ABSTRACT

KIM, HAN-JE.

DE NOVO SYNTHESIS OF STABLE BACTERIOCHLORINS.

(Under the Direction of Dr. Jonathan S. Lindsey)

Hydroporphyrins perform a wide variety of essential functions in living systems. Hydroporphyrins differ from porphyrins in having fewer π bonds along the perimeter of the macrocycle. Efficient routes for the preparation of stable, dehydrogenation-resistant analogues of naturally occurring hydroporphyrins (e.g., chlorins, bacteriochlorins, isobacteriochlorins, corrins) are essential for fundamental studies and diverse applications. To develop such routes, a collection of 24 hydrodipyrrins has been prepared wherein each hydrodipyrrin contains a pyrrole ring and a pyrroline ring. The pyrroline ring bears a geminal-dimethyl group to lock-in the hydrogenation level. The a-substituents on the pyrrole and pyrroline rings provide different reactivity combinations (Nu/E^+, E^+/E^+, or E^+/Nu). Selected hydrodipyrrins have been employed in six exploratory routes to stable bacteriochlorins. The availability of straightforward routes to various hydrodipyrrins should facilitate development of syntheses of diverse hydroporphyrins (Chapter III).

Bacteriochlorins are attractive for diverse photochemical applications owing to their strong absorption in the near-infrared spectral region, as exemplified by the bacterial photosynthetic pigment bacteriochlorophyll *a*, yet often are labile toward dehydrogenation to give the chlorin. An eight-step synthesis for preparing stable bacteriochlorins begins with *p*-tolualdehyde and proceeds to a dihydrodipyrrin–acetal (**IV-1**) bearing a geminal-dimethyl group and a *p*-tolyl substituent. Self-condensation of **IV-1** in CH_3CN containing $BF_3{\cdot}OEt_2$ at

room temperature afforded a readily separable mixture of two free base bacteriochlorins and a ring-contracted, B,D-tetradehydrocorrin. Each bacteriochlorin contains two geminal-dimethyl groups to lock-in the bacteriochlorin (tetrahydroporphyrin) hydrogenation level, *p*-tolyl substituents at opposite (2,12) β–positions, and the absence (**H-BC**) or presence (**MeO-BC**) of a methoxy group at the 5- (meso) position. The B,D-tetradehydrocorrin (**TDC**) lies equidistant between the hydrogenation levels of corrin and corrole, is enantiomeric, and contains two geminal-dimethyl groups, 2,12-di-*p*-tolyl substituents, and an acetal group at the pyrroline-pyrrole junction. Examination of the effect of the concentrations of **IV-1** (2.5 – 50 mM) and $BF_3{\cdot}OEt_2$ (10 – 500 mM) revealed a different response surface for each of **H-BC**, **MeO-BC**, and **TDC**. The highest isolated yield of each was 49%, 30%, and 67%, respectively. The hydroporphyrins are stable to routine handling in light and air. The spectral features of **H-BC** are exemplary, including strong near-IR absorption (λ_{Qy} = 737 nm, ε_{Qy} = 130,000 $M^{-1}cm^{-1}$) and emission (λ_{em} = 744 nm, Φ_f = 0.14). A crystal structure was obtained for **MeO-BC**. In summary, the ease of preparation of stable bacteriochlorins having characteristic spectral features should facilitate a wide variety of applications (Chapter IV).

DE NOVO SYNTHESIS OF STABLE BACTERIOCHLORINS

by

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DEDICATION

To My Parents and My Wife, Eun-Hee

BIOGRAPHY

Han-Je Kim was born in Heongsung of Kangwon-Do, Korea. After he graduated from Heongsung High School, he entered the Department of Chemistry at Kangwon National University in March 1990. Half way through his undergraduate studies, he joined the Korean army and completed two and a half years of military service. After he was released from the army, he worked in Daesung Block Company and Heongsung Royal Travel Hotel until returning to college. When he was a junior, he became a member of Professor Chang-Hee Lee's Lab and participated in some projects related with organic synthesis. During his under graduate career, he took some courses in the Chemistry Education program to obtain his teaching license in hope of becoming a chemistry teacher.

After graduation in 1997, he continued his study at the graduate school of his alma mater. Before finishing his graduate courses, he graduated from SDA Language (English) Institute. He received a M.S. degree in Chemistry on February 1999 with his thesis titled "Synthesis and Properties of Core-Modified Porphyrins Containing Furan or Thiophene Moiety." He continued his research at Kangwon National University as an Intern researcher supported by the Korean Government for one year. After acceptance to North Carolina State University he relocated to Raleigh, NC to pursue his Ph.D. He successfully defended his final oral exam on March 3, 2005.

He married Jun, Eun-Hee and has two sons, Dong-Hyun and Dong-Won.

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Who told me this phrase? "He will never get excited. He will never get frustrated. He will always be steady and level headed." I still keep in my mind the words and I respect you.

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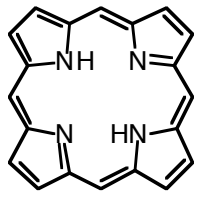
CHAPTER I. GENERAL INTRODUCTION

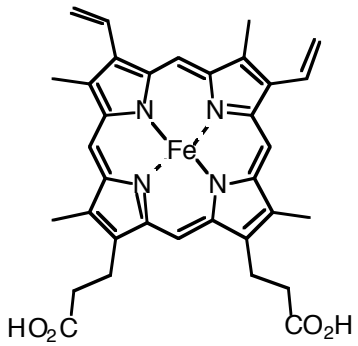
I.A. Porphyrins and Hydroporphyrins.

Porphyrinic macrocycles are ubiquitous in Nature. Formally, porphyrinic macrocycles can be divided into two main groups, porphyrins and hydroporphyrins. The porphyrins are fully unsaturated and have 22 π-electrons in the ring whereas hydroporphyrins have the same skeleton but one or more pyrrole rings are saturated at the *β*-positions. Ring-contracted analogues are also members of the porphyrinic family (e.g., corrins such as vitamin B_{12}) and will be discussed in Chapter 4. Examples of hydroporphyrins include chlorins, isobacteriochlorins, and bacteriochlorins. Porphyrins and hydroporphyrins are aromatic owing to the presence of a conjugated 18 π-electron system in each macrocycle.

1. Porphyrins. The porphyrin ring system is a biologically important unit found in *heme*, which serves as the oxygen-carrying cofactor of hemoglobin, an electron-transfer agent in respiratory chains, and the catalyst for oxidation processes carried out by cytochrome P_{450} enzymes.



porphyrin



heme

Chart I.1. Structure of a porphyrin and a biologically important porphyrin in Nature.

The porphyrin ring system is a tetrapyrrole macrocycle where the four pyrrole rings are joined by =CH– groups and the resulting ring system is aromatic (Chart I.1). The pyrrole hydrogens in the porphyrin core can be replaced by a variety of metal ions and the perimeter of the porphyrin can be substituted with various groups.

During the 20th century, great attention has been paid to the porphyrins and their metal derivatives due to their important biological functions, unique photo-physical properties, and characteristic electronic properties. In recent years, the aforementioned features in conjunction with the high stability of porphyrins have led to applications in molecular electronics (molecule-based materials are used for electronic applications). A number of covalently linked donor-acceptor porphyrin-based assemblies have been studied for opto-electronics,[I1] information storage,[I2] and solar cells.[I3] Also, the photosensitizing properties of porphyrins has led to investigations for use as sensitizers in a variety of medical applications such as photodynamic therapy (PDT),[I4] boron neutron capture therapy,[I5] radiation therapy,[I6] and magnetic resonance imaging.[I7] A vast literature exists on synthetic porphyrin-based researches.

2. Chlorins. Chlorins are one of Nature's most important cofactors, providing the basis for photosynthesis in plants (chlorophyll *a* and *b*) and various algae (bacteriochlorophylls *c*, *d*, and *e*).[I8] While photosynthesis is their dominant biological role, chlorins also mediate enzymatic redox processes in bacteria (heme *d*),[I9] serve as hormones in sea worms (bonellin),[I10] and have unknown functions in other organisms (tunichlorins).[I11, I15a]

Chorins are hydroporphyrins and differ from the porphyrin in having one pyrrole ring saturated at the β-positions (Chart I.2). Although porphyrins and chlorins have many

similarities, the altered symmetry and path of conjugation resulting from the reduced pyrrole ring give rise to differences of profound importance for photochemical applications.

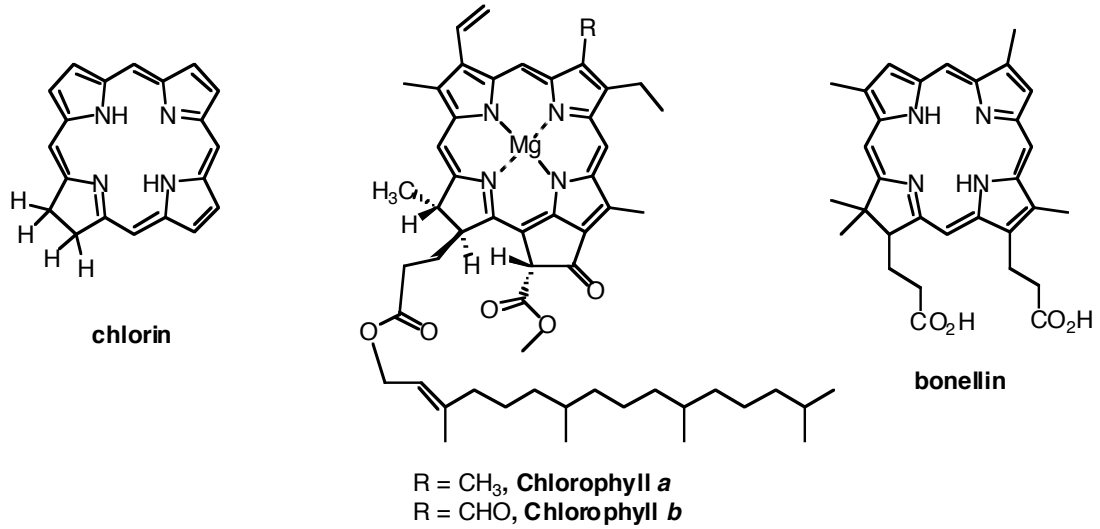


Chart I.2. Structure of a chlorin and some important chlorins in Nature.

Due to the instability of chlorophylls (*a* and *b*), many investigators have done a great amount of work to modify and to stabilize naturally occurring chlorophylls. Also, the fact that there are only a few functionalities available for modification led many research groups to concentrate on the synthesis of stable chlorins and chlorin-like chromophores.[I12]

Battersby,[I13] Montforts,[I14] and their coworkers developed selective methods for the total synthesis of some chlorin model systems, which contain the characteristic dialkylated moiety in the saturated five-membered (pyrroline) ring of the chlorin system. The knowledge gained from these investigations was later used to synthesize naturally occurring chlorins and other dialkylated chlorins.[I15]

3. Bacteriochlorins. Bacteriochlorins differ from porphyrins in having two pyrrole rings saturated at the β-positions on opposite sites of the macrocycle. The term

"bacteriochlorin" originates from the bacteriochlorophylls, which are pigments employed in bacterial photosynthesis.

Two types of naturally occurring bacteriochlorins have been reported. These are bacteriochlorophylls (*a*, *b*, and *g*) and tolyporphins (A–J).

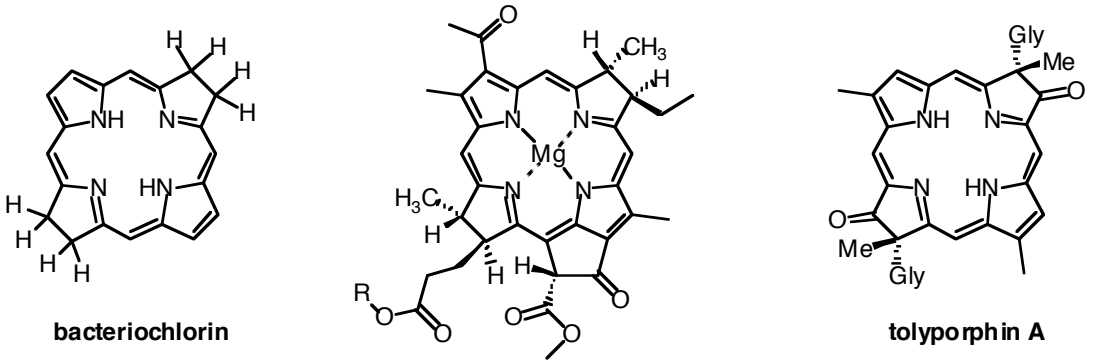


Chart I.3. Structure of a bacteriochlorin and naturally occurring bacteriochlorins.

Bacteriochlorophyll *a* (Chart I.3) is the most widely distributed bacteriochlorin pigment. It occurs in most photosynthetic bacteria and is the only bacteriochlorophyll in most strains of *Rhodospirillales*.[I8] Bacteriochlorophyll *b* differs from bacteriochlorophyll *a* by the presence of an ethylidene group at the 8-position. Bacteriochlorophyll *g* is similar with bacteriochlorophyll *b* but contains a vinyl rather than an acetyl group at the 3-position.[I16] Due to the presence of an exocyclic ethylidene group, bacteriochlorophyll *b* and *g* are particularly unstable, and their chemistry has been insufficiently explored. (The discerning reader will notice that bacteriochlorophyll *b* and *g* are actually dihydroporphyrins, not tetrahydroporphyrins; nonetheless the structures result in characteristic bacteriochlorin spectral features, as discussed in more detail in Chapter 4.)

The only naturally occurring bacteriochlorins that are known to not be involved in bacterial photosynthesis are the tolyporphins. In 1992, Moore and co-workers reported the isolation of tolyporphin A from the lipophilic extract of the cyanophyte microalga *Tolypothrix nodosa*.[I17] Tolyporphin A (a dioxobacteriochlorin) is an unsymmetrical bacteriochlorin containing ketones at the 8- and 18-positions, and two identical β-linked C-glycosyl units at the 7- and 17-positions. Subsequently, ten additional tolyporphins (B-K) have been isolated.[I18] The fundamental structure of tolyporphins A-J was a dioxobacteriochlorin, whereas tolyporphin K is an oxochlorin. The groups substituted at the 7- and 17-positions of tolyporphins include C-glycosyl, acetate, and hydroxyl groups.

Bacteriochlorins absorb light very strongly in the near-infrared spectral region. Owing to the desirable photophysical properties of bacteriochlorophylls (*a*, *b*, and *g*) and tolyporphins (A-J) for medical and materials applications, there has been increasing interest in the synthesis of stable bacteriochlorins or other similar tetrapyrrolic systems.

There are additional examples of hydroporphyrins such as isobacteriochlorins, dodecahydroporpyrins, as well as more highly saturated hydroporphyrins.[I12] Since our project particularly concerned the development of rational syntheses of chlorins and bacteriochlorins, the remaining discussion is limited to chlorins and bacteriochlorins with the exclusion of other members of the hydroporphyrins family.

I.B. Characteristic Absorption Spectra of Porphyrins and Hydroporphyrins (Chlorin and Bacteriochlorin).

Porphyrins exhibit characteristic optical spectra stemming from π-π* transitions of the aromatic macrocycle. As shown Figure I.1, the UV-visible absorption spectrum of a

porphyrin exhibits an intense peak (ε = ~450,000 $M^{-1}cm^{-1}$) at about 420 nm (the "Soret" band), followed by several weaker peaks (Q bands) at longer wavelengths (from 500 to 650 nm).

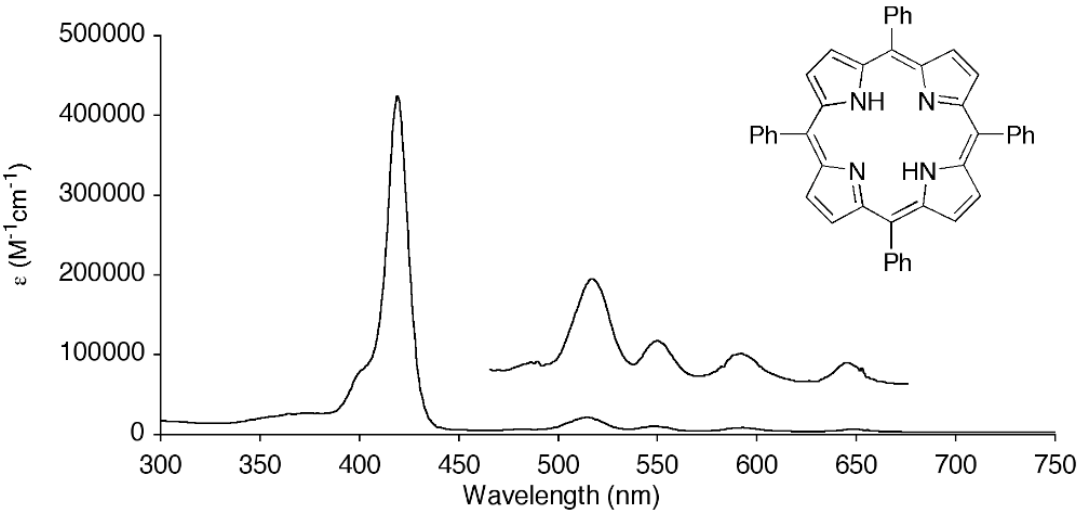
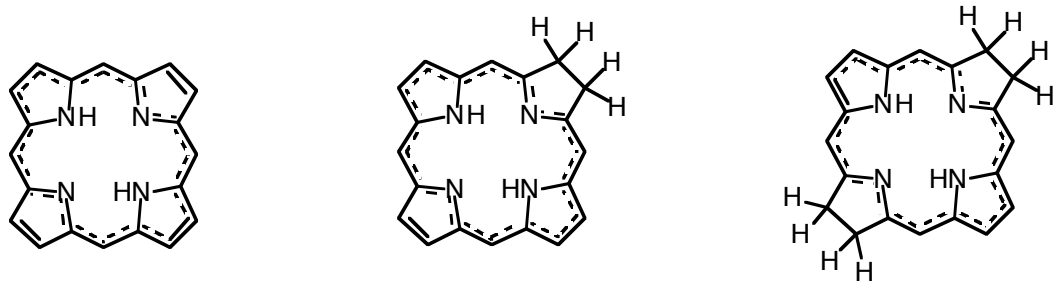


Figure I.1. Typical UV-Visible absorption spectrum of a porphyrin (TPP).

While the substitution at peripheral sites of the porphyrin ring often causes minor changes to the intensity and wavelength of the absorption features, protonation of the inner nitrogen atoms or the insertion/change of metal atoms into the porphyrin usually significantly alters the pattern of absorption bands in the region 500-700 nm.[I19]

In the porphyrin macrocyclic ring system, two of the peripheral double bonds in opposite pyrrolic rings are isolated and are not required to maintain aromaticity (Chart I.4). Thus, reduction of one or both of these isolated double bonds still maintains aromaticity; however, the change in symmetry results in red-shifted Q bands with relatively high extinction coefficients.



Porphyrin **Chlorin** **Bacteriochlorin**

Chart I.4. Aromatic path (dotted line) of porphyrin and hydroporphyrins.

Nature exploits the optical properties of the hydroporphyrins to harvest solar energy for photosynthesis, with chlorophylls and bacteriochlorophylls serving as pigments both in antenna and reaction center complexes.[I20] Comparison of the absorption spectra of a porphyrin, chlorophyll *a* (a chlorin), and bacteriochlorophyll *a* (a bacteriochlorin) shows how reduction of one or more pyrrole rings causes spectral changes (Figure I.2).

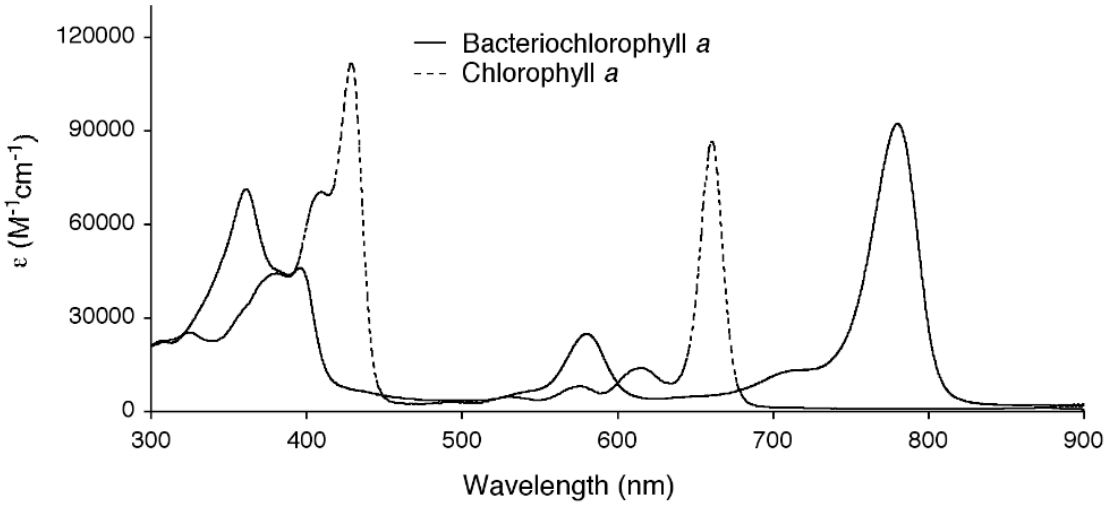


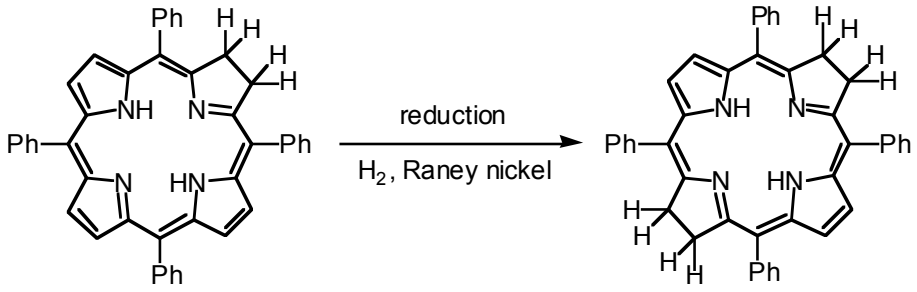
Figure I.2. Absorption spectra of a chlorophyll *a* and bacteriochloriphyll *a*.

A clearly visible difference is that hydroporphyrins absorb strongly in both the blue and red regions, while porphyrins absorb strongly only in the blue. Synthetic chlorins and bacteriochlorins have very similar spectral features as naturally occurring hydroporphyrins.[I15] The long wavelength absorption of the hydroporphyrins, particularly bacteriochlorins, naturally led to the explorations of their uses in medicinal applications.

I.C. Existing Methods for Bacteriochlorin Preparation.

Bacteriochlorins can be prepared using a few existing methods. Two distinct approaches are derivatization of porphyrins (or chlorins) and modification of naturally occurring bacteriochlorophylls. Also, a stepwise synthesis of a bacteriochlorin (a tolyporphin derivative) has been published. A recent review[I21] provides a comprehensive description of routes to almost all known synthetic bacteriochlorins. A summary of methods highlighted the disadvantages of each synthetic method.

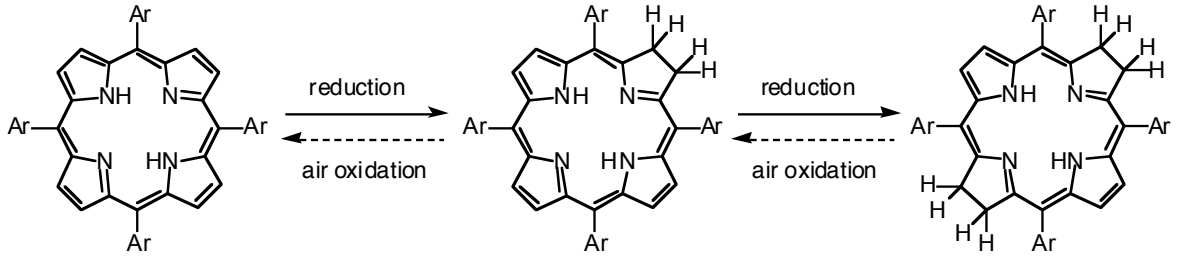
1. Derivatization of Porphyrins (or Chlorins): (a) Reduction. In 1952, Dorough and Miller attempted to convert *meso*-tetraphenylchlorin to *meso*-tetraphenylbacteriochlorin by catalytic hydrogenation.[I22] The predominant evidence for the bacteriochlorin was the similarity of the absorption spectrum of the product to that of bacteriochlorophyll *a*.



Scheme I.1. First attempt for bacteriochlorin formation via catalytic hydrogenation of a chlorin compound.

In 1969, Whitlock *et al*. extended this basic approach to a more efficient method for hydrogenation, and also described the selective preparation of bacteriochlorins and isobacteriochlorins from porphyrins.[I23] Diimide reduction (H_2N_2) of free base tetraphenylporphyrin (TPP) afforded tetraphenylbacteriochlorin (TPBC) in 50% yield, whereas reduction of zinc tetraphenylchlorin (ZnTPC) afforded the zinc tetraphenylisobacteriochlorin (ZnTP*i*BC) in 57% yield. It is noteworthy that diimide reduction of TPP and ZnTPC gave TP*i*BC and ZnTPBC respectively as side products in 2–4% yield.

The diimide reduction method has been applied to the preparation of a number of bacteriochlorins.[I24] Although diimide reduction is one of the most efficient and simple synthetic methods for the preparation of bacteriochlorin compounds, this method has two critical problems. First, diimide reduction of a porphyrin results in a mixture of porphyrin (starting material), chlorin, isobacteriochlorin, and bacteriochlorin. Since their structures are somewhat similar, separation typically is difficult. Second, even though the bacteriochlorin can be isolated by column chromatography, adventitious dehydrogenation slowly yields the chlorin and the porphyrin (Scheme I.2).



Scheme I.2. Reduction of a porphyrin (TPP) to the corresponding bacteriochlorin, and adventitious dehydrogenation of the bacteriochlorin.

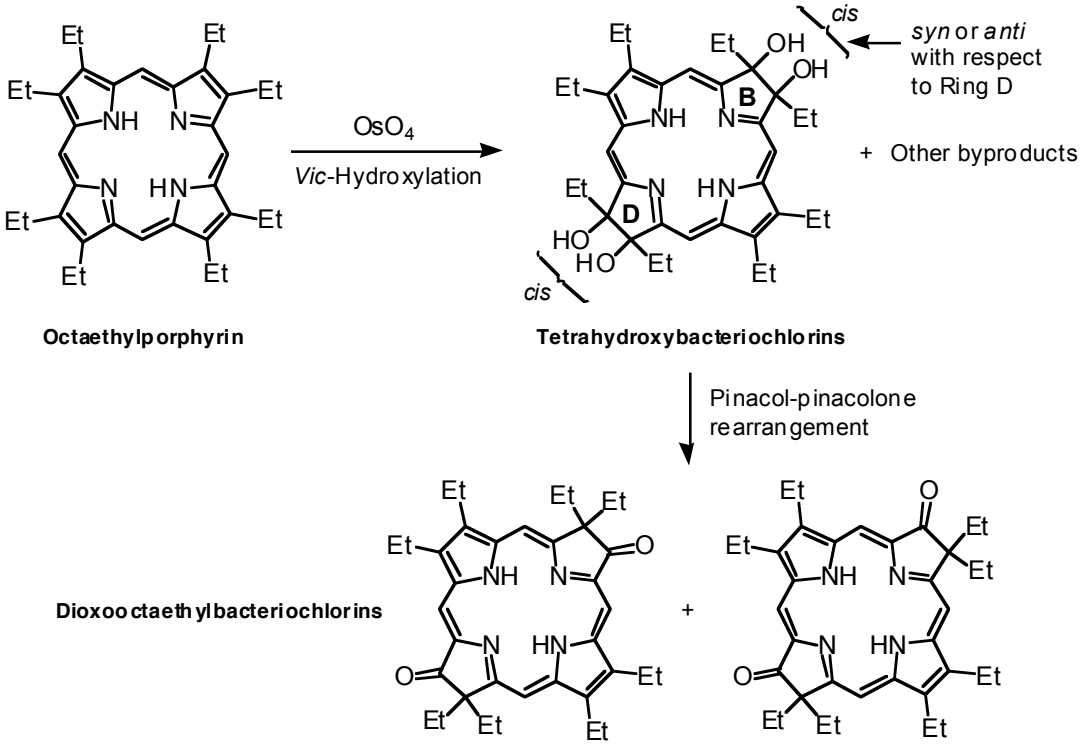
It is generally accepted that the most bacteriochlorins prepared by hydrdogenation are extremely sensitive to oxidation, resulting in rapid conversion to the chlorin and eventually the porphyrin.[I25]

(b) *Vic*-Hydroxylation. In 1930, Hans Fischer reported a method to obtain green-colored pigments from porphyrins. The proposed structure of such a green pigment was an chlorin–epoxide, where a pyrrole double bond has undergone epoxidation.[I26] Around 30 years later, Johnson and Inhoffen independently reinvestigated such oxidation reactions using symmetrical β-substituted porphyrins, and established that the true structure of the major product from hydrogen peroxide/sulfuric acid oxidation is a keto-chlorin (an oxochlorin) formed by pinacol rearrangement of a diol or epoxide.[I27]

In 1986, Chang *et al*. showed that a free base octaethylporphyrin could be selectively converted into the corresponding tetrahydroxybacteriochlorin, whereas zinc oxochlorins gave the isomeric tetrahydroxyisobacteriochlorin as a major product.[I28] The resulting tetrahydroxybacteriochlorins generally have been converted to the corresponding isomeric mixtures of dioxobacteriochlorins in reasonable yields via an acid-catalyzed pinacol-pinacolone rearrangement (Scheme I.3).[I29]

Pandey *et al*. investigated the effect of electron-withdrawing groups positioned at peripheral sites of porphyrins or chlorins toward OsO_4-mediated hydroxylation and pinacol-pinacolone rearrangements. They found that the regioselectivity of OsO_4-mediated hydroxylation in porphyrins is affected considerably by the presence of electron-withdrawing groups on the macrocycle.[I30] The vicinal hydroxy groups are *cis* owing to the use of OsO_4;

however, the two pairs of vicinal hydroxy groups on the macrocycle can exist in a *syn* or *anti* relationship given the reactivity of the two faces of the molecule.

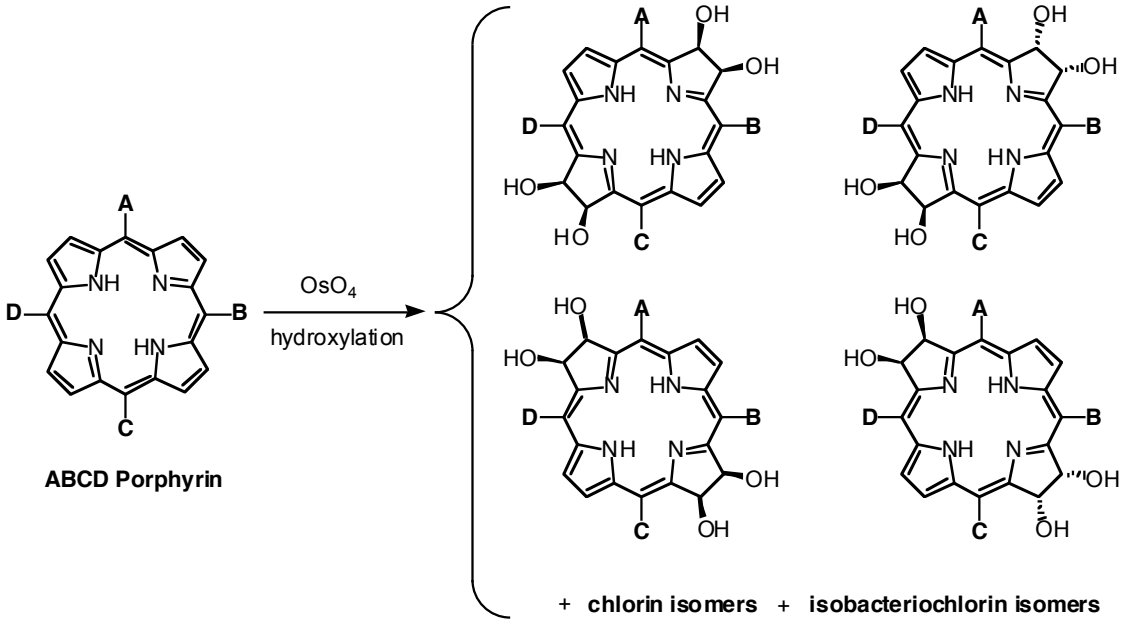


Scheme I.3. Dioxobacteriochlorins prepared by hydroxylation of a symmetrically substituted porphyrin using OsO_4 followed by pinacol-pinacolone rearrangement.

The selective formation of bacteriochlorin (versus isobacteriochlorins) in the hydroxylation method can be controlled using free base (rather than metalated) porphyrins.[I28] Moreover, the migratory aptitude of alkyl groups in the pinacol-pinacolone rearrangement can be controlled by the substitution pattern of electron-withdrawing groups at the peripheral positions of the macrocycle.[I30] The hydroxylation of porphyrin macrocycles is one of the successful methods for the preparation of bacteriochlorins. A sizable number of hydroxy- and ketobacteriochlorins have been synthesized in this manner and their biological activities

have been tested. Such bacteriochlorins showed greater stability compared with bacteriochlorins prepared by hyrogenation.

However, it should be added that the hydroxylation method has several intrinsic problems. First, only β-alkylated porphyrins afford relatively stable bacteriochlorins. (Porphyrins lacking β-substituents cannot be converted to dioxobacteriochlorins.) Second, the hydroxylation method typically generates a mixture of bacteriochlorins, chlorins, and isobacteriochlorins, each of which is composed of a mixture of isomers. Thus, the starting material should have high symmetry to give a relatively small number of isomers.



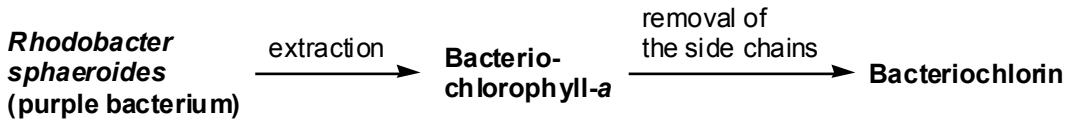
Scheme I.4. Predictable products from the hydroxylation of an ABCD-porphyrin.

For example, the hydroxylation of an ABCD-porphyrin (a porphyrin that bears a different substituent at each of the four meso positions), typically will give four bacteriochlorin diastereomers (Scheme I.4). In addition, the reaction will generate isomers of

chlorins and isobacteriochlorins as byproducts. This example, although somewhat extreme, does clearly illustrate a fundamental problem of the hydroxylation approach.

(c) Selected Methods for Derivatization of Porphyrins (or Chlorins). A number of reactions have been employed to add moieties to the β-pyrrole rings of porphyrins (or chlorins) thereby yielding bacteriochlorins. The methods include a double Diels-Alder reaction on divinylporphyrins,[I31] addition of dienophiles,[I32] 1,3 dipolar addition,[I33] etc.[I34] However, none of these methods is free from generation of isomers and/or instability of the product.

2. Alteration of Bacteriochlorophyll *a*. Bacteriochlorophyll *a* can be extracted with organic solvents from concentrated cell pastes or subcellular fractions (Scheme I.5).[I25]



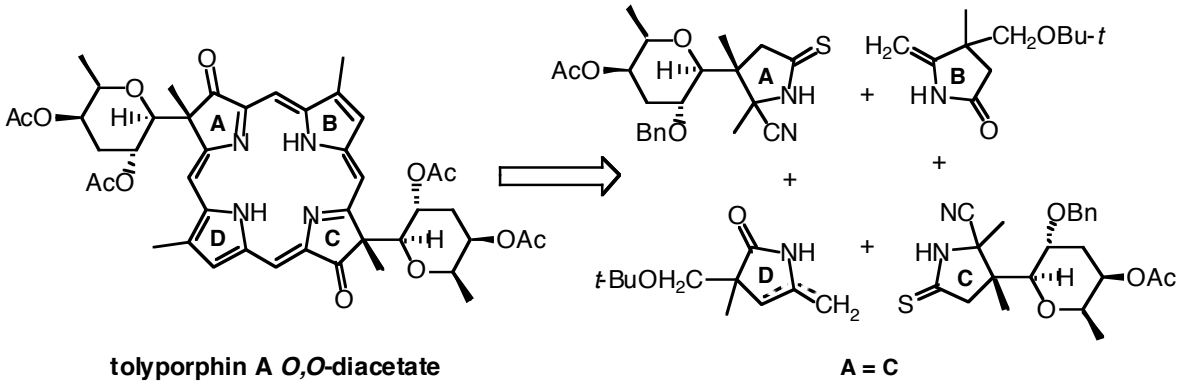
Scheme I.5. Modification of naturally occurring bacteriochlorophyll *a*.

However, it should be kept in mind that bacteriochlorophylls (especially *a*, *b*, and *g*) are exceptionally labile pigments that are subject to structural alterations when exposed to factors such as light, acids, and oxidizing chemicals. Therefore, to prevent destruction, all manipulations should be performed in the dark or at least under dim light.[I8, I20, I25]

The modification of bacteriochlorophyll *a* yields bacteriochlorin pigments but affords little synthetic flexibility.[I35] Also, the total synthesis of the bacteriochlorophyll *a* has yet to be developed.

3. Rational Synthesis of a Tolyporphin A Derivative. Examples of naturally occurring bacteriochlorins that are not involved in photosynthesis are provided by the

recently discovered tolyporphins (A-J). Kishi group has synthesized a tolyporphin derivative (tolyporphin A *O*,*O*-diacetate) by the extension of the Eschenmoser sulfide contraction and iminoester cyclization method.[I36]



tolyporphin A *O*,*O*-diacetate **A = C**

Scheme I.6. Approach to tolyporphin A by Kishi's group.

Retrosynthetic analysis (Scheme I.6) shows how the tolyporphin skeleton was assembled from monocyclic precursors. Extensive chromatographic and spectroscopic studies showed the synthetic *O*,*O*-diacetate to be identical to the *O*,*O*-diacetate derived from natural tolyporphin A, unambiguously establishing the stereochemistry of tolyporphin A.[I36]

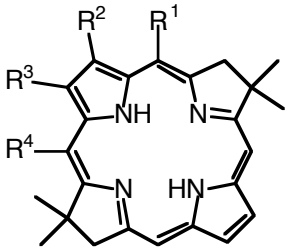
Although the stepwise synthesis of the tolyporphin A derivative provided a masterful demonstration of synthetic prowess, the synthetic method was too lengthy (more than 20 steps; < 5 mg) in practice to serve as a general method for the preparation of bacteriochlorins, particularly for fundamental studies or materials chemistry applications. For perspective, the tolyporphin synthesis is the only known *de novo* synthesis of a naturally occurring bacteriochlorin.

I.D. Overall Goal of the Research.

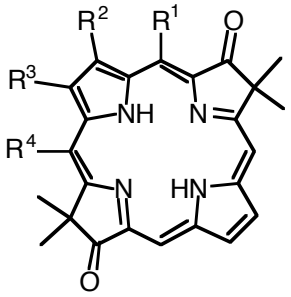
Naturally occurring bacteriochlorins absorb strongly in the spectral region 700-800 nm. Despite the desirable photophysical properties of the bacteriochlorins for medical and materials chemistry applications, few preparative methods have been developed to access these valuable macrocycles. Furthermore, none of the known methods was suitable for our research purposes.

The main goal of my research was to develop a *de novo* synthesis of bacteriochlorins. The term "*de novo*" is used to indicate that the bacteriochlorin reduction level is established by features in acyclic precursors prior to macrocycle formation, rather than by derivatization of an existing porphyrin or chlorin.

The design attributes for the target bacteriochlorin molecules were as follows: (1) resist dehydrogenation to afford chlorin and porphyrin products; (2) incorporate substituents at designated sites at the perimeter of the macrocycle; (3) be readily accessed by rational synthesis from simple starting materials; and, optionally, (4) be easy to convert to dioxobacteriochlorins.



Bacteriochlorin



Dioxobacteriochlorin

Chart I.5. Structural features of target bacteriochlorins.

This set of attributes translates into a number of specific molecular features. (i) Dehydrogenation can be prevented through the use of geminal dimethyl groups. (ii) Free methylene groups in pyrroline rings can afford the corresponding ketones to give mono- or dioxobacteriochlorins. (iii) Two hydrodipyrrin units can be prepared from simple starting materials and joining of the two units can give the bacteriochlorins.

We suggested our two target compounds having geminal-dimethyl groups to avoid dehydrogenation (Chart I.5). The dioxobacteriochlorin can be prepared from the oxidation of the corresponding bacteriochlorin. Also, the target molecules will be synthesized in a stepwise synthetic manner from simple starting materials. In developing new synthetic routes for the bacteriochlorins, the overriding goal was to achieve simplicity, scalability, and scope. In Chapter 2, I describe my work aimed at extending an existing synthesis of chlorins. In Chapter 3, I describe my exploratory work, which builds on the chlorin route, to develop a new approach to bacteriochlorins. In Chapter 4, I describe a new route to bacteriochlorins and the characterization of the synthetic bacteriochlorins.

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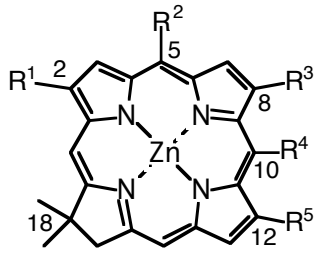
CHAPTER II. SYNTHESIS OF A SPIRO-CHLORIN AND ITS OXOCHLORIN

II.A. Introduction.

Synthetic building blocks that exhibit the spectral and photochemical properties of chlorophyll would have wide application in bioorganic and materials chemistry, particularly in areas such as photodynamic therapy, light-harvesting model systems, and molecular photonics. In many instances where chlorophyll-like molecules are desired, porphyrins have been employed as surrogates.

Chlorins are superior to porphyrins for use in photosynthetic systems and related photochemical systems wherein broad spectral coverage and/or efficient through-space contributions to energy transfer are desired. This superiority arises because the extinction coefficient of the long-wavelength absorption band of chlorins is greater than that of porphyrins.[II1]

Recently, a rational synthesis of C-methylated chlorin building blocks was developed in our group[II2–II4] following Battersby's routes.[II5] Each chlorin bears one geminal dimethyl group at the β-position in the reduced ring. For building block applications, synthetic handles have been introduced at several β-positions (2, 8, 12) and two meso-positions (5, 10). A current research objective is to create arrays containing a large number of chlorin chromophores, thereby obtaining synthetic materials with features that more closely resemble the natural light-harvesting systems.



A typical design of porphyrin building blocks employs several peripheral sites for attachment of synthetic handles and others for positioning groups that impart high solubility

in organic solvents. Methodology has been developed for introducing four different groups of wide variety at the four meso-positions of porphyrins.[II6] In the case of chlorins, methodology existed for introducing (i) two meso-substituents, (ii) two β-substituents and one meso-substituent, or (iii) two meso-substituents and one β-substituent, but not for introducing more than three different groups.[II2–II4] The chief limitation was that the two meso-substituents flanking the reduced ring were not yet accessible toward modification. Although functionality on chlorins has been introduced at five different positions (2, 5, 8, 10, and 12-positions), the solubility of chlorins remains a problem. To broaden the range of synthetic control and to increase solubility via substituents at the perimeter of the chlorin macrocycle, we sought to investigate whether the site of the geminal dialkyl group (18-position) could serve as a position for introducing substituents (Chart II.1).

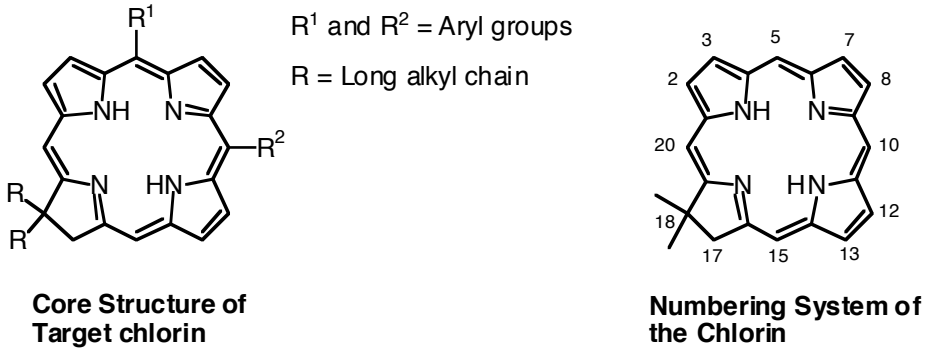
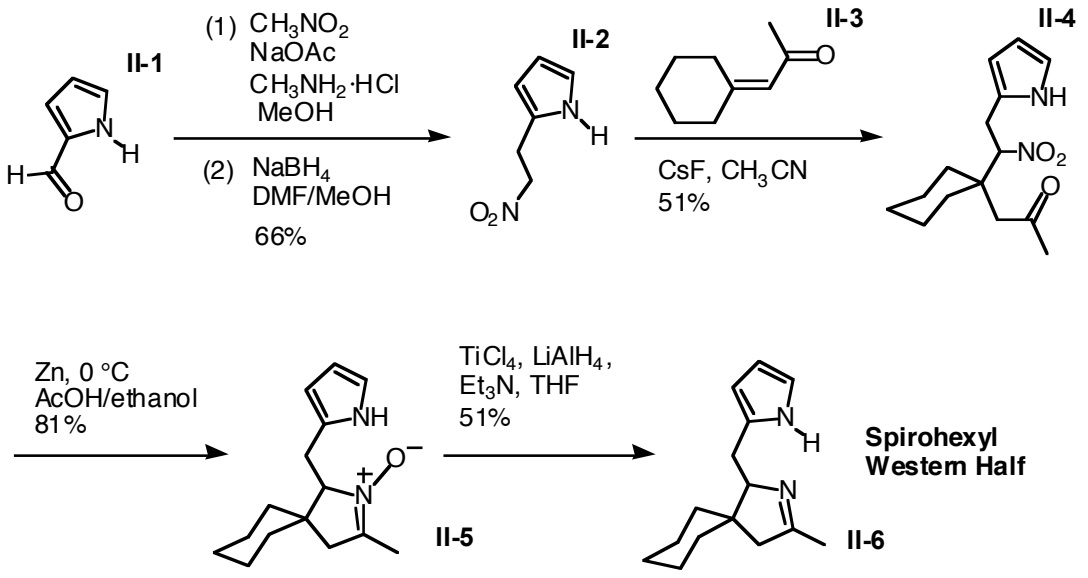


Chart II.1. Target chlorin structure and numbering system of the chlorin.

In this chapter, a synthesis of a spiro-chlorin is described, which is a chlorin that bears a spirohexyl group in lieu of a geminal dimethyl group. Also, an efficient method is illustrated for converting the spiro-chlorin to the corresponding oxochlorin.

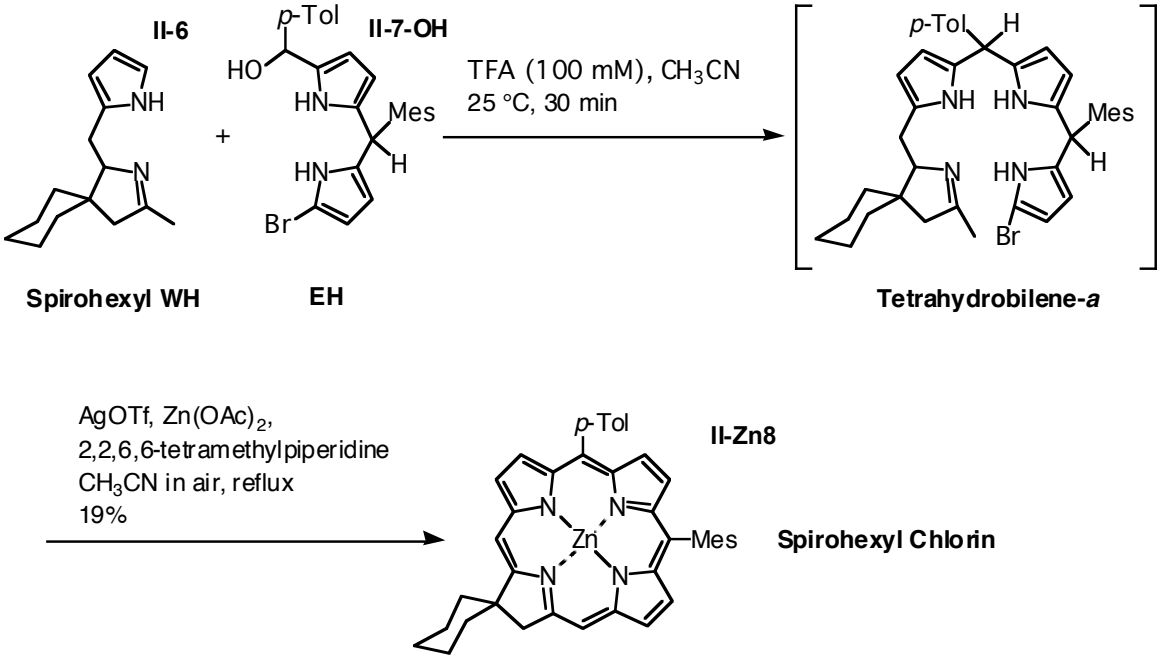
II.B. Results and Discussion.

1. Synthesis of Spirohexyl WH (Western half, II-6). A key step in the synthesis of the desired spirohexyl Western half is the Michael addition of nitroethyl pyrrole **II-2** to an α,β-unsaturated ketone **II-3** bearing a spirohexyl group at the β-position. The synthesis of a spirohexyl-substituted Western half begins in the same manner as for the geminal-dimethyl-substituted Western half, with the conversion of pyrrole-2-carboxaldehyde (**II-1**) to the nitroethyl pyrrole **II-2**. The prior synthesis of pyrrole **II-2**[II2] required two steps and a tedious work-up procedure. A simplified two-step, one-flask synthesis was developed that avoids isolation of the intermediate nitrovinyl pyrrole. In this manner, **II-2** was obtained in 66% yield compared with 45% in the prior procedure. Reaction of **II-3** with nitroethyl pyrrole **II-2** in the presence of CsF gave the Michael addition product **II-4**, from which tetrahydrodipyrrin *N*-oxide **II-5** was obtained following a straightforward procedure.[II4] The latter was deoxygenated to form the tetrahydrodipyrrin Western half **II-6**.



Scheme II.1. Synthesis of a spirohexyl Western half (**II-6**).

2. Synthesis of a Spirohexyl Chlorin (II-Zn8). The synthesis of C-alkylated chlorins entails the joining of an Eastern half and a Western half.[II4] The Eastern half **II-7-OH** was readily prepared by a known procedure.[II2] The reaction of Western half **II-6** and Eastern half **II-7-OH** under the standard two-step chlorin-forming condition[II4] gave chlorin **II-Zn8** in 19% yield (Scheme II.2). The absorption spectrum of **II-Zn8** in toluene was quite similar compared with those of previously prepared chlorins. Also, the identity of the spirohexyl chlorin **II-Zn8** was supported by data obtained from LD-MS, high-resolution mass spectrometry, and ^{1}H NMR spectroscopy.

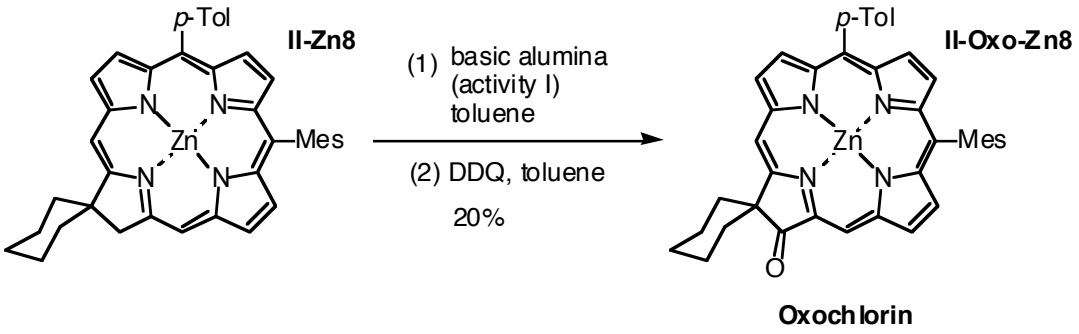


Scheme II.2. Two-step one-flask synthesis of a spirohexyl chlorin

3. Conversion of the Spirohexyl Chlorin (II-Zn8) to its Oxochlorin (II-Oxo-Zn8). A simple two-step conversion of a zinc chlorin to a zinc oxochlorin, wherein the keto group

is located in the reduced ring (17-position) of the macrocycle, has been developed.[II7] The transformation proceeds by hydroxylation of the chlorin upon exposure to alumina in air followed by dehydrogenation with DDQ.

Following the existing method, oxidation of **II-Zn8** led to the corresponding oxochlorin **II-Oxo-Zn8** in 20% yield. In this manner, the keto group was introduced at the site (17-position) adjacent to the geminal spirohexyl group (18-position), forming only one oxochlorin isomer (**II-Oxo-Zn8**) (Scheme II.3).



Scheme II.3. Conversion of a chlorin to the corresponding oxochlorin.

The chlorin and oxochlorin were characterized by absorption spectroscopy, LD-MS, high-resolution mass spectrometry, and ^{1}H NMR spectroscopy. The ^{1}H NMR spectrum of the oxochlorin was not remarkable compared with the chlorin except for the disappearance of a singlet signal (4.55 ppm) from the two protons in the reduced ring. As with the corresponding chlorin, each of the six β-protons and two meso-protons of the oxochlorin is unique and gives a distinctive resonance. The LD-MS spectrum of **II-Zn8** gave the molecule ion peak (*m/z* = 649.89), which is consistent with a molecular formula $C_{41}H_{38}N_4Zn$ (calcd 650.2388), and that of **II-Oxo-Zn8** gave the molecule ion peak (*m/z* = 664.70), which is consistent with the molecular formula $C_{41}H_{36}N_4OZn$ (calcd 664.2181). Note that the mass

difference (~14) of molecule ion peaks between **II-Zn8** and **II-Oxo-Zn8** is consistent with the presence of the keto group in the latter compound.

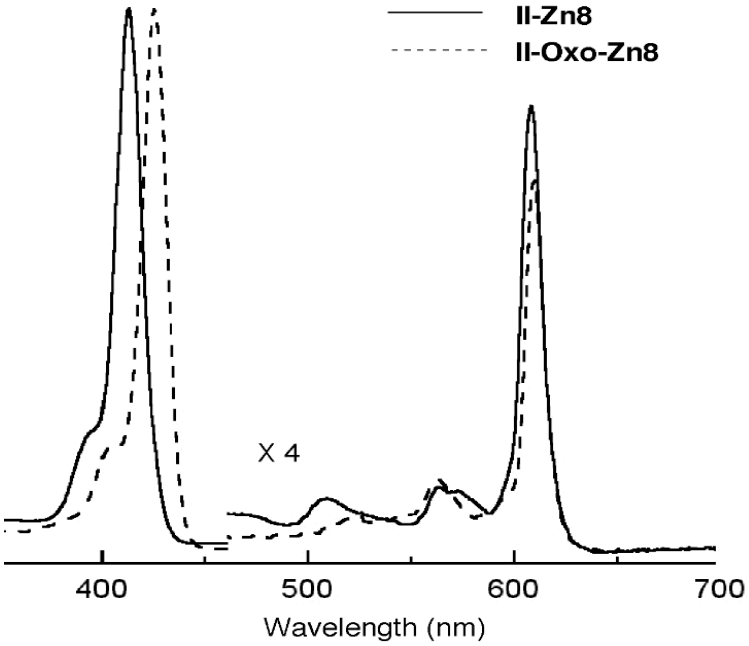


Figure II.1. Absorption spectra of chlorin **II-Zn8** and oxochorin **II-Oxo-Zn8** in toluene at room temperature.

UV-vis absorption spectra of the zinc chlorin (**II-Zn8**) and its oxochlorin (**II-Oxo-Zn8**) in toluene at room temperature are shown in Figure II.1. The strong near-UV Soret (B) band of the oxochlorin is red-shifted by ~10 nm from its chlorin counterpart, while the $Q_y(0,0)$ band is relatively unchanged (609 versus 608 nm). Both bands are slightly sharper for the oxochlorin.

Taken together, the absorption spectra, LD-MS, and ^{1}H NMR spectroscopic characterization data support the structures of the chlorin (**II-Zn8**) and the oxochlorin (**II-Oxo-Zn8**).

II.C. Conclusions.

A route to a spirohexyl-substituted chlorin/oxochlorin has been developed. The spirohexyl oxochlorin has absorption spectral features nearly identical to that of the spirohexyl chlorin, but the spirohexyl oxochlorin is more resistant to oxidation.

II.D. Experimental Section.

Synthetic Procedures. General. All ^{1}H NMR spectra (300 or 400 MHz) were obtained in $CDCl_3$ unless noted otherwise. IR spectra were obtained from films evaporated from CH_2Cl_2 on a NaCl window. Basic alumina (60-325 mesh, activity grade I) and neutral alumina (80-200 mesh) were obtained from Fisher Scientific. Activity grade V alumina was prepared from grade I alumina.[II8] Chlorins and oxochlorins were analyzed by laser desorption mass spectrometry without a matrix (LD-MS) or with the matrix POPOP (MALDI-MS).[II9] Fast atom bombardment mass spectrometry (FAB-MS) data are reported for the molecule ion or protonated molecule ion. Column chromatography was performed with flash silica (Baker).

Solvents. THF was distilled from sodium benzophenone ketyl as required. Toluene was distilled from CaH_2. CH_3CN (A.C.S. grade) for use in the condensation process was distilled from CaH_2 and stored over powdered molecular sieves. Nitromethane was stored over $CaCl_2$. Anhydrous methanol was prepared by drying over CaH_2 for 12 h followed by distillation. All other solvents were used as received.

2-(2-Nitroethyl)pyrrole (II-2). Pyrrole-2-carboxaldehyde (**II-1**) (2.85 g, 30.0 mmol) was dissolved in 90 mL of dry methanol and treated with nitromethane (4.85 mL, 90.0

mmol), sodium acetate (2.71 g, 33.0 mmol) and methylamine hydrochloride (2.23 g, 33.0 mmol). Stirring at room temperature for 12 h afforded a yellow/brown mixture. DMF (60 mL) and methanol (50 mL) were added to the reaction mixture. Sodium borohydride (3.97 g, 105 mmol) was added portionwise. The reaction mixture was stirred at room temperature for 1 h, neutralized with acetic acid (~5 mL) and evaporated. The mixture was dissolved in dichloromethane (150 mL) and washed with water. The organic layer was dried (Na_2SO_4), concentrated, and chromatographed (silica, CH_2Cl_2) to give an orange oil (2.79 g, 66%). The ^{1}H NMR spectrum and the ^{13}C NMR spectrum were identical with the literature.[II2] IR 3406, 1552, 1380 cm^{-1}; Anal. Calcd. for $C_6H_8N_2O_2$: C, 51.42; H, 5.75; N, 19.99. Found C, 51.38; H, 5.71; N, 19.92.

1-Cyclohexylidene-2-propanone (II-3). Following a standard procedure,[II10] a solution of dimethyl (2-oxopropyl)phosphonate (7.18 mL, 52.0 mmol) and KOH (3.14 g, 56.0 mmol) in ethanol/H_2O (70.0 mL, 4:1) was treated with cyclohexanone (4.15 mL, 40.0 mmol). Stirring at room temperature for 24 h afforded a light brown mixture. The mixture was extracted with petroleum ether. The organic layer was washed with water, dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (silica, dichloromethane) to give a colorless oil (5.02 g, 82%). Analytical data were consistent with the literature for the title compound prepared via a different route.[II11]

1-{1-[1-Nitro-2-(1*H*-pyrrol-2-yl)ethyl]cyclohexyl]propan-2-one (II-4). Following a general procedure,[II2–II4] cesium fluoride (3.58 g, 23.6 mmol, 3.00 mol eq, freshly dried by heating to 100 °C under vacuum for 1 h and then cooling to room temperature under argon) was placed in a flask under argon. A mixture of **II-2** (1.10 g, 7.85 mmol) and **II-3** (7.17 g, 47.1 mmol) in 50 mL of dry acetonitrile was transferred to the flask by cannula. The mixture

was heated at 70 °C for 7 h, whereupon the reaction was deemed to be complete by TLC analysis. The reaction mixture was filtered. The filtrate was evaporated and chromatographed [alumina, ethyl acetate/hexanes (1:3)], affording a light yellow oil which solidified upon storing in the freezer (1.11 g, 51%): mp 82 °C; IR 3395, 1712, 1547, 1366 cm^{-1}; ^{1}H NMR δ 1.20–1.98 (m, 10H), 2.18 (s, 3H), 2.63, 2.70 (AB, ^{2}J = 17.7 Hz, 2H), 3.10 (ABX, ^{3}J = 2.7 Hz, ^{2}J = 15.3 Hz, 1H), 3.30 (ABX, ^{3}J = 11.7 Hz, ^{2}J = 15.3 Hz, 1H), 5.18 (ABX, ^{3}J = 2.7 Hz, ^{3}J = 11.7 Hz, 1H), 5.94–5.98 (m, 1H), 6.07–6.12 (m, 1H), 6.64–6.67 (m, 1H), 8.10–8.22 (br, 1H); ^{13}C NMR δ 21.3, 25.3, 26.2, 30.9, 31.0, 32.2, 40.0, 43.8, 94.6, 107.1, 108.6, 117.7, 126.1, 207.7; Anal. Calcd. for $C_{15}H_{22}N_2O_3$: C, 64.73; H, 7.97; N, 10.06. Found C, 64.46; H, 7.88; N, 10.12.

3-Methyl-1-(1*H*-pyrrol-2-ylmethyl)-2-aza-spiro[4.5]dec-2-ene 2-oxide (II-5). Following a general procedure,[II4] a vigorously stirred solution of **II-4** (700 mg, 2.51 mmol) in 12 mL of acetic acid and 12 mL of ethanol at 0 °C was treated with Zn dust (4.11 g, 62.8 mmol) in small portions over 5 min. The reaction mixture was stirred at 0 °C for 15 min, and then was filtered through Celite. The filtrate was concentrated under high vacuum. The resulting brown solid was purified by column chromatography [silica; packed and eluted with ethyl acetate/CH_2Cl_2 (1:1), then eluted with CH_2Cl_2/methanol (9:1)] affording a brown oil that solidified to brownish crystals on standing at room temperature (498 mg, 81%): mp 109–110 °C; IR 3200, 1216 cm^{-1}; ^{1}H NMR δ 1.25–1.89 (m, 10 H), 2.01 (s, 3H), 2.28–2.44 (m, 2H), 3.00 (ABX, ^{3}J = 3.7 Hz, ^{2}J = 16.1 Hz, 1H), 3.17 (ABX, ^{3}J = 6.6 Hz, ^{2}J = 16.1 Hz, 1H), 3.83–3.91 (m, 1H), 5.92–5.96 (m, 1H), 6.04–6.09 (m, 1H), 6.66–6.71 (m, 1H), 10.35–10.60 (br, 1H); ^{13}C NMR δ 13.2, 22.4, 25.6, 25.7, 30.8, 30.9, 37.0, 40.1, 42.8, 81.3, 106.4, 107.2, 117.3, 128.3, 146.1; FAB-MS obsd 247.1813, calcd 247.1810 ($C_{15}H_{22}N_2O$).

3-Methyl-1-(1*H*-pyrrol-2-ylmethyl)-2-aza-spiro[4.5]dec-2-ene (II-6). Following a procedure for the deoxygenation of tetrahydrodipyrrin *N*-oxides,[II4] $TiCl_4$ (1.51 mL, 13.7 mmol) was slowly added with stirring to dry THF (30 mL) under argon at 0 °C. To the resulting yellow solution was slowly added $LiAlH_4$ (370 mg, 9.75 mmol). The resulting black mixture was stirred at room temperature for 15 min and then triethylamine (12.2 mL, 87.8 mmol) was added. The black mixture was then poured into a solution of **II-5** (480 mg, 1.95 mmol) in dry THF (20 mL). The mixture was stirred for 30 min at room temperature and then water (25 mL) was added. The mixture was filtered. The filtrate was extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure. The resulting yellow oil was purified by chromatography (silica, ethyl acetate) to give a pale yellow oil, which solidified to a pale yellow solid on cooling (228 mg, 51%): mp 54-55 °C; IR 3358, 1648 cm^{-1}; ^{1}H NMR δ 1.16–1.71 (m, 10H), 2.04 (s, 3H), 2.31, 2.46 (AB, ^2J = 17.6 Hz, 2H), 2.53 (ABX, ^3J = 11.0 Hz, ^2J = 14.7 Hz, 1H), 2.85 (ABX, ^3J = 2.9 Hz, ^2J = 14.7 Hz, 1H), 3.63–3.73 (m, 1H), 5.92–5.96 (m, 1H), 6.08–6.13 (m, 1H), 6.68–6.73 (m, 1H), 9.70–9.95 (br, 1 H); ^{13}C NMR δ 20.8, 23.6, 24.1, 26.4, 28.4, 31.3, 37.2, 45.9, 49.7, 81.1, 105.5, 107.5, 116.6, 131.9, 174.2; FAB-MS obsd 379.1349, calcd 379.1328 ($C_{18}H_{22}N_2O_5S$).

Spirohexylchlorin II-Zn8. Following a general procedure,[II4] a solution of **II-7**[II2] (140 mg, 0.304 mmol) in 10 mL of anhydrous THF/methanol (4:1) was treated with $NaBH_4$ (115 mg, 3.04 mmol). The resulting Eastern half (**II-7-OH**) was dissolved in 3 mL of anhydrous CH_3CN, and then the Western half (**II-6**, 70.0 mg, 0.304 mmol) and TFA (23.4 μL, 0.304 mmol) were added. The solution was stirred at room temperature for 30 min. The reaction was quenched with 10% aqueous $NaHCO_3$ (50 mL) and extracted with distilled CH_2Cl_2. The combined organic layers were washed with water, dried (Na_2SO_4) and

concentrated in vacuo without heating. The residue, which contains the crude tetrahydrobilene-*a*, was dissolved in 30 mL of toluene, to which AgOTf (137 mg, 0.534 mmol), $Zn(OAc)_2$ (490 mg, 2.67 mmol) and 2,2,6,6-tetramethylpiperidine (447 μL, 2.67 mmol) were added. The reaction mixture was refluxed for 24 h. The reaction mixture was concentrated and chromatographed [silica, hexanes/CH_2Cl_2 (2:1)] affording a blue solid (37 mg, 19%): ^{1}H NMR δ 0.80–2.70 (m, 22H), 4.55 (s, 2H), 7.20 (s, 2H), 7.47 (d, J = 8.1 Hz, 2H), 7.95 (d, J = 8.1 Hz, 2H), 8.22 (d, J = 4.5 Hz, 1H), 8.36 (d, J = 4.5 Hz, 1H), 8.48 (d, J = 4.5 Hz, 1H), 8.54–8.67 (m, 5H); LD-MS obsd 649.89; FAB-MS obsd 650.2399, calcd 650.2388 ($C_{41}H_{38}N_4Zn$); λ_{abs} 412, 610 nm; λ_{em} 610, 654, 666 nm.

Spirohexyloxochlorin II-Zn-Oxo8. A mixture of **II-Zn8** (25.0 mg, 38 μmol) and basic alumina activity I (1.70 g) in 3 mL of toluene was stirred at 85 °C for 15 h. After standard workup, the residue was dissolved in 3 mL of toluene and DDQ (16.9 mg, 76.1 μmol) was added. Standard workup and chromatography (silica, CH_2Cl_2) gave a bluish-purple solid (5.0 mg, 20%): ^{1}H NMR δ 0.85-2.70 (m, 22H), 7.23 (s, 2H), 7.51 (d, J = 8.1Hz, 2H), 7.98 (d, J = 8.1 Hz, 2H), 8.22 (d, J = 4.5 Hz, 1H), 8.45 (d, J = 4.5 Hz, 1H), 8.53 (d, J = 4.5 Hz, 1H), 8.80-8.93 (m, 3H), 8.98 (s, 1H), 9.45 (s, 1H); LD-MS obsd 664.70; FAB-MS obsd 664.2198, calcd 664.2181 ($C_{41}H_{36}N_4OZn$); λ_{abs} 424, 611 nm; λ_{em} 611, 651, 669 nm.

The contents of Chapter II have been published.[II7]

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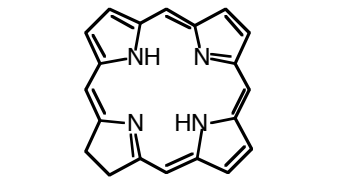
CHAPTER III. EXPLORATORY ROUTES TO BACTERIOCHLORINS

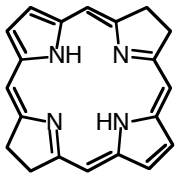
III.A. Introduction.

Hydroporphyrins perform a wide variety of essential functions in living systems. Hydroporphyrins differ from porphyrins in having fewer π bonds along the perimeter of the macrocycle. Representative hydroporphyrins are shown in Chart III.1.

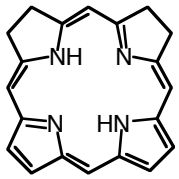
Chart III.1



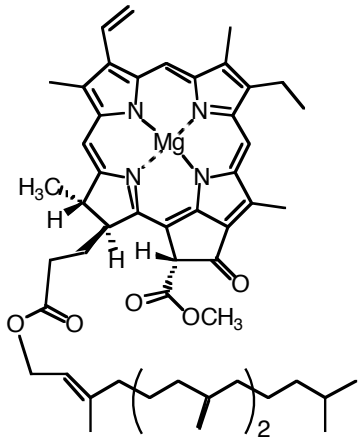
Chlorin



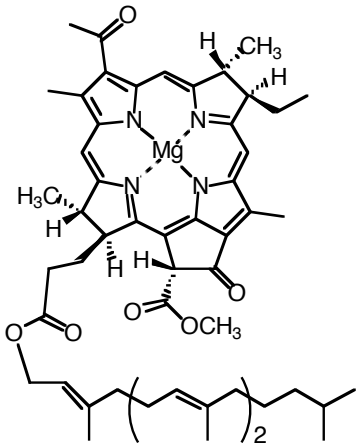
Bacteriochlorin



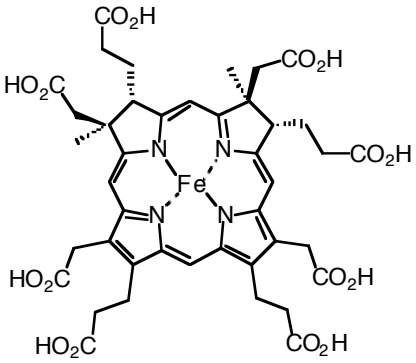
Isobacteriochlorin



Chlorophyll *a*



Bacteriochlorophyll *a*



Siroheme

Chlorophyll *a* and *b* (chlorins) and bacteriochlorophyll *a*, *b*, and *g* (bacteriochlorins) serve as the principal light-absorbing pigments in plant and bacterial photosynthetic systems.[III1] Siroheme (an isobacteriochlorin) plays an important role in the sulfur and nitrogen metabolism of numerous microorganisms.[III2] Vitamin B_{12} (a ring-contracted

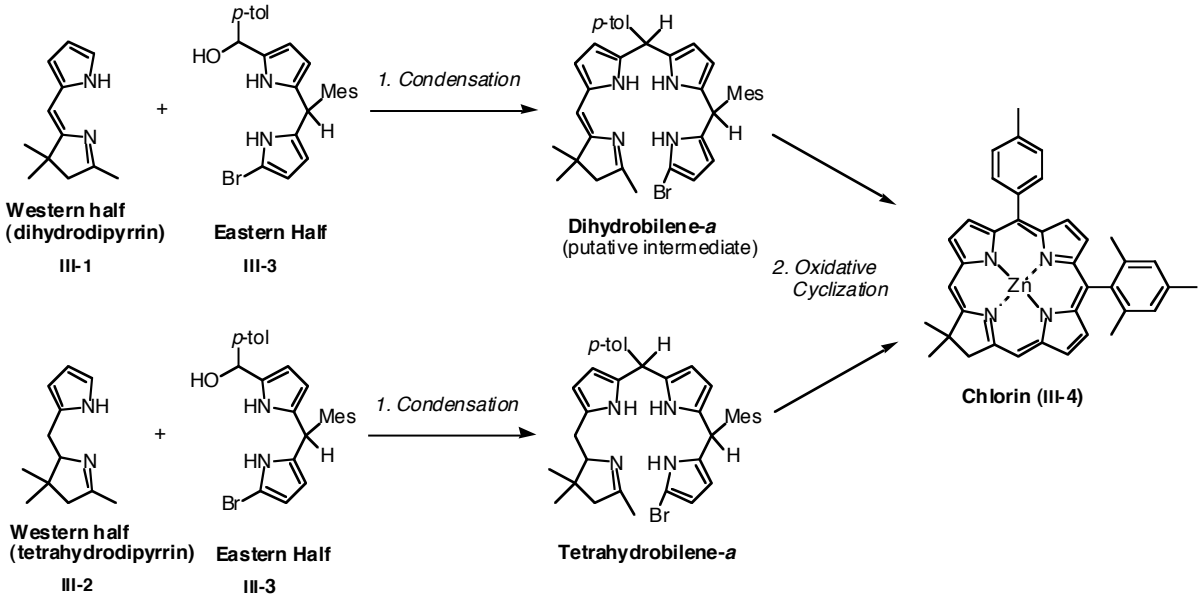
hydroporphyrin) serves as a cofactor for diverse enzymatic transformations.[III3] A wide variety of other naturally occurring hydroporphyrins (e.g., bacteriochlorophylls *c*-*e*,[III4] bonellin,[III5] F_{430},[III6] heme d,[III7] heme d_1,[III7] tolyporphins,[III8] tunichlorin[III9]) have been identified.

Significant efforts have been devoted to the development of total syntheses of naturally occurring hydroporphyrins.[III10] Two key challenges in each of the syntheses (in addition to constructing the macrocycle) concern the arrangement of eight or more distinct peripheral substituents and location of the pyrroline ring(s) to give the desired hydroporphyrin. While invariably elegant, the syntheses typically are elaborate and have afforded only minute quantities of material. By contrast, fundamental chemical studies, biological investigations, and materials chemistry applications require efficient routes for preparing the core hydroporphyrins. A trivial route to chlorins, bacteriochlorins, and isobacteriochlorins entails hydrogenation of the porphyrin.[III11] The simplicity of this approach is offset by two problems: (1) reduction in any of the four pyrrolic rings yields regioisomers if a distinct pattern of peripheral substituents is present, and (2) the hydroporphyrin is susceptible to adventitious dehydrogenation.

An alternative approach entails the *de novo* synthesis of hydroporphyrins. The chief challenges of *de novo* syntheses of non-natural hydroporphyrins are as follows: (1) afford a dehydrogenation-resistant hydroporphyrin, (2) provide control over the location of pyrroline rings, (3) enable placement of a small number of substituents at designated sites, and (4) offer a level of simplicity so that a collection of such hydroporphyrins can be prepared in ample quantities by practitioners of reasonable skill.

We began our work in hydroporphyrins by building on the pioneering syntheses developed by Battersby and coworkers of naturally occurring chlorins related to bonellin.[III12-III15] Bonellin contains a geminal-dialkyl group at one of the carbons in the pyrroline ring, thereby locking-in the hydrogenation level of the chlorin and precluding adventitious oxidative reversion to the porphyrin. We incorporated the geminal-dimethyl group as a key design feature of the non-natural chlorins. The resulting *de novo* synthesis involves the convergent joining of an Eastern half and a Western half (Scheme III.1).

Scheme III.1

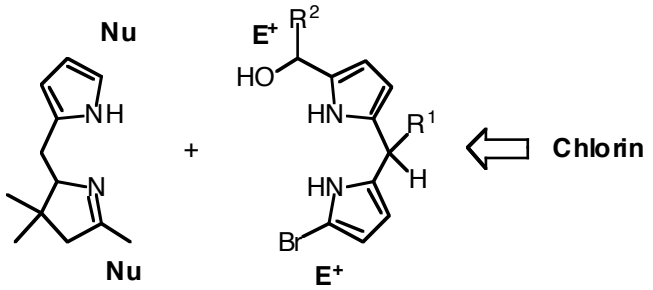


Two Western halves, a dihydrodipyrrin (**III-1**)[III16] and a tetrahydrodipyrrin (**III-2**),[III17] were each synthesized in four to five steps from pyrrole-2-carboxaldehyde. A bromo-dipyrromethane-carbinol (Eastern half, **III-3**) was prepared by sequential acylation and bromination of a 5-substituted dipyrromethane, followed by reduction. Acid-catalyzed

condensation of **III-3** + **III-1** (or **III-2**) followed by oxidative cyclization afforded the zinc chlorin **III-4**. The cyclization yield reached up to 45% depending on the presence of substituents in the components and the choice of Western half.[III16-III19]

The development of routes to bacteriochlorins and isobacteriochlorins requires the ability to introduce two geminal-dimethyl substituted pyrroline rings in each macrocycle. In the syntheses of geminal-dimethyl substituted chlorins,[III16– III19] the pyrrole unit and the α-methyl pyrroline unit of the Western half both functioned as nucleophiles, while the two complementary sites on the Eastern half (bromo-pyrrole, α-carbinol) functioned as electrophiles (Scheme III.2).

Scheme III.2



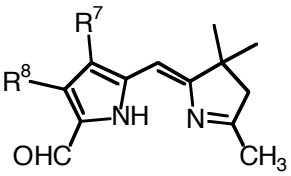
Moreover, each component provided one C_1-synthon to form the bridging carbon linking the two halves. A general strategy toward bacteriochlorins and isobacteriochlorins entails joining of two pyrrole-pyrroline synthons (i.e., hydrodipyrrins) similar to **III-1** and **III-2** employed in the chlorin synthesis. The success of such hydrodipyrrin + hydrodipyrrin reactions requires access to hydrodipyrrins with suitable reactivity at the α-positions of the respective pyrrole or pyrroline unit. All possible combinations of reactivity for the pyrrole and pyrroline rings are desirable, including Nu/Nu, Nu/E^+, E^+/E^+, and E^+/Nu. The reactivity of the pyrrole/pyrroline unit can be modified through (1) the use of a displaceable group at

the α-position, or (2) the presence of a C_1-synthon attached to the α-position that ultimately provides the bridging carbon upon formation of the hydroporphyrin macrocycle.

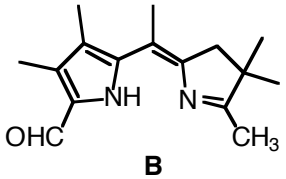
Prior studies in the synthesis of chlorins, isobacteriochlorins, and corrins have led to the development of a variety of hydrodipyrrin species with features for distinct reactivity (Nu/Nu, Nu/E^+, E^+/E^+, and E^+/Nu) at the pyrrole and pyrroline α-positions. With the exception of **III-1** and **III-2**, most such compounds bear substituents at both β-positions of the pyrrole ring (Chart III.2).

Chart III.2

E^+/Nu

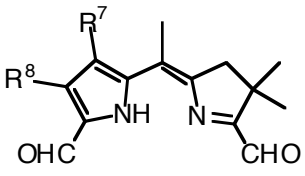


A

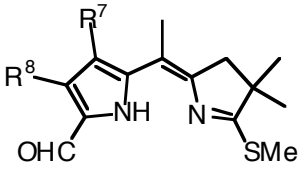


B

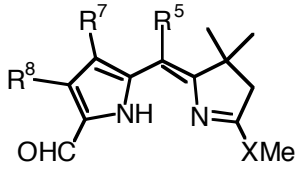
E^+/E^+



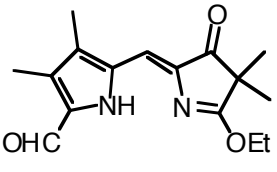
C



D

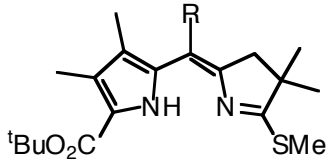


E: X = O
F: X = S

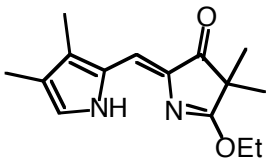


G

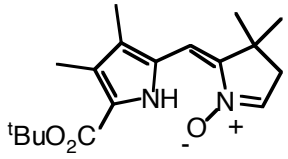
Nu/E^+



H



I



J

The hydrodipyrrins employed in chlorin syntheses (**III-1**,[III16] **III-2**,[III17] and substituted analogs[III12-III15,III18-III24]) bear nucleophilic pyrrole and pyrroline units (Nu/Nu). An electrophilic pyrrole site has been achieved by introducing a formyl group at the α-pyrrole position (**A**,[III14,III25] **B**,[III14,III25] **D**,[III25] **E**,[III20,III21-III24,III26] **F**,[III20,III21-III24,III26] **G**[III27]). An electrophilic pyrroline site has been achieved through use of a formyl group at the α-position (**C**),[III25] a (thio)alkoxide leaving group (**D**-**G**, **H**,[III28] **I**[III27]), or an α-unsubstituted pyrroline in the *N*-oxide form (**J**[III29]). In addition to differences in reactivity of the pyrrole or pyrroline units, the hydrodipyrrins also differ in number of potential bridging atoms conferred upon hydroporphyrin formation, including two (**A**-**C**), one (**D**-**G**), or zero (**H**-**J**).

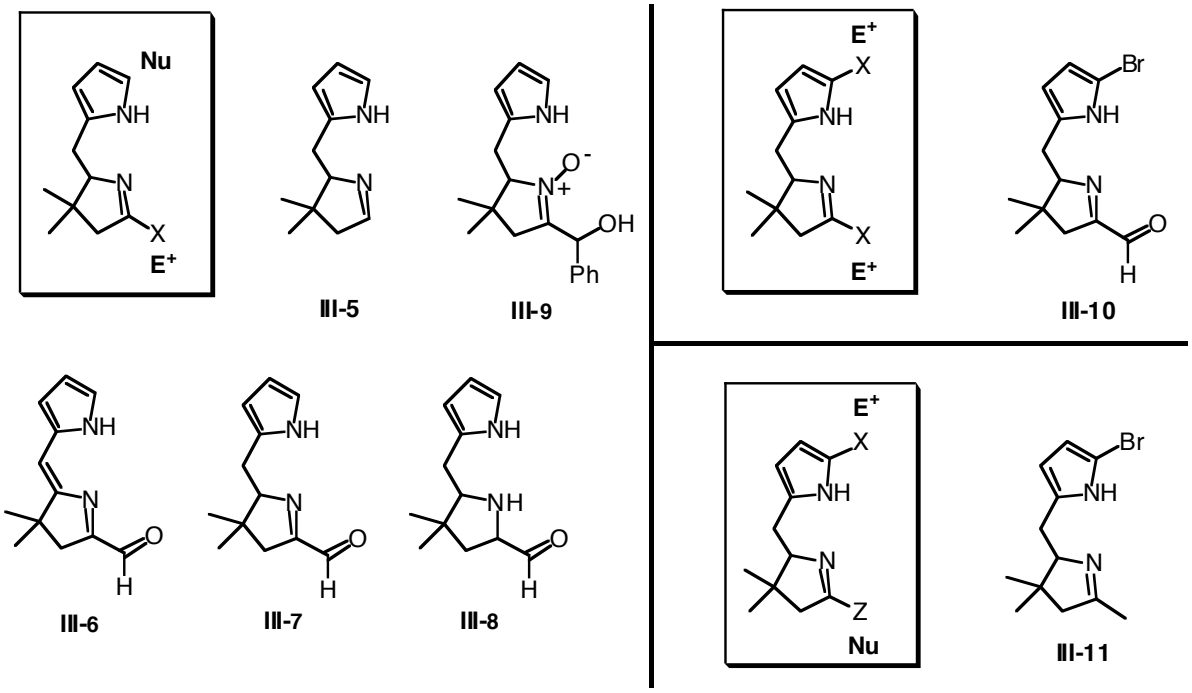
In this Chapter, we describe the synthesis of new hydrodipyrrins with normal or umpolung reactivity at the pyrrole and pyrroline α-positions. With the exception of the geminal-dimethyl group in the pyrroline ring, the hydrodipyrrins lack β-substituents. A lengthy study using hydrodipyrrins in developing a new route to bacteriochlorins is summarized. This work has established the foundation for a concise synthesis of bacteriochlorins and a B,D-tetradehydrocorrin as described in the continuing Chapter.[III30]

III.B. Results and Discussion.

1. Approach. The target hydrodipyrrins are shown in Chart III.3. The compounds with a Nu/E^+ pyrrole-pyrroline design contain pyrrole as the nucleophile, whereas the electrophilic pyrroline unit bears no substituent (**III-5**) or an aldehyde (**III-6**, **III-7**). An amino-aldehyde (**III-8**) was targeted that contains a pyrrolidine ring. Note the progressive reduction along the series **III-6** (dihydrodipyrrin), **III-7** (tetrahydrodipyrrin), and **III-8**

(hexahydrodipyrrin). A hydrodipyrrin bearing a carbinol (**III-9**) at the α-imine position also was sought. An electrophilic pyrrole was achieved with an α-bromopyrrole (**III-10**, **III-11**).

Chart III.3



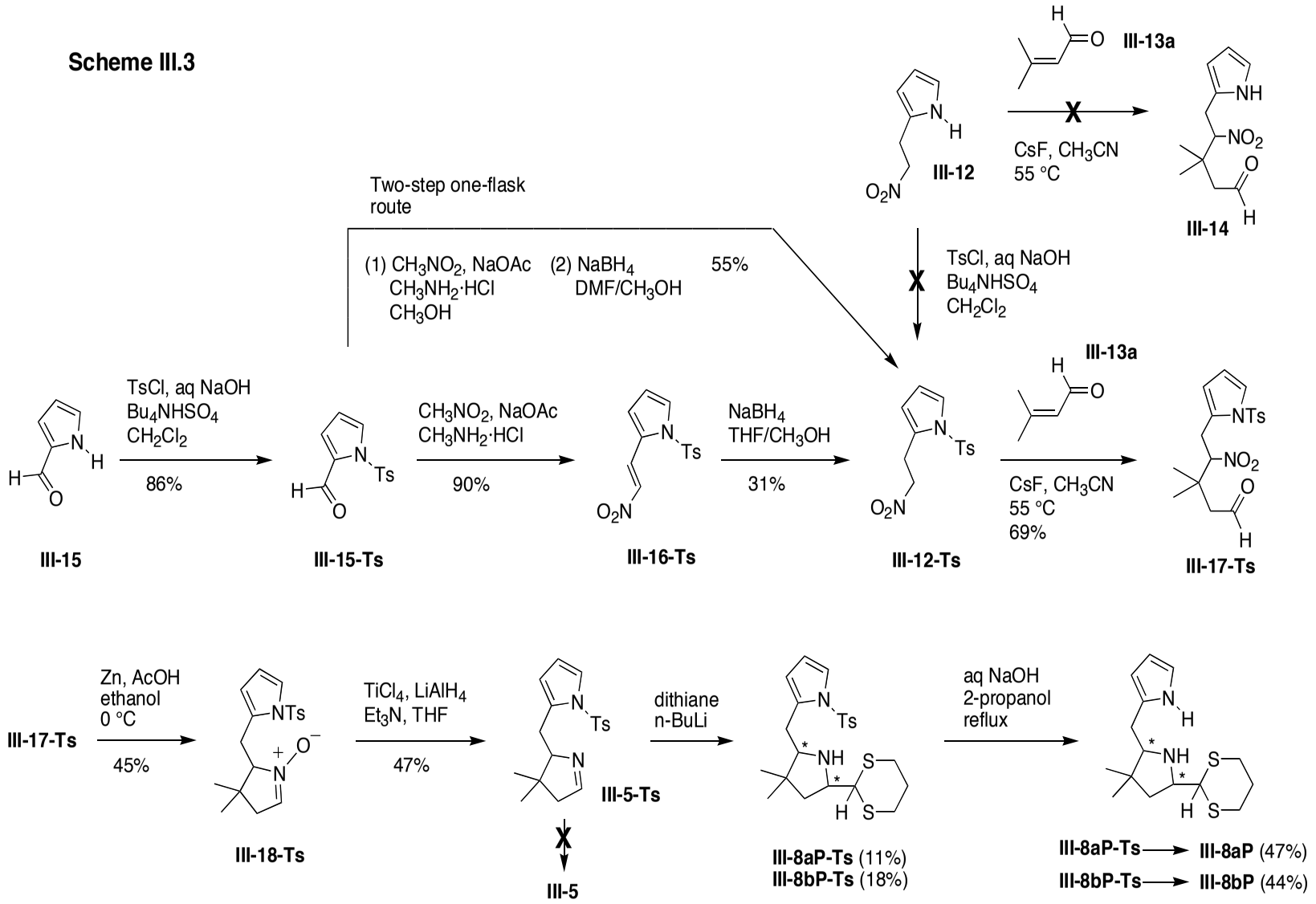
In all cases except **III-6**, the bond between the meso-position and the pyrroline ring is saturated. The rationale for this design stems from studies in chlorin chemistry[III16-III19] where hydrodipyrrins with such saturation (e.g., tetrahydrodipyrrin **III-2**) were found to be more stable than the unsaturated analogues (dihydrodipyrrin **III-1**). The following sections describe the routes that were pursued toward the synthesis of compounds **III-5**–**III-11**. Several of the target compounds were obtained whereas in some cases similar or protected analogues were obtained.

The general synthetic strategy builds on the approach employed for the synthesis of **III-1** or **III-2**, each of which contains a Nu/Nu pyrrole-pyrroline design.[III16,III17] Both compounds are prepared by elaboration of pyrrole-2-carboxaldehyde via condensation with nitromethane followed by reduction to give 2-(2-nitroethyl)pyrrole (**III-12**).[III19] Subsequent Michael addition with mesityl oxide gives the 2-alkylpyrrole bearing a γ-nitro-carbonyl unit, which can be cyclized to give the pyrroline ring as part of a dihydrodipyrrin or a tetrahydrodipyrrin. The dihydrodipyrrin is formed by reaction with NaOMe followed by $TiCl_3$ in near-neutral solution;[III16] the tetrahydrodipyrrin is obtained by reductive cyclization with Zn and acetic acid to give the *N*-oxide followed by deoxygenation with Ti(0).[III17] For the target molecules **III-5**–**III-11**, the desired functionality at the α-pyrroline position is introduced either upon elaboration of pyrrole-2-carboxaldehyde or by derivatization of the hydrodipyrrin product.

2. Synthesis of Hydrodipyrrins. A. Nu/E^+ Pyrrole-Pyrroline Units.

(i) An α-Amino-Aldehyde in Protected Form. The synthesis of the dithiane analogue (**III-8P**) of **III-8** was initially attempted via the intermediate 2-(2-nitroethyl)pyrrole (**III-12**) in the same manner as for **III-2**. However, the Michael addition of **III-12** with the aldehyde **III-13a** (instead of the ketone, mesityl oxide, **III-13b**, used in the synthesis of **III-2**) did not give the desired nitropentanal-pyrrole **III-14**. To suppress the reactivity of **III-12** we turned to the tosyl protecting group.[III31,III32] The direct tosylation of nitroethylpyrrole **III-12** to give **III-12-Ts** proved unsuccessful, requiring introduction of the tosyl group at the outset of the synthesis (Scheme III.3).

Scheme III.3

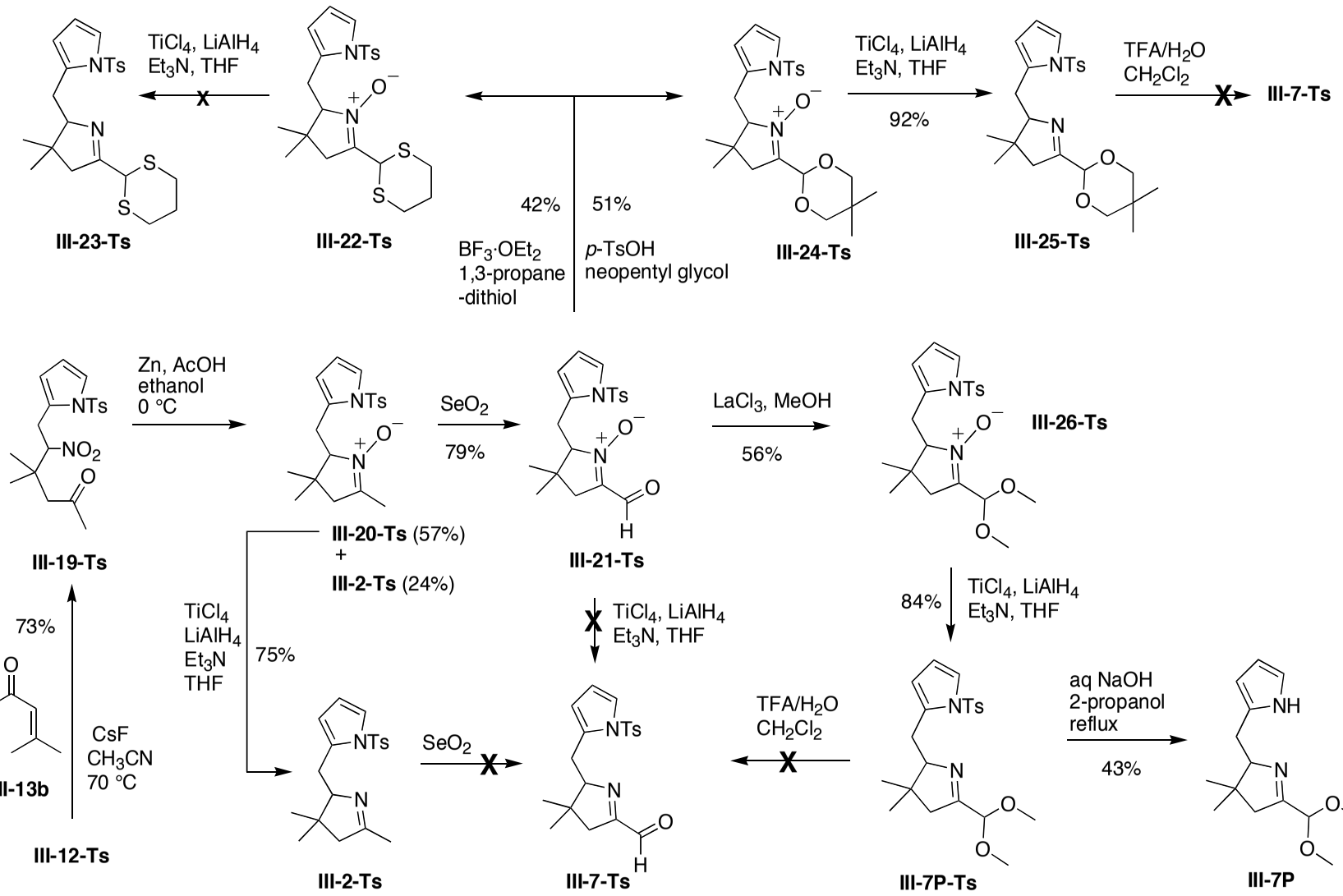

III-13a
III-12
CsF, CH3CN
55 °C
III-14
Two-step one-flask route
(1) CH3NO2, NaOAc
CH3NH2·HCl
CH3OH
(2) NaBH4
DMF/CH3OH
55%
TsCl, aq NaOH
Bu4NHSO4
CH2Cl2
III-13a
TsCl, aq NaOH
Bu4NHSO4
CH2Cl2
86%
CH3NO2, NaOAc
CH3NH2·HCl
90%
NaBH4
THF/CH3OH
31%
CsF, CH3CN
55 °C
69%
III-15
III-15-Ts
III-16-Ts
III-12-Ts
III-17-Ts
III-17-Ts
Zn, AcOH
ethanol
0 °C
45%
TiCl4, LiAlH4
Et3N, THF
47%
dithiane
n-BuLi
aq NaOH
2-propanol
reflux
III-18-Ts
III-5-Ts
III-5
III-8aP-Ts (11%)
III-8bP-Ts (18%)
III-8aP-Ts → III-8aP (47%)
III-8bP-Ts → III-8bP (44%)

Reaction of pyrrole-2-carboxaldehyde (**III-15**) and *p*-tosyl chloride under phase-transfer conditions afforded the *N*-tosyl derivative **III-15-Ts** (a known compound[III33] but with previously incomplete characterization data) in 86% yield. The subsequent nitro-aldol condensation and reduction was initially performed in two steps via the intermediate nitrovinylpyrrole **III-16-Ts** to give *N*-tosyl nitroethylpyrrole **III-12-Ts**. An alternative two-step, one-flask synthesis[III19] proved to be simpler and afforded a higher yield of **III-12-Ts**. Michael addition of the latter with **III-13a** in the presence of CsF at 55 °C gave the nitropentanal-pyrrole **III-17-Ts** in 69% yield.

Reductive cyclization of **III-17-Ts** in the presence of Zn in acetic acid and ethanol at 0 °C afforded the *N*-oxide **III-18-Ts** in 45% yield. Deoxygenation of **III-18-Ts** gave the *N*-protected **III-5-Ts** in 47% yield. However, attempts to deprotect **III-5-Ts** to give target compound **III-5** using the standard conditions (aq NaOH, 2-propanol, and reflux)[III32] were unsuccessful. On the other hand, dithiane addition[III34] to the imine of **III-5-Ts** gave two separable diastereomers **(III-8aP-Ts**, **III-8bP-Ts**) in 29% overall yield. The tosyl group of each diastereomer was removed using aqueous NaOH and 2-propanol. The resulting **III-8aP** and **III-8bP** are protected derivatives of target compound **III-8**.

(ii) Acetal Derivatives. We examined the direct conversion of pyrroline **III-2** to pyrroline-aldehyde **III-7** using SeO_2, but were unable to identify suitable conditions for this apparently simple transformation. Given that the *N*-oxide in a pyrroline ring accelerates oxidative conversion of the α-methyl group to the aldehyde,[III35] we turned to the pyrroline *N*-oxide.

Scheme III.4

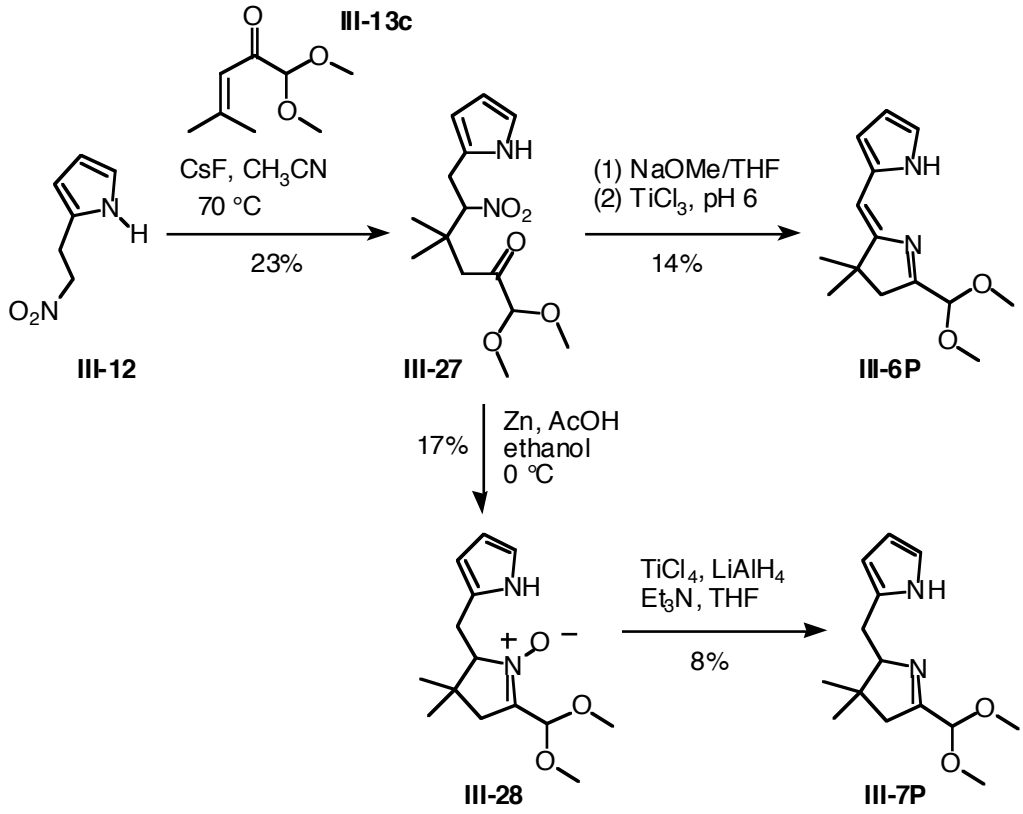

TiCl4, LiAlH4
Et3N, THF
III-23-Ts
III-22-Ts
42%
51%
BF3·OEt2
1,3-propane
-dithiol
p-TsOH
neopentyl glycol
III-24-Ts
92%
III-25-Ts
TFA/H2O
CH2Cl2
III-7-Ts
Zn, AcOH
ethanol
0 °C
III-19-Ts
III-20-Ts (57%)
+
III-2-Ts (24%)
SeO2
79%
III-21-Ts
LaCl3, MeOH
56%
III-26-Ts
84%
TiCl4, LiAlH4
Et3N, THF
73%
CsF
CH3CN
70 °C
III-13b
III-12-Ts
TiCl4
LiAlH4
Et3N
THF
75%
III-2-Ts
SeO2
TiCl4, LiAlH4
Et3N, THF
III-7-Ts
TFA/H2O
CH2Cl2
III-7P-Ts
aq NaOH
2-propanol
reflux
43%
III-7P

Michael addition of **III-12-Ts** with mesityl oxide (**III-13b**) gave **III-19-Ts**, which upon reductive cyclization gave the tetrahydrodipyrrin *N*-oxide **III-20-Ts** accompanied by the fully deoxygenated **III-2-Ts** (Scheme III.4). Treatment of **III-20-Ts** with freshly prepared Ti(0)[III19] afforded **III-2-Ts** in 75% yield. Oxidation of *N*-oxide **III-20-Ts** with SeO_2 gave the corresponding aldehyde **III-21-Ts** in 79% yield. As in the case of unactivated pyrroline **III-2**, attempted deoxygenation of both **III-2-Ts** and **III-21-Ts** failed to give **III-7-Ts**.

The failure of the direct deoxygenation of **III-21-Ts** prompted investigation of aldehyde protecting groups. Use of 1,3-propanedithiol[III36] gave compound **III-22-Ts**, which was unstable (e.g., decomposed after 24 hours in $CDCl_3$). Attempts to deoxygenate **III-22-Ts** were not successful, which can be attributed to its instability. Use of neopentyl glycol[III37,III38] gave *N*-oxide **III-24-Ts**, which upon deoxygenation gave acetal **III-25-Ts** in 92% yield. Although **III-25-Ts** was stable, the subsequent hydrolysis to give **III-7-Ts** also was unsuccessful. Finally, **III-21-Ts** was converted to the more labile dimethyl acetal (**III-26-Ts**) using $LaCl_3$[III39] in methanol in 56% yield. Deoxygenation gave **III-7P-Ts** in 84% yield. Conversion of **III-7P-Ts** to **III-7-Ts** was attempted using established methods for acetal hydrolysis [$MoO_2(acac)_2$ in aqueous acetonitrile;[III40] TFA/H_2O (3:1) in CH_2Cl_2[III37,III41]] but to no avail. ^{1}H NMR spectroscopy of the crude product obtained with aqueous TFA showed that **III-7P-Ts** had indeed reacted with water, but with addition of water across the imine rather than hydrolysis of the acetal. In summary, all four approaches to the *N*-tosyl protected target tetrahydrodipyrrin-carboxaldehyde **III-7-Ts** failed. On the other hand, removal of the tosyl protecting group in **III-7P-Ts** upon basic treatment afforded **III-7P**, the dimethyl acetal of **III-7**.

An approach to **III-7P** without use of *N*-protection is shown in Scheme III.5. The readily available 2-(2-nitroethyl)pyrrole (**III-12**) underwent Michael addition with α-keto acetal **III-13c** (instead of mesityl oxide as employed in the synthesis of **III-1** or **III-2**) in the presence of CsF, affording adduct **III-27**. Reductive cyclization of the latter in the presence of Zn and acetic acid afforded the *N*-oxide **III-28**, which upon deoxygenation with Ti(0) gave the tetrahydrodipyrrin-dimethyl acetal **III-7P**.

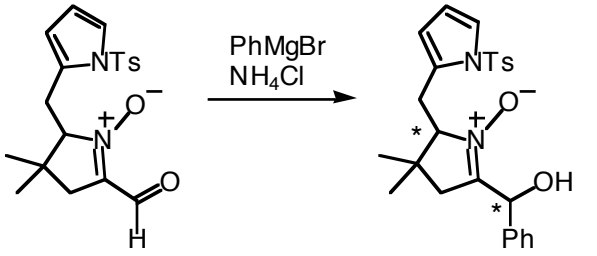
Scheme III.5



The synthesis of a dihydrodipyrrin-acetal (**III-6P**) followed the same method employed in the synthesis of dihydrodipyrrin **III-1**.[III16] Jacobi *et al.* described a related diformyl dihydrodipyrrin (**C**, Chart III.2),[III25] but given the difficulties we encountered in preparing the 1-formyl-tetrahydrodipyrrin **III-7**, we elected to prepare an acetal-protected

analogue. Thus, reductive cyclization of **III-27** upon treatment with NaOMe followed by a buffered solution of $TiCl_3$ afforded **III-6P** (Scheme III.5). The yields in both routes to **III-6P** and **III-7P** (protected derivatives of **III-6** and **III-7**) were quite low but sufficient material was obtained for subsequent exploratory studies.

(iii) Carbinol Derivative. The *N*-oxide aldehyde **III-21-Ts** appeared to be a versatile intermediate given the masked pyrrolic nitrogen, the "protected" imine unit, and the free formyl group. To explore conversion of the aldehyde to the secondary carbinol, **III-21-Ts** was treated with PhMgBr. The resulting diastereomers **III-9a-Ts** and **III-9b-Ts** were separated by column chromatography (34% total yield). The carbinols **III-9a-Ts** and **III-9b-Ts** were more stable than the corresponding dipyrromethane-based carbinols prepared previously[III42] (eq III.1).

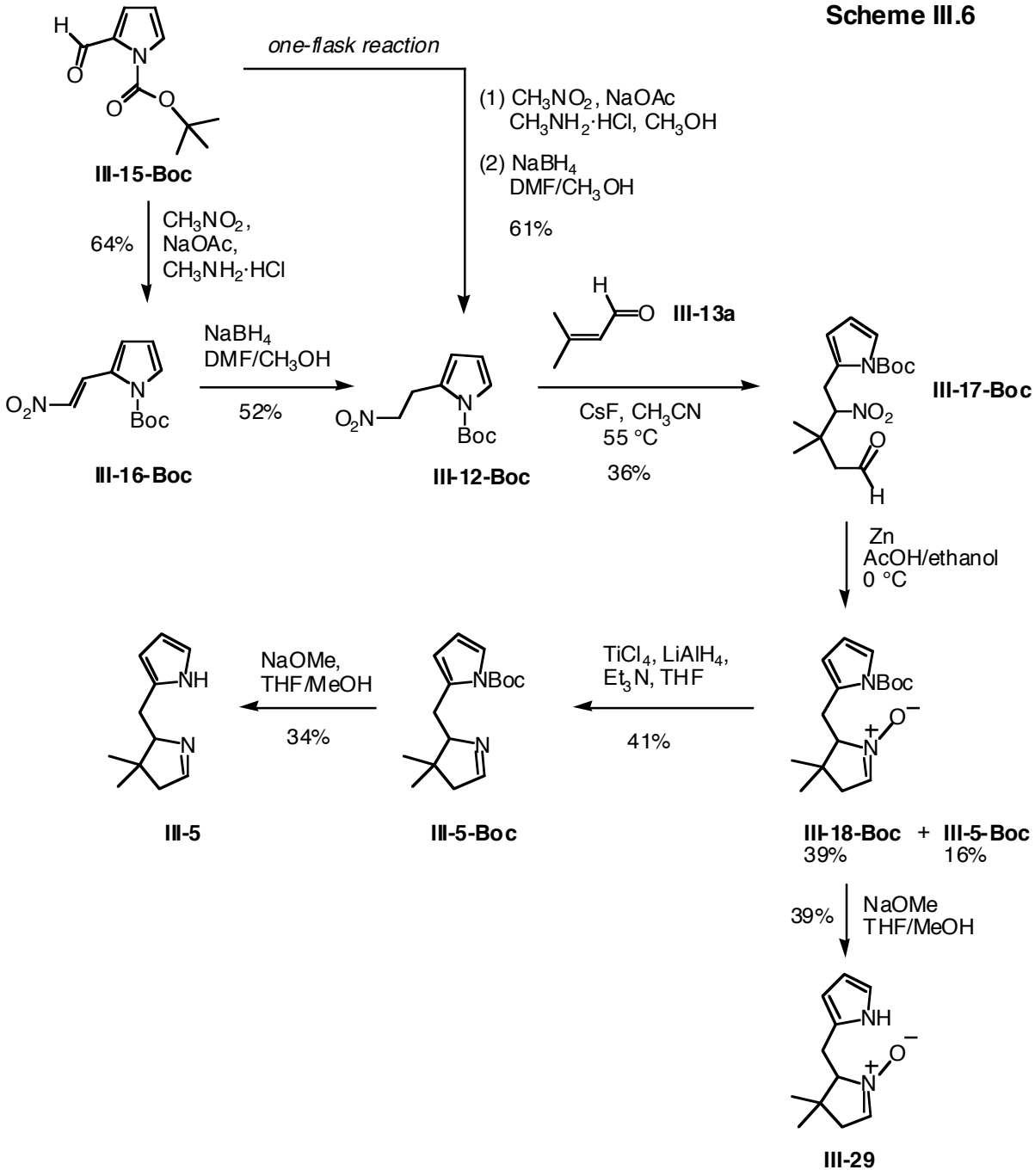


III-21-Ts **III-9a-Ts** (16%) **III-9b-Ts** (18%)

Eq III.1

(iv) Des-Methyl Imine Derivatives. An initial target was an analog of **III-2** lacking a methyl group at the α-position of the pyrroline ring (**III-5**). Such "des-methyl" species were important precursors in Battersby's synthesis of isobacteriochlorins.[III22,III23,III29] The first approach to **III-5**, by removal of the *N*-tosyl group from the tetrahydrodipyrrin **III-5-Ts**, was not successful (Scheme III.3). To facilitate deprotection, we changed from the tosyl to the Boc group for protecting the pyrrole nitrogen. The synthesis of the Boc-protected hydrodipyrrins mirrors that for the preparation of *N*-tosyl **III-5-Ts**.

Scheme III.6



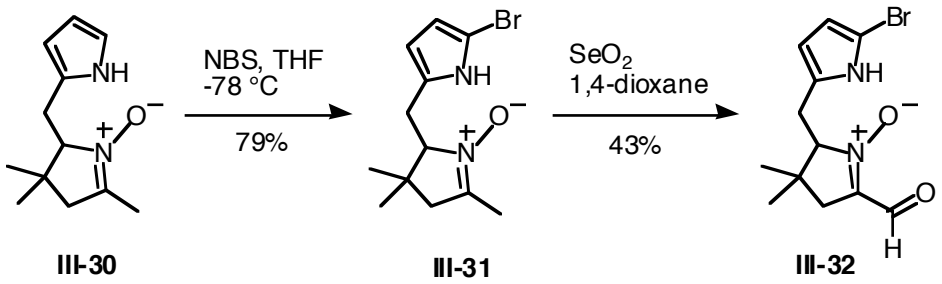
Thus, *N*-BOC pyrrole-2-carboxaldehyde (**III-15-Boc**)[III43] was converted via the intermediate nitrovinyl pyrrole **III-16-Boc** to the nitroethylpyrrole **III-12-Boc**, again either with a two-step or one-flask synthesis (Scheme III.6). Michael addition of **III-12-Boc** and 3-methyl-2-butenal (**III-13a**) gave the nitropentanal-pyrrole **III-17-Boc** (36% yield), which

upon cyclization in the presence of Zn and acetic acid afforded the expected *N*-oxide (**III-18-Boc**, 39%) and the deoxygenated *N*-Boc tetrahydrodipyrrin **III-5-Boc**. Two routes were investigated to obtain **III-5** from the *N*-oxide **III-18-Boc**, which differ in the order of deoxygenation and cleavage of the BOC group. Removal of the Boc group upon treatment with NaOMe afforded the *N*-oxide **III-29**, which proved to be slightly unstable. On the other hand, deoxygenation of **III-18-Boc** gave **III-5-Boc** (41% yield) and subsequent treatment with NaOMe gave the target compound **III-5** in 34% yield. The low yield in the deprotection steps (39% for **III-29**; 34% for **III-5**) appears to stem from the slightly unstable nature of **III-5**.

B. Synthesis of a Hydrodipyrrin with E^+/E^+ Pyrrole-Pyrroline Units. The umpolung analog of tetrahydrodipyrrin **III-2** (Nu/Nu) requires conversion of both nucleophilic units (pyrrole and methyl imine) to electrophilic units. In a previous chlorin synthesis,[III16-III19] an α-bromo-pyrrole in the Eastern half served as a key electrophilic unit in the carbon-carbon bond-forming macrocyclization process. Such an α-bromo-pyrrole and a pyrroline-aldehyde are obvious choices for the two electrophiles. However, direct conversion of the methyl imine to the aldehyde (e.g., **III-2** → **III-7**) was not viable, prompting examination of the *N*-oxide of tetrahydrodipyrrin **III-2** (i.e., **III-30**) as a surrogate for the corresponding conversion.

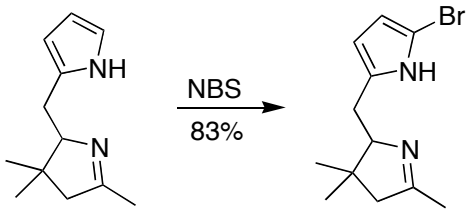
Treatment of the *N*-oxide **III-30**[III17] with NBS in THF at –78 °C gave selective bromination at the α-pyrrole position, affording bromo *N*-oxide **III-31** in 79% yield. Oxidation of **III-31** with SeO_2 gave the aldehyde **III-32** in 43% yield (Scheme III.7). It is noteworthy that the opposite order of bromination and oxidation proved difficult owing to the instability of the pyrrole *N*-oxide aldehyde.

Scheme III.7



III-30 **III-31** **III-32**

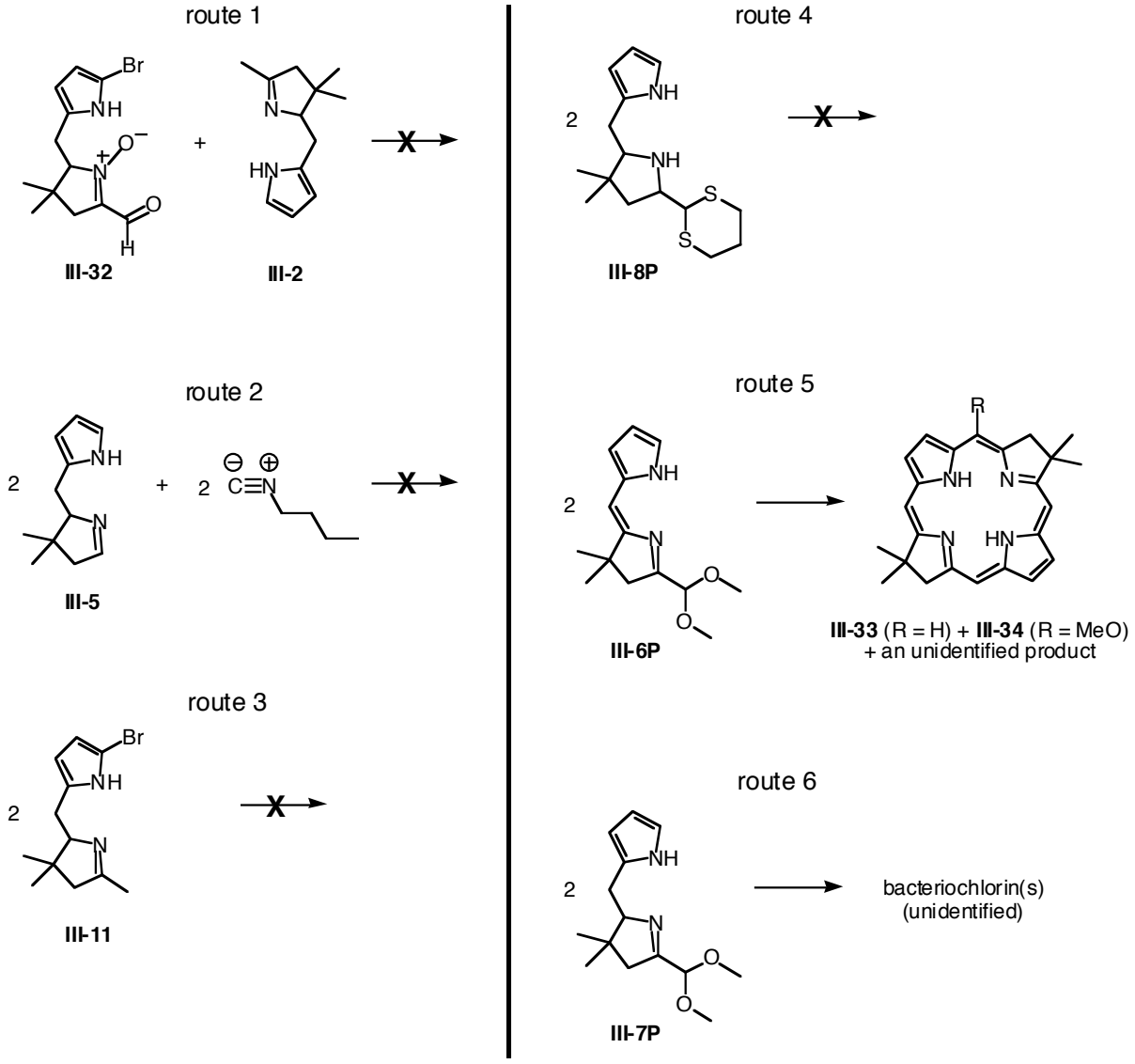
C. Synthesis of a Hydrodipyrrin with E^+/Nu Pyrrole-Pyrroline Units. The conversion of the pyrrole unit from a nucleophilic to electrophilic species can be accomplished by bromination. Thus, bromination of tetrahydrodipyrrin **III-2** with NBS proceeded selectively at the free α-pyrrole position, affording bromo tetrahydrodipyrrin **III-11** in 83% yield (eq III.2).



III-2 **III-11** **Eq III.2**

3. Exploratory Studies Toward Bacteriochlorins. Six routes were explored to access bacteriochlorins as well as gain fundamental information concerning reactivity of the various hydrodipyrrins (Scheme III.8). Route 1 entailed the reaction of 9-bromo-tetrahydrodipyrrin-1-carboxaldehyde **III-32** and 1-methyltetrahydrodipyrrin **III-2**, a bis-electrophile and a bis-nucleophile (E^+/E^+ + Nu/Nu), respectively. The latter has been employed as the Western half in a chlorin synthesis.[III17]

Scheme III.8



The reaction was carried out under conditions identical to those in chlorin synthesis (**III-2** + **III-3**), entailing acid-catalyzed condensation followed by metal-mediated oxidative cyclization.[III16-III19] Although **III-2** was consumed, no bacteriochlorin was obtained. Model studies related to the reaction of **III-32** + **III-2** were performed as follows: (1) The reaction of *N*-oxide aldehyde **III-21-Ts** and **III-2**, where the initial reactive sites are the carboxaldehyde of **III-21-Ts** and the pyrrole of **III-2**, proceeded to completion in a few

minutes under TFA catalysis but the resulting product showed severe tailing on TLC and the ^{1}H NMR spectrum was not readily assignable. The reaction was explored over a range of TFA concentrations (10 mM, 120 mM, 5.1 M) but no identifiable product was obtained. (2) In the syntheses of porphyrins and chlorins, dipyrromethane-carbinols are essential precursors.[III16-III19,III42] The carbinols normally have limited stability and are prepared immediately before use without chromatographic purification. A carbinol analog (**III-9-Ts**) of *N*-oxide **III-21-Ts** was sufficiently stable to be purified by chromatography. However, TLC analysis of the condensation of **III-9-Ts** + **III-2** showed that the carbinol **III-9-Ts** was resistant to condensation under low acid concentrations [TFA or $BF_3{\cdot}O(Et)_2$] while **III-2** slowly decomposed under high acid concentrations.

Route 2 entailed the reaction of the des-methyl-tetrahydrodipyrrin **III-5** and an alkyl isocyanide to form a 5,15-bis(butylamino)bacteriochlorin. The carbon of the isocyanide serves as both an electrophile and a nucleophile,[III44] complementing that of the pyrrole and pyrroline units of **III-5** (Nu/E^+). The reaction of **III-5** and *n*-butyl isocyanide was carried out under established conditions for reactions of isocyanides, including neutral solution[III45] or with acid catalysis[III46] [$BF_3{\cdot}OEt_2$, $CuC1_2$, $(CF_3SO_3)_3Y$, or $AlCl_3$]. No bacteriochlorin-like species were obtained even with addition of DDQ to oxidize any intermediates. These results indicate insufficient reactivity of the *n*-butyl isocyanide toward the imine group of **III-5**.

Route 3 entailed the self-condensation of 9-bromo-1-methyltetrahydrodipyrrin **III-11**, wherein the reactivity is E^+/Nu. Similar motifs appear in the Eastern half (**III-3**) and Western half (**III-2**) of chlorin syntheses.[III16-III19] However the self-condensation of **III-11** under various conditions, including use of metal templates, did not give any bacteriochlorin.

Route 4 examined the effects of reversal of polarity achieved with a hydrodipyrrin bearing a 1-formyl group and an intact pyrrole, affording Nu/E^+ reactivity. Dithiane-hexahydrodipyrrin **III-8P** was subjected to hydrolysis conditions to give the corresponding aldehyde **III-8** as a potential intermediate on the path to bacteriochlorins. Although the α-aminoaldehyde motif in compound **III-8** would be prone to tautomerization (Cf. literature[III47] on *N*-protected α-aminoaldehydes), we felt that the reaction of the free aldehyde and pyrrole in the self-condensation could be a competitive process. However, the attempted hydrolysis of the dithiane moiety in **III-8P** (or the *N*-tosyl analog **III-8P-Ts**) under various conditions ($HgO/HBF_4/THF$;[III48] $HgCl_2/MeOH$;[III49] aqueous $AgNO_3$;[III50] $AgNO_2/I_2$[III51]) including use of DDQ following oxidation gave neither aldehyde **III-8** (or the *N*-tosyl aldehyde analogue) nor a bacteriochlorin.

Route 5 envisaged hydrolysis of dihydrodipyrrin-acetal **III-6P** under acidic conditions to generate the corresponding dihydrodipyrrin-carboxaldehyde **III-6**, which also has reactivity of Nu/E^+. The unsaturated system in **III-6** precludes any tautomerization as might occur with **III-8**. Upon use of the mild Lewis acid $InCl_3$ in $CHCl_3$ at room temperature in an effort to hydrolyze the acetal, the appearance of the characteristic bacteriochlorin absorption spectrum[III11,III30] was observed with a strong sharp Q_y band at ~710 nm. The yield was ~1% on the reasonable assumption[III11,III30] that ε_{Qy} = 120,000 $M^{-1}cm^{-1}$. The reaction was scaled up using **III-6P** (10 mM) and $InCl_3$ (10 mol equiv) in $CHCl_3$ at room temperature for 24 h exposed to air. The acid-catalysis conditions resemble those used in dipyrromethane + dipyrromethane-dicarbinol condensations.[III52] Workup gave two bacteriochlorins (**III-33**, **III-34**) and one putative bacteriochlorin species in trace quantities (characterized only by absorption spectroscopy; λ_{Qy} = 720 nm). Bacteriochlorins **III-33** and

III-34 were characterized by absorption spectroscopy, laser desorption mass spectrometry, and high-resolution mass spectrometry, but the limited amount of product obtained precluded NMR characterization. The characterization data are consistent with the structures shown for **III-33** and **III-34** where the former is an unsubstituted bacteriochorin and the latter is a methoxy-bacteriochlorin; however, the structures must be considered provisional in the absence of NMR or X-ray data. Analogous bacteriochlorins have been obtained via a similar route in higher yields and have been thoroughly characterized, as described in the companion Chapter.[III30] Note that the acetal unit of compound **III-6P** serves as an electrophile for the bacteriochlorin-forming reaction. Although a masked aldehyde, examples are known where an acetal has been used as an electrophile without hydrolysis, leaving one alkyl ether unit intact.[III53]

Route 6 entailed the self-condensation of tetrahydrodipyrrin-acetal **III-7P** under acidic conditions in the presence of an oxidant. We anticipated that this route would be superior to routes 4 and 5, owing to the presence of the imine acetal (rather than the aminomethyl acetal, thereby precluding tautomerization as is possible in route 4) and the alkylpyrrole (rather than an alkenylpyrrole, thereby affording a more potent pyrrolic nucleophile). The reaction under standard porphyrin-forming conditions (condensation with $BF_3{\cdot}OEt_2$ or TFA in CH_2Cl_2 at room temperature followed by oxidation with DDQ),[III54] which are suitable for aryl acetals,[III55] did not give any bacteriochlorin. Use of $InCl_3$ in $CHCl_3$ at room temperature (as in route 5) or elevated temperature also did not give any bacteriochlorin. A series of solvents that support higher reaction temperatures at reflux (CH_3CN, ~80 °C; toluene, ~110 °C; collidine, ~170 °C) was employed with various acid catalysts and air as an oxidant. Eventually we found that use of **III-7P** (5 mM) with excess

$Zn(OAc)_2$ (50 mM) and excess $InCl_3$ (50 mM) in refluxing collidine gave an absorption band at ~720 nm that is characteristic of bacteriochlorins (≤1% yield); however, in neither case could a bacteriochlorin be purified for characterization. The origin of the different reactivity and reaction course exhibited by the tetrahydrodipyrrin-acetal **III-7P** and the dihydrodipyrrin-acetal **III-6P** is not clear and will require further study.

III.C. Conclusion.

Routes to a set of hydrodipyrrin derivatives composed of one pyrrole and one pyrroline (or pyrrolidine) unit have been developed. The reduced pyrrole ring bears a geminal-dimethyl group to lock-in the hydrogenation level of target hydroporphyrin macrocycles. The substituents at the α-pyrrole and α-pyrroline positions have been designed to afford reactivity as a nucleophile or electrophile. The α-pyrrole position is either unsubstituted or bears a bromo substituent; the α-pyrroline position is either unsubstituted or bears a formyl, acetal, or carbinol substituent; the α-pyrrolidine substituent is a dithiane unit. Hydrodipyrrins bearing distinct groups (methyl, acetal, no substituent) at the α-pyrroline position were obtained by Michael addition of 2-(2-nitroethyl)pyrrolic compounds with different α,β-unsaturated carbonyl compounds (**III-13a–III-13c**). A dihydrodipyrrin-acetal provisionally afforded two bacteriochlorins under acid catalysis in ~1% yield. Extension of this work to a more efficient synthesis of bacteriochlorins is described in the companion Chapter.[III30]

III.D. Experimental Section.

General. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were collected at room temperature in $CDCl_3$ unless noted otherwise. Melting points are uncorrected. Column chromatography was performed with flash silica or alumina (80–200 mesh). The $CHCl_3$ contained 0.8% ethanol. THF was distilled from sodium benzophenone ketyl as required. CH_3CN was distilled from CaH_2 and stored over powdered molecular sieves. Other solvents were used as received.

Noncommercial compounds. Compounds **III-2**,[III17] **III-15-Boc**,[III43] and **III-30**[III17] were prepared according to literature procedures.

2,3,4,5-Tetrahydro-1,3,3-trimethyl-(*N*^{11}-tosyl)dipyrrin (III-2-Ts). Following a procedure for the deoxygenation of *N*-oxides[III17] with slight modification, $TiCl_4$ (229 μL, 2.08 mmol) was slowly added with stirring to dry THF (6.0 mL) under argon at 0 °C. The resulting yellow solution was slowly treated with $LiAlH_4$ (56.0 mg, 1.49 mmol). The resulting black mixture was stirred at room temperature for 15 min. TEA (1.86 mL, 13.4 mmol) was added. The black mixture was poured into a solution of **III-20-Ts** (107 mg, 0.297 mmol) in dry THF (60 mL) at 0 °C. The mixture was stirred for 1 h in a water bath (~20 °C) and then water (40 mL) was added. The mixture was filtered. The filtrate was extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and concentrated. The resulting yellow oil was purified by column chromatography (silica, ethyl acetate) to give a pale yellow oil (76 mg, 75%): ^{1}H NMR δ 0.88 (s, 3H), 1.07 (s, 3H), 1.97 (s, 3H), 2.27, 2.56 (AB, ^{2}J = 17.0 Hz, 2H), 2.39 (s, 3H), 2.66 (ABX, ^{3}J = 9.8 Hz, ^{2}J = 16.2 Hz, 1H), 2.94 (ABX, ^{3}J = 4.2 Hz, ^{2}J = 16.2 Hz, 1H), 3.72–3.75 (m, 1H), 6.21–6.23 (m, 1H), 6.23–6.25 (m, 1H),

7.27 (d, J = 8.4 Hz, 2H), 7.28–7.29 (m, 1H), 7.65 (d, J = 8.4 Hz, 2H); ^{13}C NMR δ 20.7, 21.8, 22.9, 27.3, 28.3, 42.4, 54.8, 78.2, 111.9, 113.7, 122.4, 127.0, 130.1, 134.3, 136.7, 144.9, 174.7; FABMS obsd 345.1649, calcd 345.1637 [$(M+H)^+$, M = $C_{19}H_{24}N_2O_2S$]. Anal. Calcd. for $C_{19}H_{24}N_2O_2S$: C, 66.25; H, 7.02; N, 8.13. Found C, 65.93; H, 6.93; N, 8.00.

2,3,4,5-Tetrahydro-3,3-dimethyldipyrrin (III-5). Following a general procedure,[III18] a solution of **III-5-Boc** (299 mg, 1.08 mmol) in anhydrous THF (4.32 mL) under argon at room temperature was treated with methanolic NaOMe (1.50 mL, prepared by dissolving 373 mg of NaOMe in 2.00 mL of MeOH). After 25 min, the reaction was quenched with a mixture of hexanes and water (20.0 mL, 1:1). The mixture was extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried (Na_2SO_4), and chromatographed [alumina, ethyl acetate/hexanes (1:3)] to give a pale yellow oil (64 mg, 34%): IR 3380, 2958 cm^{-1}; ^{1}H NMR δ 0.95 (s, 3H), 1.13 (s, 3H), 2.39–2.41 (m, 2H), 2.60 (ABX, ^3J = 11.6 Hz, ^2J = 14.8 Hz, 1H), 2.82 (ABX, ^3J = 3.2 Hz, ^2J = 14.8 Hz, 1H), 3.63–3.69 (m, 1H), 5.95–5.97 (m, 1H), 6.10–6.12 (m, 1H), 6.69–6.71 (m, 1H), 7.63–7.65 (m, 1H), 9.52–9.68 (br, 1H); ^{13}C NMR δ 23.0, 27.4, 28.0, 40.3, 52.5, 80.9, 105.5, 107.5, 116.7, 131.5, 166.7; EI-MS obsd 176.1305, calcd 176.1313 ($C_{11}H_{16}N_2$).

(*N*^{11}-*tert*-Butoxycarbonyl)-3,3-dimethyl-2,3,4,5-tetrahydrodipyrrin (III-5-Boc). Following a general procedure,[III17] $TiCl_4$ (769 μL, 7.00 mmol) was slowly added with stirring to dry THF (25.0 mL) under argon at 0 °C. To the resulting yellow solution was slowly added $LiAlH_4$ (190 mg, 5.00 mmol). The resulting black mixture was stirred at room temperature for 25 min. TEA (6.27 mL, 45.0 mmol) was added. The resulting black mixture was stirred for 10 min at room temperature and then cooled at °C. The black mixture was

slowly poured into a solution of **III-18-Boc** (292 mg, 1.00 mmol) in dry THF (15.0 mL) at 0 °C. The mixture was stirred for 1 h at room temperature and then water (10.0 mL) was added. The mixture was filtered. The filtrate was extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), concentrated, and chromatographed (silica, ethyl acetate) to give a pale yellow oil (112 mg, 41%): IR 2958, 1740, 1333, 1126 cm^{-1}; ^1H NMR δ 0.97 (s, 3H), 1.14 (s, 3H), 1.58 (s, 9H), 2.39–2.41 (m, 2H), 2.88 (ABX, ^3J = 10.4 Hz, ^2J = 15.8 Hz, 1H), 3.15 (ABX, ^3J = 3.8 Hz, ^2J = 15.8 Hz, 1H), 3.77–3.83 (m, 1H), 6.10–6.12 (m, 1H), 6.17–6.18 (m, 1H), 7.19–7.21 (m, 1H), 7.61–7.63 (m, 1H); ^{13}C NMR δ 23.0, 27.2, 28.3, 29.7, 40.7, 52.8, 78.6, 83.2, 110.4, 112.5, 121.1, 134.6, 149.8, 166.7; FAB-MS obsd 277.1917, calcd 277.1916 $[(M+H)^+$, M = $C_{16}H_{24}N_2O_2]$.

3,3-Dimethyl-2,3,4,5-tetrahydro-(*N*[11]-tosyl)dipyrrin (III-5-Ts). Following a procedure for the deoxygenation of *N*-oxides[III17] with slight modification, $TiCl_4$ (3.18 mL, 28.9 mmol) was slowly added with stirring to dry THF (100 mL) under argon at 0 °C. To the resulting yellow solution was slowly added $LiAlH_4$ (784 mg, 20.7 mmol). The resulting black mixture was stirred at room temperature for 15 min. TEA (25.9 mL, 186 mmol) was added. The black mixture was poured into a solution of **III-18-Ts** (1.43 g, 4.13 mmol) in dry THF (60 mL) at 0 °C. The mixture was stirred for 1 h in a water bath (~20 °C) and then water (40 mL) was added. The mixture was filtered. The filtrate was extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), concentrated, and chromatographed (silica, ethyl acetate) to give a pale yellow oil. The oil solidified upon cooling to give a white solid (635 mg, 47%): mp 80–82 °C; ^1H NMR δ 0.89 (s, 3H), 1.12 (s, 3H), 2.36–2.37 (m, 2H), 2.39 (s, 3H), 2.62 (ABX, ^3J = 10.6 Hz, ^2J = 16.2 Hz, 1H), 2.98 (ABX, ^3J = 3.8 Hz, ^2J = 16.2 Hz, 1H),

3.73–3.79 (m, 1H), 6.22–6.25 (m, 2H), 7.27 (d, J = 8.4 Hz, 2H), 7.28–7.31 (m, 1H), 7.56–7.58 (m, 1H), 7.63 (d, J = 8.4 Hz, 2H); ^{13}C NMR δ 21.8, 23.0, 27.3, 28.3, 40.7, 52.7, 78.6, 112.0, 113.9, 122.6, 126.9, 130.2, 134.1, 136.8, 144.9, 166.9; FAB-MS obsd 331.1493, calcd 331.1480 [$(M+H)^+$, M = $C_{18}H_{22}N_2O_2S$].

1-(Dimethoxymethyl)-2,3-dihydro-3,3-dimethyldipyrrin (III-6P). Following a general procedure,[III16] a solution of acetal **III-27** (149 mg, 0.500 mmol) in dry THF (5.0 mL) was treated with sodium methoxide (135 mg, 2.50 mmol). The resulting mixture was stirred at room temperature under argon for 1 h to form the nitronate anion. $TiCl_3$ (8.6 wt% $TiCl_3$ in 28 wt % HCl, 3.74 mL, 2.50 mmol, 5 mol equiv) was placed in a flask to which 20 mL of water was added. Ammonium acetate (15.4 g, 200 mmol, 400 mol equiv) was added to buffer the solution to pH ~6 (pH meter) and then 1.2 mL of THF was added. The nitronate anion in THF was added to the buffered $TiCl_3$ solution. The resulting mixture was stirred at room temperature for 4.5 h. The reaction mixture was extracted with ethyl acetate. The organic layer was washed with $NaHCO_3$ (10% w/v, 40 mL) and water, dried and concentrated under reduced pressure. The resulting oil was purified by column chromatography [alumina, packed in hexanes and eluted with hexanes/ethyl acetate (2:1)] to give a yellow oil (17 mg, 14%): ^{1}H NMR δ 1.21 (s, 6H), 2.61 (s, 2H), 3.45 (s, 6H), 5.02 (s, 1H), 5.88 (s, 1H), 6.15–6.18 (m, 1H), 6.83–6.86 (m, 1H), 10.59–10.70 (br, 1H); ^{13}C NMR δ 29.3, 40.2, 48.3, 54.8, 103.0, 107.7, 108.7, 109.4, 119.6, 130.9, 159.5, 174.1; λ_{abs} (CH_2Cl_2) 341. The limited stability of this compound thwarted high-resolution mass spectrometric analysis.

1-(Dimethoxymethyl)-2,3,4,5-tetrahydro-3,3-dimethyldipyrrin (III-7P). Following a general procedure,[III32] a mixture of **III-7P-Ts** (491 mg, 1.21 mmol) in 2-propanol (12 mL) and 12 mL of 5 N aqueous NaOH was stirred under reflux for 10 days. After cooling to room temperature, water (50 mL) was added to the mixture. The mixture was extracted with ethyl acetate. The organic extract was washed with water, dried (Na_2SO_4), concentrated, and chromatographed [silica, CH_2Cl_2/ethyl acetate (4:1)] to give a colorless oil (131 mg, 43%): ^{1}H NMR δ 0.96 (s, 3H), 1.12 (s, 3H), 2.43, 2.48 (AB, ^2J = 17.2 Hz, 2H), 2.64 (ABX, ^3J = 11.4 Hz, ^2J = 14.6 Hz, 1H), 2.83 (ABX, ^3J = 3.2 Hz, ^2J = 14.6 Hz, 1H), 3.43 (s, 3H), 3.44 (s, 3H), 3.70–3.76 (m, 1H), 4.81 (s, 1H), 5.93–5.97 (m, 1H), 6.09–6.12 (m, 1H), 6.69–6.73 (m, 1H), 9.53–9.63 (br, 1H); ^{13}C NMR δ 22.9, 27.4, 28.1, 41.4, 48.8, 54.7, 54.8, 80.6, 103.1, 105.6, 107.6, 116.8, 131.4, 174.2; FAB-MS obsd 251.1753, calcd 251.1760 [$(M+H)^+$, M = $C_{14}H_{22}N_2O_2$].

1-(Dimethoxymethyl)-2,3,4,5-tetrahydro-3,3-dimethyl-*N*[11] tosyldipyrrin (III-7P-Ts). Following a general procedure,[III17] $TiCl_4$ (1.22 mL, 11.1 mmol) was slowly added with stirring to dry THF (30 mL) under argon at 0 °C. The resulting yellow solution was slowly treated with $LiAlH_4$ (280 mg, 7.39 mmol). The resulting black mixture was stirred at room temperature for 15 min. TEA (9.66 mL, 69.3 mmol) was added. The resulting black mixture was stirred for 2 min at room temperature. The black mixture was slowly poured into a solution of **III-26-Ts** (648 mg, 1.54 mmol) in dry THF (25 mL). The mixture was stirred for 30 min at room temperature and then water (30 mL) was added. The mixture was extracted with CH_2Cl_2 and ethyl acetate. The organic extract was washed with water, dried (Na_2SO_4), and chromatographed [silica, CH_2Cl_2/ethyl acetate (4:1)] to give a colorless oil (525 mg,

84%): ^{1}H NMR δ 0.90 (s, 3H), 1.08 (s, 3H), 2.40 (s, 3H), 2.37–2.49 (m, 2H), 2.72 (ABX, ^{3}J = 9.6 Hz, ^{2}J = 16.0 Hz, 1H), 2.98 (ABX, ^{3}J = 4.8 Hz, ^{2}J = 16.0 Hz, 1H), 3.38 (s, 3H), 3.39 (s, 3H), 3.81–3.85 (m, 1H), 4.79 (s, 1H), 6.21–6.24 (m, 2H), 7.27 (d, J = 8.4 Hz, 2 H), 7.29–7.31 (m, 1H), 7.65 (d, J = 8.4 Hz, 2H); ^{13}C NMR δ 21.8, 22.8, 27.3, 28.2, 41.8, 48.7, 54.8, 54.9, 78.3, 103.2, 111.9, 113.9, 122.6, 127.0, 130.2, 133.9, 136.7, 145.0, 174.2; FAB-MS obsd 405.1840, calcd 405.1848 [$(M+H)^{+}$, M = $C_{21}H_{28}N_2O_4S$]. Anal. Calcd. for $C_{21}H_{28}N_2O_4S$: C, 62.35; H, 6.98; N, 6.93. Found C, 62.20; H, 7.00; N, 6.70.

1-(1,3-Dithian-2-yl)-1,2,3,4-tetrahydro-3,3-dimethyldipyrromethane (III-8aP). Following a general procedure,[III32] a mixture of **III-8aP-Ts** (86 mg, 0.19 mmol) in 2-propanol (1.3 mL) and 10 N aqueous NaOH (2.0 mL) was stirred under reflux for 3 days. After cooling to room temperature, the mixture was concentrated at reduced pressure and the resulting residue was extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), concentrated, and chromatographed (silica, ethyl acetate) to give a colorless oil (27 mg, 47%): ^{1}H NMR δ 1.03 (s, 3H), 1.04 (s, 3H), 1.69–1.83 (m, 2H), 1.85–1.92 (m, 1H), 2.10–2.16 (m, 1H), 2.20–2.31 (br, 1H), 2.40–2.49 (m, 1H), 2.67–2.72 (m, 1H), 2.82–2.88 (m, 5H), 3.40–3.47 (m, 1H), 4.10 (d, J = 7.2 Hz, 1H), 5.88–5.91 (m, 1H), 6.09–6.11 (m, 1H), 6.69–6.71 (m, 1H), 9.40–9.67 (br, 1H); ^{13}C NMR δ 24.0, 26.4, 28.3, 30.0, 30.2, 30.3, 41.5, 44.1, 54.8, 59.6, 68.4, 105.5, 107.7, 116.7, 131.6; FAB-MS obsd 297.1462, calcd 297.1459 [$(M+H)^{+}$, M = $C_{15}H_{24}N_2S_2$].

1-(1,3-Dithian-2-yl)-1,2,3,4-tetrahydro-3,3-dimethyldipyrromethane (III-8bP). Following a general procedure,[III32] a mixture of **III-8bP-Ts** (210 mg, 0.466 mmol) in 2-propanol (3.00 mL) and 5 N aqueous NaOH (2.50 mL) was stirred at reflux for 3 days. After

cooling to room temperature, the mixture was concentrated at reduced pressure and the resulting residue was extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), concentrated, and chromatographed (silica, ethyl acetate) to give a light brown solid (61 mg, 44%): mp 108–110 °C; ^{1}H NMR δ 0.89 (s, 3H), 1.02 (s, 3H), 1.69 (ABX, ^3J = 8.4 Hz, ^2J = 12.8 Hz, 1H), 1.84 (ABX, ^3J = 7.6 Hz, ^2J = 12.8 Hz, 1H), 1.82–1.93 (m, 1H), 2.04–2.17 (m, 2H), 2.41 (ABX, ^3J = 10.4 Hz, ^2J = 15.4 Hz, 1H), 2.76 (ABX, ^3J = 2.8 Hz, ^2J = 15.4 Hz, 1H), 2.80–2.88 (m, 4H), 2.95 (ABX, ^3J = 2.8 Hz, ^3J = 10.4 Hz, 1H), 3.47–3.53 (m, 1H), 4.04 (d, J = 7.2 Hz, 1H), 5.90–5.94 (m, 1H), 6.10–6.13 (m, 1H), 6.68–6.71 (m, 1H), 9.15–9.27 (br, 1H); ^{13}C NMR δ 21.2, 25.8, 26.3, 28.2, 30.1, 42.4, 46.1, 55.0, 58.8, 67.4, 105.5, 108.1, 116.6, 130.7; FAB-MS obsd 297.1466, calcd 297.1459 [$(M+H)^+$, M = $C_{15}H_{24}N_2S_2$].

9-(1,3-Dithian-2-yl)-6,7,8,9-tetrahydro-7,7-dimethyl-(N^{10}-tosyl)dipyrromethane (III-8P-Ts). Following a procedure for organolithium addition to imines,[III34] a solution of 1,3-dithiane (919 mg, 7.64 mmol) in dry THF (8 mL) at –20 °C (salt ice bath) was treated with n-butyl lithium (3.10 mL, 2.5 M in hexane, 7.64 mmol) followed by stirring for 30 min at –20 °C. The flask was then cooled to –78 °C. A sample of **III-5-Ts** (630 mg, 1.91 mmol) was added and the mixture was stirred for 1 h at –20 °C. The flask was placed in a bath at –78 °C and stirred for 5 min. The reaction was quenched by addition of saturated aqueous NH_4Cl (20 mL). The mixture was extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated. TLC analysis [silica, ethyl acetate/hexanes (9:1)] showed two components with R_f = 0.67 (**III-8aP-Ts**, minor) and R_f = 0.47 (**III-8b-Ts**, major). Column chromatography [silica, ethyl acetate/hexanes (7:3)] afforded each isomer as

a light yellow oil. Both isomers solidified upon cooling to give light brown solids (**III-8aP-Ts**, 98 mg, 11%; **III-8bP-Ts**, 151 mg, 18%). Data for **III-8aP-Ts**: mp 103–105 °C; ^{1}H NMR δ 0.97 (s, 3H), 1.02 (s, 3H), 1.59 (ABX, ^3J = 8.0 Hz, ^2J = 13.2 Hz, 1H), 1.79 (ABX, ^3J = 8.4 Hz, ^2J = 13.2 Hz, 1H), 1.84–1.93 (m, 2H), 2.03–2.08 (m, 1H), 2.40 (s, 3H), 2.48–2.55 (m, 1H), 2.77–2.95 (m, 6H), 3.21–3.27 (m, 1H), 3.90 (d, J = 8.4 Hz, 1H), 6.11–6.13 (m, 1H), 6.18–6.20 (m, 1H), 7.25–7.28 (m, 1H), 7.27 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H); ^{13}C NMR δ 21.6, 24.5, 25.9, 27.7, 29.0, 29.3, 29.5, 39.1, 45.2, 53.2, 58.1, 66.2, 111.6, 113.5, 122.8, 126.5, 130.0, 133.9, 136.6, 144.7; FAB-MS obsd 451.1540, calcd 451.1548 [(M+H)$^+$, M = $C_{22}H_{30}N_2O_2S_3$]; Anal. Calcd. for $C_{22}H_{30}N_2O_2S_3$: C, 58.63; H, 6.71; N, 6.22. Found C, 58.42; H, 6.75; N, 5.96.

Data for **III-8bP-Ts**: mp 126–128 °C; ^{1}H NMR δ 0.90 (s, 3H), 1.00 (s, 3H), 1.65 (ABX, ^3J = 8.6 Hz, ^2J = 12.8 Hz, 1H), 1.77 (ABX, ^3J = 7.2 Hz, ^2J = 12.8 Hz, 1H), 1.83–1.90 (m, 1H), 1.93–2.01 (br, 1H), 2.03–2.10 (m, 1H), 2.39 (s, 3H), 2.39–2.46 (m, 1H), 2.71–2.86 (m, 5H), 3.02–3.05 (m, 1H), 3.42–3.48 (m, 1H), 3.90 (d, J = 7.2 Hz, 1H), 6.15–6.18 (m, 1H), 6.18–6.21 (m, 1H), 7.25–7.27 (m, 1H), 7.27 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 8.4 Hz, 2H); ^{13}C NMR δ 21.5, 21.6, 25.9, 26.0, 28.8, 29.3, 29.4, 41.2, 45.5, 54.2, 57.7, 64.8, 111.6, 113.1, 122.5, 126.6, 129.9, 133.7, 136.5, 144.7; FAB-MS obsd 451.1556, calcd 451.1548 [(M+H)$^+$, M = $C_{22}H_{30}N_2O_2S_3$].

1-(α-Hydroxy-α-phenyl-methyl)-2,3,4,5-tetrahydro-3,3-dimethyl-(*N*^{11}-tosyl)dipyrrin *N*^{10}-oxide (III-9-Ts). A solution of **III-21-Ts** (573 mg, 1.53 mmol) in dry THF (23.0 mL) at 0 °C was treated with PhMgBr (1.84 mL, 1.0 M in THF, 1.84 mmol). The mixture was stirred for 1.5 h at 0 °C. The reaction was quenched by addition of H_2O/hexanes

(20.0 mL). The reaction mixture was extracted with ethyl acetate. The organic layer was washed with water and brine. TLC analysis (silica, ethyl acetate) showed two components with R_f = 0.65 (**III-9a-Ts**) and R_f = 0.49 (**III-9b-Ts**). Column chromatography (silica, ethyl acetate) afforded the two isomers as a light brown solid (**III-9a-Ts**, 113 mg, 16%) and a white solid (**III-9b-Ts**, 126 mg, 18%). Data for **III-9a-Ts**: mp 62–64 °C; ^{1}H NMR δ 0.89 (s, 3H), 1.01 (s, 3H), 2.18, 2.32 (AB, ^2J = 17.6 Hz, 2H), 2.40 (s, 3H), 3.07 (ABX, ^3J = 9.8 Hz, ^2J = 15.8 Hz, 1H), 3.47 (ABX, ^3J = 4.2 Hz, ^2J = 15.8 Hz, 1H), 4.21–4.25 (m, 1H), 5.62 (s, 1H), 6.07–6.09 (m, 1H), 6.18–6.20 (m, 1H), 6.86–6.97 (br, 1H), 7.29 (d, J = 8.2 Hz, 2H), 7.29–7.31 (m, 1H), 7.32–7.35 (m, 1H), 7.36–7.42 (m, 2H), 7.42–7.46 (m, 2H), 7.68 (d, J = 8.2 Hz, 2H); ^{13}C NMR δ 21.8, 22.7, 24.7, 28.1, 37.9, 44.0, 70.9, 80.3, 111.9, 114.9, 123.3, 126.5, 127.0, 128.5, 128.9, 130.3, 130.4, 135.9, 139.5, 145.3, 148.2; FAB-MS obsd 453.1854, calcd 453.1848 (M = $C_{25}H_{28}N_2O_4S$).

Data for **III-9b-Ts**: mp 156–158 °C; ^{1}H NMR δ 0.96 (s, 3H), 0.97 (s, 3H), 2.23–2.26 (m, 2H), 2.40 (s, 3H), 3.15 (ABX, ^3J = 9.8 Hz, ^2J = 16.0 Hz, 1H), 3.48 (ABX, ^3J = 4.0 Hz, ^2J = 16.0 Hz, 1H), 4.13–4.19 (m, 1H), 5.60–5.62 (m, 1H), 6.09–6.11 (m, 1H), 6.20–6.22 (m, 1H), 7.01–7.03 (m, 1H), 7.30 (d, J = 8.6 Hz, 2H), 7.30–7.33 (m, 1H), 7.32–7.35 (m, 1H), 7.36–7.41 (m, 2H), 7.42–7.46 (m, 2H), 7.68 (d, J = 8.6 Hz, 2H); ^{13}C NMR δ 21.8, 22.9, 24.8, 28.3, 37.9, 44.2, 71.4, 80.7, 111.9, 114.8, 123.3, 126.6, 127.0, 128.6, 129.0, 130.3, 130.5, 136.0, 139.5, 145.4, 148.0; FAB-MS obsd 453.1859, calcd 453.1848 (M = $C_{25}H_{28}N_2O_4S$).

9-Bromo-2,3,4,5-tetrahydro-1,3,3-trimethyldipyrrin (III-11). Following a procedure for the α-bromination of pyrroles,[III16] a solution of **III-2** (95 mg, 0.50 mmol) in dry THF (10 mL) was cooled to –78 °C under argon. NBS (89 mg, 0.50 mmol) was added in

two portions. The reaction mixture was stirred for an additional 1 h at –78 °C. Hexanes (6.0 mL) and water (6.0 mL) were added and the mixture was allowed to warm to room temperature. The organic layer was extracted with ethyl acetate, dried ($MgSO_4$), and concentrated under vacuum without heating. The resulting residue was purified by gravity column chromatography (silica, ethyl acetate) to give a white solid (112 mg, 83%): mp 102–104 °C (dec.); ^{1}H NMR δ 0.92 (s, 3H), 1.11 (s, 3H), 2.04–2.06 (m, 3H), 2.29, 2.38 (AB, ^2J = 16.8 Hz, 2H), 2.53 (ABX, ^3J = 11.6 Hz, ^2J = 15.0 Hz, 1H), 2.69 (ABX, ^3J = 2.8 Hz, ^2J = 15.0 Hz, 1H), 3.55–3.62 (m, 1H), 5.85–5.87 (m, 1H), 5.98–6.00 (m, 1H), 9.84–10.00 (br, 1H); ^{13}C NMR δ 20.7, 23.0, 27.4, 28.3, 42.0, 54.5, 80.2, 95.7, 107.2, 109.4, 133.4, 175.0; FAB-MS obsd 269.0641, calcd 269.0653 [$(M+H)^+$, M = $C_{12}H_{17}BrN_2$].

***N-tert*-Butoxycarbonyl-2-(2-nitroethyl)pyrrole (III-12-Boc).** Following a general procedure,[III18] a solution of **III-16-Boc** (490 mg, 2.06 mmol) in DMF/methanol (35.0 mL, 1:2) at 0 °C was treated with sodium borohydride (117 mg, 3.09 mmol). The reaction mixture was stirred for 15 min. Water (30.0 mL) was added followed by acetic acid (~one drop). The mixture was extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), concentrated, and chromatographed [silica, CH_2Cl_2/hexanes (8:2)] to give a pale yellow oil (258 mg, 52%): IR 2980, 1736 cm^{-1}; ^{1}H NMR δ 1.60 (s, 9H), 3.57 (t, J = 7.0 Hz, 2H), 4.66 (t, J = 7.0 Hz, 2H), 6.05–6.07 (m, 1H), 6.07–6.09 (m, 1H), 7.19–7.21 (m, 1H); ^{13}C NMR δ 27.1, 28.2, 75.0, 84.4, 110.5, 114.0, 122.2, 129.2, 149.5; FAB-MS obsd 240.1126, calcd 240.1110 ($C_{11}H_{16}N_2O_4$).

One-Flask Synthesis of *N-tert*-Butoxycarbonyl-2-(2-nitroethyl)pyrrole (III-12-Boc). Following a general procedure,[III19] a solution of **III-15-Boc** (3.62 g, 18.5 mmol) in

distilled methanol (62.0 mL) was treated with nitromethane (3.00 mL, 55.6 mmol), sodium acetate (1.67 g, 20.4 mmol) and methylamine hydrochloride (1.37 g, 20.4 mmol). Stirring at room temperature for 16 h under argon afforded a yellow mixture. DMF (100 mL) and methanol (138 mL) were added to the reaction mixture. Sodium borohydride (910 mg, 24.1 mmol) was added rapidly at 0 °C. The reaction mixture was stirred at room temperature for 20 min. The mixture was neutralized with acetic acid (~0.5 mL) and then concentrated. The resulting residue was dissolved in CH_2Cl_2 (100 mL) and washed with water. The organic layer was dried (Na_2SO_4), concentrated, and chromatographed [silica, $CHCl_3$/hexanes (8:2)] to give a pale yellow oil (2.74 g, 61%). Analytical data were identical as above.

2-(2-Nitroethyl)-*N*-tosylpyrrole (III-12-Ts). Following a general procedure,[III16] a solution of **III-16-Ts** (5.30 g, 18.1 mmol) in dry THF/methanol (180 mL, 19:1) at 0 °C was treated with sodium borohydride (1.71 g, 45.3 mmol) in portions. The mixture was stirred for 50 min, neutralized with acetic acid (~2 mL), and filtered. The filtrate was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (150 mL) and washed with water. The organic layer was dried (Na_2SO_4), concentrated, and chromatographed [silica, CH_2Cl_2/hexanes (7:3)] to give a light yellow solid (1.64 g, 31%): mp 95–96 °C; ^{1}H NMR δ 2.42 (s, 3H), 3.41 (t, J = 6.8 Hz, 2H), 4.61 (t, J = 6.8 Hz, 2H), 6.09–6.11 (m, 1H), 6.21–6.23 (m, 1H), 7.30–7.32 (m, 1H), 7.32 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 8.4 Hz, 2H); ^{13}C NMR δ 21.6, 25.4, 74.4, 111.8, 114.7, 123.6, 126.5, 128.4, 130.2, 135.8, 145.3; Anal. Calcd. for $C_{13}H_{14}N_2O_4S$: C, 53.05; H, 4.79; N, 9.52. Found C, 53.08; H, 4.82; N, 9.43.

One-Flask Synthesis of 2-(2-Nitroethyl)-*N*-tosylpyrrole (III-12-Ts). Following a general procedure,[III19] a solution of **III-15-Ts** (10.9 g, 43.7 mmol) in distilled methanol (250

mL) was treated with nitromethane (7.07 mL, 131 mmol), sodium acetate (4.30 g, 52.4 mmol) and methylamine hydrochloride (3.54 g, 52.4 mmol). Stirring at room temperature for 40 h under argon afforded a yellow mixture. DMF (200 mL) and methanol (250 mL) were added to the reaction mixture. Sodium borohydride (1.98 g, 52.4 mmol) was added rapidly at 0 °C. The reaction mixture was stirred at room temperature for 20 min, neutralized with acetic acid (~2 mL) and concentrated. The mixture was dissolved in CH_2Cl_2 (100 mL) and washed with water. The organic layer was dried (Na_2SO_4), concentrated, and chromatographed [silica, CH_2Cl_2/hexanes (7:3)] to give a light yellow solid (7.00 g, 55%). Analytical data were identical as above.

***N*-Tosylpyrrole-2-carboxaldehyde (III-15-Ts).**[III33] Following a general procedure,[III31] a mixture of **III-15** (4.76 g, 50.0 mmol) and tetrabutylammonium hydrogen sulfate (1.70 g, 5.00 mmol) was added to aqueous NaOH [9.00 g (225 mmol) of NaOH in 30 mL of water]. The mixture was stirred for 10 min. *p*-Toluenesulfonyl chloride (10.5 g, 55.0 mmol) in CH_2Cl_2 (10 mL) was added rapidly. The reaction mixture was stirred for 5 h, then water (200 mL) and brine (100 mL) were added. The mixture was extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), concentrated, and chromatographed (silica, CH_2Cl_2) to give a light pink solid (10.7 g, 86%): mp 94–95 °C; ^{1}H NMR δ 2.42 (s, 3H), 6.39–6.41 (m, 1H), 7.15–7.16 (m, 1H), 7.32 (d, J = 8.6 Hz, 2H), 7.61–7.63 (m, 1H), 7.80 (d, J = 8.6 Hz, 2H), 9.98 (s, 1H); ^{13}C NMR δ 21.9, 112.6, 124.6, 127.7, 129.6, 130.3, 133.7, 135.4, 146.2, 179.2; Anal. Calcd. for $C_{12}H_{11}NO_3S$: C, 57.82; H, 4.45; N, 5.62. Found C, 58.03; H, 4.62; N, 5.64.

***N-tert*-Butoxycarbonyl-2-(*trans*-2-nitrovinyl)pyrrole (III-16-Boc).** Following a general procedure,[III16] a solution of **III-15-Boc** (772 mg, 3.70 mmol) in distilled methanol (11.0 mL) was treated with nitromethane (599 μL, 11.1 mmol), sodium acetate (334 mg, 4.07 mmol) and methylamine hydrochloride (275 mg, 4.07 mmol). The mixture was stirred at room temperature for 21 h under argon. The methanol was removed *in vacuo* without heating to give a yellow solid. The solid was dissolved in CH_2Cl_2 (100 mL) and the resulting solution was washed with water. The organic extract was dried (Na_2SO_4), concentrated, and chromatographed (silica, CH_2Cl_2) to give a yellow solid (562 mg, 64%): mp 123–124 °C; IR 2965, 1748, 1504, 1368, 1331, 1123 cm^{-1}; ^1H NMR δ 1.65 (s, 9H), 6.29–6.31 (m, 1H), 6.82–6.83 (m, 1H), 7.48 (d, J = 13.6 Hz, 1H), 7.53–7.54 (m, 1H), 8.76 (d, J = 13.6 Hz, 1H); ^{13}C NMR δ 28.2, 86.1, 112.4, 118.1, 126.3, 127.7, 130.1, 135.2, 148.7; FAB-MS obsd 239.1035, calcd 239.1032 [$(M+H)^+$, M = $C_{11}H_{14}N_2O_4$]. Anal. Calcd. for $C_{11}H_{14}N_2O_4$: C, 55.46; H, 5.92; N, 11.76. Found C, 55.40; H, 6.01; N, 11.71.

2-(*Trans*-2-Nitrovinyl)-*N*-tosylpyrrole (III-16-Ts). Following a general procedure,[III16] a solution of **III-15-Ts** (17.3 g, 69.4 mmol) in distilled methanol (300 mL) was treated with nitromethane (11.2 mL, 208 mmol), sodium acetate (6.26 g, 76.3 mmol) and methylamine hydrochloride (5.15 g, 76.3 mmol). The mixture was stirred at room temperature for 38 h under argon. The methanol was removed *in vacuo* without heating to give a yellow solid. The solid was dissolved in CH_2Cl_2 (150 mL) and the resulting solution was washed with water. The organic extract was dried (Mg_2SO_4), concentrated, and chromatographed (silica, CH_2Cl_2) to give a yellow solid (18.3 g, 90%): mp 153–154 °C; ^1H NMR (300 MHz) δ 2.42 (s, 3H), 6.39–6.41 (m, 1H), 6.81–6.83 (m, 1H), 7.33 (d, J = 8.1 Hz,

2H), 7.36 (d, J = 13.5 Hz, 1H), 7.61–7.63 (m, 1H), 7.74 (d, J = 8.1 Hz, 2H), 8.51 (d, J = 13.5 Hz, 1H); ^{13}C NMR δ 21.6, 113.3, 118.6, 125.5, 126.9, 127.0, 128.3, 130.4, 135.0, 135.6, 146.1; Anal. Calcd. for $C_{13}H_{12}N_2O_4S$: C, 53.42; H, 4.14; N, 9.58. Found C, 53.44; H, 4.17; N, 9.53.

5-(*N*-*tert*-Butoxycarbonyl-2-pyrrolyl)-3,3-dimethyl-4-nitro-1-pentanal (III-17-Boc). A mixture of **III-12-Boc** (2.50 g, 10.4 mmol) and 3-methyl-2-butenal (**III-13a**) (10.0 mL, 104 mmol, 10.0 mol eq) in dry acetonitrile (10.4 mL) was treated with CsF (4.74 g, 31.2 mmol, 3.00 mol equiv, freshly dried under vacuum for 1 h and purged with argon). The mixture was stirred at room temperature for 2.5 h, whereupon the reaction was deemed to be complete by TLC. The reaction mixture was filtered through alumina (~5 cm). The filtrate was concentrated and chromatographed [silica, ethyl acetate/hexanes (1:3)] to give a pale yellow oil. The oil solidified upon cooling to give a light brown solid (1.22 g, 36%): mp 73–75 °C; IR 2978, 1737, 1550, 1371, 1324, 1126 cm^{-1}; ^{1}H NMR 1.24 (s, 3H), 1.29 (s, 3H), 1.59 (s, 9H), 2.49–2.61 (m, 2H), 3.38 (ABX, ^3J = 11.6 Hz, ^2J = 15.2 Hz, 1H), 3.58 (ABX, ^3J = 2.0 Hz, ^2J = 15.2 Hz, 1H), 4.92 (ABX, ^3J = 2.0 Hz, ^3J = 11.6 Hz, 1H), 5.99–6.00 (m, 1H), 6.02–6.04 (m, 1H), 7.13–7.15 (m, 1H), 9.83–9.85 (m, 1H); ^{13}C NMR δ 24.1, 24.3, 28.1, 28.2, 36.8, 51.7, 84.2, 95.6, 110.5, 114.3, 122.1, 129.3, 149.5, 200.7; FAB-MS obsd 325.1759, calcd 325.1763 [(M+H)$^+$, M = $C_{16}H_{24}N_2O_5$]. Anal. Calcd. for $C_{16}H_{24}N_2O_5$: C, 59.24; H, 7.46; N, 8.64. Found C, 59.38; H, 7.46; N, 8.47.

3,3-Dimethyl-4-nitro-5-(*N*-tosyl-2-pyrrolyl)-1-pentanal (III-17-Ts). Following a general procedure,[III19] CsF (3.40 g, 22.4 mmol, 3.00 mol equiv, freshly dried by heating to 100 °C under vacuum for 1 h and then cooling to room temperature under argon) was placed

in a flask under argon. A mixture of **III-12-Ts** (2.20 g, 7.47 mmol) and 3-methyl-2-butenal (**III-13a**) (7.21 mL, 74.7 mmol, 10.0 mol equiv) in dry acetonitrile (75 mL) was cannulated into the flask containing CsF. The mixture was heated at 55 °C for 90 min, whereupon the reaction was deemed to be complete by TLC. The reaction mixture was filtered through a pad of silica (ethyl acetate). The filtrate was concentrated and chromatographed [silica, ethyl acetate/hexanes (1:3)] to give a pale yellow oil (1.96 g, 69%): ^{1}H NMR (300 MHz) δ 1.22 (s, 3H), 1.27 (s, 3H), 2.43 (s, 3H), 2.40–2.60 (m, 2H), 3.23 (ABX, ^3J = 2.2 Hz, ^2J = 15.4 Hz, 1H), 3.34 (ABX, ^3J = 11.4 Hz, ^2J = 15.4 Hz, 1H), 4.92 (ABX, ^3J = 2.2 Hz, ^3J = 11.4 Hz, 1H), 6.02–6.06 (m, 1H), 6.17–6.20 (m, 1H), 7.26–7.28 (m, 1H), 7.32 (d, J = 8.0 Hz, 2H), 7.58 (d, J = 8.0 Hz, 2H), 9.80–9.82 (m, 1H); ^{13}C NMR δ 21.9, 24.2, 24.5, 27.0, 36.9, 51.5, 95.6, 112.4, 115.7, 124.2, 126.5, 128.8, 130.5, 136.3, 145.6, 200.4; Anal. Calcd. for $C_{18}H_{22}N_2O_5S$: C, 57.13; H, 5.86; N, 7.40. Found C, 57.12; H, 5.84; N, 7.20.

(*N*^{11}-*tert*-Butoxycarbonyl)-3,3-dimethyl-2,3,4,5-tetrahydrodipyrrin *N*^{10}-oxide (III-18-Boc). Following a general procedure,[III17] a vigorously stirred solution of **III-17-Boc** (364 mg, 1.12 mmol) in 5.50 mL of acetic acid and 5.50 mL of ethanol at 0 °C was treated slowly with zinc dust (1.83 g, 28.0 mmol) in small portions for 5 min. The reaction mixture was stirred at 0 °C for 15 min and then filtered through Celite. The filtrate was concentrated under high vacuum. The resulting residue was dissolved in CH_2Cl_2 (50 mL), affording a solution that was washed with aqueous sodium carbonate (20%, 30 mL), dried (Na_2SO_4), and concentrated. The resulting light brown oil was purified by column chromatography [silica; CH_2Cl_2 → ethyl acetate → CH_2Cl_2/methanol (9:1)] affording a light brown oil (**III-5-Boc**, 49 mg, 16%) and the title compound as a light brown solid (127 mg, 39%). Data for the title compound: mp 116–118 °C; IR 3393, 2974, 1737, 1334, 1126 cm^{-1}; ^{1}H NMR δ 1.07 (s, 3H),

1.12 (s, 3H), 1.59 (s, 9H), 2.36–2.39 (m, 2H), 3.22 (ABX, ^{3}J = 9.6 Hz, ^{2}J = 15.6 Hz, 1H), 3.72 (ABX, ^{3}J = 5.2 Hz, ^{2}J = 15.6 Hz, 1H), 4.05–4.10 (m, 1H), 6.07–6.11 (m, 2H), 6.84–6.86 (m, 1H), 7.19–7.21 (m, 1H); ^{13}C NMR δ 21.8, 23.3, 24.9, 29.0, 39.4, 42.7, 79.8, 111.8, 114.3, 123.2, 127.1, 130.3, 130.8, 133.3, 136.0, 145.3; FAB-MS obsd 293.1875, calcd 293.1865 [$(M+H)^+$, M = $C_{16}H_{24}N_2O_3$].

3,3-Dimethyl-2,3,4,5-tetrahydro-(*N*^{11}-tosyl)dipyrrin *N*^{10}-oxide (III-18-Ts). Following a general procedure,[III17] a vigorously stirred solution of **III-17-Ts** (1.94 g, 5.13 mmol) in a solution of acetic acid (24.0 mL) and ethanol (24.0 mL) at 0 °C was treated slowly with zinc dust (8.39 g, 128 mmol) in small portions for 5 min. The reaction mixture was stirred at 0 °C for 15 min. The mixture was filtered through Celite. The filtrate was concentrated under high vacuum. The resulting oil was purified by column chromatography [silica, ethyl acetate/CH_2Cl_2 (1:1) → CH_2Cl_2/methanol (9:1)] affording a brown oil (796 mg, 45%): ^{1}H NMR δ 1.02 (s, 3H), 1.12 (s, 3H), 2.38–2.41 (m, 2H), 2.40 (s, 3H), 3.17 (ABX, ^{3}J = 10.6 Hz, ^{2}J = 16.2 Hz, 1H), 3.43 (ABX, ^{3}J = 3.8 Hz, ^{2}J = 16.2 Hz, 1H), 4.05–4.11 (m, 1H), 6.09–6.11 (m, 1H), 6.20–6.23 (m, 1H), 6.84–6.87 (m, 1H), 7.29 (d, J = 8.4 Hz, 2H), 7.30–7.33 (m, 1H), 7.68 (d, J = 8.4 Hz, 2H); ^{13}C NMR δ 21.8, 23.3, 24.9, 29.0, 39.4, 42.7, 79.8, 111.8, 114.3, 123.2, 127.1, 130.3, 130.8, 133.3, 136.0, 145.3; FAB-MS obsd 347.1420, calcd 347.1429 [$(M+H)^+$, M = $C_{18}H_{22}N_2O_3S$].

4,4-Dimethyl-5-nitro-6-(*N*-tosyl-2-pyrrolyl)-2-hexanone (III-19-Ts). Following a general procedure,[III16] CsF (526 mg, 3.47 mmol, 3.00 mol equiv, freshly dried by heating to 100 °C under vacuum for 1 h and then cooling to room temperature under argon) was placed in a flask under argon. A mixture of **III-12-Ts** (340 mg, 1.16 mmol) and mesityl oxide (**III-**

13b, 1.98 mL, 17.3 mmol, 15.0 mol equiv) in dry acetonitrile (12 mL) was cannulate into the flask containing CsF. The mixture was heated at 70 °C for 16 h, whereupon the reaction was deemed to be complete by TLC. The reaction mixture was filtered through a bed of silica. The filtrate was concentrated and chromatographed [alumina, ethyl acetate/hexanes (1:3)] to give a pale yellow oil. The oil solidified upon cooling (~ –6 °C) to give a pale yellow solid (330 mg, 73%): mp 92–93 °C; ^{1}H NMR δ 1.14 (s, 3H), 1.25 (s, 3H), 2.14 (s, 3H), 2.42 (s, 3H), 2.43, 2.57 (AB, ^2J = 17.4 Hz, 2H), 3.21 (ABX, ^3J = 2.2 Hz, ^2J = 16.0 Hz, 1H), 3.37 (ABX, ^3J = 12.0 Hz, ^2J = 16.0 Hz, 1H), 5.12 (ABX, ^3J = 2.2 Hz, ^3J = 12.0 Hz, 1H), 6.02–6.03 (m, 1H), 6.16–6.18 (m, 1H), 7.24–7.26 (m, 1H), 7.32 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H); ^{13}C NMR δ 21.9, 23.8, 24.3, 26.7, 32.0, 36.9, 50.9, 94.2, 112.2, 114.8, 123.9, 126.6, 129.4, 130.4, 136.4, 145.4, 206.4; Anal. Calcd. for $C_{19}H_{24}N_2O_5S$: C, 58.15; H, 6.16; N, 7.14. Found C, 58.21; H, 6.17; N, 7.10.

2,3,4,5-Tetrahydro-1,3,3-trimethyl-(N^{11}-tosyl)dipyrrin N^{10}-oxide (III-20-Ts). Following a general procedure,[III17] a vigorously stirred solution of **III-19-Ts** (225 mg, 0.57 mmol) in acetic acid (3.0 mL) and ethanol (3.0 mL) at 0 °C was treated slowly with zinc dust (932 mg, 14.3 mmol) in small portions for 5 min. The reaction mixture was stirred at 0 °C for 15 min and then filtered through Celite. The filtrate was concentrated under high vacuum. The resulting oil was purified by column chromatography [silica, ethyl acetate/CH_2Cl_2 (1:1) → CH_2Cl_2/methanol (9:1)] affording a pale yellow oil (**III-2-Ts**, 47 mg, 24%) and the title compound as a white solid (119 mg, 57%). Data for the title compound: mp 123-125 °C; ^{1}H NMR δ 0.98 (s, 3H), 1.10 (s, 3H), 2.05 (s, 3H), 2.39 (s, 3H), 2.39–2.41 (m, 2H), 3.15 (ABX, ^3J = 10.4 Hz, ^2J = 16.0 Hz, 1H), 3.49 (ABX, ^3J = 3.4 Hz, ^2J = 16.0 Hz, 1H), 4.08–4.12 (m, 1H), 6.08–6.09 (m, 1H), 6.20–6.22 (m, 1H), 7.29 (d, J = 8.2 Hz, 2H),

7.31–7.32 (m, 1H), 7.69 (d, J = 8.2 Hz, 2H); ^{13}C NMR δ 13.3, 21.8, 23.4, 25.0, 29.1, 36.8, 47.4, 79.6, 111.7, 114.2, 123.1, 127.1, 130.3, 131.1, 136.0, 143.2, 145.2; Anal. Calcd. for $C_{19}H_{24}N_2O_3S$: C, 63.31; H, 6.71; N, 7.77. Found C, 63.27; H, 6.71; N, 7.70.

1-Formyl-2,3,4,5-tetrahydro-3,3-dimethyl-(N^{11}-tosyl)dipyrrin N^{10}-oxide (III-21-Ts). Following a general procedure,[III25] a solution of **III-20-Ts** (590 mg, 1.64 mmol) in 1,4-dioxane (20.0 mL) was treated with SeO_2 (272 mg, 2.46 mmol) under argon. The mixture was stirred for 2.5 h at room temperature. The reaction mixture was treated with saturated $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2. The organic extract was washed with water, dried (Na_2SO_4), and chromatographed [silica, ethyl acetate/CH_2Cl_2 (1:9)] to give a light brown solid (448 mg, 73%): mp 140–142 °C; IR 2965, 1665, 1524, 1368 cm^{-1}; ^{1}H NMR δ 1.06 (s, 3H), 1.10 (s, 3H), 2.41 (s, 3H), 2.57–2.59 (m, 2H), 3.06 (ABX, ^3J = 9.2 Hz, ^2J = 16.0 Hz, 1H), 3.43 (ABX, ^3J = 4.4 Hz, ^2J = 16.0 Hz, 1H), 4.38–4.43 (m, 1H), 6.13–6.15 (m, 1H), 6.23–6.25 (m, 1H), 7.31 (d, J = 8.4 Hz, 2H), 7.32–7.34 (m, 1H), 7.68 (d, J = 8.4 Hz, 2H), 10.13 (s, 1H); ^{13}C NMR δ 21.8, 22.6, 24.9, 27.5, 38.1, 39.8, 83.0, 112.0, 115.6, 123.7, 127.0, 129.8, 130.3, 136.0, 141.7, 145.4, 183.4; Anal. Calcd. for $C_{19}H_{22}N_2O_4S$: C, 60.94; H, 5.92; N, 7.48. Found C, 60.91; H, 5.85; N, 7.51.

2,3,4,5-Tetrahydro-3,3-dimethyl-1-(1,3-dithian-2-yl)-N^{11} tosyldipyrrin N^{10}-oxide (III-22-Ts). Following a general procedure,[III36] a solution of **III-21-Ts** (100 mg, 0.27 mmol) and 1,3-propanedithiol (32 μL, 0.32 mmol) in CH_2Cl_2 (2.0 mL) was treated with neat $BF_3{\cdot}OEt_2$ (140 μL, 1.1 mmol) and molecular sieves (4 A, ~200 mg). The mixture was stirred for 2 h at 0 °C, warmed to room temperature, and stirred for 40 h. Saturated $NaHCO_3$ (~2 mL) was added to the reaction mixture. The mixture was extracted with CH_2Cl_2. The

organic extract was washed with water, dried (Na_2SO_4), and concentrated. The resulting residue was chromatographed [silica, CH_2Cl_2/ethyl acetate (4:1)] to give a pale yellow oil (52 mg, 42%): ^{1}H NMR δ 1.01 (s, 3H), 1.09 (s, 3H), 1.88–2.00 (m, 1H), 2.11–2.18 (m, 1H), 2.39 (s, 3H), 2.53–2.56 (m, 2H), 2.85–2.92 (m, 2H), 2.99–3.10 (m, 3H), 3.42–3.48 (m, 1H), 4.13–4.17 (m, 1H), 5.66 (s, 1H), 6.11–6.13 (m, 1H), 6.20–6.22 (m, 1H), 7.29 (d, J = 8.4 Hz, 2H), 7.30–7.32 (m, 1H), 7.70 (d, J = 8.4 Hz, 2H); ^{13}C NMR δ 21.8, 22.9, 24.8, 25.2, 28.2, 30.3, 37.7, 41.2, 43.0, 80.0, 111.8, 115.0. 123.2, 127.1, 130.3, 130.6, 135.9, 141.0, 145.3. The limited stability of this compound prevented high-resolution mass spectrometric analysis.

2,3,4,5-Tetrahydro-3,3-dimethyl-1-(5,5-dimethyl-1,3-dioxan-2-yl)-*N*^{11} tosyldipyrrin *N*^{10}-oxide (III-24-Ts). Following a general procedure,[III38] a solution of **III-21-Ts** (224 mg, 0.60 mmol) and neopentyl glycol (81.0 mg, 0.78 mmol) in benzene (30.0 mL) was treated with *p*-toluenesulfonic acid monohydrate (11.4 mg, 0.060 mmol). The mixture was refluxed for 2.5 h and then cooled. The reaction mixture was washed with saturated $NaHCO_3$ and water. The organic layer was dried (Na_2SO_4), concentrated, and chromatographed [silica, ethyl acetate/CH_2Cl_2 (1:1)] to give a light brown solid (140 mg, 51%): mp 64–65 °C; ^{1}H NMR δ 0.75 (s, 3H), 1.00 (s, 3H), 1.09 (s, 3H), 1.21 (s, 3H), 2.39 (s, 3H), 2.54–2.56 (m, 2H), 3.10 (ABX, ^3J = 10.0 Hz, ^2J = 16.0 Hz, 1H), 3.45 (ABX, ^3J = 3.6 Hz, ^2J = 16.0 Hz, 1H), 3.56–3.61 (m, 2H), 3.63–3.69 (m, 2H), 4.15–4.19 (m, 1H), 5.66 (s, 1H), 6.10–6.12 (m, 1H), 6.19–6.22 (m, 1H), 7.28 (d, J = 8.4 Hz, 2H), 7.30–7.32 (m, 1H), 7.69 (d, J = 8.4 Hz, 2H); ^{13}C NMR δ 21.8, 22.1, 23.1, 24.7, 28.5, 29.9, 30.6, 37.5, 41.4, 77.5,

80.9, 94.3, 111.7, 114.7. 123.2, 127.1, 130.3, 130.8, 136.1, 141.6, 145.2; FAB-MS obsd 461.2100, calcd 461.2110 [$(M+H)^+$, M = $C_{24}H_{32}N_2O_5S$].

1-(5,5-Dimethyl-1,3-dioxan-2-yl)-2,3,4,5-tetrahydro-3,3-dimethyl-(*N*^{11} tosyl)dipyrrin (III-25-Ts). Following a general procedure,[III17] $TiCl_4$ (222 μL, 2.02 mmol) was slowly added with stirring to dry THF (5.0 mL) under argon at 0 °C. To the resulting yellow solution was slowly added $LiAlH_4$ (51.0 mg, 1.35 mmol). The resulting black mixture was stirred at room temperature for 15 min. TEA (1.78 mL, 12.8 mmol) was added. The resulting black mixture was stirred for 2 min at room temperature. The black mixture was slowly poured into a solution of **III-24-Ts** (130 mg, 0.282 mmol) in dry THF (4.0 mL) at 0 °C. The mixture was stirred for 30 min at room temperature and then water (8.0 mL) was added. The reaction mixture was extracted with CH_2Cl_2 and ethyl acetate. The organic extract was washed with water, dried (Na_2SO_4), and chromatographed [silica, ethyl acetate/CH_2Cl_2 (1:19)] to give a colorless oil (116 mg, 92%): ^{1}H NMR δ 0.74 (s, 3H), 0.89 (s, 3H), 1.09 (s, 3H), 1.22 (s, 3H), 2.39 (s, 3H), 2.52–2.54 (m, 2H), 2.71 (ABX, ^3J = 9.6 Hz, ^2J = 16.0 Hz, 1H), 2.99 (ABX, ^3J = 4.4 Hz, ^2J = 16.0 Hz, 1H), 3.48–3.52 (m, 2H), 3.63–3.68 (m, 2H), 3.79–3.84 (m, 1H), 5.04 (s, 1H), 6.20–6.22 (m, 1H), 6.22–6.24 (m, 1H), 7.26 (d, J = 8.4 Hz, 2 H), 7.28–7.29 (m, 1H), 7.64 (d, J = 8.4 Hz, 2H); ^{13}C NMR δ 21.8, 22.0, 22.7, 23.1, 27.1, 27.8, 30.5, 41.7, 48.6, 77.2, 78.3, 99.8, 111.8, 113.8, 122.4, 127.0, 130.1, 133.9, 136.6, 144.9, 173.8; FAB-MS obsd 445.2152, calcd 445.2161 [$(M+H)^+$, M = $C_{24}H_{32}N_2O_4S$].

1-(Dimethoxymethyl)-2,3,4,5-tetrahydro-3,3-dimethyl-*N*^{11} tosyldipyrrin *N*^{10}-oxide (III-26-Ts). Following a general procedure,[III39] aldehyde **III-21-Ts** (287 mg, 0.766 mmol) was dissolved in a methanolic solution of $LaCl_3 \cdot 7H_2O$ (0.40 M, 1.9 mL) and the

resulting mixture was treated with trimethyl orthoformate (758 μL, 6.93 mmol). The reaction mixture was stirred for 3 h at room temperature and then poured into 5% aqueous $NaHCO_3$ (16 mL). The mixture was extracted with ethyl acetate. The organic extracts were combined, dried (Na_2SO_4), concentrated, and chromatographed [silica, CH_2Cl_2/ethyl acetate (4:1)] to afford a white solid (180 mg, 56%): mp 108–109 °C; ^{1}H NMR δ 1.01 (s, 3H), 1.09 (s, 3H), 2.39 (s, 3H), 2.47–2.49 (m, 2H), 3.06–3.13 (m, 1H), 3.47 (s, 6H), 3.46–3.51 (m, 1H), 4.18–4.22 (m, 1H), 5.48 (s, 1H), 6.10–6.12 (m, 1H), 6.20–6.22 (m, 1H), 7.29 (d, J = 8.4 Hz, 2H), 7.30–7.32 (m, 1H), 7.69 (d, J = 8.4 Hz, 2H); ^{13}C NMR δ 21.8, 23.1, 24.8, 28.4, 37.7, 42.1, 55.4, 55.7, 80.7, 97.9, 111.8, 114.8. 123.3, 127.1, 130.3, 130.7, 136.0, 142.8, 145.3; Anal. Calcd for $C_{21}H_{28}N_2O_5S$: C, 59.98; H, 6.71; N, 6.66. Found: C, 59.82; H, 6.70; N, 6.50.

1,1-Dimethoxy-4,4-dimethyl-5-nitro-6-(2-pyrrolyl)-2-hexanone (III-27). Following a general procedure,[III16] CsF (8.97 g, 59.1 mmol, 3.00 mol equiv, freshly dried by heating to 100 °C under vacuum for 1 h and then cooling to room temperature under argon) was placed in a flask under argon. A mixture of **III-12** (2.76 g, 19.7 mmol) and acetal **III-13c** (13.7 g, 86.6 mmol, 4.40 mol equiv) in 170 mL of dry acetonitrile was cannulated into the flask containing CsF. The mixture was heated at 65 °C for 14 h, whereupon the reaction was deemed to be complete by TLC. The reaction mixture was filtered through a bed of alumina (ethyl acetate). The filtrate was concentrated and chromatographed [silica, ethyl acetate/hexanes (1:3)], affording a brown oil containing some impurities. Chromatography (silica, CH_2Cl_2) of the brown oil gave a light brown solid (1.99 g, 34%): mp 74–75 °C; ^{1}H NMR δ 1.14 (s, 3H), 1.23 (s, 3H), 2.60, 2.72 (AB, ^2J = 18.6 Hz, 2H), 3.03 (ABX, ^3J = 2.4 Hz, ^2J = 15.6 Hz, 1H), 3.36 (ABX, ^3J = 11.8 Hz, ^2J = 15.6 Hz, 1H), 3.43 (s, 3H), 3.44 (s,

3H), 4.36 (s, 1H), 5.15 (ABX, ^{3}J = 2.4 Hz, ^{3}J = 11.8 Hz, 1H), 5.97–5.99 (m, 1H), 6.08–6.11 (m, 1H), 6.65–6.67 (m, 1H), 8.00–8.13 (br, 1H); ^{13}C NMR δ 24.4, 24.5, 26.9, 36.6, 45.3, 55.4, 95.0, 104.9, 107.5, 108.9, 117.9, 126.2, 203.8; FAB-MS obsd 299.1605, calcd 299.1607; Anal. Calcd for $C_{14}H_{22}N_2O_5$: C, 56.36; H, 7.43; N, 9.39. Found: C, 76.44; H, 7.57; N, 9.38.

2,3,4,5-Tetrahydro-1-(dimethoxymethyl)-3,3-dimethyldipyrrin N^{10}-oxide (III-28). Following a general procedure,[III17] a vigorously stirred solution of **III-27** (60 mg, 0.20 mmol) in acetic acid (1.0 mL) and ethanol (1.0 mL) at 0 °C was treated slowly with zinc dust (330 mg, 5.0 mmol) in small portions for 5 min. The reaction mixture was stirred at 0 °C for 15 min and filtered through Celite. The filtrate was concentrated under high vacuum. The resulting oil was chromatographed [alumina, ethyl acetate/CH_2Cl_2 (9:1)], affording a white solid (9.0 mg, 17%): mp 68–70 °C; ^{1}H NMR δ 1.11 (s, 3H), 1.21 (s, 3H), 2.47, 2.53 (AB, ^{2}J = 17.8 Hz, 2H), 2.96 (ABX, ^{3}J = 1.6 Hz, ^{2}J = 15.8 Hz, 1H), 3.07 (ABX, ^{3}J = 7.6 Hz, ^{2}J = 15.8 Hz, 1H), 3.43 (s, 3H), 3.46 (s, 3H), 3.95 (ABX, ^{3}J = 1.6 Hz, ^{2}J = 7.6 Hz, 1H), 5.48 (s, 1H), 5.92–5.95 (m, 1H), 6.06–6.09 (m, 1H), 6.68–6.71 (m, 1H), 10.31–10.45 (br, 1H); ^{13}C NMR δ 22.8, 25.5, 27.3, 38.4, 42.2, 55.3, 55.5, 82.9, 97.6, 106.4, 107.5, 117.8, 128.9, 145.1; FAB-MS obsd 266.1630, calcd 266.1630 (M = $C_{14}H_{22}N_2O_2$).

2,3,4,5-Tetrahydro-3,3-dimethyldipyrrin N^{10}-oxide (III-29). Following a general procedure,[III18] a solution of **III-18-Boc** (413 mg, 1.41 mmol) in anhydrous THF (9.0 mL) under argon at room temperature was treated with methanolic NaOMe (1.40 mL of a solution prepared by dissolving 486 mg of NaOMe in 2.00 mL of MeOH). After 25 min, the reaction was quenched by adding a mixture of hexanes and water (40.0 mL, 1:1). The mixture was

extracted with ethyl acetate. The organic extract was washed with water and brine, dried (Na_2SO_4), and chromatographed (silica, ethyl acetate) to give a light brown oil (106 mg, 39%): IR 3255, 2962, 1590, 1236 cm^{-1}; ^1H NMR δ 1.15 (s, 3H), 1.22 (s, 3H), 2.29–2.48 (m, 2H), 2.99 (ABX, ^3J = 3.0 Hz, ^2J = 15.8 Hz, 1H), 3.07 (ABX, ^3J = 7.4 Hz, ^2J = 15.8 Hz, 1H), 3.85–3.89 (m, 1H), 5.93–5.96 (m, 1H), 6.05–6.09 (m, 1H), 6.70–6.72 (m, 1H), 6.93–6.95 (m, 1H), 10.30–10.46 (br, 1H); ^{13}C NMR δ 23.0, 25.6, 27.8, 40.2, 42.6, 81.6, 106.5, 107.5, 117.8, 128.7, 135.5; EI-MS obsd 192.1265, calcd 192.1263 ($C_{11}H_{16}N_2O$).

9-Bromo-2,3,4,5-tetrahydro-1,3,3-trimethyldipyrrin N^{10}-oxide (III-31). Following a general procedure,[III16] a solution of **III-30** (413 mg, 2.00 mmol) in dry THF (20.0 mL) was cooled to –78 °C under argon. NBS (356 mg, 2.00 mmol) was added in two portions and the reaction mixture was stirred for 1 h at –78 °C. Hexanes (25.0 mL) and water (25.0 mL) were added and the mixture was allowed to warm to room temperature. The mixture was extracted with ethyl acetate. The organic layer was dried (Na_2SO_4), concentrated under vacuum without heat, and chromatographed (silica, ethyl acetate) to give a white solid (453 mg, 79%): mp 124–125 °C (dec.); ^1H NMR δ 1.09 (s, 3H), 1.19 (s, 3H), 2.07–2.08 (m, 3H), 2.32, 2.48 (AB, ^2J = 17.6 Hz, 2H), 2.91 (ABX, ^3J = 2.8 Hz, ^2J = 15.6 Hz, 1H), 3.00 (ABX, ^3J = 7.2 Hz, ^2J = 15.6 Hz, 1H), 3.84–3.91 (m, 1H), 5.85–5.87 (m, 1H), 5.96–5.98 (m, 1H), 10.92–11.03 (br, 1H); ^{13}C NMR δ 13.4, 23.0, 26.2, 27.8, 37.4, 47.2, 81.1, 96.8, 108.1, 109.4, 130.5, 146.3; Anal. Calcd. for $C_{12}H_{17}BrN_2O$: C, 50.54; H, 6.01; N, 9.82. Found C, 50.48; H, 6.05; N, 9.65.

9-Bromo-1-formyl-2,3,4,5-tetrahydro-3,3-dimethyldipyrrin N^{10}-oxide (III-32). A solution of **III-31** (29 mg, 0.10 mmol) in 1,4-dioxane (1.0 mL) was treated with SeO_2 (14

mg, 0.13 mmol) under argon. The mixture was stirred for 2.5 h at room temperature. The reaction mixture was then treated with saturated $NaHCO_3$ (1.0 mL) and extracted with ethyl acetate. The organic extract was washed with water, dried (Na_2SO_4), and chromatographed [silica, ethyl acetate/hexanes (1:1)] to give a light brown solid (13 mg, 43%): mp 115–117 °C (dec.); ^{1}H NMR δ 1.09 (s, 3H), 1.27 (s, 3H), 2.60, 2.66 (AB, ^2J = 17.2 Hz, 2H), 2.84 (ABX, ^3J = 2.2 Hz, ^2J = 16.0 Hz, 1H), 3.08 (ABX, ^3J = 8.2 Hz, ^2J = 16.0 Hz, 1H), 4.06–4.11 (m, 1H), 5.88–5.90 (m, 1H), 5.99–6.01 (m, 1H), 9.64–9.74 (br, 1H), 10.20 (s, 1H); ^{13}C NMR δ 22.2, 25.2, 26.4, 38.9, 39.9, 85.4, 97.4, 108.7, 110.0, 129.8, 142.7, 183.1; FAB-MS obsd 299.0385, calcd 299.0395 [$(M+H)^+$, M = $C_{12}H_{15}BrN_2O_2$].

Implementation of Route 5 (III-6P → Bacteriochlorins). A solution of dihydrodipyrrin **III-6P** (30 mg, 0.12 mmol) in $CHCl_3$ (12 mL) was treated with $InCl_3$ (267 mg, 1.2 mmol, 10 equiv). The reaction mixture was stirred at room temperature for 24 h. The reaction was monitored by absorption spectroscopy; the spectroscopic yield of bacteriochlorins was ~2%. The reaction mixture was filtered. The filtrate was washed with aqueous $NaHCO_3$, dried (Na_2SO_4), concentrated, and chromatographed (silica). Three bands were collected. The first band was eluted with CH_2Cl_2/hexanes (1:1) (green, **III-33**, < 0.5 mg, ~1%), the second band was eluted with CH_2Cl_2/hexanes (1:1) (green, **III-34**, < 0.5 mg, ~1%), and the third band was eluted with ethyl acetate (pink, trace quantity of unknown identity; λ_{abs} = 720 nm). The yields were estimated by absorption spectrometric analysis (on the basis of the reasonable assumption[11,30] that ε_{Qy} = 120,000 $M^{-1}cm^{-1}$) of the isolated fractions. Data for putative 8,8,18,18-tetramethylbacteriochlorin (**III-33**): λ_{abs} in toluene (relative intensity) 340 (0.90), 365 (1.00), 490 (0.26), 714 (0.82) nm; LD-MS obsd 370.4;

FAB-MS obsd 370.2177, calcd 370.2157 ($C_{24}H_{26}N_4$). Data for putative 5-methoxy-8,8,18,18-tetramethylbacteriochlorin (**III-34**): λ_{abs} in toluene (relative intensity) 345 (0.87), 355 (0.77), 367 (1.00), 501 (0.30), 709 (0.85) nm; LD-MS obsd 400.4; FAB-MS obsd 400.2262, calcd 400.2263 ($C_{25}H_{28}N_4O$).

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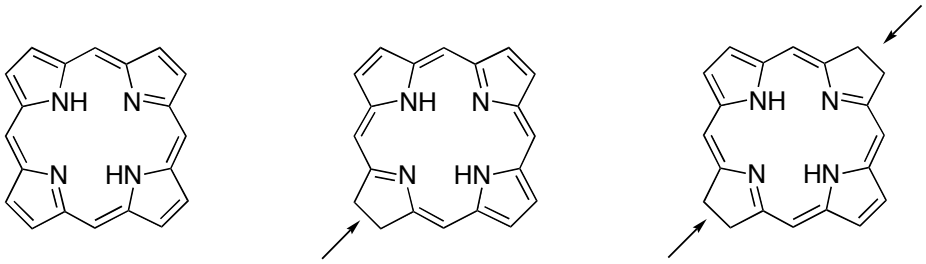
CHAPTER IV. DE NOVO SYNTHESIS OF STABLE BACTERIOCHLORINS

IV.A. Introduction.

The progressive $2e^-/2H^+$ reduction of the porphyrinic macrocycle along the series porphyrin, chlorin (a dihydroporphyrin) and bacteriochlorin (a tetrahydroporphyrin) causes profound changes in chemical and physical properties (Chart IV.1).

Chart IV.1



Porphyrin **Chlorin** **Bacteriochlorin**

The reduction alters the symmetry yet each macrocycle maintains an 18 π-electron conjugated system as required for aromaticity. One striking change upon reduction is the large increase in absorption in the red or near-IR region of the spectrum.[IV1] The changes in physical properties have been famously exploited by biological systems; the chlorin macrocycle provides the basis for chlorophyll *a* and *b* in plant photosynthesis while the bacteriochlorin macrocycle provides the basis for bacteriochlorophyll *a* in bacterial photosynthesis. The change in absorption is illustrated for a representative porphyrin,[IV2] chlorin,[IV3] and bacteriochlorin[IV4] in Figure IV.1.

Three distinct types of bacteriochlorins occur in Nature as illustrated by bacteriochlorophyll *a*, bacteriochlorophyll *b* or *g*, and tolyporphin A (Chart IV.2).

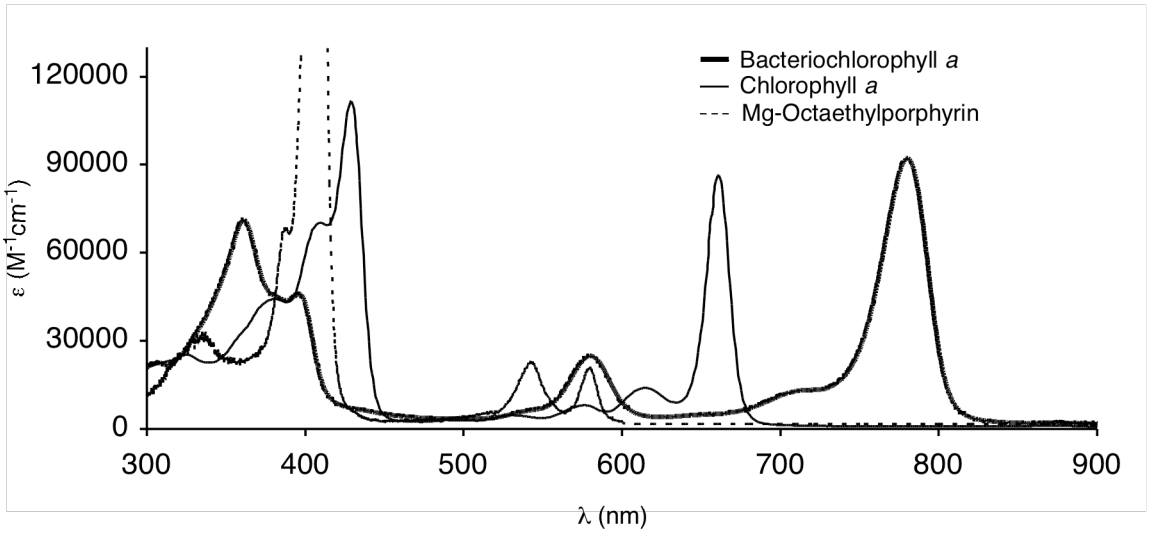
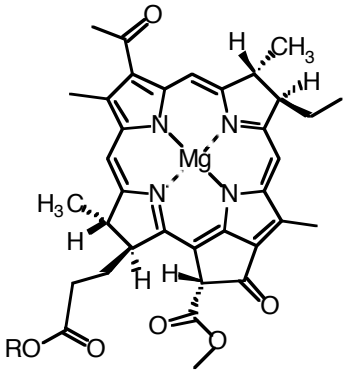


Figure IV.1. Absorption spectra of Mg-octaethylporphyrin (CH_2Cl_2, $\varepsilon_{409\ nm}$ = 408,300 $M^{-1}cm^{-1}$),[IV2] chlorophyll *a* (diethyl ether, $\varepsilon_{428.5\ nm}$ = 111,700 $M^{-1}cm^{-1}$),[IV3] and bacteriochlorophyll *a* (toluene, $\varepsilon_{781\ nm}$ = 92,300 $M^{-1}cm^{-1}$).[IV4]

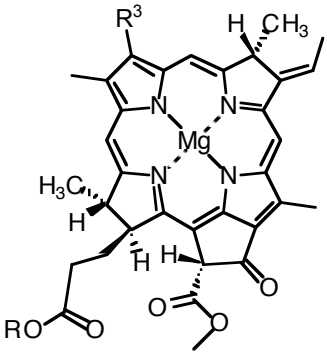
The bacteriochlorophylls serve as the principal light-absorbing pigments and energy/electron-transfer components in bacterial photosynthetic systems.

Chart IV.2



R = phytyl analogue

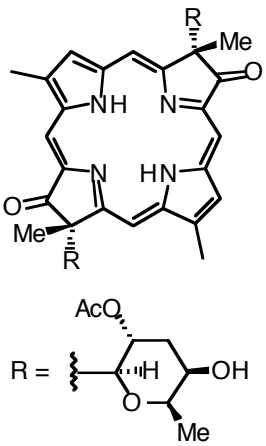
Bacteriochlorophyll *a*



R = phytyl analogue

Bacteriochlorophyll *b* (R^3 = acetyl)

Bacteriochlorophyll *g* (R^3 = vinyl)

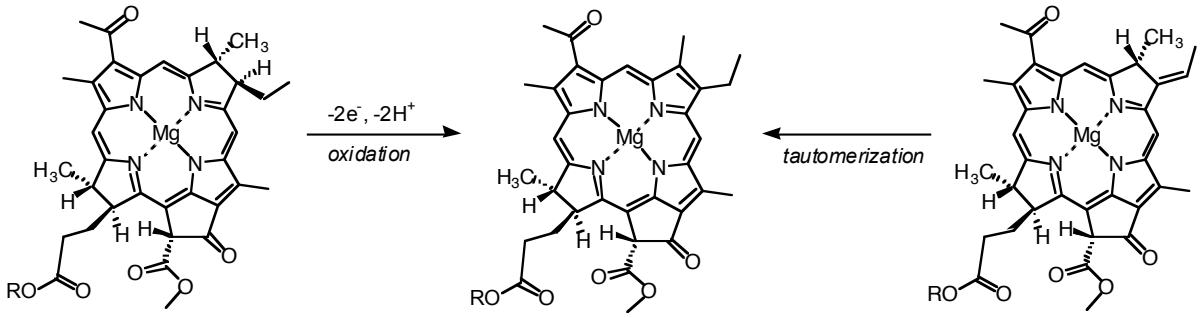


Tolyporphin A

Bacteriochlorophyll *a* is the most widely distributed bacteriochlorin pigment.[IV5] Bacteriochlorophylls *b* and *g* have spectral features characteristic of tetrahydroporphyrins (i.e., bacteriochlorins) but each is actually a dihydroporphyrin tautomer with an exocyclic double bond in ring B of the macrocycle. (Bacteriochlorophylls *c*, *d*, and *e* are dihydroporphyrins with only one reduced ring, and accordingly exhibit all the spectral features of chlorins.[IV6]) Tolyporphin A, a non-photosynthetic bacteriochlorin pigment, was isolated from the Pacific microalga *Tolypothrix nodosa* in 1992, and a number of additional tolyporphins have since been isolated.[IV7] Inspection of the structures shows that tolyporphins differ in several ways from bacteriochlorophylls. For our purposes here, it is noteworthy that a tolyporphin contains two geminal-dialkyl units that lock-in the reduction level of the bacteriochlorin.

Surprisingly few methods exist for the preparation of bacteriochlorins despite the importance of this class of compounds.[IV8] With regard to the naturally occurring bacteriochlorins, the total synthesis of the *O,O*-diacetate of tolyporphin A was reported several years ago by Kishi, entailing >20 steps and affording <5 mg of product.[IV9] To our knowledge, no total syntheses of bacteriochlorophyll *a* have been reported. A chief obstacle to handling bacteriochlorophyll *a* is its pronounced tendency to undergo dehydrogenation to give the corresponding chlorin.[IV10] Bacteriochlorophyll *b*[IV11,IV12] and bacteriochlorophyll *g*[IV13] are even more labile given their susceptibility to tautomerization, also affording the corresponding chlorin. For example, both bacteriochlorophyll *b* and *g* undergo conversion to the chlorin with half-lives of a few minutes min upon exposure to light in vitro.[IV12,IV13] Both oxidation and tautomerization processes are illustrated in Scheme IV.1.

Scheme IV.1



bacteriochlorophyll *a* **3-desvinyl-3-acetylchlorophyll *a*** **bacteriochlorophyll *b***

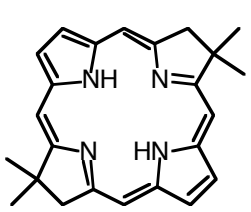
A simple method developed several decades ago for preparing synthetic bacteriochlorins entails reduction with diimide of a porphyrin or chlorin.[IV14] This direct reduction method, which has been used widely to make chlorins but less frequently to make bacteriochlorins,[IV15-IV24] is accompanied by several problems including (1) the difficulty of separating chlorin and bacteriochlorin species, (2) the adventitious dehydrogenation of the bacteriochlorin yielding the chlorin and porphyrin, and (3) the possible formation of bacteriochlorin isomers depending on the nature of meso or β-pyrrole substituents.

More resilient bacteriochlorins have been prepared by derivatization of porphyrins or chlorins. A versatile approach entails via vicinal dihydroxylation to give the tetrahydroxybacteriochlorin;[IV25] subsequent pinacol rearrangement (for porphyrins that bear β-substituents) affords the dione,[IV26] which then can be methenylated or alkylated.[IV27,IV28] Other derivatization approaches include photooxygenation of divinylporphyrins,[IV29] Diels-Alder reactions,[IV30] 1,3-dipolar cycloadditions,[IV31] and successive addition of carbon nucleophiles.[IV32,IV33] Each method has merit yet also suffers from the potential formation of

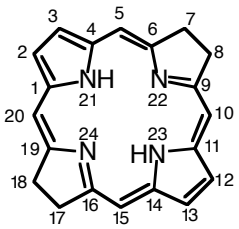
regioisomers owing to reaction at distinct pyrrole rings or at the same or opposite faces of the macrocycle.

An alternative route to bacteriochlorins entails modification of naturally occurring chlorophylls[IV34-IV36] or bacteriochlorophylls.[IV35,IV37] Elaborate bacteriochlorin derivatives have been obtained in this manner despite the inherent lability of the naturally available starting materials, but the presence of a nearly full complement of peripheral substituents restricts synthetic flexibility.

Chart IV.3



Core structure of the target bacteriochlorin



Bacteriochlorin numbering system

The strong absorption by bacteriochlorins in the near-IR region makes these pigments especially attractive for a wide variety of applications in medicine, the life sciences, and materials chemistry. Such applications require simple synthetic methods that afford access to ample quantities of stable compounds. Specific attributes of the desired methodology include the ability (1) to construct a macrocycle that is locked at the bacteriochlorin reduction level, and (2) to exercise synthetic control over the pattern of substituents arrayed around the perimeter of the macrocycle. The former objective can be met through the use of a geminal-dimethyl group in each of the two reduced, pyrroline rings. The latter objective can be met by using hydrodipyrrin precursors containing the desired pattern of substituents to be carried

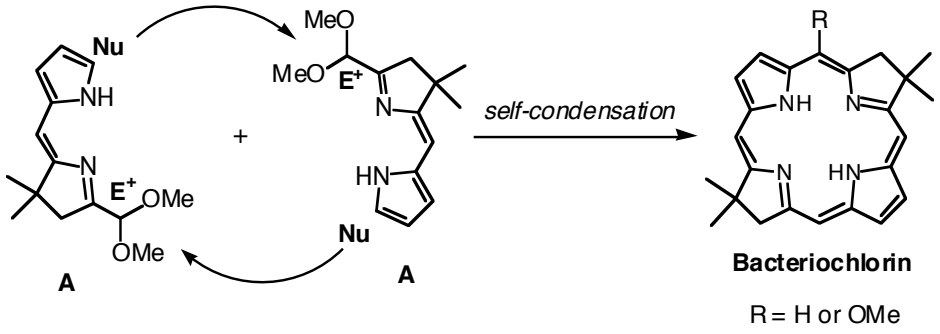
over to the target bacteriochlorin. The structure of a target bacteriochlorin core (lacking peripheral substituents other than the geminal-dimethyl groups) is shown in Chart IV.3.

In this Chapter, we describe a *de novo* synthesis of bacteriochlorins where structural features in acyclic precursors establish the bacteriochlorin reduction level. The route that we developed draws on our prior work concerning the rational synthesis of chlorins[IV38,IV39] but also required extensive development as described in the previous Chapter.[IV40] The route to bacteriochlorins employs the self-condensation of a dihydrodipyrrin–acetal wherein the pyrrolic end of the molecule functions as a nucleophile and the acetal functions as an electrophile. We describe the synthesis of the dihydrodipyrrin–acetal, a study of conditions for the self-condensation, and the characterization of the resulting tetrahydroporphyrins.

IV.B. Results and Discussion.

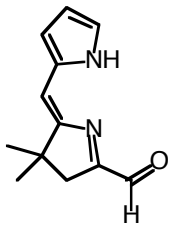
1. Strategy. During the development of a *de novo* synthesis of bacteriochlorins, we examined the reactivity of a number of hydrodipyrrins each containing one pyrrole and one pyrroline unit.[IV40]

Scheme IV.2



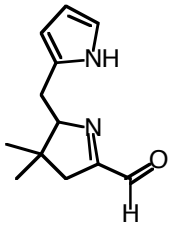
We eventually found that a dihydrodipyrrin (**A**) bearing a dimethyl acetal moiety attached to the α-pyrroline position underwent self-condensation to give bacteriochlorins (Scheme IV.2). This result validated the approach of employing pyrrole/pyrroline moieties to serve as complementary nucleophilic/electrophilic counterparts, although the yield was very low (~1%). We decided to build on this result to develop a more reliable synthesis.

Chart IV.4



B

a dihydrodipyrrin

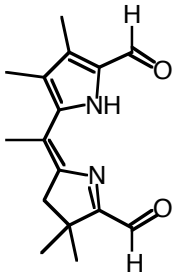


C

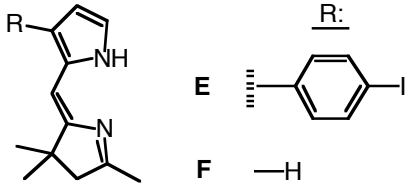
a tetrahydrodipyrrin

The initial target molecules of choice were hydrodipyrrin–carboxaldehydes rather than the acetal **A**. The hydrodipyrrin–carboxaldehydes **B** and **C** differ only in the saturation at the 4,5-position (between the meso-carbon and the pyrroline α′-carbon) (Chart IV.4).

Chart IV.5

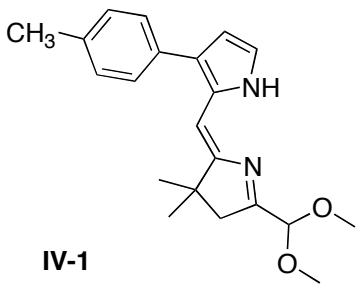


D



However, we were unable to prepare either **B** or **C**.[IV40] Two observations from the literature concerning related structures (Chart IV.5) prompted the next step in the evolution of the synthesis. First, Jacobi *et al*. employed a diformyl-dihydrodipyrrin (**D**) in a rational route to chlorins.[IV41] The dihydrodipyrrin bears the desired formyl group at the α-position of

the pyrroline group, while also incorporating a nearly full complement of substituents throughout the molecule. Second, dihydrodipyrrins bearing a β-substituent in the pyrrole ring (**E**) are known to be more stable than unsubstituted analogs (**F**).[IV39] Accordingly, we focused on the development of a route that would employ a β-pyrrole substituted dihydrodipyrrin analog (**IV-1**) of the tetrahydrodipyrrin–acetal **A**. The *p*-tolyl group was chosen as an inert substituent that is readily characterized by ^{1}H NMR spectroscopy.



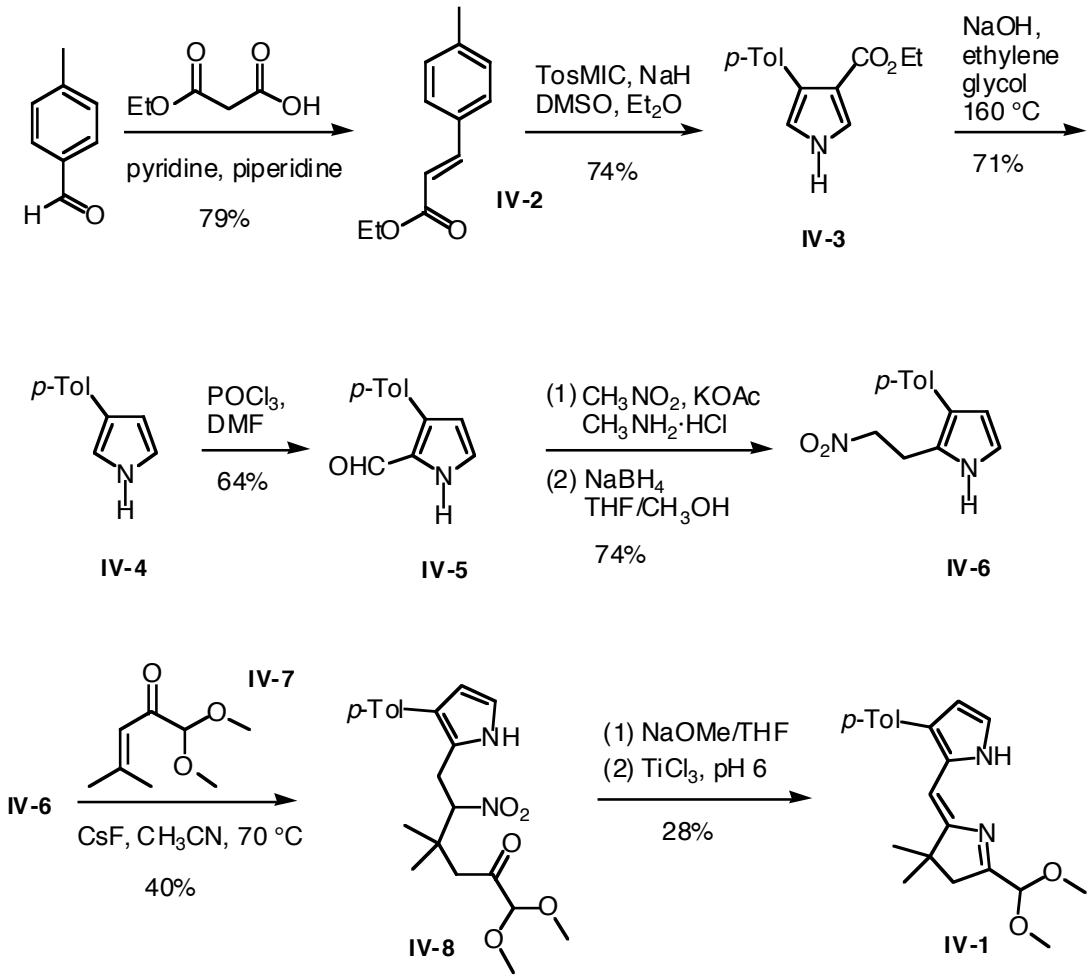
IV-1

2. Synthesis of Bacteriochlorin Precursors. The synthesis of dihydrodipyrrin–acetal **IV-1** was initiated in similar fashion to that of dihydrodipyrrin **E**.[IV39] Some of the components (**IV-2–IV-4**) of the early portion of the synthesis have been prepared via different routes or have been reported with incomplete characterization data. A full description of the synthesis is reported here.

Application of the previously unused Knoevenagel condensation[IV42] of *p*-tolualdehyde with malonic acid monoethyl ester[IV43] in pyridine containing a catalytic amount of piperidine gave the known α,β-unsaturated ester **IV-2**[IV44] in 79% yield. Subsequent reaction of **IV-2** with (*p*-tolylsulfonyl)methyl isocyanide (TosMIC) afforded β-substituted pyrrole **IV-3** (a known compound with incomplete data[IV45]) in 74% yield. Removal of the ethoxycarbonyl group of pyrrole **IV-3** by treatment with NaOH in ethylene glycol at 160 °C gave the known β-substituted pyrrole **IV-4**[IV46-IV48] in 71% yield. Vilsmeier-Haack formylation of **IV-7** yielded a mixture of regioisomers owing to substitution at the 2- or 5-position. After column chromatography, the two regioisomers were determined to be present

in ~13:1 ratio by ^{1}H NMR integration of the methyl unit of the *p*-tolyl group. Selective precipitation readily afforded the major regioisomer **IV-5** in 64% yield (Scheme IV.3).

Scheme IV.3



It is noteworthy that we previously employed the same formylation method to prepare 2-formyl-3-(4-iodophenyl)pyrrole, which was characterized by ^{1}H NMR spectroscopy and X-ray crystallography.[IV39] The chemical shift of the two peaks (δ 6.42–6.44 and 7.10–7.13 ppm) from the pyrrolic protons of the major isomer **IV-5** were quite similar to those for 2-formyl-3-(4-iodophenyl)pyrrole (δ 6.42 and 7.14 ppm)[IV39] or 2-formyl-3-phenylpyrrole (δ

6.50 and 7.30 ppm).[IV49] The minor isomer, 2-formyl-4-(4-methylphenyl)pyrrole (δ 7.20–7.22 and 7.36–7.38 ppm), also showed similar chemical shifts for the respective pyrrolic protons of the previously characterized 2-formyl-4-(4-iodophenyl)pyrrole (δ 7.21 and 7.39 ppm).[IV39]

Treatment of **IV-5** to the standard conditions[IV39] for condensation of a pyrrole-2-carboxaldehyde with nitromethane for 2.5 h afforded the crude 2-(2-nitrovinyl)pyrrole as a brown solid. Reduction of the latter with $NaBH_4$ gave the β-substituted nitroethylpyrrole **IV-6** (74% for this two-step one-flask synthesis). The α-keto acetal (**IV-7**) required for the next step, previously prepared at the 2-mmol scale by reaction of mesityl oxide with a catalytic amount of diphenyl diselenide and excess ammonium peroxydisulfate,[IV50] was carried out at the 160-mmol scale, affording **IV-7** (~7 g) in 29% yield. The Michael reaction of **IV-6** with excess **IV-7** (10 equiv) in the presence of CsF at 65 °C gave **IV-8** in 40% yield, accompanied by recovery of **IV-7** (~50%) upon bulb-to-bulb distillation and column chromatography. Treatment of **IV-8** with NaOMe followed by a buffered $TiCl_3$ solution afforded the dihydrodiyrrin–acetal **IV-1** as a yellow solid in 28% yield.

3. Investigation of Reaction Conditions for Bacteriochlorin Formation. A series of microscale studies (~1–2 mg of **IV-1** per reaction) was performed to investigate the effects of reaction parameters that are known to influence the course of condensations leading to porphyrinic macrocycles, including concentration of **IV-1**, acid composition, acid concentration, solvent, and time.[IV51] The standard conditions employed initially included 5 mM of acetal **IV-1** in CH_3CN containing 50 mM of acid at room temperature, which closely resemble those employed in the self-condensation of the unsubstituted dihydrodipyrrin–acetal **A**.[IV40] Samples were removed periodically over the course of ~24 h, neutralized with

TEA, and examined by absorption spectroscopy. Yields were calculated on the basis of the assumption that each bacteriochlorin has ε_{Qy} = 120,000 $M^{-1}cm^{-1}$, an assumption that proved reasonable (vide infra). The intense absorption of the bacteriochlorin enabled quantitative analysis of crude reaction mixtures.

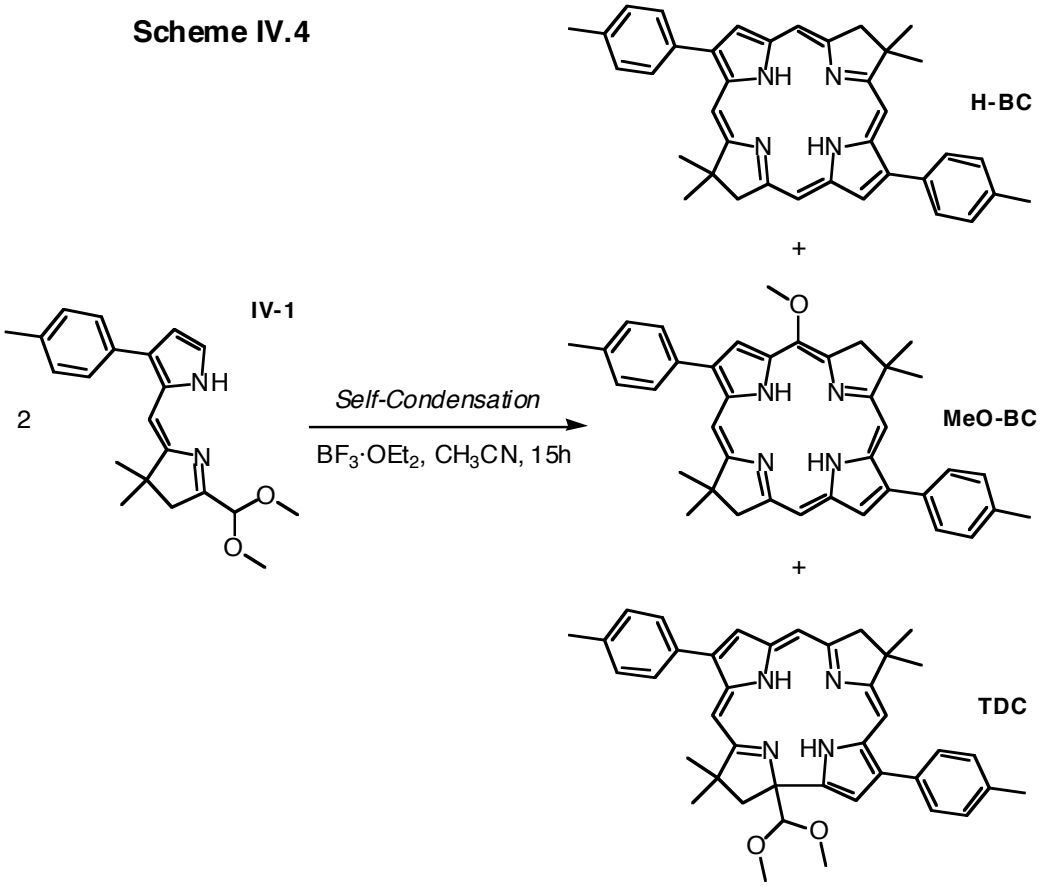
A. Acids. A screening study was performed to identify the effects of a variety of acids on the self-condensation of **IV-1**. Four Brønsted acids and eleven Lewis acids (previously employed in porphyrin chemistry)[IV52] were examined in CH_3CN exposed to air. The acids can be categorized on the basis of bacteriochlorin yields: $BF_3{\cdot}OEt_2$ (31%); $InCl_3$, $Sc(OTf)_3$, or $SnCl_4$ (18-16%); *p*-$TsOH{\cdot}H_2O$ (4.9%); $Yb(OTf)_3$, SnF_4, $TiCl_4$, BBr_3, or HCl (1.5-0.4%), and AcOH, TFA, $MgBr_2$, $ZnCl_2$, or $Zn(OAc)_2$ (~0%). The acids $InCl_3$ and $Yb(OTf)_3$ gave a slightly different reaction course, affording a free base bacteriochlorin, a metalated bacteriochlorin, and a non-bacteriochlorin macrocycle. This work will be described elsewhere.

B. Solvents. The effect of solvent on the self-condensation of **IV-1** was examined with $BF_3{\cdot}OEt_2$ catalysis under the standard conditions. The bacteriochlorin yields were ~30% (CH_3CN), <2% ($CHCl_3$ or $ClCH_2CH_2Cl$), and not detectable (CH_2Cl_2, toluene, DMF, DMSO, THF, 1,4-dioxane, methanol, ethanol).

The standard reaction was scaled-up using $BF_3{\cdot}OEt_2$ in CH_3CN at room temperature exposed to air for 6 h (Scheme IV.4). Chromatographic workup on silica followed by ^1H NMR spectroscopy and laser-desorption mass spectrometry (LD-MS) analysis led to two surprises. The first surprise was that two bacteriochlorins were isolated: one relatively nonpolar bacteriochlorin (**H-BC**) has no meso substituent while one more polar

bacteriochlorin (**MeO-BC**) has a methoxy group at the 5-position. The two bacteriochlorins were isolated in 11% and 30% yield, respectively.

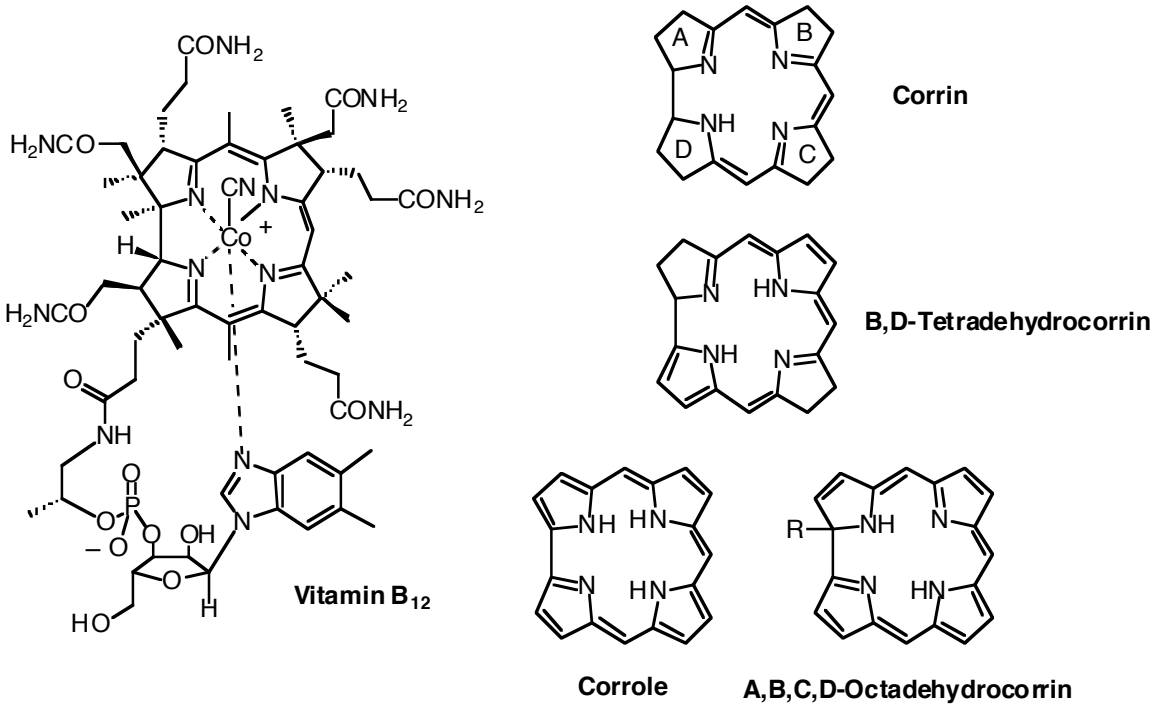
Scheme IV.4



The second surprise emerged upon carrying out the reaction at lower concentrations of $BF_3{\cdot}OEt_2$, whereupon another porphyrinic macrocycle was identified. The macrocycle proved to be a ring-contracted porphyrinic species containing two opposing pyrroline rings, termed a B,D-tetradehydrocorrin (**TDC**). The tetradehydrocorrin is a $4e^-/4H+$ oxidized analogue of a corrin, the core macrocycle of vitamin B_{12}, and hence lies equidistant between the reduction levels of a corrin and a corrole. A corrole is an aromatic tautomer of an octadehydrocorrin,[IV53] as illustrated for R = H in Chart IV.6. Each hydroporphyrin was

characterized by absorption spectroscopy, ^{1}H NMR spectroscopy, LD-MS, and high-resolution FAB-MS (vide infra).

Chart IV.6



In summary, the dramatic increase in yield (versus the <1% yield with the unsubstituted dihydrodipyrrin–acetal **A**) validated our hunch that β-substitution would afford a more stable dihydrodipyrrin and more efficient reaction.

C. Effect of Reactant and Acid Concentrations. To gain a deeper understanding of the effect of reactant concentration and acid concentration, a grid-search experiment was performed at the microscale level (0.5-2 mL reactions). The search space was defined by the dihydrodipyrrin–acetal **IV-1** concentration (2.5 – 50 mM) and the $BF_3{\cdot}OEt_2$ concentration (10 – 500 mM). Points at the corners, faces, core, and center of the search space were examined. Each reaction was monitored over time (23 h) and the yield of bacteriochlorins (but not **TDC**) was determined spectroscopically from the crude mixture. Each reaction

mixture was then separated chromatographically to determine the isolated yield (by spectrophotometry of purified fractions) of bacteriochlorins (**H-BC** and **MeO-BC**) and the tetradehydrocorrin **TDC**.

The yield of bacteriochlorins versus time for several points in the search space is shown in Figure IV.2. The bacteriochlorins form smoothly and the yields generally remain constant over time. The rates did not vary substantially with acid concentration, as shown by the curves obtained with 10, 71, or 500 mM $BF_3{\cdot}OEt_2$ in Figure IV.2.

Figure IV.2

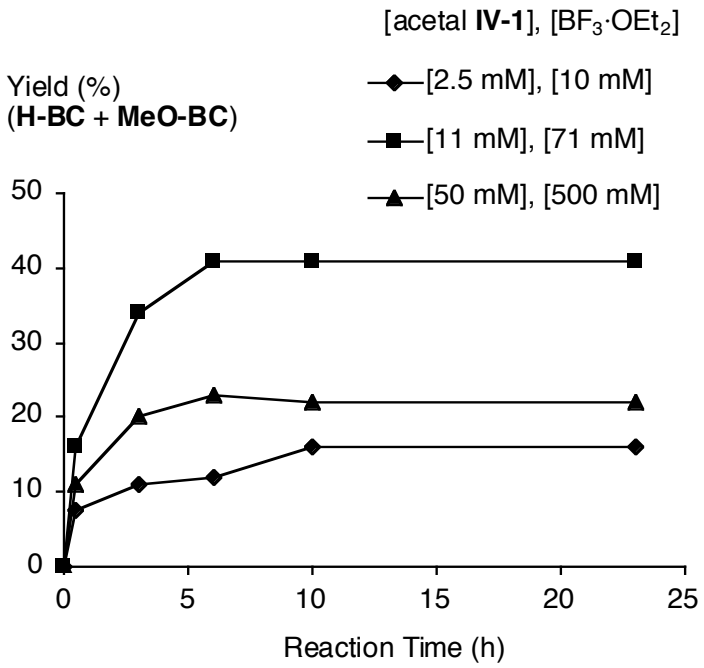
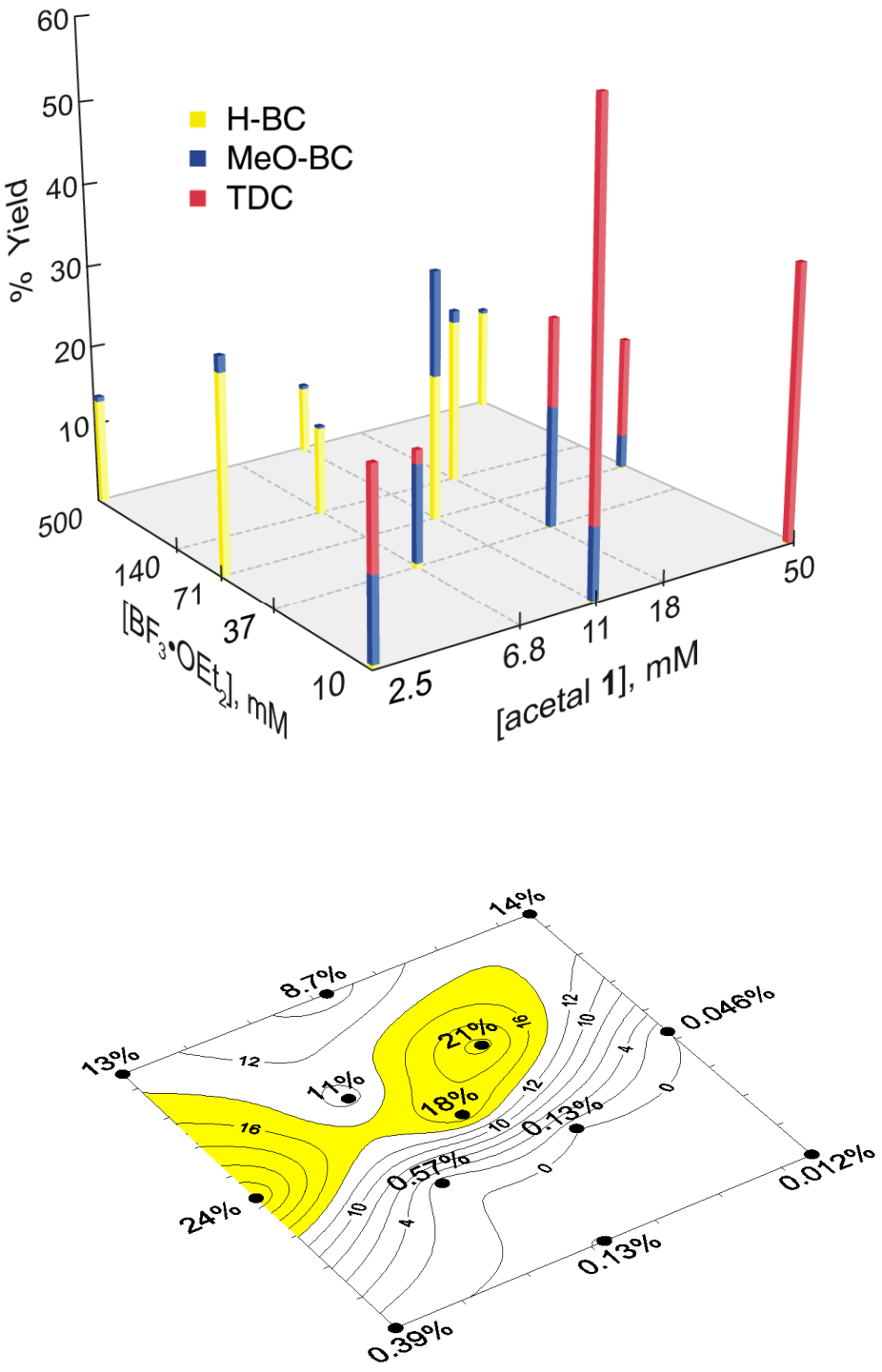


Figure IV.2. The yield of bacteriochlorins (sum of **H-BC** + **MeO-BC**) as a function of time. The data points were taken for concentrations of **IV-1** and $BF_3{\cdot}OEt_2$ located along the diagonal of the reaction space described in Figure IV.3. The data points represent the lowest, highest, and midpoint of the concentrations of both **IV-1** and $BF_3{\cdot}OEt_2$. The yields were determined by absorption spectroscopy of crude reaction samples.

The isolated yields at each point in the search space are shown in Figure IV.3.



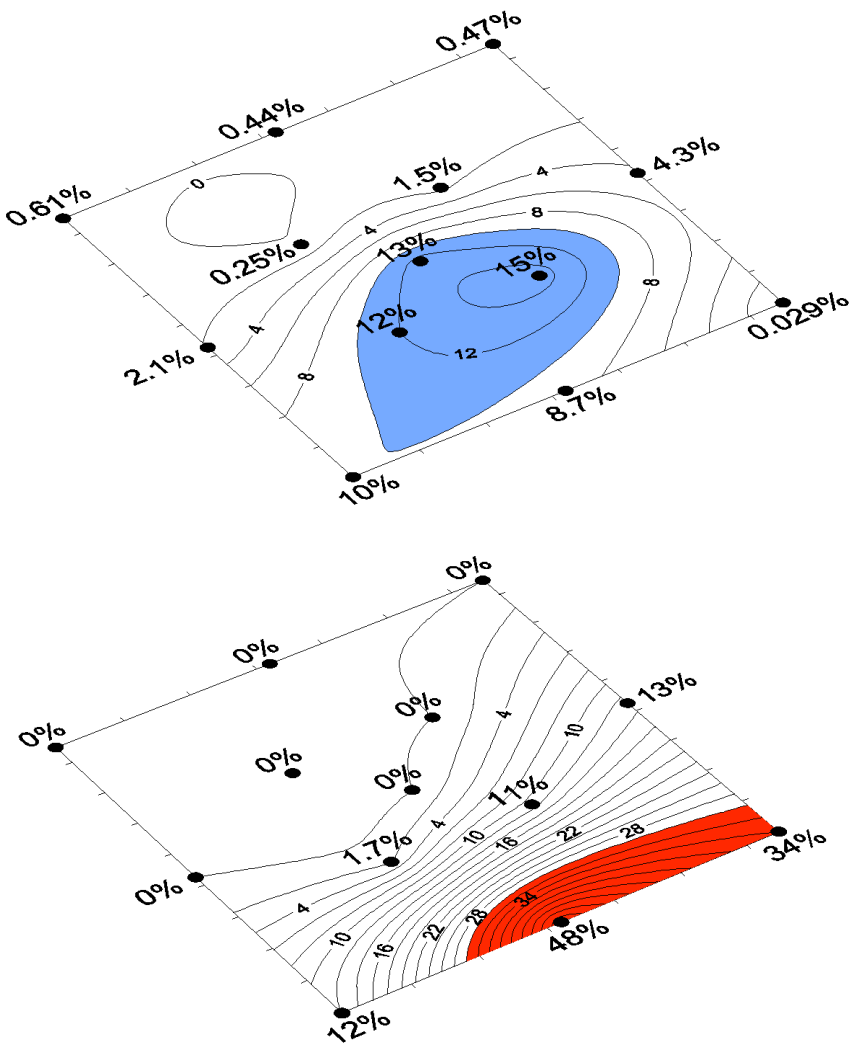


Figure IV.3. Yields of H-BC, MeO-BC, and TDC as a function of the concentrations of **IV-1** and $BF_3{\cdot}OEt_2$. The reactions were performed at the microscale level. Each reaction was worked up after 23 h. The segmented histogram at top shows the yield of each species and the summed yield of macrocycles. The contour diagrams below illustrate the yield of each species H-BC, MeO-BC, and TDC in the same search space defined by the concentrations of **IV-1** and $BF_3{\cdot}OEt_2$. The actual numerical data are listed; the contours are provided to guide the eye. In each contour, coloration is provided to illustrate the 60% cutset data (i.e., those regions that afford a yield that is at least 60% of the highest value recorded anywhere in the search space).

The histogram shows the yield of each of the three hydroporphyrins and the summed yields. Note that the ratio of **H-BC**:**MeO-BC**:**TDC** changes with alteration in the concentration of acid and reactant. The yield of **TDC** is highest at the lowest acid concentration examined and is not observed at the highest acid concentrations. On the other hand, the yield of **H-BC** generally increased with increasing acid concentration. The yield of **MeO-BC** was highest at modest concentrations of acid and reactant. From a practical standpoint, this limited study has identified conditions that afford a relatively high, albeit not exclusive, yield of each of the hydroporphyrins: (i) With 50 mM **IV-1** and 10 mM $BF_3{\cdot}OEt_2$, **TDC** is formed in 34% yield with <2% bacteriochlorins. (ii) With 6.8 mM **IV-1** and 140 mM $BF_3{\cdot}OEt_2$, **H-BC** is formed in 29% yield with <1% other hydroporphyrins. (iii) With 6.8 mM **IV-1** and 37 mM $BF_3{\cdot}OEt_2$, **MeO-BC** is formed in 20% yield with <3% other hydroporphyrins. These results augur well for relatively selective preparation of workable quantities of each hydroporphyrin.

Table IV.1. Isolated Yields of Hydroporphyrins from Semi-preparative Reactions[a]

Entry	[**IV-1**], mM	[$BF_3{\cdot}OEt_2$], mM	**H-BC** yield	**MeO-BC** yield	**TDC** yield
1[b]	18	140	49% (21%)[c]	1.9% (1.5%)[c]	---
2[d]	5.0	50	11%	30%	---
3[b]	11	10	---	6.3% (8.7%)[c]	67% (48%)[c]

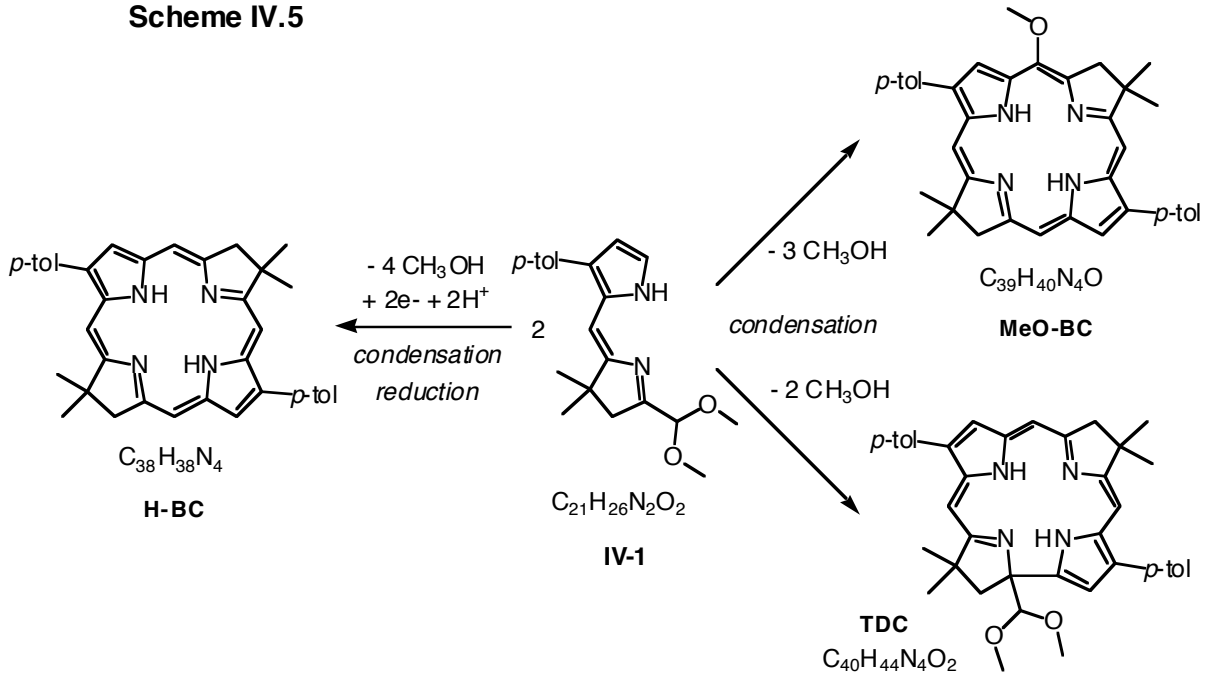
[a] Yields were determined gravimetrically. [b] The reaction was performed using 0.15 mmol of **IV-1**. [c] Yield obtained in the microscale grid-search experiment (Figure IV.3). [d] The reaction was performed using 0.27 mmol of **IV-1**.

Three semi-preparative reactions were performed. In each reaction, the concentrations of **IV-1** and $BF_3{\cdot}OEt_2$ were chosen on the basis of the response-surface data to favor one of the three hydroporphyrins (**H-BC**, **MeO-BC**, **TDC**). The results are listed in Table IV.1. The reaction designed to favor **H-BC** gave **H-BC** in 49% yield (20 mg; entry 1); the reaction designed to favor **MeO-BC** gave **MeO-BC** in 30% yield (24 mg; entry 2); the reaction to favor **TDC** gave **TDC** in 67% yield (30 mg; entry 3). In each case, the desired hydroporphyrin was readily isolated, as was a lesser amount of one (but not both) of the other hydroporphyrins. The product ratios generally mirrored the trends observed in the microscale work (Figure IV.3) although the isolated yields were somewhat higher than expected.

4. Mechanistic Considerations. At present we know very little about the mechanistic course leading from the dihydrodipyrrin–acetal to the bacteriochlorin or tetradehydrocorrin species. The balanced reaction for formation of each product is shown in Scheme IV.5. The conversion of two molecules of **IV-1** to give **MeO-BC** proceeds with elimination of three molecules of methanol. Note that the acetal unit of **IV-1** serves as an electrophile for the bacteriochlorin-forming reaction. Although a masked aldehyde, examples are known where an acetal functions as an electrophile leaving one alkyl ether unit intact.[IV54] The formation of **TDC** entails elimination of two molecules of methanol. By contrast, the formation of **H-BC** must proceed with elimination of four molecules of methanol and addition of $2e^-$ and $2H^+$. Neither the source of the reductant nor the nature of

the intermediate that undergoes reduction is known. It is worthwhile to contrast this overall transformation with that of porphyrin formation from an aldehyde and pyrrole, which proceeds via condensation to give a hexahydroporphyrin (porphyrinogen) intermediate; the latter is converted via a $6e^-/6H^+$ oxidation to give the porphyrin.[IV51] Formation of the bacteriochlorins or tetradehydrocorrin from **IV-1** does not require an oxidant. Further consideration of oxidation-state changes is likely to be important in searching for intermediates and in designing alternative precursors to give bacteriochlorins.

Scheme IV.5



The formation of **TDC** warrants additional comment. From the standpoint of oxidation-state and structural considerations, the B,D-tetradehydrocorrin (**TDC**) is to a bacteriochlorin what an octadehydrocorrin is to a porphyrin. Both the tetradehydrocorrin and bacteriochlorin are $4e^-/4H^+$-reduced analogues of the most unsaturated corresponding

porphyrinoid (i.e., porphyrin) and corrinoid (i.e., octadehydrocorrin or corrole) macrocycles. Syntheses of octadehydrocorrins were developed several decades ago,[IV53b,IV55-IV59] and more recent activity has been devoted to methodology for preparing substituted corroles,[IV60,IV61] the aromatic counterpart of octadehydrocorrins.[IV53] Recent directed routes to corroles entail cyclization of a 1,19-unsubstituted bilane,[IV62,IV63] *a,c*-biladiene,[IV64] or 22,24-dihydro-*a,b,c*-bilatriene.[IV64] The conversion of each such acyclic species to give the A-D ring junction of the corrole requires oxidation (the mechanisms of which remain under active investigation). A typical oxidant is DDQ or *p*-chloranil. By contrast, the self-condensation of **IV-1** leading to the macrocycle **TDC** does not require any change in oxidation state. While unexpected, the self-condensation of **IV-1** at low acid concentration provides a very facile entry into B,D-tetradehydrocorrins. It is interesting that corroles also have been formed in the presence of quite low acid concentrations.[IV61-IV63]

5. Characterization. A. The B,D-Tetradehydrocorrin. The absorption spectrum of **TDC** shows λ_{max} at 341 nm, a shoulder at 438 nm, and a broad, weaker band in the region 500 – 1000 nm (Figure IV.4). The absorption spectral features are similar to a Ni(II) 1-methyloctadehydrocorrin.[IV55,IV65] The absorption spectra of corrinoid macrocycles vary depending on the reduction level, path of conjugation, metalation state, and peripheral substituents.[IV56-IV58,IV65-IV68]

The ^{1}H NMR spectrum showed relatively complex features owing to the C_s symmetry of **TDC**. The pair of geminal-dimethyl groups gives rise to four apparent singlets (δ 1.04, 1.24, 1.26, and 1.33 ppm). The four protons of the methylene units in the pyrroline rings appear as pair of doublets (AB pattern) at δ 1.82 and 2.49 ppm (^2J = 13.2 Hz), and δ 2.65 and 2.71 ppm (^2J = 18.8 Hz) respectively. The methane proton of the acetal unit gives a singlet at

δ 4.26 ppm. Of the five protons at the perimeter, three give singlets (δ 5.42, 5.43, and 6.02 ppm) whereas the other two protons give multiplets (probably due to long-range coupling) at the region of δ 6.24–6.25 and 6.57–6.58 ppm. The aryl hydrogens of the *p*-tolyl groups give two pairs of doublets at δ 7.20 ppm and 7.29 ppm, and at δ 7.38 ppm and 8.42 ppm. The two NH protons exhibit two broad peaks in the region of δ 11.34–11.40 ppm and δ 11.89–11.96 ppm. The downfield shift of the NH peaks is in sharp contrast to the resonance at ~ –1-3 ppm of aromatic porphyrinic compounds.

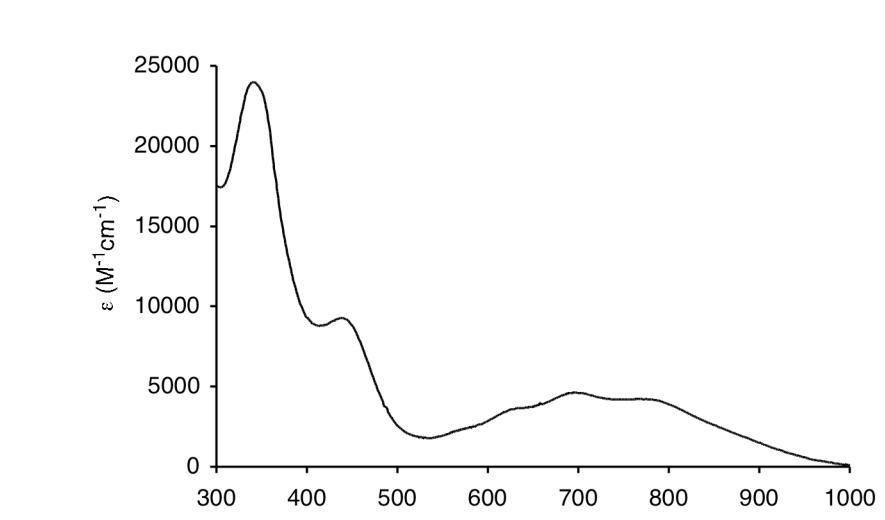


Figure IV.4. Absorption spectrum of **TDC** in toluene at room temperature.

LD-MS and FAB-MS analysis of **TDC** gave the molecule ion peak (*m/z* = 612.7 and 612.3447 respectively), consistent with the proposed structure (Scheme IV.4). Taken together, the absorption, mass spectrometric, and ^{1}H NMR spectroscopic data support the structure proposed for **TDC**.

The progressive reduction along the series from corrole to **TDC** to corrin alters the path of conjugation in the macrocycle. The reduction state of the pyrrolic rings that form the

A-D ring junction also change, including pyrrole–pyrrole (corrole), pyrroline-pyrrole (**TDC**), and pyrroline-pyrrolidine (corrin). On account of the interrupted path of conjugation and the reduction in rings A and C affording only 16 π-electrons, **TDC** is not aromatic. **TDC** in particular is a B,D-tetradehydrocorrin, where the 1-acetal substituent defines the A ring, and the B and D rings are dehydrogenated relative to corrin.[IV53] While a number of dehydrocorrins have been prepared (e.g., D-didehydrocorrin,[IV69] C,D-tetradehydrocorrin,[IV67,IV70] B,C-tetradehydrocorrin,[IV71] B,C,D-hexadehydrocorrin,[IV72] and A,B,C,D-octadehydrocorrin;[IV53b,IV55-IV59] each defined using IUPAC nomenclature[IV53]) either by direct synthesis or by reduction of an existing macrocycle,[IV73] to our knowledge there are no prior reports concerning the synthesis of B,D-tetradehydrocorrins.

B. Bacteriochlorins. Absorption Spectra. The absorption spectra of **H-BC** and **MeO-BC** in toluene are shown in Figure IV.5. Bacteriochlorin **H-BC** exhibits two Soret bands (B_y, B_x) at 351 and 374 nm, a weak $Q_x(0,0)$ band at 499 nm, and a strong $Q_y(0,0)$ band at 737 nm. Bacteriochlorin **MeO-BC** exhibits broadened Soret bands with peaks at 356 and 374 nm, a weak $Q_x(0,0)$ band at 511 nm, and a strong $Q_y(0,0)$ band at 732 nm. The overall absorption spectra of **H-BC** and **MeO-BC** resemble those of bacteriopheophytin *a* (the free base analogue of bacteriochlorophyll *a*) as well as synthetic, meso-substituted bacteriochlorins such as 5,15-diphenylbacteriochlorin[IV22] and 5,10,15,20-tetraphenylbacteriochlorin (λ_{abs} 356, 378, 520, and 742 nm; $\varepsilon_{742\ nm}$ = 130,000 $M^{-1}cm^{-1}$).[IV14,IV74] The bacteriochlorins exhibit a light green appearance in dilute solution in CH_2Cl_2 or toluene.

Fluorescence Properties. The fluorescence spectra and fluorescence quantum yields of **H-BC** and **MeO-BC** were collected in toluene at room temperature. The fluorescence

spectrum of each bacteriochlorin is dominated by a $Q_y(0,0)$ band with Stokes shift of ~ 7–9 nm (Figure IV.5). Measurements of the fluorescence quantum yield (Φ_f) using chlorophyll *a* (Φ_f = 0.325)[IV75] as a reference gave a value of 0.14 or 0.18 for **H-BC** or **MeO-BC**, respectively.

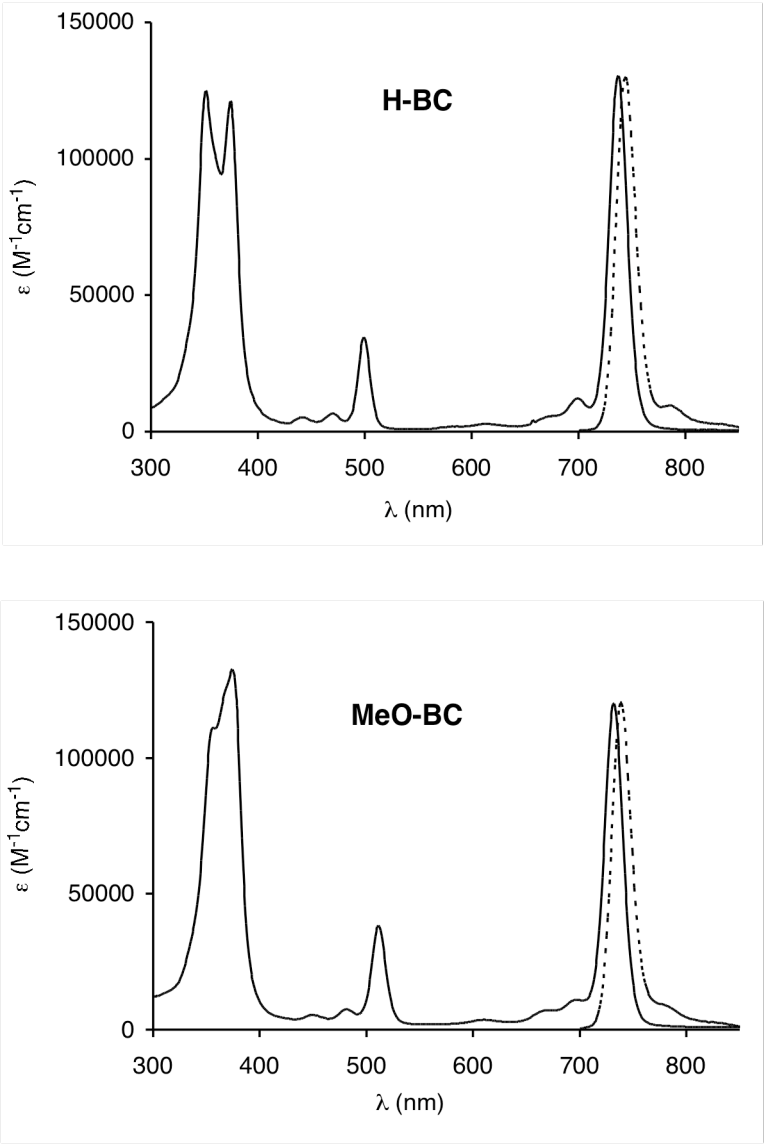


Figure IV.5. Absorption and emission spectra of **H-BC** and **MeO-BC** in toluene at room temperature.

The few data available concerning the fluorescence quantum yields (Φ_f) of free base bacteriochlorins are surprisingly varied. The free base analog of the naturally occurring bacteriochlorophyll *a* (bacteriopheophytin *a*) has Φ_f estimated to be 0.12[IV4] or 0.094,[IV76] whereas a 13[1]-deoxo-20-formyl-pyropheophorbide derivative gave Φ_f ~0.002.[IV36] Synthetic bacteriochlorins such as *meso*-tetrakis(3-hydroxyphenyl)bacteriochlorin[IV21] or 5,15-diphenylbacteriochlorin[IV22] gave Φ_f values of 0.11 or 0.14, respectively. A series of halogenated *meso*-tetraarylbacteriochlorins gave Φ_f = 0.068 (Ar = 2,6-difluorophenyl), 0.048 (Ar = 2-chlorophenyl), and 0.012 (Ar = 2,6-dichlorophenyl).[IV23] On the other hand, the dioxobacteriochlorin derived from octaethylporphyrin was reported to have Φ_f of 0.48.[IV77] A deeper understanding of the effects of substituents on the fluorescence properties of bacteriochlorins will require the examination of a larger and more systematic collection of bacteriochlorins, the synthesis of which may be enabled by the new synthesis described herein.

Laser Desorption Mass Spectrometry (LD-MS). Porphyrins typically give a strong molecule ion peak upon LD-MS analysis without requirement for use of a matrix.[IV78] LD-MS analysis of **H-BC** or **MeO-BC** gave the molecule ion peak (*m/z* = 580.1 or 550.0), consistent with the proposed structures (Scheme IV.4). The mass difference (~30) between **H-BC** and **MeO-BC** is consistent with the presence of the methoxy group in the former compound.

^{1}H NMR Spectra. The ^{1}H NMR spectra of **H-BC** and **MeO-BC** are readily assignable. In the case of **H-BC**, which has C_h symmetry, a relatively simple ^{1}H NMR spectrum is observed. A broad upfield peak (δ –1.96 ppm), singlet at δ 1.93 ppm, and singlet at δ 4.46 ppm are attributed to the two NH protons, the pair of geminal-dimethyl groups, and

the CH_2 groups of the pyrroline rings, respectively. The aryl hydrogens of the *p*-tolyl groups give a characteristic pair of doublets (J = 8.0 Hz) at δ 7.59 ppm and 8.13 ppm. A doublet (J = 2.0 Hz) at δ 8.73 ppm and two singlets at δ 8.81 and 8.86 ppm stem from the six protons (3, 5, 10, 13, 15, and 20 positions) about the perimeter of the bacteriochlorin.

Bacteriochlorin **MeO-BC** has generally similar features, but the presence of the 5-methoxy group results in C_s symmetry. Accordingly, the two NH protons (δ –1.90 and –1.78 ppm), the two pairs of geminal-dimethyl groups (δ 1.91 and 1.92 ppm), and the two methylene units in each of the reduced pyrrole rings (δ 4.40 and 4.41 ppm) are non-equivalent and appear as distinct singlets. Each *p*-tolyl group gives a pair of doublets (J = 8.0, 8.4 Hz in each case) in the region of δ 7.56–7.59 ppm and 8.09–8.15 ppm. The five peripheral protons (3, 10, 13, 15, and 20 positions) give rise to apparent singlets (δ 8.68, 8.78, and 8.81 ppm), a doublet (δ 8.94 ppm), and a partially overlapping peak at δ 8.67 ppm. Taken together, the absorption, fluorescence, LD-MS, and ^{1}H NMR spectroscopic data support the structures proposed for bacteriochlorins **H-BC** and **MeO-BC**.

Crystal Structure. To confirm the proposed structures, an X-ray structure was sought for one of the bacteriochlorins. Bacteriochlorin **MeO-BC** afforded good crystals, and the X-ray structure of a single crystal confirmed the expected 2,12-diaryl-5-methoxy-substitution pattern. The crystal structure of **MeO-BC** contains two molecules symmetry in the asymmetric unit (triclinic P-1). The structure of one of the molecules is shown in Figure IV.6. The characteristic structural features of **MeO-BC** include longer Cβ–Cβ bonds in the pyrroline rings [C7–C8 = 1.531(7) Å and C17–C18 = 1.534(8) Å] versus that in the pyrrole rings [C2–C3 = 1.376(7) Å; C12–C13 = 1.375(8) Å], slightly smaller Cα–N–Cα angles in

the pyrroline rings [C6–N2–C9 = 109.0(4)°; C16–N4–C19 = 109.2(4)°] than in the pyrrole rings [C1–N1–C4 = 110.6(4)°; C11–N3–C14 = 110.9(4)°], and location of the two inner NH moieties at the pyrrole rings. The location of the *p*-tolyl substituents at the 2- and 12-positions, relative to the geminal-dimethyl groups at the 8- and 18-positions, confirms the structure of the β-substituted dihydrodipyrrin–acetal **IV-1** and each of the precursors **IV-5**, **IV-6**, and **IV-8**. The X-ray structure of **MeO-BC** shows the characteristic hydroporphyrin macrocycle.

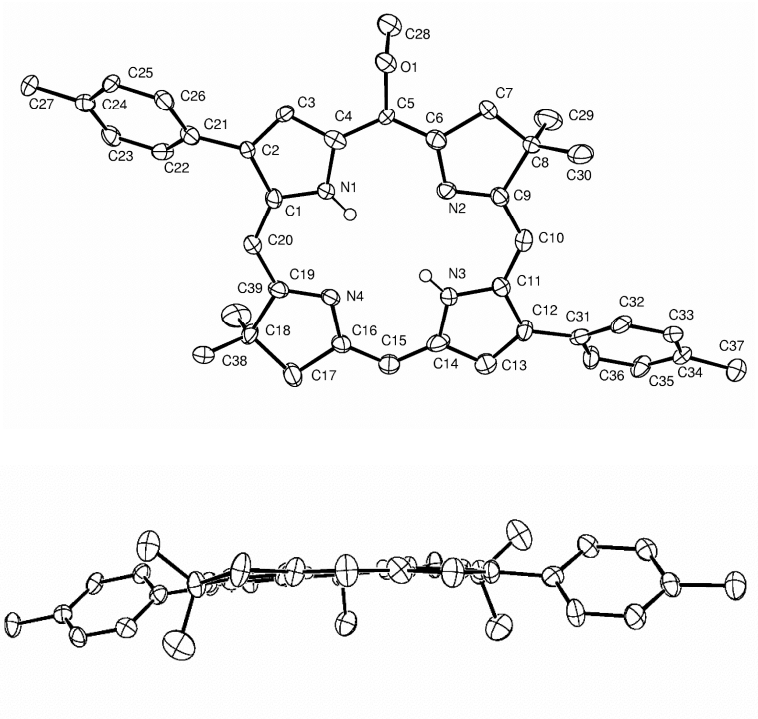


Figure IV.6. Crystal structure of bacteriochlorin **MeO-BC**.

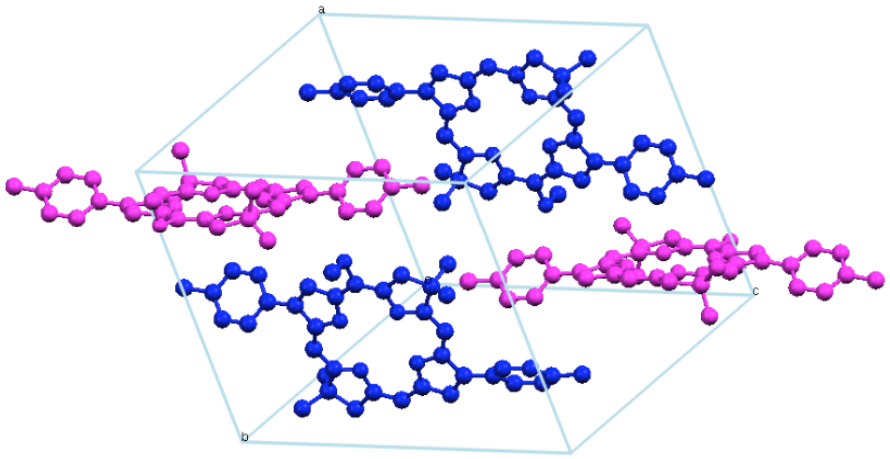
A very large number (~1000) of porphyrin single crystal X-ray structures have been reported.[IV79] By contrast, relatively few X-ray structures of bacteriochlorin single crystals have been determined (although a larger number of photosynthetic proteins containing bacteriochlorins have been characterized). The structures of bacteriochlorin single crystals

include several free base bacteriochlorins (*meso*-tetraphenylbacteriochlorin bearing four β-alkyl substituents,[IV33] *meso*-tetrabutylbacteriochlorin,[IV20] methyl bacteriopheophorbide *a*[IV80]), oxobacteriochlorins (β-substituted C-alkyl dioxobacteriochlorin,[IV35] the exomethylene analog of the dioxobacteriochlorin derived from octaethylporphyrin[IV27]), zinc bacteriochlorins (the dimer of Zn(II)-5-(2-pyridyl)-10,15,20-triarylbacteriochlorins,[IV17] the pyridine adduct of Zn(II) meso-tetraphenylbacteriochlorin[IV81]), and Ni(II) *ccc*-octaethylbacteriochlorin.[IV82,IV83] The general structural characteristics of **MeO-BC** are typical for free base bacteriochlorins.

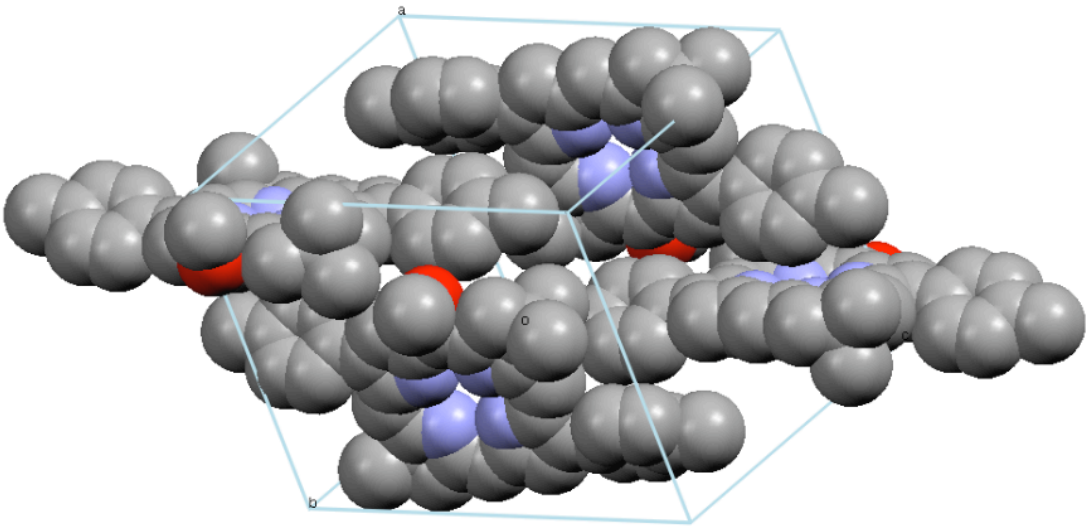
A number of hydroporphyrins are known to give substantial deformation of the macrocycle, forming a saddle-shaped conformation.[IV82] The deformation is most pronounced in porphyrinic architectures bearing a large number of substituents at the perimeter of the macrocycle, particularly with substituents at all meso and β-positions.[IV84] Ring deformation occurs to accommodate the steric hindrance of the substituents at the perimeter of the macrocycle. The ring deformations are accompanied by bathochromic spectral shifts and less positive oxidation potentials. Many hydroporphyrins typically have considerable steric congestion at the perimeter of the macrocycle; in addition, hydroporphyrins also are considered to have greater conformational flexibility than porphyrins. Even in hydroporphyrins derived from octaethylporphyrin, the deformation toward a saddle conformation is substantial.[IV82] By comparison, **MeO-BC** is nearly planar with only marginal bowing of the overall macrocycle, which may stem in part from the absence of vicinal β-substituents or flanking meso- and β-substituents. The pyrroline rings in **MeO-BC** each contain one geminal dimethyl group (rather than alkyl groups at each β-position as in naturally occurring bacteriochlorins), the 5-methoxy group is flanked by unsubstituted β-pyrrole and β-pyrroline units, and the *p*-tolyl groups have no flanking substituents. Each *p*-

tolyl group is rotated substantially toward coplanarity with the bacteriochlorin macrocycle, indicating the lack of steric hindrance at these sites.

A key objective is to learn how to control the solid-state packing pattern of the bacteriochlorins, in which case it may prove possible to exploit the assembled bacteriochlorins as a light-harvesting element in a variety of applications. Light-harvesting entails absorption of light followed by excited-state energy transfer. Electronic interactions between pigments resulting in altered electronic spectra (absorption, emission), altered properties of excited states, and efficient excited-state energy transfer depend both on the distance and orientation of interacting pigments. Accordingly, the following diagrams are provided to illustrate the packing arrangement of the bacteriochlorin molecules in the single crystal examined for **MeO-BC**.



(A)

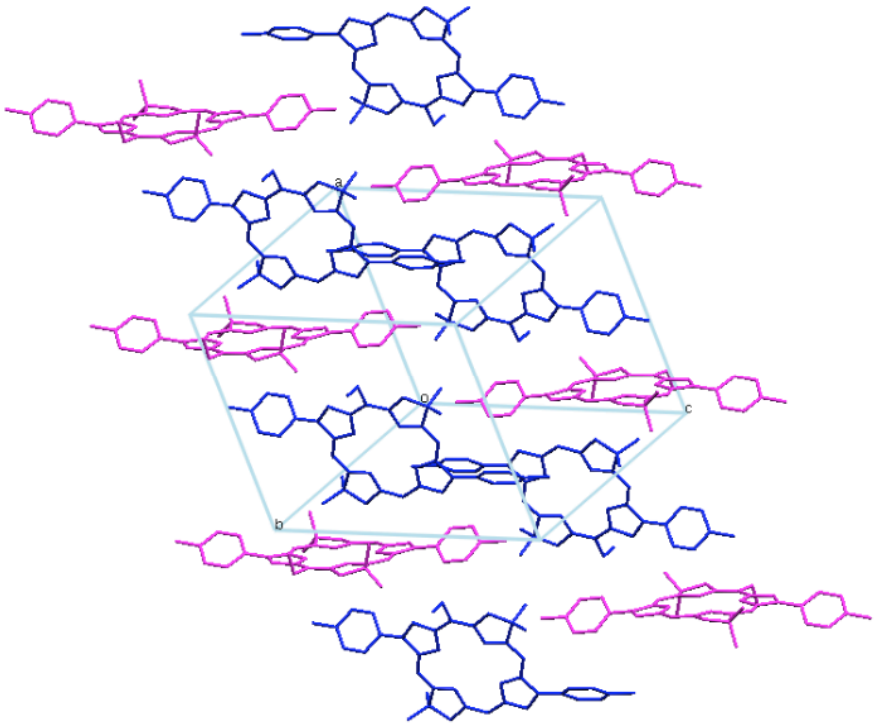


(B)

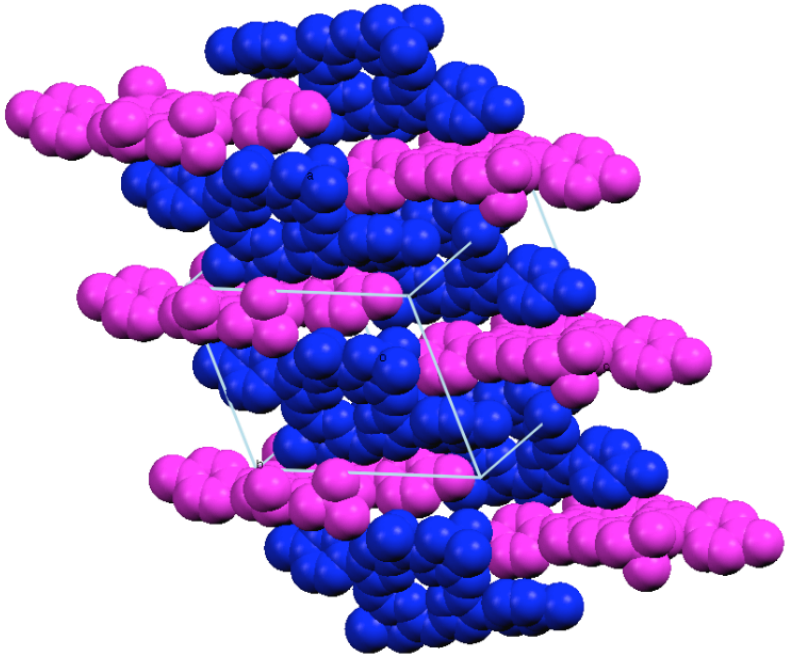
Figure IV.7. (A) Ball-and-stick display of the unit-cell packing of the two pairs of symmetry independent molecules of **MeO-BC**. Hydrogen atoms are omitted for clarity. (B) Space-filling model of the **MeO-BC** bacteriochlorin molecules.

Figure IV.7 shows the four bacteriochlorins in the unit cell, composed of two symmetry independent molecules. The long-wavelength Q_y band stems from an electronic transition that is polarized along the pyrrole-pyrrole N^{21}-N^{23} axis (orthogonal to the pyrroline-pyrroline N^{22}-N^{24} axis). Förster theory, for example, indicates that the value of the orientation term (κ^2) for resonance energy transfer depends on the orientation of the

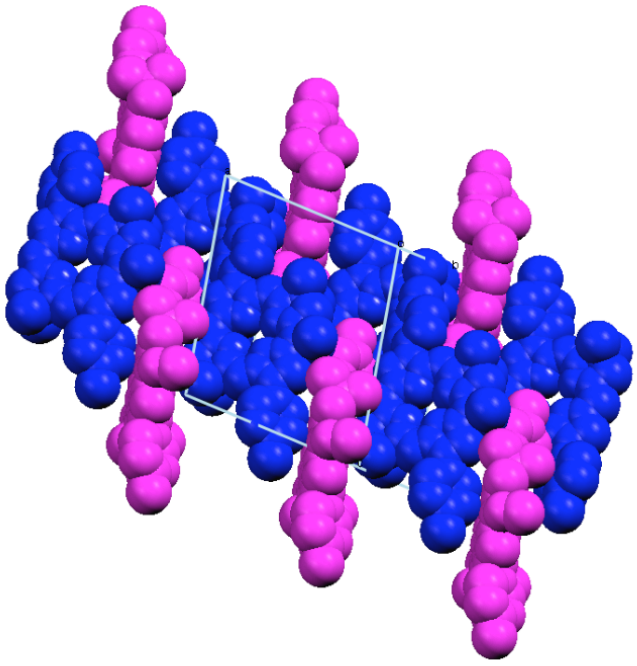
respective donor-acceptor transition dipole moments. The orientation term takes on values of 0 (perpendicular), 1 (parallel but not collinear), and a maximal value of 4 (collinear).[IV85] Note that for a given pair of symmetry equivalent molecules in the crystal lattice, the N^{21}-N^{23} axes are essentially parallel.



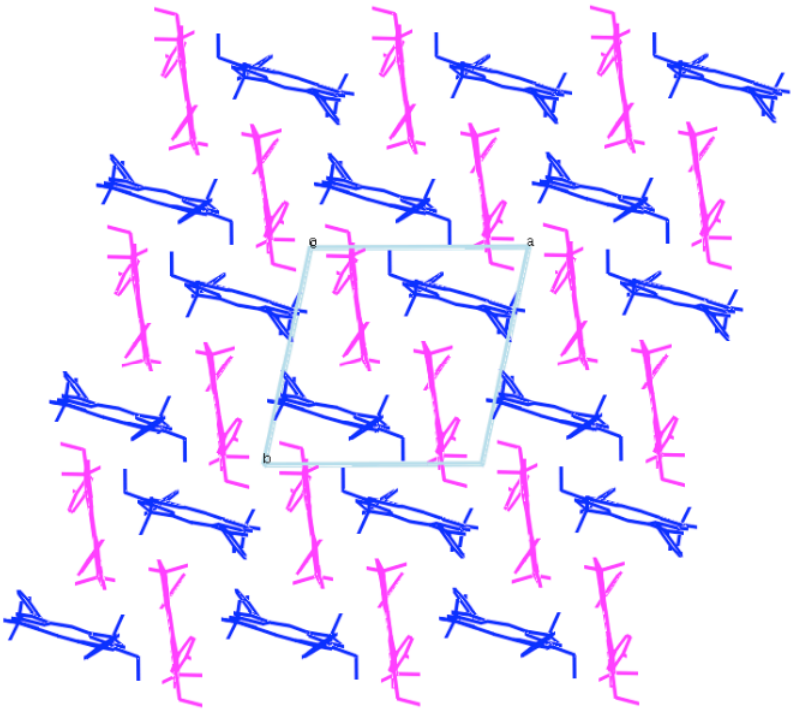
(A)



(B)



(C)



(D)

Figure IV.8. The packing diagram along the a axis of **MeO-BC** shows the two types of symmetry independent molecules. Hydrogen atoms are omitted for clarity. (A) Capped stick rendition with symmetry independent molecules in green or blue. (B) Space-filling rendition with symmetry independent molecules in green or blue. (C) Packing shown for three unit cells along the a axis and two unit cells along the b axis. (D) Expanded diagram showing the ab plane projected down the c axis.

Figure IV.8 shows the packing along the a axis of the bacteriochlorin molecules in the crystal lattice. The symmetry equivalent bacteriochlorins are positioned in a vertical stack along the a axis where each member is slightly slipped from the normal to the macrocycle

plane. Positioned between those bacteriochlorins in a vertical stack is a *p*-tolyl group of the other set of bacteriochlorin molecules. Note that the bacteriochlorin molecules of each type lie essentially in parallel planes with no rotation of the respective N^{21}-N^{23} axes. While not central to the issue of possible energy transfer, note also that the 2- and 12- *p*-tolyl groups are both rotated in the same direction toward coplanarity with the bacteriochlorin macrocycle. Also, the 5-methoxy groups in a given vertical stack of bacteriochlorins are aligned in the same direction, while those in adjacent stacks are aligned in opposite directions.

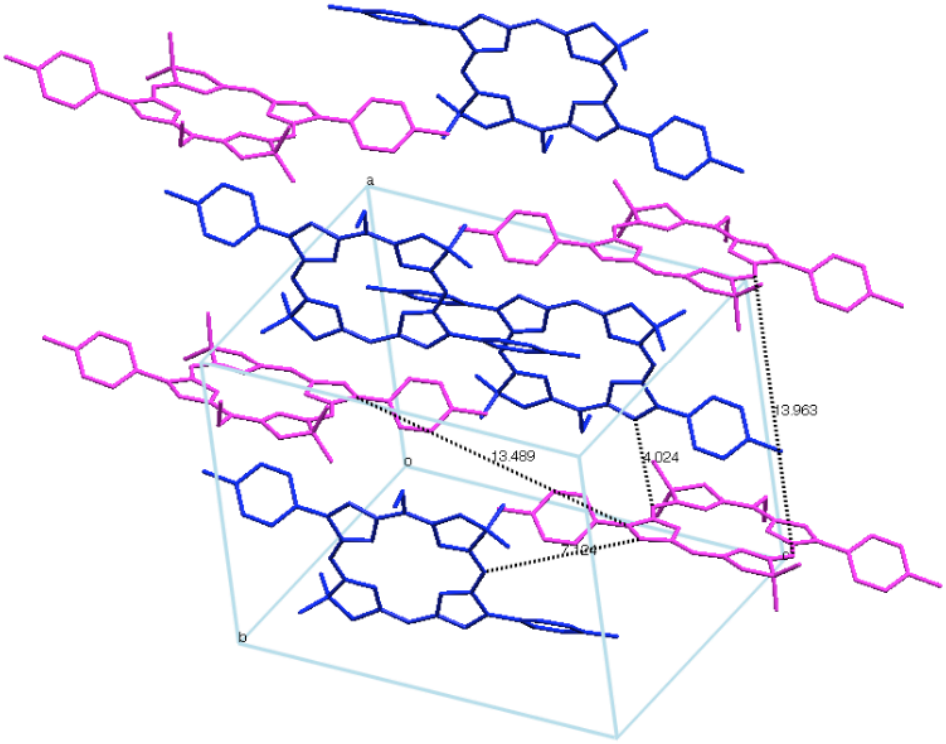


Figure IV.9. Selected distances between **MeO-BC** bacteriochlorin molecules. Hydrogen atoms are omitted for clarity. The bacteriochlorin (α) in the lower right-hand corner appears to have nearest distances with the bacteriochlorin (β) macrocycle of ~4.0 Å ($C20^{\alpha}$ – $C3^{\beta}$) and 7.1 Å ($C17^{\alpha}$ – $C10^{\beta}$). The nearest approach with the

symmetry equivalent bacteriochlorin appears to be ~13.5 Å ($C18^{\alpha}$ – $C12^{\alpha}$) and 13.96 Å ($C10^{\alpha}$ – $C10^{\alpha}$).

Figure IV.9 shows approximate distances between bacteriochlorins in the unit cell. The distance between the faces of two symmetry equivalent bacteriochlorins in a slipped vertical stack is ~14 Å (between respective C10 atoms), while that between lateral stacks is ~13.5 Å ($C18^{\alpha}$ – $C12^{\alpha}$). On the other hand, the nearest distances between symmetry independent bacteriochlorins are ~4 Å ($C20^{\alpha}$ – $C3^{\beta}$) and 7 Å ($C17^{\alpha}$ – $C10^{\beta}$).

For perspective, it is noteworthy that there are no hydrogen bond donors at the perimeter of the bacteriochlorin macrocycle. Thus, although each bacteriochlorin bears one methoxy group, which could serve as a hydrogen-bond acceptor, no complementary group is present in **MeO-BC**. In addition, the bacteriochlorin **MeO-BC** is a free base entity. The presence of a metal capable of apical coordination (e.g., zinc, four or five coordinate; magnesium, five or six coordinate) in metalloporphyrinic molecules often has a profound effect on the resulting crystal packing patterns. Indeed, naturally occurring bacteriochlorins typically are present in light-harvesting complexes as the magnesium (or zinc) chelate. It will be interesting to examine the crystals and study the light-harvesting properties of metal chelates of **H-BC** and **MeO-BC** as well as bacteriochlorin analogues containing groups situated at the perimeter of the macrocycle that are capable of apical coordination. It also will be of interest to determine whether the arrangement of respective donor-acceptor transition dipole moments can be controlled in a systematic manner through molecular design, and if so, to determine the effects of disparate orientations on energy transfer in the

crystalline assemblies. Such structures are now within the realm of possibility given the synthetic advances described in this thesis.

6. Stability. The synthetic bacteriochlorins (**H-BC** and **MeO-BC**) are quite robust. For example, the bacteriochlorins are stable upon standing on the bench top in solution exposed to air for more than 10 days, chromatography on silica in air in the presence of ambient lighting, dissolution in a variety of solvents (CH_2Cl_2, $CHCl_3$, THF, hexanes, toluene, DMF), or treatment with mild bases. Unlike bacteriochlorins derived from photosynthetic bacteria,[IV10-IV13] the synthetic bacteriochlorins do not undergo adventitious dehydrogenation upon routine handling.

IV.C. Conclusions.

A straightforward 8-step synthesis has been developed that affords two free base bacteriochlorins from simple precursors. Each bacteriochlorin bears two geminal-dimethyl groups to lock-in the bacteriochlorin reduction level, two β-substituents, and zero (**H-BC**) or one (**MeO-BC**) methoxy group in a meso-position. The self-condensation of dihydrodipyrrin–acetal **IV-1** proceeds under mild acid catalysis at room temperature without requirement for an oxidant to give the free base bacteriochlorins. A ring-contracted analogue (tetradehydrocorrin, **TDC**) was also obtained. The formation of the tetradehydrocorrin is understood in part by the recognition that a tetradehydrocorrin is to a bacteriochlorin what an octadehydrocorrin (a corrole tautomer) is to a porphyrin. The tetradehydrocorrin and bacteriochlorins lie at the same oxidation state ($4e^-/4H^+$ reduced) relative to the fully unsaturated corrinoid and porphyrinoid macrocycles. One key difference, however, is that the tetradehydrocorrin is not aromatic whereas the bacteriochlorins are aromatic

macrocycles. Workable quantities (10s of mg) of each macrocycle can be readily prepared. Mere adjustment of the concentrations of **IV-1** and $BF_3 \cdot OEt_2$ enable a given macrocycle (**H-BC**, **MeO-BC**, **TDC**) to be obtained in reasonable yield. The bacteriochlorins exhibit characteristic absorption and fluorescence properties. The bacteriochlorins are stable to a variety of reaction conditions. The design and synthesis approach described herein should provide ready access to bacteriochlorins bearing a variety of substituents, an essential feature for fundamental studies and diverse applications.

IV.D. Outlook: Potential Applications of Bacteriochlorins.

The discovery of a novel, concise pathway to stable bacteriochlorins opens the door to a number of potential applications. Here I provide an outline of a few of the possible applications of stable bacteriochlorins.

1. Medicinal Applications: (a) Photodynamic Therapy (PDT). Photodynamic therapy[IV87] is one of a number of current promising cancer treatments. Two essential components in PDT are a photosensitizer (in many cases porphyrin derivatives) and a light source (laser). The light source (laser) is readily available but the photosensitizer is in high demand. For example, one current photosensitizer (Photofrin®) exhibits relatively low efficiency and a number of side effects. The intrinsic limitations of Photofrin® (poorly defined mixture, unstable, and a weak absorption peak at about 630 nm) prompted development of second-generation photosensitizers with improved phototherapeutic properties. Currently a number of second-generation photosensitizers are undergoing various stages of clinical trails. Most are porphyrin derivatives, phthalocyanines, or chlorins.[IV88]

PDT applications require strong absorption in the red/near-IR, enabling use of red/near-IR light, which affords the best penetration of tissues by avoiding absorption by heme and other biological molecules. The ideal spectral region is 700-800 nm, where bacteriochlorins absorb strongly. Due to the strong absorption in the red/near-IR region, bacteriochlorin derivatives have been ideal photosensitizer candidates in PDT. Also, bacteriochlorophyll derivatives (bacteriochlorin) have been investigated for cancer therapy but these pigments are typically labile. Thus our synthetic work could provide the foundation for the development of stable bacteriochlorins of use as PDT drugs in the future.

(b) *Anti*-MDR (Multidrug Resistance) Drugs in Cancer Treatment. Cancer cells often develop strong resistance after a few treatments with a given anticancer drug. Sometimes the resistance encompasses even chemically unrelated anticancer drugs. This phenomenon is termed multidrug resistance (MDR).

Moor and co-workers reported that the tolyporphin derivatives possess varying degrees of anti-MDR activity.[IV7] Clearly the anti-MDR activity is accounted for by the structures of tolyporphins. Structurally, tolyporphins are mostly dioxobacteriochlorins containing β-linked C-glycosides. Our target molecules are structurally quite similar to tolyporphin analogues. The conversion of a bacteriochlorin to a dioxobacteriochlorin was quite practical in the total synthesis of a tolyporphin A derivative.[IV9] It is worthy to explore whether the bacteriochlorins described herein will have anti-MDR activity upon attachment of C-glycosyl unit to the macrocycle ring.

2. Molecule-Based Devices: (a) Molecular Wires. A wire is a device that conveys a signal or permits the flow of energy. The increasing interest in molecular scale devices has

focused attention on the synthesis of molecular wires.[IV89] In our group, various molecular photonic wires have been prepared that support excited-state energy migration. Our approach to molecular wires is inspired by the light harvesting complexes in photosynthesis, which comprise hundreds of pigments (chlorophylls) in a solid-state array. Molecular photonic wires absorb light and undergo excited-state energy transfer.

A boron-dipyrromethene dye provides an optical input at one end, a linear array of three zinc porphyrins is employed as a signal transmission element, and a free base porphyrin provides an optical output at the other end.[IV90] A molecular wire containing a perylene-monoimide (input unit), a zinc porphyrin (transmission unit), and a free base porphyrin (output unit) was recently prepared by our group.[IV91]

Because chlorins and bacteriochlorins are important photosynthetic pigments, these hydroporphyrins warrant consideration for use as components in molecular photonic wires. A molecular wire composed of bacteriochlorin, chlorin, and porphyrin pigments probably will be an attractive system in which to investigate ultrafast, efficient energy transfer.

(b) Molecule-Based Information Storage. An observation made in 1965 by Gordon Moore is that the number of transistors per square inch on integrated circuits has doubled every year since the integrated circuit was invented. In subsequent years, the pace slowed down a little, but data density has doubled approximately every 18 months, and this is the current definition of Moore's Law. While many experts expect Moore's Law to hold for the near future, it won't hold forever.

The current development roadmap for semiconductors calls for reducing the size of silicon transistors or simply driving existing transmission systems faster. This top-down approach to miniaturizing transistors and diode lasers is unlikely to be able to meet the ever-

increasing demand for higher-speed information processing and transmission. In exploring alternatives to the traditional top-down method of reducing the size of silicon transistors, some researchers realized that molecule-based devices could be built from the bottom-up with atomic precision.[IV92]

Nowadays, a number of molecules are under progress for the molecule based devices such as nanotubes,[IV93] quantum dots,[IV94] dendrimers,[IV95] porphyrins,[IV96] etc. In the Lindsey group, a molecular approach using porphyrin derivatives has been developed for information storage that has features superior to those of semiconductors.[IV96] The basic idea is to store information in distinct oxidation states of porphyrin molecules that are attached to an electroactive surface.

Bacteriochlorins are members of the porphyrin family that show similar electronic property but also are quite distinctive. Stable bacteriochlorins (or dioxobacteriochlorin analogues) could be good candidates in developing molecular based information storage, particularly because the bacteriochlorins are expected to have less positive oxidation potentials than porphyrins.

(c) Molecular-based solar cell. Photosynthesis is the process in nature by which green plants (chlorophylls) and photosynthetic bacteria (bacteriochlorophylls) use the energy from sunlight as an energy source. These reactions convert carbon dioxide and water into organic building block molecules used by the photosynthetic organism, which act as chemical factories that satisfy the plant needs.

Solar cells are designed to convert available light into electrical energy mimicking Nature's photosynthesis. Despite the rapid development of solar energy conversion in the laboratory, duplication of natural photosynthesis in the sense of efficiency is still far away.

The obvious goal of making solar cells is to mimic and reproduce the high photoconversion efficiency of the natural systems. Dye-sensitized photoelectrochemical cells (DSSCs) have emerged as a promising and interesting alternative to the established solid-state photovoltaic devices to generate cheap and feasible electricity from the sun.[IV97] A number of porphyrins have been employed as dye sensitizers in molecular-based solar cell devices.[IV98]

Chlorins and bacteriochlorins are fundamental materials for Nature's photosynthesis. However there are not many ways to prepare these pigments. Also naturally occurring chlorins and bacteriochlorins are quite sensitive to oxidation (or tautomerization). Stable chlorins and bacteriochlorins should open a number of opportunities for mimicking photosynthesis in Nature.

IV.E. Experimental Section.

General. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were collected at room temperature in $CDCl_3$. Absorption spectra were collected routinely. Melting points are uncorrected. Column chromatography was performed with flash silica or alumina (80–200 mesh). Bacteriochlorins were analyzed in neat form by laser desorption mass spectrometry (LD-MS) in the absence of a matrix. The $CHCl_3$ contained 0.8% ethanol.

Static Absorption and Emission. Static absorption and fluorescence measurements were performed as described previously.[IV86]

Molar Absorption Coefficients. The molar absorption coefficients were determined by dissolving a known quantity of each hydroporphyrin (~6 mg) in 100 mL of toluene. Then a known amount (~100 μL) of this solution was added to a quartz cuvette containing 3.0 mL of toluene. The absorption spectrum was recorded at room temperature.

Fluorescence Quantum Yields (Φ_f). The Φ_f values were determined with bacteriochlorin samples in toluene at room temperature. The maximal absorption of each sample was ~0.1 both in the B-band region and in the Q_y region, ensuring homogeneous illumination at λ_{exc} (373 nm) and avoidance of the inner filter effect by the Q_y band upon emission. Chlorophyll *a* was chosen as a reference compound because chlorophyll *a* has the following features: (i) significant absorption at 373 nm (blue shoulder of the B-band), (ii) emission in the red region (650-750 nm) with reasonable quantum efficiency (Φ_f = 0.325 in benzene[IV75]), (iii) ready availability, (iv) solubility in toluene, and (v) a sizable body of data is available concerning the fluorescence properties. All samples were degassed briefly prior to illumination. Excitation was performed using 0.5-mm excitation and emission slits (~2 nm spectral bandwidth), 1-nm steps, and 0.1 sec/nm integration time. Integrated

fluorescence emission spectra were obtained with correction for detection-system spectral response and temporal variation in light intensity. The integrated spectra were corrected for absorption and the resulting value was ratioed to the known Φ_f for chlorophyll *a* to determine the Φ_f values for the bacteriochlorins. Chlorophyll *a* was found to have $\Phi_f = 0.35$ in toluene. The bacteriochlorins also were examined with $\lambda_{exc} = 351$ nm, affording identical results as upon $\lambda_{exc} = 373$ nm (**H-BC**, $\Phi_f = 0.14$; **MeO-BC**, $\Phi_f = 0.18$).

Microscale Survey of Conditions for Bacteriochlorin-Forming Reactions. The condensations were carried out in 1-dram vials containing magnetic stir bars. A freshly prepared sample of dihydrodipyrrin–acetal **IV-1** (0.85–1.7 mg) was dissolved in a specific amount (0.50–2.0 mL) of a certain solvent. The condensation was initiated by adding the desired acid to the stirred reaction mixture at room temperature. The progress of the reaction was monitored by taking aliquots periodically from the reaction mixture via syringe and neutralizing with TEA, followed by absorption spectroscopy. In particular, for 5 mM reactions of **IV-1**, 10 μL aliquots were removed from the reaction vessel and diluted with 3 mL of CH_2Cl_2. The diluted solution was treated with one drop of TEA and the visible absorption spectrum was recorded. [In cases where the acid yielded a heterogeneous mixture (e.g., $InCl_3$, $Yb(OTf)_3$) or broadened absorption in the Q_y region, the 10 μL aliquots were passed through a 2-cm long pipet column (CH_2Cl_2/ethyl acetate). The first collected sample (green; eluted with CH_2Cl_2) and the second collected sample (pink; eluted with ethyl acetate) were separately concentrated and then diluted with 3 mL of CH_2Cl_2. The visible absorption spectrum was recorded with the diluted solutions.] The yield of bacteriochlorins was determined by the intensity of the Q_y band (above 700 nm, $\varepsilon = 120{,}000\ M^{-1}cm^{-1}$) measured from the apex to the middle point of base line, which lined from the blue edge to the red edge

of the band. This eliminated the contribution of the other components, which may have absorption band in the region of above 700 nm. In the case of insoluble acids, the dihydrodipyrrin–acetal **IV-1** and the insoluble acids were pre-weighed in the vial followed by addition of a microstir bar. The reactions were initiated by addition of the desired solvent. The reactions were monitored as described above.

Examination of Effects of Concentration (IV-1, $BF_3{\cdot}OEt_2$). Stock solutions of dihydrodipyrrin-acetal **IV-1** (100 mM, ~2 mL, ~50 mg of **IV-1**) and $BF_3{\cdot}OEt_2$ (1.0 M, 2 mL, 253 μL of $BF_3{\cdot}OEt_2$) in acetonitrile were prepared immediately before the reactions were carried out. Solutions of **IV-1** (5.0, 14, 22, 36, and 100 mM) in 0.5 mL of acetonitrile were prepared by taking a specific volume from the stock solution of **IV-1**. Similarly, the $BF_3{\cdot}OEt_2$ solutions (20, 74, 140, 280, and 1000 mM) in 0.5 mL of acetonitrile were prepared by taking specific volumes from the stock solution. Each condensation was carried out in a 1-dram vial containing acetal **IV-1** and $BF_3{\cdot}OEt_2$ in acetonitrile with stirring and exposure to air. The total volume of each reaction mixture was 1.0 mL. The condensation was initiated by adding the acid solution (0.50 mL) to the stirred acetal solution (0.50 mL) at room temperature. The progress of the reaction was monitored for 23 h by taking aliquots (5 μL) periodically from the reaction mixture via syringe. The aliquot was diluted into CH_2Cl_2 (3 mL) aliquot was neutralized with TEA (2-3 μL). The neutralized solution was examined by absorption spectroscopy. The total yield of bacteriochlorins (**H-BC** + **MeO-BC**) was determined by the intensity of the Q_y band (733-737 nm, ε = 120,000 $M^{-1}cm^{-1}$) measured from the apex to the middle point of the baseline drawn from the blue edge to the red edge of the band.

After stirring for 23 h, the reaction vials were treated with triethylamine (1-3 drops). The solvent was removed by evaporation, and the residue was chromatographed (silica). Elution with CH_2Cl_2/hexanes (1:1) gave two bacteriochlorins. The first product, **H-BC**, was non polar (R_f = 0.70). The second product, **MeO-BC**, was slightly more polar (R_f = 0.54). Subsequent elution of the column with CH_2Cl_2 gave tetradehydrocorrin **TDC**. Each isolated product was relatively pure. In each case, the isolated yield was determined by concentrating the product to dryness, then dissolving the resulting residue in a known volume of solvent (typically 3 mL). A sample from this solution was then analyzed by absorption spectroscopy using the measured molar absorption coefficients for each species: **H-BC** ($\varepsilon_{737\ nm}$ = 130,000 $M^{-1}cm^{-1}$); **MeO-BC** ($\varepsilon_{732\ nm}$ = 120,000 $M^{-1}cm^{-1}$); **TDC** ($\varepsilon_{431\ nm}$ = 24,000 $M^{-1}cm^{-1}$).

Alternatively, absorption spectroscopy of the isolated bacteriochlorins was used to determine the relative amount of product; the actual amount of bacteriochlorin produced was calculated on the basis of the spectroscopic yield of the mixture of bacteriochlorins (as described in the preceding paragraph) and the relative ratios of the two species. No such correction was possible for **TDC**; the yields of **TDC** refer to isolated material.

1-(1,1-Dimethoxymethyl)-3,3-dimethyl-7-(4-methylphenyl)-2,3-dihydrodipyrrin (IV-1). Following the procedure for preparing a β-substituted pyrrole,[IV39] a solution of **IV-8** (237 mg, 0.610 mmol) in anhydrous THF (3.00 mL) under argon was treated with NaOMe (165 mg, 3.05 mmol) and the mixture was stirred for 1 h at room temperature (first flask). In a second flask, $TiCl_3$ (8.6 wt % $TiCl_3$ in 28 wt % HCl, 4.56 mL, 3.05 mmol, 5.0 mol equiv) and H_2O (24 mL) were combined; NH_4OAc (18.8 g, 244 mmol) was added to buffer the solution to pH 6.0; and then THF (1.60 mL) was added. The solution in the first flask containing the nitronate anion of **IV-8** was transferred via a cannula to the buffered $TiCl_3$

solution in the second flask. The resulting mixture was stirred at room temperature for 6 h under argon. Then the mixture was extracted with ethyl acetate. The combined organic layers were washed with 5% aqueous $NaHCO_3$ and water, and then dried ($NaSO_4$). The solvent was removed under reduced pressure at room temperature. The crude product was passed through a short column [alumina, hexanes/ethyl acetate (2:1)] to afford a light yellow solid (57 mg, 28%): mp 104–105 °C; ^{1}H NMR δ 1.19 (s, 6H), 2.38 (s, 3H), 2.62 (s, 2H), 3.45 (s, 6H), 5.03 (s, 1H), 6.11 (s, 1H), 6.28–6.30 (m, 1H), 6.86–6.88 (m, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 10.80–10.90 (br, 1H); ^{13}C NMR δ 21.3, 29.3, 40.5, 48.3, 54.8, 103.0, 106.2, 109.3, 119.2, 124.7, 126.9, 128.7, 129.4, 134.2, 135.4, 160.1, 174.2; FAB-MS obsd 338.2020, calcd 338.1994; Anal. Calcd for $C_{21}H_{26}N_2O_2$: C, 74.52; H, 7.74; N, 8.28. Found: C, 74.46; H, 7.79; N, 8.08; λ_{abs} (CH_2Cl_2) 358.

Ethyl-3-(4-methylphenyl)prop-2-enoate (IV-2).[IV44] A solution of ethyl malonate potassium salt (27.0 g, 158 mmol) in water (20.0 mL) was treated with concentrated HCl (~35%, 15.0 mL) and the resulting mixture was stirred for 10 min at room temperature. The mixture was extracted with ether. The extracts were washed with water, dried (Na_2SO_4), and concentrated to give a colorless oil (16.7 g, 79%), which was used without characterization.[IV43] A solution of *p*-tolualdehyde (11.6 g, 96.9 mmol) and *mono*-ethyl malonate (16.7 g, 126 mmol) in pyridine (39.2 mL, 485 mmol) containing piperidine (958 μL, 9.69 mmol) was refluxed for 8 h under argon. The reaction mixture was cooled to room temperature, quenched with 2 N HCl (~250 mL), and extracted with ether. The extracts were washed with water, base ($NaHCO_3$), and water. The organic solution was dried (Na_2SO_4), concentrated, and chromatographed (silica, CH_2Cl_2) to give a colorless oil (14.6 g, 79%): ^{1}H NMR δ 1.33 (t, *J* = 7.2 Hz, 3H), 2.37 (s, 3H), 4.26 (q, *J* = 7.2 Hz, 2H), 6.39 (d, *J* = 15.8 Hz,

1H), 7.18 (d, J = 8.2 Hz, 2H), 7.42 (d, J = 8.2 Hz, 2H), 7.66 (d, J = 15.8 Hz, 1H); ^{13}C NMR δ 14.5 21.6, 60.6, 117.4, 128.2, 129.8, 131.9, 140.8, 144.8, 167.4; Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.76; H, 7.44.

3-(Ethoxycarbonyl)-4-(4-methylphenyl)pyrrole (IV-3).[IV45] A suspension of TosMIC (15.7 g, 80.5 mmol) and **IV-2** (14.6 g, 76.7 mmol) in dry ether/DMSO (2:1) (154 mL) was added dropwise under argon to a stirred suspension of NaH (2.39 g, 99.7 mmol) in ether (70 mL). The mixture started to reflux due to the exothermic reaction. After 3 h, water (200 mL) was carefully added to the mixture and the aqueous phase was extracted with ether and CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), concentrated, and chromatographed [silica, CH_2Cl_2/ethyl acetate (9:1)] to give a light brown solid (13.1 g, 74%): mp 154-155 °C (lit.[IV45] mp 135–137 °C); ^{1}H NMR δ 1.25 (t, J = 7.2 Hz, 3H), 2.36 (s, 3H), 4.22 (q, J = 7.2 Hz, 2H), 6.75–6.77 (m, 1H), 7.16 (d, J = 7.8 Hz, 2H), 7.38 (d, J = 7.8 Hz, 2H), 7.46–7.48 (m, 1H), 8.38–8.54 (br, 1H); ^{13}C NMR δ 14.5, 21.4, 59.8, 113.9, 118.3, 125.4, 126.8, 128.6, 129.4, 132.0, 136.3, 165.2; Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.11; H, 6.59; N, 6.12.

3-(4-Methylphenyl)pyrrole (IV-4).[IV46-IV48] Following a standard procedure,[IV39] a mixture of **IV-3** (6.81 g, 29.7 mmol) and ethylene glycol (76.0 mL) in a 250-mL Claisen flask was flushed with argon for 10 min, and then powdered NaOH (3.05 g, 76.2 mmol) was added. The flask was placed in an oil bath at 120 °C and the oil bath temperature was raised to 160 °C. After 2.5 h, the flask was cooled to room temperature and 10% aqueous NaCl (150 mL) was added. The aqueous layer was extracted with CH_2Cl_2. The organic layers were collected, washed with 10% aqueous NaCl, dried (Na_2SO_4), concentrated, and chromatographed (silica, CH_2Cl_2) to give a light brown solid (3.33 g, 71%): mp 92–93 °C

(lit.[IV46] mp 93–95 °C; lit.[IV47] mp 80–82 °C; lit.[IV48] mp 85–87 °C); ^{1}H NMR δ 2.34 (s, 3H), 6.51–6.54 (m, 1H), 6.82–6.84 (m, 1H), 7.05–7.08 (m, 1H), 7.15 (d, J = 7.8 Hz, 2H), 7.43 (d, J = 7.8 Hz, 2H), 8.15–8.32 (br, 1H); ^{13}C NMR δ 21.3, 106.7, 114.4, 119.0, 125.1, 125.4, 129.5, 133.1, 135.2; FAB-MS obsd 157.0885, calcd 157.0891 ($C_{11}H_{11}N$).

2-Formyl-3-(4-methylphenyl)pyrrole (IV-5). Following a standard procedure,[IV39] a solution of **IV-4** (472 mg, 3.00 mmol) in DMF (0.96 mL) and CH_2Cl_2 (30 mL) under argon was cooled to 0 °C and then $POCl_3$ (340 μL, 3.60 mmol) was added dropwise. After 1 h, the flask was warmed to room temperature and stirred overnight (~18 h). The reaction was quenched at 0 °C with 2.5 M aqueous NaOH (25 mL). The mixture was poured into water (50 mL), extracted with CH_2Cl_2, and the combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed [silica, CH_2Cl_2/ethyl acetate (9:1)] to give a brown solid. ^{1}H NMR spectroscopy showed two regioisomers in ~13:1 ratio. Cooling of the solution (ethyl acetate/hexanes) at ~ –16 °C resulted in precipitation of an orange solid, which proved to be a single regioisomer (354 mg, 64%): mp 149–150 °C; ^{1}H NMR δ 2.41 (s, 3H), 6.42–6.44 (m, 1H), 7.10–7.13 (m, 1H), 7.26 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 9.63–9.64 (m, 1H), 9.52–9.78 (br, 1H); ^{13}C NMR δ 21.4, 111.6, 126.2, 128.9, 129.3, 129.7, 130.9, 137.7, 137.9, 180.2; FAB-MS obsd 186.0907, calcd 186.0919 ($C_{12}H_{11}NO$).

2-(2-Nitroethyl)-3-(4-methylphenyl)pyrrole (IV-6). Following a standard procedure,[IV39] a mixture of **IV-5** (3.93 g, 21.2 mmol), KOAc (2.29 g, 23.3 mmol), methylamine hydrochloride (1.72 g, 25.4 mmol), and nitromethane (190 mL) under argon was stirred at room temperature. The mixture slowly became orange and yielded an orange-red precipitate. After stirring for 2.5 h, TLC showed the appearance of a new component and

the disappearance of **IV-5**. The reaction was quenched with brine, extracted with ethyl acetate, and the organic layers were dried (Na_2SO_4) and concentrated. The residue was dissolved in THF/MeOH (210 mL, 3:7) at 0 °C. $NaBH_4$ (2.41 g, 63.6 mmol) was added in portions at 0 °C. Then the mixture was stirred for 0.5 h at room temperature. The reaction mixture was neutralized with acetic acid (pH = 7), then water (150 mL) was added and the mixture was extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried (Na_2SO_4), concentrated, and chromatographed [silica, hexanes/ethyl acetate (3:1)] to give a light brown solid (3.61 g, 74%): mp 81–82 °C; ^{1}H NMR δ 2.37 (s, 3H), 3.44 (t, *J* = 6.8 Hz, 2H), 4.54 (t, *J* = 6.8 Hz, 2H), 6.27–6.29 (m, 1H), 6.73–6.75 (m, 1H), 7.20 (d, *J* = 8.2 Hz, 2H), 7.23 (d, *J* = 8.2 Hz, 2H), 8.19–8.36 (br, 1H); ^{13}C NMR δ 21.2, 24.4, 75.2, 109.6, 117.7, 121.9, 123.2, 128.0, 129.5, 133.4, 135.8; FAB-MS obsd 230.1055, calcd 230.1055 ($C_{13}H_{14}N_2O_2$).

1,1-Dimethoxy-4-methyl-3-penten-2-one (IV-7). The following procedure employs the approach described by Tiecco *et al.*[IV50] but at 80-times larger scale and with altered workup. A mixture of mesityl oxide (18.0 mL, 160 mmol), diphenyl diselenide (5.00 g, 16.0 mmol), and ammonium peroxydisulfate (109 g, 480 mmol) in anhydrous MeOH (1.20 L) was refluxed for 4 h under argon. The progress of the reaction was monitored by TLC. The reaction mixture was poured into water (1.20 L) and extracted with $CHCl_3$. The organic layer was washed with water, dried (Na_2SO_4), and concentrated to give a dark brown oil. Bulb-to-bulb distillation of the oil at 50 °C/0.04–0.05 mm Hg gave a yellow oil. The ^{1}H NMR spectrum of the oil showed the presence of unknown impurities. The oil was chromatographed [silica, hexanes/ethyl acetate (3:1)] to give a pale yellow oil (7.37 g, 29%). Analytical data were consistent with the literature[IV50] for the title compound: ^{1}H NMR δ 1.96

(d, J = 1.2 Hz, 3H), 2.21 (d, J = 1.2 Hz, 3H), 3.42 (s, 6H), 4.49 (s, 1H), 6.36–6.38 (m, 1H); ^{13}C NMR δ 21.3, 28.2, 54.5, 104.5, 119.1, 160.2, 194.2; FAB-MS obsd 159.1020, calcd 159.1021 ($C_8H_{14}O_3$) $[M + H]^+$. Note: The use of reagent grade methanol resulted in a slow reaction (required >26 h for completion) versus the relatively fast reaction (<4 h) when anhydrous methanol was used.

6-[3-(4-Methylphenyl)pyrrol-2-yl]-1,1-dimethoxy-4,4-dimethyl-5-nitro-2-hexanone (IV-8). Following a general procedure,[IV38,IV39] CsF (1.82 g, 12.0 mmol, 3.00 mol equiv, freshly dried by heating to 100 °C under vacuum for 1 h and then cooling to room temperature under argon) was placed in a flask under argon. A mixture of **IV-6** (921 mg, 4.00 mmol) and acetal **IV-7** (6.33 g, 40.0 mmol, 10 mol equiv) in dry acetonitrile (40 mL) was transferred by cannula to the flask containing CsF. The mixture was heated at 65 °C for 1.2 h, whereupon TLC analysis showed the reaction to be complete. The reaction mixture was filtered through a bed of silica (ethyl acetate) and the filtrate was concentrated. The resulting oil was subjected to bulb-to-bulb distillation at room temperature/0.04–0.05 mmHg for 3 h, affording recovery of the acetal **IV-7** (~2 g) as the distillate and the desired product in the crude undistilled residue. Purification of the residue by column chromatography [alumina, ethyl acetate/hexanes (1:3)] gave a light brown solid (626 mg, 40%): mp 98–100 °C; ^{1}H NMR δ 1.09 (s, 3H), 1.19 (s, 3H), 2.37 (s, 3H), 2.53, 2.71 (AB, ^2J = 18.8 Hz, 2H), 3.21 (ABX, ^3J = 2.4 Hz, ^2J = 15.4 Hz, 1H), 3.39 (ABX, ^3J = 11.6 Hz, ^2J = 15.4 Hz, 1H), 3.41 (s, 6H), 4.34 (s, 1H), 5.22 (ABX, ^3J = 2.4 Hz, ^3J = 11.6 Hz, 1H), 6.22–6.24 (m, 1H), 6.66–6.68 (m, 1H), 7.19 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 8.06–8.14 (br, 1H); ^{13}C NMR δ 21.3, 24.1, 24.3, 25.3, 36.8, 45.1, 55.2, 55.2, 95.0, 104.7, 109.5, 117.7, 122.1, 123.7,

128.4, 129.4, 133.5, 135.6, 203.7; Anal. Calcd for $C_{21}H_{28}N_2O_5$: C, 64.93; H, 7.27; N, 7.21. Found: C, 65.02; H, 7.34; N, 7.14.

Conversion of IV-1 → Tetrahydroporphyrins.

Preparation to Obtain MeO-BC (5 mM acetal IV-1 and 50 mM $BF_3{\cdot}OEt_2$): A solution of **IV-1** (93 mg, 0.27 mmol) in CH_3CN (54 mL) was treated with neat $BF_3{\cdot}OEt_2$ (350 μL, 2.7 mmol, 50 mM). The reaction mixture was stirred at room temperature without deaeration for 15 h. The reaction was monitored by absorption spectroscopy. TEA (1.0 mL) was added to the reaction mixture. The reaction mixture was concentrated and the residue was dissolved in CH_2Cl_2. The solution was washed (water), dried (Na_2SO_4), concentrated and chromatographed [silica, CH_2Cl_2/hexanes (1:1)]. The first band (green) was collected (**H-BC**, 8.1 mg, 11%) and then the second band (green) was collected (**MeO-BC**, 24.4 mg, 30%).

Preparation to Obtain TDC (11 mM acetal IV-1 and 10 mM $BF_3{\cdot}OEt_2$): $BF_3{\cdot}OEt_2$ (18 μL, 0.14 mmol) in CH_3CN (1.6 mL) was slowly added to a solution of **IV-1** (50 mg, 0.15 mmol) in CH_3CN (12 mL). The reaction mixture was stirred at room temperature without deaeration for 24 h. TEA (20 μL, 0.14 mmol) was added to the reaction mixture. The reaction mixture was concentrated and the residue was chromatographed [silica, CH_2Cl_2/hexanes (1:1)]. The first green band was collected (**H-BC**, <<0.1 mg, <<0.1%). Some pinkish material then eluted (not identified). The second green band was collected (**MeO-BC**, 2.7 mg, 6.3%). Further elution with CH_2Cl_2 afforded the third dark green band (**TDC**, 30.0 mg, 67%).

Preparation to Obtain H-BC (18 mM acetal IV-1 and 140 mM $BF_3{\cdot}OEt_2$): A solution of **IV-1** (50 mg, 0.15 mmol) in CH_3CN (8.3 mL) was treated with $BF_3{\cdot}OEt_2$ (150

μL, 1.2 mmol). The reaction mixture was stirred at room temperature without deaeration for 24 h. TEA (167 μL, 1.2 mmol) was added to the reaction mixture. The reaction mixture was concentrated and the residue was chromatographed [silica, CH_2Cl_2/hexanes (1:1)]. The first green band was collected (**H-BC**, 20 mg, 49%). The second green band was collected (**MeO-BC**, 0.8 mg, 2%). Further elution with CH_2Cl_2 did not afford any isolated **TDC**.

Data for **8,8,18,18-tetramethyl-2,12-bis(4-methylphenyl)bacteriochlorin (H-BC):** ^{1}H NMR δ –2.00 (br, 2H), 1.93 (s, 12H), 2.61 (s, 6H), 4.56 (s, 4H), 7.59 (d, J = 8.0 Hz, 4H), 8.13 (d, J = 8.0 Hz, 4H), 8.73 (d, J = 2.0 Hz, 2H), 8.81 (s, 2H), 8.86 (s, 2H); λ_{abs} (toluene)/nm 351 (ε = 130,000 $M^{-1}cm^{-1}$), 374 (120,000), 499 (35,000), 737 (130,000); λ_{em} (λ_{exc} 499 nm) 744 nm, Φ_f = 0.14; LD-MS obsd 550.0; FAB-MS obsd 550.3068, calcd 550.3096 ($C_{38}H_{38}N_4$).

Data for **5-Methoxy-8,8,18,18-tetramethyl-2,12-bis(4-methylphenyl)bacteriochlorin (MeO-BC):** ^{1}H NMR δ –1.90 (br, 1H), –1.78 (br, 1H), 1.91 (s, 6H), 1.92 (s, 6H), 2.61 (s, 6H), 4.40 (s, 2H), 4.41 (s, 2H), 4.49 (s, 3H), 7.58 (d, J = 8.0 Hz, 4H), 8.10 (d, J = 8.0 Hz, 2H), 8.14 (d, J = 8.0 Hz, 2H), 8.66–8.69 (m, 2H), 8.78 (s, 1H), 8.81 (s, 1H), 8.94–8.95 (m, 1H); λ_{abs} (toluene)/nm 356 (ε = 110,000 $M^{-1}cm^{-1}$), 374 (130,000), 511 (39,000), 732 (120,000); λ_{em} (λ_{exc} 511 nm) 739 nm, Φ_f = 0.18; LD-MS obsd 580.1; FAB-MS obsd 580.3232, calcd 580.3202 ($C_{39}H_{40}N_4O$).

Data for **1*H*-22*H*-24*H*-7,8,17,18-Tetradehydro--1-(1,1-dimethoxymethyl)-3,3,13,13-tetramethyl-7,17-bis(4-methylphenyl)corrin (TDC):** ^{1}H NMR δ 1.04 (s, 3H), 1.24 (s, 3H), 1.26 (s, 3H), 1.33 (s, 3H), 1.82, 2.49 (AB, ^2J = 13.2 Hz, 2H), 2.38 (s, 3H), 2.42 (s, 3H), 2.65, 2.71 (AB, ^2J = 18.8 Hz, 2H), 3.37 (s, 3H), 3.40 (s, 3H), 4.26 (s, 1H), 5.42 (s,

1H), 5.43 (s, 1H), 6.02 (s, 1H), 6.24–6.25 (m, 1H), 6.57–6.58 (m, 1H), 7.20 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 8.42 (d, J = 8.0 Hz, 2H), 11.34–11.40 (br, 1H), 11.89–11.96 (br, 1H); λ_{abs} (toluene)/nm 343 (ε = 24,000 $M^{-1}cm^{-1}$), 437 (7,400), 640 (4,300), 703 (5,400); LD-MS obsd 612.7; FAB-MS obsd 612.3447, calcd 612.3464 ($C_{40}H_{44}N_4O_2$).

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(IV53) The nomenclature of dehydrogenated corrinoids is not yet fully systematized. Many workers would refer to **TDC** as a didehydrocorrin because two double bonds have been introduced relative to the corrin; by the same token, a corrole would be a tetradehydrocorrin. In IUPAC recommendations, **TDC** is a tetradehydrocorrin ($4e^-$ /$4H^+$ removed from the corrin), and corrole is an octadehydrocorrin ($8e^-$/$8H^+$ removed from corrin).[a] A clear review concerning octadehydrocorrins is provided by Genokhova et al.[b] **TDC** could be termed a tetrahydrocorrole, perhaps clarifying the similarity with bacteriochlorins, but because the macrocycle has an interrupted path of conjugation and is not aromatic, we have chosen to name **TDC** as a dehydrogenated corrin rather than as a hydrogenated corrole. (a) *Pure Appl. Chem.*

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