents, radiosensitizer). Imidazole is also used in synthesizing ionic liquids, which are known as environment friendly solvents. The water solubility of the imidazole derivatives makes them applicable for biological purposes. In addition, a metalloporphyrin bearing an imidazole moiety can form self-assembling light harvesting arrays similar to that of the photosynthetic pigment bacteriochlorophyll *c*. Also, due to the high polarity of imidazole compounds, imidazole porphyrins can provide the basis for water-soluble porphyrinic compounds. Water-soluble, alkylated imidazolium-porphyrin species could be applied in PDT.

Self-assembly: The Photosynthetic apparatus in green photosynthetic bacteria provides a very good example of self-assembly in nature. These bacteria, in order to perform photosynthesis by capturing sunlight even 10-50 m below the surface of the ocean, have developed an organelle called a chlorosome.¹¹⁹ The chlorosome, an extramembranous antenna in green photosynthetic bacteria, is an extraordinary light-harvesting system. Chlorosomal bacteriochlorophyll -*c*, -*d* and -*e* (BChl) self-aggregate forming antennas without the use of proteinaceous scaffolding. This system is in contrast to those of the inner membrane antennas, which consist of pigment-protein complexes. These BChl molecules self-aggregate by intermolecular interaction among the 3¹-hydroxyl, central metal and 13-

carbonyl moieties, along with the π - π interactions of chlorin macrocycles.¹²⁰ The Q_y absorption band of the chlorins is red shifted due to the aggregation.¹²¹

In the literature a variety of synthetic self-assembling porphyrins are known. However, initial synthetic approaches chosen to obtain self-assembling chlorins started from porphyrins instead of employing a rational synthesis of chlorins,¹²³ or the precursors are the extracts from the natural pigments.¹²⁴ Nagata *et al.* synthesized a *trans*-A₂B₂ type imidazole porphyrin, which forms a hydrogen bonded array in non-polar solvents due to the affinity of an imidazole nitrogen in one porphyrin molecule towards the imidazole proton in an adjacent imidazole porphyrin (Figure I.2).^{18a} The same research group has synthesized arrays of imidazole metalloporphyrins (gallium and zinc). An H-bonded array was observed when ¹H NMR spectroscopy was carried out in a non-coordinating solvent (CDCl₃); the porphyrin array disappeared when a coordinating solvent (CD₃OD) was used (Figure I.3).^{18b} Recently, Kobuke's group has synthesized an imidazole porphyrin-phthalocyanine dyad which functions as a light harvesting array. In non-coordinating solvents the dyad dimerizes, and the dimer regenerates the monomeric dyad when a coordinating solvent is used.¹⁹

Figure I.2

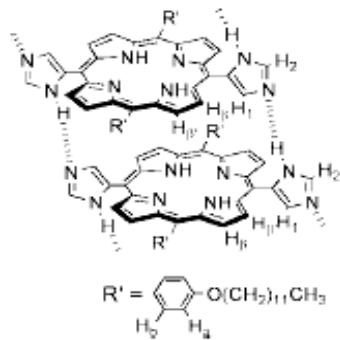


Figure I.2: Reported self-assembly of imidazol-4-yl porphyrin.

Figure I.3

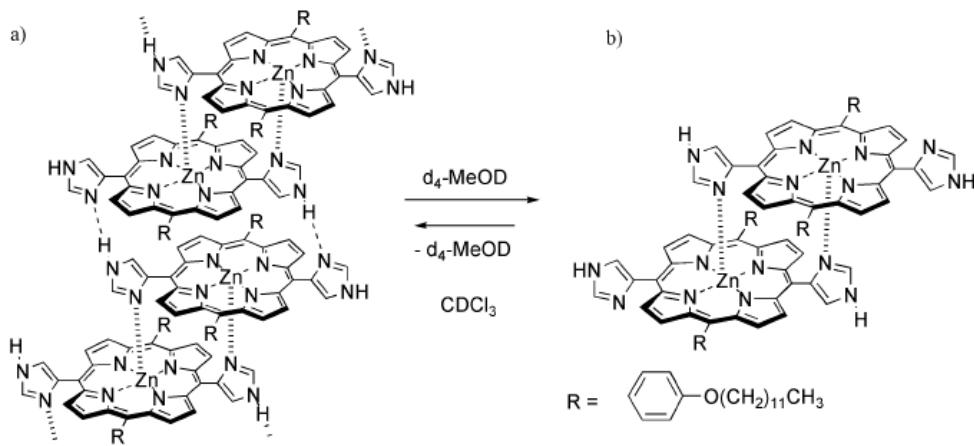
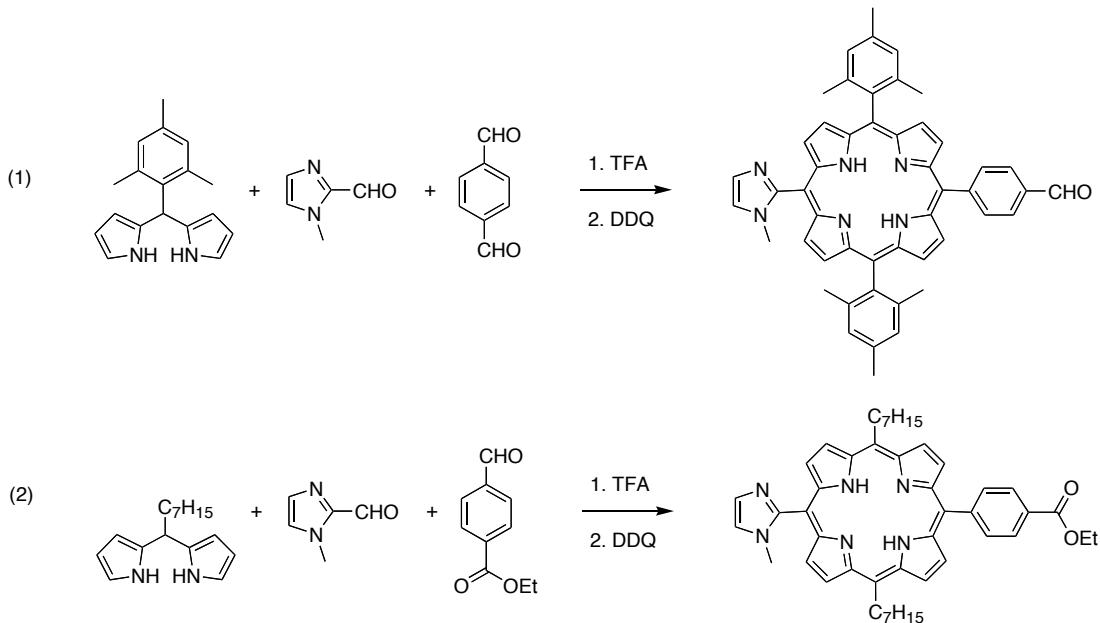


Figure I.3: Imidazol-4-yl metalloporphyrin showing self-assembly.

Synthesis : Synthesis of various imidazolyl porphyrins are known. In most cases, however the routes employed are statistical affording the desired imidazolyl porphyrin in very low yield. For instance, *trans*-AB₂C-porphyrins with one imidazole moiety have been synthesized by the reaction of a dipyrromethane, an imidazole carboxaldehyde and a second aldehyde (Chart I.4).^{I10a-b}

Chart I.4

Statistical Synthesis of Imidazole-Containing *Trans*-A₂BC-Porphyrin



In our group, we have synthesized a set of *meso*-substituted porphyrins wherein each porphyrin bears one nitrogen heterocyclic group. First, starting from a heterocyclic aldehyde (2-, 3-, 4-pyridinecarboxaldehyde, quinoline-3-carboxaldehyde, imidazole-2-carboxaldehyde or uracil-5-carboxaldehyde), the corresponding dipyrromethane has been synthesized through a pyrrole-aldehyde condensation. Second, each dipyrromethane was condensed with a dipyrromethane-dicarbinol to produce the respective porphyrin (Figure I.4). The yield of imidazole porphyrin was quite low (1.5%), whereas the other porphyrins (e.g., pyridyl, quinolyl, uracil) were obtained in higher yields. The lower yield of imidazolyl porphyrin can be attributed to the presence of the proton attached to the imidazole ring nitrogen.^{110c}

Figure I.4

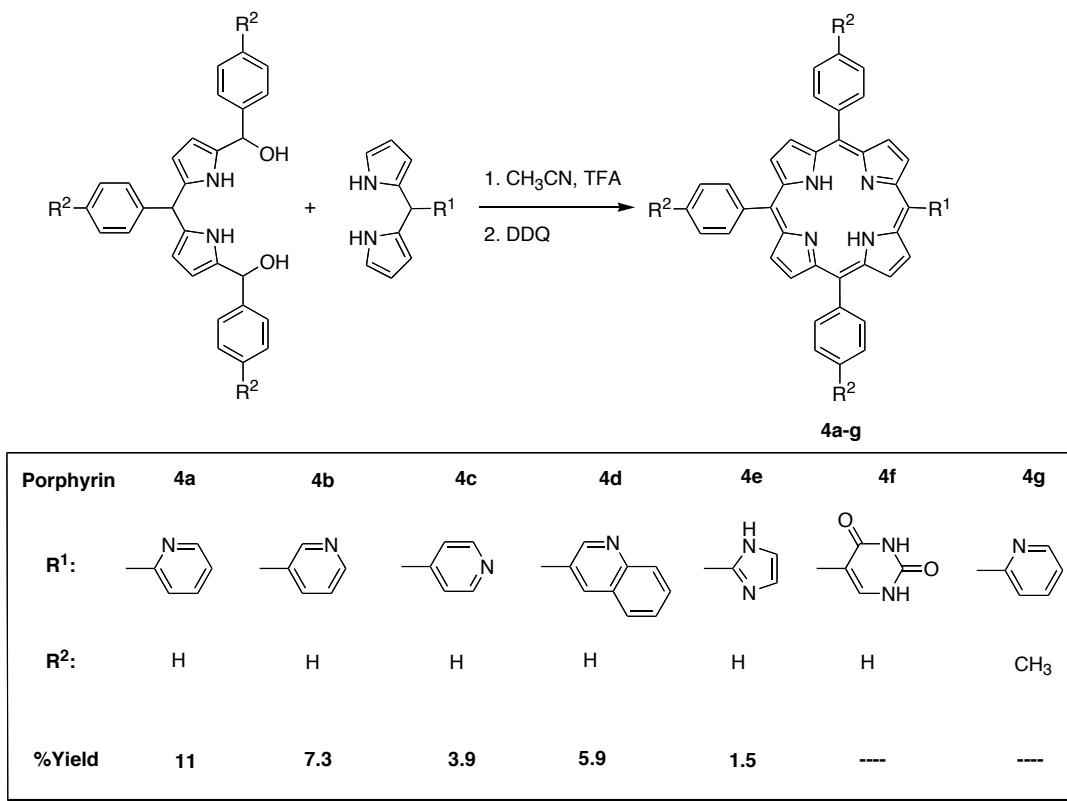
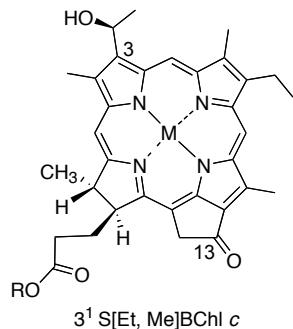


Figure I.4: Known porphyrins with *N*-heterocyclic substituents.

We have carried out research on the synthesis of self-assembling porphyrinic molecules containing one or two imidazole groups (Chapter II). The synthetic approaches are rational, resulting in a single porphyrinic product with minimal scrambling and in higher yield. Our synthetic imidazole-containing porphyrinic molecules, which contain an imidazole group and a metal (zinc or magnesium), may self-organize in either a parallel or an anti-parallel orientation through both H-bonding and coordinate bonding, and may form artificial light-harvesting antennae similar to that of the natural pigment bacteriochlorophyll *c* (Figure I.5).

Figure I.5

Self-Assembling Natural Pigments



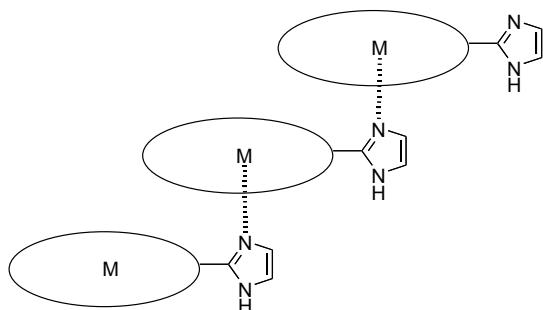
Bacteriochlorophyll *c*

Self-Assembly in Imidazolyl Metalloporphyrinic Molecules



Porphyrinic Molecule (Porphyrin/Chlorin/Bacteriochlorin)

Parallel Self-Assembly



Antiparallel Self-Assembly

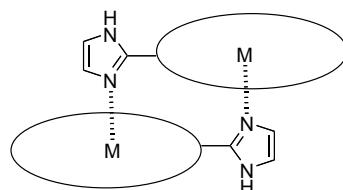


Figure I.5: Self-assembling natural pigments and imidazolyl metalloporphyrinic molecules.

I.C. Water-Soluble Imidazolium-Porphyrins

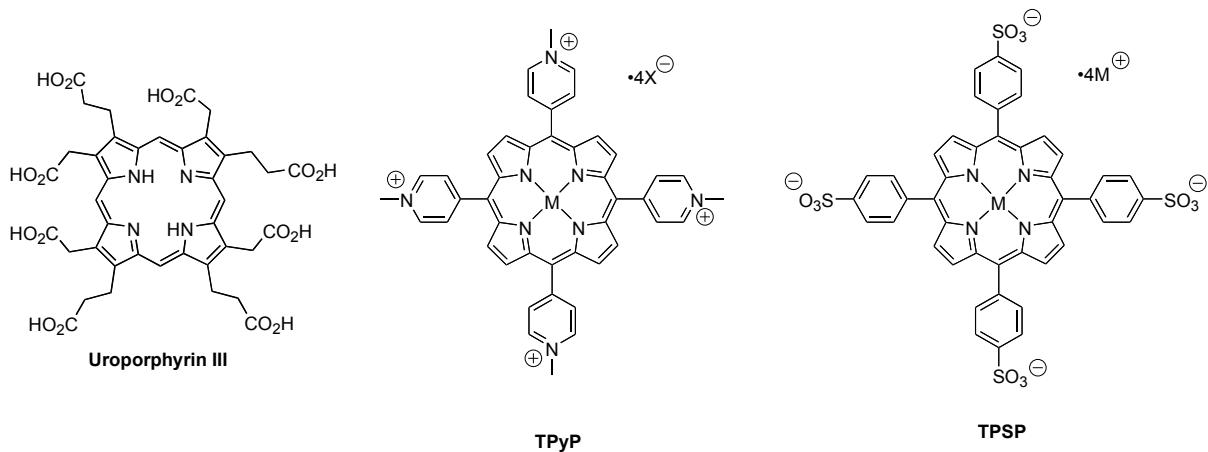
Water-soluble porphyrins are valuable for diverse biological applications. Hence, for potential biological applications of porphyrinic compounds, hydrophilicity is required. Imparting a higher degree of polarity to a nonpolar starting porphyrin results in water

solubility of the porphyrin. There are various methods of introducing polar groups to the porphyrins. One of the facile methods for the synthesis of water-soluble porphyrins is the insertion of an alkyl chain with hydrophilic tails (e. g. COO^- , PO_3^{2-} , SO_3^-).¹²⁵

In the literature, water-soluble porphyrins containing *N*-alkyl pyridinium or phenyl sulfonic acid are known (Chart I.5).¹²⁵ Even though water solubility is a requirement for the synthesis of biologically important porphyrins, the actual synthesis is complicated by challenges in the purification of water-soluble porphyrinic products. This problem can be solved by the application of reverse phase chromatography, gel permeation chromatography and so on.

Chart I.5

Reported Water Soluble Porphyrins

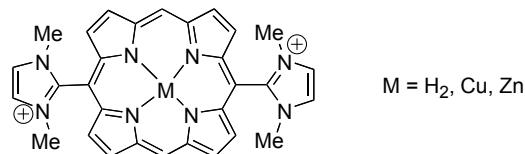


Cationic porphyrins and their non-covalent interactions with DNA are of importance from the viewpoint of their potential therapeutic use as a photosensitizer in PDT as a DNA cleavage agent. It is known that the dicationic bis(imidazoliumyl)porphyrinatometals interact with DNA¹²⁹ and cationic tetrakis(imidazoliumyl)porphyrinatometals function as a potent SOD (superoxide dismutase) mimic (Chart I.6).¹³⁰ Both alkylimidazole and alkylpyridyl substituted porphyrins were explored for SOD activity. It was observed that the

SOD activity of manganese (III) porphyrins is governed by their metal-centered redox potential, and a number of structural variations, including *meso* and β -substitution (Figure I.6), have been explored in order to control the redox potential.¹³¹

Chart I.6

Dicationic bis(imidazoliumyl)porphyrinatometals interact with DNA



Cationic tetrakis(imidazoliumyl)porphyrinatometals as a potent SOD (superoxide dismutase) mimic

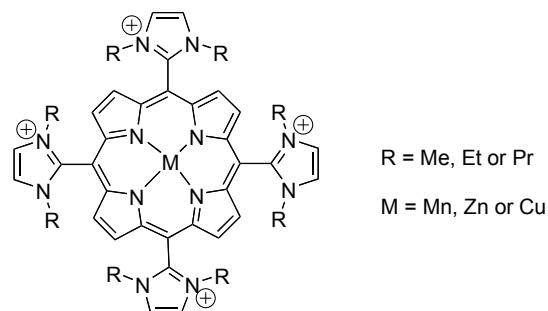


Figure I.6

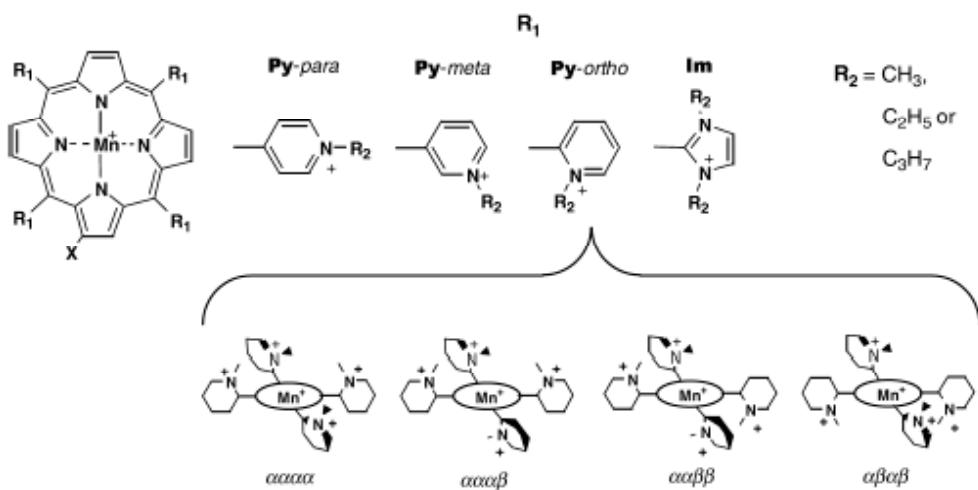


Figure I.6: Structures of manganese (III) cationic porphyrins analyzed as SOD (superoxide dismutase) mimics.

A promising route to water soluble porphyrins is found in the initial introduction of polar heterocyclic moieties such as pyridine, imidazole or pyrimidine. First, porphyrins that are not water-soluble can be synthesized from the corresponding aldehydes. Later, those porphyrins can be derivatized to obtain water-soluble analogs. One of the convenient ways to quaternize the porphyrins with heterocyclic substituents is to introduce an alkyl chain at each of the nitrogen atoms. There are various conditions that can be used to achieve such transformations. Conditions ranging from room temperature, heating, reflux, or microwave irradiation can be applied. In addition, different bases, solvents, and alkylating agents can be employed for the preparation of the water-soluble heterocyclic porphyrins.

For the synthesis of water-soluble porphyrins with biological activity, an imidazole-substituted porphyrin can be considered as a good candidate among porphyrins with heterocyclic substituents. Imidazole-substituted porphyrins can be more readily synthesized

than the corresponding pyridine or pyrimidine derivative (Chapter II). Porphyrins with heterocyclic substituents are difficult to synthesize in an acceptable yield. Imidazole derivatives can be protected with a silyl ether group that imparts nonpolarity prior to the porphyrin synthesis. The protecting group allows macrocyclization to occur with a good yield. Later, the protecting group can be removed using TBAF, and the porphyrin can be derivatized to obtain a water-soluble porphyrin.

Anionic groups are superior to cationic groups where minimization of non-specific binding of porphyrins to the cellular structures is expected. Apart from that, for achieving water solubility it is essential to minimize aggregation of porphyrins. Enforced placement of polar substituents above and below the plane of porphyrinic macrocycle suppresses cofacial aggregation. Imidazolium-porphyrins with bis-sulfoalkyl groups can accomplish the above-mentioned conditions. Hence, these water-soluble porphyrinic compounds could be a motif for cancer-targeting agents and other life sciences applications. From the literature we learned that each water-soluble imidazolium-porphyrin useful for biological applications contains two to four imidazole groups. Our research involves the synthesis of imidazolium-porphyrins with only one imidazole substituent. The synthesis was achieved by the derivatization of the imidazolyl porphyrins. Later, the extent of water-solubility of the resulting imidazolium porphyrins was investigated (Chapter III).

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Chapter II: Rational Synthesis of Imidazolyl Porphyrinic Molecules for Self-Assembly and Bioconjugation

II.A. Abstract

Imidazole-substituted metalloporphyrinic compounds are valuable for studies of self-assembly and for applications where water solubility is required. Rational syntheses of porphyrins bearing one or two imidazol-2-yl or imidazol-4-yl groups at the meso positions have been developed. The syntheses employ dipyrromethanes, 1-acyldipyrromethanes, and 1,9-diacyldipyrromethanes bearing an imidazole at the 5-position. The polar, reactive imidazole unit was successfully masked by (1) use of the 2-(trimethylsilyl)ethoxymethyl (SEM) group at the imidazole pyrrolic nitrogen, and (2) use of a dialkylboron motif bound to the pyrrole of the dipyrromethane and coordinated to the imidazole pyrrolenyl nitrogen. Such doubly masked imidazole-dipyrromethanes were relatively nonpolar and were easily employed in rational syntheses of *trans*-A₂B₂-, *trans*-A₂BC-, and *trans*-AB-porphyrins, as well as a chlorin. Each porphyrinic species contained one or more SEM-protected imidazole units. This work establishes the foundation for the rational synthesis of a variety of porphyrinic compounds containing imidazole units.

II.B. Introduction

Imidazole-porphyrins are of widespread interest in materials chemistry and the life sciences. The original impetus for preparing imidazole-porphyrins stemmed from biomimicry studies of hemoglobin,^{II1} where imidazole occupies the apical site of an iron porphyrin. Since then, a large number of porphyrins have been prepared bearing imidazole units directly attached to the porphyrin macrocycle. In the latter cases, the imidazole provides the basis for controlled self-assembly to give multimeric architectures, and upon derivatization yields water-soluble porphyrinic compounds. Indeed, some self-assembled aggregates of imidazole-porphyrins exhibit light-harvesting features,^{II2} while water-soluble imidazolium-porphyrins have been investigated for superoxide dismutase behavior^{II3-II5} and for DNA binding.^{II6} Despite these promising attributes, the methods for preparing imidazole-porphyrinic compounds remain poorly developed.

Porphyrins bearing four *meso*-imidazole groups have been prepared by condensation of an imidazole-carboxaldehyde with pyrrole via the Adler method.^{II7,II8} The same reaction with inclusion of a second aldehyde has been used in a statistical synthesis of an A₃B-porphyrin bearing one imidazole group.^{II2,II9} *Trans*-AB-porphyrins^{II10} and *trans*-AB₂C-porphyrins^{II11-II17,II18} have been prepared by statistical reaction of a dipyrromethane, an imidazole-carboxaldehyde, and a second aldehyde. The synthesis of *trans*-A₂B₂-porphyrins has been achieved in a rational manner by reaction of a dipyrromethane and an imidazole-carboxaldehyde.^{II19-II22} However, the yields of *trans*-A₂B₂-porphyrins are typically quite low (in most cases 2%).^{II19,II20}

Several years ago we began studies aimed at the rational synthesis of porphyrins bearing one nitrogen heterocyclic group at the *meso* position. A given heterocyclic aldehyde

(2-, 3-, 4-pyridinecarboxaldehyde, quinoline-3-carboxaldehyde, imidazole-2-carboxaldehyde or uracil-5-carboxaldehyde) was condensed with pyrrole to afford the corresponding dipyrromethane; reaction of the latter with a dipyrromethane-dicarbinol gave the respective A₃B-porphyrin bearing a single heterocyclic group. The yield of the imidazole-porphyrin was unacceptably low (1.5%), whereas the other porphyrins (e.g., pyridyl, quinolyl, uracil) were obtained in good yield (5-20%).^{II23} Similarly, the reaction of an imidazole-dipyrromethane and an aldehyde to give a *trans*-A₂B₂-porphyrin also proceeded in low yield (3%).^{II24}

The challenges to facile incorporation of the imidazole unit in porphyrins include the following: (1) imidazolyl compounds are very polar and streak on a chromatography column; (2) the imidazole group in a dipyrromethane interferes with 1-acylation, thereby preventing access to dipyrromethane-1-carbinols, which are valuable precursors to *trans*-A₂B₂-porphyrins^{II25,II26} and chlorins; and (3) imidazole-dipyrromethanes afford low yields of porphyrin upon reaction with a dipyrromethane-1,9-dicarbinol. We considered that these problems might be mitigated by use of a suitable protecting group for the tautomeric nitrogen of the imidazole. In one of the earliest studies of the synthesis of imidazole-substituted A₄-porphyrins, Milgrom investigated benzyl or *p*-methoxybenzyl protecting groups.^{II7} While promising, some difficulties were encountered in deprotecting the corresponding porphyrins. Despite the well-developed use of imidazole protecting groups in protein chemistry (to protect the imidazole moiety of histidine), the use of imidazole protecting groups has not been further investigated in porphyrin chemistry.

Here we report our studies aimed at developing improved methods for manipulating imidazole-dipyrromethanes. The SEM-protecting group has been employed in the synthesis

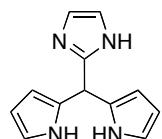
of porphyrins bearing one or two imidazol-2-yl or imidazol-4-yl groups, and a chlorin bearing one imidazol-2-yl group. Dialkylboron complexes of imidazole-dipyrromethanes also were investigated for masking the pyrrolenyl nitrogen atom. Taken together, this work provides a substantial improvement in methods for preparing porphyrinic macrocycles bearing one or two imidazole units.

II.C. Results and Discussion

A. Synthesis of Imidazol-2-yl Porphyrinic Molecules. 1. Protected Imidazolyl Dipyrromethane. The imidazole protecting groups employed in peptide chemistry and related fields include trichlorotrityl (Tct),^{II27} 2,4-dimethylpent-3-yloxycarbonyl (Doc),^{II28} 2-adamantyloxymethyl,^{II29} *p*-tosyl,^{II30} and 2-(trimethylsilyl)ethoxymethyl (SEM)^{I31} groups. We considered the following in selecting a protecting group: (1) methods of introduction and removal, (2) compatibility with conditions employed in dipyrromethane preparation and derivatization, (3) compatibility with conditions employed in porphyrin and chlorin formation, (4) hydrophobicity thereby facilitating chromatography, and (5) a solid product rather than an oil, thereby facilitating crystallization. The *p*-tosyl group appeared attractive in many of these regards, but exploratory work indicated the *p*-tolyl protected imidazole-carboxaldehyde required extensive chromatography for purification. Eventually we settled on use of the SEM group.

5-(Imidazol-2-yl)dipyrromethane (**1**) has been prepared by the solventless condensation of imidazole-2-carboxaldehyde in pyrrole under reflux.^{II23} However, the yield was very low (14%), and **1** was incompatible with subsequent Grignard-mediated acylation of the dipyrromethane. To mask the imidazole NH unit, we treated imidazole-2-

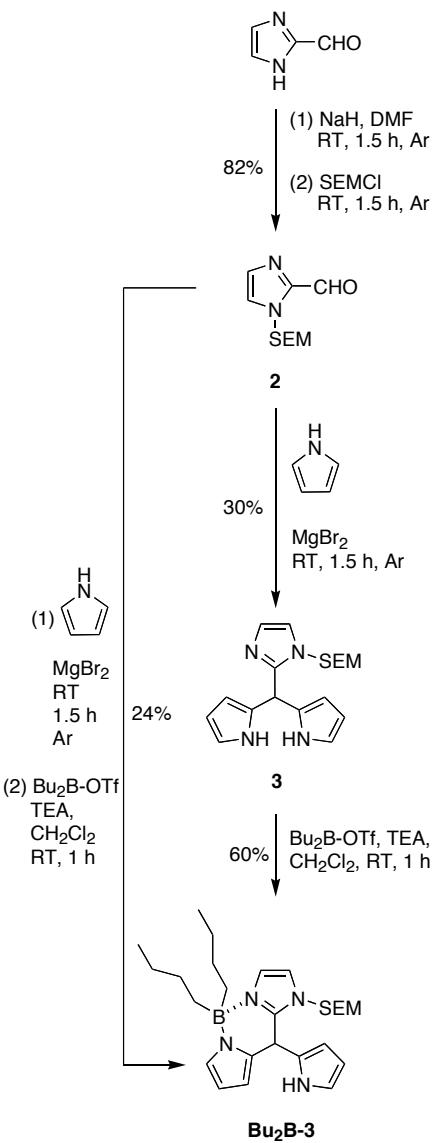
carboxaldehyde with NaH, followed by the addition of 2-(trimethylsilyl)ethoxymethyl chloride (SEMCl), which afforded the SEM-protected aldehyde **2** in 82% yield (Scheme II.1).^{II31} The condensation of aldehyde **2** with excess pyrrole at room temperature in the presence of MgBr₂ (0.5 equiv)^{II32} afforded the protected imidazole-dipyrromethane **3** in 30% yield. An attempt to synthesize **3** using InCl₃ (0.3 equiv) was also successful (by TLC), but MgBr₂ afforded a cleaner reaction mixture.



1

2. Dialkylboron Complexation of Imidazolyl Dipyrromethanes. The imidazolyl dipyrromethane **3** streaks upon chromatographic purification. Earlier we found that 1-acyldipyrromethanes, which also streak on chromatographic media, react with dialkylboron triflates to form dialkylboron complexes that are hydrophobic and readily handled.^{II33} With the same objective of achieving a hydrophobic complex, we treated dipyrromethane **3** with excess Bu₂B-OTf, which afforded the dibutylboron complex **Bu₂B-3** in 60% yield (Scheme II.1). In this complex, the boron is bonded to the pyrrole and coordinated to the imidazole pyrrolenyl nitrogen. Owing to both the dibutylboron complex and the SEM group, the imidazole nitrogens are fully masked. As expected, **Bu₂B-3** proved to be of low polarity and did not streak upon chromatography.

Scheme II.1

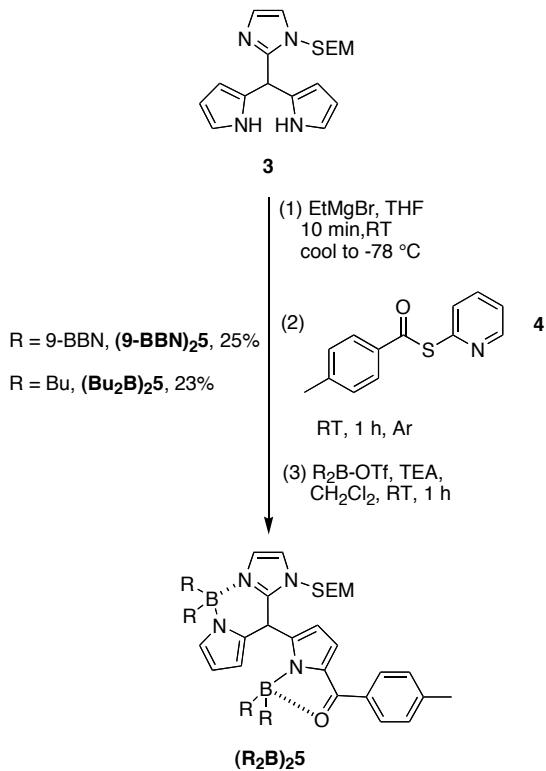


$\text{SEM} = \text{CH}_2\text{OCH}_2\text{CH}_2\text{SiMe}_3$

Later we tried to employ dialkylboron complexation as a means of purifying the crude reaction mixture upon dipyrromethane formation. After the reaction of **2** and pyrrole in the presence of MgBr_2 (0.5 equiv), the crude reaction mixture was freed of pyrrole and then treated with TEA and $\text{BBu}_2\text{-OTf}$ (3 equiv), affording **Bu₂B-3** in 24% yield. The similar process using 9-BBN-OTf was unsuccessful, which can be attributed to the instability of the 9-BBN group in the crude mixture of dipyrromethane.

3. Dialkylboron Complex of an Imidazole-1-acyldipyrromethane. The standard method for 1-acylation entails treatment of a dipyrromethane with EtMgBr followed by reaction with a 2-pyridyl thioester (Mukaiyama reagent). Application of this approach with dipyrromethane **3** and Mukaiyama reagent **4** afforded a crude mixture of the 1-acyldipyrromethane. However, the corresponding 1-acyldipyrromethane streaked extensively and was not separable on TLC. Treatment of the crude mixture with 9-BBN-OTf (2 equiv) afforded **(9-BBN)₂5** as a non-polar, crystalline solid in 25% yield (Scheme II.2). According to ¹H NMR spectroscopy, FAB-MS and elemental analysis, the product contains two 9-BBN moieties. ¹¹B NMR spectroscopy of **(9-BBN)₂5** showed two peaks (-0.04 and 12.65 ppm) for the two boron moieties, relative to the ¹¹B standard $\text{BF}_3\cdot\text{O}(\text{Et})_2$ (0 ppm), consistent with coordination of one boron atom to the carbonyl oxygen while the other boron is coordinated to the imidazole. By comparison, the boron signal in the unacylated *N*-(9-borabicyclo[3.3.1]non-9-yl)pyrrole appears at 59.9 ppm.^{II33} A similar synthesis using $\text{Bu}_2\text{B-OTf}$ gave the dibutylboron complex **(Bu₂B)₂5** in 23% yield. The low yield of boron complexation in both cases can be attributed to steric hindrance from the SEM protecting group.

Scheme II.2



X-ray structural analysis was performed on **(9-BBN)₂5** (Figure II.1). Crystals for X-ray were obtained by the slow evaporation of a solution of the boron-complex **(9-BBN)₂5** in anhydrous ether. The crystallographic data for **(9-BBN)₂5** is provided in appendix A. The molecule contains two 9-BBN moieties and one SEM group. One 9-BBN unit is bound to the pyrrolic nitrogen atom and coordinated to α -carbonyl moiety, forming a cyclic coplanar array of five atoms. The second 9-BBN unit is bound to the pyrrolic nitrogen atom and coordinated to the pyridyl nitrogen of the imidazole unit, forming a cyclic array of six atoms. The C–O bond length (1.302 Å) is longer than that in 2-benzoylpyrrole (1.234 Å),^{II33} suggesting some enolate character. At the same time, the C–C bond between the carbonyl carbon and the α -carbon of the acylpyrrole (1.404 Å) is significantly shorter than that in 2-benzoylpyrrole (1.446 Å),^{II33} suggesting partial multiple bond character. The B–N coordinate bond length (1.640 Å) is longer than the B–O coordinate bond length (1.557 Å)

due to the larger ionic radius of nitrogen than oxygen. The oxygen of the SEM group is disordered. The presence of the three protecting groups effectively masks all polar and/or hydrogen-bonding sites and thereby renders the imidazole-dipyrromethane a rather hydrophobic complex.

Figure II.1

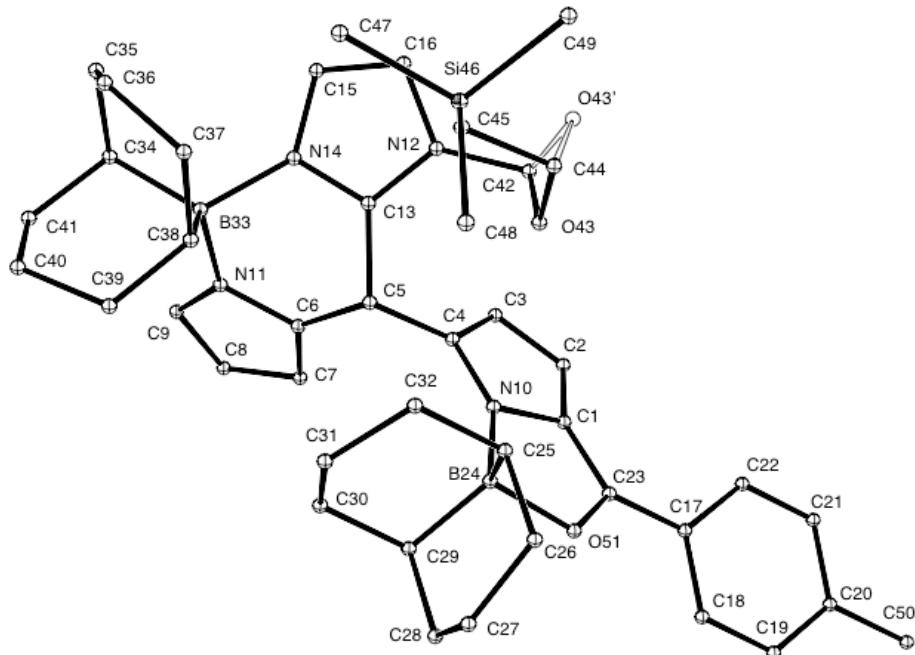


Figure II.1. X-ray structure of **(9-BBN)₂5** showing the two dialkylboron groups and one SEM group. The polar moieties (1-acylpyrrole moiety, pyrrole, and imidazole) are fully masked.

An alternative approach entailed preparation of the dialkylboron complex of the SEM-imidazole-dipyrromethane followed by acylation. Thus, a sample of protected dipyrromethane **Bu₂B-3** was treated first with MesMgBr (2 equiv) and Mukaiyama reagent **4** followed by TEA and BBu₂-OTf (2 equiv), affording **(Bu₂B)₂5** in 33% yield. When EtMgBr (2 equiv) was used instead of MesMgBr, **(Bu₂B)₂5** was obtained in 11% yield. Even though

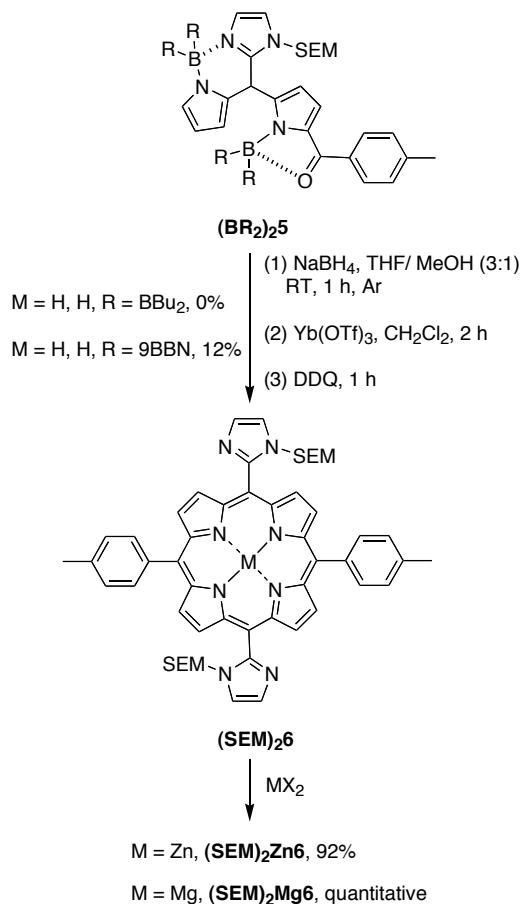
the yield is lower in the latter case, the purification is more facile due to the easier removal of products derived from EtMgBr versus MsMgBr.

4. SEM-protected Imidazol-2-yl Porphyrin (*trans*-A₂B₂). Our goal was to synthesize imidazole-porphyrin (**SEM**)₂**6** from the boron-complex of 1-acyldipyrromethane (**R**₂**B**)₂**5**. The established methods for working with dialkylboron complexes of acyldipyrromethanes entail (1) decomplexation in refluxing pentanol to give the acyldipyrromethane, which is then reduced with NaBH₄ to give the corresponding dipyrromethanecarbinol, or (2) direct reduction of the acyldipyrromethane-dialkylboron complex with NaBH₄, whereupon decomplexation occurs *in situ* yielding the dipyrromethanecarbinol. The mechanistic course of the *in situ* reduction and decomplexation is not known; it may be that reduction of the carbonyl group is followed by decomplexation (perhaps upon aqueous workup), or reduction of the dialkylboron moiety by NaBH₄ may occur, displacing a dialkylboron hydride species, after which the unveiled carbonyl group undergoes reduction.

Attempts to reduce dibutylboron-complex (**Bu**₂**B**)₂**5** with NaBH₄, even with 100 equiv for ~5 hour, were not successful. Alternatively, (**Bu**₂**B**)₂**5** was subjected to refluxing pentanol (similar to the conditions that effect decomplexation of dialkylboron complexes of 1-acyldipyrromethanes)^{II33} for 7 h, and the crude mixture was employed under conditions for porphyrin formation, but the formation of porphyrin (**SEM**)₂**6** was not observed. However, (**9-BBN**)₂**5** was reduced with excess NaBH₄ (50 equiv), affording the corresponding carbinol. The carbinol was then treated with Yb(OTf)₃ (3.2 mM) to carry out the self-condensation. Subsequent oxidation with DDQ afforded (**SEM**)₂**6** in 12% yield (Scheme II.3). Because of the affinity of imidazole towards Yb(OTf)₃, the amount of Yb(OTf)₃ employed was increased

from 0.32 mM in the general procedure^{II25} to 3.2 mM. Laser desorption mass spectrometry (LDMS) analysis of the crude reaction mixture did not show the presence of porphyrinic products derived from scrambling processes. TLC analysis of the product (**SEM**)₂**6** showed two porphyrin components, as expected for the two atropisomers. After column chromatography, only the more polar atropisomer was isolated in pure form. In accord with the literature,^{II19} the more polar atropisomer was assigned the *cis*-configuration.

Scheme II.3



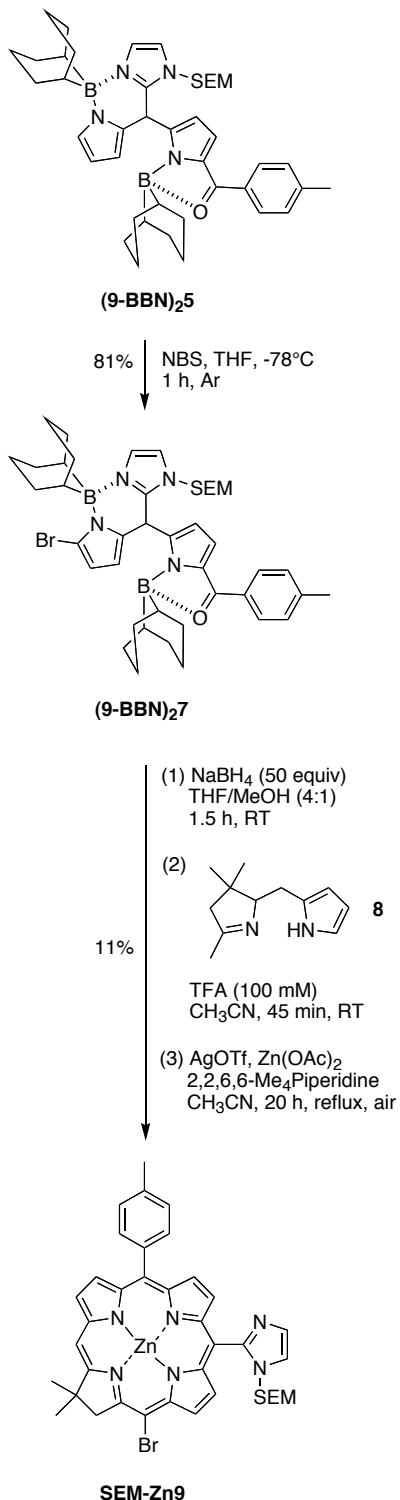
Attempts to metalate porphyrin (**SEM**)₂**6** led to aggregated samples. Treatment of the pure atropisomer (**SEM**)₂**6** with $\text{Zn(OAc)}_2 \cdot 2\text{H}_2\text{O}$ afforded (**SEM**)₂**Zn6** in 92% yield (Scheme II.3).^{II34} Crystallization of (**SEM**)₂**Zn5** from THF/ether afforded crystals which lost solvent molecules and broke apart upon attempted X-ray structural analysis. The absorption

spectrum of **(SEM)₂Zn6** in CH₂Cl₂ showed a split Soret band (415, 434 nm), which constitutes strong evidence of self-assembly arising from coordination between the lone pair of electrons on the imidazole nitrogen of one porphyrin molecule with the apical site on the zinc atom of another porphyrin molecule. Treatment of **(SEM)₂6** to the standard conditions for magnesium metalation (MgI₂ and DIEA in anhydrous ether)^{II35} gave the magnesium chelate in quantitative yield. The absorption spectrum of **(SEM)₂**Mg6 showed a split Soret band (411, 429 nm) in CH₂Cl₂. The LDMS spectrum also contained a peak at *m/z* = 1806.6 apart from a peak at 902.5, which is attributed to a dimer. After dissolving **(SEM)₂**Mg6 in CH₂Cl₂ and on standing for a few minutes, a solid thin film of self-assembled porphyrin was observed.

5. SEM-protected Imidazol-2-yl Chlorin. Synthesis of a chlorin entails the condensation of a 1-bromodipyrromethane-9-carbinol (Eastern half) with a 1,3,3-tetrahydropyrrin (Western half).^{II36-II39} Bromination of imidazol-2-yl-1-acyldipyrromethane-boron complex (**9-BBN**)₂**5** in a standard procedure^{II40} using NBS in THF at -78 °C gave the 1-bromo-9-acyldipyrromethane (**9-BBN**)₂**7** in 81% yield. Reduction with excess NaBH₄ (50 equiv) gave the corresponding Eastern half, which was condensed with Western half **8**^{II36-II39} in the presence of TFA. The resulting tetrahydrobilene-*a* was refluxed in CH₃CN for 20 hour exposed to air in the presence of Zn(OAc)₂, TMP and AgOTf. To our surprise, the chlorin (**SEM-Zn9**, 11% yield) obtained from this reaction contained a bromine atom at the 15-position (Scheme II.4). The mechanistic origin of this product remains unclear. TLC analysis showed only one chlorin, and LDMS showed the corresponding molecule ion peak. However, ¹H NMR spectroscopy indicated that **SEM-Zn9** consists of two atropisomers. The absorption spectrum showed a broad (~25 nm) and split Soret band,

which indicated self-assembly. The Soret band remained split upon examination of the sample in acetone, THF or CH₃CN, whereas a sharp band was observed in DMSO, MeOH or pyridine. Demetalation of the zinc chlorin yielded the free base chlorin, which exhibited a sharp absorption spectrum.

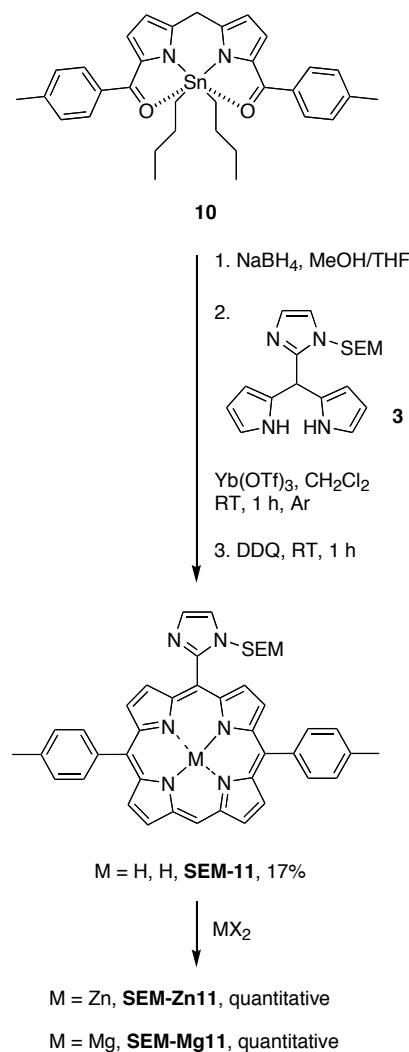
Scheme II.4



6. SEM-protected Imidazol-2-yl Porphyrin (*trans*-A₂BC). A *trans*-A₂BC-porphyrin bearing one imidazolyl group was prepared as shown in Scheme II.5. The tin-

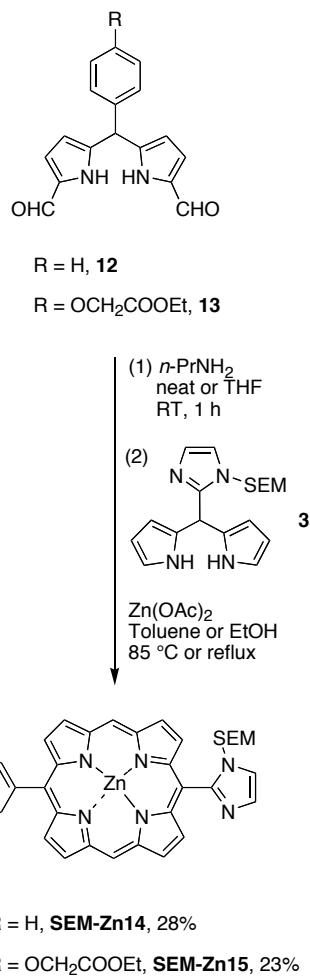
complex of a 1,9-diacyldipyrromethane (**10**)^{II41} was reduced using NaBH₄ to give the corresponding dicarbinol, which was condensed with imidazol-2-yl dipyrromethane **3** in the presence of Yb(OTf)₃. The progress of the reaction was monitored by UV-VIS spectroscopy. After 1 hour, the reaction leveled off and DDQ was added, giving porphyrin **SEM-11** in 17% yield. Metalation with Zn(OAc)₂·2H₂O afforded **SEM-Zn11** in quantitative yield. The absorption spectrum of **SEM-Zn11** showed a split Soret band (410, 427 nm), characteristic of aggregate formation. Metalation with magnesium gave **SEM-Mg11**, which also exhibited a split Soret band (406, 423 nm).

Scheme II.5



7. SEM-protected Imidazol-2-yl Porphyrins (*trans*-AB). *Trans*-AB-porphyrins are valuable for life sciences applications owing to their compact size.^{II42} Following a new synthetic route to *trans*-AB-porphyrins, 1,9-diformyldipyrromethane **12**^{II42} was treated with *n*-propylamine in THF to give the corresponding bis(iminomethyl)dipyrromethane. The latter was combined with imidazole-dipyrromethane **3** in ethanol containing Zn(OAc)₂, which upon refluxing in the presence of air for 13 h afforded **SEM-Zn14** (Scheme II.6). The isolated product consisted of a mixture of porphyrin and chlorin species. Treatment of the mixture with DDQ (1.5 equiv) at room temperature afforded **SEM-Zn14** in 28% yield. Similar treatment of 1,9-diformyldipyrromethane **13**^{II43} and imidazole-dipyrromethane **3** gave porphyrin **SEM-Zn15** in 23% yield. In this case ethanol was replaced by toluene. Each of these porphyrins (**SEM-Zn14** and **SEM-Zn15**) showed a split Soret band in CH₂Cl₂ due to the coordination between zinc and imidazole species.

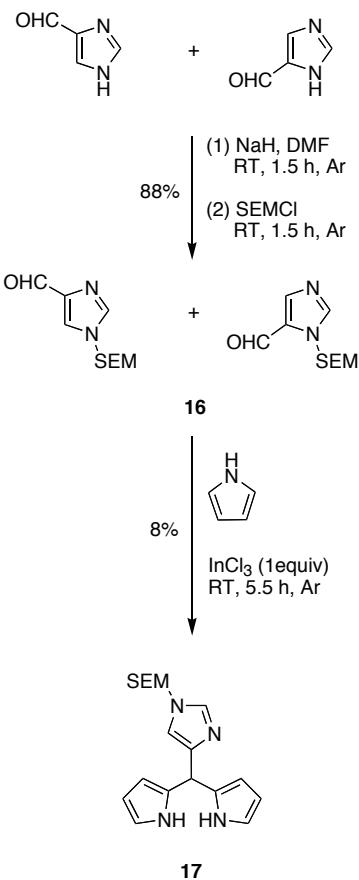
Scheme II.6



B. Imidazol-4-yl Porphyrin. The synthesis of SEM-protected imidazolecarboxaldehyde was achieved by the treatment of 4(5)-imidazolecarboxaldehyde with NaH followed by addition of SEMCl.^{II31} A mixture of two isomers of **16** (1:1 ratio by ¹H NMR analysis) was obtained in 88% overall yield (Scheme II.7). The mixture of isomers of **16** was reacted with excess pyrrole in the presence of InCl₃.^{II32} With 0.1 equiv of InCl₃, a mixture of a dipyrromethane and an unreacted aldehyde (by TLC and crude ¹H NMR analysis) was obtained, which was difficult to separate. In the presence of 1.0 equiv of InCl₃, a mixture of two isomers of the protected imidazole-dipyrromethane was obtained. The less

polar isomer (**17**) was isolated by chromatography in 8% yield upon small-scale reaction, or 4% yield at larger scale. The more polar regioisomer was not isolated in pure form.

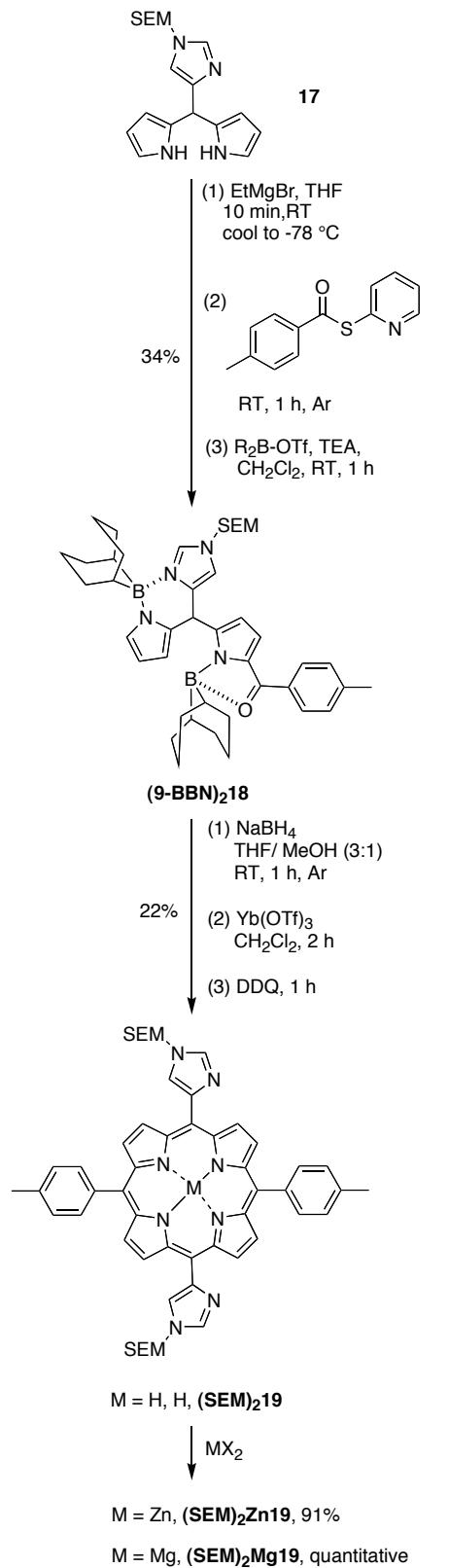
Scheme II.7



SEM = $\text{CH}_2\text{OCH}_2\text{CH}_2\text{SiMe}_3$

Dipyrrromethane **17** was treated with EtMgBr followed by Mukaiyama reagent **4** in the standard approach for 1-acylation. The crude mixture was treated directly with TEA and 9-BBN-OTf affording $(\mathbf{9}\text{-BBN})_2\mathbf{18}$ in 34% yield (Scheme II.8).^{II33} According to ^1H NMR spectroscopy and FAB-MS analysis, the compound contains two 9-BBN moieties. ^{11}B NMR spectroscopy of $(\mathbf{9}\text{-BBN})_2\mathbf{18}$ showed two distinct peaks (1.4 and 12.1 ppm), consistent with coordination of one boron atom to the carbonyl oxygen and one boron atom to the imidazole nitrogen atom.

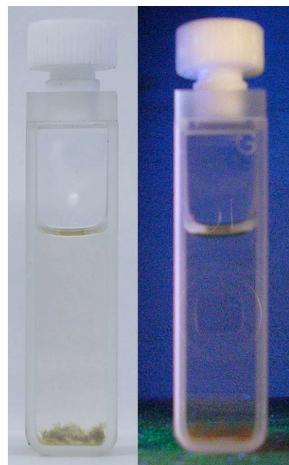
Scheme II.8



Reduction of **(9-BBN)₂18** with NaBH₄ gave the corresponding carbinol, which underwent self-condensation upon exposure to Yb(OTf)₃ (3.2 mM). Subsequent oxidation with DDQ afforded **(SEM)₂19** in 22% yield (Scheme II.8). LDMS analysis of the crude reaction mixture did not show the presence of any scrambled porphyrins. Treatment of **(SEM)₂19** with Zn(OAc)₂·2H₂O afforded **(SEM)₂Zn19** in 91% yield.^{II34} A satisfactory FABMS analysis was obtained for **(SEM)₂Zn19**, but the ¹H NMR spectrum in THF was complicated. This is due to the aggregation of **(SEM)₂Zn19**. The absorption spectrum of **(SEM)₂Zn19** in THF showed a split Soret band (417, 433 nm) which also implies the formation of an aggregate.

Treatment of **(SEM)₂19** to the standard conditions for magnesium insertion^{II35} afforded the magnesium chelate **(SEM)₂Mg19**. LDMS analysis of the crude product showed the expected molecule ion peak. The absorption spectrum showed a very broad peak at 422 nm. The sample in CH₂Cl₂ solution afforded a porphyrin precipitated at the bottom of the glass cuvette on standing for less than ten minutes, consistent with self-assembly yielding aggregates (Figure II.2).

Figure II.2



Self-assembly of **(SEM)₂Mg19** in CH₂Cl₂

Figure II.2. Left panel: the formation of precipitate of porphyrin **(SEM)₂Mg19** from CH₂Cl₂ solution on standing for a few minutes. Right panel: the same cuvette (illuminated with long-wave UV light) shows the fluorescent precipitate of porphyrin **(SEM)₂Mg19**, whereas the CH₂Cl₂ solution remains non-fluorescent. Therefore all porphyrin is in the precipitate.

II.D. Conclusions

Imidazolyl porphyrins and chlorins containing one or two imidazole units have been prepared in reasonable yields by employing two masking agents for the imidazole nitrogens. The SEM group blocks the pyrrole-like NH site while the dialkylboron group blocks the pyridyl-like nitrogen, thereby affording nonpolar, crystalline species that are more readily handled. Self-assembly of the zinc metalated imidazolyl porphyrins was observed in non-polar solvents. This work builds the foundation for the rational synthesis of a variety of porphyrinic compounds containing imidazole units with reasonable yields.

II.E. Experimental Section

General. All ^1H NMR spectra (400 MHz) and ^{13}C NMR spectra (100 MHz) were collected in CDCl_3 unless noted otherwise. ^{11}B NMR spectra (128 MHz) were obtained in $\text{THF}-d_8$ with inclusion of inner tube containing $\text{BF}_3\cdot\text{O}(\text{Et})_2$ as an external standard. Melting points are uncorrected. Absorption and fluorescence spectra were collected in CH_2Cl_2 at room temperature unless noted otherwise. Silica gel (40 μm average particle size) was used for column chromatography. THF was freshly distilled from sodium/benzophenone as required. Toluene was distilled from CaH_2 . CHCl_3 was stabilized with 0.8% ethanol. Anhydrous MeOH, CH_2Cl_2 and CHCl_3 (stabilized with 0.8% EtOH) were reagent grade and were used as received.

The magnesium-porphyrins that contain an imidazole group proved difficult to characterize (by NMR spectroscopy and often mass spectrometry) owing to extensive aggregation.

Noncommercial compounds. Mukaiyama reagent **4**,^{II40} tetrahydrodipyrin **8**,^{II36-II39} tin-complex **10**,^{II41} diformyldipyrromethane **12**,^{II42} and diformyldipyrromethane **13**^{II43} were prepared as described in the literature.

1-[2-(Trimethylsilyl)ethoxymethyl]imidazole-2-carboxaldehyde (2). Following a general procedure,^{II31} NaH (60% dispersion in mineral oil, 0.800 g, 20.0 mmol) was washed with hexanes (2×25 mL) under argon. The flask was charged with dry DMF (30 mL), and 2-imidazolecarboxaldehyde (1.92 g, 20.0 mmol) was added in small portions. After stirring at room temperature for 1.5 h, the above solution was treated dropwise with 2-(trimethylsilyl)ethoxymethyl chloride (SEMCl) (3.53 g, 21.2 mmol). The reaction mixture became slightly warm on the addition of SEMCl. The reaction mixture was stirred for 2.5 h,

quenched with water and extracted with ethyl acetate. The organic layers were combined and washed several times with water. The organic layer was then dried (Na_2SO_4) and concentrated to give a yellow oil (3.7 g, 82%): ^1H NMR (300 MHz) δ –0.12 (s, 9H), 0.83 (t, J = 8.7 Hz, 2H), 3.48 (t, J = 11.2 Hz, 2H), 5.70 (s, 2H), 7.24–7.29 (m, 2H), 9.75 (s, 1H); ^{13}C NMR δ –1.4, 17.8, 66.9, 75.7, 125.5, 132.0, 143.5, 182.3; FABMS calcd. 227.1216, obsd 227.1221 [(M + H)⁺, M = C₁₀H₁₈N₂O₂Si].

5-[1-(2-(Trimethylsilyl)ethoxymethyl)imidazol-2-yl]dipyrromethane (3).

Following a general procedure^{II32} with modification, pyrrole (104 mL, 1.50 mol) and aldehyde **2** (3.39 g, 15.0 mmol) were added to a 250-mL single neck round-bottomed flask containing a magnetic stir bar. The solution was degassed with a stream of argon for 10 min. A sample of MgBr₂ (1.38 g, 7.50 mmol) was added, and the mixture was stirred under argon at room temperature for 1.5 h. The mixture turned dark yellow during the course of the reaction. NaOH (3.00 g, 75.0 mol, 20-40 mesh beads) was added to quench the reaction. Stirring for 45 min afforded a light brown mixture. The mixture was filtered through a Büchner funnel. The contents of the flask and the filtered material were washed with a small amount of pyrrole. The filtrate was concentrated using a rotary evaporator under vacuum (0.2 mm Hg). Traces of pyrrole were removed by performing the following procedure three times: the crude viscous residue in the evaporation flask was triturated with hexanes (50 mL), and the volatile components were evaporated. The resulting light brown viscous liquid was purified by column chromatography [silica, CH₂Cl₂ → CH₂Cl₂/ethyl acetate (4:1)]. Concentration of the eluted product gave a brown viscous liquid (1.55 g, 30.1%): ^1H NMR δ –0.03 (s, 9H), 0.89 (t, J = 8.0 Hz, 2H), 3.45 (t, J = 8.0 Hz, 2H), 5.27 (s, 2H), 5.73 (s, 1H), 5.96–6.00 (s, 2H), 6.09–6.11 (m, 2H), 6.66–6.70 (m, 2H), 6.92–6.98 (m, 1H), 7.03–7.05 (m,

1H), 9.14–9.24 (br, 2H); ^{13}C NMR δ –1.4, 17.9, 35.4, 66.5, 75.1, 106.2, 108.2, 117.7, 119.9, 127.6, 129.9, 148.0; Anal. calcd. for $\text{C}_{18}\text{H}_{26}\text{N}_4\text{OSi}$: C, 63.12; H, 7.65; N, 16.36; found C, 62.63; H, 7.74; N, 15.73; FABMS obsd 343.1960, calcd 343.1954 $[(\text{M} + \text{H})^+, \text{M} = \text{C}_{18}\text{H}_{26}\text{N}_4\text{OSi}]$.

10-(Dibutylboryl)-5-[1-(2-(trimethylsilyl)ethoxymethyl)imidazol-2-yl]dipyrromethane (Bu₂B-3).

A solution of **3** (17 mg, 0.050 mmol) in CH_2Cl_2 (0.1 mL) was treated with TEA (17 μL , 0.12 mmol) followed by treatment with Bu₂B-OTf (0.10 mL, 0.10 mmol, 1.0 M in CH_2Cl_2) and the mixture was stirred at room temperature. After 1 h, the mixture was poured onto a pad of silica eluted with CH_2Cl_2 . The product eluted as a fast moving red band, which upon concentration afforded a dark red viscous solid (14 mg, 60%): ^1H NMR δ –0.03 (s, 9H), 0.41–0.52 (m, 4H), 0.71–0.76 (m, 16H), 3.41–3.50 (m, 2H), 5.21 (d, $J = 10.8$ Hz, 1H), 5.45 (d, $J = 10.0$ Hz, 1H), 5.79 (s, 1H), 5.94–5.98 (m, 1H), 6.01–6.03 (m, 1H), 6.07–6.09 (m, 1H), 6.23–6.25 (m, 1H), 6.61–6.63 (m, 1H), 6.76–6.78 (m, 1H), 7.11–7.13 (m, 2H), 7.94–8.10 (br, 1H); ^{13}C NMR δ –1.1, 14.3, 18.0, 26.4, 26.6, 27.4, 28.7, 33.9, 67.4, 76.3, 104.6, 106.3, 107.9, 108.6, 118.4, 120.3, 121.2, 121.7, 144.9; FABMS obsd 467.3377, calcd 467.3372 $[(\text{M} + \text{H})^+, \text{M} = \text{C}_{26}\text{H}_{43}\text{BN}_4\text{OSi}]$; λ_{abs} (THF) 296 nm.

10-(Dibutylboryl)-5-[1-(2-(trimethylsilyl)ethoxymethyl)imidazol-2-yl]dipyrromethane (Bu₂B-3).

A solution of **3** (0.22 g, 0.64 mmol) in CH_2Cl_2 (1.3 mL) was treated with TEA (0.22 mL, 1.6 mmol) followed by the treatment with Bu₂B-OTf (1.3 mL, 1.3 mmol, 1.0 M in CH_2Cl_2) and the mixture was stirred at room temperature. After 1 h, the mixture was poured onto a pad of silica eluted with CH_2Cl_2 . The product eluted as a fast moving red band, which upon concentration afforded a dark red viscous liquid (0.24 g, 81%). Characterization data (^1H NMR) were consistent with the values reported above.

10,11-Bis(9-borabicyclo[3.3.1]non-9-yl)-1-(4-methylbenzoyl)-5-[1-(2-(trimethylsilyl)ethoxymethyl)imidazol-2-yl]dipyrromethane [(9-BBN)₂5]. Following a published procedure^{II33} with slight modification, a solution of EtMgBr (9.50 mL, 9.50 mmol, 1.0 M in THF) was added slowly to a solution of **3** (1.63 g, 4.75 mmol) in THF (4.8 mL) under argon. The resulting mixture was stirred at room temperature for 10 min, and then cooled to -78 °C. A solution of S-2-pyridyl 4-methylbenzothioate (**4**, 1.09 g, 4.75 mmol) in THF (4.8 mL) was added. The solution was stirred at -78 °C for 10 min, then warmed to room temperature and stirred for 1.5 h. The reaction was quenched by addition of saturated aqueous NH₄Cl (20 mL). The mixture was extracted with ethyl acetate. The organic layer was washed (water and brine), dried (Na₂SO₄) and filtered. The filtrate was concentrated. The crude product (a red-orange oil) thus obtained was dissolved in CH₂Cl₂ (9.5 mL) and treated with TEA (1.59 mL, 11.4 mmol) followed by 9-BBN-OTf (19 mL, 9.5 mmol, 0.5 M in hexane) with stirring at room temperature. After 1 h the mixture was poured onto a pad of silica (3 cm x 15 cm) eluting with CH₂Cl₂. The fast moving yellow band was concentrated and further purification [silica, hexanes/CH₂Cl₂ (1:1)] afforded a yellow solid (846 mg, 25.4%): mp 170–172 °C; ¹H NMR δ –0.07 (s, 9H), 0.74–0.93 (m, 6H), 1.50–2.43 (m, 24H), 2.52 (s, 3H), 3.16–3.27 (m, 2H), 4.35 (d, *J* = 10.0 Hz, 1H), 4.62 (d, *J* = 10.0 Hz, 1H), 5.57 (s, 1H), 6.01–6.04 (m, 1H), 6.21–6.26 (m, 1H), 6.53 (d, *J* = 4.0 Hz, 1H), 7.01–7.06 (m, 1H), 7.34–7.37 (m, 1H), 7.41–7.43 (m, 3H), 7.66–7.69 (m, 1H), 8.19 (d, *J* = 8.4 Hz, 2H); ¹³C NMR δ –1.5, 18.1, 21.5, 22.1, 23.4, 23.6, 23.7, 25.0, 25.7, 26.2, 30.0, 31.01, 31.05, 31.7, 34.2, 34.41, 34.44, 34.8, 39.8, 67.2, 105.8, 107.4, 117.3, 118.1, 121.3, 124.3, 124.4, 127.7, 129.9, 130.0, 130.1, 134.7, 145.9, 146.4, 147.4, 175.7; ¹¹B NMR δ –0.04, 12.65; Anal. calcd.

for C₄₂H₅₈B₂N₄O₂Si: C, 72.00; H 8.34; N, 8.00. Found: C, 71.97; H 8.32; N, 7.90; FABMS obsd 700.4572, calcd 700.4515 (C₄₂H₅₈B₂N₄O₂Si); λ_{abs} (THF) 298 nm.

10,11-Bis(dibutylboryl)-1-(4-methylbenzoyl)-5-[1-(2-(trimethylsilyl)ethoxymethyl)imidazol-2-yl]dipyrromethane [(Bu₂B)₂5]. Following a published procedure^{II33} with slight modification, a solution of EtMgBr (0.620 mL, 0.620 mmol, 1.0 M in THF) was added slowly to a solution of **3** (106 mg, 0.310 mmol) in THF (0.31 mL) under argon. The resulting mixture was stirred at room temperature for 10 min, and then cooled to -78 °C. A solution of *S*-2-pyridyl-4-methylbenzothioate (**4**, 71 mg, 0.31 mmol) in THF (0.31 mL) was added. The solution was stirred at -78 °C for 10 min, then warmed to room temperature and stirred for 1 h. The reaction was quenched by addition of saturated aqueous NH₄Cl (4 mL). The mixture was extracted with ethyl acetate. The organic layer was washed (water and brine), dried (Na₂SO₄) and filtered. The filtrate was concentrated. The crude product (a red-orange oil) thus obtained was dissolved in CH₂Cl₂ (0.62 mL) and treated with TEA (105 μL, 0.750 mmol) followed by Bu₂B-OTf (0.62 mL, 0.62 mmol, 1.0 M in hexane) with stirring at room temperature. After 1 h, the mixture was poured onto a pad of silica (2 cm x 16 cm) eluted with CH₂Cl₂. The product eluted as a fast moving orange band, which upon concentration afforded a orange-red viscous solid (50 mg, 23%): ¹H NMR δ -0.08 (s, 9H), 0.40–0.60 (m, 2H), 0.72–1.31 (m, 36H), 2.49 (s, 3H), 3.16–3.19 (m, 1H), 3.30–3.35 (m, 1H), 4.89 (d, *J* = 10.4 Hz, 1H), 5.13 (d, *J* = 10.4 Hz, 1H), 5.83 (s, 1H), 5.90–5.92 (m, 1H), 6.20–6.22 (m, 2H), 6.74–6.76 (m, 1H), 7.18–7.22 (m, 3H), 7.38 (d, *J* = 8.0 Hz, 2H), 8.12 (d, *J* = 8.4 Hz, 2H); ¹³C NMR (75 MHz) δ -1.3, 14.3, 14.4, 14.5, 18.1, 22.1, 23.6, 26.2, 26.4, 26.5, 26.8, 27.1, 27.6, 28.3, 28.6, 35.1, 67.4, 76.0, 106.2, 108.2, 118.7, 118.9, 119.9, 120.9, 122.0, 124.9, 127.7, 130.0, 130.1, 134.4, 143.4, 145.8,

147.3, 176.5; FABMS obsd 709.5203 calcd 709.5219 [(M + H)⁺, M = C₄₂H₆₆B₂N₄O₂Si]; λ_{abs} (THF) 360 nm.

5,15-Bis(4-methylphenyl)-10,20-bis[1-(2-(trimethylsilyl)ethoxymethyl)imidazol-2-yl]porphyrin [(SEM)₂6]. Following general procedures^{II25,II33} with slight modification, a sample of NaBH₄ (0.95 g, 25 mmol, 50 molar equiv) was slowly added in small portions to a stirred solution of (**9-BBN**)₂**5** (0.35 g, 0.50 mmol) at 0 °C in THF/MeOH (3:1, 20 mL). The reaction was monitored by TLC (silica, CH₂Cl₂). After 1.5 h, the reaction was quenched by pouring the reaction mixture into a stirred solution of saturated aqueous NH₄Cl and ethyl acetate (1:1, 100 mL). The organic layer was isolated, washed with water, and then dried (Na₂SO₄). The solvent was then removed to afford the carbinol as an orange oil. The carbinol (~0.5 mmol) was immediately dissolved in CH₂Cl₂ (100 mL), and Yb(OTf)₃ (0.20 g, 0.32 mmol, 3.2 mM) was added. The solution slowly darkened and the reaction was monitored by absorption spectroscopy. After 4 h, the spectroscopic yield of porphyrin had essentially leveled off, and then DDQ (0.17 g, 0.75 mmol) was added and the mixture was stirred at room temperature for 1 h. Then TEA (89 µL, 0.64 mmol) was added, and the entire reaction mixture was filtered through a pad of alumina [5 cm x 10 cm, CH₂Cl₂/MeOH (19:1) → CH₂Cl₂/MeOH (19:1)] until the eluent was no longer dark. Removal of solvent gave a dark solid, which under purification by column chromatography [silica, 3 cm x 20 cm, CH₂Cl₂/ethyl acetate (9:1) → CH₂Cl₂/ethyl acetate (1:1)] gave purple solid (24 mg, 12%): ¹H NMR (300 MHz) δ -2.84 to -2.81 (br, 2H), -0.42 (s, 9H), -0.38 (s, 9H), 0.38–0.44 (m, 4H), 2.73 (s, 6H), 2.87–2.94 (m, 4H), 5.06 (s, 2H), 5.12 (s, 2H), 7.57–7.61 (m, 4H), 7.69–7.75 (m, 4H), 8.02–8.15 (m, 4H), 8.80–8.83 (m, 4H), 8.93 (d, *J* = 6.4 Hz, 4H); LDMS obsd 881.7;

FABMS obsd 883.4243, calcd 883.4300 [$(M + H)^+$, $M = C_{52}H_{58}N_8O_2Si_2$]; λ_{abs} 419, 516, 552, 589 nm; λ_{em} 655, 720 nm.

Zn(II)-5,15-Bis(4-methylphenyl)-10,20-bis[1-(2-

(trimethylsilyl)ethoxymethyl]imidazol-2-yl]porphyrin [(SEM)₂Zn6]. Following a general procedure,^{II34} a solution of porphyrin **(SEM)₂6** (14 mg, 16 μ mol) in CHCl₃/MeOH (8 mL, 3:1) was treated with Zn(OAc)₂·2H₂O (0.35 g, 1.6 mmol, 100 equiv). The reaction mixture was stirred at room temperature for 4 h. The reaction was quenched with water and extracted with ethyl acetate. The organic layer was separated, dried (Na₂SO₄), concentrated and chromatographed [silica, CH₂Cl₂/ethyl acetate (4:1) containing 1% TEA] to afford a purple-green solid (14 mg, 92%): ¹H NMR (300 MHz, THF-*d*₈) δ –0.90 (s, 9H), –0.84 (s, 9H), –0.40 (s, 2H), –0.02 (s, 2H), 0.28–0.40 (m, 1H), 2.50 (s, 6H), 3.25–3.35 (m, 1H), 5.08 (s, 2H), 5.63–5.65 (m, 2H), 5.80–5.88 (m, 2H), 7.57 (d, *J* = 4.5 Hz, 2H), 7.70–7.76 (m, 4H), 7.78 (s, 2H), 7.90 (s, 2H), 7.96 (d, *J* = 4.2 Hz, 2H), 8.33–8.35 (m, 2H), 8.52–8.62 (m, 2H), 8.93–9.00 (m, 4H); LDMS obsd 945.0; FABMS obsd 944.3364, calcd 944.3356 ($C_{52}H_{56}N_8O_2Si_2Zn$); λ_{abs} 415, 434, 562 nm; λ_{em} 615, 670 nm.

Mg(II)-5,15-Bis(4-methylphenyl)-10,20-bis[1-(2-

(trimethylsilyl)ethoxymethyl]imidazol-2-yl]porphyrin [(SEM)₂Mg6]. Following a general procedure for magnesium metalation,^{II35} a solution of **(SEM)₂6** (2 mg, 2 μ mol) in anhydrous CH₂Cl₂ (0.5 mL) was treated with a solution of MgI₂–DIEA in anhydrous ether (1 mL) and the reaction mixture was stirred at room temperature for 24 h. TLC showed the formation of a single porphyrinic product. The crude reaction mixture was diluted with CH₂Cl₂ and washed with 5% aqueous NaHCO₃ solution. The organic layer was dried over Na₂SO₄ and concentrated to obtain the product in quantitative yield (2.0 mg, 99%): LDMS

obsd 902.5, 1806.6; calcd 904.3915 ($C_{52}H_{56}N_8O_2Si_2Mg$); λ_{abs} 411, 429, 562 nm; λ_{em} 620, 670 nm.

10,11-Bis(9-borabicyclo[3.3.1]non-9-yl)-1-bromo-9-(4-methylbenzoyl)-5-[1-(2-(trimethylsilyl)ethoxymethyl)imidazol-2-yl]dipyrromethane [(9-BBN)₂7]. Following a procedure reported for the bromination of a 1-acyldipyrromethane-BBN complex,^{II40} a solution of **(9-BBN)₂5** (0.21 g, 0.30 mmol) in THF (3 mL) was cooled to -78 °C under argon. NBS (53 mg, 0.30 mmol) was added, and the reaction mixture was stirred for 1 h at -78 °C. Hexanes (4 mL) and water (4 mL) were added, and the mixture was allowed to warm to room temperature and diluted with ether. The organic phase was separated, dried (Na_2SO_4), and concentrated under reduced pressure without heating. The resulting yellow residue was chromatographed [silica, hexanes/ CH_2Cl_2 (1:1)] to afford a yellow powder (0.19 g, 81%): mp 170 °C (dec.); ¹H NMR δ -0.08 (s, 9H), 0.76–0.88 (m, 6H), 1.25–2.30 (m, 24H), 2.52 (s, 3H), 3.19–3.20 (m, 2H), 4.21 (d, J = 10.4 Hz, 1H), 4.61 (d, J = 10.4 Hz, 1H), 5.57 (s, 1H), 6.19–6.22 (m, 1H), 6.49 (d, J = 4.0 Hz, 1H), 7.05–7.07 (m, 1H), 7.26 (d, J = 5.6 Hz, 1H), 7.39–7.43 (m, 3H), 7.65–7.67 (m, 1H), 8.19 (d, J = 8.4 Hz, 2H); ¹³C NMR δ -1.6, 18.0, 21.1, 22.1, 23.2, 23.5, 24.9, 25.6, 26.1, 29.7, 30.1, 30.7, 30.8, 31.6, 34.0, 34.2, 34.3, 34.4, 34.5, 39.4, 67.2, 92.8, 109.7, 117.5, 118.1, 121.0, 123.9, 124.3, 127.6, 130.0, 130.1, 130.2, 134.7, 145.2, 146.1, 146.8, 176.0; FABMS obsd 778.3664, calcd 778.3620 ($C_{42}H_{57}B_2BrN_4O_2Si$).

Zn(II)-15-Bromo-17,18-dihydro-18,18-dimethyl-5-(4-methylphenyl)-10-[1-(2-(trimethylsilyl)ethoxymethyl)imidazol-2-yl]porphyrin (SEM-Zn9). Following a general procedure for one-flask two-step synthesis of chlorin,^{II38} a solution of **(9-BBN)₂7** (0.191 g, 0.245 mmol) in THF/MeOH [25 mL, (4:1)] was treated portionwise with $NaBH_4$ (0.465 g,

12.3 mmol, 50 equiv). The progress of the reaction was monitored by TLC (silica, CH₂Cl₂) and upon completion after 1.5 h the reaction was quenched with saturated aqueous NH₄Cl (50 mL). The organic layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried (Na₂SO₄) and concentrated. Upon initial work up, the monobromo-carbinol was the only product visible by TLC (short wavelength). The crude product was directly used in the chlorin-forming reaction due to limited stability. The crude product was dissolved in anhydrous CH₃CN (2.5 mL), and then **8** (47.0 mg, 0.245 mmol) and TFA (0.0190 mL, 0.245 mmol) were added. The reaction mixture was stirred at room temperature for 45 min under argon. The reaction mixture was treated with CH₃CN (22 mL), AgOTf (0.189 g, 0.735 mmol, 3 equiv), Zn(OAc)₂ (0.676 g, 3.68 mmol, 15 equiv), and 2,2,6,6-tetramethylpiperidine (1.25 mL, 7.35 mmol, 30 equiv). The resulting mixture was refluxed for 20 h exposed to air. The reaction mixture was concentrated under reduced pressure. The residue was chromatographed [silica, hexanes/CH₂Cl₂ (1:1)] affording **SEM-Zn9** as a dark-green solid (20 mg, 90% pure, 11% yield): ¹H NMR (THF-*d*₈) δ -0.76 (s, 9H), -0.23 (t, *J* = 8.8 Hz, 2H), 1.99 (s, 3H), 2.0 (s, 1H), 2.34 (s, 3H), 2.40 (s, 1H), 2.72 (s, 3H), 2.77 (s, 1H), 2.89 (d, *J* = 1.6 Hz, 1H), 3.35 (d, *J* = 10.4 Hz, 1H), 4.53–4.86 (m, 2H), 5.43 (s, 1H), 5.52 (d, *J* = 4.4 Hz, 1H), 6.13 (d, *J* = 1.6 Hz, 1H), 7.42 (d, *J* = 7.2 Hz, 1H), 7.68–7.72 (m, 2H), 8.10 (d, *J* = 4.4 Hz, 1H), 8.65–8.71 (m, 3H), 8.77 (d, *J* = 4.4 Hz, 1H), 8.87 (s, 1H); LDMS obsd 765.9; FABMS obsd 767.1569, calcd 767.1508 [(M + H)⁺, M = C₃₈H₃₉N₆BrOSiZn]; λ_{abs} 402, 416, 426, 526, 599, 629 nm; λ_{em} 655, 725 nm.

5,15-Bis(4-methylphenyl)-10-[1-(trimethylsilyl)ethoxymethyl]imidazol-2-yl|porphyrin (SEM-11). Following general procedures^{II25} with slight modification, a sample of NaBH₄ (0.568 g, 15.0 mmol, 50 molar equiv) was slowly added in small portions

to a stirred solution of **10** (0.184 g, 0.300 mmol) in THF/MeOH (5:1, 12 mL). The reaction was monitored by TLC analysis (silica, CH₂Cl₂). After 4.5 h, the reaction was quenched by slow addition of saturated aqueous NH₄Cl (60 mL). The reaction mixture was extracted with CH₂Cl₂, the organic layer was dried (K₂CO₃) and concentrated to afford the dicarbinol. The dicarbinol (~0.3 mmol) was immediately dissolved in CH₂Cl₂ (120 mL), then **3** (103 mg, 0.300 mmol) and Yb(OTf)₃ (0.242 g, 0.390 mmol, 3.2 mM) were added. The solution slowly darkened and the reaction was monitored by absorption spectroscopy. After 1 h, the spectroscopic yield of porphyrin had essentially leveled off. DDQ (0.204 g, 0.900 mmol) was added and the mixture was stirred at room temperature for 1 h. Then TEA (0.11 mL, 0.78 mmol) was added, and the entire reaction mixture was concentrated which under purification by column chromatography [silica, 3 cm x 18 cm, CH₂Cl₂/ethyl acetate (1:1) containing 1% TEA] gave a purple solid (35 mg, 17%): ¹H NMR δ -3.01 to -2.99 (br, 2H), -0.41 (s, 9H), -0.39 (t, *J* = 8.0 Hz, 2H), 2.72 (s, 6H), 2.86 (t, *J* = 8.0 Hz, 2H), 5.04 (s, 2H), 7.59 (d, *J* = 8.0 Hz, 4H), 7.68–7.69 (m, 1H), 7.72–7.73 (m, 1H), 8.08–8.15 (m, 4H), 8.81 (d, *J* = 8.0 Hz, 2H), 8.97 (d, *J* = 4.8 Hz, 2H), 9.05 (d, *J* = 4.4 Hz, 2H), 9.35 (d, *J* = 4.8 Hz, 2H), 10.28 (s, 1H); LDMS obsd 685.6; FABMS obsd 687.3288, calcd 687.3268 [(M + H)⁺, M = C₄₃H₄₂N₆OSi]; λ_{abs} 414, 510, 582 nm; λ_{em} 645, 710 nm.

Zn(II)-5,15-Bis(4-methylphenyl)-10-(2-(trimethylsilyl)ethoxymethyl)imidazol-2-ylporphyrin (SEM-Zn11). Following a general procedure,^{II34} a solution of porphyrin **SEM-11** (21 mg, 0.03 mol) in CHCl₃/MeOH (12 mL, 3:1) was treated with Zn(OAc)₂·2H₂O (0.33 g, 1.5 mmol, 50 equiv). The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was washed with saturated NaHCO₃ solution and water and extracted with ethyl acetate. The organic layer was separated, dried (Na₂SO₄), concentrated and

chromatographed [silica, CH₂Cl₂/ethyl acetate (3:1)] affording a purple-green solid (23 mg, quantitative): ¹H NMR δ -0.88 (s, 9H), -0.42 (t, *J* = 8.0 Hz, 2H), 1.53 (t, *J* = 8.8 Hz, 2H), 1.82 (t, *J* = 2.0 Hz, 1H), 2.86 (s, 6H), 3.15 (s, 2H), 5.50 (d, *J* = 4.4 Hz, 2H), 5.65 (d, *J* = 1.6 Hz, 1H), 7.57 (d, *J* = 7.2 Hz, 2H), 7.73 (d, *J* = 7.2 Hz, 2H), 8.01 (d, *J* = 7.6 Hz, 2H), 8.36 (d, *J* = 4.4 Hz, 2H), 8.56 (d, *J* = 7.2 Hz, 2H), 9.18 (d, *J* = 4.4 Hz, 2H), 9.50 (d, *J* = 4.4 Hz, 2H), 10.43 (s, 1H); LDMS obsd 749.6; FABMS obsd 749.2389, calcd 749.2403 [(M + H)⁺, M = C₄₃H₄₀N₆OSiZn]; λ_{abs} 410, 427, 558 nm; λ_{em} 610, 660 nm.

Mg(II)-5,15-Bis(4-methylphenyl)-10-(2-(trimethylsilyl)ethoxymethyl)imidazol-2-ylporphyrin (SEM-Mg11). Following a general procedure for magnesium metalation,^{II35} a solution of (SEM)₂11 (2 mg, 3 μmol) in anhydrous CH₂Cl₂ (1 mL) was treated with a solution of MgI₂-DIEA in anhydrous ether (1 mL) and the reaction mixture was stirred at room temperature for 18 h to obtain an orange colored solution. TLC showed the formation of a single porphyrinic product. The crude rection mixture was diluted with CH₂Cl₂ and washed with 5% NaHCO₃ solution. The organic layer was dried over Na₂SO₄ and concentrated to obtain the product in quantitative yield (2.0 mg, 99%): LDMS obsd 707.5, 1415.9 (dimer); FABMS obsd 709.2967, calcd 709.2962 [(M + H)⁺, M = C₄₃H₄₀N₆OSiMg]; λ_{abs} 406, 423, 559 nm.

Zn(II)-5-Phenyl-10-[1-(2-(trimethylsilyl)ethoxymethyl)imidazol-2-yl]porphyrin (SEM-Zn14). Following a general procedure^{II42} with slight modification, a solution of 1,9-diformyldipyrromethane 12 (56 mg, 0.20 mmol) and *n*-propylamine (0.04 mL, 0.50 mmol) in THF (1 mL) was stirred at room temperature for 1 h. After removal of the excess *n*-propylamine and THF under vacuum, the residue and dipyrromethane 3 (69 mg, 0.20 mmol) were dissolved in ethanol (20 mL). The mixture was then treated with Zn(OAc)₂ (0.367 g,

2.00 mmol) and refluxed open to the air for 13 h. After removing the solvent the residue was chromatographed [silica, CH₂Cl₂ → CH₂Cl₂/ethyl acetate (4:1)] to afford a dark purple solid (24 mg, 19%): ¹H NMR (300 MHz, CD₂Cl₂) δ -0.81 (s, 9H), -0.40 (t, *J* = 7.8 Hz, 2H), 1.55–1.61 (m, 2H), 1.91 (s, 1H), 3.16 (s, 2H), 5.54 (d, *J* = 3.9 Hz, 2H), 5.76 (s, 1H), 7.86–8.02 (m, 3H), 8.27 (d, *J* = 6.6 Hz, 1H), 8.77 (d, *J* = 6.9 Hz, 1H), 8.83 (d, *J* = 3.6 Hz, 2H), 9.24 (d, *J* = 3.9 Hz, 2H), 9.51 (d, *J* = 3.9 Hz, 2H), 10.23 (s, 2H); LDMS obsd 644.2; FABMS obsd 644.1740, calcd 644.1698 (C₃₅H₃₂N₆OSiZn); λ_{abs} 402, 422, 551 nm; λ_{em} 595, 645 nm.

Large Scale Synthesis of SEM-Zn14. Following a general procedure^{II42} with slight modification, a solution of 1,9-diformyldipyrromethane **12** (0.278 g, 1.00 mmol) in *n*-propylamine (4.11 mL, 50.0 mmol) was stirred at room temperature for 1 h. After removal of the excess *n*-propylamine, the residue and dipyrromethane **3** (0.343 g, 1.00 mmol) were dissolved in ethanol (20 mL). The mixture was then treated with Zn(OAc)₂ (1.84 g, 10.0 mmol) and refluxed in air for 18 h. After removing the solvent, the residue was chromatographed over a short pad of silica (CH₂Cl₂) to afford a non-polar reduced porphyrinic species (chlorin). After removal of the solvent, the residue (~200 mg) was dissolved in CH₂Cl₂ (28 mL) and treated with DDQ (0.16 g, 0.70 mmol) and the mixture was stirred at room temperature for 1 h. The mixture was then concentrated and the residue was chromatographed [silica, CH₂Cl₂ → CH₂Cl₂/ethyl acetate (4:1)] to afford a dark purple solid (0.18 g, 28%). The characterization data (UV-VIS, ¹H NMR, LDMS, FABMS) were consistent with the values reported above for **SEM-Zn14**.

Zn(II)-5-(4-(Ethoxycarbonylmethoxy)phenyl)-10-[1-(2-(trimethylsilyl)ethoxymethyl)imidazol-2-yl]porphyrin (SEM-Zn15). Following a general

procedure^{II42} with slight modification, a solution of 1,9-diformyldipyrromethane **13** (76 mg, 0.20 mmol) and *n*-propylamine (0.040 mL, 0.50 mmol) in THF (1 mL) was stirred at room temperature for 1 h. After removal of the excess *n*-propylamine and THF, the residue and dipyrromethane **3** (69 mg, 0.20 mmol) were dissolved in toluene (20 mL). The mixture was then treated with Zn(OAc)₂ (0.37 g, 2.0 mmol) and heated at 85 °C open to the air for 17 h. After removal of the solvent the residue was chromatographed [silica, CH₂Cl₂ → CH₂Cl₂/ethyl acetate (1:1)] to afford a dark purple solid (35 mg, 23%): ¹H NMR δ -0.83 (s, 9H), -0.42 to -0.39 (m, 2H), 1.50–1.54 (m, 5H), 1.94 (d, *J* = 1.6 Hz, 1H), 3.13 (s, 2H), 4.50–4.55 (m, 2H), 5.06 (s, 2H), 5.56 (d, *J* = 4.4 Hz, 2H), 5.71 (d, *J* = 1.6 Hz, 1H), 7.38–7.41 (m, 1H), 7.57–7.60 (m, 1H), 8.16–8.18 (m, 1H), 8.71–8.74 (m, 1H), 8.81 (d, *J* = 4.4 Hz, 2H), 9.28 (d, *J* = 4.0 Hz, 2H), 9.51 (d, *J* = 4.4 Hz, 2H), 10.21 (s, 2H); LDMS obsd 745.7; FABMS obsd 746.2070, calcd 746.2015 (C₃₉H₃₈N₆O₄SiZn); λ_{abs} 402, 423, 552 nm; λ_{em} 600, 650 nm.

1-[2-(Trimethylsilyl)ethoxymethyl]imidazole-4(5)-carboxaldehyde (16).

Following a general procedure,^{II31} NaH (60% dispersion in mineral oil, 1.00 g, 25.0 mmol) was washed with hexanes (2 x 25 mL) under argon. The flask was charged with dry DMF (36 mL) and 4(5)-imidazolecarboxaldehyde (2.40 g, 25.0 mmol) was added in small portions. After stirring at room temperature for 1.5 h, the above solution was treated dropwise with 2-(trimethylsilyl)ethoxymethyl chloride (SEMCl) (4.42 g, 25.0 mmol). The reaction mixture became slightly warm. The mixture was stirred for 1.5 h, then quenched with water and extracted with ethyl acetate. The organic layers were combined and washed repeatedly with water. The organic layer was then dried (Na₂SO₄) and concentrated to give a yellow oil (4.97 g, 87.8%): ¹H NMR δ -0.04 (s, 9H), 1.19–1.28 (m, 2H), 3.45–3.60 (m, 2H), 5.37–5.73 (m, 2H), 7.74–7.87 (m, 2H), 9.82–9.94 (br, 1H); ¹³C NMR δ -1.5, -1.4, 17.6, 17.7, 66.9, 67.0,

75.4, 76.5, 124.6, 138.8, 143.5, 143.7, 179.3, 186.0; FABMS obsd 227.1207, calcd 227.1216
[(M + H)⁺, M = C₁₀H₁₈N₂O₂Si].

Large Scale Synthesis of 16. Following a general procedure,^{II31} NaH (60% dispersion in mineral oil, 4.28 g, 107 mmol) was washed with hexanes (3 x 50 mL) under argon. The flask was charged with dry DMF (154 mL) and 4(5)-imidazolecarboxaldehyde (10.3 g, 107 mmol) was added in small portions. After stirring at room temperature for 2.5 h, the above solution was treated dropwise with 2-(trimethylsilyl)ethoxymethyl chloride (SEMCl) (19.6 g, 118 mmol). The reaction mixture became slightly warm and was stirred for 4 h and then quenched with water and extracted with ethyl acetate. The combined organic layers were washed with water, separated, dried (Na₂SO₄) and concentrated to give a yellow oil (21 g, 87%). Characterization data (¹H NMR, FABMS) were consistent with the values reported above.

5-[1-(2-(Trimethylsilyl)ethoxymethyl)imidazol-4-yl]dipyrromethane (17). Following a general procedure^{II32} with modification, pyrrole (139 mL, 2.00 mol) and aldehyde **16** (4.53 g, 20.0 mmol) were added to a 250-mL single neck round-bottomed flask containing a magnetic stir bar. The solution was degassed with a stream of argon for 10 min. InCl₃ (4.42 g, 20.0 mmol) was added, and the mixture was stirred under argon at room temperature for 5.5 h. The mixture turned brown during the course of the reaction. NaOH (24.0 g, 60.0 mol, 20-40 mesh beads) was added to quench the reaction. Stirring for 45 min afforded a brown mixture. The mixture was filtered through Büchner funnel. The contents of the flask and the filtered material were washed with a small amount of pyrrole. The filtrate was concentrated using a rotary evaporator under vacuum (0.2 mm Hg). Traces of pyrrole were removed by performing the following procedure three times: the crude viscous

residue in the evaporation flask was triturated with hexanes (50 mL), and the volatile components were evaporated. The resulting brown viscous liquid was purified by column chromatography [silica, 6 cm x 14 cm, CHCl₃ → CHCl₃/ethyl acetate (1:4)]. Concentration of the eluted product gave a light brown solid (0.55 g, 8.0%): mp 82 °C; ¹H NMR δ 0.00 (s, 9H), 0.90 (t, *J* = 8.4 Hz, 2H), 3.48 (t, *J* = 8.0 Hz, 2H), 5.20 (s, 2H), 5.41 (s, 1H), 5.95–5.97 (m, 2H), 6.11–6.13 (m, 2H), 6.68–6.70 (m, 2H), 6.81–6.82 (m, 1H), 7.57–7.58 (m, 1H), 8.84–8.96 (br, 2H); ¹³C NMR δ –1.2, 17.9, 36.8, 66.7, 76.2, 106.0, 108.2, 116.3, 117.1, 132.3, 137.4, 143.9; Anal. calcd. for C₁₈H₂₆N₄OSi: C, 63.12; H 7.65; N, 16.36. Found: C, 63.05; H 7.83; N, 15.92, FABMS obsd 343.1959, calcd 343.1954 [(M + H)⁺, M = C₁₈H₂₆N₄OSi].

Large Scale Synthesis of 17. Following a general procedure with modification,^{II26,II33} pyrrole (902 mL, 13.0 mol) and aldehyde **16** (29.4 g, 130 mmol) were added to a 2 L single neck round-bottomed flask containing a magnetic stir bar. The solution was degassed with a stream of argon for 30 min. InCl₃ (28.8 g, 130 mmol) was added, and the mixture was stirred under argon at room temperature for 5.5 hours. The mixture turned brown during the course of the reaction. NaOH (156 g, 3.90 mol, 20–40 mesh beads) was added to quench the reaction. Stirring for 1 h afforded a brown mixture. The mixture was filtered through a Büchner funnel. The contents of the flask and the filtered material were washed with a small amount of pyrrole. The filtrate was concentrated for 2.5 h using a rotary evaporator under vacuum (0.2 mm Hg). The collected pyrrole was set aside. Traces of pyrrole were removed by performing the following procedure three times: the crude viscous residue in the evaporation flask was triturated with hexanes (150 mL), and the volatile components were evaporated. The resulting brown viscous liquid was purified by column chromatography

[silica, CHCl₃ containing 1% TEA → CHCl₃/ethyl acetate (1:4) each containing 1% TEA] to afford a light brown solid (1.8 g, 4.0%). Characterization data (¹H NMR, FABMS) were consistent with the values reported above.

10,11-Bis(9-borabicyclo[3.3.1]non-9-yl)-1-(4-methylbenzoyl)-5-[1-(2-trimethylsilyl)ethoxymethyl]imidazol-4-yl]dipyrromethane [(9-BBN)₂18]. Following a published procedure^{II26,II33} with slight modification, a solution of EtMgBr (0.5 mL, 0.5 mmol, 1.0 M in THF) was added slowly to a solution of **17** (86 mg, 0.25 mmol) in THF (0.5 mL) under argon. The resulting mixture was stirred at room temperature for 10 min, and then cooled to -78 °C. A solution of S-2-pyridyl 4-methylbenzothioate (**4**, 57 mg, 0.25 mmol) in THF (0.5 mL) was added. The solution was stirred at -78 °C for 10 min, then warmed to room temperature and stirred for 1 h. The reaction was quenched by addition of saturated aqueous NH₄Cl (2 mL). The mixture was extracted with ethyl acetate (10 mL). The organic layer was washed (water and brine), dried (Na₂SO₄) and filtered. The filtrate was concentrated. The crude product (a red-orange oil) thus obtained was dissolved in CH₂Cl₂ (0.5 mL) and treated with TEA (84 µL, 0.6 mmol) followed by 9-BBN-OTf (1 mL, 0.5 mmol, 0.5 M in hexane) with stirring at room temperature. After 1 h the mixture was poured onto a pad of silica (2 cm x 4 cm) eluting with CH₂Cl₂. The product eluted as a fast moving yellow band, which upon concentration afforded a yellow-orange solid (60 mg, 34%): mp 170–172 °C; ¹H NMR δ -0.02 (s, 9H), 0.62–0.88 (m, 4H), 0.86–0.91 (m, 2H), 1.69–1.83 (m, 12H), 1.92–2.27 (m, 12H), 2.50 (s, 3H), 3.45–3.50 (m, 2H), 5.22 (d, *J* = 2.8 Hz, 2H), 5.70 (s, 1H), 6.04–6.05 (m, 2H), 6.45–6.55 (m, 1H), 6.66 (d, *J* = 4.4 Hz, 1H), 7.28–7.30 (m, 1H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.40–7.45 (m, 1H), 8.17 (d, *J* = 8.0 Hz, 2H), 8.28–8.29 (m, 1H); ¹³C NMR δ -1.3, 17.9, 21.8, 22.1, 23.4, 23.8, 23.9, 25.2, 26.2, 26.4, 29.8, 30.5, 30.6, 30.7, 31.0,

34.4, 34.5, 34.6, 34.7, 38.2, 67.7, 105.5, 105.9, 115.9, 117.9, 120.8, 123.8, 129.1, 129.7, 129.8, 130.0, 131.9, 133.8, 134.8, 142.0, 145.2, 149.2, 174.3; ^{11}B NMR δ 1.44, 12.06; Anal. calcd. for $\text{C}_{42}\text{H}_{58}\text{B}_2\text{N}_4\text{O}_2\text{Si}$: C, 72.00; H 8.34; N, 8.00. Found: C, 71.20; H 8.47; N, 7.39; FABMS obsd 700.4520, calcd 700.4515 ($\text{C}_{42}\text{H}_{58}\text{B}_2\text{N}_4\text{O}_2\text{Si}$); λ_{abs} (THF) 370 nm.

Large Scale Synthesis of $(9\text{-BBN})_2\text{18}$. Following a published procedure^{II26,II33} with slight modification, a solution of EtMgBr (7.7 mL, 7.7 mmol, 1.0 M in THF) was added slowly to a solution of **17** (1.31 g, 3.82 mmol) in THF (3.8 mL) under argon. The resulting mixture was stirred at room temperature for 10 min and then cooled to -78 °C. A solution of S-2-pyridyl 4-methylbenzothioate (**4**, 876 mg, 3.82 mmol) in THF (3.8 mL) was added. The solution was stirred at -78 °C for 10 min then warmed to room temperature and stirred for 1 h. The reaction was quenched by addition of saturated aqueous NH₄Cl (20 mL). The mixture was extracted with ethyl acetate (100 mL). The organic layer was washed (water and brine), dried (Na₂SO₄) and filtered. The filtrate was concentrated. The crude product (a red-orange oil) thus obtained was dissolved in CH₂Cl₂ (7.7 mL) and treated with TEA (1.28 mL, 9.17 mmol) followed by 9-BBN-OTf (15.3 mL, 7.65 mmol, 0.5 M in hexane) with stirring at room temperature. After 1 h, the mixture was poured onto a pad of silica (4 cm x 20 cm) eluting with CH₂Cl₂. The product eluted as a fast-moving yellow band, which upon concentration afforded a yellow-orange solid (0.80 g, 30%). Characterization data (mp, ¹H NMR, FABMS) were consistent with the values reported above.

5,15-Bis(4-methylphenyl)-10,20-bis[1-(2-(trimethylsilyl)ethoxymethyl)imidazol-4-yl]porphyrin [(SEM)₂19**].** Following general procedures^{II25,II33} with slight modification, a sample of NaBH₄ (0.047 g, 1.25 mmol, 25 molar equiv) was carefully added in small portions to a stirred solution of $(9\text{-BBN})_2\text{18}$ (0.029 g, 0.040 mmol) at 0 °C in THF/MeOH (3:1, 1.2

mL). The reaction was monitored by TLC (silica, CH₂Cl₂). The reaction was complete after 1 h, so the reaction was quenched with saturated aqueous NH₄Cl solution and then poured into CH₂Cl₂ (10 mL). The organic layer was separated, washed with water, and then dried (Na₂SO₄). The solvent was then removed to afford the carbinol as orange oil. The carbinol (~0.040 mmol) was immediately dissolved in CH₂Cl₂ (10 mL), and Yb(OTf)₃ (20 mg, 32 μmol, 3.2 mM) was added. The solution instantly darkened, and the reaction was monitored by absorption spectroscopy. After 2 h, the spectroscopic yield of porphyrin had essentially leveled off, and then DDQ (17 mg, 75 μmol) was added and the mixture was stirred at room temperature for 1 h. Then TEA (10 μL) was added, and the entire reaction mixture was filtered through a pad of silica (CH₂Cl₂ → ethyl acetate) until the eluent was no longer dark. Removal of solvent gave a dark solid, which upon purification by column chromatography [silica, CH₂Cl₂/ethyl acetate (1:1)] gave a purple solid (4.0 mg, 22%): ¹H NMR δ –2.75 to –2.71 (br, 2H), 0.10 (s, 18H), 1.11 (t, *J* = 8.0 Hz, 4H), 2.72 (s, 6H), 3.86 (t, *J* = 8.0 Hz, 4H), 5.67 (s, 4H), 7.57 (d, *J* = 8.0 Hz, 4H), 7.80–7.82 (s, 2H), 8.11 (d, *J* = 8.0 Hz, 4H), 8.15–8.17 (m, 2H), 8.87 (d, *J* = 4.8 Hz, 4H), 9.20 (d, *J* = 4.8 Hz, 4H); LDMS obsd 883.0; FABMS obsd 883.4362, calcd 883.4300 [(M + H)⁺, M = C₅₂H₅₈N₈O₂Si₂]; λ_{abs} (THF) 422, 517, 558 nm; λ_{em} (CH₂Cl₂) 670, 725 nm.

Zn(II)-5,15-Bis(4-methylphenyl)-10,20-bis[1-(2-(trimethylsilyl)ethoxymethyl]imidazol-4-yl]porphyrin [(SEM)₂Zn19]. Following a general procedure,^{II34} a solution of porphyrin (SEM)₂**19** (12 mg, 14 μmol) in CHCl₃/MeOH (4 mL, 3:1) was treated with Zn(OAc)₂·2H₂O (77 mg, 0.35 mmol, 25 equiv). The reaction mixture was stirred at room temperature for 12 h. The reaction was quenched with water and extracted with ethyl acetate. The organic layer was separated, dried (Na₂SO₄), concentrated

and chromatographed [silica, CH₂Cl₂ → CH₂Cl₂/ethyl acetate (1:1)] affording a purple-green solid (12 mg, 91%): ¹H NMR δ -0.14 (s, 9H), 0.17 (s, 9H), 0.55 (t, *J* = 8.4 Hz, 2H), 1.86–1.88 (m, 2H), 2.45 (s, 1H), 2.62 (t, *J* = 7.6 Hz, 2H), 2.85 (s, 6H), 3.94 (t, *J* = 7.6 Hz, 2H), 4.25 (s, 2H), 5.66 (s, 1H), 5.74 (s, 2H), 5.89 (d, *J* = 4.4 Hz, 2H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.70 (d, *J* = 6.4 Hz, 2H), 7.89 (s, 1H), 7.98 (d, *J* = 6.8 Hz, 2H), 8.24 (s, 1H), 8.29 (d, *J* = 4.0 Hz, 2H), 8.55 (d, *J* = 7.2 Hz, 2H), 9.01 (d, *J* = 4.4 Hz, 2H), 9.28 (d, *J* = 4.8 Hz, 2H); LDMS obsd 945.6; FABMS obsd 944.3358, calcd 944.356 (C₅₂H₅₆N₈O₂Si₂Zn); λ_{abs} (THF) 417, 433, 572 nm; λ_{em} (CH₂Cl₂) 620, 675 nm.

Mg(II)-5,15-Bis(4-methylphenyl)-10,20-bis[1-(2-(trimethylsilyl)ethoxymethyl]imidazol-4-yl]porphyrin [(SEM)₂Mg19]. Following a general procedure for magnesium metalation,^{II35} a solution of (SEM)₂**19** (2 mg, 2 μmol) in anhydrous CH₂Cl₂ (1 mL) was treated with a solution of MgI₂–DIEA in anhydrous ether (1 mL) and the reaction mixture was stirred at room temperature for 18 h. TLC showed the formation of a single porphyrinic product. The crude was diluted with CH₂Cl₂ and washed with 5% aqueous NaHCO₃ solution. The organic layer was dried over Na₂SO₄ and concentrated to obtain the product in quantitative yield (2 mg): LDMS obsd 903.5, 1807.5; calcd 904.3915 (C₅₂H₅₆N₈O₂Si₂Mg); λ_{abs} 424, 513, 585 nm.

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Chapter III: Investigation of Water Soluble Imidazolium-Porphyrins

III.A. Abstract

Water-soluble porphyrins are valuable for various biological and medicinal applications. A series of porphyrins each bearing a single imidazole group was prepared. Each imidazole-porphyrin was treated with an alkylation reagent (ethyl iodide, 1,3-propane sultone, or 1,4-butane sultone) to afford the corresponding imidazolium-porphyrin. The water solubility of these porphyrins was investigated at various pH values (0, 7, 8). Each porphyrin was dissolved in water at a given pH value mentioned above, and UV-VIS spectroscopic analysis was carried out. Each imidazolium-porphyrin was soluble in at least one of these aqueous solutions (pH 0, 7, or 8). The triflate salt of a *trans*-AB porphyrin was soluble at pH 0, whereas most of the porphyrins were soluble at pH 7 or 8 or at both pH 7 and 8. The presence of sulfoalkyl groups instead of alkyl groups in the imidazolium-porphyrins afforded a significant increase in water solubility (0.05 mM vs. 0.001 mM). A *trans*-AB-porphyrin bearing one carboxylic acid and one imidazolium group was prepared for bioconjugation applications. This work establishes the foundation for the rational synthesis of a variety of water-soluble porphyrinic compounds containing imidazole units.

III.B. Introduction

Water solubility of organic molecules is frequently required for biological applications. Water-soluble porphyrins are invaluable as photosensitizers in biological applications. Imidazolyl iron-porphyrins are important mimics of heme-containing proteins. In heme-containing systems, an imidazole side chain typically binds to the apical iron site *via* an imidazole-iron coordinate bond. Synthetic imidazolyl metalloporphyrins with water solubilizing groups might serve as more appropriate mimics of heme in natural systems. Imidazolyl-porphyrins are also important due to the mimicry of self-assembly in photosynthetic bacteria (*bacteriochlorophyll c*), where metal-imidazole coordination serves to drive supramolecular interactions in the self-assembled architecture. While not directly related to the porphyrin application, it should be mentioned that water-soluble dialkylimidazoles also serve as novel solvents (e.g., ‘ionic liquids’^{III1,III2}) for various organic reactions.

In the literature, water solubility of porphyrins is typically regarded as “some solubility of a compound at a pH range 0 to 14”.^{III3} The extent of water solubility of a porphyrin depends on a number of attributes. Among them, the presence of charge impacts considerably on water solubility. The order of water solubility is $\pm 4 > \pm 3 > \pm 2 > \pm 1$, where \pm stands for the charge present in a porphyrin.^{III3} In the case of an imidazolyl-porphyrin, the imidazole unit requires derivatization to form a charged species, thereby imparting water solubility. In a dialkylimidazolium-porphyrin, at least one or two charges are present to impart water-solubility. A variety of dialkylimidazolyl-porphyrins have been described in the literature. Most of these water-soluble porphyrins contained either two^{III4} or four^{III5} dialkylimidazolyl substituents at the *meso*-positions. The alkyl groups were either methyl or

ethyl. These porphyrins showed water solubility over the pH range of 6-8. Bis(sulfoalkyl)imidazolyl-porphyrins have not been described previously. Some examples of room temperature ionic liquids based on imidazoles have been reported that contain bis(sulfoalkyl) substituents.^{III6} Such compounds are water-soluble. The synthesis of these compounds was achieved under a variety of conditions (room temperature, reflux or microwave conditions).^{III1,III2,III6}

Sulfoalkyl groups have been employed extensively to improve hydrophilicity and aqueous solubility of a variety of compounds such as dyes, nucleosides, proteins and polymers. Sulfoalkyl derivatives of fatty acids have been shown to have antistatic properties. *N*-Sulfopropylated acridines were recently introduced as chemiluminescent probes in the diagnostic industry.^{III7} Sulfoalkyl groups can be introduced by the reaction of a nucleophile with an alkane sultone. A variety of alkane sultones are commercially available at low cost.^{III7} The presence of alkyl or sulfoalkyl groups in the imidazolyl-porphyrins can potentially impart water solubility and make these porphyrins valuable for biological applications.

Here we report the synthesis and solubility properties of bis-alkylated imidazolyl-porphyrins. Each porphyrin bears only one imidazole moiety and is of the *trans*-A₂B or *trans*-AB type. A series of studies was performed to alkylate *trans*-A₂B and *trans*-AB porphyrins bearing one imidazole group, including one porphyrin suitable for bioconjugation applications. Various groups (ethyl, 4-sulfobutyl, 3-sulfopropyl) were attached to the imidazolyl-porphyrins to achieve water solubility. The degree of water solubility of these porphyrins at various pH values was assessed by absorption spectroscopy. This work provides a substantial improvement in methods for preparing water-soluble imidazolium-

porphyrins bearing one imidazole unit. The availability of porphyrins bearing a defined number of imidazole groups opens a variety of new research opportunities, including the possibility of preparing compact water-soluble bioconjugatable porphyrins for applications in the life sciences.

III.C. Results and Discussion

A. Control Reactions with Various Substituted Imidazoles.

To understand the reactivity of imidazoles with sultones under microwave^{III7} and room temperature conditions, a variety of control reactions were carried out (Chart III.1). Those that gave promising results were subsequently applied to imidazolyl-porphyrins. The results are summarized below:

(i) 1-Butyl imidazole was reacted with two equivalents of 1,4-butane sultone (neat) under microwave conditions (Emerson household microwave oven, power 800 W) for 30 sec, affording a brownish solution. Water was added to this crude mixture, and the mixture was then filtered. The filtrate was then extracted with ether and toluene to remove any unreacted starting material. The resulting aqueous layer was dried to afford 3-sulfonyl-1-butyl imidazole **A1** in 90% yield. ¹H NMR analysis was performed using D₂O.

(ii) Imidazole-2-carboxaldehyde was reacted with 1,4-butane sultone (neat) under microwave irradiation for 30 sec. Water was added to this crude mixture, and the mixture was then filtered. The aqueous layer was then extracted with ether and toluene to remove any unreacted starting material. The resulting aqueous layer was concentrated to dryness. ¹H NMR analysis (D₂O) revealed the presence of a mixture of monosulfoalkyl and

bis(sulfoalkyl) product (**B2** and **B1**) in a 1:4 ratio. This reveals that the major component formed was a bis(sulfoalkyl) product.

(iii) To assess the effect of substitution on alkylation, 4(5)-bromoimidazole was reacted with 1,4-butane sultone under microwave conditions for 30 sec. Washing of the residue with ether and toluene followed by ^1H NMR analysis (D_2O) showed the formation of monosulfoalkyl and bis(sulfoalkyl) products **C2** and **C1** in 1:4 ratio. Hence, irrespective of the substituents, microwave treatment generated a mixture of products.

(iv) To observe the effect of microwave irradiation on the SEM-protecting group, a sample of imidazole-2-carboxaldehyde **2** was reacted with 1,4-butane sultone (neat) under microwave conditions for 30 sec. After adding water, the crude mixture was extracted with ether and toluene to remove any starting material. The aqueous layer was separated and concentrated. The ^1H NMR spectrum in D_2O showed the product **D1** along with large amounts of water-soluble byproducts. We suspect partial decomposition of the SEM-group under microwave conditions generated extensive amount of byproducts.

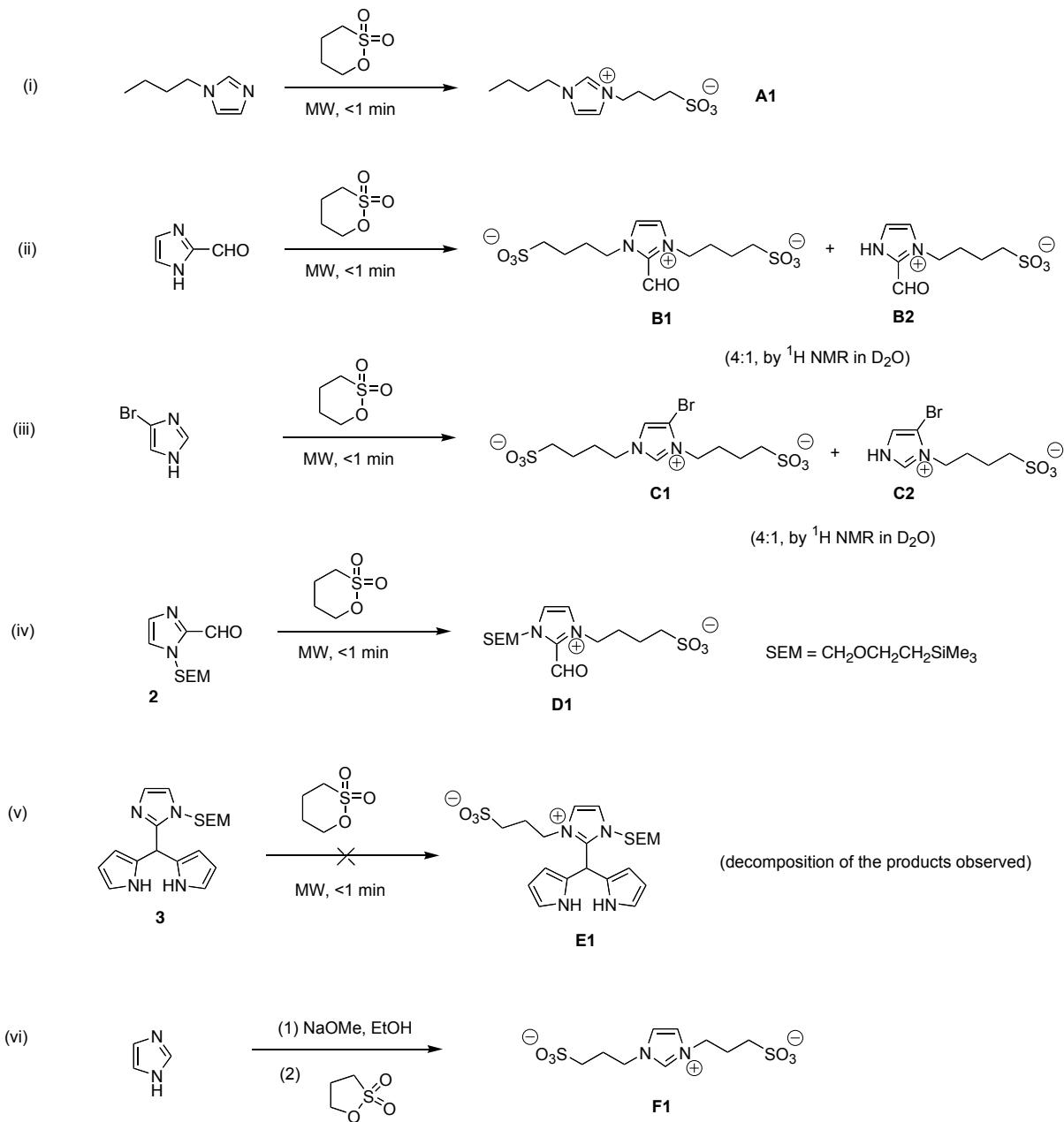
(v) We also carried out a reaction between 5-(imidazol-2-yl)-dipyrromethane **3** and 1,4-butane sultone (neat) under microwave conditions for 30 sec. Washing of the crude mixture with organic solvents (ether and toluene) followed by ^1H NMR study (D_2O) revealed the presence of extensive byproducts with no formation of the desired sulfoalkyl product **E1**. This experiment indicates extensive decomposition or polymerization of the dipyrromethane under microwave conditions.

(vi) Since the microwave conditions proved to be too drastic for dipyrromethanes, we performed control reactions under milder conditions.^{III6} Imidazole was treated with NaOMe in EtOH for 3.5 h at room temperature. 1,3-Propane sultone was then added to the mixture

and the resulting mixture was stirred for 20 h at room temperature. The resulting product was washed twice with EtOH and then dried in a vacuum oven at 60 °C for 3 hours to afford **F1**. ¹H NMR analysis (D₂O) showed only the bis(sulfoalkyl)imidazolium compound. The formation of the desired product was also confirmed by ESI-MS. Since this procedure does not produce the monosulfoalkyl product as a byproduct, this method can be applied for bis(sulfoalkylation) of the nitrogen atoms of the imidazolyl-metallocporphyrins.

Chart III.1

Control Reactions with Various Imidazole Derivatives



B. Solubility Test for Imidazolium-Porphyrins.

We tested the solubility of the porphyrins in various solvents in the following way:

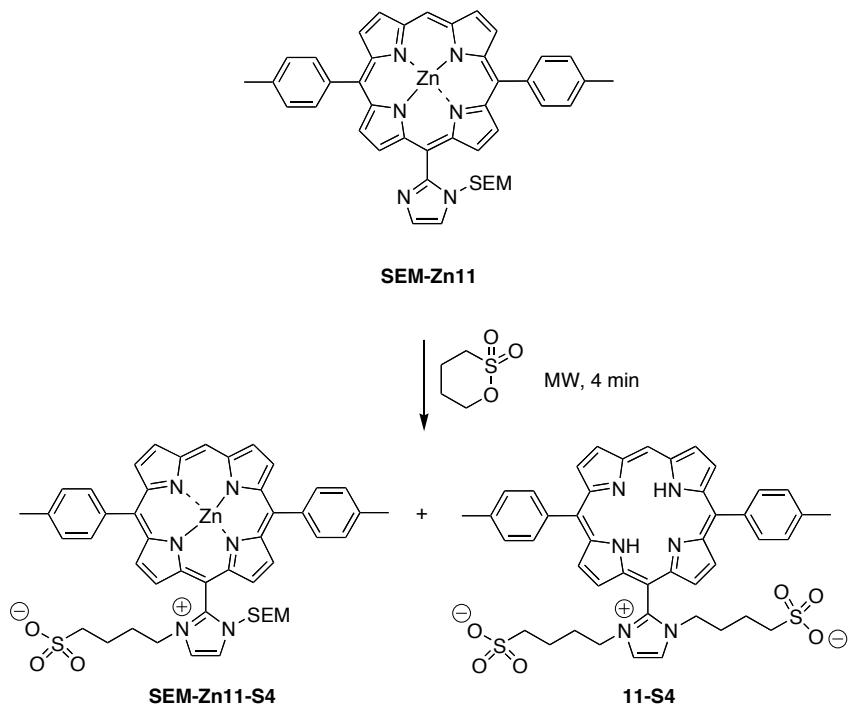
Each of the derivatized porphyrins was dissolved in a solvent in a cuvette. UV-VIS

spectroscopic analysis was performed in that solvent. If a strong Soret band (with a clear base line and with minimum noise) was observed, the porphyrin is considered to be soluble. In the case of observation of a weak Soret band from a porphyrin in water, 2-3 drops of saturated NaHCO₃ solution were added (pH 8, as obsd using pH paper) and then UV-VIS spectroscopic analysis was carried out. In a few cases, the porphyrin was found to be soluble at pH 0 (by the addition of HOTf to the aqueous suspension of porphyrin).

C. Survey of the Synthesis and the Solubility of Various Dialkylimidazolium-Porphyrins.

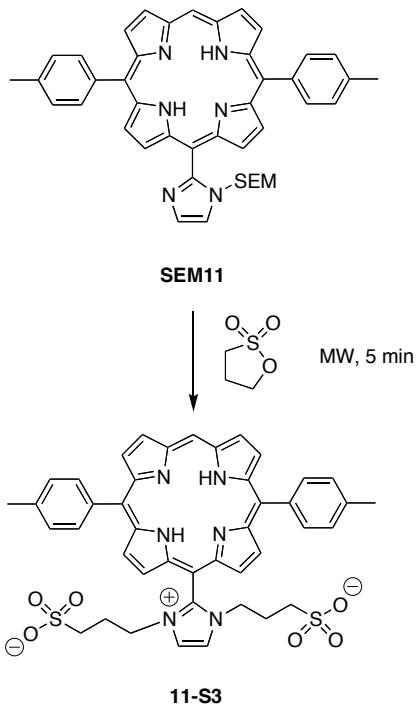
1. SEM-Protected *Trans*-A₂B Zinc-Imidazolium-Porphyrin. SEM-protected porphyrin **SEM-Zn11** was reacted with neat 1,4-butane sultone under microwave conditions for 4 min. The crude mixture was analyzed by LDMS analysis, which showed peaks at *m/z* = 828.1 and 886.1 (Scheme III.1). The latter peak is consistent with the formation of **SEM-Zn11-S4** as a major product, whereas the former peak represents **11-S4** as a minor product. The crude mixture was water soluble at pH 8, and UV-VIS analysis in water showed the Soret band at 413 nm (Table III.1). However, due to the presence of only one sulfoalkyl group and one SEM-group on the imidazole, **11-S4** was not a compound of interest, and hence the products were not analyzed further.

Scheme III.1



2. SEM-Protected *Trans*-A₂B Imidazolium-Porphyrin. We have also reacted free base imidazolyl-porphyrin **SEM-11** with neat 1,3-propane sultone under microwave conditions for 5 min (Scheme III.2). The LDMS analysis of the crude mixture revealed the presence of three porphyrins: (i) the starting porphyrin, (ii) a peak at $m/z = 799.9$ corresponding to the desired porphyrin **11-S3** and (iii) a peak at $m/z = 1007.9$ implies the presence of a higher analog of a sulfoalkyl porphyrin, presumably due to excessive alkylation of one of the pyrrolic nitrogen atoms in the porphyrin. The crude porphyrinic mixture was water soluble at pH 8, but the absence of control over the alkylation of pyrroles of the free base porphyrin precluded use of this route (Table III.2).

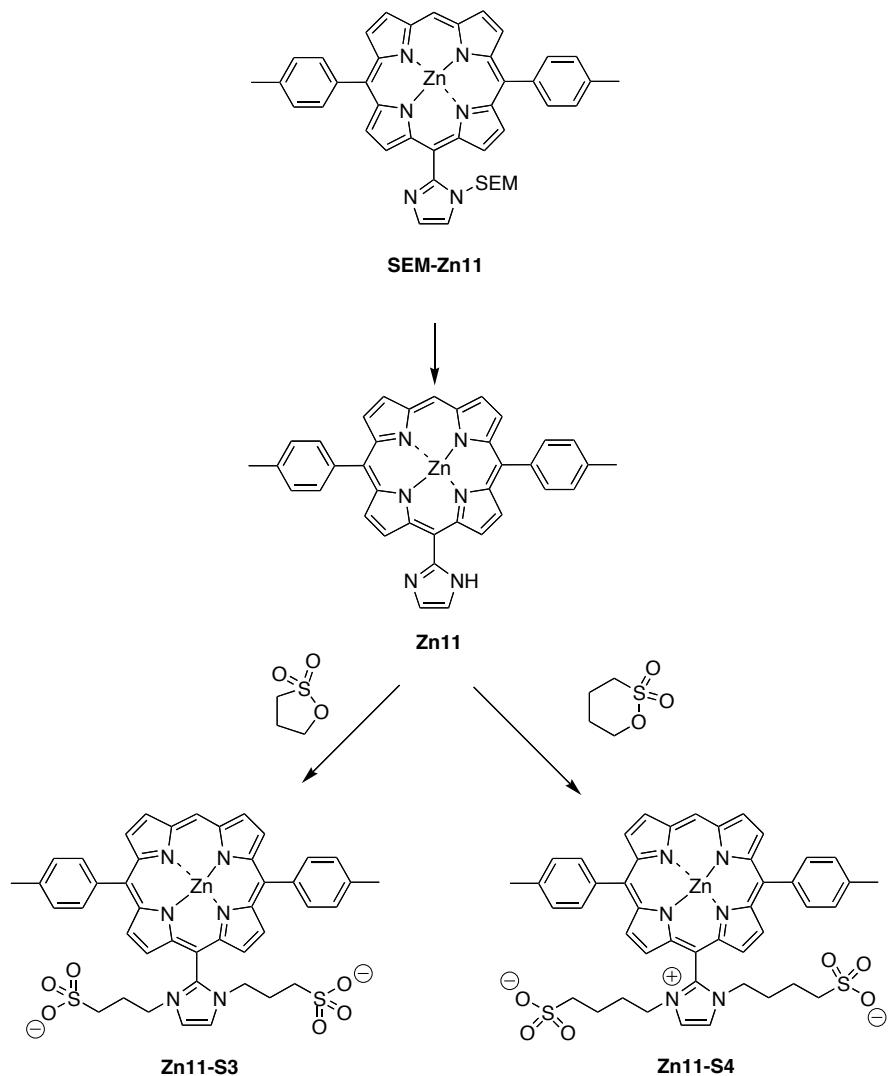
Scheme III.2



3. Removal of the SEM-Group from the *Trans*-A₂B Imidazolyl Porphyrin SEM-Zn11. The SEM-protected porphyrin **SEM-Zn11** was unsuitable for the synthesis of the water-soluble porphyrins under microwave conditions. Thus, we removed the SEM-group from **SEM-Zn11** to obtain **Zn11** (Scheme III.3). First, **SEM-Zn11** was treated with LiBF₄ and NaOH in water. The mixture was then refluxed for 15 h in MeCN (Entry 1, Table III.3). Upon TLC analysis, a small amount of the desired product was observed along with the presence of the starting material. Afterwards, MeCN was removed from the reaction mixture. THF was added to the solid residue, and the mixture was refluxed for 20 h. This approach also failed to achieve complete consumption of the starting material and thereby afford the deprotected porphyrin. So, water was added and the mixture was extracted with ethyl acetate. The organic layer was then separated and concentrated. The resulting solid residue was treated with THF and TBAF, and the mixture was then refluxed for 22 h (Entry

2, Table III.3). In this case, complete consumption of the starting material along with the formation of the desired product **Zn11** was confirmed by TLC and LDMS analysis. To the crude mixture, buffer (pH 7) was added. The aqueous layer was extracted with ethyl acetate. The organic layer was then separated and concentrated. Purification of the crude product by column chromatography afforded porphyrin **Zn11**. A single peak corresponding to porphyrin **Zn11** was observed on LDMS analysis, but a satisfactory ^1H NMR spectrum could not be obtained, probably due to extensive aggregation.

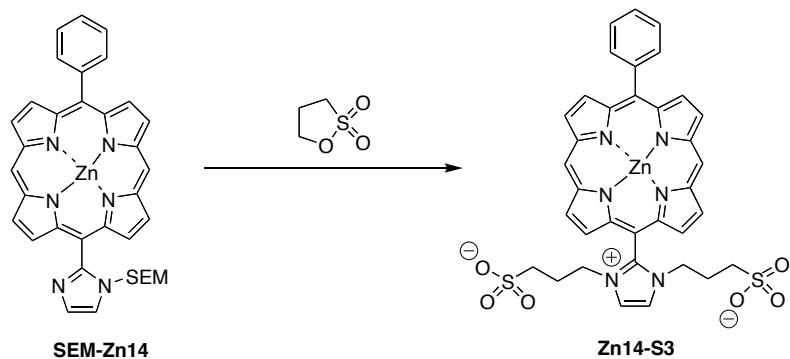
Scheme III.3



4. Sulfoalkylation of SEM-Deprotected *Trans*-A₂B Zinc Imidazolyl Porphyrin. A series of experiments (Scheme III.3) was performed using **Zn11** to synthesize the sulfoalkyl porphyrin products (**Zn11-S3** or **Zn11-S4**) and examine their water solubility. The results of the synthetic attempts are summarized in Table 4. There were instances where the desired porphyrins were formed. But the resulting porphyrins are not promising candidates for biological applications due to their sparing solubility in water.

5. Sulfoalkylation of SEM-Protected *Trans*-AB Imidazolyl Porphyrin. The *trans*-A₂B-type sulfoalkyl metalloporphyrins were sparingly soluble in water. Hence we moved to free-base *trans*-AB porphyrins for the synthesis of water-soluble porphyrins. *Trans*-AB porphyrin **SEM-Zn14** was treated with several sulfoalkylation reagents under various conditions (Scheme III.4). The results for the formation of the sulfoalkyl-porphyrin **Zn14-S3** are tabulated below (Table III.5). In most cases, starting material or extensive byproducts were observed upon LDMS analysis. The only instance where the product was observed on ESI-MS analysis was accompanied by the presence of the starting material (Entry 1, Table III.5). Hence, we abandoned the synthesis of water-soluble porphyrins from the SEM-protected porphyrin **SEM-Zn24**.

Scheme III.4



6. Deprotection of the SEM-Group from *Trans*-AB Imidazolyl Porphyrin. SEM-protected porphyrin **SEM-Zn14** was found to not be a suitable candidate for the synthesis of a water-soluble porphyrin. We decided to remove the SEM-group from **SEM-Zn14**. A mixture of porphyrin **SEM-Zn14** and TBAF was refluxed in THF for 26 h to afford **Zn14** (Scheme III.5).^{III8} After concentrating the reaction mixture, the solid residue was washed repeatedly with water. Insolubility of **Zn14** in organic solvents (CH_2Cl_2 and ethyl acetate) restricted us to extraction using organic solvents. The product was sparingly soluble in THF and in hot DMF. TLC and LDMS showed only one porphyrin **Zn14**. However, ^1H NMR spectrum was too complicated.

Porphyrin **Zn14** was found to be insoluble in neutral water, but the addition of a drop of HOTf to the aqueous suspension of porphyrin **Zn14** brought the porphyrin into solution (Chart III.2). The pH of the resulting solution was 0. The observation of a sharp Soret band at 417 nm on UV-VIS spectroscopic analysis at pH 0 implied the water solubility of **Zn14-T**. The formation of the porphyrin was confirmed by ESI-MS analysis. Due to the solubility of the porphyrin **Zn14-T** in highly acidic medium, the product was not analyzed further.

Scheme III.5

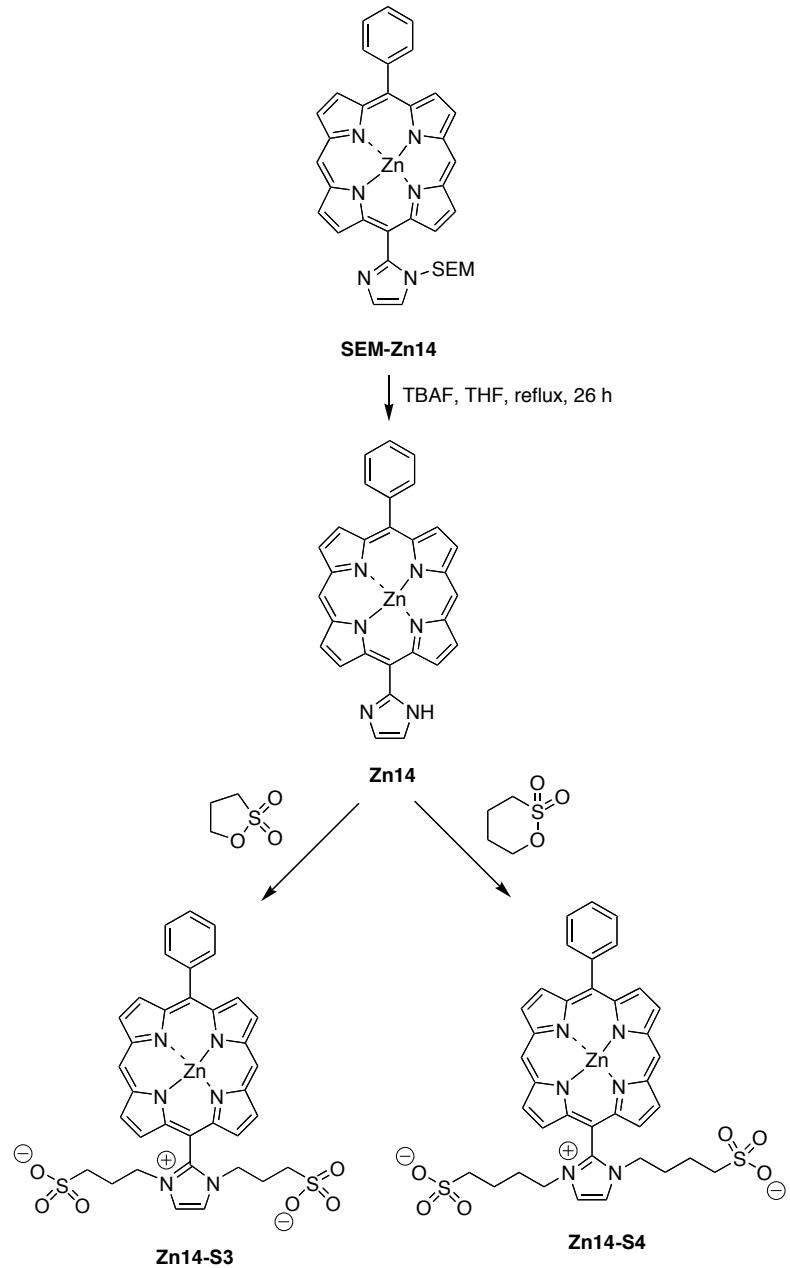
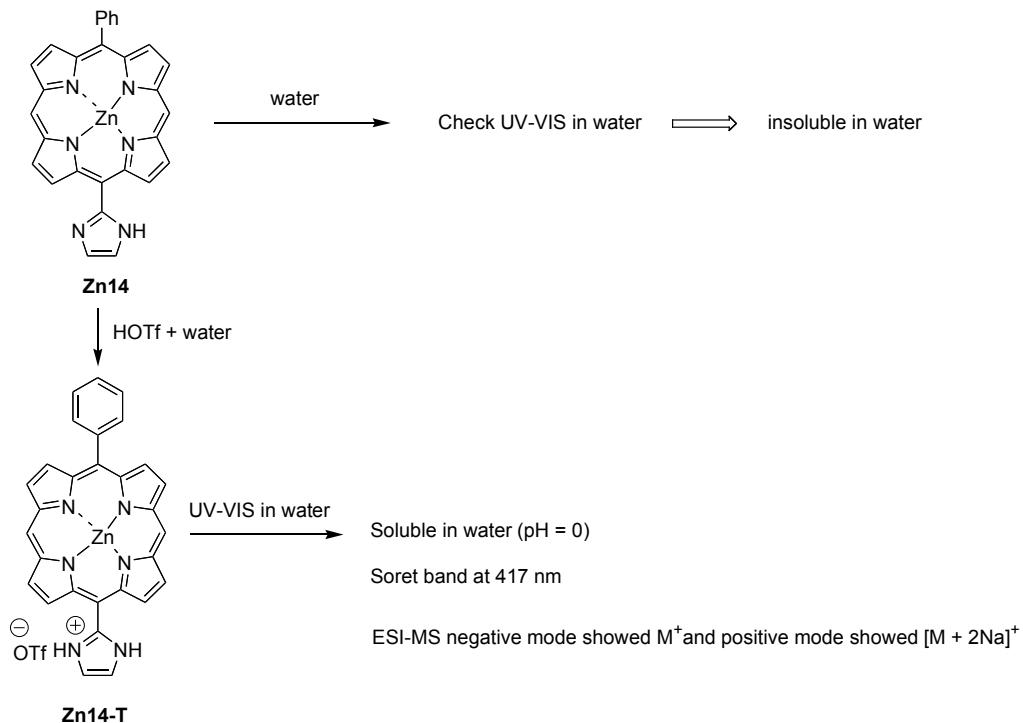


Chart III.2

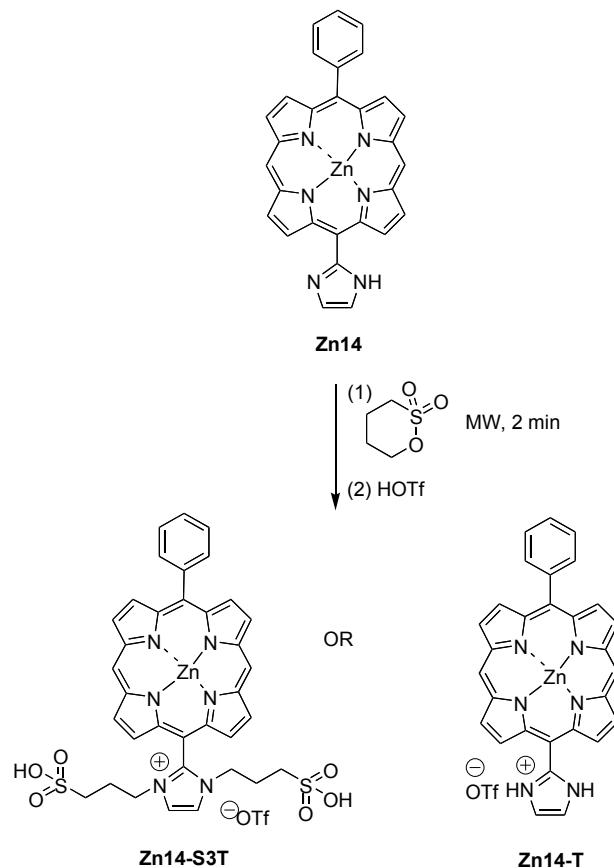


7. Sulfoalkylation of *Trans*-AB Imidazolyl Porphyrin. After successful deprotection of the SEM-group^{III8} to obtain **Zn14**, a sample of **Zn14** was treated with 1,3-propane sultone under various reaction conditions (Scheme III.5). The results are summarized below (Table III.6). Only one reaction was found promising (Entry 1) where the product was observed in ESI-MS analysis, but the product was formed in trace amounts. Porphyrin **Zn14** was reacted with 1,4-butane sultone in DMF under various reaction conditions (Scheme III.5). The results are listed below (Table III.8). In many reactions (Entry 1, 2 and 3), formation of the water-soluble product was noticed.

Porphyrin **Zn14** was reacted with neat 1,4-butane sultone under microwave conditions for 2 min (Table III.8). The crude mixture was then washed with toluene and water. On addition of HOTf to the resulting mixture, the immediate formation of a greenish color in the aqueous layer was observed (Chart III.3). This resulting aqueous layer was

separated which had a pH = 0. The UV-VIS analysis revealed water solubility of the resulting porphyrin at pH = 0 whereas it was insoluble at pH 8. ESI-MS analysis revealed a peak at m/z = 710.8, which is consistent either with the absence of one SO₃ group from the desired product **Zn14-S3T**, or with **Zn14-T** cationized with two Na⁺ ions. Since the solubility of the resulting porphyrin in water was at highly acidic pH, the porphyrin was not suitable for biological applications. Hence no further characterization was performed.

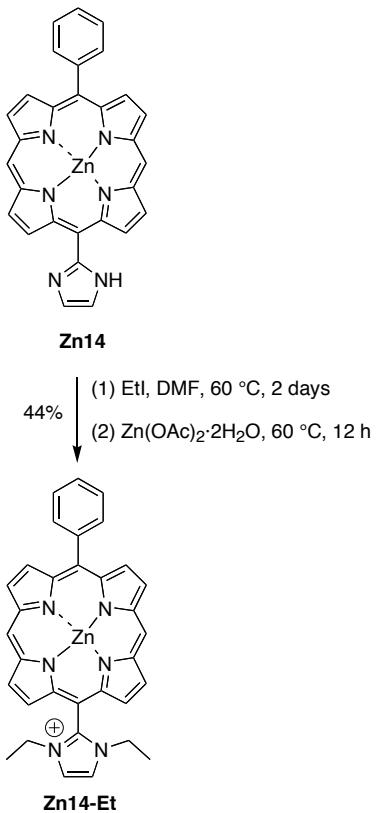
Chart III.3



8. Diethylation of *Trans*-AB Imidazolyl Porphyrin. From a series of experiments, sulfoalkyl imidazolyl-porphyrins were found to be water-soluble. Subsequently, we were interested in investigating the water-solubilizing effect of diethylation of imidazolyl-porphyrins. For this purpose, **Zn14** was treated with excess EtI (25 equiv) in DMF and the

mixture was heated at 60 °C for 2 days. After 2 days, LDMS showed the formation of the product along with the formation of the demetalated species. Hence, the crude mixture was treated with excess Zn(OAc)₂·2H₂O (25 equiv) and the mixture was heated at 60 °C for 12 h. LD-MS analysis of the crude product showed the product **Zn14-Et**. Chromatographic purification afforded **Zn14-Et** in 44% yield (Scheme III.6). This resulting porphyrin was found to be soluble in water at pH 8. A satisfactory ¹H NMR spectrum was observed in CD₃OD.

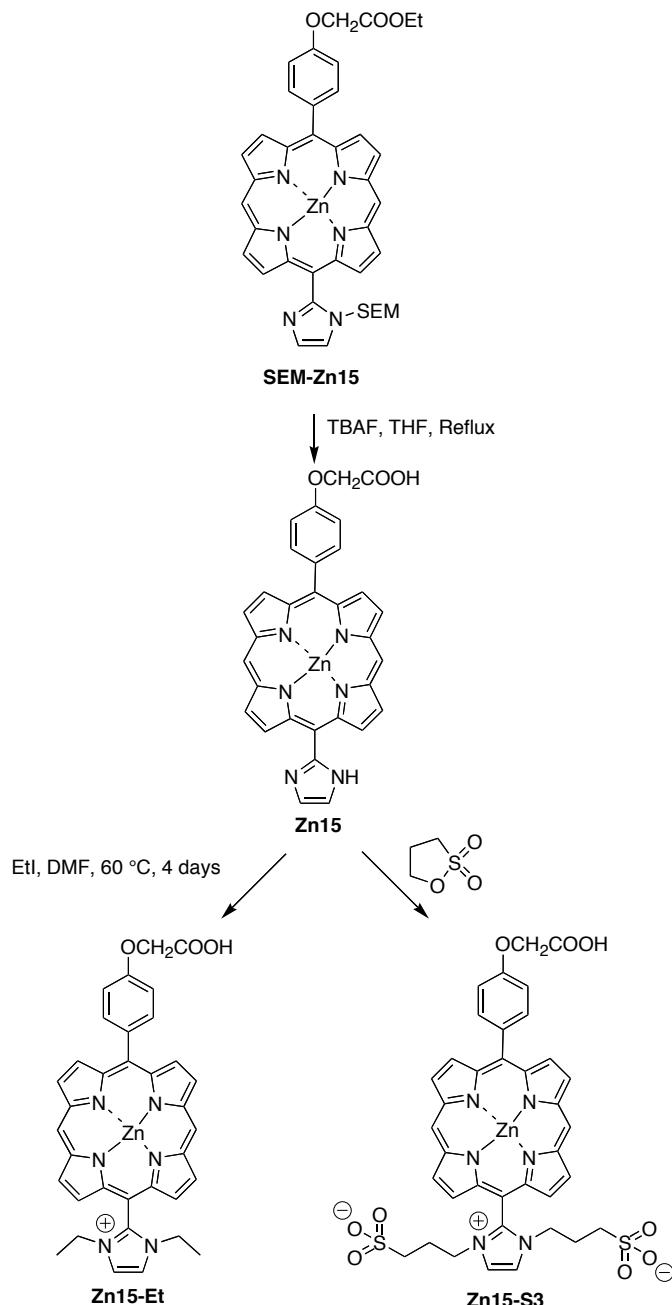
Scheme III.6



9. Removal of the SEM-Group from the Imidazolyl Porphyrin SEM-Zn15. A mixture of porphyrin **SEM-Zn15** and TBAF was refluxed in THF for 2 days.^{III8} The crude mixture was diluted with water and ethyl acetate. The organic layer was separated and

concentrated affording **Zn15** (Scheme III.7). The resulting porphyrin **Zn15** was found to be sparingly water soluble at pH 8.

Scheme III.7



10. Bisalkylation of Imidazolyl Porphyrin **Zn15.** Porphyrin **Zn15** was treated with EtI (25 equiv) in DMF and the mixture was heated at 60 °C for 4 days. LD-MS analysis of

the crude product showed the desired diethylated product **Zn15-Et** (Scheme III.7) and other unknown byproducts. The crude mixture of porphyrin **Zn15-Et** was sparingly soluble in water at both pH 7 and 8 (Table III.9).

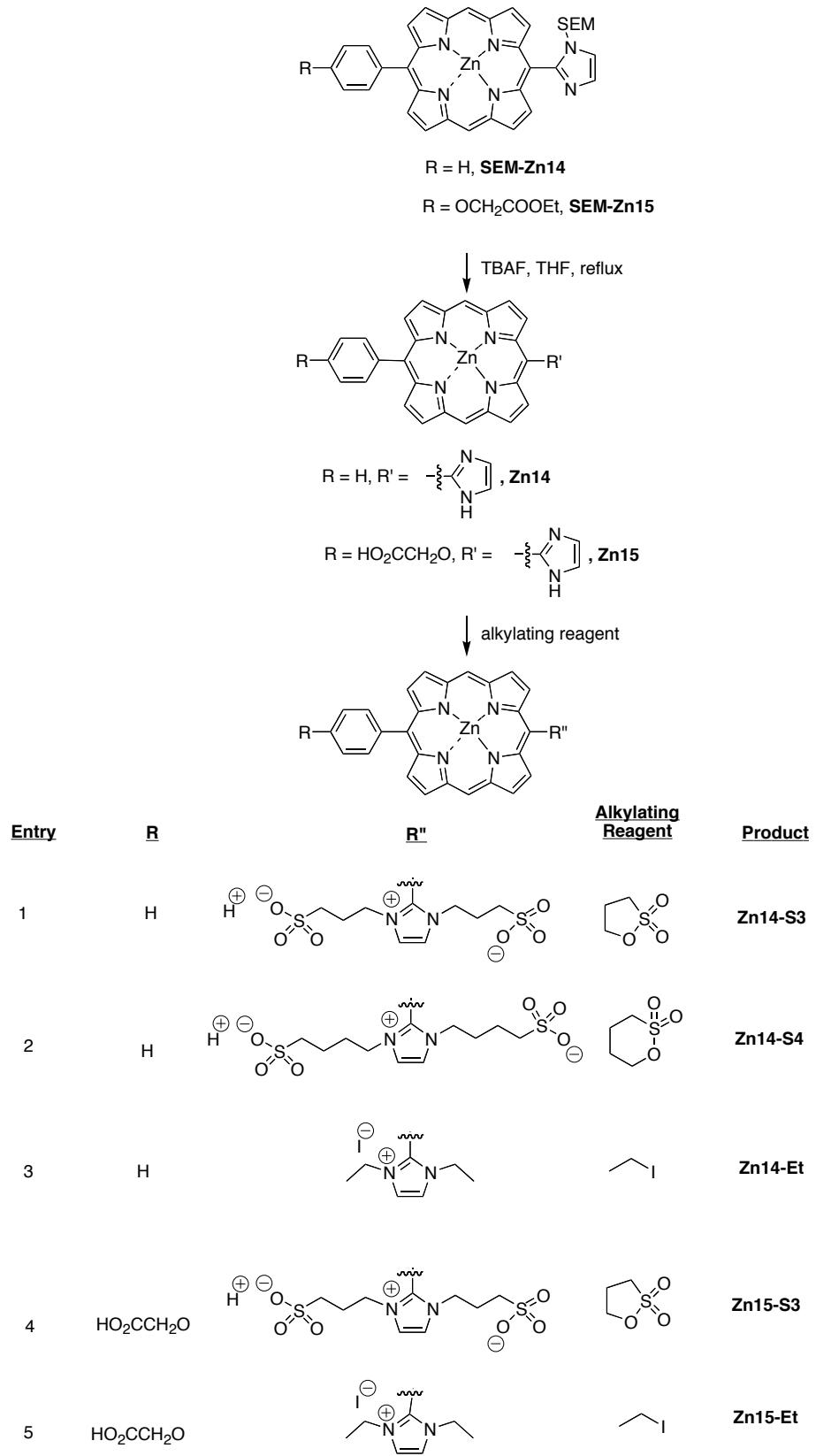
11. Sulfopropylation of Imidazolyl Porphyrin Zn15. A mixture of porphyrin **Zn15** and NaH was heated at 60 °C in DMF for 15 h (Scheme III.7). The resulting mixture was then treated with 1,3-propane sultone and heating was continued for 4 days (Entry 1, Table III.10). LDMS analysis of the crude reaction mixture indicated that **Zn15-S3** was not formed. A mixture of porphyrin **Zn15** and 1,3-propane sultone (25 equiv) was heated at 60 °C in DMF for 4 days (Entry 2, Table III.10). After removal of the solvent under high vacuum, water was added to the crude mixture. ESI-MS analysis showed the formation of porphyrin **Zn15-S3** as a single product. UV-VIS spectroscopic analysis in water showed a sharp peak at 413 nm (Soret band), indicating the water solubility of porphyrin **Zn15-S3**. The addition of 2-3 drops of saturated NaHCO₃ solution to the aqueous solution of porphyrin resulted in a red shift to 418 nm of the Soret band.

D. Synthesis of Water-Soluble *Trans*-AB Imidazolium-Porphyrins.

We have carried out an extensive search for finding the optimum conditions for the synthesis of the water-soluble dialkylimidazolium-porphyrins as well as the best water-solubilizing motif for the imidazolium-porphyrins. The results are summarized below. From the survey, the best conditions for the synthesis of the water-soluble imidazolium-porphyrins were identified and were applied to scale up and obtain characterization data of the water-soluble porphyrins.

The two *trans*-AB porphyrins **SEM-Zn14** and **SEM-Zn15** were deprotected by treatment with TBAF in refluxing THF,^{III8} affording **Zn14** and **Zn15**, respectively (Chart III.4). In each case, evaporation of the solvent yielded a solid residue that had poor solubility in organic solvents (CH₂Cl₂, ethyl acetate, THF and DMF). The porphyrin residue showed a single component by TLC and the expected molecule ion peak by LDMS analysis, but did not afford a satisfactory ¹H NMR spectrum (MeOH, DMF). The sample was washed repeatedly with water to remove excess TBAF and then used directly in derivatization reactions.

Chart III.4



Porphyrins **Zn14** and **Zn15** were subjected to alkylation with excess alkylating reagents, including ethyl iodide, 1,3-propane sultone, and 1,4-butane sultone. The reaction conditions examined include use of various bases (NaOMe, NaH), solvents (methanol, DMF, acetone, neat), and reaction conditions (room temperature, ≥ 80 °C, microwave) over various durations (5 min to 3 days). Porphyrins **Zn14** and **Zn15** each bear a single imidazole group. Bis-alkylation of the imidazole is required to impart charge. Direct evidence for bis-alkylation was sought primarily by mass spectrometry (LD-MS, FAB-MS and/or ESI-MS) (Table III.11). Supporting evidence was sought by TLC analysis. In addition, the porphyrin samples were examined by dissolution in CH₂Cl₂, a solvent where the presence of a free imidazole nitrogen results in aggregation of the metalloporphyrin. In bis-alkylated porphyrins, the samples gave a sharp absorption spectrum, indicative of a homogeneously dispersed sample.

The preferred reaction conditions employed include (1) EtI in (25 equiv) in DMF at 60 °C; (2) NaOMe and THF followed by alkane sultone in DMF at 60 °C (for **Zn14**); and (3) alkane sultone in refluxing CH₃CN (for **Zn15**). Application of these conditions afforded the products shown in chart III.4. The specific results are as follows:

- The reaction of **Zn14** with 1,3-propane sultone under a variety of reaction conditions afforded only a trace amount of product **Zn14-S3**.
- The treatment of **Zn14** with NaOMe and THF followed by the reaction with 1,4-butane sultone in DMF gave the bis-alkylated product **Zn14-S4** in 40% yield.
- The treatment of **Zn14** with excess EtI (25 equiv) in DMF at 60 °C gave the product along with the demetalated species after 2 days of reaction. Hence the

crude mixture was treated with excess Zn(OAc)₂·2H₂O (25 equiv) at 60 °C for 12 h. Chromatographic purification afforded **Zn14-Et** in 44% yield.

- The treatment of **Zn15** with EtI (25 equiv) in DMF at 60 °C for 4 days afforded the desired diethylated product **Zn15-Et**.
- The treatment of **Zn15** with 1,3-propane sultone (25 equiv) in CH₃CN at reflux for 3 days afforded **Zn15-S3** in 32% yield.

The mass spectral characterization of the quaternized porphyrins proved erratic. In some cases the product was observed by LD-MS, in others by FAB-MS, yet others by ESI-MS (see Experimental Section) analysis. The diethylimidazolium-porphyrin **Zn14-Et** was the only product that gave a satisfactory ¹H NMR spectrum (in CD₃OD). The porphyrins that gave sharp absorption bands in CH₂Cl₂ include **Zn14-S4**, **Zn14-Et**, and **Zn15-S3**. All five of the porphyrins showed some degree of water solubility (pH 8). The solubility increased in the order **Zn15-Et** < **Zn14-Et** < **Zn15-S3** < **Zn14-S3** ~ **Zn14-S4**. The extent of solubility of these porphyrins in various solvents is summarized below (Table III.12).

III.D. Conclusion

New water-solubilizing motifs have been developed for solubilizing porphyrinic macrocycles. These porphyrins were synthesized in one or two steps starting from non-polar imidazolyl-porphyrins. The bis-alkylation of porphyrins with only one imidazole moiety with an alkyl or sulfoalkyl group was achieved in moderate yields (30-40%). Each dialkylated imidazolium-porphyrin showed some extent of water solubility. Even the sulfoalkyl derivatives of *trans*-A₂B imidazolyl-porphyrins bearing one imidazole and two aryl moieties demonstrated some solubility in water (0.001-0.005 mM). *Trans*-AB

imidazolyl-porphyrins with one imidazole and one aryl group were found to be better precursors than *trans*-A₂B-porphyrins with one imidazole and two aryl groups for the synthesis of water-soluble porphyrins. The triflate derivative of a *trans*-AB imidazolyl-porphyrin was found to be water soluble at pH 0. All other alkyl or sulfoalkyl substituted *trans*-AB imidazolyl-porphyrins were found to be water soluble at pH 7 and 8. The dialkylated *trans*-AB porphyrins had higher solubility in water at pH 8 than at pH 7, whereas the bis-sulfoalkyl *trans*-AB-porphyrins showed better water solubility at pH 7 than at pH 8. However, *trans*-AB-porphyrins with sulfoalkyl chains with ~0.05 mM solubility in water are better candidates for water solubility compared to the alkyl derivatized species with water solubility ~0.001 mM at pH 7. Hence sulfoalkyl-derivatized *trans*-AB-porphyrins can be better candidates for biological applications. Taken together, the requirement for only one dialkylimidazole motif to achieve water solubility opens up an opportunity to design porphyrin-based molecular architectures for various applications in the life sciences.

III.E. Experimental Section

Zn(II)-5-[1,3-bis(4-sulfobutyl)imidazol-2-i um]-10-phenylporphyrin (Zn14-S4).

Following a general procedure,^{III8} a mixture of porphyrin **SEM-Zn14** (32 mg, 0.050 mmol) and TBAF (0.75 mL, 0.75 mmol, 1.0 M in THF) was heated to reflux for 40 h. After removal of the solvent, the solid residue was repeatedly washed with water to remove excess TBAF, affording **Zn14** as a single porphyrinic product (confirmed by LDMS analysis). The sample of **Zn14** (~0.05 mmol) was then treated with NaOMe (11 mg, 0.20 mmol) in THF (5 mL) and the mixture was stirred for 3.5 h at room temperature. The reaction mixture was cooled using an ice bath. A sample of 1,4-butane sultone (0.10 mL, 1.0 mmol) was added, and the mixture was heated to reflux for 2 days. LDMS analysis of the crude reaction mixture did not show formation of the product. The reaction mixture was concentrated to dryness under reduced pressure. 1,4-Butane sultone (0.05 mL, 0.5 mmol) and DMF (5 mL) was added and the mixture was heated at 60 °C for 3 days. After removal of DMF under high vacuum, the residue was washed with ethanol to extract the porphyrinic product. The ethanol-soluble part was concentrated and repeatedly washed with ether to remove excess 1,4-butane sultone. The title compound was obtained as a red solid (16 mg, 40%): LDMS obsd 649.3 [(M – CH₂CH₂CH₂CH₂SO₃)⁺]; ESI-MS obsd 784.0; calcd 785.1 (C₃₇H₃₃N₆O₆S₂Zn²⁺); λ_{abs} (MeOH) 410, 544, 580 nm, λ_{abs} (water) 409, 555 nm.

Zn(II)-5-(1,3-Diethylimidazol-2-i um)-10-phenylporphyrin (Zn14-Et). Following a general procedure,^{III8} porphyrin **SEM-Zn14** (26 mg, 0.040 mmol) was treated with TBAF (1.0 mL, 1.0 mmol, 1.0 M in THF) and the reaction mixture was heated to reflux for 26 h. After removal of the solvent, the solid residue was repeatedly washed with water to remove excess TBAF affording **Zn14** as a single product (confirmed by TLC and LDMS analysis).

Zn14 (~0.04 mmol) was then treated with EtI (0.100 mL, 1.25 mmol) in DMF (0.4 mL) and the reaction mixture was heated at 60 °C for 2 days. Since LDMS of the crude sample showed the formation of the demetalated species along with the desired product **Zn14-Et**, the crude material was treated with Zn(OAc)₂·2H₂O (0.22 g, 1.0 mmol) and the resulting mixture was heated at 60 °C for another 12 h. After removal of DMF under high vacuum, the crude mixture was purified by column chromatography [silica, CH₂Cl₂/MeOH (99:1) → CH₂Cl₂/MeOH (3:1)] to afford a purple solid (10 mg, 44%): ¹H NMR (300 MHz, CD₃OD) δ 0.90 (t, *J* = 6.6 Hz, 6H), 3.96–4.01 (m, 4H), 7.71–7.73 (m, 3H), 8.12 (d, *J* = 6.6 Hz, 2H), 8.29 (s, 2H), 8.72 (d, *J* = 4.8 Hz, 2H), 8.94 (d, *J* = 4.2 Hz, 2H), 9.35 (d, *J* = 4.5 Hz, 2H), 9.52 (d, *J* = 4.5 Hz, 2H), 10.33 (s, 2H); LDMS obsd 571.0; FABMS obsd 571.1609, calcd 571.1589 (C₃₃H₂₇N₆Zn); λ_{abs} (MeOH) 413, 544, 578 nm; λ_{abs} (water at pH 8) 408, 540, 574 nm; λ_{em} (MeOH) 540, 640 nm.

Zn(II)-5-[1,3-bis(3-sulfopropyl)imidazol-2-iun]-10-(4-(carboxymethoxy)phenyl)porphyrin (Zn15-S3). Following a general procedure,^{III8} porphyrin SEM-**Zn15** (22 mg, 0.030 mmol) was treated with TBAF (0.15 mL, 0.15 mmol, 1.0 M in THF) and the reaction mixture was first stirred at room temperature for 2 days and then heated to reflux for 20 h. After removal of the solvent, the solid residue was repeatedly washed with water to remove excess TBAF affording **Zn15** as a single product (confirmed by TLC and LDMS analysis). Porphyrin **Zn15** (~0.03 mmol) was treated with 1,3-propane sultone (55 mg, 0.45 mmol) in CH₃CN (6.0 mL) and the reaction mixture was stirred at room temperature for 2 days followed by reflux for 3 days. After the removal of CH₃CN, the crude mixture was washed repeatedly with ether to remove excess 1,3-propane sultone affording a dark red solid (8.0 mg, 32%): LDMS obsd 708.5 [(M – CH₂CH₂CH₂SO₃)⁺]; ESIMS obsd

416.0 (M/2, positive ionization), calcd 831.1 ($C_{37}H_{31}N_6O_9S_2Zn^-$); λ_{abs} (MeOH) 410, 544, 580 nm, λ_{abs} (water) 412, 558, 587 nm.

III.F. References

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Table III.1. Conditions for the synthesis of a water-soluble porphyrin from an SEM-protected *trans*-A₂B zinc-imidazolyl-porphyrin.

Entry	Reagent	Solvent	Temp.	Time	Formation of Product
1	1,4-BS ^a	neat	MW ^b	4 min	SEM-Zn11-S4 + 11-S4 (4:1)^c

^a1,4-Butane sultone. ^bEmerson household microwave oven (800 watt). ^cThe mixture of products was water soluble at pH 8.

Table III.2. Conditions for the synthesis of a water-soluble porphyrin from an SEM-protected *trans*-A₂B imidazolyl-porphyrin.

Entry	Reagent	Solvent	Temp.	Time	Formation of Product
1	1,3-PS ^a	neat	MW	5 min	11-S3^c

^a1,3-Propane sultone. ^bEmerson household microwave oven (800 watt). ^cThe product was water soluble at pH 8.

Table III.3. Deprotection of an SEM-protected *trans*-A₂B zinc-imidazolyl-porphyrin.

Entry	Reagent	Solvent	Temp.	Time	Formation of Product
1	LiBF ₄ , NaOH	(i) Water, MeCN	Reflux	15 h	No product
		(ii) THF			
2	TBAF	THF	Reflux	22 h	Zn11

Table III.4. Conditions for the synthesis of sulfoalkylated *trans*-A₂B zinc-imidazolyl-porphyrin from an SEM-protected *trans*-A₂B zinc-imidazolyl-porphyrin.

Entry	Reagent	Solvent	Temp.	Time	Formation of Product ^a
1	1,4-BS ^b	Neat	MW ^c	5 min	Zn11-S4 Formed ^d
2	1,4-BS ^b	DMF	Reflux	3 days	Zn11-S4 Formed ^e
3	1,4-BS ^b	DMF	MW ^c	5 min	Zn11-S4 Formed ^f
4	(a) NaOMe;1,4-BS ^b	EtOH	RT	2 h	
	(b) 1,3-PS ^g		RT	2 h	Zn11-S3 did not form

^aFormation on the basis of different analyses. ^b1,4-Butane sultone. ^cEmerson household microwave oven (800 watt). ^dLD-MS showed peaks consistent with (M - SO₃)⁺, (M - 2SO₃)⁺ and (M - 2SO₃C₄H₈)⁺. Purification entailed washing with ether and toluene. The product was sparingly soluble in water at pH = 7. ^eLD-MS showed peaks consistent with (M⁺-23) and (M⁺+18) as well as other unassigned peaks. ^fLD-MS showed (M⁺-23). After washing the crude product with water, the product was soluble in water at pH = 8. Attempts to record a ¹H NMR spectrum in various deuterated solvents (MeOH, THF, DMSO) were unsuccessful. ^g1,3-Propane sultone.

Table III.5. Conditions for the synthesis of a sulfoalkylated *trans*-AB imidazolyl-porphyrin from SEM-protected *trans*-AB zinc-imidazolyl-porphyrin.

Entry	Reagent	Solvent	Temp.	Time	Formation of Zn14-S3^a
1	(a) NaOMe	MeOH	RT	1 day	
	(b) 1,3-PS ^b			1 day	Formed ^c
2	1,3-PS ^b	Acetone	RT	3 days	S.M. ^d
3	1,3-PS ^b	(i) Acetone	RT	36 h	
		(ii) DMF	RT	12 h	
			80 °C	1 day	
			Reflux	2 days	S.P. ^e

^aFormation on the basis of different analyses. ^b1,3-Propane sultone. ^cM⁺ for the product along with the starting material was observed in ESI-MS analysis. ^dStarting material was recovered. ^eS.P. = extensive side products formed.

Table III.6. Conditions for the synthesis of a sulfopropylated *trans*-AB zinc-imidazolyl-porphyrin from *trans*-AB zinc-imidazolyl-porphyrin.

Entry	Reagent	Solvent	Temp.	Time	Formation of Zn14-S3^a
1	(a) NaOMe	EtOH	RT	1 day	
	(b) 1,3-PS ^b		RT	3 days	Trace ^d
2	(a) NaH	DMF	RT	2 h	
	(b) 1,3-PS ^b		80 °C	18 h	
			Reflux	3 days	Unknown ^e
3	(a) NaH	DMF	RT	1 h	
	(b) 1,3-PS ^b		RT	18 h	
			MW ^c	5 min	-- ^f
4	(a) NaH	DMF	RT	1 h	
	(b) 1,3-PS ^b		MW ^c	5 min	S.M. ^g
5	1,3-PS ^b	Acetone	RT	3 days	None ^h
6	1,3-PS ^b	Acetone	RT	36 h	
		DMF	RT	12 h	
			80 °C	1 day	
			Reflux	2 days	None ⁱ
7	1,3-PS ^b	Neat	MW	5 min	S.P. ^k

^aFormation on the basis of different analyses. ^b1,3-Propane sultone. ^cEmerson household microwave oven (Power: 800 watt). ^dNo peak resembling starting material was observed in LDMS analysis; ESI-MS showed small peak of the product. ^eLDMS showed peaks for unidentified products, ^gA peak for the starting material observed in LDMS analysis. ^fwas not

determined. ^hNo product formed. ^jNo peak revealing starting material was observed in LDMS. ^kNo peak from the starting material was observed in LDMS, removal of zinc was observed in UV-VIS analysis, hence the crude was used for metalation.

Table III.7. Conditions for the synthesis of a sulfobutylated *trans*-AB zinc-imidazolyl-porphyrin from *trans*-AB zinc-imidazolyl-porphyrin.

Entry	Reagent	Solvent	Temp.	Time	Formation of Zn14-S4^a
1	1,4-BS ^b	DMF	MW ^c	5 min	Formed ^d
2	1,4-BS ^b	DMF	Reflux	3 days	Formed ^e
3	1,4-BS ^b , TEA	DMF	RT	3 days	Formed ^f
4	(a) NaH	DMF	60 °C	18 h	
	(b) 1,4-BS ^b			2 days	S.P. ^g
5	1,4-BS ^b	DMF	60 °C	3 days	S.P. ^g

^aFormation on the basis of different analyses. ^b1,4-Butane sultone. ^cEmerson household microwave oven (Power: 800 watt). ^dUpon LDMS analysis a peak from the product similar to (M⁺-SO₃) was observed. ^eIn LDMS a peak resembling demetalated product (M⁺-Zn) was observed, UV-VIS analysis showed red shifted Soret band in water. ^fproduct was water soluble (UV-VIS in water showed broad Soret band). ^gCrude LDMS showed a peak for the mono-alkylated product, ESI-MS did not show peaks from mono or di-alkylated product.

Table III.8. Water solubility of a *trans*-AB imidazolyl-porphyrin at pH 0.

Entry	Reagent	Solvent	Temp.	Time	Formation of Product
1	(i) 1,4-BS ^a	neat	MW ^b	2 min	
	(ii) HOTf				Zn14-S4 formed ^c

^a1,4-Butane sultone. ^bEmerson household microwave oven (Power: 800 watt). ^cWater soluble at pH 0 and insoluble in water at pH 8.

Table III.9. Conditions for the synthesis of water-soluble porphyrin from a SEM-protected *trans*-AB imidazolyl-porphyrin.

Entry	Reagent	Solvent	Temp.	Time	Formation of Product
1	TBAF	THF	RT	2 days	Zn15 (WS, pH8) ^a
2	(i) TBAF	THF	RT	2 days	Zn15
	(ii) EtI	DMF	60 °C	4 days	Zn15-Et (Sp Sol) ^b
3	(i) TBAF	THF	RT	2 days	Zn15
	(ii) NaH	DMF	60 °C	15 h	
4	(iii) 1,3-PS ^c	DMF	60 °C	4 days	Zn15-S3 (WS) ^a
	1,3-PS ^c	DMF	60 °C	3 days	Zn15-S3 (WS) ^a

^aWS = water soluble. ^bSp. Sol. = sparingly soluble in water. ^c1,3-Propane sultone.

Table III.10. Conditions for the synthesis of water-soluble porphyrin *trans*-AB imidazolyl-porphyrin.

Entry	Reagent	Solvent	Temp.	Time	Formation of Zn15-S3
1	(i) NaH	DMF	60 °C	4 days	
	(ii) 1,3-PS ^a				No product
2	1,3-PS ^a	DMF	60 °C	4 days	Formed

^a1,3-Propane sultone.

Table III.11: Evidence of dialkylation in imidazolium-porphyrins.

Compound	¹ H NMR	LD-MS	FAB-MS	ESI	TLC	Water Solubility ^b	UV-VIS (CH ₂ Cl ₂) ^a
Zn14-S3	NA ^h	M ⁺ obsd in crude	NA ^h	- ^c	Polar	X	NA ^h
Zn14-S4	Complicate d ^e	M ⁺ – 1BS	- ^c	M ⁺ obsd	Polar (silica, 4:1 CH ₂ Cl ₂ /Me OH)	X	Sharp Soret band
Zn14-Et	Clean NMR in CD ₃ OD	M ⁺ obsd	M ⁺ obsd	NA ^g	Polar ^d (silica, 4:1 CH ₂ Cl ₂ /Me OH)	X ^f	Sharp Soret band
Zn15-S3	Complicate d ^e	M ⁺ – 1PS	- ^c	M ⁺ /2 obsd	Polar (RP 18 silica, 1:1 MeCN/H ₂ O)	X	Sharp Soret band
Zn15-Et	NA ^h	M ⁺ obsd in crude	NA ^g	- ^c	Polar	X ^g	NA ^h

^aIn case of monoalkyl imidazole substituent metalloporphyrin undergoes dimerizaion and generates split Soret band. Conversely, corresponding dialkyl imidazole derivative does not form dimer and hence generates a sharp Soret band. ^bX = compound soluble in water. ^cNot informative. ^dBy TLC analysis of the crude reaction mixture monoalkyl product was observed, which was removed by chromatography. ^eSolvents for NMR analysis are CD₃OD, DMSO-*d*₆, DMF- *d*₆, D₂O. ^fCompound was soluble in water at pH 8. ^gSparingly soluble in water. ^hNA = not applicable.

Table III.12: Solubility of imidazolium-porphyrins.

Compound	DMSO	DMF	Water	MeOH	THF
Zn14-S3	H	H	M	M	I-L
Zn14-S4	H	H	M	M	I-L
Zn14-Et	H	M-H	L-M	H	M
Zn15-S3	M	M	L-M	L	I
Zn15-Et	M	M	I-L	M-H	M

I = Insoluble = $<10^{-6}$ mM

L = Low Solubility = 0.001 - 0.01 mM

M = Medium Solubility = 0.01 - 0.05 mM

H = High Solubility = > 0.1 mM

Chapter IV: Refined Synthesis of 2,3,4,5-Tetrahydro-1,3,3-trimethyldipyrrin, a Deceptively Simple Precursor to Hydroporphyrins

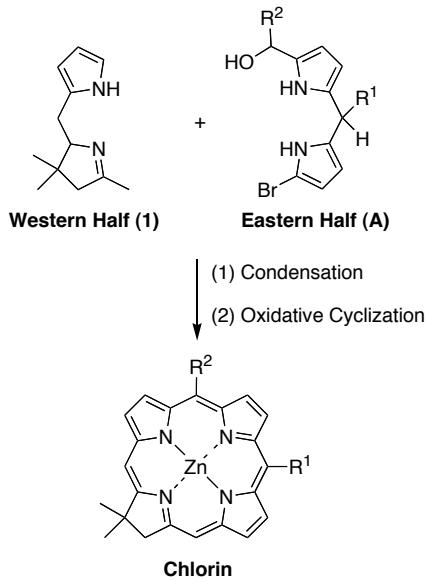
IV.A. Abstract

2,3,4,5-Tetrahydro-1,3,3-trimethyldipyrrin (**1**) is a crucial building block in the rational synthesis of chlorins and oxochlorins. The prior 5-step synthesis of **1** from pyrrole-2-carboxaldehyde (**2**) employed relatively simple and well-known reactions yet suffered from several drawbacks, including limited scale (≤ 0.5 g of **1** per run). A streamlined preparation of **1** has been developed that entails four steps: (i) nitro-aldol condensation of **2** and nitromethane under neat conditions to give 2-(2-nitrovinyl)pyrrole (**3**), (ii) reduction of **3** with NaBH₄ to give 2-(2-nitroethyl)pyrrole (**4**), (iii) Michael addition of **4** with mesityl oxide under neat conditions or at high concentration to give γ -nitrohexanone-pyrrole **5**, and (iv) reductive cyclization of **5** with zinc/ammonium formate to give **1**. Several multistep transformations have been established, including the direct conversion of **2** \rightarrow **1**. The advantages of the new procedures include (1) fewer steps, (2) avoidance of several problematic reagents, (3) diminished consumption of solvents and reagents, (4) lessened reliance on chromatography, and (5) scalability. The new procedures facilitate the preparation of **1** at the multigram scale.

IV.B. Introduction

Hydroporphyrins (e.g., chlorins, bacteriochlorins, isobacteriochlorins) are naturally occurring pigments with diverse functions. Methods for preparing chlorins have been aimed at total syntheses of naturally occurring compounds as well as more simple syntheses of chlorins for use in a variety of applications.^{IV1} We recently developed rational syntheses of non-natural chlorins^{IV2- IV4} (Scheme IV.1) and oxochlorins^{IV5} by extending routes developed by Battersby for the synthesis of naturally occurring hydroporphyrins.^{IV6} The synthesis entails reaction of an Eastern half (**A**) with a Western half (**1**) to form a tetrahydobilene-*a*, which upon oxidative cyclization affords the zinc chlorin. The Eastern half is easily available.^{IV2, IV4, IV7} However, the synthesis of the Western half has presented a number of challenges.

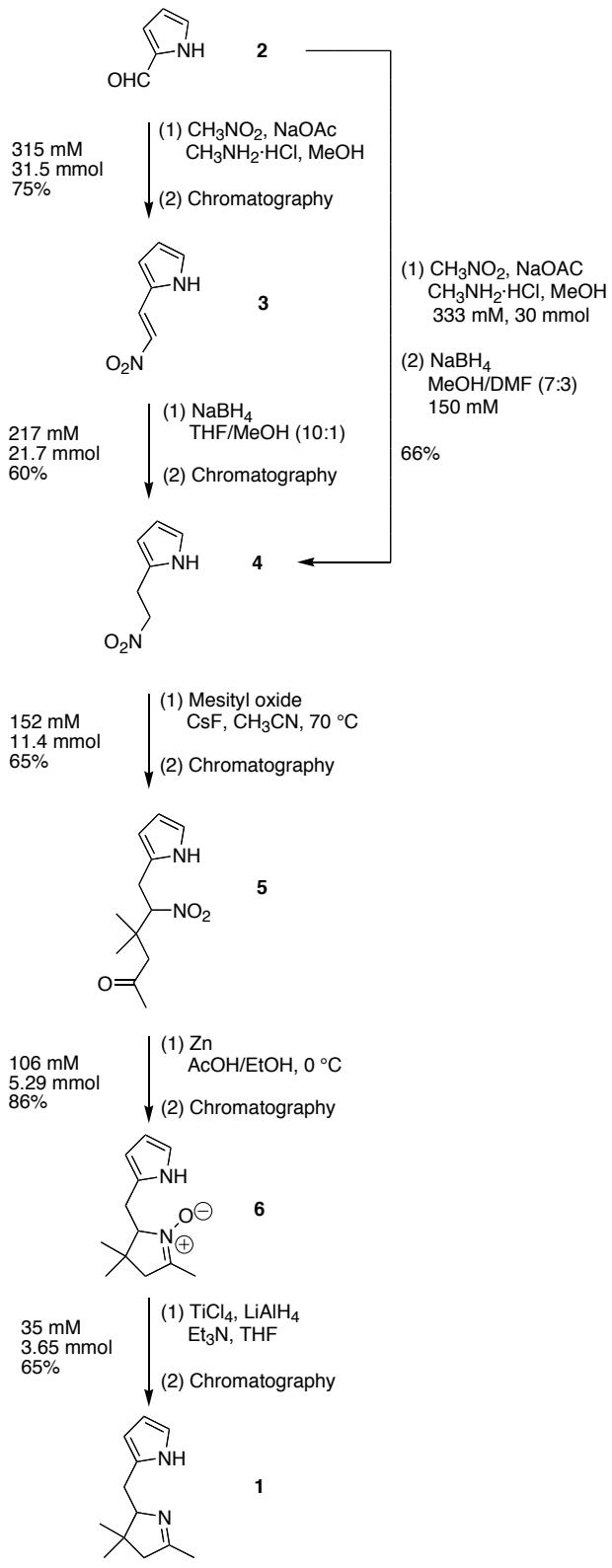
Scheme IV.1



Our previous route to **1**, which entailed five steps, is summarized in Scheme IV.2. The synthesis involved (i) nitro-alcohol condensation of pyrrole-2-carboxaldehyde (**2**) with nitromethane,^{IV2} (ii) NaBH₄ reduction of nitrovinylypyrrole **3**,^{IV2} (iii) Michael addition of

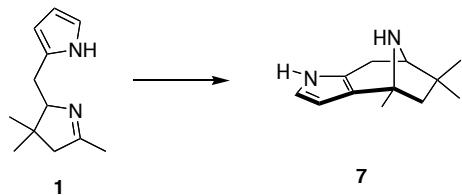
nitroethylpyrrole **4** to mesityl oxide,^{IV2} (iv) reductive cyclization of nitrohexanone **5** by Zn/AcOH,^{IV4} and (v) deoxygenation of *N*-oxide **6** using Ti(0) prepared *in situ*.^{IV2}

Scheme IV.2



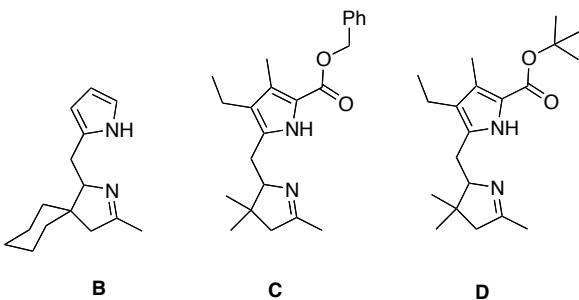
Compound **1** appears quite simple, but the appearance is deceptive because the two different heterocycles (pyrrole, pyrroline) present quite distinct reactivity. The complexity of the chemistry presented by **1** is as follows: (1) the pyrrole contains three open sites for electrophilic substitution, (2) the pyrrole is activated toward electrophiles by the 2-alkyl substituent, (3) the imine is susceptible to reduction and addition, (4) the imine nitrogen can coordinate to metals, (5) the pyrrole is a weak acid whereas the pyrroline is a weak base, and (6) the α -pyrrolic methylene is susceptible to oxidation. In addition, tetrahydrodipyrin **1** undergoes intramolecular cyclization in the presence of acid, forming a pyrrolo[3.2.1]azabicyclooctane byproduct (**7**) (eqn IV.1).^{IV4} Precursors **2-6** also are sensitive to a number of reaction conditions. Thus, the scope of suitable synthetic methods is limited.

Eqn IV.1



One of the significant structural differences between **1** and tetrahydrodipyrinic analogues reported earlier by Battersby (Chart IV.1, compounds **B** and **C**)^{IV6} is that the latter have two β -substituents in the pyrrolic ring, whereas **1** and derivatives thereof (**D**)^{IV5} typically have no pyrrolic β -substituents.

Chart IV.1



In general, tetrahydrodipyrins lacking β -pyrrolic substituents have been prepared in lower overall yield, and have required milder reaction conditions than the more stable β -substituted species. Indeed, treatment of **C** in neat TFA at room temperature yields the decarboxylated tetrahydrodipyrin, which is stable to the strong acid,^{IV6} whereas **1** undergoes slow cyclization in the presence of dilute TFA to afford the byproduct **7**^{IV4} (eqn IV.1). In addition, the byproduct **7** was observed upon reductive cyclization of nitrohexanone **5** in AcOH, and was the main product upon attempted deoxygenation of **5** using Ti(III) at pH 6.^{IV4} Thus, deoxygenation methods developed for β -substituted pyrrolic derivatives provided a low yield of **1**. Regardless, each tetrahydrodipyrin was prepared at relatively small scale (448 mg of **1**,^{IV4} 139 mg of **B**,^{IV6} 914 mg of **C**,^{IV6} 228 mg of **D**^{IV5}). Attempts to increase the scale of synthesis of **1** met with several obstacles. First, each intermediate was purified by chromatography. Some synthetic steps required low concentrations and a large excess of reagents, hence increasing the scale was prohibitive in terms of solvent and materials consumption. Moreover, the yields of most of the synthetic steps decreased substantially upon increasing the scale, which we attributed to the instability of the various reactants under the conditions employed.

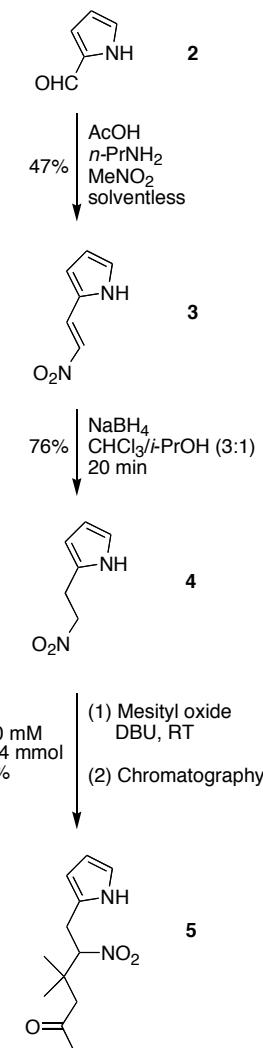
Here we report a refined preparation of **1** that proceeds in reasonable yield, with limited chromatography, and diminished consumption of solvents and reactants. The number of steps in the synthesis has been reduced from five to four, two or one. Taken together, the improvements have enabled the routine preparation of **1** at 60-mmol scale to afford 2.5 g of product in shorter time (3 days), or at medium scale (0.4 mol) to give 11 g of **1** (22 times more than reported previously). Application of this methodology to substituted analogues of **1** will be described elsewhere.

IV.C. Results and Discussion

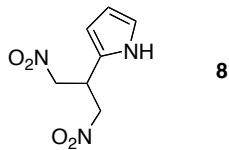
I. Refinement of Individual Transformations. A. Nitro-alcohol Condensation (2** → **3**).** The typical conditions for the nitro-alcohol condensation of pyrrole-2-carboxaldehyde require the presence of an ammonium salt and/or weak base. The condensation of pyrrole-2-carboxaldehyde with a nitroalkane typically is done in the presence of one of the following: ammonium acetate,^{IV8} ammonium acetate with microwave irradiation,^{IV9} ethylenediamine,^{IV10} sodium acetate,^{IV11} or a mixture of methylamine hydrochloride and sodium acetate.^{IV2-IV6} The latter reagent affords superior results for *N*-unprotected pyrrole-2-carboxaldehydes, whereas the former reagents are more suitable for *N*-substituted pyrrolic derivatives. However, methylamine hydrochloride is scrutinized by U. S. drug enforcement agencies owing to use in methamphetamine syntheses; hence, we searched for a comparable reagent for the first step of the synthesis. The amine must be easily removed from the reaction mixture (to proceed to the next step without laborious workup) and enable reaction at high concentration or even under solventless conditions (to diminish the use of solvents in large-scale preparations).

Various catalytic systems for the nitro-alcohol condensation were examined to identify conditions that meet three objectives: (1) complete consumption of **2**, (2) good yield of product **3**, and (3) little or no black byproducts. The cleanest reaction and the mildest condition were obtained with **2** dissolved in a 3-fold excess of nitromethane (no other solvent) containing AcOH/*n*-PrNH₂ (0.60 equiv/0.55 equiv) at room temperature (Scheme IV.3).

Scheme IV.3



The reaction is complete within 2-3 h. The ratio of AcOH/*n*-PrNH₂ is critical. A slight excess of *n*-propylamine caused formation of a significant amount of dark byproducts, which interfered with the work-up and resulted in a lower yield. On the other hand, a slight excess (0.57-0.60 equiv) of acetic acid provided a relatively clean product with minor amounts of dark byproducts. The small excess of acid also diminished the Michael addition of nitromethane to the 2-(2-nitrovinyl)pyrrole (**3**), which forms the ostensible byproduct (2-(2-pyrrolyl)-1,3-dinitropropane (**8**)).



An analogous byproduct was observed upon similar reaction of a 3-(4-iodophenyl)-2-(2-nitrovinylypyrrole.^{IV3} A small amount of **8**, which was detected in the crude reaction mixture, can be easily separated by precipitation of **3** from CH₂Cl₂/hexanes. Another problem encountered was an exothermic reaction between AcOH and *n*-PrNH₂. Therefore, the salt was prepared in a small amount of methanol in a separate flask and then transferred to the solution of pyrrole-2-carboxaldehyde.

Another issue was the choice of workup procedure suitable for the next step. 2-(2-Nitrovinylypyrrole (**3**) is somewhat unstable, therefore for this reason alone, chromatography should be avoided. Treatment of the crude reaction mixture with NaBH₄ (in an appropriate solvent) did not prove fruitful, as 2-(2-nitroethyl)pyrrole (**4**) was obtained in low yield accompanied by several byproducts. An effective workup was achieved by washing the crude mixture containing **3** with water and then removing excess MeNO₂ under high vacuum.

B. Reduction of 2-(2-Nitrovinylypyrrole (3** → **4**).** The previous synthetic route utilized NaBH₄ in DMF/THF or MeOH/THF.^{IV2,IV4} This procedure required a large excess of NaBH₄ (3.5 mol equiv) and gave a non-reproducible yield at larger scale owing to the formation of byproducts. Moreover, the abundant boron salts caused difficulties in purification of the final product. Use of a different solvent system (CHCl₃/isopropanol, 3:1) in the presence of silica^{IV12} enabled use of a lesser quantity of NaBH₄ (2 mol equiv), diminished the amount of byproducts, and gave the desired product in 76% yield (Scheme IV.3). Additionally, the presence of silica in the reaction mixture facilitated purification.

Most of the impurities were absorbed on the silica, and filtration through a pad of silica afforded the pure **4**.

C. Michael Addition with Mesityl Oxide (4** → **5**).** The previously reported procedures for Michael addition of mesityl oxide and 2-(2-nitroethyl)pyrroles utilized fluoride anion (e.g., TBAF^{IV13} or CsF^{IV2-IV5}) to effect reaction (entry 1, Table IV.1). We examined CsF and other reagents in the reaction of **4** with excess mesityl oxide (10 equiv) that have been reported to be effective for the Michael addition of α,β -enones and nitroalkanes (Al_2O_3 ,^{IV14} DBU,^{IV15} and TMG^{IV16}). The ideal reagent should give a clean reaction, a good yield at high concentration (or even neat conditions), and be easily removed from the reaction mixture. The reaction with CsF in refluxing CH₃CN gave 61% yield (entry 2) but reaction under neat conditions either at 60 °C (entry 3) or room temperature (entry 4) gave no product. Reaction with alumina under neat conditions also gave no product (entry 5). Replacement of CsF with DBU in refluxing CH₃CN gave 50% yield (entry 6). Replacing CH₃CN with THF gave only a trace of product (entries 7 and 8). On the other hand, the reaction with DBU under neat conditions at room temperature gave **5** in high yield (entries 9 and 10). Attempts to use tetramethylguanidine (TMG) in place of DBU gave little or no product (entries 11-13).

The advantages of DBU versus CsF include slightly higher yield, lower cost, absence of solvent, and greater ease of handling (no requirement for desiccation). The results shown in Table IV.1 employ 10 equiv of mesityl oxide and were performed using 1 mmol of **4**. Although mesityl oxide is inexpensive, an excess is unattractive for applications envisaged with more valuable enones. We found that the Michael addition also proceeded well with lesser quantities of mesityl oxide as long as the reaction time was prolonged. Thus,

application of the best conditions (DBU, solventless, room temperature; entry 10) with 10.0 mmol of **4** but only 1.1 equiv of mesityl oxide for 24 h afforded **5** in 78% yield.

D. Reductive Cyclization (5** → **1**).** The previous reduction of nitrohexanone **5** to the tetrahydrodipyrrin **1** was performed in two-steps: cyclization to the *N*-oxide **6** followed by deoxygenation of **6**. This procedure suffers from several problems: (1) the yield of both steps decreased substantially with increasing scale, (2) both steps required a large excess of metal reagents (25 equiv of zinc, 7 equiv of TiCl₄), and (3) the deoxygenation step was done at relatively low concentration (35 mM). To scale-up the synthesis of **1** necessitated a significant improvement in each step.

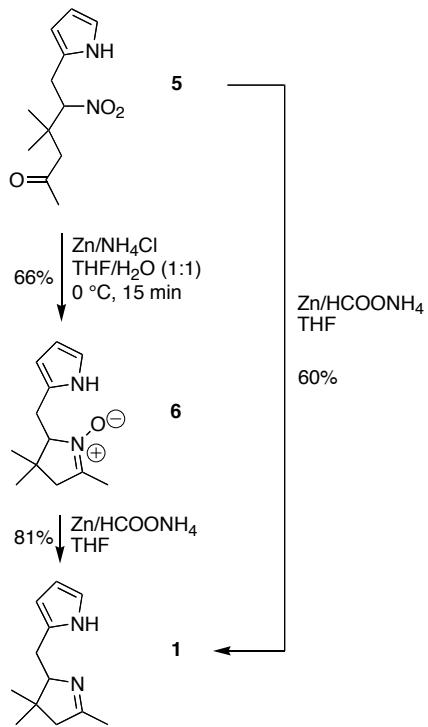
Several mild methods are known for direct reductive cyclization of γ -nitro-ketones to the corresponding cyclic imines,^{IV16} reduction of nitroalkanes to the corresponding amines,^{IV17} or the deoxygenation of *N*-oxides.^{IV18} Some recent pertinent examples include the following:

- (a) γ -nitro-ketones → cyclic imines: Zn/NH₄Cl,^{IV16a} Fe/NH₄Cl,^{IV16b} NiCl₂·H₂O/NaBH₄/NH₂NH₂·H₂O,^{IV16c} Pd-C/HCOONH₄,^{IV16d} and Zn/HCOOH;^{IV16e}
- (b) nitroalkanes → amines: NH₂NH₂·H₂O/graphite,^{IV17a} NH₂NH₂·H₂O/Raney Ni,^{IV17b} Zn/HCOONH₄,^{IV17c} Mg/HCOONH₄,^{IV17d} Mg/NH₂NH₂,^{IV17e} Zn/NH₂NH₂/HCOOH,^{IV17f} and ZrCl₄/NaBH₄;^{IV17g}
- (c) deoxygenation of *N*-oxides: Pd-C/HCOONH₄,^{IV18a} Zn/HCOONH₄,^{IV18b} In/NH₄Cl,^{IV18c} InCl₃,^{IV18d} Ga/H₂O,^{IV18e} and formic pivalic anhydride.^{IV18f} Earlier methods have been reviewed.^{IV18g}

A survey of reducing agents and conditions was carried out for the direct conversion of the γ -nitro-ketone **5** to the tetrahydrodipyrrin **1** (Scheme IV.4). Generally, we searched for

mild conditions with an aim toward application at >10-g scale. Selected results are shown in Table IV.2. The use of Zn/HCOONH₄ gave preferentially the desired target **1** accompanied by limited amounts of *N*-oxide **6** (entries 1-9). The choice of solvent was critical. Although methanol appeared to provide a good conversion of **5** to **1**, the isolated yield was very low (~10%). We reasoned that the low yield might stem from the formation of a complex between zinc(II) and **1**, as zinc(II) is known to coordinate with the related dipyrin species forming bis(dipyrinato)zinc(II) complexes.^{IV19} Accordingly, THF was used and the isolated yield increased to 60%. The reaction was clean, proceeded at relatively high concentration, and workup was straightforward. Large-scale applications appear viable because the yield remains high upon increasing the scale (up to 0.4 mol), inexpensive off-the-shelf reagents (zinc dust and ammonium formate) are employed, and the reaction is quite robust in not requiring dry solvents or special precautions.

Scheme IV.4



E. Reductive Cyclization and Deoxygenation (5** → **6** → **1**).** In the previous synthesis,^{IV1,IV2} nitrohexanone **5** was converted to *N*-oxide **6** using Zn in the presence of acetic acid. Such conditions are incompatible with a number of functional groups. In the synthesis of **1**, we were content to bypass the preparation of the *N*-oxide **6**. However, *N*-oxides are valuable intermediates in syntheses of functionalized tetrahydropyrrins.^{IV20} Accordingly, we investigated alternatives for the preparation and deoxygenation of *N*-oxide **6**. During the survey of conditions for conversion of **5** → **1**, we found that Zn/NH₄Cl in THF/H₂O preferentially gave the *N*-oxide **6** (Table IV.2, entries 10-17). For the preparative scale, nitrohexanone **5** was dissolved in THF/H₂O (1:1) and treated with Zn/NH₄Cl at 0 °C for 15 min. GC analysis showed 70% of *N*-oxide **6** and 19% of **1**. Chromatography afforded **6** in 66% yield. For the direct deoxygenation of *N*-oxide **6**, we examined a number of reagents (InCl₃, PPh₃/toluene, (MeO)₃P/toluene, CS₂, HCOONH₄/pivaloyl chloride, and Zn/HCOONH₄). Most of the methods caused extensive decomposition of **6** or no reaction. Again, the best result was obtained using Zn/HCOONH₄ in THF, affording **1** in 81% yield.

II. Investigation of Multistep Transformations. Here we investigated a number of approaches to obtain intermediates or the target compound **1** in an expeditious manner.

A. Conversion of **2 → **4**.** Pyrrole-2-carboxaldehyde (**2**) in excess nitromethane was treated with *n*-propylammonium acetate, affording the crude 2-(2-nitrovinylyl)pyrrole (**3**). Workup entailed diluting the crude mixture with CH₂Cl₂, removing the ammonium salt by washing with water, and removing excess nitromethane under high vacuum. The crude **3** was dissolved in CHCl₃/isopropanol (3:1) and treated with 2.0 mol equiv of NaBH₄ in the presence of silica, affording 2-(2-nitroethyl)pyrrole (**4**) in 40% yield.

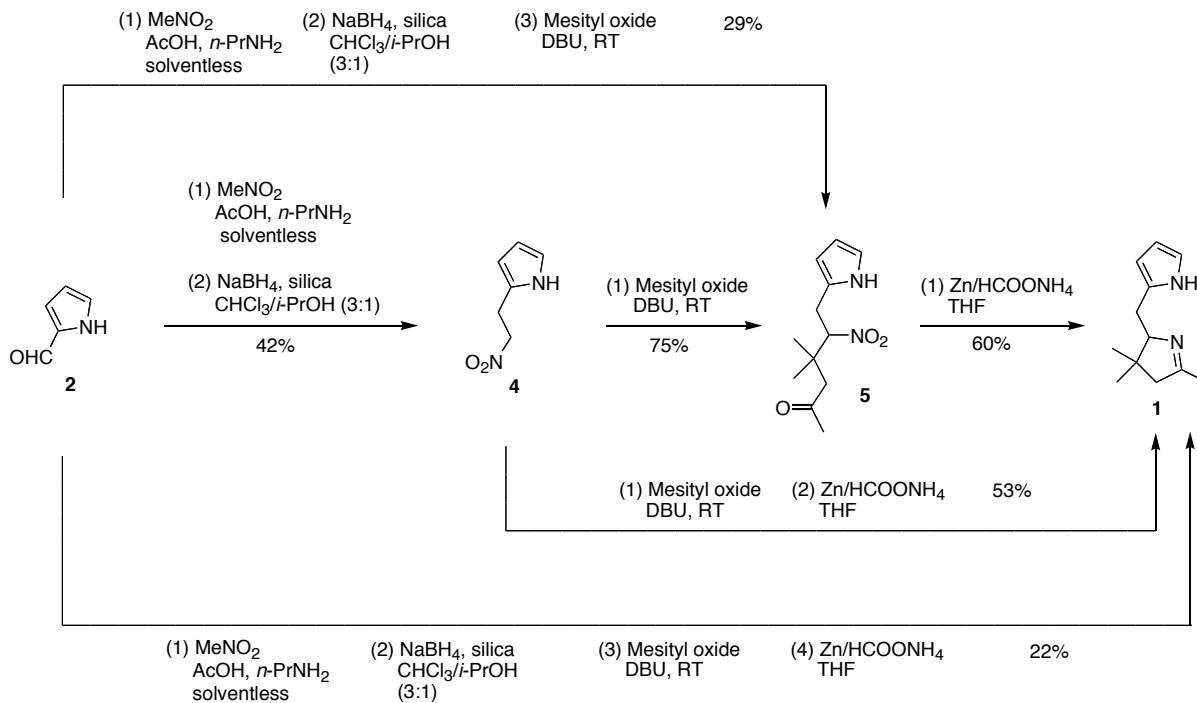
B. Conversion of 4 → 1. The conversion of 2-(2-nitroethyl)pyrrole (**4**) to the desired tetrahydropyrrin **1** was prompted by the observation that GC and TLC analyses of the crude reaction mixture following Michael addition of **4** and mesityl oxide did not show any significant side products. Therefore we employed a two-step, one-flask procedure entailing Michael addition followed by reduction of the crude nitrohexanone **5**. The crude reaction mixture was diluted with ethyl acetate and washed with water; the organic layer was dried; excess mesityl oxide was removed under high vacuum; and the resulting oil was subjected to reductive cyclization using Zn/HCOONH₄. The yield of **1** was 53%.

C. Conversion of 2 → 5. The conversion of pyrrole-2-carboxaldehyde (**2**) to the nitrohexanone-pyrrole (**5**) was carried out by solventless condensation with nitromethane, reduction with NaBH₄, Michael addition with mesityl oxide, and workup including chromatography. The desired **5** was obtained in 29% yield.

D. Conversion of 2 → 1. Taking together all improvements in each of the four steps, the direct conversion of pyrrole-2-carboxaldehyde (**2**) to **1** was investigated (Scheme IV.5). Treatment of a solution of **2** in MeNO₂ with propylammonium acetate afforded crude 2-(2-nitrovinyl)pyrrole **3**. After workup (dilution with CH₂Cl₂, washing with water, removal of excess MeNO₂ under high vacuum), the crude **3** was dissolved in CHCl₃/isopropanol, to which silica was added followed by NaBH₄ (2 mol equiv). After workup (filtration, concentration of the filtrate), the crude **4** (brown-greenish oil) was dissolved in excess mesityl oxide (1.5 equiv), excess DBU (3 equiv) was added, and the Michael addition was performed overnight at room temperature. After workup (dilution with ethyl acetate, washing with water and brine, removal of solvent and excess mesityl oxide under reduced pressure), the crude **5** was dissolved in THF (ACS grade) and treated with excess

Zn/HCOONH₄ for 2 h. Workup (filtration, concentration of the filtrate, and chromatography on silica) afforded **1** as a light-brown solid in 22% overall yield. The tetrahydrodipyrin obtained in this manner from **2** was slightly darker than upon synthesis from a pure sample of the immediate precursor **5**, although the ¹H NMR spectrum did not show any noticeable impurities.

Scheme IV.5



The entire synthesis at the 60-mmol scale afforded 2.5 g of **1** (22% yield) in a 3-day period. The procedure at the 0.4 mol-scale provided ~11 g of **1** (14.5% yield) in one batch, which is 22 times more than reported previously. Compound **1** gave satisfactory elemental analysis data in only one instance (upon preparation from **6**); in all other cases, all other characterization data were satisfactory, and samples of **1** were successfully employed in several syntheses of chlorins. In summary, the valuable tetrahydrodipyrin **1** can be obtained in a stepwise manner *via* streamlined procedures. In addition, a straightforward method has been developed for the direct conversion of pyrrole-2-carboxaldehyde (**2**) to **1** that is

relatively fast, affords reasonable overall yield, employs simple reagents and methods, and has limited reliance on chromatography. Taken together, the availability of expedient routes to multigram quantities of **1** should facilitate entry into numerous hydroporphyrin architectures.

IV.D. Experimental Section

General. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were collected at room temperature in CDCl_3 . Melting points are uncorrected. Column chromatography was performed with flash silica or alumina (80–200 mesh). The CHCl_3 contained 0.8% ethanol. All solvents and reagents were used as received. Zinc was employed in the form of zinc dust. In all cases when a salt (e.g., HCOONH_4) and zinc dust were added to a reaction mixture, the salt was added first. All procedures were performed at room temperature unless noted otherwise.

2-(2-Nitrovinyl)pyrrole (3). A stirred solution of acetic acid (2.00 mL, 35.0 mmol) in methanol (5 mL) under argon at 0 °C was treated dropwise with *n*-propylamine (2.71 mL, 33.0 mmol). The resulting *n*-propylammonium acetate solution was stirred at 0 °C for 5 min, then added dropwise to a stirred solution of **2** (5.70 g, 60.0 mmol) in nitromethane (9.70 mL, 90.0 mmol) at 0 °C. The resulting mixture was stirred at 0 °C. After 15 min, the cooling bath was removed and stirring was continued at room temperature. The color changed from yellow to dark orange during the course of reaction. After 2 h, CH_2Cl_2 (100 mL) was added and the organic phase was washed with water and brine. The organic layer was dried (Na_2SO_4) and concentrated under high vacuum to afford an orange-brown solid. Filtration through a silica pad (CH_2Cl_2) afforded an orange solid, which was dissolved in a minimal volume of CH_2Cl_2 and precipitated with hexanes to afford orange crystals (3.93 g, 47%): mp 110–112 °C (lit.^{IV1} 112–114 °C); ^1H NMR δ 6.38–6.40 (m, 1H), 6.81–6.83 (m, 1H), 7.12–7.13 (m, 1H), 7.48 (d, $^5J = 3.8$ Hz, $^3J = 13.6$ Hz, 1H), 7.99 (d, $J = 13.6$ Hz, 1H), 9.04–9.15 (br. s, 1H); ^{13}C NMR δ 112.9, 119.4, 124.1, 126.5, 129.9, 131.0; Anal. Calcd for

$C_6H_6N_2O_2$: C, 52.17; H, 4.38; N, 20.28. Found: C, 52.31; H, 4.40; N, 20.22; FAB-MS obsd 139.0500, calcd 139.00508 [$(M + H)^+$, $M = C_6H_6N_2O_2$].

2-(2-Nitroethyl)pyrrole (4). Following a published procedure,^{IV12} a solution of **3** (0.138 g, 1.00 mmol) in $CHCl_3$ (9.0 mL) and isopropanol (3.0 mL) was treated with silica (1.2 g). The resulting suspension was treated in one portion with $NaBH_4$ (0.0760 g, 2.00 mmol) under vigorous stirring. The mixture was stirred at room temperature for 20 min, accompanied by a color change from deep yellow to pale brown. The mixture was filtered. The filter cake was washed with CH_2Cl_2 . The combined filtrate was concentrated. The resulting oil was dissolved in CH_2Cl_2 . The organic solution was washed with water and brine. The organic layer was dried (Na_2SO_4), concentrated and subjected to high vacuum to remove traces of isopropanol. The residue was dissolved in a small quantity of CH_2Cl_2 and filtered through a silica pad (CH_2Cl_2) to afford a pale yellow oil (0.106 g, 76%): 1H NMR data were consistent with previously reported values;^{IV2} 1H NMR δ 3.31 (t, $J = 6.8$ Hz, 2H), 4.60 (t, $J = 6.8$ Hz, 2H), 6.00–6.09 (m, 1H), 6.14–6.18 (m, 1H), 6.71–6.73 (m, 1H), 8.20–8.24 (br, 1H); ^{13}C NMR δ 25.6, 75.5, 107.0, 108.9, 118.0, 126.1; Anal. Calcd for $C_6H_8N_2O_2$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.54; H, 5.88; N, 19.84.

3,3-Dimethyl-2-nitro-1-(2-pyrrolyl)-5-hexanone (5). A mixture of **4** (1.40 g, 10.0 mmol) and mesityl oxide (1.26 mL, 11.0 mmol) was treated with DBU (4.57 g, 30.0 mmol). The temperature rose immediately and the reaction mixture darkened. The reaction mixture was stirred at room temperature for 24 h, diluted with ethyl acetate (100 mL) and washed with water and brine. The organic layer was dried (Na_2SO_4) and concentrated. Excess mesityl oxide was removed under high vacuum. The resulting oil was dissolved in a minimal amount of CH_2Cl_2 and filtered through a silica pad [ethyl acetate/hexanes (1:3)] to afford a

light brown oil which solidified to a light-brown solid (1.85 g, 78%): mp 59–61 °C (lit.^{IV2} 54–55°C); ¹H NMR (CDCl₃) δ 1.12 (s, 3H), 1.25 (s, 3H), 2.14 (s, 3H), 2.41 (AB, *J* = 17.4 Hz, 1H), 2.59 (AB, *J* = 17.4 Hz, 1H), 3.04 (ABX, ³*J* = 2.4 Hz, ²*J* = 15.6 Hz, 1H), 3.35 (ABX, ³*J* = 11.6 Hz, ²*J* = 15.6 Hz, 1H), 5.13 (ABX, ³*J* = 2.4 Hz, ²*J* = 11.6 Hz, 1H), 5.95–5.99 (m, 1H), 6.08–6.10 (m, 1H), 6.65–6.67 (m, 1H), 8.10–8.13 (br s, 1H); ¹³C NMR δ 24.3, 24.6, 26.8, 32.1, 36.9, 51.6, 94.9, 107.5, 108.9, 118.0, 126.2, 207.2; Anal. Calcd for C₁₂H₁₈N₂O₃: C, 60.49; H, 7.61; N, 11.76. Found: C, 60.42; H, 7.61; N, 11.48.

Screening Protocol for Reductive Cyclization of 5. Reactions were done at the 0.1-mmol scale. Compound **5** was stirred in an appropriate solvent (0.2 mL) in the presence of the reagents for reductive cyclization for the given time. The reaction mixture was diluted with ethyl acetate (2 mL), filtered through a plug of cotton and analyzed by GC.

2,3,4,5-Tetrahydro-1,3,3-trimethylpyrrin N-oxide (6). A mixture of **5** (2.38 g, 10.0 mmol), THF (25 mL) and water (25 mL) was treated with NH₄Cl (1.60 g, 30.0 mmol) and zinc dust (9.8 g, 150 mmol) at 0 °C. The resulting suspension was stirred vigorously at 0 °C for 15 min, then was diluted with ethyl acetate and filtered. The filter cake was washed with ethyl acetate. The combined filtrate was washed with water and brine. The organic phase was dried (Na₂SO₄) and concentrated under vacuum. The resulting oil was chromatographed [silica, ethyl acetate then CH₂Cl₂/MeOH (10:1)] to afford a pale yellow oil which solidified to a white solid (1.36 g, 66%): mp 99–102 °C (lit.^{IV4} 85–87 °C; ¹H NMR (CDCl₃) δ 1.12 (s, 3H), 1.19 (s, 3H), 2.05–2.06 (m, 3H), 2.27–2.32 (m, 1H), 2.42–2.48 (m, 1H), 2.98–3.08 (m, 2H), 3.88–3.91 (m, 1H), 5.93–5.94 (m, 1H), 6.06–6.08 (m, 1H), 6.69–6.70 (m, 1H), 10.55–10.65 (br, 1H); ¹³C NMR δ 13.5, 23.0, 25.8, 27.9, 37.3, 47.2, 81.3, 106.3, 107.4, 117.6, 128.9; Anal. Calcd for C₁₂H₁₈N₂O: C, 69.87; H, 8.80; N, 13.58. Found:

C, 69.xx; H, 8.xx; N, 13.xx; FAB-MS obsd 207.1479, calcd 207.1497 $[(M + H)^+, M = C_{12}H_{18}N_2O]$.

2-(1,3-Dinitroprop-2-yl)pyrrole (8). A small sample was isolated from the reaction of pyrrole-2-carboxaldehyde with excess nitromethane, as an orange oil. Limited data were obtained: 1H NMR δ 4.34–4.41 (m, 1H), 4.70–4.79 (m, 5H), 6.05–6.07 (m, 1H), 6.15–6.17 (m, 1H), 6.73–6.75 (m, 1H), 8.30–836 (br s, 1H); ^{13}C NMR δ 35.4, 76.4, 106.9, 109.5, 119.3, 124.5.

2,3,4,5-Tetrahydro-1,3,3-trimethyldipyrin (5 → 1). A stirred suspension of $HCOONH_4$ (9.45 g, 150 mmol) and nitrohexanone **5** (2.38 g, 10.0 mmol) in THF (40 mL) was treated in one portion with zinc dust (9.76 g, 150 mmol). The resulting mixture was stirred vigorously at room temperature. After 2 h, ethyl acetate (40 mL) was added and the mixture was filtered. The filter cake was washed with ethyl acetate. The filtrate was washed with water, brine and dried (Na_2SO_4). The solvent was concentrated to afford a light brown oil, which slowly solidified upon standing. The crude product (1.65 g) was chromatographed (silica, ethyl acetate) to afford a light brown oil which solidified to a pale yellow-orange solid (1.15 g, 60%): mp 55–56 °C (lit.^{IV2} 53–54 °C) 1H NMR δ 0.96 (s, 3H), 1.13 (s, 3H), 2.05–2.06 (m, 3H), 2.31 (AB, $J = 16.8$ Hz, 1H), 2.39 (AB, $J = 16.8$ Hz, 1H), 2.62 (ABX, $^3J = 11.6$ Hz, $^2J = 14.8$ Hz, 1H), 2.80 (ABX, $^3J = 3.2$ Hz, $^2J = 14.8$ Hz, 1H), 3.64–3.67 (m, 1H), 5.95–5.97 (m, 1H), 6.11–6.13 (m, 1H), 6.70–6.72 (m, 1H), 9.75–983 (br. s, 1H); ^{13}C NMR δ 20.6, 23.0, 42.0, 54.4, 80.4, 105.3, 107.4, 116.5, 131.8, 174.6; FAB-MS obsd 191.1534, calcd 191.1548 $[(M + H)^+, M = C_{12}H_{18}N_2]$.

2,3,4,5-Tetrahydro-1,3,3-trimethyldipyrin (6 → 1). A solution of **6** (1.03 g, 5.0 mmol) in THF (20 mL) was treated with $HCOONH_4$ (4.78 g, 75 mmol) and zinc dust (4.88 g,

75 mmol). The resulting suspension was stirred at room temperature. After 2 h the mixture was diluted with ethyl acetate and filtered. The filter cake was washed with ethyl acetate. The combined filtrate was washed with water and brine. The organic phase was dried (Na_2SO_4) and concentrated. The resulting oil was chromatographed (silica, ethyl acetate) to afford a yellow oil which solidified to white crystals (0.62 g, 81%): The ^1H and ^{13}C NMR spectra were identical as described above; mp 52-53 °C (lit.^{IV4} 53-54 °C). Anal. Calcd for $\text{C}_{12}\text{H}_{18}\text{N}_2$: C, 75.74; H, 9.53; N, 14.72. Found: C, 75.61; H, 9.71; N, 14.63.

Direct Conversion of 2 → 4. A stirred solution of acetic acid (2.00 mL, 35.0 mmol) in methanol (5 mL) under argon at 0 °C was treated dropwise with *n*-propylamine (2.71 mL, 33.0 mmol). The resulting *n*-propylammonium acetate mixture was stirred at 0 °C for 5 min, then added dropwise to a stirred solution of **2** (5.70 g, 60.0 mmol) in nitromethane (9.70 mL, 180.0 mmol) at 0 °C. The resulting mixture was stirred at 0 °C. After 15 min, the cooling bath was removed and stirring was continued at room temperature. The color changed from yellow to dark orange during the course of reaction. After 2 h (see note below), CH_2Cl_2 (100 mL) was added and the organic phase was washed with water and brine. The organic layer was dried (Na_2SO_4) and concentrated under high vacuum to afford an orange-brown solid. The crude 2-(2-nitrovinyl)pyrrole was dissolved in a mixture of CHCl_3 (300 mL) and isopropanol (100 mL), to which silica (72 g) was added. The mixture was stirred vigorously and NaBH_4 (4.54 g, 120 mmol) was added in one batch. After 30 min, TLC analysis showed complete consumption of the starting 2-(2-nitrovinyl)pyrrole. The mixture was filtered. The filter cake was washed with CH_2Cl_2 . The filtrate was concentrated and the resulting dark oil was filtered through a silica pad (CH_2Cl_2) to afford an orange oil (3.52 g, 40%). The ^1H NMR data were consistent with reported values.^{IV2}

Note: The time for completion of the reaction varied from 1 h to 3 h. It is recommended to monitor the progress of the reaction with TLC and carry out the work-up immediately upon disappearance of the starting material.

Direct Conversion of 2 → 5. A stirred solution of acetic acid (2.00 mL, 35.0 mmol) in methanol (5 mL) under argon at 0 °C was treated dropwise with *n*-propylamine (2.71 mL, 33.0 mmol). The resulting *n*-propylammonium acetate mixture was stirred at 0 °C for 5 min, then added dropwise to a stirred solution of **2** (5.70 g, 60.0 mmol) in nitromethane (9.71 mL, 90.0 mmol) at 0 °C in a 100 mL flask. The resulting mixture was stirred at 0 °C. After 15 min, the cooling bath was removed and the stirring was continued at room temperature for 2 h. CH₂Cl₂ (100 mL) was added and the organic phase was washed with water and brine. The organic layer was dried (Na₂SO₄) and concentrated under high vacuum to afford a brownish oil. The brownish oil was placed in a 1 L flask and a mixture of CHCl₃ (300 mL) and isopropanol (100 mL) was added, followed by silica (72 g). The mixture was stirred vigorously and NaBH₄ (4.54 g, 120 mmol) was added in one batch. After 1 h, TLC analysis showed the presence of starting material. Hence, another batch of NaBH₄ (2.80 g, 74.0 mmol) was added and stirring was continued. After 2 h, TLC analysis showed the complete consumption of starting material, and GC analysis showed the formation of **4**. The mixture was filtered and the filter cake was washed with CH₂Cl₂. The filtrate was concentrated. The resulting dark oil was dissolved in mesityl oxide (20 mL) and then DBU (13.7 g, 90.0 mmol) was added. The resulting solution was stirred for 13 h. The crude was then filtered through a silica pad [ethyl acetate/hexanes (1:3)] to afford a light brown oil (4.2 g, 29%): ¹H NMR data were identical with values reported above; Anal. Calcd for C₁₂H₁₈N₂O₃: C, 60.49; H, 7.61; N, 11.76. Found: C, 60.73; H, 7.79; N, 11.83.

Direct Conversion of 4 → 1. A solution of **4** (2.10 g, 15.0 mmol) in mesityl oxide (2.83 mL, 22.5 mmol) was treated with DBU (6.86 g, 45.0 mmol). The resulting dark mixture was stirred for 14 h. The reaction mixture was diluted with ethyl acetate (50 mL) and washed with water and brine. The organic phase was dried (Na_2SO_4) and concentrated. Excess mesityl oxide was removed under high vacuum. The resulting brown oil was dissolved in THF (40 mL), then HCOONH_4 (14.2 g, 225 mmol) and zinc dust (17.7 g, 225 mmol) were added. The resulting mixture was stirred vigorously at room temperature. After 2 h, GC analysis showed complete consumption of hexanone **5** and *N*-oxide **6**. Ethyl acetate (50 mL) was added and the mixture was filtered through filter paper. The filter cake was washed with ethyl acetate. The combined filtrate was washed with water and brine. The organic phase was dried (Na_2SO_4) and concentrated. The resulting oil was chromatographed (silica, ethyl acetate) to afford a brown oil which solidified to a pale brown solid (1.51 g, 53%). The mp, ^1H NMR, ^{13}C NMR, and FAB-MS data were identical as described above.

Direct Conversion of 2 → 1 (60 mmol scale). A stirred solution of acetic acid (2.00 mL, 35.0 mmol) in methanol (5 mL) under argon at 0 °C was treated dropwise with *n*-propylamine (2.71 mL, 33.0 mmol). The resulting *n*-propylammonium acetate solution was stirred at 0 °C for 5 min, then added dropwise to a stirred solution of **2** (5.70 g, 60.0 mmol) in nitromethane (9.70 mL, 90.0 mmol) at 0 °C. The resulting mixture was stirred at 0 °C. After 15 min, the cooling bath was removed and stirring was continued at room temperature. The color changed from yellow to dark orange during the course of reaction. After 2 h (Note 1), CH_2Cl_2 (100 mL) was added and the organic phase was washed with water and brine. The organic layer was dried (Na_2SO_4) and concentrated under high vacuum to afford an orange oil that solidified to give an orange-brown solid. The crude 2-(2-nitrovinyl)pyrrole was

dissolved in a mixture of CHCl₃ (300 mL) and isopropanol (100 mL), to which silica (72 g) was added. The mixture was stirred vigorously and NaBH₄ (4.54 g, 120 mmol) was added in one batch. After 30 min, TLC analysis showed complete consumption of the starting 2-(2-nitrovinyl)pyrrole. The mixture was filtered. The filter cake was washed with CH₂Cl₂. The filtrate was concentrated. The resulting dark oil was dissolved in mesityl oxide (20 mL) and then DBU (13.7 g, 90.0 mmol) was added. The resulting dark solution was stirred for 14 h. The reaction mixture was diluted with ethyl acetate (150 mL) and washed with water and brine. The organic phase was dried (Na₂SO₄) and concentrated. Excess mesityl oxide was removed under high vacuum, followed by entrainment with hexanes (2x). The resulting brown oil was dissolved in THF (160 mL), then HCOONH₄ (37.8 g, 600 mmol) and zinc dust (39.2 g, 600 mmol) were added. The resulting mixture was stirred vigorously at room temperature. After 3 h, GC analysis did not show the presence of hexanone **5** and *N*-oxide **6**. Ethyl acetate (200 mL) was added and the mixture was filtered through Celite. The filter cake was washed with ethyl acetate. The combined filtrate was washed with water and brine. The organic phase was dried (Na₂SO₄) and concentrated. The resulting oil was chromatographed (silica, ethyl acetate) to afford a brown oil which solidified to a pale brown solid (2.54 g, 22%). The characterization data (mp, ¹H NMR data) were identical with that described above.

Direct Conversion of **2 → **1** (0.40 mol scale).** A mixture of acetic acid (12.88 mL, 225 mmol) in MeOH (20 mL) was treated dropwise with *n*-propylamine (16.44 mL, 200 mmol) at 0 °C (see note i below). The resulting mixture was stirred at room temperature for 15 min, and then transferred to the solution of pyrrole-2-carboxaldehyde (38.0 g, 0.400 mol) in MeNO₂ (64.5 mL, 1.20 mol) under argon at 0 °C. The mixture was stirred at room

temperature until TLC showed complete consumption of the starting aldehyde (~5 h, see note ii below). Excess MeNO₂ was removed under high vacuum (water bath, 40 °C). The resulting oil was triturated with hexanes (50 mL), and the volatile components were evaporated. This procedure was repeated three times. The resulting brown oil was dissolved in CHCl₃ and filtered through a pad of silica (3 x 7 cm). The filter cake was washed with CHCl₃ (the total volume of solvent used was 2000 mL, see note iii below). The filtrate was transferred to a 5 L flask. Isopropanol (667 mL) and silica (480 g) were added. Under vigorous stirring, NaBH₄ (38 g, 1.0 mmol) was added over the course of 1 min. The mixture was stirred for 45 min, then another batch of NaBH₄ (10.0 g, 264 mmol) was added and stirring was continued for 75 min. TLC showed complete consumption of 2-(2-nitrovinyl)pyrrole (**3**). The mixture was filtered through filter paper and the filter cake was washed with CH₂Cl₂ (~4000 mL). The filtrate was concentrated to afford a dark brown oil. The resulting crude 2-(2-nitroethyl)pyrrole (**4**) was dissolved in mesityl oxide (130 mL, 1.13 mol). DBU (91 g, 585 mmol) was added and the mixture was stirred overnight. Ethyl acetate (500 mL) was added and mixture was washed with water (3 x 200 mL) and brine (100 mL). The organic phase was dried (Na₂SO₄). Removal of the solvent and excess mesityl oxide under high vacuum afforded crude **5** as a brown oil. The crude oil was dissolved in THF (1000 mL) and the resulting solution was transferred to a three-necked 2-L flask. HCOONH₄ (252 g, 3.90 mol) and zinc dust (261 g, 3.90 mol) were added and resulting suspension was vigorously stirred using a mechanical stirrer (see note iv below). After 2 h, GC analysis did not show any starting hexanone (**5**) or intermediate *N*-oxide (**6**). The mixture was filtered through filter paper and the filter cake was washed with ethyl acetate (2500 mL). The resulting brown solid was chromatographed (6 x 22 cm, 260 g of

silica) using ethyl acetate (3000 mL, ~8 h), affording a brown oil which slowly crystallized to a pale brown solid (8.80 g). The mixed fractions were rechromatographed on a small silica column to afford an additional 2.26 g of title compound (total yield 11.06 g, 14.5%; see note v below). The characterization data (mp, ^1H NMR data) were identical with that described above.

Notes:

- (i) Excess acetic acid is necessary because the use of equimolar amounts of AcOH and propylamine in some experiments causes extensive decomposition of starting material.
- (ii) The time for completion of the reaction varied from 4 – 7 h. It is recommended to monitor the progress of the reaction with TLC and carry out the work-up immediately upon disappearance of the starting material.
- (iii) Alternatively, the reaction mixture was diluted with CH_2Cl_2 (~300 mL), washed with water and brine. The organic phase was dried (Na_2SO_4). The CH_2Cl_2 was removed under low vacuum, and then excess MeNO_2 was removed under high vacuum (water bath, 40 °C). The resulting oil was triturated with hexanes (50 mL), and the volatile components were removed. This procedure was repeated three times. The resulting brown-orange solid was subjected to reduction as described above.
- (iv) The reductive cyclization was done under heterogeneous conditions and required a large amount of solid material (Zn/HCOONH₄). The heterogeneous mixture caused difficulties in stirring, which affected the reaction time required for completion. A mechanical stirrer is recommended for effective stirring.

(v) Most intermediates (especially **3** and **4**) were relatively unstable upon standing in the crude reaction mixtures; therefore, all operations as well as subsequent reaction steps should be carried out promptly.

IV.E. References

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Table IV.1. Conditions for the Michael addition for the synthesis of nitrohexanone derivative (4** → **5**).^a**

Entry	Base (equiv)	4 : equiv, solvent (conc.)	Temp.	Time	Yield of 5 ^b
1 ^c	CsF (5.7)	5.0, CH ₃ CN (150 mM) ^d	70 °C	16 h	65% ^e
2	CsF (3.0)	10., CH ₃ CN (350 mM) ^f	80 °C	18 h	61% ^e
3	CsF (3.0)	10., neat	60 °C	14 h	None ^g
4	CsF (3.0)	10., neat	RT	18 h	Trace ^g
5	Al ₂ O ₃	1.0, neat	RT	14 h	None
6	DBU (1.0)	2.0, CH ₃ CN (200 mM)	Reflux	4 h	50%
7	DBU (1.0)	1.1, THF (500 mM)	RT	3h	Trace
8	DBU (1.0)	1.1, THF (500 mM)	Reflux	1 h	Trace
9	DBU (1.0)	10., neat	RT	14 h	75%
10	DBU (3.0)	10., neat	RT	16 h	78% ^e
11	TMG (0.25)	1.1, THF (250 mM)	RT	14 h	None
12	TMG (1.25)	1.1, THF (250 mM)	RT	1 h	Trace
13	TMG (0.25)	1.1, CH ₃ CN (250 mM)	RT	14 h	Trace

^aThe reactions were carried out with 1 mmol of **4** unless noted otherwise. ^bYields were

estimated on the basis of GC. ^cConditions employed previously.² ^d11.4 mmol scale.

^eIsolated yield. ^f25 mmol scale. ^gExtensive byproducts.

Table IV.2. Conditions for the reductive cyclization for the synthesis of tetrahydroadipyrin (5** → **1**).**

Entry	Zn (equiv)	NH ₄ X (equiv)	Solvent	Temp., Time	5 : 6 : 1 ^a
1	15	HCOONH ₄ (3)	MeOH	RT, 30 min	0 : 44 : 34
2	2	HCOONH ₄ (15)	MeOH	RT, 30 min	0 : 42 : 40
3	15	HCOONH ₄ (15)	MeOH	RT, 30 min	0 : 27 : 63
4	15	HCOONH ₄ (15)	MeOH	RT, 2 h	0 : 5 : 68
5	15	HCOONH ₄ (15)	MeOH	Reflux, 20 min	0 : 0 : 51
6	15	HCOONH ₄ (15)	MeCN	RT, 2 h	0 : 4 : 64
7	15	HCOONH ₄ (15)	THF	RT, 2 h	1 : 0 : 76
8	15	HCOONH ₄ (15)	Ethyl acetate	RT, 2 h	0 : 18 : 54
9	15	HCOONH ₄ (15)	CH ₂ Cl ₂	RT, 2 h	0 : 37 : 48
10	15	NH ₄ Cl (3)	THF/H ₂ O, 1:1	RT, 30 min	0 : 61 : 21
11	15	NH ₄ Cl (3)	THF/H ₂ O, 1:1	RT, 1 h	0 : 65 : 22
12	15	NH ₄ Cl (6)	THF/H ₂ O, 1:1	RT, 30 min	2 : 70 : 23
13	25	NH ₄ Cl (3)	THF/H ₂ O, 1:1	RT, 30 min	2 : 68 : 17
14	15	NH ₄ Cl (3)	THF/H ₂ O, 1:1	Reflux, 30 min	<1 : 66 : 25
15	15	NH ₄ Cl (3)	THF/H ₂ O, 4:1	RT, 30 min	1 : 72 : 20
16	5	NH ₄ Cl (3)	THF/H ₂ O, 1:1	RT, 30 min	4 : 72 : 17
17	15	NH ₄ Cl (3)	MeOH/THF, 1:1	RT, 30 min	34 : 33 : 9

^aRatio determined by GC analysis. The data do not sum to 100%, because of side products and/or impurities.

Appendix A (Chapter III)

Appendix A (Chapter III)

X-Ray Crystallographic Data for (9-BBN)₂5

X-Ray Structural Determination for (9-BBN)₂5

Data Collection. The sample was mounted on 20 micron nylon loop with a small amount of immersion oil. All X-ray measurements were made on a Bruker-Nonius X8 Apex2 CCD diffractometer at 110K. The temperature of the sample was controlled with a cold stream of nitrogen from an Oxford Cryosystems 700 Series Cryostream Cooler. The unit cell dimensions were determined from a symmetry constrained fit of 5934 reflections with $4.52^\circ < 2(\theta) < 48.44^\circ$. The data collection strategy was a number of w and j scans which collected data up to 49.5° ($2(\theta)$). The frame integration was performed using SAINT+.^{A1} The resulting raw data was scaled and absorption corrected using a multi-scan averaging of symmetry equivalent data using SADABS.^{A2}

Structure Solution and Refinement. The structure was solved by direct methods using SIR92.^{A3} All non-hydrogen atoms were obtained from the initial E-map. The hydrogen atoms were introduced at idealized positions and were allowed to refine isotropically. All non-hydrogen atoms were allowed to refine anisotropically. The etheric oxygen, O43, was disordered over two sites. The displacement parameters were fixed and the occupancies were refined, normalized then fixed. Atom sites O43 and O43' were then both refined anisotropically. The ether of solvation also exhibited some disorder, but due to a lack of large well-defined peaks in the difference map in the vicinity of the ether molecule, no attempt was made to find and refine a positional order model. The structural model was fit to the data using full matrix least-squares based on F. The calculated structure factors included corrections for anomalous dispersion from the usual tabulation. A secondary extinction correction was included in the final refinements. The structure was refined, final tables and graphic plots were produced using the NRCVAX crystallographic program suite.^{A4}

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Crystallographic data and structure refinement for (9-BBN)₂5.

Empirical formula	C46 H68 B2 N4 O3 Si	
Formula weight	774.76	
Temperature	110K	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 11.1750(9)Å b = 13.0823(10)Å c = 16.1471(12)Å 2193.1(3)Å ³	α = 78.820(3)° β = 71.278(3)° γ = 85.826(3)°
Volume		
Z	2	
Density (calculated)	1.173 Mg/m ³	
Absorption coefficient	0.10mm ⁻¹	
F(000)	840.58	
Crystal size	0.24 x 0.08 x 0.04 mm ³	
Diffractometer	Bruker-Nonius X8 Apex2	
2Theta range for intensity data collection	4.52 to 48.44°	
Index ranges	-13<=h<=13, 0<=k<=15, -18<=l<=19	
Reflections collected	28845	
Independent reflections	7502	
Observed reflections (I >1sigma(I))	5977	
Solution method	Direct methods (SIR 92)	
Refinement method	Full matrix least-squares based on F	
Data/parameters	5953 /515	
Goodness-of-fit	2.01	
Final R indices (based on F)	R = 0.082, Rw = 0.091	
R indices (all data)	R = 0.102, Rw = 0.096	

Atomic coordinates and equivalent isotropic displacement parameters (\AA^2) for (9-BBN)₂5.

Name	x	y	z
C1	0.80231(32)	0.66631(26)	0.28590(21)
C2	0.77560(34)	0.62574(27)	0.37652(21)
C3	0.67026(34)	0.56522(28)	0.39990(22)
C4	0.63404(32)	0.56834(26)	0.32375(21)
C5	0.52262(32)	0.51706(27)	0.31768(21)
C6	0.40101(33)	0.56838(26)	0.36569(21)
C7	0.38200(35)	0.65633(27)	0.40417(22)
C8	0.25176(35)	0.66155(26)	0.44865(22)
C9	0.19662(33)	0.57740(27)	0.43676(21)
N10	0.71287(26)	0.63125(21)	0.25411(17)
N11	0.28753(26)	0.52012(21)	0.38445(17)
N12	0.60353(27)	0.33222(23)	0.36846(18)
C13	0.51135(32)	0.40046(27)	0.35683(21)
N14	0.39999(26)	0.35277(21)	0.38702(17)
C15	0.42318(35)	0.25079(27)	0.42132(22)
C16	0.54731(37)	0.23699(28)	0.41006(23)
C17	0.99417(32)	0.78750(26)	0.21736(21)
C18	1.03501(34)	0.87828(27)	0.15437(22)
C19	1.14083(35)	0.92944(27)	0.14981(23)
C20	1.21267(34)	0.89075(28)	0.20491(23)
C21	1.17323(35)	0.79899(28)	0.26756(23)
C22	1.06468(34)	0.74945(27)	0.27408(23)
C23	0.88563(32)	0.73424(26)	0.21677(22)
B24	0.73966(38)	0.68422(31)	0.15186(25)
C25	0.78374(33)	0.60939(27)	0.07918(21)
C26	0.84891(36)	0.67910(29)	-0.01140(22)
C27	0.77084(37)	0.77335(28)	-0.03788(22)
C28	0.70102(36)	0.83282(28)	0.03677(23)
C29	0.63604(34)	0.76318(27)	0.12745(22)
C30	0.52067(35)	0.70382(28)	0.12692(23)
C31	0.55494(35)	0.61798(28)	0.06970(23)
C32	0.67016(36)	0.55090(27)	0.07713(22)
B33	0.28118(39)	0.41171(31)	0.35795(25)
C34	0.14359(34)	0.35820(28)	0.39981(22)
C35	0.14633(37)	0.24555(30)	0.38247(25)
C36	0.20865(39)	0.23415(30)	0.28468(26)
C37	0.32643(35)	0.30080(30)	0.23548(23)
C38	0.31748(32)	0.41398(26)	0.25201(22)
C39	0.22381(35)	0.48377(30)	0.21409(23)
C40	0.08635(35)	0.45232(30)	0.25844(24)
C41	0.04798(33)	0.42587(30)	0.36051(23)
C42	0.74209(35)	0.34894(32)	0.33331(25)

O43	0.78082(36)	0.38626(30)	0.24786(25)
O43'	0.81146(57)	0.27270(48)	0.30080(38)
C44	0.81680(45)	0.29847(52)	0.19288(33)
C45	0.70162(38)	0.25183(32)	0.18531(25)
Si46	0.73492(10)	0.19325(7)	0.08250(6)
C47	0.59232(38)	0.12331(31)	0.09059(26)
C48	0.77340(39)	0.29669(29)	-0.01814(25)
C49	0.86728(38)	0.09748(30)	0.08149(24)
C50	1.33185(38)	0.94444(30)	0.19707(26)
O51	0.85621(21)	0.74844(17)	0.14355(14)
O1s	0.71501(38)	-0.00719(26)	0.43528(32)
C1s	0.76969(98)	0.04704(57)	0.55768(55)
C2s	0.83163(69)	0.02631(45)	0.45738(51)
C3s	0.75933(92)	-0.03177(45)	0.35939(38)
C4s	0.63817(80)	-0.06598(40)	0.34159(37)
H2	0.82182(0)	0.63750(0)	0.41464(0)
H3	0.62799(0)	0.52698(0)	0.45800(0)
H5	0.52858(0)	0.52549(0)	0.25609(0)
H7	0.44540(0)	0.70388(0)	0.40114(0)
H8	0.20907(0)	0.71464(0)	0.48139(0)
H9	0.10844(0)	0.56087(0)	0.46093(0)
H15	0.36026(0)	0.19800(0)	0.44943(0)
H16	0.58900(0)	0.17361(0)	0.42755(0)
H18	0.98846(0)	0.90492(0)	0.11395(0)
H19	1.16586(0)	0.99295(0)	0.10785(0)
H21	1.22250(0)	0.77051(0)	0.30578(0)
H22	1.03650(0)	0.68840(0)	0.31854(0)
H25	0.84401(0)	0.55988(0)	0.09503(0)
H26a	0.86754(0)	0.63703(0)	-0.05664(0)
H26b	0.92621(0)	0.70454(0)	-0.00943(0)
H27a	0.70873(0)	0.74864(0)	-0.05859(0)
H27b	0.82596(0)	0.82098(0)	-0.08527(0)
H28a	0.76107(0)	0.87593(0)	0.04459(0)
H28b	0.63746(0)	0.87601(0)	0.01855(0)
H29	0.60740(0)	0.80632(0)	0.17200(0)
H30a	0.46629(0)	0.75356(0)	0.10412(0)
H30b	0.47612(0)	0.67212(0)	0.18686(0)
H31a	0.57148(0)	0.65090(0)	0.00865(0)
H31b	0.48363(0)	0.57293(0)	0.08718(0)
H32a	0.64368(0)	0.50007(0)	0.13082(0)
H32b	0.69812(0)	0.51621(0)	0.02687(0)
H34	0.11693(0)	0.35632(0)	0.46283(0)
H35a	0.19200(0)	0.20216(0)	0.41751(0)
H35b	0.06080(0)	0.22199(0)	0.40097(0)
H36a	0.14757(0)	0.25394(0)	0.25392(0)
H36b	0.23204(0)	0.16226(0)	0.28335(0)

H37a	0.39569(0)	0.26677(0)	0.25318(0)
H37b	0.34335(0)	0.30361(0)	0.17292(0)
H38	0.39971(0)	0.44438(0)	0.22492(0)
H39a	0.24564(0)	0.48089(0)	0.15203(0)
H39b	0.23182(0)	0.55398(0)	0.22095(0)
H40a	0.03354(0)	0.50865(0)	0.24215(0)
H40b	0.07244(0)	0.39184(0)	0.23741(0)
H41a	0.03727(0)	0.49060(0)	0.38183(0)
H41b	-0.03108(0)	0.38999(0)	0.38211(0)
H42a	0.78277(0)	0.28261(0)	0.34350(0)
H42b	0.76475(0)	0.39592(0)	0.36456(0)
H44a	0.85712(0)	0.24369(0)	0.22356(0)
H44b	0.87397(0)	0.32405(0)	0.13493(0)
H45a	0.66519(0)	0.19972(0)	0.23661(0)
H45b	0.64239(0)	0.30832(0)	0.18241(0)
H47a	0.57216(0)	0.06973(0)	0.14265(0)
H47b	0.52294(0)	0.17191(0)	0.09452(0)
H47c	0.60757(0)	0.09252(0)	0.03874(0)
H48a	0.70303(0)	0.34416(0)	-0.01476(0)
H48b	0.84645(0)	0.33382(0)	-0.02180(0)
H48c	0.79049(0)	0.26556(0)	-0.06999(0)
H49a	0.94161(0)	0.13321(0)	0.07736(0)
H49b	0.84451(0)	0.04635(0)	0.13516(0)
H49c	0.88393(0)	0.06362(0)	0.03117(0)
H50a	1.36854(0)	0.90693(0)	0.24047(0)
H50b	1.39075(0)	0.94574(0)	0.13859(0)
H50c	1.31224(0)	1.01449(0)	0.20732(0)
H1sa	0.83283(0)	0.06832(0)	0.57930(0)
H1sb	0.70648(0)	0.10090(0)	0.55814(0)
H1sc	0.73106(0)	-0.01588(0)	0.59521(0)
H2sa	0.89415(0)	-0.02835(0)	0.45504(0)
H2sb	0.86957(0)	0.08843(0)	0.41796(0)
H3sa	0.79829(0)	0.02704(0)	0.31560(0)
H3sb	0.81946(0)	-0.08814(0)	0.35866(0)
H4sa	0.66252(0)	-0.08568(0)	0.28414(0)
H4sb	0.59990(0)	-0.12419(0)	0.38641(0)
H4sc	0.57873(0)	-0.00901(0)	0.34335(0)

Bond lengths [Å] for (9-BBN)₂5.

Bond	Length	Bond	Length
C1-C2	1.398(5)	B33-C34	1.618(5)
C1-N10	1.400(5)	B33-C38	1.621(5)
C1-C23	1.404(5)	C34-C35	1.549(5)
C2-C3	1.375(5)	C34-C41	1.552(5)
C2-H2	0.960(4)	C34-H34	0.960(3)
C3-C4	1.405(5)	C35-C36	1.540(6)
C3-H3	0.960(3)	C35-H35a	0.960(4)
C4-C5	1.495(5)	C35-H35b	0.960(4)
C4-N10	1.352(4)	C36-C37	1.533(5)
C5-C6	1.514(5)	C36-H36a	0.960(4)
C5-C13	1.531(5)	C36-H36b	0.960(4)
C5-H5	0.960(3)	C37-C38	1.545(5)
C6-C7	1.383(5)	C37-H37a	0.960(4)
C6-N11	1.376(4)	C37-H37b	0.960(4)
C7-C8	1.404(5)	C38-C39	1.536(5)
C7-H7	0.960(4)	C38-H38	0.960(3)
C8-C9	1.373(5)	C39-C40	1.521(5)
C8-H8	0.960(3)	C39-H39a	0.960(3)
C9-N11	1.375(4)	C39-H39b	0.960(4)
C9-H9	0.960(4)	C40-C41	1.538(5)
N10-B24	1.602(5)	C40-H40a	0.960(4)
N11-B33	1.571(5)	C40-H40b	0.960(4)
N12-C13	1.349(5)	C41-H41a	0.960(4)
N12-C16	1.384(5)	C41-H41b	0.960(4)
N12-C42	1.485(5)	C42-O43	1.310(6)
C13-N14	1.335(4)	C42-O43'	1.304(7)
N14-C15	1.382(4)	C42-H42a	0.960(4)
N14-B33	1.640(5)	C42-H42b	0.960(4)
C15-C16	1.343(6)	O43-O43'	1.636(7)
C15-H15	0.960(3)	O43-C44	1.539(6)
C16-H16	0.960(4)	O43'-C44	1.692(8)
C17-C18	1.402(5)	O43'-H42a	0.694(6)
C17-C22	1.392(5)	O43'-H44a	1.306(6)
C17-C23	1.446(5)	C44-C45	1.513(6)
C18-C19	1.375(5)	C44-H44a	0.960(7)
C18-H18	0.960(4)	C44-H44b	0.960(5)
C19-C20	1.385(6)	C45-Si46	1.881(4)
C19-H19	0.960(3)	C45-H45a	0.960(4)
C20-C21	1.407(5)	C45-H45b	0.960(5)
C20-C50	1.509(5)	Si46-C47	1.851(4)
C21-C22	1.382(5)	Si46-C48	1.855(4)
C21-H21	0.960(4)	Si46-C49	1.866(4)
C22-H22	0.960(3)	C47-H47a	0.960(4)

C23-O51	1.302(4)	C47-H47b	0.960(4)
B24-C25	1.607(5)	C47-H47c	0.960(4)
B24-C29	1.589(6)	C48-H48a	0.960(4)
B24-O51	1.557(5)	C48-H48b	0.960(4)
C25-C26	1.548(5)	C48-H48c	0.960(4)
C25-C32	1.541(5)	C49-H49a	0.960(4)
C25-H25	0.960(4)	C49-H49b	0.960(4)
C26-C27	1.531(6)	C49-H49c	0.960(4)
C26-H26a	0.960(3)	C50-H50a	0.960(4)
C26-H26b	0.960(4)	C50-H50b	0.960(4)
C27-C28	1.529(5)	C50-H50c	0.960(4)
C27-H27a	0.960(4)	O1s-C2s	1.569(8)
C27-H27b	0.960(3)	O1s-C3s	1.261(8)
C28-C29	1.548(5)	C1s-C2s	1.612(12)
C28-H28a	0.960(4)	C1s-H1sa	0.960(9)
C28-H28b	0.960(4)	C1s-H1sb	0.960(9)
C29-C30	1.556(5)	C1s-H1sc	0.960(8)
C29-H29	0.960(3)	C2s-H2sa	0.960(7)
C30-C31	1.541(5)	C2s-H2sb	0.960(6)
C30-H30a	0.960(4)	C3s-C4s	1.582(12)
C30-H30b	0.960(3)	C3s-H3sa	0.960(6)
C31-C32	1.528(6)	C3s-H3sb	0.960(8)
C31-H31a	0.960(3)	C4s-H4sa	0.960(6)
C31-H31b	0.960(4)	C4s-H4sb	0.960(6)
C32-H32a	0.960(3)	C4s-H4sc	0.960(7)
C32-H32b	0.960(3)		

Bond angles [°] for (9-BBN)₂5.

Bond	Angle	Bond	Angle
C2-C1-N10	109.7(3)	C34-C35-H35a	108.3(3)
C2-C1-C23	141.1(3)	C34-C35-H35b	108.2(4)
N10-C1-C23	109.2(3)	C36-C35-H35a	108.2(4)
C1-C2-C3	106.1(3)	C36-C35-H35b	108.1(3)
C1-C2-H2	126.9(3)	H35a-C35-H35b	109.5(4)
C3-C2-H2	127.0(3)	C35-C36-C37	114.6(3)
C2-C3-C4	108.3(3)	C35-C36-H36a	108.2(4)
C2-C3-H3	126.4(4)	C35-C36-H36b	108.0(4)
C4-C3-H3	125.2(3)	C37-C36-H36a	108.1(4)
C3-C4-C5	127.4(3)	C37-C36-H36b	108.5(4)
C3-C4-N10	109.4(3)	H36a-C36-H36b	109.5(4)
C5-C4-N10	123.1(3)	C36-C37-C38	116.0(3)
C4-C5-C6	110.4(3)	C36-C37-H37a	107.8(3)
C4-C5-C13	114.8(3)	C36-C37-H37b	107.7(3)
C4-C5-H5	108.3(3)	C38-C37-H37a	108.0(3)
C6-C5-C13	106.9(3)	C38-C37-H37b	107.8(3)
C6-C5-H5	108.4(3)	H37a-C37-H37b	109.5(4)
C13-C5-H5	107.9(3)	B33-C38-C37	108.9(3)
C5-C6-C7	130.1(3)	B33-C38-C39	110.3(3)
C5-C6-N11	119.7(3)	B33-C38-H38	106.8(3)
C7-C6-N11	109.9(3)	C37-C38-C39	114.3(3)
C6-C7-C8	106.2(3)	C37-C38-H38	108.2(3)
C6-C7-H7	126.7(4)	C39-C38-H38	108.1(3)
C8-C7-H7	127.1(4)	C38-C39-C40	114.3(3)
C7-C8-C9	107.8(3)	C38-C39-H39a	108.1(3)
C7-C8-H8	126.0(4)	C38-C39-H39b	108.5(3)
C9-C8-H8	126.2(4)	C40-C39-H39a	108.2(3)
C8-C9-N11	109.4(3)	C40-C39-H39b	108.2(3)
C8-C9-H9	125.6(3)	H39a-C39-H39b	109.5(4)
N11-C9-H9	125.0(3)	C39-C40-C41	113.7(3)
C1-N10-C4	106.5(3)	C39-C40-H40a	108.7(3)
C1-N10-B24	109.0(3)	C39-C40-H40b	108.5(3)
C4-N10-B24	144.5(3)	C41-C40-H40a	108.4(3)
C6-N11-C9	106.8(3)	C41-C40-H40b	108.0(3)
C6-N11-B33	121.4(3)	H40a-C40-H40b	109.5(4)
C9-N11-B33	131.3(3)	C34-C41-C40	116.0(3)
C13-N12-C16	107.5(3)	C34-C41-H41a	107.4(3)
C13-N12-C42	127.6(3)	C34-C41-H41b	108.2(3)
C16-N12-C42	124.5(3)	C40-C41-H41a	107.3(3)
C5-C13-N12	128.3(3)	C40-C41-H41b	108.3(3)
C5-C13-N14	121.5(3)	H41a-C41-H41b	109.5(3)
N12-C13-N14	110.2(3)	N12-C42-O43	112.5(3)
C13-N14-C15	106.2(3)	N12-C42-O43'	116.6(4)

C13-N14-B33	118.4(3)	N12-C42-H42a	107.6(4)
C15-N14-B33	133.5(3)	N12-C42-H42b	109.3(3)
N14-C15-C16	109.5(3)	O43-C42-O43'	77.5(4)
N14-C15-H15	125.3(4)	O43-C42-H42a	108.3(4)
C16-C15-H15	125.1(4)	O43-C42-H42b	109.4(4)
N12-C16-C15	106.6(3)	O43'-C42-H42a	31.3(3)
N12-C16-H16	126.6(4)	O43'-C42-H42b	126.4(4)
C15-C16-H16	126.8(4)	H42a-C42-H42b	109.6(4)
C18-C17-C22	118.3(3)	C42-O43-O43'	51.1(3)
C18-C17-C23	118.6(3)	C42-O43-C44	111.5(4)
C22-C17-C23	123.0(3)	O43'-O43-C44	64.3(4)
C17-C18-C19	120.8(3)	C42-O43'-O43	51.4(3)
C17-C18-H18	119.5(3)	C42-O43'-C44	103.1(5)
C19-C18-H18	119.7(3)	C42-O43'-H42a	45.9(4)
C18-C19-C20	121.0(3)	C42-O43'-H44a	137.4(5)
C18-C19-H19	119.9(4)	O43-O43'-C44	55.0(3)
C20-C19-H19	119.0(4)	O43-O43'-H42a	96.9(6)
C19-C20-C21	118.5(3)	O43-O43'-H44a	87.5(4)
C19-C20-C50	121.0(3)	C44-O43'-H42a	147.5(7)
C21-C20-C50	120.6(3)	C44-O43'-H44a	34.4(3)
C20-C21-C22	120.5(3)	H42a-O43'-H44a	172.9(8)
C20-C21-H21	119.6(4)	O43-C44-O43'	60.6(3)
C22-C21-H21	119.9(3)	O43-C44-C45	111.8(4)
C17-C22-C21	120.8(3)	O43-C44-H44a	107.9(4)
C17-C22-H22	119.1(3)	O43-C44-H44b	110.1(5)
C21-C22-H22	120.0(4)	O43'-C44-C45	108.5(4)
C1-C23-C17	129.2(3)	O43'-C44-H44a	50.2(3)
C1-C23-O51	112.2(3)	O43'-C44-H44b	140.3(5)
C17-C23-O51	118.6(3)	C45-C44-H44a	106.8(5)
N10-B24-C25	117.6(3)	C45-C44-H44b	110.5(4)
N10-B24-C29	117.5(3)	H44a-C44-H44b	109.6(5)
N10-B24-O51	96.6(3)	C44-C45-Si46	113.5(3)
C25-B24-C29	107.9(3)	C44-C45-H45a	110.7(4)
C25-B24-O51	107.8(3)	C44-C45-H45b	106.0(4)
C29-B24-O51	108.0(3)	Si46-C45-H45a	109.0(3)
B24-C25-C26	107.0(3)	Si46-C45-H45b	108.1(3)
B24-C25-C32	110.8(3)	H45a-C45-H45b	109.5(4)
B24-C25-H25	108.1(3)	C45-Si46-C47	108.34(18)
C26-C25-C32	112.1(3)	C45-Si46-C48	110.40(18)
C26-C25-H25	109.3(3)	C45-Si46-C49	107.19(19)
C32-C25-H25	109.4(3)	C47-Si46-C48	109.56(19)
C25-C26-C27	115.1(3)	C47-Si46-C49	109.00(18)
C25-C26-H26a	108.1(3)	C48-Si46-C49	112.24(18)
C25-C26-H26b	108.6(3)	Si46-C47-H47a	109.7(3)
C27-C26-H26a	107.7(3)	Si46-C47-H47b	109.0(3)
C27-C26-H26b	107.8(3)	Si46-C47-H47c	109.6(3)

H26a-C26-H26b	109.5(4)	H47a-C47-H47b	109.5(4)
C26-C27-C28	115.2(3)	H47a-C47-H47c	109.5(4)
C26-C27-H27a	107.6(3)	H47b-C47-H47c	109.5(4)
C26-C27-H27b	108.6(4)	Si46-C48-H48a	109.4(3)
C28-C27-H27a	107.6(3)	Si46-C48-H48b	109.6(3)
C28-C27-H27b	108.2(3)	Si46-C48-H48c	109.4(3)
H27a-C27-H27b	109.5(3)	H48a-C48-H48b	109.5(4)
C27-C28-C29	114.8(3)	H48a-C48-H48c	109.5(4)
C27-C28-H28a	107.9(3)	H48b-C48-H48c	109.5(4)
C27-C28-H28b	108.0(3)	Si46-C49-H49a	109.5(3)
C29-C28-H28a	108.3(3)	Si46-C49-H49b	109.7(3)
C29-C28-H28b	108.2(3)	Si46-C49-H49c	109.3(3)
H28a-C28-H28b	109.5(4)	H49a-C49-H49b	109.5(4)
B24-C29-C28	107.6(3)	H49a-C49-H49c	109.5(4)
B24-C29-C30	111.0(3)	H49b-C49-H49c	109.5(4)
B24-C29-H29	108.0(3)	C20-C50-H50a	109.2(3)
C28-C29-C30	112.8(3)	C20-C50-H50b	109.5(3)
C28-C29-H29	108.8(3)	C20-C50-H50c	109.7(4)
C30-C29-H29	108.4(3)	H50a-C50-H50b	109.5(4)
C29-C30-C31	114.5(3)	H50a-C50-H50c	109.5(4)
C29-C30-H30a	108.1(3)	H50b-C50-H50c	109.5(4)
C29-C30-H30b	108.7(3)	C23-O51-B24	113.0(3)
C31-C30-H30a	108.0(3)	C2s-O1s-C3s	105.5(6)
C31-C30-H30b	108.1(3)	C2s-C1s-H1sa	110.7(8)
H30a-C30-H30b	109.5(4)	C2s-C1s-H1sb	108.7(7)
C30-C31-C32	115.2(3)	C2s-C1s-H1sc	109.0(6)
C30-C31-H31a	108.0(3)	H1sa-C1s-H1sb	109.5(7)
C30-C31-H31b	108.1(3)	H1sa-C1s-H1sc	109.5(8)
C32-C31-H31a	108.0(3)	H1sb-C1s-H1sc	109.5(10)
C32-C31-H31b	108.1(3)	O1s-C2s-C1s	102.6(6)
H31a-C31-H31b	109.5(4)	O1s-C2s-H2sa	111.4(5)
C25-C32-C31	116.0(3)	O1s-C2s-H2sb	111.7(5)
C25-C32-H32a	108.1(3)	C1s-C2s-H2sa	110.6(6)
C25-C32-H32b	107.8(3)	C1s-C2s-H2sb	110.9(6)
C31-C32-H32a	107.7(3)	H2sa-C2s-H2sb	109.5(8)
C31-C32-H32b	107.6(3)	O1s-C3s-C4s	103.1(7)
H32a-C32-H32b	109.5(3)	O1s-C3s-H3sa	110.8(6)
N11-B33-N14	99.1(3)	O1s-C3s-H3sb	111.9(6)
N11-B33-C34	114.2(3)	C4s-C3s-H3sa	110.6(7)
N11-B33-C38	114.8(3)	C4s-C3s-H3sb	110.8(6)
N14-B33-C34	118.7(3)	H3sa-C3s-H3sb	109.5(9)
N14-B33-C38	105.6(3)	C3s-C4s-H4sa	109.3(7)
C34-B33-C38	104.5(3)	C3s-C4s-H4sb	109.4(6)
B33-C34-C35	112.2(3)	C3s-C4s-H4sc	109.6(5)
B33-C34-C41	109.4(3)	H4sa-C4s-H4sb	109.5(5)
B33-C34-H34	107.7(3)	H4sa-C4s-H4sc	109.5(6)

C35-C34-C41	109.9(3)	H4sb-C4s-H4sc	109.5(8)
C35-C34-H34	108.8(3)	C42-H42a-O43'	102.9(6)
C41-C34-H34	108.7(3)	O43'-H44a-C44	95.4(4)
C34-C35-C36	114.5(3)		

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