ABSTRACT

MCDOWELL, BRIAN. De Novo Synthetic Approaches to Hydroporphyrins. (Under the direction of Dr. Jonathan S. Lindsey.)

Hydroporphyrins are aromatic macrocycles that possess useful photochemical and electronic properties. Some notable naturally occurring hydroporphyrins that play important biological roles in nature include chlorophylls \(a\) and \(b\), the tolyporphins, and bacteriochlorophylls. Consequently, these compounds may have application in several biomedical and materials applications such as photodynamic therapy and information storage, respectively. Herein, the synthesis of simple hydroporphyrins (chlorins and bacteriochlorins) is described. The chemistry described should help facilitate the development of more elaborate and complex hydroporphyrins that may be used for the aforementioned applications.

Chlorins possessing zero or one meso-substituent were obtained by the acid-catalyzed condensation of a 1,3,3-trimethyltetrahydrodipyrrin and a 1-bromo-9-formyldipyrromethane to give tetrahydrobiladienes that are subsequently cyclized affording zinc-chlorins in 14-42% yield. Aryl substitution at the meso-positions of the chlorin macrocycle afforded slightly red-shifted \(Q_y\) bands that do not mimic the intense, long-wavelength absorption band characteristic of chlorophyll \(a\). However, the chemistry employed has recently resulted in the synthesis of several chlorins possessing substituents at the 3,13-positions with spectral properties similar to those of chlorophyll.

Bacteriochlorins absorb strongly in the near-infrared region and are attractive candidates for use in photodynamic therapy. The synthesis of a stable bacteriochlorin bearing 2,4,6-trimethylphenyl (mesityl) substituents at the 3,13-positions was achieved
through the self-condensation of the corresponding 3-aryl substituted dihydrodipyrrin acetal to afford the bacteriochlorin in 6% yield. X-ray crystal analysis verified the 3,13-disubstitution pattern. This 3,13-dimesityl bacteriochlorin exhibits spectral features \((Q_y = 726 \text{ nm}, \lambda_{em} = 729 \text{ nm})\) characteristic of naturally occurring bacteriochlorins but is far more stable.

Dihydrodipyrrins are important compounds that have been used extensively in chlorin and bacteriochlorin-forming reactions. Recently, enelactones have been shown to be useful synthetic intermediates in the synthesis of dihydrodipyrrins. Consequently, several exploratory routes to enelactones were examined. Among the routes examined, it was found that 2-Iodo-\(N\)-phenylsulfonylpyrrole could be efficiently coupled with 4-pentynoic acid to give the \(N\)-protected enelactone in >40% yield. The development of this new methodology may provide access to new dihydrodipyrrins. The dihydrodipyrrins may be used to access simple chlorins via a northern-southern approach.
De Novo Synthetic Approaches to Hydroporphyrins

By
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A dissertation submitted to the Graduate Faculty of
North Carolina State University
In partial fulfillment for the Degree of
Doctor of Philosophy

Chemistry

Raleigh, North Carolina, USA
2007

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DEDICATION

I like to give a special dedication to Dr. Alan S. Wingrove (Professor of Chemistry, Towson University) who passed away comfortably January 2007.
BIOGRAPHY

Brian Edward McDowell was born in Washington, D.C. on June 26, 1978. He is the oldest of three handsome sons of James and Acquanette McDowell.

He began his undergraduate studies at Morgan State University in the fall of 1996. After spending a year at Morgan, he transferred to Towson University in the fall of 1997 to study pre-medicine. Brian had taken organic chemistry with professor Dr. Alan Wingrove that year and was fascinated by the subject. Consequently, he graduated with honors from Towson University in 2001 with an undergraduate degree in chemistry.

Brian continued his higher education at the University of Virginia with Dr. James Marshall, where he studied the art of total synthesis using enantioenriched alkyltin reagents. In the summer of 2003, he graduated from Virginia with a MS in organic chemistry.

In the fall of 2003, he began his doctoral studies with Dr. Jonathan Lindsey. His research focused on the development of de novo synthetic approaches to hydroporphyrins that could be used in medicinal and materials applications.
ACKNOWLEDGMENTS

First, I would like to thank God and the blessings that were given to me. Secondly, I like to thank my parents and family for their support throughout my undergraduate and graduate career.

Special thanks to Dr. Jonathan Lindsey for allowing me to conduct research in this upcoming and exciting field of chemistry. I especially would like to thank Drs. Masahiko Taniguchi, Han-Je Kim, and Yao Zhen for advice on various issues. Additional thanks go out to all Lindsey lab members (old and present) for conducting themselves professionally and allowing for a pleasant work environment. I would also like to thank all of those who took their time to serve on my committee (Dr. Comins, Dr. Gorman, Dr. Wahl, and Dr. Peters). I also would like to thank Pfizer, Inc. for a predoctoral fellowship and NIH for supplying a supplemental grant for support.
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Chapter I. Introduction to Porphyrinic Molecules

IA. Structure and Properties.

In nature, porphyrinic macrocycles are ubiquitous. Some notable biological representatives of these important molecules include heme and the chlorophylls. Porphyrinic macrocycles may be categorized into two main groups, porphyrins and hydroporphyrins. Porphyrins and hydroporphyrins incorporate tetapyrrole units that are either fully unsaturated (porphyrins) or partially unsaturated (hydroporphyrins). Both porphyrins and hydroporphyrins are considered to be aromatic due to the conjugated 18 $\pi$-electron system present in each macrocycle.

1. Porphyrins.

The porphyrin macrocycle constitutes the main structure of heme as depicted in Figure I.1. Heme is an important molecule that serves as the oxygen-carrying cofactor of hemoglobin and also serves as an electron-transfer agent in respiratory chains.

![Figure I.1. Structure of the Biologically Important Porphyrin Heme.](image)

Porphyrins are heterocyclic molecules made up of four pyrrole rings that are linked on opposite sides ($\alpha$-position) through 4 methine bridges (=CH-) (Figure I.2). In regard to porphyrin nomenclature, the positions on the pyrrole ring that are not attached to the methine
bridges (α-position) are called the β-positions. Additionally, each methine bridge is referred to as a meso-position.

Porphyrians have received considerable attention due to their important roles in biological functions and their unique photo-physical and electronic properties. In recent years, porphyrin-based assemblies have been studied in various applications such as optoelectronics\textsuperscript{11} and solar cells\textsuperscript{12}. Porphyrins have also been extensively studied in biomedical applications such as photodynamic therapy (PDT)\textsuperscript{13} and magnetic resonance imaging.\textsuperscript{14}

![Figure I.2. Porphyrin Nomenclature.](image)

2. Chlorins.

Chlorins are categorized into the class of porphyrinic compounds known as the hydroporphyrins. Chlorins differ from porphyrins in possessing a reduced pyrrole ring in the macrocycle. The most recognized hydroporphyrins would be the chlorophylls (Figure I.3). Chlorophylls are considered one of nature’s most important cofactors by providing the basis for photosynthesis in plants. Although chlorins closely resemble porphyrins in structure, the reduced pyrrole ring alters the symmetry and path of conjugation in the molecule. This perturbation gives rise to profound differences in regards to their photochemical properties. This perturbation will be discussed more in depth in the following section.

The bacteriochlorins are also hydroporphyrins. Bacteriochlorins differ from porphyrins in possessing two reduced pyrrole rings that are located opposite to each other in the macrocycle. Some naturally occurring bacteriochlorophylls that are responsible for photosynthesis in bacteria include the bacteriochlorophylls (a, b, and g).

Bacteriochlorophyll a (Figure I.4) is the most widely distributed bacteriochlorin pigment among the bacteriochlorins mentioned.
Other naturally occurring bacteriochlorins include the tolyporphins such as tolyporphin A. Tolyporphin A (a dioxobacteriochlorin) was isolated by Moore and co-workers from the lipophilic extract of the cyanophyte microalga *Tolypothrix nodosa*. Additional tolyporphins that have been isolated include tolyporphins B-K.

In addition to the aforementioned hydroporphyrins, there are isobacteriochlorins, dodecahydroporphyrins, and other highly reduced hydroporphyrins that will not be discussed in detail here.

4. **Spectral Properties of Porphyrins and Hydroporphyrins.**

The porphyrin is a highly conjugated aromatic macrocycle. Due to the highly conjugated nature of these macrocycles, porphyrins and hydroporphyrins show strong absorption bands in the UV-visible absorption spectrum. For example, porphyrins strongly absorb around 400 nm (known as the Soret or B band). Porphyrins also weakly absorb in the range of 450-700 nm (known as Q bands). These absorption bands arise from electronic transitions via the molecular orbitals (HOMO-LUMO) of the porphyrin. For the Q band (made up of $Q_x$ and $Q_y$), the transition dipoles nearly cancel each other, giving rise to weak absorption bands. In Figure I.5, the absorption spectrum of a representative porphyrin (Mg-octaethylporphyrin, $\varepsilon = 408,000$ for B band) is displayed for comparison purposes.

The absorption spectra of hydroporphyrins are considerably different upon comparison to their porphyrin analogues. In particular, chlorins absorb more strongly in the red region of the spectrum versus that of porphyrins. As mentioned before, the prototypical chlorins are chlorophyll $a$ and $b$, which play a critical role in the process of photosynthesis.
The absorption spectrum of chlorophyll $a$ is shown in Figure I.5 (dashed line), whereas the $Q_y$ band is observed at 660 nm.

Bacteriochlorins absorb strongly in the red or near-IR region of the absorption spectrum when compared to both porphyrins and chlorins. Reduction of the second pyrrole ring affords a significant red-shifted $Q$ band. Another distinct difference is that bacteriochlorins absorb strongly in both the blue and red regions, while porphyrins only absorb strongly in the blue region. A representative bacteriochlorophyll (bacteriochlorophyll $a$) is shown in Figure I.5, where the $Q_y$ band is seen near 800 nm. Due to their strong absorption in the red region, bacteriochlorins are ideal candidates for medicinal applications such as photodynamic therapy (PDT), which will be described in the following section.

In summary, the reduction of porphyrinic macrocycles (porphyrins $\rightarrow$ hydroporphyrins) gives rise to profound changes in photochemical properties.
IB. Potential Biomedical Application.

1. Photodynamic Therapy.

Bacteriochlorins absorb strongly in the near-IR region. Consequently, these macrocycles may serve as photosensitizers in a variety of biomedical applications. One useful application is photodynamic therapy (PDT).

Photodynamic therapy is a medical technique that involves the selective uptake of a photosensitizer in cancerous or other diseased tissue. The technique involves a drug (photosensitizer) that is initially introduced into the patient’s body. After an appropriate ratio of the drug is accumulated in the tumor, the tissue is irradiated with light that leads to tumor necrosis. Presumably, cell necrosis occurs by initial excitation of the photosensitizer, followed by formation of toxic singlet oxygen ($^1O_2$).

![Figure 1.6. Structure of Photofrin.](image)

One of the first-generation photosensitizers, derived from hematoporphyrin-IX by treatment with acid, is called Photofrin® (Figure 1.6). Unfortunately, Photofrin® absorbs
weakly around 620 nm, and is a complex and inseparable mixture of monomers, dimers, and oligomers. In addition, Photofrin® is not very selective and results in skin photosensitivity.

Ideally, the photosensitizer should be easy to administer into the bloodstream (water-soluble) and also be hydrophobic to transverse the lipid membrane to gain access inside the cell. Lastly, the sensitizer should be able to absorb at longer wavelengths (particularly from 700-900 nm). The tetrapyrrolic core of bacteriochlorins is generally non-polar, but the polarity of the molecule may be tuned by attaching polar residues such as phosphates or amino acids to the perimeter of the macrocycle. Therefore, bacteriochlorins possessing water-solubilizing motifs could be employed as PDT drugs in the near future.

In summary, porphyrins and hydroporphyrins have received considerable attention due to their fascinating photochemical and electronic properties. The reduced pyrrole rings in chlorins and bacteriochlorins give rise to intense red-shifted Q bands (long-wavelength) in the UV-visible absorption spectrum. As a consequence of their strong absorption in the blue and near-IR region, these hydroporphyrins are very attractive for use in biomedical and materials applications. In the following chapters, several new synthetic routes to simple chlorins and bacteriochlorins will be described in detail. The chemistry employed should lead to the development of more elaborate and complex hydroporphyrins that may have use in a range of applications.
References


1. Introduction.

The rational synthesis of substituted porphyrins and chlorins relies heavily on dipyrromethane building blocks (II-1). Functionalization of the dipyrromethane at the 1- and 9-positions is possible due to the high reactivity of both α-pyrrolic positions towards electrophiles. Consequently, 1,9-difunctionalization (acylation, aminomethylation, bromination, chlorination, and formylation) of dipyrromethanes can be done in a relatively straightforward manner.

![Scheme II.1. Selective 1-Acylation of Dipyrromethanes.](image)

A more challenging task is the selective synthesis of 1-substituted dipyrromethanes, given the comparable reactivity of the 1- and 9-positions. Indeed, treatment of a dipyrromethane with an equimolar amount of an electrophilic reagent usually results in a statistical mixture of unreacted starting material, the desired 1-substituted product, and the 1,9-disubstituted derivative. Our lab has previously developed a selective method for 1-acylation of dipyrromethanes, employing a S-2-pyridyl thioate (Mukaiyama reagent) as an acylating agent for use with the magnesium salt of the dipyrromethane (Scheme II.1). On the other hand, no methods for selective 1-formylation of dipyrromethanes have been developed. Battersby reported a rational, albeit lengthy, six-step synthesis of 1-
formyldipyrromethane \textbf{II-2a} by using \textit{N}-mesyl-2-chloromethylpyrrole and an acetal of pyrrole-2-carboxaldehyde as building blocks (Scheme II.2).\textsuperscript{17} The most direct method at present for preparing 1-formyldipyrromethanes entails statistical Vilsmeier formylation of a dipyrromethane followed by extensive chromatography. Here we report two simple methods for more expeditious syntheses of 1-formyldipyrromethanes.\textsuperscript{18} The work reported here stems from a collaborative effort with Dr. Marcin Ptaszek in our lab.

![Scheme II.2. Battersby's Approach to 1-Formyldipyrromethane II-2a.](image)

2. Selective Tin-Complexation Approach.

The first approach to 1-formyldipyrromethanes relies on the selective tin-complexation and subsequent facile removal of the resulting 1,9-diformyldipyrromethane-dibutyltin species. Using standard Vilsmeier conditions, treatment of dipyrromethane \textbf{II-1a}\textsuperscript{19} afforded a mixture of the 1-formyldipyrromethane (\textbf{II-2a}) and the unwanted 1,9-diformyldipyrromethane (\textbf{II-3a}) (Scheme II.3). To facilitate separation of the formyldipyrromethane species, the mixture was treated with Bu$_2$SnCl$_2$ and TEA in CH$_2$Cl$_2$ at room temperature. The tin-complexation process\textsuperscript{110} is selective for the 1,9-diformyl species, yielding a hydrophobic 1,9-diformyldipyrromethane-dibutyltin complex (Bu$_2$Sn-\textbf{II-3a}) and the uncomplexed 1-formyldipyrromethane. The mixture was separated by flash chromatography to afford the desired 1-formyldipyrromethane \textbf{II-2a}. Similar treatment of
dipyrromethane II-1b\textsuperscript{II9} or II-1c\textsuperscript{II9} afforded 1-formyldipyrromethane II-2b\textsuperscript{II5} or II-2c in 27\% and 23\% yield, respectively. This procedure proved viable for small-scale preparations but partial decomplexation of the diformyl dipyrromethane-dibutyltin complex upon chromatographic separation limited larger scale implementation.

![Scheme II.3. Tin-Complexation Approach to 1-Formyldipyrromethanes.](image)

<table>
<thead>
<tr>
<th>R</th>
<th>Compd.</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>II-2a</td>
<td>28</td>
</tr>
<tr>
<td>phenyl</td>
<td>II-2b</td>
<td>27</td>
</tr>
<tr>
<td>mesityl</td>
<td>II-2c</td>
<td>23</td>
</tr>
</tbody>
</table>


This complementary method to the tin-complexation approach, which was developed in our lab by Dr. Marcin Ptaszek, employs the Grignard-mediated formylation of
dipyrromethanes. Only salient excerpts are described here. A more detailed investigation is described within the manuscript. This method provided 1-formyldipyrromethanes in moderate yields (28-65%). In addition, this method could be extended to various 5-

![Chemical Structure](image)

1-formyldipyrromethanes as depicted in Table II.1.

In summary, the two methods for 1-formylation are complementary both in conditions (acidic versus basic) and in selectivity (statistical Vilsmeier versus directed Grignard reaction). The Grignard-mediated reaction is particularly attractive owing to its simplicity, lack of formation of 1,9-diformyldipyrromethane, and broad scope. The recently described synthesis of 1-formyldipyrromethanes has allowed facile access to various chlorin
precursors (eastern halves). As a consequence, the synthesis of chlorins bearing zero or few substituents will be described in the next chapter.
Representative Experimental Procedures

General Procedure for Vilsmeier Formylation and Tin Complexation, Exemplified for 1-Formyl dipyrromethane (II-2a). Following a procedure for the formylation of dipyrromethanes,\textsuperscript{115} DMF (10 mL) was treated with POCl\textsubscript{3} (1.50 mL, 16.4 mmol) at 0 °C under argon and the resulting solution was stirred for 10 min (Vilsmeier reagent). A solution of II-1a (1.00 g, 6.84 mmol) in DMF (23 mL) at 0 °C under argon was treated with the freshly prepared Vilsmeier reagent (5.16 mL, 1.08 mol equiv) and the resulting solution was allowed to stir for 1.5 h at 0 °C. Saturated aqueous sodium acetate solution (76 mL) was added and the ice bath was removed. The mixture was then stirred for 4 h and allowed to warm to room temperature. The mixture was extracted with ethyl acetate. The organic extract was washed with brine, dried (MgSO\textsubscript{4}) and filtered. The filtrate was concentrated to afford a brown oil. Following a procedure for the dialkyltin complexation of 1,9-diacyldipyrromethanes,\textsuperscript{10} the crude oil was dissolved in CH\textsubscript{2}Cl\textsubscript{2} (34 mL) and treated with TEA (2.85 mL, 20.5 mmol) and Bu\textsubscript{2}SnCl\textsubscript{2} (2.08 g, 6.84 mmol). The mixture was stirred for 30 min at room temperature. The solvent was removed and the resulting oil was chromatographed [silica, hexanes/ethyl acetate (9:1 → 1:1 containing 1% TEA)] to afford a brown solid (338 mg, 28% overall): mp 115–116 °C (lit.\textsuperscript{117} 118 °C); \textsuperscript{1}H NMR \(\delta\) 4.04 (s, 2H), 6.06–6.13 (m, 1H), 6.14–6.18 (m, 2H), 6.70–6.72 (m, 1H), 6.93–6.95 (m, 1H), 8.62 (br s, 1H), 9.36 (s, 1H), 10.07 (br s, 1H); \textsuperscript{13}C NMR \(\delta\) 26.9, 106.9, 108.7, 110.9, 117.9, 124.9, 127.7, 132.4, 142.5, 179.1. Anal Calcd for C\textsubscript{10}H\textsubscript{10}N\textsubscript{2}O: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.72; H, 5.77; N, 15.97.

General Procedure for the Grignard-Mediated Formylation Exemplified for 1-Formyl-5-phenyl dipyrromethane (II-2b). A sample of II-1b (1.11 g, 5.00 mmol) in THF
(10 mL) was treated with MesMgBr (10.0 mL, 1 M in THF, 10 mmol). After 10 min, the mixture was cooled to –78 °C. Phenyl formate (1.09 mL, 10.0 mmol) was added in one portion. The reaction mixture was stirred at –78 °C for 1 h. The cooling bath was removed and stirring was continued for 1 h. The reaction was quenched by adding saturated aqueous NH₄Cl (~30 mL). The resulting mixture was extracted with CH₂Cl₂. The organic extract was washed (water, brine) and concentrated. The resulting oil was dissolved in CH₃CN (30 mL) and treated with 2 M aqueous NaOH (30 mL). The resulting mixture was stirred vigorously at room temperature for 1 h. Water (50 mL) was added and mixture was extracted with CH₂Cl₂. The organic phase was washed (saturated aqueous NH₄Cl, water, brine), dried (Na₂SO₄) and concentrated. The resulting dark oil was chromatographed [silica, CH₂Cl₂ → CH₂Cl₂/ethyl acetate (10:1)] to afford a light brown powder (0.457 g, 37%). The characterization data (¹H NMR, elemental analysis) were consistent with those obtained for the title compound prepared via Vilsmeier formylation (see manuscript).
References


Chapter III. Sparsely Substituted Chlorins as Core Constructs for Chlorophyll Analogue Chemistry

IIIA. Introduction.

The dihydroporphyrins known as chlorins constitute the chromophore of plant chlorophylls. In comparison with porphyrins, chlorins absorb more strongly in the red region of the spectrum. The prototypical chlorins are chlorophyll \( a \) and chlorophyll \( b \), whose structure and absorption spectra are shown in Figure III.1. The spectra differ owing to the presence of the methyl group or the formyl group at the 7-position. Thus, chlorin spectra can be significantly altered upon modification of even a single substituent.

![Absorption Spectra of Chlorophyll a and b and Chlorin Numbering System](image)

Figure III.1. Absorption Spectra of Chlorophyll a and b and Chlorin Numbering System.

To gain a deep understanding of the effects of substituents on the spectral properties of chlorins requires the ability to prepare chlorins bearing diverse patterns of substituents. To tailor chlorins for use in diverse applications also requires a fundamental understanding of how substituents alter reactivity. A comprehensive treatment of the effects of substituents requires access to chlorins bearing a systematic progression of substituents, beginning with no substituents and proceeding to one, two, or more groups at designated locations.
Surprisingly few systematic studies are available concerning the effects of substituents on chlorin properties. The dearth stems largely from synthetic limitations. Two simple routes to chlorins entail (1) derivatization of naturally occurring chlorins, and (2) reduction/derivatization of synthetic porphyrins. The former route is constrained by the numerous substituents present in the naturally occurring macrocycles. The lack of regioselectivity of the latter route typically limits the scope to the reduction of porphyrins having substitution patterns (giving 4-fold or 2-fold symmetry) wherein regioisomers cannot form. Benchmark chlorins of the latter type include meso-tetraphenylchlorin (H₂TPC) and octaethylchlorin (H₂OEC), which are commercially available, and 5,15-diphenylchlorin. Analogues such as meso-tetrakis(3-hydroxyphenyl)chlorin, 2,3-vic-dihydroxy-meso-tetraphenylchlorin, and diverse 5,15-diarylchlorins have been prepared for studies of photodynamic therapy.

The chlorin lacking any substituents, 2,3-dihydroporphine (known as “chlorin” itself, here termed H₂Chlorin; Figure III.2), has been the subject of theoretical calculations and numerous spectroscopic studies. The latter include fundamental studies to probe chlorin features, as well as spectral hole-burning experiments to probe the utility of chlorins in optical information storage applications. However, such a potentially valuable benchmark has not been employed for studies of reactivity (other than dehydrogenation), presumably owing to the limited quantities of available material. The only reported synthesis of H₂Chlorin entails Grignard-mediated cyclization of 2-(N,N-dimethylaminomethyl)pyrrole. Photoreduction of zinc porphine affords the corresponding ZnChlorin, but no preparative procedure has been reported. Regardless, all of the hydroporphyrins shown in Figure III.2 are susceptible in an aerobic environment to
adventitious dehydrogenation to give the porphyrin, and thus have limited stability toward routine handling in the laboratory.

![Diagram of some simple hydroporphyrins](image)

Figure III.2. Structure of Some Simple Hydroporphyrins.

The naturally occurring chlorins bonellin (a non-photosynthetic pigment) and Faktor I (a biosynthetic intermediate) each contain a geminal-dialkyl group in the pyrroline ring, which stabilizes the chlorin to dehydrogenation (Figure III.3). Total syntheses of these “C-methylated chlorins” and other naturally occurring chlorins have been developed; however, such syntheses are necessarily elaborate owing to the challenges of installing the multiple \( \beta \)-pyrrolic and pyrrolinic substituents.\(^{114}\)

![Diagram of bonellin and Faktor I](image)

Figure III.3. Structure of Bonellin and Faktor I.
The methodology developed for preparing bonellin and Faktor I has been extended to gain access to synthetic chlorins bearing more simple substituent patterns (while retaining the geminal-dimethyl group). Two routes that we developed in this regard include (I) reaction of a 9-bromodipyrromethane-1-carbinol (Eastern half) and a 1,3,3-trimethyltetrahydrodipyrrin (Western half), and (II) reaction of a 9-bromodipyrromethane-1-carboxaldehyde (Eastern half) and the same 1,3,3-trimethyltetrahydrodipyrrin (Western half). The two routes are shown in Scheme III.1. The Western half incorporates a geminal dimethyl group that ensures the presence of the reduced, pyrroline ring in the resulting chlorin, thereby precluding adventitious dehydrogenation leading to the porphyrin. In each case, the reaction proceeds in a two-step process of condensation of the Eastern and Western halves to give a 1-methyl-19-bromo-bilane derivative, and metal-mediated oxidative cyclization of the latter to give the corresponding chlorin.
The two routes are similar in a number of respects but also differ in the conditions for condensation, nature of the acyclic intermediate, and substituent patterns in the resulting chlorins. Route I has provided access to chlorins bearing two substituents (5,10-, III15 5,12-, III16 5,8- III16) or three substituents (2,5,12-, III16 5,10,15-, III17 5,10,20- III17) at sites other than the pyrroline ring, and each chlorin has contained a 5-substituent (see Figure III.1 for chlorin numbering system). Reasonable yields of chlorin macrocycle formation (12-45%) have facilitated preparation of 5,10-disubstituted chlorins in >100-mg quantities, as required for a variety of applications. Route II, developed very recently and described herein, has been applied to access zinc chlorins bearing two substituents (3,13-), three substituents (3,10,13-), and no meso- or β-pyrrole substituents. III15 By contrast with route I, where each chlorin contains a 5-substituent, the development of route II for the synthesis of sparsely substituted, 5-unsubstituted chlorins has presented a number of unexpected challenges.

In the following section, the synthesis of sterically uncongested, stable chlorins possessing no β-pyrrole substituents and no or only one meso-substituent (at the 5- or 10-position) is described. This work stems from a collaborative effort with Dr. Marcin Ptaszek, Dr. Masahiko Taniguchi, Dr. Han-Je Kim, and Dr. Paul Boyle.
IIIB. Synthesis.

1. Synthesis of Chlorins bearing 0-1 Substituents at the 10-Position.

We investigated five routes (I–V) to the target chlorin bearing no substituents (R = H) or one substituent at the 10-position (R = aryl), as shown in Scheme III.2. The 2 + 2 synthesis of a chlorin entails condensation of an Eastern half (composed of two pyrrole units) and a Western half (composed of one pyrrole and one pyrroline unit). The two halves must have complementary sets of reactive nucleophilic and electrophilic positions.

![Scheme III.2. Routes to 10-Substituted or Unsubstituted Chlorins.](attachment:Scheme III.2)
The routes differ from each other in the placement of reactive groups on the two halves: the α-pyrrolic position and the pyrrolinic methyl group react as nucleophiles, whereas the α-bromo-, formyl, and hydroxymethylpyrrolic groups serve as electrophiles.

The routes also differ in the nature of the intermediates expected upon condensation of the Eastern half and Western half. The intermediates are shown in the retrosynthetic scheme. Intermediate A is a 2,3,4,5-tetrahydrobilene-α, B is a 2,3,4,5-tetrahydrobiladiene-ab, and C is a 2,3,4,5-tetrahydrobilatriene-abc. While the intermediates obtained upon condensation are typically not characterized but instead are treated to the conditions for metal mediated oxidative cyclization, the differing oxidation state of A, B, and C are expected to give rise to different properties and ease of oxidation.

A key issue in the condensation concerns the lability of the Eastern half and Western half under the reaction conditions employed, particularly the level of acid employed in the condensation. A requirement for stronger acidic conditions is expected for the condensation in each of Routes I–V (pyrrolic-carboxaldehyde or 1° pyrrole-carbinol) to give a 5-unsubstituted chlorin versus that employed to give a 5-substituted chlorin (2° pyrrole-carbinol in Route I). However, strong acid causes the Western half (III-1) to undergo irreversible rearrangement to a bicyclic product, and Eastern halves can undergo cleavage. The liberation of free pyrrolic species upon acidolysis of an Eastern half opens the door to the formation of chlorin byproducts as well as porphyrin species. Dipyrrromethanes bearing meso-aryl substituents are more prone to acidolysis than those lacking a meso-substituent. Even in the absence of acid, bromo-dipyrrromethanes (e.g., many of the Eastern halves) are inherently reactive. Thus, conditions to force the reaction of Eastern and Western halves, such as strong acid or elevated temperature, are of limited utility.
(a) Route I:

Access to a 5-unsubstituted chlorin via route I (Scheme III.2) requires use of a 1° carbinol rather than a 2° carbinol. The synthesis of such chlorins required preparation of 1-formyldipyrromethanes. The 1-formyldipyrromethanes (II-2a-c) were prepared by the Vilsmeier-tin-complexation or the Grignard-mediated formylation method described in the previous chapter. Treatment of 1-formyldipyrromethanes II-2a-c with NBS gave the 1-bromo-9-formyldipyrromethanes II-3a-c in 55-78% yield (Scheme III.3).

\[
\begin{align*}
\text{II-2a-c} & \xrightarrow{\text{NBS, THF, -78 °C}} \text{II-3a-c} \\
\end{align*}
\]

Scheme III.3. Selective Bromination of 1-Formyldipyrromethanes.

Dr. Han-Je Kim and Dr. Marcin Ptaszek of this laboratory implemented the condensation-cyclization procedure with III-1 and II-3c-OH, the latter obtained by reduction of II-3c with NaBH₄. Reaction of II-3c-OH with III-1 under the standard conditions of TFA catalysis followed by metal-mediated oxidative cyclization afforded the corresponding chlorin ZnC-M¹⁰ in <1% yield (Scheme III.4). We attributed the low yield to the poor reactivity of the 1° carbinol. Related studies of the reaction of similar dipyrromethane-carbinols in porphyrin-forming conditions have also given quite low yields.¹¹¹⁹
(b) Route II.

We next turned our attention towards Route II, which utilizes a 1-bromo-9-formyldipyrromethane (Eastern half) and the tetrahydrodipyrrin (Western half). Initially, the condensation of 9-bromo-1-formyldipyrromethane (II-3a) and Western half III-1 was carried out with 1 equiv of BF$_3$·O(Et)$_2$ in CH$_3$CN, which gave no reaction after 15 minutes, while excess BF$_3$·O(Et)$_2$ resulted in decomposition of III-1. Battersby reported the condensation of a 1-formyldipyrromethane and a tetrahydrodipyrrin using $p$-toluenesulfonic acid monohydrate ($p$-TsOH) in MeOH, affording an intermediate 2,3,4,5-tetrahydrobiladiene-$ab$ on the path to a copper chlorin. Note that the Eastern half and Western half reactants employed by Battersby contained several $\beta$-substituents and no meso-substituents. We performed the condensation of II-3a and III-1 using 13.5 mM reactants and 5 molar equiv (68 mM) of $p$-TsOH in methanol. The putative protonated 2,3,4,5-tetrahydrobiladiene-$ab$ was observed with a maximum absorption centered at 480 nm (to be compared with Battersby’s tetrahydrobiladiene-$ab$ at 496 nm), an absorption characteristic of dipyrrin chromophores.
The crude mixture was then subjected to the standard conditions for metal-mediated oxidative cyclization, affording the desired zinc chlorin ZnC in 9% yield. The similar reaction of 9-bromo-1-formyldipyrrromethane II-3b or II-3c afforded ZnC-P or ZnC-M in 10% or 12% yield, respectively. A number of conditions were examined in an attempt to increase the overall yield of the condensation-cyclization sequence (Table III.1). The best conditions were found when employing an excess of p-TsOH (5 equiv) and increasing the concentration to 26 mM, which gave ZnC in 24% yield (Entry 8).

**Table III.1. Microscale Condensation Study in Chlorin Formation.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid</th>
<th>Molar equiv. of acid&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Solvent</th>
<th>Concentration [III-I] = [II-3a], mM</th>
<th>Yield of chlorin&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BF&lt;sub&gt;3&lt;/sub&gt;·O(Et)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>3</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CN</td>
<td>13.5</td>
<td>Decomposition of III-1</td>
</tr>
<tr>
<td>2</td>
<td>InCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>5</td>
<td>MeOH</td>
<td>26.3</td>
<td>No reaction&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>p-TsOH</td>
<td>5</td>
<td>MeOH</td>
<td>26.3</td>
<td>11%</td>
</tr>
<tr>
<td>4</td>
<td>p-TsOH</td>
<td>1</td>
<td>MeOH</td>
<td>100</td>
<td>No reaction&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>p-TsOH</td>
<td>5</td>
<td>MeOH</td>
<td>100</td>
<td>7%</td>
</tr>
<tr>
<td>6</td>
<td>p-TsOH</td>
<td>5</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;/MeOH (4:1)</td>
<td>6.92</td>
<td>10%</td>
</tr>
<tr>
<td>7</td>
<td>p-TsOH</td>
<td>5</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;/MeOH (4:1)</td>
<td>13.5</td>
<td>9%</td>
</tr>
<tr>
<td>8</td>
<td>p-TsOH</td>
<td>5</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;/MeOH (4:1)</td>
<td>26.3</td>
<td>24%</td>
</tr>
<tr>
<td>9</td>
<td>p-TsOH</td>
<td>10</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;/MeOH (4:1)</td>
<td>26.3</td>
<td>21%</td>
</tr>
<tr>
<td>10</td>
<td>p-TsOH</td>
<td>5</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;/MeOH (4:1)</td>
<td>51.3</td>
<td>22%</td>
</tr>
</tbody>
</table>

<sup>a</sup> Relative to concentration of [III-I] = [II-3a].<sup>b</sup> Isolated yield. Oxidative cyclization was performed with the putative tetrahydrobiladiene-<i>ab</i> (assumed 10 mM for quantitative formation), AgOTf (5 equiv), 2,2,6,6-tetramethylpiperidine (15 equiv), and Zn(OAc)<sub>2</sub> (15 equiv) in CH<sub>3</sub>CN (4 mL) exposed to air at 70 °C for 19 h.
Little or no biladiene observed by absorption spectroscopy; chlorin formation was not attempted.

Thus, the reaction was scaled-up employing 26 mM of each Eastern and Western half to afford workable quantities (66–104 mg) of $\text{ZnC}$, $\text{ZnC-P}^{10}$ or $\text{ZnC-M}^{10}$ in 16%, 33% or 42% yield, respectively (Scheme III.5). This procedure may be streamlined into a 3-step procedure. For example, Ptaszek later showed that \textbf{II-3a} can be brominated with NBS and the crude reaction mixture may be subjected to the condensation-cyclization procedure described above to afford $\text{ZnC}$ in 18% yield. The streamlined three-step procedure is advantageous in avoiding chromatography following step one, and employing a simple workup in step two.
(c) Routes III-IV.

The remaining routes III-V, which were attempted by Dr. Ptaszek, utilized several derivatives of the Eastern and Western halves employed in Route II. For example, route III utilized a dipyrrin analogue of the Eastern half instead of the typical 9-bromo-1-formyldipyrromethane. While routes IV and V utilized a 9-formyltetrahydrodipyrrin as the requisite Western half (Scheme III.2). Unfortunately, these routes only provided the desired chlorins in low yield (<10%) and were eventually abandoned. A more detailed description of these investigations may be found in the manuscript\textsuperscript{III21}. We chose route II as the most efficient route to chlorins and extended this methodology to gain access to various metallochlorins.

2. Modified AgOTf-Free Route to Metallochlorins.

We next turned to investigate alternative conditions for the metal-mediated, oxidative cyclization of the tetrahydrobiladiene-\textit{ab}. The traditional method employs Zn(OAc)$_2$, AgOTf and 2,2,6,6-tetramethylpiperidine in refluxing acetonitrile exposed to air. Prior omission/reconstitution experiments concerning route I revealed that omission of Zn(OAc)$_2$ or 2,2,6,6-tetramethylpiperidine resulted in failure to form any detectable chlorin, whereas omission of AgOTf gave chlorin, albeit in diminished yield.\textsuperscript{III15} Here, Ptaszek explored the cyclization in the presence of various metal salts and bases in refluxing solvents exposed to air, but without any AgOTf (i.e., a AgOTf-free step 3 in route II). In each case, the $p$-TsOH-catalyzed condensation of \textbf{III-1} and \textbf{II-3b} gave the crude reaction mixture containing \textbf{II-3b-Br}. The latter was neutralized with an appropriate base, dissolved in a given solvent, and treated with a base and metal salt (Scheme III.6). The resulting reaction mixture was
refluxed until the absorption spectrum remained relatively unchanged. The results are summarized in Table III.2.

![Scheme III.5. AgOTf-Free Synthesis of Metallochlorins.](image)

With a number of metal salts, the (AgOTf-free) metal-mediated oxidative cyclization of **II-3b-Br** gave the corresponding metallochlorin. Each metal reagent examined gave an absorption spectrum consistent with the metal complex of **II-3b-Br**, regardless of whether the chlorin ultimately was obtained. The metal reagents that successfully gave chlorin include Zn(II) (entries 1-3), Pd(II) (entries 4-6), Cu(II) (entries 7 and 8), In(III) (entries 9 and 10), and Sn(II) (entry 11) but not Mg(II), Co(II), Ni(II), Cd(II) or no metal (entries 12-17) under the conditions examined. The best yield typically was observed when 2,2,6,6-tetramethylpiperidine was used in acetonitrile. In the case of Cu(II), a better yield was observed for KOH/EtOH, conditions (entry 8) developed previously for the synthesis of palladium porphyrins. The procedure of acid-catalyzed condensation followed by AgOTf-free metal-mediated oxidation was applied to give milligram quantities of **CuC**, **PdC**, **CuC-P**₁⁰, **ZnC-P**₁⁰, and **PdC-P**₁⁰. Tetrapyrrolic complexes of Pd(II) and In(III) are
potentially useful in the life sciences for photodynamic therapy, and $^{111}$In chelates may be used for photosensitization, imaging, and/or radiotherapy applications.

**Table III.2.** Exploration of the Metal-mediated Oxidative Cyclization of a Tetrahydrobiladiene-$ab^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Metal salt</th>
<th>Base</th>
<th>Solvent</th>
<th>Product</th>
<th>Yield $^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Zn(OAc)$_2$</td>
<td>TMPi</td>
<td>MeCN</td>
<td>ZnC-P$^{10}$</td>
<td>37%</td>
</tr>
<tr>
<td>2</td>
<td>Zn(OAc)$_2$</td>
<td>DBU</td>
<td>MeCN</td>
<td>ZnC-P$^{10}$</td>
<td>9%</td>
</tr>
<tr>
<td>3</td>
<td>Zn(OAc)$_2$</td>
<td>DIEA</td>
<td>MeCN</td>
<td>ZnC-P$^{10}$</td>
<td>10%</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)$_2$</td>
<td>TMPi</td>
<td>MeCN</td>
<td>PdC-P$^{10}$</td>
<td>12%$^c$</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)$_2$</td>
<td>KOH$^d$</td>
<td>EtOH</td>
<td>PdC-P$^{10}$</td>
<td>5.6%$^c$</td>
</tr>
<tr>
<td>6</td>
<td>Pd(MeCN)$_2$Cl$_2$</td>
<td>KOH$^d$</td>
<td>EtOH</td>
<td>PdC-P$^{10}$</td>
<td>6.2%$^c$</td>
</tr>
<tr>
<td>7</td>
<td>Cu(OAc)$_2$</td>
<td>TMPi</td>
<td>MeCN</td>
<td>CuC-P$^{10}$</td>
<td>4%$^b$</td>
</tr>
<tr>
<td>8</td>
<td>Cu(OAc)$_2$</td>
<td>KOH$^d$</td>
<td>EtOH</td>
<td>CuC-P$^{10}$</td>
<td>14%$^c$</td>
</tr>
<tr>
<td>9</td>
<td>InCl$_3$</td>
<td>TMPi</td>
<td>MeCN</td>
<td>‘InC-P$^{10}$</td>
<td>29%</td>
</tr>
<tr>
<td>10</td>
<td>InCl$_3$</td>
<td>DIEA</td>
<td>MeCN</td>
<td>‘InC-P$^{10}$</td>
<td>8%</td>
</tr>
<tr>
<td>11</td>
<td>SnCl$_2$</td>
<td>TMPi</td>
<td>MeCN</td>
<td>SnC-P$^{10}$</td>
<td>5%</td>
</tr>
<tr>
<td>12</td>
<td>MgBr$_2$</td>
<td>TMPi</td>
<td>MeCN</td>
<td>--</td>
<td>0%</td>
</tr>
<tr>
<td>13</td>
<td>Co(OAc)$_2$</td>
<td>TMPi</td>
<td>MeCN</td>
<td>--</td>
<td>0%</td>
</tr>
<tr>
<td>14</td>
<td>NiCl$_2$</td>
<td>TMPi</td>
<td>MeCN</td>
<td>--</td>
<td>0%</td>
</tr>
<tr>
<td>15</td>
<td>CdCl$_2$</td>
<td>TMPi</td>
<td>MeCN</td>
<td>--</td>
<td>0%</td>
</tr>
<tr>
<td>16</td>
<td>No metal</td>
<td>TMPi</td>
<td>MeCN</td>
<td>--</td>
<td>0%</td>
</tr>
<tr>
<td>17</td>
<td>No metal</td>
<td>DBU</td>
<td>MeCN</td>
<td>--</td>
<td>0%</td>
</tr>
<tr>
<td>18</td>
<td>No metal</td>
<td>DIEA</td>
<td>MeCN</td>
<td>--</td>
<td>0%</td>
</tr>
</tbody>
</table>

$^a$The crude biladiene II-3b-Br was prepared by p-TsOH-catalyzed condensation of III-1 and II-3b under standard conditions. The reaction mixture was then neutralized by the base to be used in the metal-mediated oxidative cyclization (when KOH was used as a base in metal-mediated cyclization, crude II-3b-Br was neutralized by Et$_3$N). Unless noted otherwise each reaction was performed at 10 mM concentration with 15 equiv of metal salt and 30 equiv of base. $^b$Spectroscopic yield (from II-3b) unless noted otherwise, assuming a fixed molar absorption coefficient in all cases (see Experimental Section). $^c$Isolated yield. $^d$5 Equiv was employed. $^e$The chelate is In(III) with unknown counterion. $^f$Column chromatography (silica, ethyl acetate then THF) revealed the presence of two chlorin species, which proved difficult to separate and were not further characterized.

In summary, the reaction of 1-formyl-9-bromo-dipyrromethane and 2,3,4,5-tetrahydro-1,3,3-trimethyldipyrrin affords the corresponding chlorin bearing only a geminal dimethyl group at the 18-position. The reaction can be carried out in a three-step process (9-bromination of the 1-formylpyrrromethane, acid-catalyzed condensation to form the tetrahydrobiladiene-$ab$, and metal-mediated oxidative cyclization), in a streamlined manner
where the 1-formyl-9-bromo-dipyrromethane is used in crude form, and/or with an AgOTf-
free metal-mediated oxidative cyclization process. The AgOTf-free route provides direct
access to a selection of metallochlorins. Similar reaction enables synthesis of a chlorin
bearing one additional substituent at the 10-position. In conjunction with other synthetic
methods, simple routes are now available for preparing stable chlorins that bear no
substituents, a single substituent at the 5- or 10-position, or two or three distinct meso
substituents. All of the synthetic chlorins prepared herein were stable upon routine handling
in aerobic environments, including use of procedures such as chromatography,
recrystallization, and standing in solution on the open benchtop. The ready synthesis and
stability of the chlorins enabled the studies of reactivity and spectroscopic properties that will
be described in the upcoming sections.
IIIC. Reactivity.

The availability of stable chlorins bearing few or no meso substituents opens the door to a series of fundamental studies of reactivity as well as spectroscopic characterization. Studies of these sparsely substituted chlorins may serve as benchmarks for the naturally occurring chlorophylls, which bear a full complement of β-substituents. The presence of the geminal dimethyl group in the pyrroline ring renders these new synthetic chlorins more resilient toward synthetic manipulation than the existing model synthetic chlorins including meso-tetraphenylchlorin\textsuperscript{III14}, octaethylchlorin\textsuperscript{III15}, and chlorin\textsuperscript{III12}.

Here, we describe the examination of sparsely substituted synthetic chlorins in studies of fundamental reactivity. The studies include measuring the kinetics of deuteration for chlorins that bear 0, 1, 2, or 3 meso-substituents and no β-substituents, and assessing the regioselectivity of bromination in a series of chlorins that bear 0 or 1 meso-substituents. Selected bromo-chlorins have been subjected to Suzuki coupling reactions. Other reactions carried out include demetalation of zinc chlorins to give free base chlorins, metalation of a free base chlorin to give the magnesium chlorin, and oxochlorin formation. The following investigations were a collaborative effort with Dr. Marcin Ptaszek and Dr. Masahiko Taniguchi.

The shorthand nomenclature for the chlorins described herein employs the following abbreviations with superscripts to denote substituents and their positions: B (3,5-di-tert-butylphenyl), P (phenyl), M (mesityl), and T (p-tolyl). The chlorins examined include those bearing no meso substituents (ZnC); one meso substituent [(ZnC-B\textsuperscript{5}), (ZnC-T\textsuperscript{5})]; two meso substituents (H\textsubscript{2}C-T\textsuperscript{5}M\textsuperscript{10} and ZnC-T\textsuperscript{5}M\textsuperscript{10}); and
three meso substituents ($\text{H}_2\text{C-T}^5\text{M}^{10}\text{P}^{15}$ and $\text{ZnC-T}^5\text{M}^{10}\text{P}^{15}$). One oxochlorin ($\text{Oxo-H}_2\text{C-T}^5\text{M}^{10}$) also was examined.

1. Oxochlorin Formation.

Oxochlorins have more positive oxidation potentials compared with chlorins. To gain information regarding spectral properties, the chlorin benchmarks $\text{ZnC-B}^5$ and $\text{ZnC}$ were converted to their corresponding oxochlorins using an established procedure. Accordingly, $\text{ZnC-B}^5$ or $\text{ZnC}$ was heated in the presence of basic alumina followed by oxidation with DDQ, giving $\text{Oxo-ZnC-B}^5$ or $\text{Oxo-ZnC}$ in 47% or 56% yield, respectively (Scheme III.7).
2. Demetalation and Metalation of Chlorins.

Free base chlorins are valuable compounds and also serve as precursors to diverse metallochlorins. In this regard, the availability of zinc chlorins from the chlorin synthesis is particularly attractive given the facile demetalation of the zinc chelates in the presence of weak acid. Thus, treatment of each member of a series of zinc chlorins and a zinc oxochlorin (ZnC, ZnC-T⁵, ZnC-M¹⁰, ZnC-P¹⁰, or Oxo-ZnC) with TFA in CH₂Cl₂ afforded the corresponding free base species (H₂C, H₂C-T⁵, H₂C-M¹⁰, H₂C-P¹⁰, or Oxo-H₂C) in good yield (Scheme III.8).
The free base chlorin \( \text{H}_2\text{C} \) provided a convenient building block for the synthesis of simple metallochlorins that may be compared to naturally occurring chlorophylls. Therefore, we treated \( \text{H}_2\text{C} \) to a mild method for magnesium insertion\(^\text{III23} \) (MgI\(_2\) in CH\(_2\)Cl\(_2\) containing DIEA at room temperature), which afforded the magnesium chelate \( \text{MgC} \), a benchmark compound for comparison with chlorophylls (Scheme III.9). \( \text{MgC} \) underwent partial demetalation upon chromatography on basic alumina, or on standing in CH\(_2\)Cl\(_2\) solution, but was stable in toluene. Analysis of the isolated sample of \( \text{MgC} \) by \(^1\text{H} \) NMR spectroscopy showed the presence of H\(_2\)O, THF, and \( \text{MgC} \) in \(~\)12:1:2 ratio. Magnesium chlorins are often isolated as solids in conjunction with coordinative molecules.

![Scheme III.9. Synthesis of a Magnesium Chlorin.](image)

3. **Deuteration of Chlorins.**

Woodward first reported that chlorins possessing no meso substituents and a partial or full complement of \( \beta \)-substituents undergo deuteration preferentially at the meso sites (15- and 20-positions) flanking the pyrrole ring.\(^\text{III24} \) However, conclusions concerning relative
reactivity were restricted to the four meso sites owing to the presence of the blocking β-substituents. We recently examined the deuteration of chlorins bearing substituents only at the 5- and 10-positions and found that deuteration occurred preferentially at the 15- and 20-positions, but the presence of substituents at the 5- and 10-positions also limited the conclusions that could be drawn. Here we carried out analogous studies using the free base chlorin $\text{H}_2\text{C}$ and free base oxochlorin $\text{Oxo-H}_2\text{C}$, which has 10 sites potentially open to electrophilic aromatic substitution (six β-pyrrole and four meso-sites).

The following investigation was performed by Dr. Taniguchi. Five chlorins ($\text{H}_2\text{C}$, $\text{H}_2\text{C-T}^5$, $\text{H}_2\text{C-M}^{10}$, $\text{H}_2\text{C-T}^5\text{M}^{10}$, and $\text{H}_2\text{C-T}^5\text{M}^{10}\text{P}^{15}$) and two oxochlorins ($\text{Oxo-H}_2\text{C}$ and $\text{Oxo-H}_2\text{C-T}^5\text{M}^{10}$) were exposed to neat TFA-$d$ at 50 °C, and the exchange progress was measured by $^1\text{H}$ NMR spectroscopy (Scheme III.10).

![Scheme III.10. Deuteration of Chlorins.](image-url)
For example, dissolution of $\text{H}_2\text{C}$ in neat TFA-$d$ at 50 °C resulted in a steady decrease over a few hours in the intensity of the resonances from $\text{H}^{15}$ (9.26 ppm) and $\text{H}^{20}$ (9.19 ppm) (Figure III.4). By contrast, the resonances from the 5, 10-, and all $\beta$-protons remained intact over the duration of the experiment (up to 24 h). No deuteration other than at the 15- or 20-positions was observed with the chlorin samples examined herein.

![Figure III.4. $^1$H NMR spectra over time showing the deuteration of the 15- and 20-positions of chlorin $\text{H}_2\text{C}$ in TFA-$d$ at 50 °C.](image)

The data obtained obeyed first-order rate expressions quite closely; thus, rate constants ($k$) and half-lives ($t_{1/2}$) were calculated. The deuterium exchange of each proton was monitored to at least 50% conversion (except for $\text{H}^{15}$ of $\text{Oxo-H}_2\text{C}$ or $\text{Oxo-H}_2\text{C-T}^5\text{M}^{10}$, which was deuterated up to 40% conversion). These data were used to determine the correlation coefficient $R$ ($\geq 0.998$ in each case). This data, along with a more detailed discussion may be found in the manuscript. A brief summary of the findings is described below.
The major findings from the kinetic study of deuteration are as follows:

1. 15- versus 20-positions: The 15-position was ~3 times more reactive than the 20-position toward deuterium exchange in chlorins, versus the equivalent reactivity of the 15- and 20-positions in the symmetric H$_2$OEC (2,3,7,8,12,13,17,18-octaethylchlorin). This difference stems from the steric effect of the geminal-dimethyl group at the 18-position. On the other hand, the 15-position was ~3-times less reactive than the 20-position toward deuterium exchange in oxochlorins (Oxo-H$_2$C, Oxo-H$_2$OEC, and Oxo-H$_2$C-T$^5$M$^{10}$). The lesser reactivity of the 15-position in oxochlorins shows that the electron-withdrawing effect of the carbonyl group outweighs the steric effects of the 18-geminal dimethyl group. In summary, the order of reactivity toward deuterium exchange in the benchmark chlorin H$_2$C is 15 > 20 >> all other meso and β-positions, and the order for the benchmark oxochlorin Oxo-H$_2$C is 20 > 15 >> all other meso and β-positions.

2. Effects of meso-aryl substituents: The rate of the exchange of 15- and 20-positions depends largely on the number of meso-aryl substituents. The rate constants for H$_2$C, H$_2$C-T$^5$, and H$_2$C-M$^{10}$ showed almost identical values. The rate constants increase ~5-fold (15-position) and ~2-fold (20-position) upon introduction of two aryl groups in chlorins (H$_2$C-T$^5$M$^{10}$ versus H$_2$C). Similar effects are observed for oxochlorins, where the rate constants are increased 6.4-fold (15-position) and 4.4-fold (20-position) upon introduction of two aryl groups (Oxo-H$_2$C-T$^5$M$^{10}$ versus Oxo-H$_2$C). Introduction of three meso-aryl groups (H$_2$C-T$^5$M$^{10}$P$^{15}$) causes the rate constant to increase 10-fold (20-position). A tentative interpretation is that the meso-aryl groups stabilize the transition state (by inductive and/or resonance effects) more so than the ground state, thereby increasing the rate of reaction. High-level calculations are required to gain further insight into the origin of the
regiospecificity of deuteration and the role of meso-aryl groups in accelerating the rate of deuteration.

4. Halogenation and Coupling of Chlorins.

Prior studies have shown that chlorins undergo electrophilic halogenation at the meso sites flanking the pyrrole ring. Electrophilic bromination of ZnC was carried out using NBS in THF at room temperature (Scheme III.11). The 15-bromochlorin ZnC-Br\textsuperscript{15} was obtained accompanied by a small amount of dibromochlorins, as indicated by LD-MS analysis of the crude mixture. Substitution at the 15-position was confirmed upon \textsuperscript{1}H NMR spectroscopy. Trace amounts of dibrominated products in the purified fraction were observed by LD-MS and \textsuperscript{1}H NMR spectroscopy.

![Scheme III.11. Bromination of Metallochlorins.](image-url)
The purification of ZnC-Br\textsuperscript{15} proved to be difficult; therefore, we treated the crude reaction mixture to conditions for demetalation (TFA/CH\textsubscript{2}Cl\textsubscript{2}). Chromatographic separation of the free-base chlorin species proved easier than the corresponding zinc complexes. In this manner, H\textsubscript{2}C-Br\textsuperscript{15} was obtained in 56% yield, together with unreacted starting material (~5%) and one isolated (unidentified) dibromochlorin (~1%). Similar bromination of ZnC-P\textsuperscript{10} provided ZnC-P\textsuperscript{10}Br\textsuperscript{15} together with an unidentified (non-bromo) chlorin. Complete purification again was not achieved, and LD-MS analysis of the isolated sample of ZnC-P\textsuperscript{10}Br\textsuperscript{15} (95% purity, 51% yield) revealed the presence of traces of dibromochlorins. The chromatographic retention of otherwise hydrophobic zinc chlorins is dominated by the polar apical site of the zinc chelated macrocycle. Accordingly, we turned to the bromination of free base chlorins (Scheme III.12).
Thus, bromination of $\text{H}_2\text{C}$ under the same conditions employed for $\text{ZnC}$ provided $\text{H}_2\text{C-Br}^{15}$ in 51% yield (with recovery of 27% of starting material) without detectable formation of any dibrominated chlorin. Bromination of $\text{H}_2\text{C-M}^{10}$ provided the corresponding 15-bromochlorin $\text{H}_2\text{C-M}^{10}\text{Br}^{15}$ in 55% yield, together with traces of an unidentified dibromochlorin (~5%).

The availability of regioselective bromination has been exploited in the synthesis of a variety of substituted chlorins. Here, 15-bromination opens the door for further derivatization of sparsely substituted chlorins. Thus, Ptaszek showed that several free base and zinc chlorins could be successfully coupled to give the corresponding 15-substituted chlorins as depicted in Scheme III.13.

![Scheme III.13. Suzuki Coupling of Chlorins.](image-url)
In summary, reactivity studies of the unsubstituted chlorin $\text{H}_2\text{C}$ showed that the positions flanking the pyrroline ring (15- and 20-position) are most reactive (among four meso sites and six β-pyrrolic sites) toward deuteration in acidic media, with the 15-position reacting ~3-times faster than the 20-position. A single aryl group at the 5- or 10-position has little effect on the rate of deuteration, whereas two aryl groups (5- and 10-positions) increases the rate by ~5.5 fold. The 15-position of free base or zinc chlorins also was the most reactive site in the macrocycle toward electrophilic bromination. The sequence of bromination and palladium-mediated coupling provided access to chlorins with substituents at the 15- or 10,15-positions. Compared with prior benchmark chlorins, the unsubstituted chlorin $\text{H}_2\text{C}$ prepared herein and its metal chelates are more accessible, more stable, and therefore more amenable for diverse fundamental studies. The chlorins prepared herein also have been examined spectroscopically. This spectroscopic data will be discussed in the next section.
IIID. Structure and Properties.

The availability of stable chlorins bearing few or no meso substituents opens the door to a series of fundamental spectroscopic studies. Such studies may provide data that serve as benchmarks for the naturally occurring chlorophylls (which bear a full complement of β-substituents) and for complex molecular architectures containing synthetic chlorins.

Here, we describe the examination of a collection of sparsely substituted synthetic chlorins including the free base chlorin bearing no meso- or β-pyrrolic substituents (H₂C), its zinc chelate (ZnC), and analogues thereof. The studies include characterization of the ¹H NMR spectral properties of free base chlorins bearing 0–3 meso substituents; full assignment of the ¹³C NMR spectral properties of H₂C and ZnC accompanied by comparison with data for other model compounds and for chlorophyll a; characterization of the absorption spectra of H₂C, metal chelates thereof [Mg(II), Cu(II), Zn(II), Pd(II)], and determination of the X-ray structure of ZnC and the oxochlorin Oxo-ZnC. The results obtained from the synthetic chlorins begin to fill a lacuna that exists between the structurally complex chlorophylls and the simple synthetic chlorin model compounds prepared to date. Here, only the spectroscopic trends and X-ray data will be described. A full description of ¹H NMR and ¹³C NMR data can be found in the manuscript.¹²³⁷

1. Absorption and Fluorescence Properties.

The fully unsubstituted chlorins H₂C, MgC, and ZnC exhibit absorption and fluorescence spectral features similar to those of the corresponding derivatives of chlorin itself (H₂Chlorin, MgChlorin, and ZnChlorin, refer to Figure III.2). These data are displayed in Table III.3. On the other hand, the synthetic chlorins prepared herein lack
auxochromes at the 3- and 13-positions, which accentuate the long-wavelength transition of chlorophylls (which contain a 3-vinyl and 13-keto group). Hence the spectra of the synthetic chlorins typically exhibit less red absorption than the chlorophylls. The availability of the synthetic chlorins enables these differences to be probed in detail.

Table III.3. Spectral properties of chlorins.

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\lambda_B$ in nm (log $\varepsilon$)</th>
<th>$\lambda_{Qy}$ in nm (log $\varepsilon$)</th>
<th>$I_B/I_Q$</th>
<th>$\lambda_{em}$ in nm</th>
<th>$\Phi_f$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$H_2C$</td>
<td>389 (5.20)</td>
<td>634 (4.82)</td>
<td>2.4</td>
<td>636</td>
<td>0.19</td>
</tr>
<tr>
<td>$H_2$Chlorin</td>
<td>388 (5.11)$^d$</td>
<td>638 (4.70)$^d$</td>
<td>2.6</td>
<td>--</td>
<td>0.20$^e$</td>
</tr>
<tr>
<td>Pheo $a$</td>
<td>409 (5.06)$^f$</td>
<td>667 (4.74)$^f$</td>
<td>2.1</td>
<td>--</td>
<td>0.175$^g$</td>
</tr>
<tr>
<td>MgC</td>
<td>402 (5.35)</td>
<td>607 (4.65)</td>
<td>4.4</td>
<td>610</td>
<td>0.26</td>
</tr>
<tr>
<td>MgChlorin</td>
<td>402 (5.49)$^g$</td>
<td>610 (4.75)$^g$</td>
<td>5.5</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Chl $a$</td>
<td>429 (5.05)$^h$</td>
<td>661 (4.94)$^h$</td>
<td>1.3</td>
<td>666$^i$</td>
<td>0.325$^g$</td>
</tr>
<tr>
<td>ZnC$^a$</td>
<td>399 (5.38)</td>
<td>603 (4.84)</td>
<td>3.5</td>
<td>605</td>
<td>0.062</td>
</tr>
<tr>
<td>ZnChlorin</td>
<td>402$^i$</td>
<td>603$^i$</td>
<td>3.6</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Zn-Pheo $a$</td>
<td>423 (5.09)$^m$</td>
<td>653 (4.96)$^m$</td>
<td>1.38</td>
<td>657</td>
<td>0.23</td>
</tr>
<tr>
<td>OxoZnC</td>
<td>412 (5.19)</td>
<td>602 (4.65)</td>
<td>3.5</td>
<td>605</td>
<td>0.026$^n$</td>
</tr>
<tr>
<td>PdC</td>
<td>390</td>
<td>586</td>
<td>1.7</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>CuC</td>
<td>397</td>
<td>596</td>
<td>3.9</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

$^a$In toluene at room temperature unless noted otherwise. $^b$Ratio of the intensity of the B and Qy bands. $^c$Each $\Phi_f$ value was determined in toluene at room temperature with $\lambda_{exc}$ at the B band maximum using chlorophyll $a$ as a standard ($\Phi_f = 0.322$) unless noted otherwise (see text). $^d$Ref III12 (in benzene). $^e$Ref III29 (in propanol). $^f$Ref III1 (in diethyl ether). $^g$Ref III30 (in benzene). $^h$Ref III12 (in benzene). $^i$Ref III28 (in diethyl ether). $^j$Ref III15. $^k$Ref III32 (in n-octane). $^m$Ref III33 (in diethyl ether). $^n$Ref III34 (in diethyl ether).

An example of the difference in absorption spectra is provided by $H_2C$ and pheophytin $a$, the free base analogue of chlorophyll $a$ (Pheo $a$), as is shown in Figure III.5. The ratio of the intensity of the B and Qy bands ($I_B/I_Q$ ratio), which provides a measure of the relative amount of blue:red absorption, is greater for the synthetic chlorins than the chlorophylls. The most pronounced difference occurs in the magnesium chelates, where MgC exhibits an $I_B/I_Q$ ratio of 4.4 versus 1.3 for that of chlorophyll $a$. 46
The fluorescence quantum yields of the synthetic chlorins can be compared with those of other chlorins, including chlorophyll and its metalated analogues. The fluorescence quantum yield of \( \text{H}_2\text{C} \) is nearly identical with that of \textbf{Pheo} \( \text{a} \) (\( \Phi_f = 0.19 \) vs. 0.175), the yields for \textbf{MgC} and chlorophyll \( \text{a} \) are similar (0.26 versus 0.325), but a sizable disparity occurs for \textbf{ZnC} and \textbf{Zn-Pheo} \( \text{a} \) (0.062 vs. 0.23). The zinc-oxochlorins (\textbf{Oxo-ZnC}, \textbf{Oxo-ZnC-B}_5) exhibit even lower fluorescence yields (0.026, 0.029). The fluorescence quantum yield for \( \text{H}_2\text{C} \) and \( \text{H}_2\text{Chlorin} \) are nearly identical (\( \Phi_f \approx 0.20 \)). To our knowledge, fluorescence yield data are not available for \textbf{MgChlorin} and \textbf{ZnChlorin}.

\[ 
\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{absorption_spectra.png}
\caption{Absorption spectra of \( \text{H}_2\text{C} \) (solid line in toluene) and \textbf{Pheo} \( \text{a} \) (dashed line, in diethyl ether).}
\end{figure} 
\]

Thus, the geminal-dimethyl-substituted chlorins exhibit spectral attributes resembling those of the less stable analogues that have been prepared previously. The availability of diverse synthetic chlorins enables a number of spectral studies. The comparisons presented here concern the effects of core modification (metalation), and the effects of increasing number of meso substituents in free base chlorins.

The absorption spectra of several metallochlorins (\textbf{ZnC}, \textbf{CuC}, \textbf{MgC}, and \textbf{PdC}) are shown in Figure III.6. The absorption spectra of \textbf{CuC}, \textbf{MgC}, and \textbf{ZnC} exhibit the following
characteristic features: (i) blue shift of the $Q_y$ band (27 to 38 nm) compared to $H_2C$, (ii) narrower $B$ band ($fwhm = 10$ to $13$ nm) compared to $H_2C$ ($fwhm = 33$ nm), (iii) larger $I_B/I_Q$ ratio (3.5 to 4.4) compared to $H_2C$ (2.4).  

$PdC$ shows the following distinctive features versus $ZnC$: (i) a further blue shift of the $Q_y$ band (17 nm), (ii) broadening of the $B$ band ($fwhm = 26$ nm), and (iii) a smaller $I_B/I_Q$ ratio (1.7).

![Figure III.6](image)

**Figure III.6.** Absorption spectra of metallochlorins in toluene at room temperature. Legend: $PdC$ (a, purple), $CuC$ (b, red), $ZnC$ (c, blue), $MgC$ (d, green), and $H_2C$ (e, black).

The absorption spectra of free base chlorins with 0-3 substituents are displayed in Figure III.7 and the data is summarized in Table III.4.  The $B$ band and $Q_y$ band of the free base meso-substituted chlorins are steadily red shifted with increasing number of aryl substituents from 0 to 3, while the $I_B/I_Q$ ratio increases from 2.4 (unsubstituted) to 3.8 (trisubstituted).  The following observations concern the additive effects of meso-aryl groups giving rise to the red shift for both the $B$ and $Q_y$ bands: (i) The $Q_y$ band of chlorins is red shifted $\sim$4 nm by the introduction of each meso-aryl substituent regardless of the type or position of the substituent.  This effect was additive, giving a total red shift of $\sim$11 nm for the
Q_y band of the triaryl-substituted chlorin $\text{H}_2\text{C-}^5\text{T}^{10}\text{M}^{15}$. (ii) The magnitude of the red shift of the B band depends on both the type and position of the substituents: 5-position (14 nm for $p$-tolyl), 10-position (14 nm for phenyl, 11 nm for mesityl), and 15-position (6 nm for phenyl). Spectral trends similar to those described herein for chlorins also have been observed with porphyrins. Senge and co-workers reported absorption spectra of porphyrins that bear 1 to 4 meso-aryl substituents and noted a continual red shift of the absorption spectra with increasing number of aryl substituents.

![Figure III.7](image)

**Figure III.7.** Absorption spectra of free base chlorins with 0-3 meso-substituents in toluene at room temperature. Legend: $\text{H}_2\text{C}$ (a, black), $\text{H}_2\text{C-}^5\text{T}^{15}$ (b, green) $\text{H}_2\text{C-}^5\text{M}^{15}$ (c, purple), $\text{H}_2\text{C-}^5\text{P}^{15}$ (d, light blue), $\text{H}_2\text{C-}^5\text{P}^{15}$ (e, blue), and $\text{H}_2\text{C-}^5\text{T}^{15}\text{M}^{15}$ (f, yellow), and $\text{H}_2\text{C-}^5\text{T}^{15}\text{P}^{15}$ (g, red).
Table III.4. Spectral properties of free base chlorins with 0-3 substituents.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Number of</th>
<th>Compound</th>
<th>$\lambda_B$ (nm)</th>
<th>$\Delta\lambda_B$ (nm)\textsuperscript{b}</th>
<th>$\lambda_Qy$ (nm)</th>
<th>$\Delta\lambda_Qy$ (nm)\textsuperscript{b}</th>
<th>$I_B/I_Q$\textsuperscript{c}</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>H\textsubscript{2}C</td>
<td>389</td>
<td>-</td>
<td>634</td>
<td>-</td>
<td>2.4</td>
</tr>
<tr>
<td>1</td>
<td>H\textsubscript{2}C-T\textsuperscript{3}</td>
<td>403</td>
<td>+14</td>
<td>637</td>
<td>+3</td>
<td>2.9</td>
</tr>
<tr>
<td>1</td>
<td>H\textsubscript{2}C-M\textsuperscript{10}</td>
<td>400</td>
<td>+11</td>
<td>638</td>
<td>+4</td>
<td>2.5</td>
</tr>
<tr>
<td>1</td>
<td>H\textsubscript{2}C-P\textsuperscript{10}</td>
<td>403</td>
<td>+14</td>
<td>637</td>
<td>+3</td>
<td>2.8</td>
</tr>
<tr>
<td>1</td>
<td>H\textsubscript{2}C-P\textsuperscript{15}</td>
<td>395</td>
<td>+6</td>
<td>638</td>
<td>+4</td>
<td>2.6</td>
</tr>
<tr>
<td>2</td>
<td>H\textsubscript{2}C-T\textsuperscript{3}M\textsuperscript{10}</td>
<td>414</td>
<td>+25</td>
<td>641</td>
<td>+7</td>
<td>3.3</td>
</tr>
<tr>
<td>2</td>
<td>H\textsubscript{2}C-P\textsuperscript{10}P\textsuperscript{15}</td>
<td>408</td>
<td>+19</td>
<td>641</td>
<td>+7</td>
<td>3.1</td>
</tr>
<tr>
<td>3</td>
<td>H\textsubscript{2}C-T\textsuperscript{3}M\textsuperscript{10}P\textsuperscript{15}</td>
<td>418</td>
<td>+29</td>
<td>645</td>
<td>+11</td>
<td>3.8</td>
</tr>
</tbody>
</table>

\textsuperscript{a}In toluene at room temperature unless noted otherwise. \textsuperscript{b}Shift in peak wavelength from that of H\textsubscript{2}C. \textsuperscript{c}Ratio of the intensity of the B and Q\textsubscript{y} bands.

A deep understanding of the origin of the differences in spectral attributes and fluorescence yields will require additional spectroscopic and other physical studies. Such studies are now possible given the availability of the benchmark chlorins described herein as well as analogous chlorins bearing substituents at designated locations.

2. X-ray Crystal Structures.

More than 75 crystal structures of chlorins have been reported.\textsuperscript{III36} To our knowledge, however, there are no reported X-ray crystal structures of a chlorin lacking any substituents at the meso and $\beta$-pyrrolic positions, nor are there crystal structures of chlorins possessing relatively few (1-3) substituents. The typical synthetic chlorins that have been examined by X-ray crystallography contain a full complement of aryl or alkyl substituents at the meso or $\beta$-positions. Moreover, only a few crystal structures of oxochlorins have been reported, and these are for the iron or nickel chelate.\textsuperscript{III37}

Single crystals of the unsubstituted chlorin (ZnC) and the unsubstituted oxochlorin (Oxo-ZnC) were grown from dichloromethane/cyclohexane and subjected to X-ray crystallographic analysis. Key structural parameters are listed in the manuscript.\textsuperscript{III27} ORTEP
drawings of ZnC and Oxo-ZnC are shown in Figure III.8, together with the bond distances. The carbon-carbon bond lengths in the pyrroline ring are distinct from those in the three pyrrole rings due to the sp$^3$ versus sp$^2$ hybridization. In ZnC, for example, the C17-C18 distance (1.507 Å) or the C16-C17 distance (1.500 Å) is longer than the average of the corresponding bond distances in the pyrrole rings (1.340 or 1.434 Å, respectively). The distances between the zinc atom and the four nitrogen atoms resemble those of other chlorins. The distance between the zinc atom to the pyrroline nitrogen atom (2.103 Å for ZnC and 2.098 Å for Oxo-ZnC) in each case is longer than that between the zinc atom and the pyrrole nitrogen atom by ~0.04 to ~0.09 Å. Similar observations were reported for other metallochlorins (e.g., ZnTPC, PdOEC, FeOEC, NiTMC). The core size (pairwise distances between the four nitrogen atoms N1-N2, N2-N3, N3-N4, N4-N1) of ZnC, Oxo-ZnC, and ZnTPC give values that are similar to each other, with average nitrogen-nitrogen distances of 2.896, 2.908, and 2.906 Å, respectively. In each molecule, the N3-N4 and N4-N1 distances are slightly longer (~0.03 Å) than those for N1-N2 and N2-N3.

Figure III.8. Projection view of ZnC (left) and Oxo-ZnC (right), showing bond distances. The thermal ellipsoids are drawn at the 50% probability level. Hydrogen atoms are omitted for clarity. Estimated standard deviations on bond distances are 0.002 - 0.005 Å.
ZnC and Oxo-ZnC each crystallized with inclusion of cyclohexane in the unit cell (ZnC:cyclohexane = 2:1; Oxo-ZnC:cyclohexane = 1:1). Each unit cell of ZnC contains 8 chlorin molecules and 4 cyclohexane molecules, whereas each unit cell of Oxo-ZnC contains 4 chlorin molecules and 4 cyclohexane molecules. The molecular packing patterns in the unit cell of ZnC (left) and Oxo-ZnC (right) are shown in Figure III.9.

![Figure III.9. View of the molecular packing diagram of ZnC (left) and Oxo-ZnC (right). In the diagram for Oxo-ZnC, solvent molecules are omitted for clarity.]

The ZnC macrocycles are arranged as slipped cofacial dimers without any apical ligand at the zinc site; each zinc atom is tetracoordinate with a very slight out-of-plane distortion from square planar geometry. The presence of the 17-oxo group profoundly changes the packing pattern. The Oxo-ZnC macrocycles are arranged in a polymeric network owing to coordination of the carbonyl oxygen atom of one oxochlorin to the apical zinc atom of an adjacent oxochlorin. Each oxochlorin in a given polymer also forms a cofacial interaction with an oxochlorin in a neighboring polymer.

In summary, the unsubstituted chlorin (H₂C, ZnC), oxochlorin (Oxo-ZnC), and sparsely substituted analogues constitute benchmark macrocycles against which more complex hydroporphyrins can be compared. The absorption spectral data provide quantitative reference points for understanding how substituents alter electronic properties.
and shift spectral bands. The $^1$H NMR data and $^{13}$C NMR data may prove useful for characterizing more highly substituted chlorins. The X-ray data may establish the foundation for studies of crystal engineering, where substituents are employed to alter crystal-packing patterns and elicit desirable photophysical and electronic features.
Representative Experimental Procedures

**Bromination of 1-Formyldipyrrromethanes:**

1-Bromo-9-formyl-5-mesityldipyrrromethane (II-3c). Following the standard procedure, a solution of II-2c (43.5 mg, 0.149 mmol) in dry THF (4 mL) at -78 °C under argon was treated with NBS (26.5 mg, 0.149 mmol) and stirred for 30 min. Hexanes (4 mL) and water (4 mL) were added and the cooling bath was removed. The mixture was allowed to warm to room temperature and extracted with ethyl acetate, dried (MgSO₄) and filtered. The filtrate was concentrated to give a brown solid that was chromatographed [silica, ethyl acetate/hexanes (1:9 → 1:3)] and recrystallized (4:1 EtOH/H₂O) to afford light brown crystals (37 mg, 67%): mp 159 °C (dec.); ¹H NMR (THF-d₈) δ 2.05 (s, 6H), 2.22 (s, 3H), 5.49-5.52 (m, 1H), 5.74 (s, 1H), 5.80-5.85 (m, 1H), 5.89-5.92 (m, 1H), 6.76-6.78 (m, 1H), 6.80 (s, 2H) 9.38 (s, 1H), 10.45 (br s, 1H), 11.09 (br s, 1H); ¹³C NMR δ 22.2, 31.9, 41.5, 98.4, 110.7, 111.4, 112.2, 121.9, 131.9, 134.5, 135.3, 136.2, 138.0, 139.2, 143.6, 179.2; FAB-MS obsd 370.0664, calcd 370.0681 [M+H], (M = C₁₉H₁₉BrN₂O).

1-Bromo-9-formyldipyrrromethane (II-3a). Following the procedure for the preparation of II-3c, bromination of II-2a (200 mg, 1.15 mmol) and purification [silica, hexanes/ethyl acetate (3:1)] afforded a brown solid (226 mg, 78%): mp 88 °C (dec.); ¹H NMR δ 4.01 (s, 2H), 5.97–5.99 (m, 1H), 6.01–6.03 (m, 1H), 6.20–6.22 (m, 1H), 7.03–7.04 (m, 1H), 9.36 (s, 1H), 9.92 (br s, 1H), 11.35 (br s, 1H); ¹³C NMR δ 27.1, 97.5, 108.6, 110.3, 111.2, 125.6, 129.0, 132.4, 142.3, 179.3; FAB-MS obsd 251.9878, calcd 251.9898 [(M + H)⁺, M = C₁₀H₉BrN₂O].

**Chlorin Formation via Route II: Zn(II)-17,18-Dihydro-18,18-dimethylporphyrin (ZnC).** A solution of III-1 (308 mg, 1.62 mmol) and II-3a (411 mg, 1.62 mmol) in CH₂Cl₂
(50 mL) under argon was treated with a solution of $p$-TsOH·H$_2$O (1.56 g, 8.21 mmol) in distilled MeOH (12 mL). The resulting red mixture was stirred for 30 min under argon. A solution of 10% aqueous NaHCO$_3$ (100 mL) was added. The mixture was extracted with CH$_2$Cl$_2$. The organic extract was washed with water, dried (Na$_2$SO$_4$), and filtered. The filtrate was concentrated. The resulting brown solid was dissolved in CH$_3$CN (162 mL) and subsequently treated with Zn(OAc)$_2$ (4.46 g, 24.3 mmol), AgOTf (1.24 g, 4.86 mmol), and 2,2,6,6-tetramethylpiperidine (4.12 mL, 24.3 mmol). The reaction mixture was heated at 70 °C for 19 h in the presence of air. The mixture was concentrated and the resulting black residue was chromatographed [silica, CH$_2$Cl$_2$] to afford a bluish-green solid (104 mg, 16%): $^1$H NMR (THF-$d_8$) δ 2.05 (s, 6H), 4.58 (s, 2H), 8.67 (s, 1H), 8.70 (s, 1H), 8.69–8.72 (m, 1H), 8.75–8.77 (m, 1H), 8.90–8.94 (m, 2H), 9.05–9.08 (m, 2H), 9.61 (s, 1H), 9.63 (s, 1H); LD-MS obsd 403.9; FAB-MS obsd 402.0820, calcd 402.0823 (C$_{22}$H$_{18}$N$_4$Zn); $\lambda$$_{abs}$ 399 (log $\varepsilon$ = 5.38), 603 (4.84) nm; $\lambda$$_{em}$ 606 nm.

**AgOTf-free Route II to Metallochlorins: Pd(II)-17,18-Dihydro-18,18-dimethylporphyrin (PdC).** Following the AgOTf-free route, samples of III-1 (95 mg, 0.50 mmol) and II-3a (126 mg, 0.500 mmol) were dissolved in CH$_2$Cl$_2$ (15 mL). A solution of $p$-TsOH·H$_2$O (475.0 mg, 2.50 mmol) in anhydrous MeOH (5 mL) was added. The resulting mixture was stirred for 30 min and then treated with 2,2,6,6-tetramethylpiperidine (2.50 mL). The mixture was concentrated. The resulting yellow solid was dissolved in CH$_3$CN (50 mL). Samples of 2,2,6,6 tetramethylpiperidine (2.54 mL, 15.0 mmol) and Pd(OAc)$_2$ (0.338 g, 1.50 mmol) were added. The resulting mixture was refluxed exposed to air for 1 h. The resulting dark-green mixture was concentrated and chromatographed [silica, hexanes/CH$_2$Cl$_2$ (1:1)] to afford a violet-green solid (7.5 mg, 3%): $^1$H NMR δ 2.02 (s, 6H), 4.62 (s, 2H), 8.98 (d, $J$ =
4.4 Hz, 1H), 8.73 (s, 1H), 8.74 (d, \(J = 4.4\) Hz, 1H), 8.81 (s, 1H), 8.95–8.96 (m, 2H), 8.98 (d, \(J = 4.4\) Hz, 1H), 8.99 (d, \(J = 4.4\) Hz, 1H), 9.72 (s, 1H), 9.74 (s, 1H); LD-MS obsd 443.7; FAB-MS obsd 444.0557, calcd 444.0566 (C\(_{22}\)H\(_{18}\)N\(_4\)Pd); \(\lambda_{abs}\) 388, 585 nm.

**Oxochlorin Formation: Zn(II)-17,18-Dihydro-18,18-dimethyl-17-oxoporphyrin (Oxo-ZnC).** Following a general procedure, a mixture of ZnC (39 mg, 0.097 mmol) and basic alumina (activity I, 3.58 g) in toluene (4.5 mL) was stirred for 7 h at 50 °C exposed to air. After standard workup, the residue was dissolved in toluene (44 mL). DDQ (44 mg, 0.19 mmol) was added. Standard workup and chromatography [silica, CH\(_2\)Cl\(_2\)ÆCH\(_2\)Cl\(_2\)/MeOH (19:1)] gave a bluish-green solid (25 mg, 56%): \(^1\)H NMR \(\delta\) 2.04 (s, 6H), 8.65–8.68 (m, 2H), 8.83–8.86 (m, 2H) 8.98–8.99 (m, 2H), 9.05–9.07 (m, 1H), 9.30 (s, 1H), 9.36 (s, 1H), 9.44 (s, 1H); \(^{13}\)C NMR \(\delta\) 23.3, 49.4, 94.5, 96.0, 106.9, 109.4, 129.0, 129.6, 129.9, 130.7, 132.2, 132.9, 142.7, 147.1, 147.4, 148.7, 149.1, 150.8, 153.5, 163.9, 208.7; LD-MS obsd 415.5; FAB-MS obsd 416.0605, calcd 416.0616 (C\(_{22}\)H\(_{16}\)N\(_4\)OZn); \(\lambda_{abs}\) 412 (log \(\varepsilon = 5.19\)), 602 (4.65) nm; \(\lambda_{em}\) 605 nm.

**Demetalation of Zn-Chlorins: 17,18-Dihydro-18,18-dimethylporphyrin (H\(_2\)C).** Following a general procedure, a solution of ZnC (15.0 mg, 0.0371 mmol) in anhydrous CH\(_2\)Cl\(_2\) (13 mL) was treated with TFA (284 \(\mu\)L, 3.68 mmol). The mixture was stirred for 30 min at room temperature. The reaction mixture was quenched by addition of 10% aqueous NaHCO\(_3\) (50 mL) and extracted with CH\(_2\)Cl\(_2\). The organic extract was washed with water, dried (Na\(_2\)SO\(_4\)), and filtered. The filtrate was concentrated. Purification on a short column [silica, CH\(_2\)Cl\(_2\)] afforded a green solid (8.5 mg, 67%): \(^1\)H NMR \(\delta\) –2.60 to –2.44 (br, 2H), 2.07 (s, 6H), 4.66 (s, 2H), 8.94 (d, \(J = 4.4\) Hz, 1H), 8.98 (s, 1H), 8.99 (d, \(J = 4.4\) Hz, 1H), 9.06–9.10 (m, 2H), 9.08 (s, 1H), 9.24 (d, \(J = 4.4\) Hz, 1H), 9.26 (d, \(J = 4.4\) Hz, 1H), 9.86 (s,
1H), 9.89 (s, 1H); $^{13}$C NMR δ 31.5, 46.8, 52.2, 94.7, 96.7, 106.5, 106.9, 123.66, 123.72, 128.12, 128.20, 132.6, 132.8, 134.7, 135.0, 139.7, 140.5, 151.6, 151.9, 163.3, 174.9; LD-MS obsd 339.7; FAB-MS obsd 340.1692, calcd 340.1688 (C$_{22}$H$_{20}$N$_{4}$); λ$_{abs}$ 389 (log ε = 5.20), 634 (4.82) nm; λ$_{em}$ 636 nm.

**Bromination of Chlorins: Zn(II)-15-Bromo-17,18-dihydro-18,18-dimethylporphyrin (ZnC-Br$^{15}$).** Following a general procedure,$^{1117}$ a solution of ZnC (9.00 mg, 0.0223 mmol) in dry THF (11 mL) under argon was treated with NBS (3.97 mg, 0.0223 mmol). The mixture was stirred at room temperature for 30 min. CH$_2$Cl$_2$ (20 mL) was added. The mixture was washed with aqueous NaHCO$_3$. The organic extract was dried (Na$_2$SO$_4$) and filtered. The filtrate was concentrated. Purification on a short column [silica, hexanes/CH$_2$Cl$_2$ (1:1)] afforded a green solid (8.4 mg) that was ~85% pure: $^1$H NMR (THF-$d_8$) δ 2.05 (s, 6H), 4.64 (s, 2H), 8.62 (s, 1H), 8.74 (d, $J = 4.4$ Hz, 1H), 8.89 (d, $J = 4.4$ Hz, 1H), 8.93 (d, $J = 4.4$ Hz, 1H), 9.02–9.06 (m, 2H), 9.10 (d, $J = 4.4$ Hz, 1H), 9.57 (s, 1H), 9.63 (s, 1H); LD-MS obsd 479.9; ESI-MS obsd 479.9913, calcd 479.9928 (C$_{22}$H$_{17}$BrN$_4$Zn); λ$_{abs}$ 406, 607 nm.

**Suzuki Coupling of Bromochlorins: 17,18-Dihydro-18,18-dimethyl-10,15-diphenylporphyrin (H$_2$C-P$^{15}$).** Following a general procedure,$^{1117}$ samples of H$_2$C-Br$^{15}$ (42 mg, 0.10 mmol), 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (207 mg, 1.00 mmol), Pd(PPh$_3$)$_4$ (35 mg, 0.030 mmol), and K$_2$CO$_3$ (111 mg, 0.800 mmol) were weighed in a Schlenk flask. The flask was pump-purged with argon three times. A degassed mixture of toluene/DMF (3:1, 10 mL) was added. The resulting mixture was stirred at 90-95 °C for 20 h. The reaction mixture was diluted with CH$_2$Cl$_2$ and filtered. The filtrate was concentrated. Column chromatography [silica, hexanes/CH$_2$Cl$_2$ (1:3)] afforded a trace amount of putative
PdC-P$_{15}$ (first fraction, violet, < 1 mg) and the title compound (second fraction, green, 35 mg, 83%). Data for H$_2$C-P$_{15}$: $^1$H NMR $\delta$ –2.48 to –2.38 (br, 1H), –2.36 to –2.24 (br, 1H), 1.99 (s, 6H), 4.25 (s, 2H), 7.67–7.76 (m, 2H), 7.90–7.95 (m, 2H), 8.42 (d, $J = 4.4$ Hz, 1H), 8.99 (s, 1H), 9.00 (d, $J = 4.4$ Hz, 1H), 9.06–9.09 (m, 2H), 9.13 (d, $J = 4.4$ Hz, 1H), 9.24 (d, $J = 4.4$ Hz, 1H), 9.84 (s, 1H), 9.89 (s, 1H); $^{13}$C NMR $\delta$ 31.6, 46.4, 52.3, 94.9, 106.2, 107.4, 112.2, 123.6, 124.2, 127.70, 127.83, 128.2 (two peaks are overlapped), 132.5, 132.7, 133.0, 134.5, 135.4, 140.2, 140.4, 143.0, 151.4, 152.3, 162.6, 174.7; LD-MS obsd 415.9; FAB-MS obsd 416.1985, calcd 416.2001 (C$_{28}$H$_{24}$N$_4$); $\lambda_{abs}$ 395, 638 nm.
References


Chapter IV. Synthesis of a Bacteriochlorin Bearing Substituents at the 3,13-Positions

1. Introduction.

Bacteriochlorins are attractive compounds owing to their strong absorption in the red/near-IR spectral region. In particular, these reduced tetrapyrrolic macrocycles are ideal candidates for diverse photochemical applications and would serve as valuable components in molecular-based solar cells. The ability to prepare light-harvesting systems primarily depends on several factors that include: (1) readily accessible syntheses of stable bacteriochlorins bearing a variety of substituents, (2) the identification of simple bacteriochlorins which afford functionally active assemblies, and (3) the alignment of the transition dipole moment for the long-wavelength transition of the respective bacteriochlorins to give enhanced energy transfer.

There are only a few synthetic methods available for the preparation of bacteriochlorins. Early methods for preparing bacteriochlorins include the reduction of porphyrins or chlorins. Several examples include the reduction of meso-tetraphenylchlorin to meso-tetraphenylbacteriochlorin using Raney nickel,\textsuperscript{IV1} or the selective reduction of porphyrins employing diimide.\textsuperscript{IV2} Even though diimide reduction is a simple method for the preparation of bacteriochlorins, three distinct problems are evident: (1) the reduction of porphyrins with diimide affords a mixture of starting material, chlorins, bacteriochlorins and isobacteriochlorins; (2) separation and isolation of the bacteriochlorin is difficult; and (3) adventitious dehydrogenation affords the more stable chlorin and porphyrin species as illustrated in Figure IV.1.
Another established method for the preparation of bacteriochlorins involves the dihydroxylation of porphyrins to give tetrahydroxybacteriochlorins. In particular, Pandey et al. examined the effects of electron-withdrawing groups at the peripheral positions in the OsO₄-mediated hydroxylation of porphyrins to generate dioxobacteriochlorins after pinacol-

![Scheme IV.1. Preparation of Dioxobacteriochlorins using OsO₄.](image-url)
pinacolone rearrangement.\textsuperscript{IV3} The vicinal hydroxyl groups are cis owing to the use of OsO$_4$, but the two pairs of vicinal hydroxyl groups may adopt a syn or anti relationship owing to the two faces of the macrocycle (Scheme IV.1). A significant drawback of this method is that only porphyrins bearing $\beta$-substituents afford relatively stable bacteriochlorins. In addition, the hydroxylation method affords a mixture of isomers comprised of bacteriochlorins, chlorins, and isobacteriochlorins.

A number of cycloaddition reactions with porphyrins and chlorins have been reported to afford bacteriochlorins. For example, Yon-Hin and co-workers employed a double Diels-Alder reaction on divinylporphyrins to afford bacteriochlorin-like chromophores.\textsuperscript{IV4} Other well-precedented transformations include conjugate additions of $\beta$-nitrochlorins to give bacteriochlorins\textsuperscript{IV5} and 1,3-dipolar cycloadditions\textsuperscript{IV6} of meso-substituted chlorins to give glycoconjugated bacteriochlorins. Again, the aforementioned methods described usually afford a mixture of isomers and the resulting bacteriochlorins are rather labile.

A recent total synthesis of a nonphotosynthetic bacteriochlorin has been described by Kishi and co-workers.\textsuperscript{IV7} The total synthesis of the $O,O$-diacetate of tolyporphin A was carried out in $>20$ steps, affording $<5$ mg of product. After extensive studies, it was revealed that the synthetic derivative was identical to the $O,O$-diacetate derived from the naturally occurring tolyporphin A. Although the chemistry employed by Kishi was highly impressive, his synthetic method proved to be too lengthy and could not be used as a general method for preparing bacteriochlorins in significant quantities for fundamental studies.
Our lab has recently developed a *de novo* synthesis of stable bacteriochlorins. The approach relies on the self condensation of a dihydrodipyrrin-acetal in the presence of BF₃·O(Et)₂, which affords two free base bacteriochlorins (H-BC and MeO-BC) and a free base B,D-tetra(dehydro)corrin (TDC) as depicted in Scheme IV.2. The free base bacteriochlorins contained *p*-tolyl substituents at opposing (2,12) β-positions, and the absence or presence of a methoxy group at the 5-meso position (see Figure IV.2 for numbering system).

Pursuing a similar synthetic route, we were interested in stable bacteriochlorins bearing the 2,4,6-trimethylphenyl (mesityl) group at the 3,13-positions. We sought this particular bacteriochlorin because (1) our prior bacteriochlorins were substituted at the 2,12-positions and we wanted to establish methodology for gaining access to the 3,13-positions, and (2) the previous substituents were *p*-tolyl groups, and we wanted to probe the spectral effects of groups that were forced into a conformation more perpendicular to the bacteriochlorin framework. In addition, we anticipated that the 3,13-analogue would serve as
a convenient starting point for the synthesis of various metallobacteriochlorins (metal = Mg, Zn, Cu, Ni, Pd, Al). Spectroscopic studies of these benchmark compounds would set the stage for the preparation of more complex and elaborate bacteriochlorins that may be suitable for light-harvesting applications.

2. Synthesis.

We envisioned the 3,13-disubstituted bacteriochlorin Mes-BC would be readily obtained from the self-condensation of dihydrodipyrrin acetal IV-7, the latter derived from 3-mesitylpyrrole (IV-3) as illustrated in Scheme IV.3.

The synthesis of Mes-BC began with the attempted Knoevenagel condensation of mesitaldehyde with malonic acid monoethyl ester in refluxing pyridine utilizing a catalytic amount of piperidine (10 mol %), which afforded a 1:1 mixture of starting material and the
desired ester IV-1. Literature preparation of IV-1\textsuperscript{10}, which employed Wittig homologation of mesitaldehyde using commercially available (carboethoxymethylene)triphenylphosphorane proved superior and afforded the α,β-unsaturated ester (IV-1) in quantitative yield (Scheme IV.4).

![Scheme IV.4. Synthesis of β-Substituted Pyrrole IV-2.]

Subsequent cyclization of IV-1 employing van Leusen’s method\textsuperscript{IV10} with (p-tolylsulfonyl)methylisocyanide (TosMIC) under the standard conditions (NaH/Et\textsubscript{2}O) afforded the desired β-substituted pyrrole IV-2, albeit in rather low yield (28%). Improved yields were observed with THF as a co-solvent (Scheme IV.4).

![Scheme IV.5. Synthesis of Pyrrole Aldehyde IV-4.]

Decarboxylation of IV-2 using an excess of NaOH in ethylene glycol gave pyrrole IV-3 in 61% yield (Scheme IV.5).\textsuperscript{IV11} Initially, standard Vilsmeier-Haack formylation\textsuperscript{IV12} conditions with IV-3 produced a mixture of regioisomers, where formylation occurred at
both α-positions, to give the 2,4- and 2,3-isomers in a 2:1 ratio, respectively. Slightly improved regioselectivity (4:1) was observed upon slow dropwise addition of the Vilsmeier reagent to a solution of the pyrrole in DMF at 0 °C to afford predominantly the 2,4-isomer. Recrystallization (MeOH/H₂O) afforded exclusively the 2,4-isomer (IV-4) in 66% yield.

We next examined the Henry reaction of aldehyde IV-4 under various conditions. Recently, a new route for the synthesis of 2-(2-nitrovinyl)pyrrole that involves the dropwise addition of n-propylammonium acetate to a solution of pyrrole-2-carboxaldehyde in nitromethane has been described.¹⁴

Thus, treatment of IV-4 under the latter conditions, followed by reduction with NaBH₄ in a mixture of silica in CHCl₃/i-PrOH afforded a mixture of the 2-(2-nitroethyl)pyrrole and a significant amount of unidentified byproducts. Fortunately, the previously used Henry reaction and reduction procedure¹¹ using nitromethane in the presence of KOAc and methylamine hydrochloride, followed by reduction with NaBH₄ in THF/MeOH cleanly gave the desired 2-(nitroethyl)pyrrole. The 2-(2-nitroethyl)pyrrole was found to be labile and decomposition was observed within a few hours. Thus, we immediately treated the crude 2-(2-nitroethyl)pyrrole with acetal IV-5⁴¹ in DBU, which afforded hexanone IV-6 as a black oil in three steps (49% overall yield). Treatment of IV-6
with NaOMe, followed by treatment with a buffered TiCl$_3$ solution afforded the dihydrodipyrrin-acetal IV-7 in 32% yield (Scheme IV.6).

Acetal IV-7 was found to decompose immediately upon removal of solvent (~85% pure by $^1$H NMR spectroscopy). Accordingly, the acetal was immediately subjected to

\[
\text{Mes} \quad \text{IV-7} \quad 6\% \quad \text{BF}_3\cdot\text{O(Et)}_2 \quad \text{CH}_3\text{CN}
\]

\[
\text{Mes-BC}
\]

Scheme IV.7. Synthesis of Mes-BC.

bacteriochlorin formation using BF$_3$·O(Et)$_2$ in CH$_3$CN. After stirring for 24 h and subsequent purification by flash chromatography, bacteriochlorin Mes-BC was isolated as the only product, albeit in 6% yield (Scheme IV.7). Again, no other porphyrinic species were obtained (i.e., 5-methoxy substituted bacteriochlorin or the corresponding tetradehydrocorrin). It is unclear whether the low yield and the lack of formation of other porphyrinic species stems from the instability of IV-7, and/or steric considerations at the $\alpha$-position imposed by the mesityl group.

Although the yield in the macrocycle formation step was low, valuable information was gained regarding the spectral properties of \textbf{Mes-BC}. \textbf{Mes-BC} exhibited spectral properties that are characteristic of naturally occurring bacteriochlorins (Figure IV.3). A noteworthy feature of \textbf{Mes-BC} is the following: The $Q_y$ band appears at 726 nm, versus 744 nm for the 2,12-di-$p$-tolylsubstituted bacteriochlorin (\textbf{H-BC}, which lacks a methoxy group at the 5-meso position). The blue-shifted $Q_y$ band may result from (1) the preferred perpendicular alignment of the mesityl groups with respect to the macrocycle, which results in diminished $\pi$-conjugation with the bacteriochlorin macrocycle, or (2) the placement of aryl substituents at the 3,13-positions. Further studies will be needed to understand substituent effects on the long-wavelength absorption band ($Q_y$) in bacteriochlorins.

![Absorption Spectrum of Mes-BC](image)

\textit{Figure IV.3. Absorption Spectrum of Mes-BC in Toluene.}

In addition, the 3,13-dimesityl substituted bacteriochlorin gave considerably sharper Soret and $Q_y$ bands in the absorption spectrum (Figure IV.3) versus that of the 2,12-di-$p$-tolylbacteriochlorin analogue \textbf{H-BC}. As a result of the sharp absorption bands, water-soluble
bioconjugatable analogues of Mes-BC could serve as markers in flow cytometry. The sharp bands may stem from the rigidification of the bacteriochlorin macrocycle due to the steric nature of the mesityl groups.

![Figure IV.4. X-ray Structure of Mes-BC.](image)

A single crystal X-ray structure of Mes-BC was obtained, which verified the 3,13-substitution pattern (Figure IV.4). As expected, each mesityl group is forced into a perpendicular arrangement with respect to the macrocyle to minimize any potential steric interaction. Due to the C$_{2h}$ symmetry of the molecule, a simple $^1$H NMR spectrum was observed. The spectrum includes characteristic NH- and gem-dimethyl protons at –2.16 ppm and 1.96 ppm, respectively. In addition, this synthetic bacteriochlorin is stable upon routine handling in light and an aerobic environment.

In summary, the ability to construct self-assembling architectures relies on readily accessible syntheses of bacteriochlorins that allow for the introduction of various substituents at designated sites. Following our established route for the synthesis of stable bacteriochlorins, the synthesis of a bacteriochlorin bearing mesityl groups at the 3,13-
position was achieved. A regioselective Vilsmeier-Haack formylation was employed to set the 3,13-substitution pattern in the macrocycle. Introduction of aryl substituents at the 3,13-position resulted in a slightly blue-shifted Qy band (726 nm versus 744 nm for H-BC). Although Mes-BC was not ideal for the preparation of various metallobacteriochlorins, water-soluble bioconjugatable analogues of Mes-BC could potentially serve as markers in flow cytometry or other life sciences applications.
Experimental Procedures

3-(Ethoxycarbonyl)-4-(2,4,6-trimethylphenyl)pyrrole (IV-2). Following Van Leusen’s method, a suspension of TosMIC (12.0 g, 61.5 mmol) and the known α,β-unsaturated ester IV-1 (12.8 g, 58.6 mmol) in anhydrous Et₂O/DMSO (2:1) (281 mL) was added dropwise under argon into a stirred suspension of NaH (3.07 g, 60% dispersion in mineral oil, 76.8 mmol) in anhydrous THF (118 mL). After stirring for 2.5 h, water (260 mL) was carefully added. The mixture was extracted with ether and CH₂Cl₂. The extracts were dried (Na₂SO₄) and filtered. The filtrate was concentrated to afford a yellow oil. Purification [silica, ethyl acetate/hexanes (1:9 → 1:3) gave a white solid (9.13 g, 60%): mp 164–165 °C; ¹H NMR δ 1.08 (t, J = 7.2 Hz, 3H), 2.03 (s, 6H), 2.30 (s, 3H), 4.07 (q, J = 7.2 Hz, 2H), 6.54–6.56 (m, 1H), 6.89 (s, 2H), 7.53–7.55 (m, 1H), 8.47 (br s, 1H); ¹³C NMR δ 14.3, 21.0, 21.3, 59.5, 117.9, 124.6, 127.7, 129.7, 130.6, 132.3, 136.3, 137.7, 165.2; FAB-MS obsd 257.1414, calcd 257.1416 (C₁₆H₁₉NO₂).

3-(2,4,6-Trimethylphenyl)pyrrole (IV-3). Following a standard procedure, a mixture of IV-2 (7.00 g, 27.2 mmol) in ethylene glycol (70 mL) was degassed with argon for 10 min. Powdered NaOH (10.9 g, 272 mmol) was added, and the mixture was placed in an oil bath at 120 °C. The oil bath was raised to 160 °C, and the resulting mixture was heated under argon for 3 h. The mixture was then cooled to room temperature, and 10% aqueous NaCl (90 mL) was added. The aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with 10% aqueous NaCl, dried (Na₂SO₄) and filtered. The filtrate was concentrated to afford a brown oil. Purification on a column [deactivated silica (2.5% TEA), CH₂Cl₂] gave a brown solid (3.05 g, 61%). Note: Purification with alumina affords a colorless solid which can be stored up to several months.
at 0 °C with negligible decomposition versus to the fast decomposition of IV-3 when using deactivated silica (1-2 weeks): mp 105–106 °C; ¹H NMR δ 2.34 (s, 6H), 2.50 (s, 3H), 6.28–6.29 (m, 1H), 6.72–6.73 (m, 1H), 6.97–6.98 (m, 1H), 7.12 (s, 2H), 8.23 (br s, 1H); ¹³C NMR δ 21.4, 21.6, 110.4, 116.7, 117.8, 122.4, 128.4, 133.9, 136.3, 138.1; FAB-MS obsd 185.1201, calcd 185.1204 (C₁₃H₁₅N).

2-Formyl-4-(2,4,6-trimethylphenyl)pyrrole (IV-4). Following a similar procedure, anhydrous DMF (20 mL) was treated with freshly distilled POCl₃ (3.0 mL, 32.8 mmol) at 0 °C under argon and stirred for 10 min. A solution of IV-3 (2.75 g, 14.8 mmol) in DMF (51 mL) at 0 °C under argon was treated with the freshly prepared Vilsmeier reagent (11.2 mL, 1.08 equiv), and the resulting solution stirred for 1.5 h at 0 °C. Saturated aqueous sodium acetate solution (165 mL) was added, and the ice bath was removed. The mixture was then stirred for 4 h, slowly warming to room temperature. The mixture was extracted with ethyl acetate. The combined organic extracts were washed with water, dried (Na₂SO₄), and filtered. The filtrate was concentrated. The resulting oil was chromatographed [silica, CH₂Cl₂ → CH₂Cl₂/ethyl acetate (9:1)] to afford a light brown solid. ¹H NMR spectroscopy revealed a ~4:1 mixture of regioisomers. The resulting solid was recrystallized twice (MeOH/H₂O) to afford exclusively the 2,4-regioisomer (2.08 g, 66%): mp 154–155 °C; ¹H NMR δ 2.19 (s, 6H), 2.38 (s, 3H), 6.94–6.95 (m, 1H), 7.01 (s, 2H), 7.12–7.14 (m, 1H), 9.59 (s, 1H), 11.0 (br s, 1H); ¹³C NMR δ 21.3, 21.4, 123.4, 125.5, 127.0, 128.5, 131.5, 133.1, 137.2, 137.7, 179.9; FAB-MS obsd 214.1214, calcd 214.1232 [M+H], (M = C₁₄H₁₅NO).

1,1-Dimethoxy-4,4-dimethyl-6-[4-(2,4,6-trimethylphenyl)pyrrol-2-yl]-5-nitro-2-hexanone (IV-6). Following an established procedure, a mixture of IV-4 (2.00 g, 9.38
mmol), KOAc (1.01 g, 10.3 mmol), methyamine hydrochloride (760 mg, 11.3 mmol) in nitromethane (84 mL) and anhydrous THF (10 mL) under argon was stirred for 3 h. The reaction mixture was quenched with brine and extracted with ethyl acetate. The extracts were dried (Na$_2$SO$_4$) and filtered. The filtrate was concentrated to give an orange solid. The solid was subsequently dissolved in THF/MeOH (98 mL, 9:1), and the solution was brought to 0 °C. NaBH$_4$ (1.07 g, 28.2 mmol) was added in portions, and the ice bath was removed. The mixture was stirred for 45 min at room temperature and immediately quenched with acetic acid (1.6 mL). Water was added, and the mixture was extracted with ethyl acetate. The extracts were then dried (Na$_2$SO$_4$) and filtered. The filtrate was passed through a pad of silica (eluted with ethyl acetate). The solvent was then concentrated to give a yellow oil. Due to the instability of the nitroethylpyrrole, the oil was immediately used in the next step. Following the general procedure, the crude nitroethylpyrrole and acetal IV-5 (2.22 g, 14.1 mmol) were subsequently treated with DBU (4.22 mL, 28.2 mmol). The reaction mixture was then stirred for 18 h at room temperature. The mixture was then diluted with ethyl acetate and washed with water. The organic layer was dried (Na$_2$SO$_4$) and filtered. The filtrate was concentrated. The resulting oil was chromatographed [silica, ethyl acetate/hexane (1:9 → 1:3)] to give a dark orange oil (1.92 g, 49% over 3 steps): $^1$H NMR δ 1.17 (s, 3H), 1.25 (s, 3H), 2.10 (s, 6H), 2.30 (s, 3H), 2.59–2.78 (m, 2H), 3.09 (d, $J = 15.4$ Hz, 1H), 3.33–3.38 (m, 1H), 3.44 (s, 6H), 4.38 (s, 1H), 5.17–5.21 (m, 1H), 5.84 (s, 1H), 6.45 (s, 1H), 6.90 (s, 2H) 8.10 (br s, 1H); $^{13}$C NMR δ 21.3, 24.5, 27.2, 36.7, 45.3, 55.4, 95.2, 104.9, 109.3, 116.4, 122.7, 125.8, 128.1, 133.5, 136.1, 137.8, 203.9; FAB-MS obsd 417.2395, calcd 417.2389 [(M + H)$^+$, M = C$_{23}$H$_{32}$N$_2$O$_5$].
1-(1,1-Dimethoxymethyl)-3,3-dimethyl-8-(2,4,6-trimethylphenyl)-2,3 dihydrodipyrrin (IV-7). Following the standard procedure, a solution of IV-6 (1.23 g, 2.95 mmol) in anhydrous THF (14 mL) under argon was treated with NaOMe (799 mg, 14.8 mmol) and the resulting mixture stirred for 1 h at room temperature. In a separate flask, a freshly prepared solution of TiCl₃ (8.6 wt % TiCl₃ in 28 wt % HCl, 22.1 mL, 14.8 mmol, 5 mol equiv) and H₂O (114 mL) were combined; NH₄OAc (91.0 g, 1.18 mol) was added to buffer the solution to pH 6, and then THF (8 mL) was added. The solution containing the nitronate anion was then transferred via a cannula to the freshly prepared buffered TiCl₃ solution and the resulting mixture was stirred for 6.5 h at room temperature under argon. The mixture was then extracted with ethyl acetate. The combined organic extracts were washed with 10% aqueous NaHCO₃ and water, dried (Na₂SO₄), and filtered. The filtrate was concentrated. The crude product was chromatographed [alumina, CH₂Cl₂/hexane (1:1) → CH₂Cl₂ → ethyl acetate] to give an orange oil (343 mg, 32%). Note that decomposition of IV-7 was observed by TLC immediately after purification (~85% pure by ¹H NMR spectroscopy): ¹H NMR δ 1.28 (s, 6H), 2.22 (s, 6H), 2.35 (s, 3H), 2.67 (s, 2H), 3.50 (s, 6H), 5.07 (s, 1H), 5.95 (s, 1H), 6.08 (s, 1H), 6.70 (s, 1H), 6.95 (s, 2H), 10.7 (br s, 1H); ¹³C NMR δ 21.3, 21.5, 29.4, 40.4, 48.4, 54.9, 103.1, 107.8, 111.2, 118.7, 122.6, 128.2, 130.6, 133.8, 136.1, 137.9, 159.4, 174.2.

8,8,18,18-Tetramethyl-3,13-bis(2,4,6-trimethylphenyl)bacteriochlorin (Mes-BC). Following a similar procedure, a solution of IV-7 (322 mg, 0.879 mmol) in 21 mL of CH₃CN was treated with BF₃·O(Et)₂ (891 µL, 7.03 mmol). The resulting mixture was then stirred for 24 h at room temperature. TEA (1 mL) was added, and the reaction mixture was concentrated to dryness. The resulting residue was chromatographed [silica, CH₂Cl₂/hexane
(1:3) → CH₂Cl₂] to afford a green solid (16 mg, 6%): ¹H NMR δ –2.16 (br s, 2H), 1.96 (s, 12H), 2.12 (s, 12H), 2.56 (s, 6H), 4.35 (s, 4H), 7.25 (s, 4H) 8.35 (s, 2H), 8.55–8.57 (m, 2H), 8.71 (s, 2H); LD-MS obsd 607.7; FAB-MS obsd 606.3754, calcd 606.3722 (C₄₂H₄₆N₄); λₐₙₐₑₜₜₑₜₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑ euler 346, 370, 493, 726 nm; λₑₑₘₘₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑ℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮℮耪uala 729, 770 nm.
References


Chapter V. Exploratory Studies Toward a Northern-Southern Approach to Chlorins

1. Introduction.

Over the past several years, our lab has developed several syntheses of chlorins based on a Western half + Eastern half approach.\textsuperscript{V1} Most recently, the synthesis of several chlorins possessing few or no substituents entailed the acid-catalyzed condensation of a 9-bromoformyldipyrromethane (Eastern half) with 2,3,4,5-tetrahydro-1,3,3-trimethylidipyrrin (Western half)\textsuperscript{V2} as illustrated in Scheme V.1.

\begin{center}
\includegraphics[width=0.7\textwidth]{scheme_v1}
\end{center}

\textit{Scheme V.1. Western + Eastern Half Approach to Chlorins.}

In an effort to expand on our existing chlorin methodology, we had envisioned that substituted chlorins may also be obtained in a Northern-Southern fashion as shown in Scheme V.2.

\begin{center}
\includegraphics[width=0.7\textwidth]{scheme_v2}
\end{center}

\textit{Scheme V.2. Proposed Northern + Southern Route to Chlorins.}
A representative example of the Northern + Southern approach to chlorins is shown below. Applying this strategy, chlorins possessing substituents at the 3, 7, or 10-position are readily accessible using the desired carbinol\textsuperscript{V3} (Northern half) shown in Scheme V.3.

\begin{scheme}
\begin{center}
\begin{align*}
\text{Northern Half} & \quad \text{Southern Half} \\
\end{align*}
\end{center}
\end{scheme}

\textbf{Scheme V.3.} Northern + Southern Route to 3, 7, and 10-Substituted Chlorins.

In addition, chlorins possessing one meso substituent at the 5-position or completely unsubstituted derivatives may be accessible using the appropriate 1-formyl-9-bromo-dipyrrromethane\textsuperscript{V2} (Scheme V.4).

\begin{scheme}
\begin{center}
\begin{align*}
\text{Northern Half} & \quad \text{Southern Half} \\
\end{align*}
\end{center}
\end{scheme}

\textbf{Scheme V.4.} Northern + Southern Route to Sparsely Substituted Chlorins.
2. Synthesis.

To access chlorins using the proposed Northern + Southern approach, new methodology that would allow facile access to the desired Southern half (dihydrodipyrrin) would be required. Traditional routes to dihydrodipyrrins usually employ a nitroaldol condensation (Henry reaction) of a nitroalkane with a substituted pyrrole carboxaldehyde to give the corresponding (nitrovinyl)pyrrole derivative. The resulting olefin is then reduced to give a nitroalkane that is subjected to a Michael addition with an enone, followed by a reductive cyclization procedure to afford the dihydrodipyrrin, albeit in low yield (Scheme V.5).V4 This route generally affords dihydrodipyrrins possessing the gem-dimethyl group at the 3-position of the pyrroline ring, instead of the desired 2-position that is needed for our approach. The gem-dimethyl group is an important feature that prevents adventitious dehydrogenation in the chlorin macrocycle.

![Scheme V.5. Michael Addition-Cyclization Approach to 3-Gem-Dimethyl Substituted Dihydrodipyrrins.](image-url)
Recently, enelactones have been exploited as useful synthetic intermediates in the synthesis of chlorins.\textsuperscript{V5} In addition to chlorins, enelactones have been shown to be valuable intermediates in the synthesis of biologically important corrins and meso-substituted semicorrins.\textsuperscript{V6} The most recent approach, described by Jacobi and co-workers,\textsuperscript{V5} utilizes a Pd(0)-initiated coupling-cyclization procedure of an alkyne acid and iodopyrrole that affords enelactones in near quantitative yield. The enelactones are then transformed into dihydridipyrrins after several synthetic manipulations (Scheme V.6). A significant drawback of this procedure is the difficult task in obtaining the iodopyrrole coupling moiety, which relies on several, often laborious synthetic steps. In an effort to develop more conventional routes to enelactones that could serve as precursors to our desired Southern half, we investigated several new routes to enelactones.

\begin{center}
\includegraphics[width=\textwidth]{SchemeV6.png}
\end{center}

\textbf{Scheme V.6.} Jacobi's Approach to Enelactones.

\textbf{(a) Enelactones via an Alkylation-Desulfonation Sequence of Pyrrole Methyl Halides and Sulfones:}

Ley and co-workers successfully demonstrated that 2-benzenesulfonyl tetrahydropyrans smoothly reacted with halides to give cyclic enol ethers after elimination of benzenesulfinic acid.\textsuperscript{V7} Based on this successful alkylation-desulfonation sequence, we
examined the potential coupling of a \( N \)-protected pyrrole carboxaldehyde and known aryl sulfone (\( V-1 \))\(^{Vr} \) (Scheme V.7). After several well-precedented transformations, the desired Southern half possessing the \( \text{gem} \)-dimethyl group at the 2-position is readily obtained.

\[
\begin{align*}
\text{X} = & -\text{CH}_2\text{Cl} \text{ or } -\text{CH}_2\text{I}, \\
\text{R} = & \text{tosyl, Boc}
\end{align*}
\]

Scheme V.7. Proposed Route to Dihydridopyrrins via Enelactones.

Initially, attempts were made to access several \( N \)-protected pyrrole methyl halides that would serve as potential electrophiles. Consequently, known Boc-protected pyrrole \( V-2 \)\(^{V9} \) was treated with mesyl chloride and DIPEA to give the pyrrole methyl chloride (\( V-3 \)), which immediately polymerized upon removal of solvent (Scheme V.8).

\[
\begin{align*}
\text{MsCl, DIPEA} & \\
\text{CH}_2\text{Cl}_2 & 0 \degree \text{C to RT}
\end{align*}
\]

Scheme V.8. Attempted Synthesis of Boc-Protected Pyrrole \( V-3 \).

We reasoned that converting \( V-3 \) to its sulfonamide derivative would suppress the reactivity and potentially afford a stable precursor. Consequently, a mixture of pyrrole-2-carboxaldehyde and \( \text{Bu}_4\text{NHSO}_4 \)\(^{V10} \) was treated with an aqueous solution of NaOH in water
followed by $p$-tosyl chloride to afford sulfonamide V-4 (Scheme V.9). Reduction of the latter with LiBH$_4$ gave the desired alcohol (V-5) in 91% yield. Surprisingly, initial attempts to convert alcohol V-5 to the desired halide resulted in either decomposition (KI/BF$_3$·O(Et)$_2$), recovered starting material (SOCl$_2$, Et$_3$N), or inseparable mixtures of starting material along with the desired product (MsCl, DIPEA).

(b) Enelactones via Julia Olefination of Pyrrole Carboxaldehydes and Sulfones:

We next examined the potential coupling reaction of a $N$-protected pyrrole carboxaldehyde (V-4) with sulfone V-1 employing the traditional Julia-Lythgoe reaction.\textsuperscript{10a} It was anticipated that alkylation of V-4 with aryl sulfone V-1 would readily afford the intermediate $\beta$-hydroxysulfone. The $\beta$-hydroxysulfone is then converted to the acetate, followed by subsequent treatment with an appropriate reducing agent to give the $N$-protected enelactone as depicted in Scheme V.10.
Initial alkylation attempts resulted in the recovery of aldehyde V-4 and the decomposition of sulfone V-1. Due to the instability of the anion derived from sulfone V-1, we sought an alternative nucleophile. Therefore, in an attempt to enhance the stability of the resulting anion, a (phenyl tetrazole)-analogue of V-1 was synthesized (Scheme V.11).

Accordingly, known alcohol V-6 was converted to sulfide V-7 using standard Mitsunobu conditions. Initial attempts to oxidize V-7 to the desired sulfone using oxone or mCPBA resulted in decomposition of the sulfide. We later found that sulfide V-7 could be smoothly oxidized with (NH₄)₂MoO₄ to afford sulfone V-8, albeit in 21% yield. Unfortunately, the reaction of sulfone V-8 and V-4 in THF with KHMDS resulted in the decomposition of V-8 (Scheme V.12). As a consequence, this route was abandoned.
(c) Enelactones via Coupling of N-Protected Pyrroles with Alkyne Acids:

A palladium (II) catalyzed C-H alkenylation reaction of deactivated pyrroles with olefins employing tert-butylperoxybenzoate (TBPB) as an oxidant has been recently described.\textsuperscript{11} Encouraged by these results, we next investigated the potential coupling of N-tosyl pyrroles with alkyne acids to give enelactones. Both V-9 and V-10 were commercially available. Several reaction conditions were investigated and are summarized in Table V.1. Despite several attempts employing different conditions, only the starting N-tosylpyrrole was recovered.

![Diagram of enelactone formation](image)

**Table V.1. Model Coupling Study of N-Tosylpyrrole with Alkyne Acid V-10.\textsuperscript{a}**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Reaction Time</th>
<th>Chloride Source\textsuperscript{b}</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)\textsubscript{2}</td>
<td>Dioxane/DMSO (9:1)</td>
<td>35 °C</td>
<td>24 h</td>
<td>none</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)\textsubscript{2}</td>
<td>Dioxane/DMSO (9:1)</td>
<td>35 °C</td>
<td>24 h</td>
<td>Bu\textsubscript{4}NCl</td>
<td>NR</td>
</tr>
<tr>
<td>3\textsuperscript{d}</td>
<td>Pd(OAc)\textsubscript{2}</td>
<td>Dioxane/DMSO (9:1)</td>
<td>35 °C</td>
<td>24 h</td>
<td>Bu\textsubscript{4}NCl</td>
<td>NR</td>
</tr>
<tr>
<td>4\textsuperscript{d}</td>
<td>Pd(OAc)\textsubscript{2}</td>
<td>CH\textsubscript{3}CN</td>
<td>reflux</td>
<td>24 h</td>
<td>Bu\textsubscript{4}NCl</td>
<td>NR</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Reactions were performed employing V-9 (2.0 equiv) and V-10 (1.0 equiv) under an argon atmosphere in the appropriate solvent along with the Pd-catalyst (10 mol%), TBPB (1.0 equiv) and Et\textsubscript{3}N (10 equiv) unless otherwise noted. Concentration of V-10 was 0.66 M.\textsuperscript{b} 1.0 equiv was used.\textsuperscript{c} No reaction.\textsuperscript{d} Reaction was performed with V-9 (1.0 equiv, 0.66 M) and V-10 (1.5 equiv)
(d) Enelactones via Coupling of N-Protected 2-Iodopyrroles with Alkyne Acids:

We then turned our attention to the coupling of N-protected 2-iodopyrroles as potential coupling partners with alkyne acids to afford enelactones. Iodopyrrole V-12 was prepared by the method described by Dinsmore et al.\textsuperscript{12} Again, we began our initial investigation using commercially available 4-pentynoic acid (V-10) as the alkyne acid and subsequently screened several coupling conditions as depicted in Table V.2.

![Diagram of reaction between V-12 and V-10]

**Table V.2. Model Coupling Study of 2-Iodo-N-Phenylsulfonylpyrrole V-12 with Alkyne Acid V-10.\textsuperscript{a}**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Reaction Time</th>
<th>Chloride Source\textsuperscript{b}</th>
<th>Yield of V-13 (%)\textsuperscript{c}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1\textsuperscript{d}</td>
<td>Pd(PPh\textsubscript{3})\textsubscript{4}</td>
<td>CH\textsubscript{3}CN</td>
<td>reflux</td>
<td>18 h</td>
<td>Bu\textsubscript{4}NCl</td>
<td>NR\textsuperscript{e}</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)\textsubscript{2}</td>
<td>CH\textsubscript{3}CN</td>
<td>reflux</td>
<td>18 h</td>
<td>Bu\textsubscript{4}NCl</td>
<td>NR</td>
</tr>
<tr>
<td>3</td>
<td>Pd(PPh\textsubscript{3})\textsubscript{4}</td>
<td>DMSO</td>
<td>75 °C</td>
<td>18 h</td>
<td>Bu\textsubscript{4}NCl</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>Pd(PPh\textsubscript{3})\textsubscript{4}</td>
<td>DMSO</td>
<td>75 °C</td>
<td>45 min</td>
<td>Bu\textsubscript{4}NCl</td>
<td>46</td>
</tr>
<tr>
<td>5</td>
<td>Pd(PPh\textsubscript{3})\textsubscript{4}</td>
<td>DMSO</td>
<td>75 °C</td>
<td>45 min</td>
<td>none</td>
<td>43</td>
</tr>
</tbody>
</table>

\textsuperscript{a} All reactions were performed employing V-12 (0.3 mmol) and V-10 (0.5 mmol) under an argon atmosphere in the appropriate solvent along with the Pd-catalyst (7 mol% with respect to V-12) and Et\textsubscript{3}N (10 equiv with respect to V-12) unless otherwise noted. Concentration of V-12 was 0.33M. \textsuperscript{b} 1.5 equiv with respect to V-12 was used. \textsuperscript{c} Isolated yield. \textsuperscript{d} Reaction was performed using 1 equiv (0.3 mmol) of V-10. \textsuperscript{e} No reaction.

Employing acetonitrile as the solvent gave no reaction as evidenced by TLC and \textsuperscript{1}H NMR spectroscopy. Fortuitously, we observed that employing DMSO as a solvent and heating the reaction mixture at 75 °C for approximately 1 hour afforded enelactone V-13 in 46% yield. Prolonged heating resulted in a significant amount of unidentified byproducts and a decrease in product yield (Entry 3). We also were pleased to find that this
transformation could be carried out without the presence of a chloride source (Entry 5). In similar transformations involving palladium-catalyzed reactions of vinyl triflates with 4-pentynoic acids, it is speculated that the chloride ions undergo a ligand exchange mechanism in the catalytic cycle, resulting in enhanced reactivity and product yield.\textsuperscript{13} In our case, it is apparent that the presence of chloride ions does not play a significant role in the overall catalytic cycle. Therefore, applying this coupling methodology using the appropriate alkyne acid bearing the \textit{gem}-dimethyl group\textsuperscript{5} and following several reported transformations, the enelactone is eventually transformed into a suitable Southern half (Scheme V.13).

![Scheme V.13. Proposed Synthesis of the Southern Half.]

In summary, a convenient synthesis of \textit{N}-protected enelactones has been described. Palladium catalyzed coupling of readily available 2-iodo-\textit{N}-phenylsulfonylpyrrole with commercially available 4-pentynoic acid afforded the (\textit{E})-\textit{N}-protected enelactone in >40\% yield. Coupling times were relatively fast (<1 h) and did not require the use of a chloride source. The facile synthesis of \textit{N}-protected enelactones should facilitate the preparation of simple dihydridipyrrins that may used to access chlorins in a Northern + Southern fashion.
Experimental Procedures

N-Tosylpyrrole-2-carboxaldehyde (V-4). Following a general procedure for the tosylation of pyrrole derivatives, a mixture of pyrrole-2-carboxaldehyde (4.76 g, 50.0 mmol) and tetrabutylammonium hydrogen sulfate (1.70 g, 5.00 mmol) was added to a solution of NaOH (9.00 g, 225 mmol) in water (30 mL). The mixture was stirred for 10 min, and a mixture of p-toluenesulfonyl chloride (10.5 g, 55.0 mmol) in CH$_2$Cl$_2$ (10 mL) was added. After stirring for 5 h, water (200 mL) and brine (100 mL) were added. The reaction mixture was extracted with CH$_2$Cl$_2$. The combined organic extracts were dried (Na$_2$SO$_4$) and filtered. The filtrate was concentrated and chromatographed (silica, CH$_2$Cl$_2$) to afford a pale pink solid (7.32 g, 59%): mp 94–96 °C (lit.$^{14}$ 94 °C); $^1$H NMR δ 2.40 (s, 3H), 6.38–6.40 (m, 1H), 7.14–7.15 (m, 1H), 7.31 (d, $J$ = 8.6 Hz, 2H), 7.61–7.62 (m, 1H), 7.79 (d, $J$ = 8.3 Hz, 2H), 9.96 (s, 1H); $^{13}$C NMR δ 21.9, 112.7, 124.8, 127.7, 129.7, 130.4, 133.7, 134.5, 146.2, 179.2. Anal. Calcd for C$_{12}$H$_{11}$NO$_3$S: C, 57.82; H, 4.45; N, 5.62. Found: C 57.83; H, 4.41; N, 5.72.

[1-(4-Methylphenylsulfonyl)pyrrol-2-yl]methanol (V-5). Following a general procedure, a stirred solution of V-4 (1.00 g, 4.01 mmol) in anhydrous THF (23 mL) at 0 °C under argon was treated with LiBH$_4$ (0.348 g, 16.0 mmol). The resulting mixture was stirred for 1.5 h at 0 °C, and then poured into water (300 mL). The mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine and dried (Na$_2$SO$_4$). The filtrate was filtered and concentrated. Purification by flash chromatography [silica, hexanes/ethyl acetate (1:2)] afforded a colorless solid (0.916 g, 91%): mp 97 °C (lit.$^{14}$ 97 °C); $^1$H NMR δ 2.41 (s, 3H), 2.73 (t, $J$ = 7.0 Hz, 1H), 4.59 (d, $J$ = 7.0 Hz, 2H), 6.22–6.26 (m, 2H), 7.26–7.31 (m, 3H), 7.71 (d, $J$ = 8.3 Hz, 2H); $^{13}$C NMR δ 21.9, 57.1, 112.1, 115.4, 123.8,
Anal. Calcd for $C_{12}H_{13}NO_3S$: C, 57.35; H, 5.21; N, 5.57. Found: C 57.43; H, 5.15; N, 5.59.

**Sulfide V-7.** Following a reported procedure,$^{15}$ a solution of dihydro-5-hydroxy-3,3-dimethyl-2(3H)-furanone (V-6)$^9$ (400 mg, 3.07 mmol), triphenylphosphine (890 mg, 3.38 mmol), and 2-phenyl-2$H$-tetrazole-5-thiol (600 mg, 3.38 mmol) in dry THF (36 mL) under an atmosphere of argon was treated with DEAD (0.540 mL, 3.38 mmol) dropwise over 10 min. The resulting yellow solution was allowed to stir at room temperature for 18 h. Water (20 mL) was added, and the mixture was extracted with ethyl acetate. The organic extracts were dried ($Na_2SO_4$) and filtered. The filtrate was concentrated. Purification by flash chromatography [silica, ethyl acetate/hexanes (1:9 to 1:4)] gave a colorless solid (271 mg, 30%): mp 92–95 °C; $^1H$ NMR $\delta$ 1.46 (s, 3H), 1.53 (s, 3H), 2.68 (dd, $J = 13.5, 7.5$ Hz, 1H), 2.97 (dd, $J = 13.7, 7.1$ Hz, 1H), 6.94 (t, $J = 7.0$ Hz, 1H), 7.52–7.61 (m, 3H), 7.89–7.93 (m, 2H); $^{13}C$ NMR $\delta$ 24.9, 26.2, 29.9, 40.4, 81.0, 124.2, 129.6, 130.2, 134.4, 164.6, 179.1. Anal. Calcd for $C_{13}H_{14}N_4O_2S$: C, 53.78; H, 4.86; N, 19.30. Found: C 54.13; H, 4.92; N, 18.91.

**Sulfone V-8.** Following a reported procedure,$^{15}$ an ice-cooled solution of sulfide V-7 (100.0 mg, 0.344 mmol) in EtOH/ethyl acetate (9:1, 11 mL) at 0 °C was treated with ammonium molybdate (17.0 mg, 0.086 mmol) and 30% aqueous $H_2O_2$ (330 $\mu$L, 3.44 mmol). The bath was removed, and the solution was stirred overnight at room temperature. The yellow solution was poured into saturated aqueous $Na_2S_2O_3$. The mixture was extracted with ethyl acetate. The organic extracts were washed with brine and dried ($Na_2SO_4$). The filtrate was filtered and concentrated. Purification by flash chromatography [silica, ethyl acetate/hexanes (1:3)] gave a light brown solid (23 mg, 21%): mp 125–126 °C; $^1H$ NMR $\delta$ 1.43 (s, 3H), 1.52 (s, 3H), 2.59 (dd, $J = 13.8, 7.7$ Hz, 1H), 2.98 (dd, $J = 13.4, 7.4$ Hz, 1H),
6.40 (t, \( J = 7.4 \) Hz, 1H), 7.38–7.55 (m, 3H), 7.87–7.91 (m, 2H); \(^{13}\text{C} \text{NMR} \delta 24.9, 26.0, 39.8, 40.5, 79.2, 119.8, 128.5, 129.8, 134.3, 169.6, 179.1.

**\( E-5-(5\text{-oxo-dihydrofuran-2-ylidenemethyl})\text{-N-phenylsulfonylpyrrole} \) (V-13).**

Following a reported procedure,\(^{13}\) a solution of iodopyrrole \( V-12 \) (100 mg, 0.300 mmol), alkyne acid \( V-10 \) (44.0 mg, 0.450 mmol), and Et\(_3\)N (0.44 mL, 3.2 mmol) in dry DMSO (0.9 mL) under argon was treated with Pd(PPh\(_3\))\(_4\) (23 mg, 0.02 mmol). The reaction mixture was heated under reflux and stirred at 75 °C for 45 min. The mixture was then allowed to cool to room temperature, and quenched by addition of saturated aqueous NH\(_4\)Cl. The mixture was extracted with ethyl acetate. The organic extracts were washed with brine and dried (Na\(_2\)SO\(_4\)). The filtrate was filtered and concentrated. Purification by flash chromatography [silica, hexanes/ethyl acetate (9:1 to 3:1)] afforded a brown film (39 mg, 43%): IR (NaCl) 1185, 1802, 2931, 3149 cm\(^{-1}\); \(^1\text{H} \text{NMR} \delta 2.60–2.65 (m, 2H), 2.77–2.81 (m, 2H), 6.06 (s, 1H), 6.29–6.31 (m, 1H), 6.60–6.62 (m, 1H), 7.38–7.39 (m, 1H), 7.48–7.52 (m, 2H), 7.58–7.62 (m, 1H), 7.80 (d, \( J = 9.2 \) Hz, 2H); \(^{13}\text{C} \text{NMR} \delta 25.1, 27.5, 96.6, 112.4, 113.5, 116.4, 123.1, 127.2, 129.6, 134.2, 139.0, 152.5, 174.3; \text{FAB-MS} \text{ obsd} \text{ 303.0570, calcd 303.0565 (C}_{13}\text{H}_{13}\text{NO}_{4}\text{S).} \)}}
References


