ABSTRACT

ZHANG, SHAOFEI. Synthesis of Bacteriochlorins and the Full Skeleton of Bacteriochlorophylls. (Under the direction of Professor Jonathan S. Lindsey.)

Bacteriochlorins, the core macrocycle ring of natural bacteriochlorophylls, are characterized by their ability to absorb near infrared light (700 – 900 nm), which makes them attractive candidates in variety of photophysical studies and applications. The previously established de novo synthesis, which relies on the acid-catalyzed self-condensation of dihydrodipyrrin–acetal, provides access towards diverse bacteriochlorins, but has its limitations. This dissertation describes the development of new strategies for bacteriochlorin synthesis. Firstly, a route towards previously unknown tetra-alkyl bacteriochlorins (e.g., alkyl = Me, or –CH₂CO₂Me) is established (Ch. 2). Secondly, explorations of synthetic approaches to unsymmetrically substituted bacteriochlorins through electrocyclic reactions of linear tetrapyrrole intermediates are described. Four new unsymmetrically substituted bacteriochlorins and one new tetradehydrocorrin were produced, albeit in low yields (Ch. 3). Thirdly, a new method to construct bacteriochlorin macrocycle with concomitant Nazarov cyclization to form the annulated isocyclic ring, is established. Five new bacteriochlorins, which are closely anlogues of bacteriochlorophyll a, bearing various substituents (alkyl/alkyl, aryl, and alkyl/ester) at positions 2 and 3 and 13² carboalkoxy groups (R = Me or Et) were constructed in 37–61% yield from the bilin analogues (Ch. 4). Taken together, these studies expand the scope of available bacteriochlorins for fundamental studies and applications, and provide the synthetic pathway to full skeleton of bacteriochlorophylls.
Synthesis of Bacteriochlorins and the Full Skeleton of Bacteriochlorophylls

by
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DEDICATION

To my wife Kaimeng

and my son Jason
Shaofei Zhang was born in Baoji, China in 1988. He received his B.Sc. degree in chemistry from Peking University, in 2011, after conducting research under the guidance of Professor Yuguo Ma and Jianbin Huang. Upon entering North Carolina State University in 2011 as a graduate student in chemistry, he joined the laboratory of Professor Jonathan S. Lindsey where he has been working on synthesis of tetrapyrrole macrocycles.
ACKNOWLEDGMENTS

The heart and beauty of synthesis chemistry lies in its creative nature. The request to the designed molecule is a long-term adventure filled with challenges, frustration, joys and opportunities. Luckily, I am not alone in this journey. First, I would like to thank my advisor and mentor, Dr. Jonathan Lindsey, for his guidance, encouragement and support. Besides, I would like to thank every faculty and staffs that I worked with in our chemistry department, for their teaching, assistance and collaboration. Also, I am grateful to work with all past and present members in our lab. I will treasure our friendship forever. At last, there are no words to express how grateful I am and how much I love for my family.
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CHAPTER I

General Introduction of Bacteriochlorins

1. Bacteriochlorophylls and Bacteriochlorins

Tetrapyrrole macrocycles play central roles in living life. The most famous examples are heme B (the red blood pigment), chlorophyll a (the green pigment in photosynthetic systems of plant), bacteriochlorophyll a (the green pigment in anoxygenic bacterial photosynthetic systems), and vitamin B_{12} (the red pigment essential for biochemically important rearrangement reactions). The basis for their biochemical or photophysical functions is their macrocycle structures and central metal ions. In heme, the macrocycle takes the form of an unsaturated 18\pi aromatic porphyrin. In chlorophyll a or bacteriochlorophyll a, the macrocycle framework is chlorin or bacteriochlorin, which have one (in chlorin) or two (in bacteriochlorin) reduced pyrrole ring(s) saturated at the \beta-position(s) compared to their parent porphyrin. Vitamin B_{12} is a highly reduced corrin that precisely adjusts the reactivity at the central cobalt ion. Porphyrin, chlorin, bacteriochlorin, and corrin are four mainly representatives of skeletons for the class of porphinoid natural products (Figure 1.1). Nomenclature about numbering C-atoms about the peripheral macrocycle and labeling of pyrrole/pyrroline rings are also illustrated in Figure 1.1.
Photosynthesis is crucial for life on the earth, since it provides food and oxygen and is the basis for most energy resource (e.g. fossil fuels). Photosynthetic organisms have different strategies to convert sunlight into chemical energy, relying on the participation of photosynthetic pigments. In order to absorb light, nature has chosen chlorophylls (harvesting visible light in plants) and bacteriochlorophylls (harvesting infrared light in anoxygenic bacteria) as pigments for photosynthesis. The chlorin macrocycle provides the skeleton for chlorophyll $a$ and $b$, and the bacteriochlorin macrocycle provides the skeleton for bacteriochlorophyll $a$. The increased saturation of the macrocycle leads to stronger
absorption in longer wavelength regions. Thus, bacteriochlorophylls are distinguished by their intense long-wavelength absorption band ranging from 700 nm to 1000 nm.\textsuperscript{2-4} The absorption spectra of a porphyrin (magnesium octaethylporphyrin), chlorophyll \textit{a} and \textit{b}, and bacteriochlorophyll \textit{a} are compared in Figure 1.1.\textsuperscript{5} Porphyrin strongly absorbs in the blue spectra region (B band) and only moderately in the red region around 620 nm (Q\textsubscript{y} band). Chlorophylls \textit{a} and \textit{b} display a relative strong Q\textsubscript{y} absorption at the red region (600 – 700 nm) while bacteriochlorophyll \textit{a} shows intense NIR (near-infrared region) absorption at 772 nm. The ability to absorb NIR light is important for organisms (e.g. green or purple bacteria) that perform photosynthesis, so that they can live in deep water where little light penetrates. In LH1 and LH2 complexes (two major type pf bacteriochlorophyll \textit{a}-containing photosynthetic systems), aggregates of pigments and pigment-protein interactions extensively tune broad absorption bands to around 800, 850 (LH1) and 875 nm (LH2).\textsuperscript{3,4}

\textbf{Figure 1.2.} Absorption spectra of magnesium octaethylporphyrin (blue line), chlorophyll \textit{a} (green) and \textit{b} (dashed green), and bacteriochlorophyll \textit{a} (red).\textsuperscript{5}
The name “bacteriochlorophylls (BChl)” refers to the pigments that were isolated from various anoxygenic photosynthetic bacteria, of which early studies were reviewed by C. B. van Neil in 1944. Figure 1.3 shows the structures of bacteriochlorophyll $a$ – $g$, accomplishing the full aspect of natural bacteriochlorophylls so far. Among them, BChl $c$, $d$, $e$ and $f$ are actually chlorins (dihydroporphyrins). BChl $c$, $d$, and $e$ were isolated in the 1960–1970s from photosynthetic bacteria and BChl $f$ was produced very recently by deliberate mutation. BChl $a$, $b$, and $g$ are true bacteriochlorins (7,8-trans, 17,18-trans-tetrahydroporphyrins). BChl $a$ is the most widely distributed BChl and is present in reaction center and the core-antennas of most anoxygenic photosynthetic bacteria (e.g. *Rhodobacter sphaeroides*). In some bacteria (e.g. *Rp. viridis*), the role of BChl $a$ is replaced by BChl $b$, which differs structurally from BChl $a$ by an exocyclic ethyldene group at position-8. BChl $b$ enable bacteria to use light beyond 1000 nm. BChl $g$, found in the antenna and reaction center of *Hb. Chlorum*, also contains the exocyclic ethyldene group in ring B but carries a vinyl rather than an acetyl group at position-3.

The fine X-ray structure of a derivative of BChl $a$ (methyl bacteriopheophorbide $a$, which is obtained upon demetalation and transesterification of BChl $a$) was reported by Barkigia *et al.* in 1989, confirming the stereochemistry of natural BChl $a$. However, total syntheses of BChl $a$, $b$, or $g$ have not been reported so far. One of the main obstacle to handling photosynthetic bacteriochlorophylls is their instability. Chemical or photochemical oxidations of BChl $a$ can occur easily to give the corresponding 2-desvinyl-2-acetylchlorophyll $a$. BChl $b$ and $g$ are even more labile to tautomerization, affording corresponding chlorins. For example, during column chromatography, BChl $b$ and $g$ decompose easily and give transformation products exposed to air and light.
Figure 1.3. Structures of natural bacteriochlorophylls.

Not all bacteriochlorins found in nature are unstable. Tolyporphins, nonphotosynthetic bacteriochlorins isolated from a blue-green alga *Tolypothrix nodosa*, are stable against oxidization.\(^{17-19}\) The total synthesis of tolyporphin A \(^{20}\) \(O,O\)-diacetate was reported by Kishi *et al.* in 1999, which established the stereochemistry of tolyporphin A. Structure of tolyporphin A \(^{20}\) \(O,O\)-diacetate is shown in Figure 1.4. The main difference between tolyporphins and photosynthetic bacteriochlorophylls is the geminal dialkyl groups located in each of the reduced pyrroline ring (ring B/ring D). This unique structure prevents the pyrroline ring from undergoing dehydrogenation. Similar structural units have also been
found in other natural hydroporphyrin pigments, such as vitamin B\textsubscript{12}, siroheme (a natural isobacteriochlorin), bonellin (a natural chlorin), etc. (Figure 1.4. Geminal dialkyl groups are in red). Total synthesis of the above compounds have been accomplished in 1970s – 1990s.\textsuperscript{1}

\textbf{Figure 1.4.} Natural hydroporphyrins with geminal dialkyl motif.

We have established and developed a \textit{de novo} route to synthetic bacteriochlorins during the past decades in our lab.\textsuperscript{21–24} Figure 1.5 shows the core structure of our synthetic bacteriochlorins, which have several features compared to those natural bacteriochlorophylls. (1) Their macrocycle contain geminal dialkyl groups at the pyrroline rings, which block adventitious dehydrogenation and therefore make them oxidatively stable. (2) Synthetic manipulation enables the ability to install different substituents at the 2-, 3-, 12-, and 13-positions.\textsuperscript{22} Further synthetic transformation can provide bacteriochlorins wherein the 15-substituent is altered.\textsuperscript{23,24} The resulting palette of synthetic bacteriochlorins represents a
significant extension of the properties of natural bacteriochlorophylls.  

(3) Various of metallobacteriochlorins are accessible.  

(4) Procedures are robust and efficient, giving synthetic bacteriochlorins in hundreds of milligrams-scale.

Figure 1.5. Core structure of synthetic bacteriochlorins.

Studies on natural bacteriochlorophylls and synthetic bacteriochlorins can help us understand a number of fundamental questions in natural photosynthesis process, which might be roughly divided into two types.  

(1) Why does nature choose bacteriochlorophylls? What are the advantages of the bacteriochlorophyll over other structures? These questions concern the relationship between molecular structures and photophysical features. One example is that investigation of synthetic bacteriochlorin might elucidate the effect of the peripheral substituents (as well as ones in the isocyclic ring) on the spectral and photophysical properties of chromophores.  

Another example is that resonance Raman spectra of synthetic copper bacteriochlorin isotopologues can reveal the vibronic characteristics and spin-density distribution in bacteriochlorin macrocycles.  

(2) How do these pigments function in light harvesting and EET (energy and electron transfer)? This question concerns the interactions and EET within pigment-pigment, as well as pigment-protein. One example is that studies of synthetic bacteriochlorin-containing arrays might delineate molecular factors affecting EET phenomena.  

Another example is
that biohybrid light-harvesting architectures incorporated with various synthetic bacteriochlorins can exploit the self-constituting features of the natural systems such as LH1 or LH2.31–33

In addition to fundamental studies, strong absorption in the NIR region makes bacteriochlorophylls and synthetic bacteriochlorins attractive candidates in a variety of photochemical studies and applications, including the following:

(1) *Artificial photosynthesis.*34–37 A significant fraction of the solar spectrum falls in the red and NIR region. Bacteriochlorophylls and synthetic bacteriochlorins have the capability to capture the NIR light. Moreover, fine-tuning of the position of the Q_y band in synthetic bacteriochlorins enables absorption covering a significant portion of NIR regions. Hence, synthetic bacteriochlorins might provide a palette of chromophores as basic building blocks for enhancing artificial or biohybrid photosynthetic system.

(2) *Photodynamic therapy (PDT).*13,38–44 Bacteriochlorophylls and synthetic bacteriochlorins are efficient sensitizers with optimal light-harvesting properties: (1) They have very high extinction coefficients at long wavelengths (λ_{max} = 700–800 nm, \( \varepsilon = (4 – 12) \times 10^4 \text{ M}^{-1} \text{ cm}^{-1} \)), where light penetration into tissues is maximal.13 (2) They can generate reactive oxygen species at high quantum yield.39 Compared with native bacteriochlorophylls, synthetic bacteriochlorins are better candidates for PDT research. Firstly, they are stable towards dehydrogenation. Secondly, they exhibit amenability toward synthetic tailoring for cell uptake and delivery to diverse target sites.

(3) *Optical imaging.*45–47 Effective molecular imaging requires molecular probes with the following properties: (i) intense absorption and efficient emission in the red or near-infrared (NIR) spectral region, (ii) sharp absorption and emission bands, (iii) large
absorption-fluorescence spacing (Stokes shift), (iv) long excited-state lifetime and (v) photo-stability. Other desirable features include ease of synthesis, high stability, tailorable solubility, provisions for bioconjugation, absence of toxicity, biological targetability and systemic clearance. Development of energy-transfer dyads recently makes bacteriochlorin very appealing as building block for consideration in optical imaging applications.46,47

(4) Flow cytometry. Synthetic bacteriochlorins are distinguished from many other NIR chromophores by their relative strong and sharp NIR absorption/fluorescence emission, as well as the ability to tune the absorption band. Recent work on the synthesis of bioconjugatable bacteriochlorins bearing PEG groups and flow cytometry tests of corresponding bacteriochlorin-labeled antibodies indicated that synthetic bacteriochlorins may afford valuable attributes as labels for polychromatic flow cytometry.48

2. Synthesis of Bacteriochlorins

I. Early Methods for Bacteriochlorin Synthesis

Synthetic manipulation of bacteriochlorophylls (mainly BChl a) afforded a number of derivative, such as bacteriopheophorbide a, bacteriopyropheophorbide a, bacteriopurpurin, bacteriopurpurinimides, etc.13,38,49–53 Figure 1.6 shows the structures of these derivatives. There are two significant problems handling these compounds or using them in photochemical applications. (1) The native starting BChls and their derivatives have poor stability. (2) A nearly full complement of substituents about the perimeter of the macrocycle restricts the synthetic flexibility.
Figure 1.6. Typical derivatives of BChl a.

In an early era, most known synthetic bacteriochlorins were prepared from porphyrins and chlorins. These works have been reviewed by Montforts and Pandey, including: (1) hydrogenation of porphyrin or chlorin to bacteriochlorin, using simple catalytic hydrogenation, electrochemical reduction, or diimide reduction method; (2) OsO₄ oxidation and subsequent pinacol rearrangement of porphyrins; (3) intramolecular cyclization, and (4) cycloaddition reactions (e.g., D-A reaction, and 1,3-dipolar cycloaddition). Scheme 1.1 shows an overview about concepts of each method (each entry describes only concepts rather than reaction; substituents on the macrocycle have been simplified or omitted for clarification). Problems of these methods includes: (1) some methods still give unstable bacteriochlorins; (2) most methods suffer from the formation of structural isomers (e.g. bacteriochlorin/isobacteriochlorins, etc.) and (3) none of these
methods can tailor synthetic bacteriochlorins with diverse peripheral substituents or more sophisticated modification/functionalization.

**Scheme 1.1.** Early Methods to Synthetic Bacteriochlorins

Kishi et al. completed the total synthesis of a derivative of tolyporphin A, which is the only reported example about the total synthesis of a natural bacteriochlorophyll.\(^{20,65–68}\) Firstly, they extended the Eschenmoser sulfide contraction/iminoester cyclization method, developed by Eschenmoser during the vitamin B\(_{12}\) synthesis, to the synthesis of the core macrocycle of tolyporphin.\(^{66}\) The basic building blocks are four monocyclic precursors, corresponding to the four pyrrole or pyrroline rings in the macrocycle. An
octahydroporphyrin was assembled first, followed by elimination of substituents, to give the desired bacteriochlorin (tetrahydroporphyrin). Oxidation afforded the tolyporphin macrocycle, which is actually a dioxo-bacteriochlorin (Scheme 1.2). Next, synthesis of tolyporphin A O,O-diacetate was completed several years later, establishing the absolute configuration of this natural product.²⁰,⁶⁸

Scheme 1.2. Construction of Tolyporphin Macrocycle

II. Hydrodipyrrins: Building Blocks of Tetrapyrrole Macrocycle

There are three types of hydrodipyrrins important for tetrapyrrole synthesis (Scheme 1.3, top): dipyrromethane, dihydrodipyrrin (DHDP) and tetrahydrodipyrrin (THDP). Dipyrromethane and dihydrodipyrrin are isomers, which differ in the location of the double bonds. Reductions or additions of the double bond in DHDP, which joins the pyrrole ring and pyrroline ring, lead to THDP. In contrast, however, oxidation conditions converting THDP to DHDP have not been reported so far. Reactivities of these compounds serve as the foundation for constructing porphyrin, chlorin and bacteriochlorin macrocycles, of which details are beyond our discussion in this chapter. Here, we will only focus on dihydrodipyrrins and tetrahydrodipyrrins.

Both dihydrodipyrrins and tetrahydrodipyrrins consist of a pyrrole ring and a pyrroline ring, which bring two distinct reaction sites (Scheme 1.3). (1) The reactivity of the
pyrrole ring is dominated by a readiness to undergo electrophilic aromatic substitutions, preferentially at the α-position. In some situations (diakylboron-dihydridipyrrin complexes), substitution at a β-position is preferred. Moreover, the pyrrole rings, especially substituted with electron-donating groups, are unstable towards photo- or chemical- oxidation. In fact, a dihydrodipyrrin-acetal bearing two electron-donating groups decomposed quite easily (see dihydrodipyrrin-acetal 1-EtEt in reference 22). (2) On the other hand, an imine unit within pyrroline ring can serve as a good electrophile and undergo nucleophilic addition. In addition, the imine unit can be reduced to an amine by a reducing agent such as LiAlH₄ or NaBH₄.

Due to the absence of a double bond, a methylene linker (-CH₂-) between pyrrole and pyrroline ring in THDP affords more flexibility. Therefore, N-protected THDP can be easily prepared while preparation of N-protected DHDP was difficult. Besides, THDP carried out an arrangement in the presence of strong acid, wherein a β-position of the pyrrole attacks the imine unit in pyrroline and affords a bicyclic compound. In addition, because of the conjugation between pyrrole and pyrroline rings in DHDP, reactivities of DHDP and THDP are quite different. For example, self-condensation of DHDP-acetal can afford bacteriochlorin, while self-condensation of THDP-acetal cannot.

A substituent (Z) located at the α-position of pyrroline afford a third reaction site. The substituent can be a methyl, dimethoxymethyl, aldehyde, secondary carbinol, dithiane, phenoxyethyl, etc. Among them, the dimethoxymethyl group or the aldehyde group in a DHDP-acetal or DHDP-carboxaldehyde can condense with the α-pyrrolic position in other dihydrodipyrrins, resulting in self-condensation and affording synthetic
bacteriochlorins. Modification of this substituent can provide different reactivities to self-condensation or access to new reactions.

Scheme 1.3. Hydrodipyrrens (top) and their Typical Reactions (mid and bottom)
Synthetic routes to dihydrodipyrrin and tetrahydrodipyrrin were established by Battersby et al. in 1980s. This method was modified, improved and widely applied in our research. Another route to dihydrodipyrrins was developed by Jacobi et al., involving Pd(0)-catalyzed coupling-cyclization. We recently applied this method in synthesis of bacteriochlorins via a Northern-Southern route.

**III. Construction of Bacteriochlorins**

Scheme 1.4 shows a *De novo* synthesis of bacteriochlorins developed in our lab. This route employs an acidic self-condensation of a dihydrodipyrrin-acetal, wherein a geminal dimethyl group is attached to the β-pyrroline position while the acetal group is located at the α-pyrroline position. Under distinct acidic catalysis, the self-condensation can dominantly or even exclusively produce one of three macrocycles: the preparative synthesis with BF₃·OEt₂ (50 – 500 mM) gave predominantly HBC (20 – 30%); Trimethylsilyl triflate (TMSOTf) in the presence of 2,6-di-tert-butylpyridine (DTBP) gave exclusively MeOBC (40%); and Yb(OTf)₃ gave exclusively TDC (70%). Treating TDC with a Lewis acid produced HBC or MeOBC.
Scheme 1.4. *De novo* Synthesis of Bacteriochlorins

The mechanism of the *de novo* synthesis might be a straightforward process. Scheme 1.5 shows a possible pathway for the formation of MeOBC. Activated by a Lewis acid, the $\alpha$-carbon in the acetal unit of one dihydrodipyrrin serves as an electrophile, and is attacked by the pyrrole of the other dihydrodipyrrin, giving the linear tetapyrrole intermediate. During this process, one molecule of methanol is eliminated. Repetition of the same process eliminates the second molecule of methanol, closes the ring and affords the 5,15-dimethoxy-5,15-dihydrobacteriochlorin. Elimination of methanol again gives the aromatic bacteriochlorin macrocycle, with one methoxy substituent left at the 5-position. Formation of the HBC-type macrocycle may be more complicated, since a $2H^+/2e^-$ reduction is involved (not shown).
Since the establishment of the de novo synthesis, some significant progress has been achieved in our lab. Firstly, bacteriochlorins with diverse substituents at the β-pyrrolic and meso- position have been prepared.\textsuperscript{23,24} Secondly, annulated rings (five-membered isocyclic ring as occurs in all bacteriochlorophylls, or the six-membered imide ring of bacteriopurpurinimides) have been introduced to the bacteriochlorin macrocycle.\textsuperscript{23} Thirdly, a variety of metallobacteriochlorins have been prepared.\textsuperscript{26} Lastly, preparation of water-soluble and bioconjugatable bacteriochlorins have been developed.\textsuperscript{48,81,82} Moreover, recently a Northern-Southern route to synthetic bacteriochlorin was reported, giving access to meso-dialkyl, meso-diaryl, and meso-trisubstituted bacteriochlorins.\textsuperscript{79}

3. Summary and Overview

Bacteriochlorophylls, pigments found in anoxygenic photosynthetic bacteria, are characterized by their strong absorption in the NIR region. Studies of bacteriochlorophylls not only provide insight into fundamental scientific problems but also enable applications in
photochemical fields such as artificial photosynthesis, PDT, molecular imaging, etc. Natural bacteriochlorophylls are usually unstable against chemical- or photo-oxidations. Development of synthetic bacteriochlorins, which are stable toward adventitious dehydrogenation due to the presence of a geminal dialkyl group in each pyrroline ring, can overcome such limitations.

The synthetic chemistry of bacteriochlorin was relatively undeveloped before 2005. During the past decades, our lab established and developed the *de novo* route to bacteriochlorins, which relies on the acidic-catalyzed self-condensation of dihydropyrrin-acetals, wherein a wide variety of substituents can be appended to the macrocycle at preselected locations. The method opens access bacteriochlorins with a variety of functions, such as wavelength-tunability, water-solubility, and bioconjugatability.

Despite these successes, large numbers of bacteriochlorins are still inaccessible through the present route. One of the greatest limitations is that the *de novo* synthesis is a dimerization process, meaning that substituents on two opposite pyrroles have to be identical (2-/3-position vs. 12-/13-position, Figure 1.7). In order to get access to unsymmetrically substituted bacteriochlorins, new strategies of constructing the macrocycle are required. My work has focused on developing new bacteriochlorin synthesis methodology, to provide access to new bacteriochlorins, especially unsymmetrical ones.
Figure 1.7. Symmetrically and unsymmetrically substituted bacteriochlorin.

Firstly, a synthetic route to access tetra-alkyl bacteriochlorins was developed (Chapter II). The alkyl groups examined include methyl and methyl acetate. Such synthetic bacteriochlorins, while previously unknown, provide valuable models of the natural chromophores. Next, explorations and synthetic approaches to unsymmetrically substituted bacteriochlorins through linear tetrapyrrole intermediates are described in Chapter III. In this chapter, 7 new target hydrodipyrrins have been prepared bearing diverse α-pyrrole (-H, -SMe, -Br, -Me, and -CO₂Et) and α-pyrroline (methyl, carboxaldehyde, acetal, and imino) substituents. The hydrodipyrrins were examined for use in a directed synthesis of bacteriochlorins, taking inspiration from a directed route to chlorins. At last, a new method to construct the bacteriochlorin macrocycle with concomitant Nazarov cyclization to form the annulated isocyclic ring is reported in Chapter IV. Five new bacteriochlorins bearing various substituents (alkyl/alkyl, aryl, and alkyl/ester) at positions 2 and 3 (β-pyrrole sites, ring A) and 13² carboalkoxy groups (R = Me or Et) were constructed in 37–61% yield from the bilin analogues.
References


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7750–7767.


2725–2732.


Chapter II

Synthesis and Photophysical Characteristics of 2,3,12,13-Tetraalkylbacteriochlorins

Preamble

The full contents of this chapter have been published (Zhang, S.; Kim, H.-J.; Tang, Q.; Yang, E.; Bocian, D. F.; Holten, D.; Lindsey, J. S. New J. Chem. 2016, 40, 5942–5956.), with contributions from the following individuals: Han-Je Kim on the synthesis of compound 1-CHO; Qun Tang (Bocian group, UC-Riverside) and Eunkyung Yang (Holten group, WUSTL) on spectra and photophysical studies of bacteriochlorins.

Introduction

Bacteriochlorophylls are Nature’s chosen chromophores for light-harvesting in the near-infrared (NIR) spectral region.\textsuperscript{1,2} The bacteriochlorin chromophore of bacteriochlorophylls is a tetrahydroporphyrin wherein two reduced pyrrole rings are located at the opposite sides of the macrocycle. The structure of bacteriochlorophylls a, b and g are shown in Figure 2.1. Bacteriochlorins characteristically exhibit a strong (\(\varepsilon \sim 10^5 \text{ M}^{-1}\text{cm}^{-1}\)) long-wavelength absorption band (Q\(_y\) band) located around 700–900 nm.\textsuperscript{3} The strong NIR absorption makes bacteriochlorins attractive for fundamental studies as well as applications in solar-energy conversion and in photomedicine.\textsuperscript{4–9}
Figure 2.1. Natural bacteriochlorophylls.

Over some years now, a *de novo* synthesis route has been developed to gain access to diverse substituted bacteriochlorins. The synthetic method relies on the self-condensation of a dihydrodipyrrin-acetal (1-acetal), which contains a dimethyl group integral to the reduced, pyrroline ring and an acetal unit located at the pyrroline α-position (Scheme 2.1). The gem-dimethyl group secures the pyrroline ring from adventitious oxidation that would lead to unsaturated products (i.e., chlorins and porphyrins). By modification of the substituents attached to the pyrrolic units and/or the meso-positions, the bacteriochlorins can be tailored with regards to the position of the long-wavelength absorption band (ranging from 690 nm to 900 nm), polarity (hydrophobic, amphiphilic, or hydrophilic) and the presence of derivatizable groups for bioconjugation or building-block applications.
A key aspect of the self-condensation of a dihydrodipyrrin-acetal is that different acidic conditions (acid composition and concentration) and dihydrodipyrrin-acetal concentrations can lead to distinct outcomes with regards to the macrocycles formed: a free base 5-unsubstituted bacteriochlorin (HBC-type macrocycle), a free base 5-methoxybacteriochlorin (MeOBC-type macrocycle), a free base $B,D$-tetrahydrocorrin (TDC-type macrocycle).\textsuperscript{10,11,22} As a general rule, the use of BF$_3$·OEt$_2$ at modest concentrations in CH$_3$CN typically provides a mixture of two if not all three macrocycles, but with 140 mM BF$_3$·OEt$_2$ and 18 mM dihydrodipyrrin-acetal, the HBC-type macrocycle is the dominant macrocyclic product (20–30% yield).\textsuperscript{184} On the other hand, TMSOTf and 2,6-di-$\textit{tert}$-butylpyridine (DTBP) in CH$_2$Cl$_2$ exclusively give the MeOBC-type macrocycle (40% 

**Scheme 2.1** Self-condensation of a Dihydrodipyrrin-acetal
yield), whereas Yb(OTf)₃ in CH₂Cl₂ exclusively gives the corresponding TDC-type macrocycle in high yield (70%).

One of our research objectives has been to install architectural features about the bacteriochlorin for wavelength tuning, water-solubilization, and bioconjugation. An opposite thrust has been to create sparsely substituted macrocycles, in particular to systematically “build up” the substituent pattern of bacteriochlorophylls beginning with the fully unsubstituted bacteriochlorin. A progression of such synthetic, free base bacteriochlorins is shown in Figure 2.2. The progression begins with the fully unsubstituted HBC-type bacteriochlorin BC0 and would add in (i) β-pyrrole substitution without potent auxochromes (four methyl groups, BC-MM), (ii) a single auxochrome (acetyl, BC-A³), (iii) the isocyclic ring, which contains a single auxochrome in the bacteriooxophorbine (BOP), (iv) perhaps other structures of intermediate complexity, and finally (v) a structure (BOP-MA³) that contains two methyl groups, one acetyl group, and the isocyclic ring as in methyl bacteriopheophorbide a, the free base analogue of BCHl a where the phytol group has been transesterified. While access to BC0 was achieved via the de novo route, we were unsuccessful in preparing the tetraethyl analogue of the next compound in the progression, the seemingly simple tetramethylbacteriochlorin.¹¹ We felt the origin of the failure stemmed from the instability of the diethylidihydrodipyrrin-acetal under the acidic reaction conditions. Thus, the synthesis of the seemingly simple tetraalkylbacteriochlorins, paradoxically, has proved more difficult than constructing architecturally elaborate bacteriochlorins.
Figure 2.2. Progression of structural complexity along the path to a free base derivative of BChl $a$.

In this paper, we report the synthesis of new $\beta$-dialkyldihydrodipyrrins and their conversion to tetraalkylbacteriochlorins. The $\beta$-dialkyldihydrodipyrrins differ from the dihydrodipyrrin-acetals used previously in two regards: (1) the acetal is replaced with a carboxaldehyde, and (2) the pyrrole is stabilized at the $\alpha$-position with an acid-cleavable ester unit. The new $\beta$-dialkyldihydrodipyrrins have provided access to two new 2,3,12,13-tetraalkylbacteriochlorins (as well as one copper chelate), including BC-MM as desired in a step along the progression of structural complexity. The electronic spectral, vibrational, and excited-state properties of the bacteriochlorins have been investigated. In all, the present work should provide a convenient route to a variety of 2,3,12,13-tetraalkylbacteriochlorins that heretofore have been inaccessible.

Results and Discussion

(I) Synthesis. (A) Reconnaissance. In our prior attempt to prepare
tetraalkylbacteriochlorins,\textsuperscript{11} pyrrole–nitrohexanone 2, which bears two ethyl groups at the β-pyrrole positions, was subjected to the standard conditions for cyclization (via TiCl\textsubscript{3}) to form the dihydrodipyrrin-acetal 3 (Scheme 2.2). The yield of the latter was 7.6%, to be compared with typical yields of 20-30% for diverse substrates; but even worse, the product began decomposing within minutes. Dihydrodipyrrin-acetal 3 was quickly purified (with limited characterization) and submitted to the bacteriochlorin-forming process under a handful of acid-catalysis conditions. In the best condition, only a slim signature (absorption bands, molecular ion peak) of the HBC- and MeOBC-type bacteriochlorins was observed, and the yield of each on the basis of absorption spectroscopy was <1%. From this result we surmised that a viable synthesis of tetraalkylbacteriochlorins would require a strategy for stabilizing the dialkyl-substituted precursors.
The synthesis of porphyrins bearing an alkyl group at each β-pyrrole position has been known since the first half of the 20th century. One general synthetic approach has employed pyrroles, dipyrrins or dipyrromethanes that are stabilized by the presence of ester substituents at the α-position(s). The electron-withdrawing effect of the esters counterbalances the electron-releasing effect of the β-alkyl groups. The same approach has been employed in rational routes to chlorins. Battersby incorporated an α-ester to stabilize the β-alkyl-substituted dihydridopyrrin I Western half precursor, and Jacobi similarly incorporated an α-ester with the β-alkyl-substituted dihydridopyrrin II for use as a Southern
half precursor\textsuperscript{26} (Figure 2.3). Note that II differs subtly from the dihydrodipyrins employed in Schemes 2.1 and 2.2 in the position of the gem-dimethyl group in the pyrroline ring.

\begin{center}
\begin{tikzpicture}
\node (I) at (0,0) {\includegraphics[width=0.4\textwidth]{figure2.3.png}};
\end{tikzpicture}
\end{center}

\textbf{Figure 2.3.} Dihydrodipyrins used in chlorin syntheses.

The general approach shown in Scheme 2.2 has provided access to diverse bacteriochlorins from the corresponding dihydrodipyrin-acetals, none of which contained pyrrole $\alpha$-ester stabilization. Two strategies for preparing such dihydrodipyrin-acetals (III) have been developed (Scheme 2.3). The original method employs Michael addition of a 2-(2-nitroethyl)pyrrole and a $\alpha,\beta$-unsaturated ketone-acetal (4-acetal) following by reductive cyclization. A more recent method relies on Michael addition of a 2-(2-nitroethyl)pyrrole (IV) and mesityl oxide (4-Me) to form the dihydrodipyrin-Me (V). Subsequent oxidation (SeO\textsubscript{2}) gives the dihydrodipyrin-carboxaldehyde (VI), which is finally converted to the dihydrodipyrin-acetal (III).\textsuperscript{13} In the two reported examples of the second route (for $\beta$-pyrrole substituents = ethyl and carboethoxy), the intermediate dihydrodipyrin-carboxaldehyde was not isolated or purified but instead converted to the desired target, the dihydrodipyrin-acetal.\textsuperscript{13} Here, we adopted the latter route to prepare and utilize two $\alpha$-ester stabilized dihydrodipyrin-carboxaldehydes.
(B) Preparation of dihydrodipyrrin-carboxaldehydes. We began the methodology studies with a substrate for which data were in hand concerning synthesis of the dihydrodipyrrin and conversion to a bacteriochlorin. Thus, the known $p$-tolyl-substituted nitroethylpyrrole 5$^{11}$ was used in the synthesis of a dihydrodipyrrin-carboxaldehyde and the corresponding bacteriochlorin. Michael addition$^{27}$ of nitroethylpyrrole 5 with mesityl oxide (4-Me) in the presence of DBU gave $\gamma$-nitrohexanone 6 in 74% yield. Subsequent treatment of 6 with NaOMe followed by a buffered TiCl$_3$ solution to achieve reductive cyclization$^{10}$ afforded dihydrodipyrrin 1-Me as a yellow solid in 25% yield. Oxidation of dihydrodipyrrin 1-Me with SeO$_2$ in 1,4-dioxane at room temperature, a procedure first reported by Jacobi and
coworkers\textsuperscript{13,28} gave the corresponding dihydrodipyrrin-carboxaldehyde 1-CHO in 47\% yield (Scheme 2.4). The formation of the carboxaldehyde is readily observed by absorption spectroscopy given the bathochromic shift into the visible region of the dihydrodipyrrin chromophore.\textsuperscript{13} Dihydrodipyrrin-carboxaldehyde 1-CHO was prone to decomposition in chlorinated solvents and during silica column chromatography, but was stable for several days upon storage in solid form at \(-20\) °C. Compound 1-CHO was characterized by \textsuperscript{1}H NMR spectroscopy and ESI-MS; however, a satisfactory \textsuperscript{13}C NMR spectrum was not obtained. The \textsuperscript{1}H NMR spectrum of the purified product indicated the presence of a minor impurity.

For the synthesis of the analogous dimethylidihydrodipyrrin-carboxaldehyde, a tert-butyl ester was introduced to the \(\alpha\)-position in the dihydrodipyrrin. Prior synthetic work in this area had resulted in transformations along the series of known compounds 7–9 and 10-Me for use in formation of chlorins, where the dihydrodipyrrin-methyl compound 10-Me suffices, but not for bacteriochlorins. Thus, 8\textsuperscript{29} was prepared beginning with acyclic precursors to 7\textsuperscript{30} following the literature, whereas 9\textsuperscript{31} and 10-Me\textsuperscript{31} were prepared via modified literature methods.\textsuperscript{11,27} Treatment of the ester-substituted dimethylidihydrodipyrrin 10-Me with SeO\textsubscript{2} in \(p\)-dioxane at room temperature afforded the corresponding dihydrodipyrrin-carboxaldehyde 10-CHO in 63\% yield (Scheme 2.4). Unlike dihydrodipyrrin-carboxaldehyde 1-CHO, 10-CHO was relatively stable in a variety of solvents (including CH\textsubscript{2}Cl\textsubscript{2} and CHCl\textsubscript{3}) as well as during silica column chromatography.
Scheme 2.4 Preparation of Dihydodipyrrin-carboxaldehydes.

(C) Self-Condensation Study of Dihydodipyrrin-carboxaldehyde. The typical conditions for the self-condensation of dihydodipyrrin-acetals were used for the reactions with the dihydodipyrrin-carboxaldehydes 1-CHO and 10-CHO. The two acidic conditions chosen for the self-condensation study with 18 mM dihydodipyrrin-carboxaldehyde were as
follows: (1) 140 mM BF$_3$·OEt$_2$, or (2) 72 mM TMSOTf/144 mM DTBP (Table 2.1, entries 1 and 2).
Table 2.1 Acid survey for the self-condensation of dihydrodipyrrin-carboxaldehydes $^a$

<table>
<thead>
<tr>
<th>entry</th>
<th>reactant</th>
<th>$R^1$</th>
<th>$R^2$</th>
<th>$R^3$</th>
<th>acidic condition</th>
<th>time (h)</th>
<th>bacteriochlorin</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1-CHO</td>
<td>$p$-tolyl</td>
<td>H</td>
<td>H</td>
<td>BF$_3$·OEt$_2$ in CH$_3$CN</td>
<td>19</td>
<td>BC-T</td>
<td>12%</td>
</tr>
<tr>
<td>2</td>
<td>1-CHO</td>
<td>$p$-tolyl</td>
<td>H</td>
<td>H</td>
<td>TMSOTf/DTBP in CH$_2$Cl$_2$</td>
<td>19</td>
<td>BC-T</td>
<td>$^b$</td>
</tr>
<tr>
<td>3</td>
<td>1-CHO</td>
<td>$p$-tolyl</td>
<td>H</td>
<td>H</td>
<td>Neat TFA</td>
<td>1</td>
<td>BC-T</td>
<td>0.2%</td>
</tr>
<tr>
<td>4</td>
<td>10-CHO</td>
<td>Me</td>
<td>Me</td>
<td>CO$_2$Bu</td>
<td>BF$_3$·OEt$_2$ in CH$_3$CN</td>
<td>19</td>
<td>BC-MM</td>
<td>11%</td>
</tr>
<tr>
<td>5</td>
<td>10-CHO</td>
<td>Me</td>
<td>Me</td>
<td>CO$_2$Bu</td>
<td>TMSOTf/DTBP in CH$_2$Cl$_2$</td>
<td>19</td>
<td>BC-MM</td>
<td>$^c$</td>
</tr>
<tr>
<td>6</td>
<td>10-CHO</td>
<td>Me</td>
<td>Me</td>
<td>CO$_2$Bu</td>
<td>Neat TFA$^d$</td>
<td>1</td>
<td>BC-MM</td>
<td>24%</td>
</tr>
</tbody>
</table>

$^a$All reactions were carried out (1.0 mL scale) with 18 mM dihydrodipyrrin-carboxaldehyde at room temperature. Concentrations of acid were 140 mM BF$_3$·OEt$_2$ or 72 mM TMSOTf/144 mM DTBP. Yields were determined by absorption spectroscopy of samples isolated by chromatography. $^b$Not detected. $^c$Unreacted dihydrodipyrrin-carboxaldehyde remained. $^d$The same reaction in TFA-$d$ (0.068 mmol 10-CHO) also gave BC-MM in comparable yield with no isotopic incorporation.
The self-condensation of 1-CHO gave BC-T in 12% yield with BF₃·OEt₂ in CH₃CN, but little or no product with the other two acids (entries 1–3). No other macrocycles, including the HOBC-type or TDC-type species, were reliably observed by TLC analysis or laser-desorption mass spectrometry (LD-MS) of the crude sample from entry 1. The self-condensation of 10-CHO gave nearly identical results in BF₃·OEt₂ in CH₃CN, with 11% yield for BC-MM (entry 4). TMSOTf/DTBP gave no product but resulted in recovery of starting material, indicating the stability of the dihydrodipyrrin-carboxaldehyde (entry 5). On the other hand, the use of neat TFA gave BC-MM in 24% yield (entry 6). No other macrocycles were detected based on TLC analysis or attempted isolation. A convenient feature of this latter result is that reaction occurred in 1 h rather than 19 h for BF₃·OEt₂. The disparity in yield of bacteriochlorin (0.2% versus 24%) in neat TFA despite identical reacting motifs for 1-CHO and 10-CHO is striking (entries 3 and 6). Regardless of mechanistic origin, the acid survey confirmed the viability of the ester-substituted dihydrodipyrrin-carboxaldehyde as a means to access a tetraalkylbacteriochlorin.

**(D) Preparation of 2,3,12,13-Tetramethylbacteriochlorin.** The self-condensation of dihydrodipyrrin-carboxaldehyde 10-CHO at ~10-fold increased scale (0.21 mmol) afforded BC-MM in 29% yield (Scheme 2.5). Again, no other macrocycles were observed or isolated. Following a standard procedure for metalation of bacteriochlorins, treatment of BC-MM with a large excess of sodium hydride and Cu(OAc)₂ in THF at 60 °C for 16 h under argon afforded CuBC-MM. Prolonging the reaction caused extensive byproducts. CuBC-MM was unstable on silica column chromatography (conversion to Cu(II)oxobacteriochlorins as found upon LD-MS, or undergoing decomposition) but could
be purified on a short column, albeit in low yield. Upon purification, CuBC-MM was stable under dry conditions for an extended period.

**Scheme 2.5.** Preparation of BC-MM and CuBC-MM.

The bacteriochlorin BC-MM was characterized by $^1$H NMR spectroscopy, $^{13}$C NMR spectroscopy, high-resolution mass spectrometry (ESI-MS) and absorption spectroscopy. The structure of BC-MM also was determined by single-crystal X-ray analysis (Figure 2.4, CCDC# 1453311). Comparison of the structure of BC-MM with that of BC$^{32}$ leads to the following findings. (1) The average nitrogen-centroid distance of BC-MM is 2.099 Å, which is slightly longer than that of BC (2.096 Å), indicating that the core size is slightly larger. (2) The torsion angle of the four carbons in the pyrroline ring (C6-C7-C8-C9; C16-C17-C18-C19) in BC-MM is 11.60°, which is much larger than that of BC (1.11°). The out-of-plane
twists of the two pyrrole rings in BC-MM are in opposite directions with respect to the macrocycle plane, imparting overall C$_i$ symmetry.

**Figure 2.4.** ORTEP drawing of BC-MM. Ellipsoids are at the 50% probability level and hydrogen atoms (except N–H) are omitted for clarity.

(E) A Bacteriochlorin with Acetate Side-chains. The successful synthesis of BC-MM prompted exploration of the synthesis of more elaborate alkyl substituents. Thus, the bacteriochlorin BC-AmAm was synthesized following the strategy reported above (Scheme 2.6). Compounds 11, 12, 13 are known but 12 and 13 were prepared here via alternative routes. Thus, a rapid transesterification of pyrrole 11 at 220 °C gave the tribenzyl ester 12 in 68% yield, following by a selective base-catalyzed transesterification at room temperature to give the dimethyl monobenzyl ester 13. Next, hydrogenolysis followed by esterification of the resulting carboxylic acid with tert-butyl alcohol and DCC along with 4-(N,N-dimethylamino)pyridine (DMAP) gave the new pyrrole 14. Treatment of the latter with thionyl chloride followed by hydrolysis caused oxidation of the α-methyl group in the presence of the three alkyl esters to give the corresponding pyrrole-carboxaldehyde 15. Subsequent nitro-aldol condensation and reduction by NaBH$_4$ afforded nitroethylpyrrole 16.
in 39% yield. The Michael addition of 16 and mesityl oxide (4-Me) in the presence of TBAF at room temperature\textsuperscript{38} afforded 17 in 70% yield. Reductive cyclization of 17 gave the desired dihydridopyrrin 18-Me in 18% yield. Finally, oxidation\textsuperscript{13,28} of dihydridopyrrin 18-Me gave the resulting dihydridopyrrin-carboxaldehyde 18-CHO, which was sufficiently pure for direct use in the next step. To our surprise, treatment with neat TFA only afforded a trace amount of BC-AmAm. On the other hand, BF$_3$·OEt$_2$-mediated self-condensation gave BC-AmAm in 6.7% yield for the two steps from 18-Me. The bacteriochlorin was characterized by absorption spectroscopy, $^1$H NMR spectroscopy, and mass spectrometry (ESI-MS). We note that established chemistry exists for the preparation of related dialkylpyrroles such with substituents such as 3-Me/4-Et,\textsuperscript{39} 3-Et/4-Me,\textsuperscript{40} 3-Me/4-CH$_2$CH$_2$CO$_2$Me,\textsuperscript{41} and 3-CH$_2$CH$_2$CO$_2$Me/4-Me,\textsuperscript{42} all of which may be potential starting materials to make tetraalkylbacteriochlorins.

(II) Photophysical Characterization. The photophysical data obtained upon characterization of the new bacteriochlorins were compared with three benchmark bacteriochlorins (Figure 2.5). One benchmark is the fully unsubstituted bacteriochlorin BC0. Two others (BC-MEs and BC-EEs) have alkyl (methyl or ethyl) groups at the 2,12-positions and carboethoxy groups attached directly to the 3,13-positions of the macrocycle. Note that
the four carbomethoxy groups of BC-AmAm are each removed from the macrocycle by a methylene group and thus do not directly interact with bacteriochlorin $\pi$-system.

![Chemical structure of bacteriochlorins](attachment:chemical_structure.png)

**Figure 2.5.** New and benchmark bacteriochlorins.

**(A) Absorption and Fluorescence Spectra.** Electronic ground-state absorption spectra of parent BC0, new tetraalkyl derivatives BC-MM and BC-AmAm, and copper chelate CuBC-MM are shown in Figure 2.6 (solid lines). The figure also shows fluorescence spectra of the free base bacteriochlorins (dashed lines). Table 2.2 lists the spectral characteristics of the free base compounds along with those of additional benchmarks BC-MEs and BC-EEs studied previously. The new tetraalkylbacteriochlorins BC-MM and BC-AmAm are quite soluble in toluene and remain stable even upon prolonged illumination without noticeable photoaggregation, an adverse phenomenon that has occurred with other bacteriochlorins.
Figure 2.6. Absorption (solid) and fluorescence (dashed) spectra of bacteriochlorins in toluene.
Table 2.2 Spectral characteristics of bacteriochlorins in toluene at room temperature

<table>
<thead>
<tr>
<th>Compound</th>
<th>$B_y(0,0)$ abs (nm)</th>
<th>$B_x(0,0)$ abs (nm)</th>
<th>$Q_y(1,0)$ abs (nm)</th>
<th>$Q_x(0,0)$ abs (nm)</th>
<th>$I_{Q_y(0,0)}/I_{Q_x(1,0)}$</th>
<th>$Q_y(1,0)$ abs (nm)</th>
<th>$Q_x(0,0)$ abs (nm)</th>
<th>$Q_y(0,0)$ abs FWHM (nm)</th>
<th>$Q_y(0,0)$ em FWHM (nm)</th>
<th>$Q_y(0,0)$ em FWHM (cm$^{-1}$)</th>
<th>$Q_y(0,0)$ em FWHM (cm$^{-1}$)</th>
<th>$I_{Q_y}/I_{B_{\text{max}}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>BC-MM</td>
<td>346</td>
<td>374</td>
<td>462</td>
<td>490</td>
<td>1.9</td>
<td>685</td>
<td>721</td>
<td>11.9</td>
<td>229</td>
<td>723</td>
<td>15.5</td>
<td>296</td>
</tr>
<tr>
<td>BC-AmAm</td>
<td>347</td>
<td>373</td>
<td>466</td>
<td>495</td>
<td>4.8</td>
<td>694</td>
<td>732</td>
<td>13.0</td>
<td>243</td>
<td>733</td>
<td>16.7</td>
<td>308</td>
</tr>
<tr>
<td>BC0</td>
<td>340</td>
<td>365</td>
<td>462</td>
<td>489</td>
<td>7.9</td>
<td>678</td>
<td>714</td>
<td>12.0</td>
<td>236</td>
<td>716</td>
<td>16.0</td>
<td>312</td>
</tr>
<tr>
<td>BC-MEs$^a$</td>
<td>354</td>
<td>384</td>
<td>488</td>
<td>520</td>
<td>17.0</td>
<td>719</td>
<td>760</td>
<td>19.0</td>
<td>337</td>
<td>764</td>
<td>20.0</td>
<td>350</td>
</tr>
<tr>
<td>BC-EEs$^a$</td>
<td>354</td>
<td>383</td>
<td>489</td>
<td>521</td>
<td>8.3</td>
<td>721</td>
<td>761</td>
<td>20.0</td>
<td>343</td>
<td>775</td>
<td>21.0</td>
<td>368</td>
</tr>
</tbody>
</table>

$^a$ Data are from ref. 14.
The absorption spectrum of each bacteriochlorin consists of four major bands: $B_y$, $B_x$ in the near ultraviolet, $Q_x$ in the green-yellow and $Q_y$ in the NIR region. Each origin, or (0,0), feature is accompanied by at least one weaker vibronic satellite band to higher energy. The $Q_y$ band of BC-AmAm (732 nm) and BC-MM (721 nm) is bathochromically shifted from parent BC0 (714 nm) but is hypsochromically shifted from benchmarks BC-MEs (760 nm) and BC-EEs (761 nm), which contain 2,3-dimethyl or 2,3-diethyl plus 3,13-dicarboethoxy groups (Table 2.2). Similar trends are observed for the wavelength (nm) positions of the $Q_x$ origin bands: BC0 (489) < BC-MM (490) < BC-AmAm (495) < BC-MEs (520) < BC-EEs (521). Like the $Q_y$ feature, the Soret ($B_y$, $B_x$) bands (in nm) of BC-AmAm (347, 373) and BC-MM (346, 374) are bathochromically shifted from parent BC0 (340, 365) and hypsochromically shifted from benchmarks BC-MEs (354, 384) and BC-EEs (354, 383). These trends thus reflect a general shift in the center of gravity of the spectrum among the compounds.

Several additional spectral characteristics are noteworthy: (1) The full-width-at-half-maximum (FWHM) of the $Q_y$ absorption band of BC-AmAm and BC-MM is small and comparable to benchmark BC0, being in the range 12–13 nm or 229–243 cm$^{-1}$ (Table 2.2). These features are about 30% narrower than for benchmarks BC-MEs and BC-EEs (19–20 nm, 337–343 cm$^{-1}$) and bacteriochlorins with substituents that impart an even longer wavelength $Q_y$ band. The ratio of the $Q_y$ and Soret ($B_y$, $B_x$) maximum for the new tetra-substituted bacteriochlorins are comparable to the benchmarks (0.85–1.1). Compared to the parent and benchmarks, the $Q_x(1,0)$ vibronic satellite band of BC-MM and BC-AmAm has gained considerable intensity relative to the $Q_x(0,0)$ origin band. The $Q_x(0,0)/Q_x(1,0)$ peak-intensity ratio follows the trend BC-MM (1.9) < BC-AmAm (4.8) < BC0 (7.9). Thus, the
2,3,12,13-tetraalkyl substituent pattern tends to turn on vibronic activity, whether Franck-Condon or Herzberg-Teller in origin.

The fluorescence spectra of **BC-MM** and **BC-AmAm** and parent **BC0** are shown in Figure 2.6 (dashed lines). The fluorescence spectrum of each bacteriochlorin is dominated by the Q_y(0,0) feature, which is positioned only 1–2 nm (19–29 cm\(^{-1}\)) to longer wavelength than the corresponding Q(0,0) absorption maximum. Such “Stokes shift” is smaller than for **BC-MEs** or **BC-EEs** (Table 2.2) or other bacteriochlorins bearing simple substituents (e.g., methyl, ethyl, phenyl, ester, acetyl, ethynyl) at the 2,3,12,13-positions, which give an average shift of ~4 nm (~90 cm\(^{-1}\)).\(^\text{14}\) The FWHM (in cm\(^{-1}\)) of the Q_y emission feature of **BC-MM** and **BC-AmAm** (296–308) is small, even slightly reduced from parent **BC0** (312) and smaller still versus benchmarks **BC-MEs** and **BC-EEs** (350 and 368) (Table 2.2) and other bacteriochlorins bearing simple β-pyrrole substituents.\(^\text{14}\)

**(B) Resonance Raman Studies of CuBC-MM.** Resonance Raman measurements round out the static studies of the ground-state properties of the new tetraalkylbacteriochlorin constructs. The low- and mid-frequency regions (150–1700 cm\(^{-1}\)) of the Q_y-excitation RR spectrum of **CuBC-MM** (\(\lambda_{ex} = 737\) nm) is compared with that previously reported\(^\text{45}\) for **CuBC0** (\(\lambda_{ex} = 730\) nm) in Figure 2.7. For **CuBC-MM**, more noise is evident in the low-frequency than mid-frequency region of the spectrum owing to the fact that a weak fluorescence background underlies the low-frequency region (see Experimental Section). The striking aspect of the Q_y-excitation RR spectrum of **CuBC0** is that it is extremely sparse in both the low- and mid-frequency regions and is dominated by a single strong band at 727 cm\(^{-1}\). The mid-frequency region (800-1700 cm\(^{-1}\)) of the RR spectrum of **CuBC-MM** is similar to that of **CuBC0** in the exhibition of relatively few weak bands. In contrast, the low-
frequency region (150–800 cm\(^{-1}\)) of the RR spectrum of CuBC-MM is much richer than that of CuBC0, exhibiting relatively strong bands at 359, 482, 602, 612, 736, and 768 cm\(^{-1}\) and somewhat weaker bands at 219, 652, 692, and 768 cm\(^{-1}\). The 736-cm\(^{-1}\) band of CuBC-MM is likely the analogue of the 727-cm\(^{-1}\) band of CuBC0. However, the 736-cm\(^{-1}\) band of CuBC-MM is not the strongest feature in the spectrum, being less intense than either the 482- or 612-cm\(^{-1}\) bands.

**Figure 2.7.** Low- and mid-frequency regions of the Q\(_y\)-excitation RR spectra of CuBC0 (\(\lambda_{\text{ex}} = 730\) nm; CH\(_2\)Cl\(_2\) solution) and CuBC-MM (\(\lambda_{\text{ex}} = 737\) nm; benzene solution).

The rationale for examining the Q\(_y\)-excitation RR spectrum of CuBC-MM was to determine whether addition of the four methyl substituents at the \(\beta\)-pyrrolic positions of the
macrocycle would substantially alter the general characteristics of the spectrum from that observed for CuBC0. As was previously noted, the $Q_y$-excitation RR spectrum is quite unusual, exhibiting only a single strong band at 727 cm$^{-1}$ plus a few other weak features in both the low- and mid-frequency regions. These characteristics of the $Q_y$-excitation RR spectrum of CuBC0 are strikingly different from those of the $Q_y$-excitation RR spectra of natural bacteriochlorophylls, both in solution and in proteins,$^{46-51}$ and a Cu-bacteriochlorophyll model complex,$^{52}$ all of which exhibit dozens of bands that span the low- and mid-frequency regions of the spectra. The BChl a macrocycle differs from that of CuBC0 in that the former contains four $\beta$-pyrrolic substituents, including two methyl groups, an acetyl group, and a keto group embedded in the five-membered, isocyclic ring. The isocyclic ring spans the 13- and 15-positions and also contains a carbomethoxy substituent (Figure 2.1). Accordingly, addition of four $\beta$-pyrrolic substituents to CuBC0, yielding CuBC-MM, was viewed as one step in increasing the complexity of the macrocycle towards that found in BChl a.

The results reported herein reveal that addition of the four $\beta$-pyrrolic substituents does indeed increase the richness of the RR spectra, but only in the low-frequency region. Thus, other structural characteristic of the natural pigment must also come into play in ultimately determining the overall RR spectral pattern. The detailed analysis of the RR spectrum of CuBC-MM is beyond the scope of this paper; however, the data acquired for this complex serve as a starting point for our program aimed at examining the RR spectra of a series of model complexes wherein the substituents present in BChl a are systematically added to the parent bacteriochlorin macrocycle.
(C) **Excited-State Properties.** The $S_1$ lifetime ($\tau_S$) and yields of $S_1 \rightarrow S_0$ fluorescence ($\Phi_f$) and $S_1 \rightarrow T_1$ intersystem crossing ($\Phi_{isc}$), the triplet yield, were measured to fully characterize the decay properties of the $S_1 (Q_y)$ excited state. The yield of $S_1 \rightarrow S_0$ internal conversion ($\Phi_{ic}$) is obtained by the simple calculation $\Phi_{ic} = 1 - \Phi_f - \Phi_{isc}$. The rate constants for the three processes are then obtained using the expression $k_i = \Phi_i / \tau_S$, where $i = f, isc, and ic$. The values of the photophysical properties are collected in Table 2.3.

### Table 2.3 Photophysical properties of bacteriochlorins $^a$

<table>
<thead>
<tr>
<th>Compound</th>
<th>$Q_y$ (eV) $^b$</th>
<th>$\tau_S$ (ns)</th>
<th>$\Phi_f$</th>
<th>$\Phi_{isc}$</th>
<th>$\Phi_{ic}$</th>
<th>$k_f^{-1}$ (ns)</th>
<th>$k_{isc}^{-1}$ (ns)</th>
<th>$k_{ic}^{-1}$ (ns)</th>
<th>$\Sigma_{Q_y}/\Sigma_{Tot}$ $^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>BC-MM</td>
<td>1.72</td>
<td>2.9</td>
<td>0.10</td>
<td>0.58</td>
<td>0.32</td>
<td>26</td>
<td>5</td>
<td>9</td>
<td>0.11</td>
</tr>
<tr>
<td>BC-AmAm</td>
<td>1.69</td>
<td>3.2</td>
<td>0.16</td>
<td>0.52</td>
<td>0.32</td>
<td>22</td>
<td>7</td>
<td>11</td>
<td>0.13</td>
</tr>
<tr>
<td>BC0</td>
<td>1.74</td>
<td>4.0</td>
<td>0.14</td>
<td>0.62</td>
<td>0.24</td>
<td>29</td>
<td>7</td>
<td>17</td>
<td>0.09</td>
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<tr>
<td>BC-MEs</td>
<td>1.63</td>
<td>3.0</td>
<td>0.13</td>
<td>0.52</td>
<td>0.35</td>
<td>23</td>
<td>6</td>
<td>9</td>
<td>0.15</td>
</tr>
<tr>
<td>BC-EEs</td>
<td>1.61</td>
<td>3.3</td>
<td>0.14</td>
<td>0.55</td>
<td>0.31</td>
<td>24</td>
<td>6</td>
<td>11</td>
<td>0.13</td>
</tr>
</tbody>
</table>

$^a$All measurements were made in toluene at room temperature. Data for BC-MEs and BC-EEs are from ref. 14. The typical errors (percent of value) of the photophysical properties are as follows: $\tau_S$ (±7%), $\Phi_f$ (±5%), $\Phi_{isc}$ (±15%), $\Phi_{ic}$ (±20%), $k_{f}$ (±10%), $k_{isc}$ (±20%), $k_{ic}$ (±25%). The error bars for $\tau_S$, $\Phi_f$, and $\Phi_{isc}$ were determined from select repeat measurements, and those for the $\Phi_{ic}$, $k_{f}$, $k_{isc}$ and $k_{ic}$ were obtained from propagation of errors. $^b$Average energy of the $Q_y$ absorption and fluorescence bands. $^c$Integrated intensity of $Q_y$ absorption manifold [$Q_y(0,0)$ and $Q_y(1,0)$] versus that of the total spectrum (300–900 nm) when plotted in wavenumbers.

The $\Phi_f$ values for BC-MM (0.10) and BC-AmAm (0.16) are comparable to those of parent BC0 (0.14) and benchmarks BC-MEs (0.13) and BC-EEs (0.14). The $\tau_S$ values (in ns) for BC-MM and BC-AmAm (2.9 and 3.2 ns) are modestly shorter than those of parent BC0.
(4.0 ns) and more similar to benchmarks BC-MEs and BC-EEs (3.0 and 3.3 ns). The intersystem-crossing (triplet) yield values of BC-MM and BC-AmAm (0.58, 0.52) are comparable to those for the parent and benchmarks (0.62, 0.52, 0.55). The internal-conversion yields for BC-MM and BC-AmAm (both 0.32) are slightly higher than that for parent BC0 (0.24) but comparable to benchmarks BC-MEs and BC-EEs (0.35, 0.31).

Although the internal-conversion yields carry large (cumulative) error because they derive from a series of measurements, the differences appear to be significant and underlie the above-noted modestly shorter than expected τs values for BC-MM and BC-AmAm. In general, as the Qy band of bacteriochlorins bearing simple substituents (mostly at the 2,3,12,13-positions) moves to lower energy (longer wavelength), the τs values are progressively reduced. However, as noted above and in Table 2.3 the S1 lifetime and energy for BC-MM (2.9 ns, 1.72 eV) and BC-AmAm (3.2 ns, 1.69 eV) are slightly smaller than that for BC0 (4.0 ns, 1.74 eV) but comparable to those for BC-MEs (3.0 ns, 1.63 eV) and BC-EEs (3.3 ns, 1.61 eV). The τs values for the latter three compounds (parent and benchmarks) follow the trend of decreasing value with decreasing S1 energy (increasing Qy wavelength), but the lifetimes for BC-MM and BC-AmAm are shorter rather than longer than that for parent BC0.

Although this result could reflect in part differences (or errors) in radiative rate constant (k_r), those values (derived from τs and Φr) are consistent with the integrated intensity of the Qy band relative to the total spectrum (Figure 2.5), as expected from the relationship of the Einstein coefficients. The differences do not appear to reflect changes in intersystem-crossing rate constants (Table 2.3). The apparent origin is that BC-MM and BC-AmAm have more facile internal conversion [k_{ic} = (9 ns)^{-1} and (11 ns)^{-1}] than BC0 [k_{ic} = (4.0 ns)^{-1} and (3.3 ns)^{-1}].
= (17 ns)^{-1}\), even though the opposite is expected on the basis of the lower S\(_1\) (Q\(_y\)) energy of the parent bacteriochlorin. The expected trend is shown by BC0 [\(k_{ic} = (17 \text{ ns})^{-1}\)] and BC-MEs and BC-EEs [\(k_{ic} = (9 \text{ ns})^{-1}\) and \(11 \text{ ns})^{-1}\)] because the two benchmarks have lower S\(_1\) (Q\(_y\)) energy than the parent. It is interesting to speculate whether the more facile internal conversion of the two new 2,3,12,13-tetraalkylbacteriochlorins is connected with the increased vibronic activity manifest in the absorption spectrum and RR spectrum of CuBC-MM versus CuBC0 (\textit{vide supra}).
Figure 2.8. Integrated intensity of $Q_y$ absorption manifold [$Q_y(0,0)$ and $Q_y(1,0)$] versus that of the total spectrum (300–900 nm) when plotted in wavenumbers (vertical axis) versus the radiative rate constant $k_f$ obtained from the $\tau_s$ and $\Phi_f$ values (x-axis). The overall linear relationship reflects the consistency of the measurements and analysis.

Conclusions

The use of a deactivating group at the $\alpha$-position of the pyrrole unit of a dihydrodipyrrin-acetal has enabled (1) the incorporation of two alkyl groups at the pyrrole $\beta$-positions, and (2) the smooth oxidation of the 9-methyl group to the corresponding aldehyde. This synthetic approach blends features of longstanding routes to natural porphyrins, where dialkylpyrrole-$\alpha$-esters are commonplace, with gem-dimethyl-substituted dihydrodipyrrins to prepare tetraalkylbacteriochlorins. The tetraalkylbacteriochlorins provide close synthetic analogues of the natural chromophores.
Experimental Section.

General Methods. $^1$H NMR (300 MHz) and $^{13}$C NMR (100 MHz) spectra were collected at room temperature in CDCl$_3$ unless noted otherwise. Absorption spectra were obtained in toluene at room temperature unless noted otherwise. Electrospray ionization mass spectrometry (ESI-MS) data are reported for the molecular ion or protonated molecular ion. THF used in all reactions was freshly distilled from Na/benzophenone ketyl. Compounds 5$^{11}$, 7, 8$^{29}$ and 11$^{33}$ were prepared as described in the literature.

Self-Condensation Study of Dihydrodipyrrin-carboxaldehydes. Each reaction (1.0 mL) was carried out in a microreaction vial equipped with a stir bar and cap; the latter was sealed with Teflon tape to limit solvent evaporation. Reactions were done on a 0.018 mmol scale of dihydrodipyrrin-carboxaldehyde. Anhydrous solvents (CH$_2$Cl$_2$, CH$_3$CN) were reagent grade and were used as received.

The acids used were (1) BF$_3$·OEt$_2$ in CH$_3$CN, (2) TMSOTf/DTBP in CH$_2$Cl$_2$, and (3) neat TFA. The procedures for each condition are as following: (i) The dihydrodipyrrin-carboxaldehyde (0.018 mmol) in CH$_3$CN (1.0 mL) was treated with BF$_3$·OEt$_2$ (17 µL, 140 µmol) under argon using a microsyringe. The reaction mixture was stirred at room temperature for 19 h. TEA (60 µL, 0.043 mmol) was added to the reaction mixture. Then the reaction mixture was concentrated. (ii) The dihydrodipyrrin-carboxaldehyde (0.018 mmol) in CH$_2$Cl$_2$ (1.0 mL) was treated with DTBP (33 µL, 144 µmol, 8 molar equiv) followed by TMSOTf (13 µL, 72 µmol, 4 molar equiv) under argon. The reaction mixture was stirred at room temperature for 19 h. The reaction mixture was concentrated. (iii) The dihydrodipyrrin-carboxaldehyde (0.018 mmol) was dissolved in TFA (1.0 mL) under argon flow. The resulting solution was stirred at room temperature for 1 h. Then the reaction
mixture was poured into saturated aqueous NaHCO₃ solution and extracted with CH₂Cl₂. The extract was washed (brine), dried (Na₂SO₄) and concentrated.

The crude samples were checked by TLC, UV-vis spectroscopy and LD-MS. For TLC analysis, a tiny amount of the crude sample in CH₂Cl₂ was spotted directly onto the TLC plate [silica, hexanes/CH₂Cl₂ (1:1)]. TLC showed the consumption of starting material, and the formation of HBC-type and/or other macrocycles (if any). The diagnostic feature in the absorption spectrum was the characteristic bacteriochlorin Q_y absorption band. If present, the bacteriochlorin was isolated by column chromatography [silica, hexanes/CH₂Cl₂ (1:1)]. The fractions containing bacteriochlorins were collected, concentrated and the yield was determined spectroscopically (ε_Q_y = 120,000 M⁻¹cm⁻¹ for HBC-type bacteriochlorins.)

6-[3-(4-Methylphenyl)pyrrol-2-yl]-4,4-dimethyl-5-nitro-2-hexanone (6).

Following a standard procedure,²⁷ a mixture of 5 (460 mg, 2.00 mmol) and mesityl oxide (458 µL, 4.00 mmol) in CH₃CN (4.0 mL) was treated with DBU (897 µL, 6.00 mmol). The reaction mixture was stirred for 24 h at room temperature, diluted with ethyl acetate (15.0 mL) and washed with water and brine. The organic layer was dried (Na₂SO₄) and concentrated. Excess mesityl oxide was removed under high vacuum. The resulting oil was chromatographed [silica, hexanes/ethyl acetate (2:1)] to afford a light brown oil (486 mg, 74%): ¹H NMR (400 MHz) δ 1.08 (s, 3H), 1.19 (s, 3H), 2.10 (s, 3H), 2.37 (s, 3H), 2.37, 2.55 (AB, ²_J = 17.6 Hz, 2H), 3.21 (ABX, ³_J = 2.6 Hz, ²_J = 15.6 Hz, 1H), 3.38 (ABX, ³_J = 11.6 Hz, ²_J = 15.6 Hz, 1H), 5.18 (ABX, ³_J = 2.6 Hz, ³_J = 11.6 Hz, 1H), 6.22–6.24 (m, 1H), 6.67–6.69 (m, 1H), 7.20 (d, ³_J = 8.0 Hz, 2H), 7.24 (d, ³_J = 8.0 Hz, 2H), 8.05–8.20 (br, 1H); ¹³C NMR δ 21.0, 23.7, 23.9, 25.1, 31.4, 36.7, 50.8, 94.4, 109.1, 117.5, 121.8, 123.1, 128.0, 129.1, 133.4, 135.3, 206.9; ESI-MS obsd 329.1852, calcd 329.1860 [(M + H)⁺, M = C₁₉H₂₄N₂O₃].

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1,3,3-Trimethyl-7-(4-methylphenyl)-2,3-dihydropyrrin (1-Me). Following a standard procedure,\textsuperscript{10} a solution of 6 (256 mg, 0.780 mmol) in anhydrous THF (7.8 mL) under argon was treated with NaOMe (210 mg, 3.90 mmol). The mixture was bubbled with argon for 10 min and then was stirred under argon for 1 h at room temperature (first flask). In a second flask, TiCl\textsubscript{3} [8.6 wt\% TiCl\textsubscript{3} in 28 wt\% HCl (d = 1.2), 5.83 mL, 3.90 mmol, 5.0 mol equiv] and H\textsubscript{2}O (31 mL) were combined. The solution was bubbled with argon for 10 min. NH\textsubscript{4}OAc (22.9 g, 297 mmol) was slowly added to buffer the solution to pH 6.0; and then THF (2.2 mL) was added under argon bubbling (~20 min). The solution in the first flask containing the nitronate anion of 6 was transferred via a cannula to the buffered TiCl\textsubscript{3} solution in the second flask. The resulting mixture was stirred at room temperature for 6 h under argon. Then the mixture was slowly poured into a stirred mixture of saturated aqueous NaHCO\textsubscript{3} solution (120 mL) and ethyl acetate (40 mL). After 10 min, the mixture was extracted with ethyl acetate. The combined organic extract was washed with water and then dried (NaSO\textsubscript{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 yellow solid (55 mg, 25\%): mp 112–113 °C; \textsuperscript{1}H NMR δ 1.18 (s, 6H), 2.21 (s, 3H), 2.38 (s, 3H), 2.51 (s, 2H), 5.97 (s, 1H), 6.27–6.28 (m, 1H), 6.84–6.86 (m, 1H), 7.21 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 10.99–11.10 (br, 1H); \textsuperscript{13}C NMR (75 MHz) δ 20.7, 21.2, 29.1, 41.2, 53.7, 102.9, 108.9, 118.3, 123.3, 127.2, 128.5, 129.2, 134.4, 134.9, 161.2, 176.6; ESI-MS obsd 279.1853, calcd 279.1856 [(M + H)\textsuperscript{+}, M = C\textsubscript{19}H\textsubscript{22}N\textsubscript{2}].

1-Formyl-3,3-dimethyl-7-(4-methylphenyl)-2,3-dihydrodipyrrin (1-CHO). Following a general procedure,\textsuperscript{13,28} a solution of 1-Me (45 mg, 0.16 mmol) in 1,4-dioxane (3.2 mL) was treated with SeO\textsubscript{2} (27 mg, 0.24 mmol) under argon. The mixture was stirred
for 1.5 h at room temperature. The reaction mixture was treated with saturated aqueous NaHCO₃ solution (4.0 mL) and extracted with ethyl acetate. The organic extract was washed with water, dried (Na₂SO₄), and chromatographed [silica, hexanes/ethyl acetate (3:1)] to give a dark orange solid (22 mg, 47%): ¹H NMR δ 1.22 (s, 6H), 2.41 (s, 3H), 2.72 (s, 2H), 6.34–6.35 (m, 1H), 6.38 (s, 1H), 7.00–7.02 (m, 1H), 7.25 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 10.0 (s, 1H), 10.71–10.82 (br, 1H); FAB-MS obsd 293.1654, calcd 293.1654 [(M + H)+, M = C₁₉H₂₀N₂O].

4,4-Dimethyl-6-(5-tert-butoxycarbonyl-3,4-dimethylpyrrol-2-yl)-5-nitrohexan-2-one (9). Following a standard procedure²⁷ with modification, mixture of 8 (4.02 g, 15.0 mmol) and mesityl oxide (4-Me, 4.40 g, 45.0 mmol) was treated with DBU (6.7 mL, 45.0 mmol) at room temperature. After 16 h, the reaction mixture was diluted with ethyl acetate and washed with HCl (0.5 M), saturated aqueous NaHCO₃ solution and brine. The organic layer was dried and filtered. The filtrate was concentrated. The residue was crystallized from hexane (20 mL) to give a light brown solid (1.95 g, 35%): mp 118–119 °C; ¹H NMR (400 MHz) δ 1.13 (s, 3H), 1.27 (s, 3H), 1.55 (s, 9H), 1.91 (s, 3H), 2.15 (s, 3H), 2.18 (s, 3H), 2.38–2.64 (AB, ²J = 18.3 Hz, 2H), 2.94 (ABX, ³J = 2.4 Hz, ²J = 13.2 Hz), 3.26 (ABX, ³J = 11.4 Hz, ²J = 15.3 Hz), 5.08 (ABX, ³J = 3.3 Hz, ²J = 14.1 Hz), 8.40–8.50 (brs, 1H); ¹³C NMR δ 8.92, 10.74, 24.29, 24.64, 25.20, 28.73, 32.07, 37.00, 51.59, 80.62, 93.71, 118.45, 119.83, 126.29, 161.24, 206.99; ESI-MS obsd 367.2221, calcd 367.2228 [(M + H)+, M = C₁₉H₃₀N₂O₅]. Compound 9 has been prepared via an earlier route.³¹

2,3-Dihydro-1,3,7,8-pentamethyl-9-tert-butoxycarbonyldipyrrin (10-Me). Following a general procedure¹¹ with modification, a solution of 9 (1.95 g, 5.33 mmol) in THF/methanol (10:1, 10 mL) under argon was treated with NaOMe (0.86 g, 15.9 mmol).
The mixture was stirred at room temperature for 30 min. In a second flask, NH₄OAc (20.0 g, 266 mmol) in distilled THF (72 mL) was bubbled with argon for 15 min. Then TiCl₃ (27 mL, 20 wt% in 3% HCl solution) was added, and the mixture was degassed by bubbling with argon for 30 min. Then, the contents of the first flask mixture were transferred via cannula to the buffered TiCl₃ solution. The resulting mixture was stirred at room temperature for 20 h under argon. The mixture was then filtered through a pad of Celite, which washed with ethyl acetate. The filtrate was washed with saturated aqueous NaHCO₃ solution, brine and water. The organic layer was dried and filtered. The filtrate was concentrated. Column chromatography (silica, CH₂Cl₂) afforded a light yellow solid (1.17 g, 69%): mp 143–144 °C; ¹H NMR δ 1.21 (s, 3H), 1.58 (s, 9H), 2.02 (s, 3H), 2.22 (s, 3H), 2.26 (s, 3H), 2.52 (s, 2H), 5.67 (s, 1H), 11.10 (brs, 1H); ¹³C NMR δ 8.89, 10.46, 20.91, 28.61, 29.19, 41.51, 53.78, 79.64, 101.30, 118.28, 119.60, 126.22, 130.60, 161.20, 163.51, 178.35; ESI-MS obsd 317.2218, calcd 317.2223 [(M + H)+, M = C₁₉H₂₈N₂O₂]. Compound 10-Me has been prepared via an earlier route.⁳¹

9-tert-Butoxycarbonyl-1-formyl-2,3-dihydro-3,3,7,8-pentamethyldipyrin (10-CHO). Following a general procedure,¹³,²⁸ a solution of dihydrodipyrrin 10-Me (95 mg, 0.30 mmol) in 6.0 mL of 1,4-dioxane was treated with SeO₂ (100 mg, 0.90 mmol) under argon. The reaction mixture was stirred at room temperature and monitored via absorption spectroscopy for the characteristic bathochromic shift that accompanies oxidation of the pyrroline α-methyl group to the carboxaldehyde.¹³ After 90 min, ethyl acetate was added. The reaction mixture was washed with aqueous NaHCO₃ solution and then brine. The organic layer was dried, concentrated and chromatographed (silica, CH₂Cl₂) to give an orange oil (63 mg, 63%): λ_abso(CH₂Cl₂) 468 nm; ¹H NMR δ 1.26 (s, 6H), 1.59 (s, 9 H), 2.09 (s,
3H), 2.26 (s, 3H), 2.73 (s, 2H), 6.14 (s, 1H), 9.98 (s, 1H), 10.81 (brs, 1H); \(^{13}\)C NMR \(\delta\) 9.15, 10.38, 28.58, 29.27, 41.27, 46.16, 80.62, 110.98, 122.75, 126.23, 129.63, 160.93, 162.38, 170.19, 190.28; ESI-MS obsd 331.2011, calcd 331.2016 [(M + H)\(^+\), M = C\(_{19}\)H\(_{26}\)N\(_2\)O\(_3\)].

**2,3,8,12,13,18,18-Octamethylbacteriochlorin (BC-MM).** A sample of 10-CHO (69.0 mg, 0.208 mmol) was dissolved in TFA (10.0 mL) under argon and stirred for 1 h at room temperature. Then the reaction mixture was poured into saturated aqueous NaHCO\(_3\) solution (200 mL). The resulting mixture was extracted with CH\(_2\)Cl\(_2\) (200 mL). The organic extract was washed with brine and water, dried (Na\(_2\)SO\(_4\)), and concentrated. Column chromatography [silica, hexanes/CH\(_2\)Cl\(_2\) (1:1)] afforded a green solid (13.0 mg, 29%): \(^1\)H NMR (400 MHz) \(\delta\) -2.43 (brs, 2H), 1.96 (s, 12H), 3.31 (s, 6H), 3.34 (s, 6H), 4.45 (brs, 4H), 8.57 (s, 2H), 8.71 (s, 2H); \(^{13}\)C NMR \(\delta\) 11.3, 11.4, 29.9, 31.3, 46.1, 51.9, 92.6, 95.1, 127.8, 133.7, 134.5, 156.4, 168.7; ESI-MS obad 427.2850, calcd 427.2856 [(M + H)\(^+\), M = C\(_{28}\)H\(_{34}\)N\(_4\)] ; \(\lambda_{abs}\)(toluene) 347, 374, 490, 722 nm.

**Benzyl 3,4,5-tris(benzyloxy carbonylmethyl)pyrrole-2-carboxylate (12).** Following a reported procedure,\(^{36}\) a solution of the trimethyl ester 11 (7.32 g, 25.9 mmol) in benzyl alcohol (40 mL) in a 100 mL round-bottom flask was stirred under an argon stream and heated to reflux. After a few minutes, a solution of sodium (0.52 g) in benzyl alcohol (10.0 mL) was added dropwise; heating was continued throughout and a few minutes later (20 min from start of process) the hot solution was poured into a mixture of water (50 mL), acetic acid (1.0 mL) and methanol (100 mL). The solid product was collected, washed with water and then dissolved in CH\(_2\)Cl\(_2\) (100 mL). After washed with water, the organic phase was dried (Na\(_2\)SO\(_4\)) and filtered. The filtrate was concentrated to a yellow oil. Recrystallization (hexanes/ether/CH\(_2\)Cl\(_2\), 100 mL/20 mL/20 mL) gave a white solid (9.03 g,
Compound 12 has been prepared via an earlier route.\textsuperscript{34}

**Benzyl 3,4-bis(methoxycarbonylmethyl)-5-methylpyrrole-2-carboxylate (13).**

Following a reported procedure,\textsuperscript{36} the triester 12 (12.78 g, 25.0 mmol) in THF (40 mL) and dry methanol (80 mL) was treated with sodium methoxide (1.08 g, 20.0 mmol). The reaction was monitored by TLC analysis. After 3 h, glacial acetic acid (3.0 mL) was added and the solution was concentrated. Then, water (200 mL) was added, and the mixture was extracted with CH$_2$Cl$_2$ (200 mL). The organic layer was washed, dried ($\text{Na}_2\text{SO}_4$) and concentrated. The crude product was recrystallized from hexanes/ether (100 mL/50 mL) to give white crystals (7.73 g, 82%): mp 90–91 °C; $^1$H NMR (400 MHz) $\delta$ 2.21 (s, 3H), 3.40 (s, 2H), 3.58 (s, 3H), 3.86 (s, 2H), 5.26 (s, 2H), 7.35 (m, 5H), 9.38 (br, 1H); $^{13}$C NMR $\delta$ 11.6, 30.1, 30.9, 51.9, 52.0, 65.9, 114.9, 117.7, 123.7, 128.2, 128.3, 128.6, 131.9, 136.2, 161.0, 171.9, 172.0; ESI-MS obsd 360.1428, calcd 360.1442 [(M + H)$^+$, M = C$_{19}$H$_{21}$NO$_6$].

Compound 13 has been prepared via an earlier route.\textsuperscript{35}

**tert-Butyl 3,4-bis(methoxycarbonylmethyl)-5-methylpyrrole-2-carboxylate (14).**

Following a reported procedure,\textsuperscript{37} a solution of 13 (0.825 g, 2.30 mmol) in 20 mL of methanol was reduced overnight with hydrogen (balloon pressure) over 83 mg of 10% Pd/C. The catalyst was removed by filtration, and the filtrate was concentrated to dryness. The resulting residue was dissolved in 10 mL of dry tert-butyl alcohol and 10 mL of dry THF. DCC (0.473 g, 2.30 mmol) and a catalytic amount of DMAP were added, and the mixture
was stirred for 18 h at room temperature. The precipitate was removed by filtration, and the filtrate was concentrated. Chromatography (silica, CH$_2$Cl$_2$) afforded a light yellow solid (522 mg, 70%): mp 130–131 °C; $^1$H NMR (400 MHz) δ 1.54 (s, 9H), 2.25 (s, 3H), 3.41 (s, 2H), 3.65 (s, 3H), 3.67 (s, 3H), 3.84 (s, 2H), 9.65 (br, 1H); $^{13}$C NMR δ 11.7, 28.6, 30.3, 31.1, 52.1, 56.0, 81.1, 114.5, 120.0, 122.2, 131.2, 161.3, 172.2, 172.3; ESI-MS obsd 348.1405, calcd 348.1418 [(M + Na)$^+$, M = C$_{16}$H$_{23}$NO$_6$].

**tert-Butyl 3,4-bis(methoxycarbonylmethyl)-5-(2-nitroethyl)pyrrole-2-carboxylate (16).** Following a reported procedure,$^{31}$ a solution of the methylpyrrole 14 (0.975 g, 3.00 mmol) in CH$_2$Cl$_2$ (30 mL) was stirred vigorously at 0 °C with K$_2$CO$_3$ (4.55 g, 33.0 mmol) during dropwise addition of SOCl$_2$ (510 μL, 6.3 mmol). The mixture was stirred for 10 min at 0 °C and 10 min at 20 °C before filtration through Celite. The filtrate was concentrated to yield the crude dichloromethylpyrrole. A solution of this product in acetone (30 mL) and water (15 mL) was kept for 1 h before dilution with water (30 mL) and extraction with CH$_2$Cl$_2$ (50 mL). The combined organic extract was washed with saturated aqueous NaHCO$_3$ solution, dried (Na$_2$SO$_4$) and concentrated to give the crude formylpyrrole 15, which was used in the next step without further purification: $^1$H NMR (400 MHz) δ 1.56 (s, 9H), 3.69 (s, 3H), 3.70 (s, 3H), 3.82 (s, 2H), 3.87 (s, 2H), 9.80 (s, 1H), 10.22 (br, 1H); $^{13}$C NMR δ 28.2, 29.5, 30.0, 52.0, 52.4, 83.0, 122.6, 125.6, 126.6, 130.2, 160.0, 170.7, 171.2, 179.8; ESI-MS obsd 362.1199, calcd 362.1210 [(M + Na)$^+$, M = C$_{16}$H$_{21}$NO$_7$]. Following a standard procedure,$^{11}$ the crude formylpyrrole 15, nitromethane (0.48 mL, 9.0 mmol), potassium acetate (0.35 g, 3.6 mmol) and methylamine hydrochloride (0.24 g, 3.6 mmol) were stirred together in methanol (10.0 mL) for 5 h. Then the mixture was diluted with water (50 mL) and extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined organic extract was washed
with water, dried (Na$_2$SO$_4$) and concentrated to give the crude (2-nitrovinyl)pyrrole. The residue was dissolved in methanol (40 mL) and DMF (4 mL) containing acetic acid (0.18 g, 3.0 mmol). The solution was treated with sodium borohydride (0.37 g, 10 mmol) in one portion. Then the mixture was cooled to 0 $^\circ$C, acidified to pH 2 with HCl solution (2 M), diluted with water (200 mL) and extracted with ether (2 × 100 mL). The combined organic extract was washed [saturated aqueous NaHCO$_3$ solution and brine (50 mL)], dried and concentrated. Chromatography [silica, hexanes/ethyl acetate (1:1)] gave a yellow oil (0.580 g, 50%): $^1$H NMR (400 MHz) $\delta$ 1.53 (s, 9H), 3.30 (t, $J = 7.2$ Hz, 2H), 3.45 (s, 2H), 3.66 (s, 3H), 3.68 (s, 3H), 3.82 (s, 2H), 4.61 (t, $J = 7.2$ Hz, 2H), 10.06 (br, 1H); $^{13}$C NMR $\delta$ 23.7, 28.3, 29.9, 30.7, 51.8, 52.1, 73.9, 81.5, 115.8, 121.2, 121.8, 128.5, 160.9, 171.8, 171.9; ESI-MS obsd 407.1415, calcd 407.1425 [(M + Na)$^+$, M = C$_{17}$H$_{24}$N$_2$O$_8$].

4,4-Dimethyl-6-(5-tert-butoxycarbonyl-3,4-bis(methoxycarbonylmethyl)pyrrol-2-yl)-5-nitro-hexan-2-one (17). Following a standard procedure,$^{38}$ the nitroethylpyrrole 16 (0.580 g, 1.51 mmol), mesityl oxide (0.740 g, 7.50 mmol), TBAF (1.0 M in THF, 1.51 mL, 1.51 mmol) and 4 Å molecular sieves (1.5 g) were stirred together in DMF (30 mL) for 3 h. The mixture was then diluted with water (120 mL) and extracted with ether (4 × 30 mL). The combined organic extract was washed [HCl solution (2 M, 20 mL), saturated aqueous NaHCO$_3$ solution (20 mL) and brine (20 mL)], dried (Na$_2$SO$_4$) and concentrated. Chromatography [silica, CH$_2$Cl$_2$, then CH$_2$Cl$_2$/ethyl acetate (1:1)] afforded a yellow oil (393 mg, 54%): $^1$H NMR (400 MHz) $\delta$ 1.13 (s, 3H), 1.25 (s, 3H), 1.53 (s, 9H), 2.17 (s, 3H), 2.43, 2.60 (AB, $^2$J = 17.6 Hz, 2H), 3.07 (ABX, $^3$J = 2.0 Hz, $^2$J = 15.2 Hz, 1H), 3.33 (ABX, $^3$J = 12.4 Hz, $^2$J = 16.0 Hz, 1H), 3.41 (s, 2H), 3.66 (s, 3H), 3.67 (s, 3H), 3.80 (s, 2H), 5.19 (ABX, $^3$J = 2.6 Hz, $^2$J = 12.0 Hz, 1H), 8.93 (br, 1H); $^{13}$C NMR $\delta$ 24.0, 24.1, 24.7, 28.3, 29.8, 30.6,
31.8, 36.8, 51.2, 51.7, 52.0, 81.1, 93.5, 115.8, 121.2, 121.6, 128.2, 160.3, 171.7, 171.8, 207.0; ESI-MS obsd 505.2144, calcd 505.2157 [(M + Na)^+], M = C_{23}H_{34}N_{2}O_{9}].

9-tert-Butoxycarbonyl-2,3-dihydro-7,8-bis(methoxycarbonylmethyl)-1,3,3-
trimethylidipyrrin (18-Me). Following a standard procedure,^{11} a solution of 17 (393 mg, 0.815 mmol) in THF/methanol (2.0 mL/0.20 mL) under argon was treated with sodium methoxide (221 mg, 4.08 mmol). The mixture was stirred at room temperature for 30 min. In a second flask, ammonium acetate (6.13 g, 81.5 mmol) in distilled THF (20 mL) was bubbled with argon for 15 min before TiCl_{3} solution (8.37 g of 12 wt% in 5–10% HCl solution) was added. The mixture was degassed by bubbling with argon for 30 min. Then, the solution in the first flask was transferred via cannula to the buffered TiCl_{3} solution. The resulting mixture was stirred for 20 h at room temperature under argon. The mixture was poured into 200 mL of saturated aqueous NaHCO_{3} solution and extracted with ethyl acetate (2 × 200 mL). The organic extract was filtered through Celite. The filtrate was washed with brine, dried (Na_{2}SO_{4}) and concentrated. Chromatography [silica, CH_{2}Cl_{2}/ethyl acetate (3:1)] gave a yellow oil (65 mg, 18%): ^{1}H NMR (400 MHz) δ 1.21 (s, 6H), 1.55 (s, 9H), 2.23 (s, 3H), 2.53 (s, 2H), 3.52 (s, 2H), 3.64 (s, 3H), 3.66 (s, 3H), 3.90 (s, 2H), 5.71 (s, 1H), 11.46 (br, 1H); ^{13}C NMR δ 21.0, 28.5, 29.1, 30.2, 30.7, 41.6, 51.9, 52.1, 53.9, 80.5, 100.8, 115.0, 120.9, 131.9, 165.0, 172.1, 172.2, 179.5; ESI-MS obsd 433.2327, calcd 433.2333 [(M + H)^+], M = C_{23}H_{32}N_{2}O_{6}].

2,3,12,13-Tetrakis(methoxycarbonylmethyl)-8,8,18,18-
tetramethylbacteriochlorin (BC-AmAm). Following a standard procedure,^{13,28} a solution of dihydrodipyrrin 18-Me (20 mg, 0.046 mmol) in 1,4-dioxane (1.0 mL) was treated with SeO_{2} (15 mg, 0.139 mmol) with vigorously stirring at room temperature. After 2 h, the
reaction mixture was poured into saturated aqueous NaHCO₃ solution and then extracted with ethyl acetate (100 mL). The organic extract was washed with brine, dried (Na₂SO₄) and concentrated. The residue was passed through a short silica column [hexanes/ethyl acetate (3:1)] to give 18-CHO as a yellow-orange oil. The oil was dissolved in dry CH₃CN (2.50 mL) and treated with BF₃·OEt₂ (45 µL, 0.37 mmol) under argon. The vial was sealed with Parafilm and stirred at room temperature for 20 h. Then trimethylamine (50 µL) was added to quench the reaction. The mixture was concentrated and chromatographed [silica, hexanes/CH₂Cl₂ (3:1)] to give a green solid (1.0 mg, 6.6%): ^1H NMR (400 MHz) δ -2.13 (br, 2H), 1.95 (s, 12H), 3.73 (s, 6H), 3.75 (s, 6H), 4.44 (s, 4H), 4.89 (s, 2H), 4.91 (s, 2H), 8.67 (s, 2H), 8.76 (s, 2H); ω₅ (toluene) 347, 373, 495, 732 nm; ESI-MS obsd 659.3052, calcd 659.3075 [(M + H)^+, M = C₉₂H₃₂N₄O₈].

**Cu(II)-2,3,8,8,12,13,18,18-Octamethylbacteriochlorin (CuBC-MM).** Following a reported procedure,^{32} BC-MM (2.0 mg, 4.7 µmol), sodium hydride (24 mg, 0.94 mmol, 60% dispersion in mineral oil) and copper(II) acetate (43 mg, 0.24 mmol) were placed in a Schlenk tube and flushed with argon. Freshly distilled THF (1.2 mL) was added, and the reaction mixture was heated at 60 °C under argon for 16 h. Then the mixture was diluted with CH₂Cl₂ and washed with saturated aqueous NaHCO₃ solution. The organic layer was washed with brine, dried (Na₂SO₄) and concentrated. Flash chromatography [silica, hexanes/CH₂Cl₂ (2:1), with 1% trimethylamine] afforded a green solid (6.0%, determined by absorption spectroscopy assuming equal molar absorptivity of the respective free base and metallobacteriochlorins at the Q_(5,0) (0,0) band): ω₅ (toluene) 336, 385, 506, 736 nm; LD-MS obsd 488.6; ES-MS obsd 487.1900, calcd 487.1918 [M^+, M = C₂₈H₃₂CuN₄].
X-ray structure determination. X-ray measurement of BC-MM was made on a Bruker-Nonius X8 Apex2 CCD diffractometer at a temperature of 110 K. The frame integration was performed using SAINT+. The resulting raw data were scaled and absorption corrected by multiscan averaging of symmetry equivalent data using SADABS. The structures were solved using direct methods from SIR92 and refined using the NRCVAX crystallographic suite. The structure was refined using the SHELXL program from the SHELX2013 package, and graphic plots were produced using Mercury 3.5.

RR Spectroscopy. The RR spectrum of CuBC-MM was obtained at room temperature on a sample (~0.2 mM) in deoxygenated benzene solution contained in a 5 mm diameter NMR tube which had been cut to a length of ~4 cm. The NMR tube was spun to mitigate photodamage. Spectra were initially acquired in CH₂Cl₂ solution; however, CuBC-MM was quite photolabile in this solvent and tended to demetalate, resulting in severe interference from fluorescence emission from the free base. CuBC-MM was much less prone to demetalation in benzene, albeit a small amount of demetalation occurred during the course of data acquisition, as was evidenced by increasing fluorescence emission.

The RR spectrum was acquired with a red-optimized triple spectrograph (Spex 1877) equipped with a holographically etched 1200 groove/mm grating in the third state. A back-illuminated (CCD) was used as the detector (Princeton Instruments LN/CCD equipped with a Tektronix chip). The excitation wavelength was provided by the discrete output of a Ti:sapphire laser (Coherent 890), pumped by a diode-pumped solid-state laser (Coherent Verdi-V6). The laser powers were typically in the 6–7 mW range; the beam diameter was ~0.5 mm. The scattered light was collected in a 90° configuration by using a 50 mm, f/1.2 camera lens. The spectra were acquired with 2 h of signal averaging (60 × 120 s or 120 × 60
s scans, depending on the spectral window). The spectral resolution was ~ 2 cm⁻¹ at a Raman shift of 200 cm⁻¹. The spectral data were calibrated using the known frequencies of indene⁵⁹ and fenchone.⁶⁰

**Photophysical Measurements.** Static absorption (Shimadzu UV-1800), fluorescence (Horiba Nanolog), and time-resolved measurements were performed at room temperature. Measurement of the fluorescence quantum yield (Φᵢ) and singlet excited-state lifetime (τₛ) utilized dilute (μM) Ar-purged toluene solutions. Static emission measurements employed 2–4 nm excitation and detection bandwidths. Emission spectra were corrected for detection-system spectral response. Samples for Φᵢ measurements generally had an absorbance of < 0.05 for BC-MM and BC-AmAm in the Qᵧ band to minimize inner-filter effects associated with the very small (1–2 nm) fluorescence-absorption (Stokes) shifts. For analogues with larger (up to 6 nm) Stokes shifts, the Qᵧ absorbance could be increased somewhat but never > 0.15. The Φᵢ measurements employed an integrating sphere in which the ratio of excitation and emission bands were compared for a blank and a sample to calculate the absolute fluorescence quantum yield (Horiba, Quanti-Phi). Fluorescence lifetimes were obtained using several methods and then averaged. The first method utilized a stroboscopic fluorescence decay technique on an apparatus with an approximately Gaussian instrument response function with a FWHM of ~1 ns (Photon Technology International, LaserStrobe TM-3). Samples were excited in the blue to green spectral regions by a dye laser pumped by a nitrogen laser at 337 nm. The second method utilized transient absorption decay measurements in which difference spectra (450–750 nm) were measured as a function of time following a 130-fs excitation flash in the Qₓ or Qᵧ band. One set up utilized 130-fs white-light probe pulse and delay times to 8 ns (Ultrafast Systems, Helios). The second
method used a continuum probe laser with a pulse width of ~1 ns and data acquisition in 100-ps bins to a delay time of ~0.5 ms (Ultrafast Systems, EOS). The values from the various measurements were in good agreement with those obtained previously\textsuperscript{14} for benchmarks using a fluorescence modulation technique (Spex Tau2). The EOS was also used for measurements of the yield of $S_1 \rightarrow T_1$ intersystem crossing (i.e., the triplet yield). In particular, from the transient absorption difference spectra, time profiles for bleaching of the ground-state Q bands relative to the basically featureless excited-state absorption were fit to an exponential (the excited-state lifetime) and the amplitude at the asymptote of the decay (due to $T_1$) was compared to the value at $t = 0$ (due to $S_1$).
### References


CHAPTER III

Synthetic Approaches Towards Unsymmetrically Substituted Bacteriochlorins

Preamble

The full contents of this chapter are in preparation for publication with contributions from the following individuals: Hen-Je Kim on early studies on exploration towards unsymmetrically substituted bacteriochlorins; Olga Mass and Muthyala Nagarjuna Reddy on synthesis of In-BC-1.

Introduction

Bacteriochlorins, which contain alternating pyrrole and pyrroline rings about the macrocycle, are distinctive members in the tetrapyrrole family. Bacteriochlorins exhibit a strong absorption band in the near-infrared (NIR) region from 700 to 900 nm, thereby giving rise to potential applications in solar energy conversion and photomedicine (e.g., imaging, flow cytometry, photodynamic therapy).\textsuperscript{1,2} In nature, bacteriochlorophylls $a$, $b$ and $g$ are the key pigments in anoxygenic bacterial photosynthesis. However, there are two main obstacles to handling bacteriochlorophylls: (1) purple bacteria, as a source of Bchl $a$, require special conditions for large-scale cultivation and hence afford limiting production. (2) Bacteriochlorophylls undergo adventitious dehydrogenation (Bchl $a^3$) or tautomerization (Bchl $b^{4-6}$ and $g^7$) to give the corresponding chlorins, which lack the characteristic NIR absorption band. Thus, robust and practical methods of synthesis are essential for fundamental studies of the chemical and photophysical properties pertaining to bacteriochlorophylls.
Early syntheses of bacteriochlorins have relied on hydrogenation of (or addition to) synthetic porphyrins and chlorins. Kishi reported the first example of a de novo synthesis of bacteriochlorins, obtaining an analogue of the naturally occurring (but likely non-photosynthetic) bacteriochlorin tolyporphin A. Tolyporphin A is more stable than bacteriochlorophylls, as the former contains a geminal dialkyl group in each pyrrole ring; the geminal dialkyl group blocks adventitious dehydrogenation. In Kishi’s route, the bacteriochlorin macrocycle was prepared from monocyclic precursors using an Eschenmoser sulfide contraction (Scheme 3.1A). While an elegant solution for the architecturally complex tolyporphin, the length of the synthesis has stymied application to a broader set of bacteriochlorins. Over the past few years, our research has been focused on developing robust, versatile and efficient routes to synthetic bacteriochlorins. A de novo synthesis (Scheme 3.1B, top), which relies on the self-condensation of a dihydrodipyrrin–acetal or dihydrodipyrrin–carboxaldehyde, opens access to stable bacteriochlorins bearing diverse substituents at the β-pyrrolic and meso-positions. A complementary route (Scheme 3.1B, bottom) employs a Northern-Southern (N-S) self-condensation of a dihydrodipyrrin–acetal, which affords the same bacteriochlorins as the Eastern-Western (E-W) route but affords expanded scope owing to the method for construction of the dihydrodipyrrin–acetal. Recently, we reported a new de novo route for constructing bacteriochlorins (Scheme 3.1C). The bacteriochlorin macrocycle as well as the isocyclic ring are created in a one-flask reaction from a linear tetra-pyrrole, which includes Nazarov cyclization and electrophilic aromatic substitution. The linear tetra-pyrrole in turn is prepared by Knoevenagel condensation starting from two dihydrodipyrrins.
Scheme 3.1. Building Bacteriochlorin Macrocycles: (A) Kishi’s route to tolyporphin A analogues, (B) de novo Eastern-Western strategy (top) and Northern-Southern strategy (bottom), and (C) Knoevenagel–Nazarov strategy

A significant challenge in bacteriochlorin synthesis concerns access to unsymmetrically substituted macrocycles with diverse groups on the respective pyrrole and pyrroline rings. In contemplating routes to achieve this goal, a de novo synthesis of chlorins
was instructive (Scheme 3.2).\textsuperscript{16,17} The chlorin synthesis entails the directed joining of two dipyrrolic species, a dipyrromethane (Eastern half) and a hydrodipyrrin (Western half). The joining of the two halves begins by condensation at the \( \alpha \)-pyrrole position of the Western half and the \( \alpha \)-carbon (carboxaldehyde or carbinol unit) of the Eastern half to form a linear tetrapyrrole (a bilin\textsuperscript{17,18} analogue); subsequent oxidation and cyclization give the chlorin. The directed nature of the synthesis enables distinct substitution in the respective halves, giving any desired location of peripheral substituents. The oxidative cyclization in this process entails a complex cascade of individual steps, involving (1) dehydrogenation, (2) tautomerization of the imine to the enamine, (3) complexation with a metal ion, (4) ring closure via a putative 18\( \pi \)-electrocyclization, and (5) elimination of HBr.\textsuperscript{16} While very little is known about the exact sequence of steps and the reactivity of specific intermediates, the process is reliable and the overall efficiency is reasonably good.

Scheme 3.2. \textit{De novo} Synthesis of Chlorins
Previously, we attempted to prepare an unsymmetrically substituted bacteriochlorin by the above strategy. The route employed a dihydrodipyrrin–CH$_3$ entity as the Western half and a bromodihydrodipyrrin–acetal as the Eastern half (Scheme 3.3). Neither of the halves could undergo self-condensation. Yet, treatment of the mixture of the Eastern half and Western half with a Lewis acid did not give the desired linear tetrapyrrole, but rather a green product that was found to be a $B,D$-tetrahydrocorrin bearing a methyl group at the A–D ring junction. The $B,D$-tetrahydrocorrin contains a linear polyene chromophore (coincidentally embedded in a macrocycle) and as such lacks the intense bands characteristic of bacteriochlorins. The tetrahydrocorrin stands intermediate between the corrin (ligand of cobalamin) and the fully unsaturated corrin (an octahydrocorrin); the latter is a formal tautomer of the well known corrole, itself an isomer of porphyrin. Approaches to modify this process to obtain bacteriochlorins could entail the following: (1) employ tetrahydrodipyrrins rather than dihydrodipyrrins as the Eastern half and Western half to impart different reactivity, (2) locate blocking groups other than bromo- at the $\alpha$-pyrrolic position in hydrodipyrrins, and (3) examine electrophiles other than the acetal unit.
In this paper, we describe exploratory studies of directed syntheses of bacteriochlorins. The synthetic plan remains based on the *de novo* route to chlorins. The paper is divided into three parts. In part I, we describe the preparation of all hydrodipyrrin building blocks, which bear distinct groups at the $\alpha$-pyrrole or $\alpha$-pyrroline position. Part II describes systematic studies of approaches to bacteriochlorins starting from those building blocks, including screening of conditions for condensations and cyclizations for each route. Part III describes the chemical characterization of the resulting new tetradehydrocorrin and bacteriochlorins.

**Scheme 3.3.** Directed Route to *BD*-tetradehydrocorrins (left) and terminology (right)
Results

Retrosynthetic analysis. The retrosynthetic analysis for the preparation of unsymmetrically substituted bacteriochlorins is shown in Scheme 3.4. Compared to the route to chlorins, the Eastern half is hydrodipyrrin (a dihydrodipyrrin-1-CH$_3$ or tetrahydrodipyrrin-1-CH$_3$) versus a dipyrromethane, while the Western half is the same or similar in both routes – a dihydrodipyrrin in the bacteriochlorin route versus a dihydrodipyrrin or tetrahydrodipyrrin in the chlorin route. Further issues in the retrosynthesis are as follows.

Scheme 3.4. Retrosynthetic Analysis

Condensation of the Eastern half and Western half under acidic conditions produces the desired hydrobilin. Self-condensation of the Eastern half, a possible undesired side-reaction, can be thwarted by the following two strategies: (1) If the pyrrole substituent “Z” is hydrogen, an electron-withdrawing group (e.g., ethoxycarbonyl) at the β-pyrrole positions in
the dihydrodipyrrin–acetal (Eastern half) could be employed to decrease the reactivity of the pyrrole ring, so that the condensation between Eastern half and Western half would proceed preferentially versus the self-condensation of the Eastern half. (2) For the pyrrole substituent “Z” to be an entity that blocks the α-pyrrole position also requires a method of cleavage of the blocking unit to complete the subsequent ring closure.

To explore the aforementioned issues, a set of 7 hydrodipyrrins has been prepared (Figure 3.1). The hydrodipyrrins include one Western half, a tetrahydrodipyrrin (2) and six Eastern halves, all of which are dihydrodipyrrins. In the latter, the pyrrole “Z” substituent includes ethoxycarbonyl- (8a), methyl- (8b), H- (7c, 17), methylthio- (14), and bromo- (16) whereas the pyrroline “Y” substituent includes (MeO)$_2$CH- (8a, 8b, 14), OHC- (7c, 16) and tert-butylimino- (17).

**Figure 3.1.** Hydrodipyrrins for studies of bacteriochlorin formation.
**Synthesis of hydrodipyrrins.** The synthesis of tetrahydrodipyrrins bearing 1-methyl groups is well established. Here, reductive cyclization of nitrohexanone 1 in the presence of zinc dust/HCO₂NH₄ in THF gave tetrahydrodipyrinn-1-CH₃ 2 in 63% yield (Scheme 3.5).

![Scheme 3.5. Synthesis of Tetrahydrodipyrinn-1-CH₃](image)

Scheme 3.5 shows the preparation of new dihydrodipyrrins with blocking units at the α-pyrrole position. Blocking units can be introduced at the very beginning of this route. Pyrrole–carboxaldehydes 3a, 3b, and 3c are known compounds; 3a and 3b were prepared in a two-step procedure starting from a Paal-Knorr synthesis, whereas 3c was prepared in a two-step procedure starting from a van Leusen synthesis. An electron-withdrawing group is necessary in 3b to stabilize the pyrrole ring.

Following a general approach, pyrrole–carboxaldehydes 3a–c were converted to nitroethylpyrroles 4a–c through a Henry reaction and reduction with NaBH₄. Treatment of 4a–c with mesityl oxide in the presence of DBU at room temperature afforded the corresponding nitrohexanones 5a–c. Subsequent TiCl₃-mediated reductive cyclization afforded dihydrodipyrinn-1-CH₃ compounds 6a–c, which upon oxidation with selenium
dioxide gave dihydrompyrrin–carboxaldehydes 7a–c.\textsuperscript{13} Aldehydes 7a,b were converted to the corresponding dihydrompyrrin–acetals 8a,b by exposure to trimethyl orthoformate in the presence of \textit{p}-toluenesulfonic acid (TsOH).\textsuperscript{14}
Scheme 3.6. Synthesis of Dihydrodipyrrins
Another established approach\textsuperscript{12} to dihydrodipyrrin–acetals (Scheme 3.7) was employed to prepare the new Eastern half 14, which contains a methylthio group as blocking unit. Thus, 2- methylthiopyrrole 9 gave the corresponding (2-nitroethyl)pyrrole 11 in two steps. Then, 11 was reacted with 1,1-dimethoxy-4-methyl-3-penten-2-one (12), giving nitrohexanone 13 in 48% yield. TiCl\textsubscript{3}-mediated reductive cyclization gave dihydrodipyrrin–acetal 14.

\textbf{Scheme 3.7. Synthesis of Dihydrodipyrrin–acetal 14.}
The bromination of hydrodipyrrin–carboxaldehyde 15 was achieved most effectively by using 1 molar equivalent of NBS in THF at −78 °C, affording 16 in 45% yield (Scheme 3.8). Compound 16 was prone to decomposition upon dissolution in chlorinated solvents and during chromatography on silica, but was stable in the solid state at −20 °C.

![Scheme 3.8. Bromination of a Dihydrodipyrrin–carboxaldehyde](image)

**Scheme 3.8.** Bromination of a Dihydrodipyrrin–carboxaldehyde

Distinct groups located at the α-pyrroline position (acetal or carboxaldehyde) in dihydrodipyrrins could provide a range of chemical reactivity during self-condensation to give the bacteriochlorin. Herein, treatment of the dihydrodipyrrin–carboxaldehyde 7c with t-BuNH$_2$ in dichloromethane at room temperature for 2 h gave the corresponding dihydrodipyrrin–imine (17) in 63% yield (Scheme 3.9). The imine (a yellow solid) was quite stable compared to the precursor carboxaldehyde (a yellow oil).

![Scheme 3.9. Synthesis of a Dihydrodipyrrin–imine](image)

**Scheme 3.9.** Synthesis of a Dihydrodipyrrin–imine

**Exploration of bacteriochlorin formation.** *Eastern half without a blocking unit.*

The condensation of 18 and 8c was carried out with the expectation that the electron-
withdrawing group (-CO₂Et) at the β-pyrrole position in dihydrodipyrrin **8c** would decrease the reactivity of the pyrrole ring and suppress the self-condensation of **8c**. The condensation of dihydrodipyrrin **8c** and **18** in the presence of 2 molar equiv of Bi(OTf)₃ in CH₂Cl₂ followed by treatment with 10 molar equiv of InCl₃ and 10 molar equiv of 2,2,6,6-tetramethylpiperidine (TMPi) in CH₃CN exposed to air resulted in bacteriochlorin **In-BC-1** upon detection by absorption spectroscopy and LD-MS analysis. Conditions to optimize this process were investigated starting with a parallel screening of metal salts with analysis by LD-MS (see Experimental section). The metal salts screened in addition to InCl₃ included NiCl₂, Zn(OAc)₂, Pd(OAc)₂, CdCl₂, MgBr₂, YbCl₃·6H₂O, CoCl₂, Cu(OAc)₂, ErCl₃ and SnCl₂·H₂O. A bacteriochlorin macrocycle was detected only when InCl₃ was used. Further screening of reaction parameters was performed in the same manner, and the results are shown in Table 3.1. During this process, attempts to isolate the linear tetrapyrrole intermediate failed, and the second reaction (cyclization) was performed directly using crude products from the first step (condensation).

**Table 3.1. Survey of conditions to prepare bacteriochlorin In-BC-1**

<table>
<thead>
<tr>
<th>Entry</th>
<th>condensation conditions</th>
<th>cyclization conditions</th>
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<tr>
<td></td>
<td>LA Molar equiv solvent base T, °C Yield, %</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>InCl₃⁵ 5 CH₃CN TMPi 83 0.8</td>
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Table 3.1. Continued

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<th>Entry</th>
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<th>Base</th>
<th>Solvent</th>
<th>TMPi</th>
<th>Yield</th>
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<td>2</td>
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<tr>
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<tr>
<td>5</td>
<td>Bi(OTf)$_3$</td>
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<td>toluene</td>
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</tr>
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<td>90</td>
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</tr>
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<td>Cs$_2$CO$_3$</td>
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<td></td>
</tr>
</tbody>
</table>

*The condensation was performed for 20 min using 18 (10 mM) and 8c (10 mM) in the presence of Lewis acid in CH$_2$Cl$_2$ at room temperature. Then the reaction was neutralized with 2.2 molar equiv of Et$_3$N and concentrated to a solid. The crude solid was treated with InCl$_3$ (10 mol equiv) and base (10 mol equiv) in 0.5 mL of solvent for 1.5–2 h. *Isolated yield determined by absorption spectroscopy ($\varepsilon_{775} = 100,000$ M$^{-1}$cm$^{-1}$) in toluene. *The condensation was carried out for 40 min. *The condensation was carried out for 150 min.

The best result (entry 8) was obtained using InCl$_3$ and TMPi in toluene at 90 °C whereupon the AB-bacteriochlorin In-BC-1 was obtained in 8% yield (the isolated yield was
determined spectroscopically). Some amount of tetradehydrocorrin and a trace of a free base A₂-bacteriochlorin, a side-product obtained from self-condensation of 8c, were also observed.

The dihydrodipyrrin–imine 17 also was examined in the synthesis of AB-bacteriochlorin In-BC-1. Following the above conditions, the condensation of imine 17 and tetrahydrodipyrrin 2 in the presence of Bi(OTf)₃, followed by cyclization using InCl₃/TMPi in toluene, gave In-BC-1 in 2% yield (Scheme 3.10). Screening of several factors (e.g., concentration of reactants, equivalents of metal triflates) did not lead to improved yields. In short, the dihydrodipyrrin–imine as the Eastern half in bacteriochlorin synthesis did not show any advantage compared with use of a dihydrodipyrrin–acetal.

Scheme 3.10. Preparation of Bacteriochlorin In-BC-1

**Eastern half with -Br as blocking unit.** To avoid production of a tetradehydrocorrin,¹⁹ a tetrahydrodipyrrin-1-CH₃ was examined as the Western half instead of a dihydrodipyrrin-1-CH₃. An earlier attempt to use a bromodihydrodipyrrin–acetal 20 as the Eastern half and tetrahydrodipyrrin-1-CH₃ 19 as the Western half to prepare a
bacteriochlorin was not successful (Scheme 3.11A). However, the reaction of
dihydrodipyrrin–carboxaldehyde 16 as the Eastern half and tetrahydrodipyrrin-1-CH$_3$ 2 as the
Western half afforded **In-BC-2** in 1% yield (Scheme 3.11B). The 1% yield was obtained
after screening various conditions, which entailed TsOH·H$_2$O (5 equiv) in CH$_2$Cl$_2$/methanol
at room temperature for the condensation (akin to that in the *de novo* synthesis of chlorins$^{28}$),
and thermal cyclization under the above conditions (InCl$_3$/TMPi in toluene at 80 °C).

**Scheme 3.11.** Preparation of **In-BC-2**
Eastern half with -SMe as Blocking Unit. An analogue of 16 containing a methylthio rather than bromo group was examined next. A broad set of acidic conditions was investigated to support the condensation of dihydrodipyrrin 18 and 14 (analogue of 16) including BF\(_3\)·OEt\(_2\), TMSOTf/DTBP, Bi(OTf)\(_3\), Ga(OTf)\(_3\), Sc(OTf)\(_3\), and Yb(OTf)\(_3\) (all in CH\(_2\)Cl\(_2\), except BF\(_3\)·OEt\(_2\) in CH\(_3\)CN). The progress of the reaction was monitored by TLC and by LD-MS. All these conditions failed to afford the expected hydrobilin. Surprisingly, Yb(OTf)\(_3\) and Sc(OTf)\(_3\) gave a tetradehydrocorrin directly (Scheme 3.12). The effects of the concentration of reagents, equivalents of Lewis acid, solvent, and presence/absence of proton scavenger (DTBP) were also studied. The best result was obtained using dilute reactants (1 mM) in CH\(_2\)Cl\(_2\) containing Yb(OTf)\(_3\) (5 mM) at room temperature for 16 h, which afforded a 50% isolated yield of tetradehydrocorrin TDC-1.

![Scheme 3.12. Attempted Bacteriochlorin Formation Yields a Tetradehydrocorrin](image)

The location of the methylthio group at the pyrrole α-position in dihydrodipyrrin 14 was expected on the basis of the synthesis from known pyrrole 9. Further confirmation by COSY spectra revealed a strong coupling signal between the two neighboring β-pyrrolic protons, as expected for the methylthio group located at the α-pyrrolic position. With regards to TDC-1, the ESI-MS spectrum gave the molecular ion peak (m/z = 509.2733), which is consistent with the molecular formula C\(_{32}\)H\(_{36}\)N\(_4\)S (calcd 509.2733 for M + H\(^+\)).
\(^{1}\)H NMR spectrum indicated only five peripheral alkenyl protons (five singlets in the range \(\delta \) 5.3 – 6.6 ppm). 2-Dimensional NMR experiments and absorption spectroscopy confirmed the tetradehydrocorrin chromophore. NOESY or COSY experiments did not give any direct evidence concerning the location of the methylthio group on the macrocycle, hence the proposed structure must be regarded as provisional absent a single-crystal X-ray diffraction analysis. A possible mechanism for the rearrangement is provided in the Discussion section.

**Eastern half with \(-\text{CO}_2\text{Et as Blocking Unit}\).** Montforts et al. reported a synthetic route to chlorins from a linear tetrapyrrole–metal complex, wherein an ester group was employed as a blocking unit.\(^{29}\) The ester group was cleaved through a high-temperature decarbobenzoxylolation in refluxing 1,2,4-trichlorobenzene (214 °C). Thus, we explored a synthetic route to bacteriochlorin using Eastern half 8a.

**Scheme 3.13A.** Condensation between 21 and 8a
First, the acids that were examined for the condensation step included BF$_3$·OEt$_2$, Sc(OTf)$_3$, Bi(OTf)$_3$, Ga(OTf)$_3$, InCl$_3$, Yb(OTf)$_3$, TMSOTf/DTBP and TFA. Reactions were conducted with 10 mM dihydrodipyrrin 21 and 8a (0.010 mmol scale) and 20 mM acid in CH$_2$Cl$_2$ (except for BF$_3$·OEt$_2$ in CH$_3$CN). The reaction was followed by LD-MS and absorption spectroscopy. The targeted hydrobilin was not detected under these conditions; however, MALDI-MS and ESI-MS of crude product displayed a major peak at m/z = 966, which might be corresponding to the molecular ion peak of bilene 22 (m/z found 966.2792 calcd 966.2826 [(M + H)$^+$, M = C$_{53}$H$_{56}$Br$_2$N$_6$O$_2$] (Scheme 3.13A). To verify this observation, acid catalyzed condensation of dihydrodipyrrin 21 and 4-bromobenzaldehyde was found to give tetrahydrobiladiene 23 in 88% yield (Scheme 3.13B). Tetrahydrobiladiene 23 underwent facile oxidation during column chromatography or in solution open to the air. Following a reported method to prepare a nickel tetradehydrocorrin,$^{30}$ treatment of 23 with nickel acetate tetrahydrate and sodium acetate in refluxing methanol for 30 min followed by dilute hydrochloric acid afforded a tetradehydrocorrin nickel chloride (Ni-TDC-2) in 82% yield.
Scheme 3.13B. Preparation of Ni-TDC-2

Secondly, during these studies, Cu\(^{2+}\) was found to afford a relatively stable copper complex (24) as a purple-red solid (Scheme 3.14). This complex was characterized by mass spectrometry (LD-MS and ESI-MS) and absorption spectroscopy; a meaningful \(^1\)H NMR spectrum could not be obtained. The complex was quite stable over time, and treatment with TFA in methanol did not cause demetalation. Treatment of 24 with sodium hydroxide at high temperature gave saponification and decarboxylation followed by cyclization. Several
reaction variables, including temperature, solvents or inert environment, were examined. For each reaction, products were purified chromatographically to determine the isolated yield of Cu-BC-1. The highest spectroscopic yield (2%) was obtained by using NaOH in ethylene glycol at 160 °C under argon. The major by-products detected (by absorption spectroscopy) were the oxobacteriochlorins and tetradehydrocorrins.

![Scheme 3.14](image)

**Scheme 3.14.** Synthesis of a Tetrpyrrole–copper (II) Complex

**Eastern half with -Me as blocking unit.** The cyclization of a 1,8-dimethyl-α,ε-biladiene in refluxing DMF containing a copper(II) reagent to give the corresponding copper(II)porphyrin is well established. Here, we explored analogous ring-closure strategies in bacteriochlorin synthesis. First, condensation of 21 and 8b in the presence of Cu(OTf)$_2$ in CH$_2$Cl$_2$ for 2 h gave the desired copper(II) complex 25, for which the molecular
mass was confirmed by ESI-MS. Heating 25 in DMF containing CuCl₂ (15 equiv) under argon gave the dioxobacteriochlorin Cu-OxoBC in 2% overall yield starting from the dihydrodipyrrins (Scheme 3.15). A similar observation was made in Battersby’s pioneering studies of the conversion of tetrahydrobiladienes to the corresponding chlorin, in which a copper oxochlorin rather than the copper chlorin was obtained.\[32\]

\[
\text{Scheme 3.15. Preparation of Cu-OxoBC}
\]

Characterization. The synthetic studies described above led to two new tetradehydrocorrins and four new bacteriochlorins, the latter in minute yields. The tetradehydrocorrin TDC-1 exhibits an absorption spectrum (Figure 3.2, top) with \( \lambda_{\text{max}} \) at 318 nm, a weak shoulder at 438 nm, and a weak, broad band from 500–800 nm, all of which are
characteristic of tetradehydrocorrin macrocycles. The $^1$H NMR, $^{13}$C NMR, gHMOC, and NOESY spectra of TDC-1 were obtained, and all protons were assigned. Distinctive features in the $^1$H NMR spectrum include the following: (1) an AB splitting pattern assigned to the two methylene protons of the C pyrroline unit; (2) five singlets in the range $\delta$ 5.3 – 6.6 ppm assigned to the five peripheral alkenyl protons; and (3) two broad peaks in the low-field region assigned to the NH protons.

The tetradehydrocorrin nickel chloride (Ni-TDC-2) was characterized by $^1$H and $^{13}$C NMR spectroscopy, ESI-MS and absorption spectroscopy. Ni-TDC-2 has a C$_2$ axis (assuming the 1,19-dimethyl groups are trans to one another; if cis, there is a plane of symmetry) bisecting the A–D ring junction, hence the two meso-protons are identical with each other, and the two $\beta$-pyrrolic protons are identical with each other. Two singlets (6.86, 7.30 ppm) are observed in the $^1$H NMR spectrum, assigned to the meso-protons and the $\beta$-pyrrolic protons, respectively. An AB splitting pattern, assigned to the two methylene protons of both pyrroline units, was also observed ($\delta$ 2.44, 2.64 ppm). A high-resolution mass spectrum showed an intense molecular ion with loss of chloride at m/z 904.9973, with the expected isotopic pattern for nickels. The absorption spectrum showed $\lambda_{\text{max}}$ at 601 nm (Figure 3.2, bottom).
Figure 3.2. Absorption spectrum of TDC-1 (top) and Ni-TDC-2 (bottom) in CH₂Cl₂ at room temperature.

Copper (II) complex 23 and 24 were characterized by mass spectrometry (LD-MS and ESI-MS) and absorption spectroscopy; the $^1$H NMR spectrum could not be obtained. The absorption spectrum of copper complex 23 displayed $\lambda_{max}$ at 540–550 nm (Figure 3.3).

Figure 3.3. Absorption spectrum of copper complex 23 in CH₂Cl₂ at room temperature.
The indium bacteriochlorins In-BC-1 and In-BC-2 were characterized by \(^1\)H NMR spectroscopy, LD-MS, ESI-MS, absorption spectroscopy, and fluorescence spectroscopy. Because both macrocycles are unsymmetrically substituted, each peripheral proton resonates uniquely (apparent singlet) in the range δ 8.5–10.0 ppm. In addition, the two geminal dimethyl groups give rise to four singlets, and the CH\(_2\) group in each pyrrole ring gives rise to a pair of doublets in the range δ 4.4–4.7 ppm. Mass spectrometric analysis in each case gave the molecular ion peak as well as a peak consistent with loss of chloride. The absorption and fluorescence spectra of In-BC-1 and In-BC-2 in toluene are shown in Figure 3.3, with the respective Q\(_y\)(0,0) absorption band at 773 and 765 nm, and the Q\(_y\)(0,0) fluorescence maximum at 789 and 775 nm.

The copper bacteriochlorins Cu-BC-1 and Cu-OxoBC were characterized by LD-MS, ESI-MS, and absorption spectroscopy. \(^1\)H NMR spectroscopy typically is not applicable for copper(II) bacteriochlorins. Fluorescence is not expected (and none was found) in these two cases. The absorption spectra of Cu-BC-1 and Cu-OxoBC in toluene are shown in Figure 3.3, with the Q\(_y\)(0,0) band at 744 and 711 nm, respectively. The absorption spectrum of Cu-OxoBC showed typical features of oxobacteriochlorin, including (1) a hypsochromic shift of the Q\(_y\) band, and (2) a bathochromic shift and apparent hypochromic effect in the B\(_y\) band.
Figure 3.4. Absorption spectra (A) and fluorescence spectra (B) of bacteriochlorins in toluene at room temperature (normalized at the Q_y band). The labels and colors in graph are as follows: In-BC-1 (a, red), In-BC-2 (b, black), Cu-BC-1 (c, magenta) and Cu-OxoBC (d, blue). The emission spectra are drawn in dashed lines.

The spectral data including the position, intensity, and full-width at half-maximum (fwhm) of the long-wavelength absorption band and emission band; and intensity ratios of the Q_y to B band are listed in Table 3.2. The spectral data of indium (III) bacteriochlorins (In-BC-T and In-BC-MeEs) are also listed as benchmarks (Figure 3.5). Comparison of
these spectral data leads to some interesting findings: (1) The wavelength of the Qy bands are in the following order: **In-BC-MeMs** (782 nm) > **In-BC-1** (773 nm) > **In-BC-2** (765 nm) ~ **In-BC-T** (763 nm), indicating that an unsymmetrically substituted bacteriochlorins can finely tune the position of the Qy band with narrow bandwidths (fwhm ~20 nm). (2) The Stokes shifts are in the following order: **In-BC-1** (263 cm\(^{-1}\)) > **In-BC-2** (163 cm\(^{-1}\)) > **In-BC-T** (103 cm\(^{-1}\)) ~ **In-BC-MeEs** (49 cm\(^{-1}\)). The larger Stokes shifts of unsymmetrically substituted bacteriochlorin, compared with those of symmetrically substituted ones, indicate more substantial structure changes upon photoexcitation.

**Figure 3.5.** Benchmark bacteriochlorins
<table>
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<tr>
<th>bacteriochlorins</th>
<th>$B_x(0, 0)^b$ abs $\lambda$ (nm)</th>
<th>$B_y(0, 0)^b$ abs $\lambda$ (nm)</th>
<th>$Q_x(0, 0)$ abs $\lambda$ (nm)</th>
<th>$Q_y(0, 0)$ abs $\lambda$ (nm)</th>
<th>$Q_y(0, 0)$ em $\lambda$ (nm)</th>
<th>$Q_y(0, 0)$ em fwhm (nm)</th>
<th>$\Delta$ abs-em (cm$^{-1}$)</th>
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<td>711</td>
<td>24</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>In-BC-T$^d$</td>
<td>350</td>
<td>388</td>
<td>539</td>
<td>763</td>
<td>23</td>
<td>769</td>
<td>31</td>
<td>103</td>
</tr>
<tr>
<td>In-BC-MeEs$^d$</td>
<td>354</td>
<td>395</td>
<td>559</td>
<td>782</td>
<td>21</td>
<td>785</td>
<td>23</td>
<td>49</td>
</tr>
</tbody>
</table>

$^a$ In toluene at room temperature. $^b$ The two Soret features are labeled $B_x(0,0)$ and $B_y(0,0)$, but the bands may be of mixed parentage.

$^c$ Ratio of the peak intensities of the $Q_y(0,0)$ band to the Soret (B) maximum. $^d$ Data from reference 34.
Discussion

The directed routes to bacteriochlorins explored herein – inspired by a de novo synthesis of chlorins – consist primarily of two steps: (1) condensation of an Eastern half and a Western half to produce a hydrobilin, and (2) ring closure of the hydrobilin to form the bacteriochlorin. Although unsymmetrically substituted bacteriochlorins can be prepared through this general approach, the overall yields of the two steps are quite low (<10%). Here we discuss the two steps in turn.

**Joining the Eastern half and Western half.** Scheme 3.16 compares the condensations used in de novo syntheses of hydroporphyrins, including chlorins, an isobacteriochlorin and a bacteriochlorin. In the first example (route A), condensation occurs between a pyrrole α-position and a carbinol group, affording the corresponding tetrahydrobilene in high yield (72%). The resulting tetrahydrobilene is sufficiently stable for isolation and purification. In the second (route B) and third (route C) examples, condensation occurs between a pyrrole α-position and an aldehyde. Both intermediates were used in the following cyclization step without purification or full characterization. This reaction can be considered as a condensation between a pyrrole-2-carboxaldehyde and a pyrrole to afford a dipyrrin, which has been known in pyrrole and porphyrin chemistry for almost one century.
It also has been known for a long time that condensation between pyrrole and an aromatic or aliphatic aldehyde in the presence of an acid usually gives a cationic intermediate, which is a reactive electrophile and will be attacked by another molecule of pyrrole to afford a dipyrromethane (Scheme 3.17). This route has been widely applied in the preparation of dipyrromethanes and porphyrins. Typically, such pyrrole-carbinol species are generated and consumed in situ; the cationic intermediates are considered to be even more labile. Herein, in route D, the reaction used to join the Eastern half and Western half is between an acetal/carboxaldehyde group located at the α-pyrroline position in the Eastern half and the pyrrole ring in the Western half. Attempts at isolation and characterization of the expected
hydrobilin intermediate \((M = \text{H, H in route D})\) failed. On the other hand, a product from condensation of two mols of Western half and one mol of Eastern half was detected (e.g., 22 in Scheme 3.13A). The instability of those intermediates or the low efficiency of this reaction may contribute to the low yield of bacteriochlorin. Similar condensation in the presence of \(\text{Cu(OTf)}_2\) afforded the stabilized copper(II)–hydrobilin complexes (23, 24). In this process, the copper ion serves as template to form the complex as well as a Lewis acid to promote the condensation. We note that while the knowledge base concerning naturally occurring or naturally derived bilins is quite vast,\(^{42}\) far less information is available about synthetic bilins and in particular the hydrobilins as described herein.

**Scheme 3.17.** Condensation of Pyrrole and an Aldehyde

**Ring Closure.** The electrocyclization of an \(18\pi\)-system has been described in Battersby’s synthesis of isobacteriochlorins and chlorins\(^{35,43}\) as well as in our *de novo*
synthesis\textsuperscript{44} of chlorins. The electrocyclization could occur via a photochemical or thermal process. An alternative 16\(\pi\)-electrocyclization process is also possible, which produces a corrin-like macrocycle, with two adjacent quaternary centers. Early studies on the synthesis of vitamin B\(_{12}\) proposed a 16\(\pi\)-electrocyclization of a secocorrin-diradical to construct the corrin macrocycle, wherein the diradical was created upon H-atom abstraction.\textsuperscript{45} While more recent analysis has turned away from this mechanism,\textsuperscript{46} we note that the tetradehydrocorrins reported herein do not require the H-atom abstraction. Scheme 3.18 shows these two competitive processes, starting from a hydrobilin (assuming M\(^{2+}\) as the metal center) to produce bacteriochlorins or corrins. Herein, attempted formation of \textbf{In-BC-1} and \textbf{Cu-BC-1} gave tetradehydrocorrin by-products, which may stem from 16\(\pi\)-electroyclic pathways. Besides, the pathway to prepare \textbf{Ni-TDC-2} was provided, which is a similar 16\(\pi\)-electroyclic pathway, with difference in location of the double bond. Also, this process can explain the formation of the tetradehydrocorrin shown in Scheme 3.3, which may involve a thermal 16\(\pi\)-electrocyclization process, considering the high reactivity of the 2-bromopyrrole species. Moreover, a 16\(\pi\)-electrocyclization is not the only possible pathway leading to the tetradehydrocorrin. In some examples (e.g., formation of \textbf{TDC} in Scheme 3.19), the tetradehydrocorrin might be produced through a simple condensation between pyrrole and imines activated by the Lewis acid in the ring-closure process.

While our interests lie strongly toward bacteriochlorins rather than corrin analogues, we note that the synthesis of corrin analogues has been relatively unexplored.\textsuperscript{47} Access to the entire slate of dehydrocorrins (hexadehydro-, tetradehydro-, and didehydrocorrins) ranging from A,B,C,D-octadehydrocorrins to corrins themselves would be exceptionally valuable for probing the structural features leading to the emergence of corrin-like properties. A strong
motivation for the study of such cobalt complexes stems from the growing interest in using earth-abundant metals as catalysts for transformations such as photosynthetic hydrogen evolution.\textsuperscript{48}

\textbf{Scheme 3.18A.} 16\pi/18\pi-Electrocyclization of a Hydrobilin
Leaving group and methylthio shift. The choice of the blocking/leaving group in the hydrobilin is a key aspect of a successful macrocyclization. If $Z$ is not a good leaving group, ring closure (or the follow-on aromatization process) requires forcing conditions, which may promote side-reactions and even destroy the bacteriochlorin macrocycle. For example, conversion from copper complex 24 to Cu-OxoBC occurs in the presence of a strong base (NaOH) and high temperature (140 °C in DMF), whereupon the ethoxycarbonyl group is cleaved. This might be another cause for the low yield of the bacteriochlorin-forming reaction. If $Z$ is insufficiently stable, duty as a blocking unit may be compromised, exemplified by the route leading to TDC-1. To improve yields beyond those reported herein, at least two advances are required: (1) a new reaction to join the Western half and Eastern half; and (2) a new blocking unit in the hydrobilin.
A possible explanation for formation of the β-methylthiotetrahydrocorrin TDC-1 is shown in Scheme 3.19. Condensation of 14 and 18 produces the hydrobilin intermediate I, which is likely to assume more of a lockwasher rather than planar conformation owing to the steric bulk of the juxtaposed methyl and methylthio groups across the A–D gap. Further cyclization ensues as shown in II to give the A–D ring closure of the corrin analogue III. Thiooxirane formation gives IV, which upon loss of the β-proton gives the β-methylthio tetradehydrocorrin TDC-1. This proposed mechanism is precedented by arylthio migration from the α- to β-position of pyrrole, as shown in the bottom of Scheme 3.19. Protonation of α-arylthiopyrrole II-pyr affords III-pyr, which undergoes thiooxirane formation to give IV-pyr; subsequent rearrangement gives the β-arylthiopyrrole. The rearrangement of I leading to TDC-1 is driven by reaction of the pyrrole α-position with the electrophilic iminium ion (shown for II), whereas the rearrangement of II-pyr is driven by an analogous electrophilic process, protonation of the pyrrole α-position. The proposed mechanism suggests calculations to address relative energies of intermediates as well as the conformation of the hydrobilin(s).
Access to unsymmetrically substituted bacteriochlorins remains challenging. Herein, 7 new hydrodipyrrins (1 tetrahydrodipyrrins and 6 dihydrodipyrrins) equipped with various entities at the \( \alpha \)-pyrrole (H, methylthio, bromo-, methyl, and ethoxycarbonyl) or the \( \alpha \)-pyrroline (methyl, carboxaldehyde, acetal, and imine) position have been prepared to examine the effects of distinct reactivity at these sites. The hydrodipyrrins serve as building blocks for the exploration of new approaches towards bacteriochlorins. Unsymmetrically substituted bacteriochlorins were prepared by using Eastern halves installed with different \( \alpha \)-pyrrolic substituents (hydrogen, bromo-, methyl-, and ethoxycarbonyl-). Also, tetradehydrocorrins were produced using these building blocks through 16\( \pi \)-electrocyclic reactions. These studies provide insights into the synthetic chemistry of hydrodipyrrins and
hydrobilins as well as processes leading to tetrapyrrole macrocycles. A number of proposed intermediates and associated mechanisms should be amenable to calculation to gauge energetics and hence their chemical likelihood. Although low yields and small quantities of bacteriochlorin severely limit present applications in synthetic chemistry, some research opportunities may be available. Examples include (1) incorporation of $^{13}$C/$^{15}$N isotopes at one or more specific sites on the $\pi$-system of the bacteriochlorin for vibronic studies, (2) preparation and photophysical studies of unsymmetrically substituted dioxobacteriochlorins (analogues of native tolyporphin A), and (3) introduction of distinct substituents (e.g. hydrophobic/hydrophilic substituents) on the opposite sides of the macrocycle for self-assembly and photophysical studies.
Experimental Section

General Methods. $^1$H NMR and $^{13}$C NMR spectra were collected at room temperature in CDCl$_3$ unless noted otherwise. Electrospray ionization mass spectrometry (ESI-MS) data are reported for the molecular ion or protonated molecular ion. Bromination was performed using freshly recrystallized NBS (from water). THF used in all reactions was freshly distilled from Na/benzophenone ketyl. All commercially available materials were used as received. Non-commercial compounds $^1$, $^{12}$, $^{26}$, $^{27}$, $^{3a}$, $^{3b}$, $^{3c}$, $^{4c}$, $^9$, $^{12}$, $^{15}$, $^{18}$, $^{19}$, $^{20}$, $^{21}$ and $^{22}$ were prepared as described in the literature and assessed for purity by $^1$H NMR spectroscopy.

2,3,4,5-Tetrahydro-1,3,3-trimethyl-7-(p-tolyl)dipyrrin (2). Following a general procedure,$^{53}$ a mixture of 1 (22 mg, 0.060 mmol) and NH$_4$OAc (16 mg, 0.24 mmol) in THF (6.0 mL) was treated with zinc dust (16 mg, 0.24 mmol) under argon. The resulting mixture was stirred at room temperature. After 2 h, ethyl acetate was added, and the mixture was filtered. The filtrate cake was washed with ethyl acetate. The filtrate was washed with water/brine, dried (Na$_2$SO$_4$), concentrated and chromatographed (silica, ethyl acetate) to afford a viscous yellow oil (16 mg, 63%): $^1$H NMR (300 MHz) $\delta$ 0.95 (s, 3H), 1.11 (s, 3H), 2.07 (s, 3H), 2.36–2.39 (m, 5H), 2.63 (ABX, $^2$J = 15.3 Hz, $^3$J = 12.3, 1H), 3.02 (ABX, $^2$J = 15.3 Hz, $^3$J = 2.4, 1H), 3.70 (AB, $J$ = 11.7 Hz, 1H), 6.31 (t, $J$ = 2.4 Hz), 6.77 (t, $J$ = 2.4 Hz), 7.21 (d, $J$ = 8.2 Hz), 7.32 (d, $J$ = 8.2 Hz, 1H), 10.2 (br, 1H); $^{13}$C NMR (75 MHz) $\delta$ 20.6, 21.2, 22.9, 26.5, 27.2, 42.0, 54.3, 80.1, 108.1, 116.0 127.8, 128.1, 129.1, 134.4, 134.7, 174.5; ESI-MS obsd 281.2017, calcd 281.2012 [(M + H)$^+$, M =C$_{26}$H$_{33}$N$_3$O$_2$].

2-Ethoxycarbonyl-3,4-dimethyl-5-(2-nitroethyl)pyrrole (4a). Samples of 3a (24 g, 0.12 mol), nitromethane (19 mL, 0.36 mol), KOAc (13 g, 0.13 mol) and CH$_3$NH$_2$·HCl (8.8 g,
0.13 mol) were stirred in MeOH (150 mL) for 3 h. The mixture was diluted with water (500 mL) and extract with CH₂Cl₂ (100 mL × 3). The combined extract was washed with brine (100 mL), dried and concentrated to give an orange-red solid, which was dissolved in absolute ethanol (500 mL) and treated with NaBH₄ (7.5 g, 0.20 mol). After 30 min, the mixture was concentrated. The residue was taken up in water (200 mL), and the solution was acidified with acetic acid to pH ~5. The mixture was extracted with CH₂Cl₂. The extract was washed with water and brine, dried (Na₂SO₄) and concentrated. Chromatography [silica, hexanes/ethyl acetate (3:1)] gave a yellow solid (10.3 g, 36%): mp 118–119 °C; ¹H NMR (300 MHz) δ 1.35 (t, J = 7.2 Hz, 3H), 1.95 (s, 3H), 2.24 (s, 3H), 3.28 (t, J = 6.9 Hz, 2H), 4.30 (q, J = 7.2 Hz, 2H), 4.54 (t, J = 7.2 Hz, 2H), 8.80 (br, 1H); ¹³C NMR (75 MHz) δ 8.9, 10.9, 14.7, 24.4, 60.4, 74.4, 118.6, 118.7, 127.5, 127.6, 162.7; ESI-MS obsd 241.11828, calcd 241.11761 [(M + H)⁺, M = C₁₁H₁₆N₂O₄].

3-Ethoxycarbonyl-2,4-dimethyl-5-(2-nitroethyl)pyrrole (4b). Samples of 3b (7.35 g, 37.7 mmol), nitromethane (6.0 mL, 0.11 mol), KOAc (4.44 g, 45.2 mmol) and CH₃NH₂·HCl (3.05 g, 45.2 mmol) were stirred together in MeOH (40 mL) for 6 h. The mixture was diluted with water (300 mL) and extracted with CH₂Cl₂ (100 mL × 3). The combined extract was washed with brine (100 mL), dried and concentrated to give an orange-red solid, which was dissolved in absolute ethanol (200 mL) and treated with NaBH₄ (2.83 g, 75.4 mmol). After 30 min, the mixture was concentrated. The residue was taken up in water (200 mL), and the solution was acidified with acetic acid. The mixture was extracted with CH₂Cl₂. The extract was washed with water and brine, dried (Na₂SO₄), concentrated and chromatographed [silica, hexanes/ethyl acetate (1:1)] to give a yellow solid (5.72 g, 63%): mp 127–129 °C; ¹H NMR (300 MHz) δ 1.34 (t, J = 7.2 Hz, 3H), 2.17 (s, 3H), 2.44 (s, 3H), 2.17 (s, 3H), 2.44 (s, 3H), 2.17 (s, 3H), 2.44 (s, 3H), 2.17 (s, 3H), 2.44 (s, 3H), 2.17 (s, 3H), 2.44 (s, 3H), 2.17 (s, 3H), 2.44 (s, 3H).
3.20 (t, \(J = 6.9\) Hz, 2H), 4.27 (q, \(J = 7.2\) Hz, 2H), 4.50 (t, \(J = 6.6\) Hz, 2H), 8.35 (br, 1H); \(^{13}\)C NMR (100 MHz) \(\delta 10.9, 14.0, 14.5, 23.3, 59.3, 75.0, 111.2, 118.4, 120.6, 135.4, 166.5;\) ESI-MS obsd 241.11762, calcd 241.11828 [(M + H)\(^+\), M = C\(_{11}\)H\(_{16}\)N\(_2\)O\(_4\)].

**6-(5-Ethoxycarbonyl-3,4-dimethylpyrrol-2-yl)-4,4-dimethyl-5-nitrohexan-2-one** (5a). Following a general procedure,\(^{13}\) a mixture of 4a (6.69 g, 27.9 mmol) and mesityl oxide (8.23 g, 84.0 mmol) was treated with DBU (12.5 mL, 84.0 mmol) at room temperature. After 16 h, the reaction mixture was diluted with ethyl acetate and washed with aqueous HCl (0.5 M), saturated aqueous NaHCO\(_3\) solution, and then brine. The organic layer was dried (Na\(_2\)SO\(_4\)) and filtered. The filtrate was concentrated. The resulting residue was chromatographed (silica, dichloromethane) to give a pale-yellow solid (3.70 g, 44%): mp 130–131 °C; \(^1\)H NMR (300 MHz) \(\delta 1.13\) (s, 3H), 1.27 (s, 3H), 1.34 (t, \(J = 7.2\) Hz, 3H), 1.92 (s, 3H), 2.15 (s, 3H), 2.21 (s, 3H), 2.50 (AB, \(^2\)J = 17.4 Hz, 2H), 2.98 (ABX, \(^2\)J = 15.3 Hz, \(^3\)J = 2.4 Hz, 1H), 3.27 (ABX, \(^2\)J = 15.3 Hz, \(^3\)J = 11.7 Hz, 1H), 4.27 (q, \(J = 7.2\) Hz, 2H), 5.12 (ABX, \(^2\)J = 11.7 Hz, \(^3\)J = 2.4 Hz, 1H), 8.65 (br, 1H); \(^{13}\)C NMR (100 MHz) \(\delta 8.9, 10.7, 14.7, 24.2, 24.6, 25.2, 32.0, 37.0, 51.5, 60.1, 93.6, 118.5, 118.6, 127.1, 127.5, 161.8, 207.0;\) ESI-MS obsd 339.19145, calcd 339.19091 [(M + H)\(^+\), M = C\(_{17}\)H\(_{26}\)N\(_2\)O\(_5\)].

**6-(4-Ethoxycarbonyl-3,5-dimethylpyrrol-2-yl)-4,4-dimethyl-5-nitrohexan-2-one** (5b). Following a general procedure,\(^{13}\) a mixture of 4b (5.72 g, 23.8 mmol) and mesityl oxide (7.00 g, 71.4 mmol) was treated with DBU (10.7 mL, 71.4 mmol) at room temperature. After 16 h, the reaction mixture was diluted with ethyl acetate and washed with brine and water (200 mL \(\times\) 3). The organic layer was dried, filtered, concentrated and chromatographed [silica, hexanes/ethyl acetate (1:1)] to give a yellow oil (6.08 g, 75%): \(^1\)H NMR (300 MHz) \(\delta 1.12\) (s, 3H), 1.24 (s, 3H), 1.33 (t, \(J = 7.2\) Hz, 3H), 2.15 (s, 6H), 2.40 (s, 3H), 2.50 (AB, \(^2\)J =
17.4 Hz, 2H), 2.94 (ABX, $^2J = 15.3$ Hz, $^3J = 2.1$ Hz, 1H), 3.22 (ABX, $^2J = 15.3$ Hz, $^3J = 11.4$ Hz, 1H), 4.25 (q, $J = 7.2$ Hz, 2H), 5.05 (ABX, $^2J = 11.4$ Hz, $^3J = 2.7$ Hz, 1H), 8.26 (br, 1H); $^{13}$C NMR (100 MHz) $\delta$ 10.7, 13.8, 14.4, 23.9, 24.0, 24.2, 31.7, 36.6, 51.1, 59.0, 94.1, 110.8, 118.3, 120.5, 135.3, 166.3, 207.3; ESI-MS obsd 339.19178, calcd 339.19145 [(M + H)$^+$, M = C$_{17}$H$_{26}$N$_2$O$_5$].

6-(4-Ethoxycarbonyl-3-p-tolylpyrrol-2-yl)-4,4-dimethyl-5-nitrohexa-2-one (5c). Following a general procedure,$^{13}$ a mixture of 4c (1.81 g, 6.00 mmol) and mesityl oxide (0.820 mL, 7.20 mmol) was treated with DBU (2.70 mL, 18.0 mmol) at room temperature. The reaction mixture became dark and was stirred for 16 h at room temperature. Ethyl acetate (100 mL) was added. The mixture was washed with water and brine. The organic layer was dried (Na$_2$SO$_4$) and concentrated. Column chromatography [silica, hexanes/ethyl acetate (3:2)] afforded a light yellow solid (1.22 g, 51%): mp 150–152 °C; $^1$H NMR (300 MHz) $\delta$ 0.99 (s, 3H), 1.03 (s, 3H), 1.16 (t, $J = 7.2$ Hz, 3H), 2.04 (s, 3H), 2.36 (s, 3H), 2.27, 2.45 (AB, $J = 17.7$ Hz, 2H), 2.95 (ABX, $^2J = 15.6$ Hz, $^3J = 2.4$ Hz, 1H), 3.19 (ABX, $^2J = 15.6$ Hz, $^3J = 11.4$ Hz, 1H), 4.12 (q, $J = 7.2$ Hz, 2H), 4.97 (ABX, $^2J = 11.4$, $^3J = 2.4$ Hz, 1H), 7.13–7.17 (m, 4H), 7.31 (d, $J = 3.0$ Hz, 1H), 8.65 (br, 1H); $^{13}$C NMR (100 MHz) $\delta$ 14.4, 21.5, 23.9, 24.2, 24.9, 31.8, 37.0, 51.2, 59.6, 94.9, 115.2, 124.1, 124.7, 125.2, 128.7, 130.4, 131.5, 136.5, 164.8, 206.8; ESI-MS obsd 401.2085, calcd 401.2071 [(M + H)$^+$, M = C$_{22}$H$_{28}$N$_2$O$_5$].

9-Ethoxycarbonyl-2,3-dihydro-1,3,3,7,8-pentamethylidpyrrin (6a). Following a general procedure,$^{13}$ in a first flask, a solution of 5a (3.70 g, 10.9 mmol) in THF/methanol (10:1, 20. mL) under argon was treated with NaOMe (1.78 g, 33.0 mmol). The mixture was stirred at room temperature for 50 min. In a second flask, NH$_4$OAc (41 g, 0.54 mol) in
distilled THF (140 mL) was bubbled with argon for 15 min. Then TiCl₃ (20 wt% in 3 wt% HCl solution, 56 mL, 87 mmol) was added, and the mixture was degassed by bubbling argon for another 30 min. Then, the first flask mixture was transferred via cannula to the buffered TiCl₃ solution. The resulting mixture was stirred at room temperature for 16 h under argon. The mixture was then filtered through a pad of Celite, and the filtered material was washed with ethyl acetate. The eluent was washed with saturated aqueous NaHCO₃, then brine and water. The organic layer was dried, filtered and concentrated. Chromatography (silica, CH₂Cl₂) afforded a light yellow solid (1.02 g, 32%): mp 116–118 °C; ¹H NMR (300 MHz) δ 1.21 (s, 6H), 1.37 (t, J = 6.9 Hz, 3H), 2.03 (s, 3H), 2.24 (s, 3H), 2.27 (s, 3H), 2.52 (s, 2H), 4.29 (q, J = 6.9 Hz, 2H), 5.68 (s, 1H), 11.16 (br, 1H); ¹³C NMR (75 MHz) δ 8.9, 10.5, 14.6, 21.0, 29.2, 41.5, 53.9, 59.5, 101.2, 118.4, 118.4, 126.8, 131.3, 161.8, 163.9, 178.7; ESI-MS obsd 289.19105, calcd 289.19081 [(M + H)+, M = C₁₇H₂₄N₂O₂].

8-Ethoxycarbonyl-2,3-dihydro-1,3,3,7,9-pentamethyldipyrrin (6b). Following a general procedure,¹³ a solution of 5b (6.08 g, 18.0 mmol) in THF/methanol (10:1, 20 mL) under argon was treated with NaOMe (2.92 g, 54.0 mmol). The mixture was stirred at room temperature for 50 min. In a second flask, NH₄OAc (68 g, 0.88 mol) in distilled THF/water (150 mL/50 mL) was bubbled with argon for 30 min. Then TiCl₃ (20 wt% in 3 wt% HCl solution, 93 mL, 0.14 mol) was added, the mixture was degassed by bubbling argon for another 30 min. Then, the first flask mixture was transferred via cannula to the buffered TiCl₃ solution. The resulting mixture was stirred at room temperature for 16 h under argon. The mixture was then filtered through a pad of Celite, washed with ethyl acetate. The eluent was washed with saturated aqueous NaHCO₃, then brine and water. The organic layer was dried, filtered and concentrated. Column chromatograph (silica, CH₂Cl₂) afforded a light
yellow solid (3.32 g, 59%): mp 98–99 °C; $^1$H NMR (300 MHz) $\delta$ 1.20 (s, 6H), 1.35 (t, $J = 7.2$ Hz, 3H), 2.20 (s, 3H), 2.29 (s, 3H), 2.49 (s, 2H), 2.53 (s, 3H), 4.26 (q, $J = 7.2$ Hz, 2H), 5.68 (s, 1H), 10.88 (br, 1H); $^{13}$C NMR (100 MHz) $\delta$ 11.2, 14.7, 14.8, 20.9, 21.3, 24.9, 41.2, 53.9, 59.1, 101.5, 110.0, 119.0, 126.4, 136.4, 160.4, 166.8, 176.5; ESI-MS obsd 289.19102, calcd 289.19105 [(M + H)$^+$, M = C$_{17}$H$_{24}$N$_2$O$_2$].

**8-Ethoxycarbonyl-2,3-dihydro-1,3,3-trimethyl-7-(p-tolyl)dipyrrin (6c).** Following a general procedure, in a first flask, a solution of 5c (1.20 g, 3.00 mmol) in freshly distilled THF (30.0 mL) was treated with NaOMe (825 mg, 15.0 mmol). The reaction mixture was stirred and degassed by bubbling argon through the solution for 45 min. In a second flask purged with argon, TiCl$_3$ (20 wt% in 2N HCl solution, 21 mL, 33 mmol) and 120 mL of H$_2$O were combined under argon, and the mixture was degassed by bubbling argon for 10 min. Then, NH$_4$OAc (92.4 g, 1.20 mol) was slowly added under argon bubbling to buffer the mixture to pH 6.0. The mixture was further bubbled with argon for 30 min. The mixture in the first flask was transferred via cannula to the buffered TiCl$_3$ mixture. The resulting mixture was stirred at room temperature for 16 h under argon. Then saturated aqueous NaHCO$_3$ (250 mL) was added. The mixture was filtered over a pad of Celite and eluted with ethyl acetate. The filtrate was washed with water and brine. The organic layer was dried (Na$_2$SO$_4$), concentrated and chromatographed [silica, hexanes/ethyl acetate (9:1)] to afford a yellow solid (422 mg, 40%): mp 83–85 °C; $^1$H NMR (300 MHz) $\delta$ 1.13 (s, 6H), 1.21 (t, $J = 7.2$ Hz, 3H), 2.23 (s, 3H), 2.40 (s, 3H), 2.51 (s, 2H), 4.17 (q, $J = 7.2$ Hz, 2H), 5.67 (s, 1H), 7.19–7.30 (m, 4H), 7.51 (d, $J = 2.7$ Hz, 1H), 11.4 (br, 1H); $^{13}$C NMR (100 MHz) $\delta$ 14.3, 20.7, 21.3, 29.0, 41.2, 53.8, 59.2, 102.2, 114.2, 123.4, 124.7, 128.2, 129.9, 130.8, 131.8,
135.7, 162.5, 165.0, 177.7; ESI-MS obsd 351.2075, calcd 351.2067 [(M + H)^+, M = C_{22}H_{26}N_{2}O_{2}]; \lambda_{\text{abs}} (\text{CH}_2\text{Cl}_2) 330 nm.

9-Ethoxycarbonyl-1-formyl-2,3-dihydro-3,3,7,8-tetramethyldipyrpin (7a). A solution of 6a (50 mg, 0.18 mmol) in 1,4-dioxane (5.0 mL) was treated with SeO_2 (60. mg, 0.54 mmol) under argon and stirred at room temperature. The progress of the reaction was monitored by absorption spectroscopy. After 30 min, the reaction mixture was dilute with ethyl acetate, washed with water and brine, dried (Na_2SO_4) and concentrated. Chromatography [silica, CH_2Cl_2] gave a red-orange solid (32 mg, 59%): 1H NMR (400 MHz) \(\delta\) 1.27 (s, 6H), 1.37 (t, \(J = 7.2\) Hz, 3H), 2.09 (s, 3H), 2.28 (s, 3H), 2.73 (s, 2H), 4.32 (q, \(J = 7.2\) Hz, 2H), 6.14 (s, 1H), 10.00 (s, 1H), 10.84 (br, 1H); 13C NMR (100 MHz) \(\delta\) 9.1,10.4, 14.6, 29.3, 41.2, 46.2, 60.1, 110.8, 121.5, 122.7, 126.8, 130.2, 161.6, 162.7, 170.5, 190.3; ESI-MS obsd 303.1699, calcd 303.1703 [(M + H)^+, M = C_{17}H_{22}N_{2}O_{3}]; \lambda_{\text{abs}} (\text{CH}_2\text{Cl}_2) 459 nm.

8-Ethoxycarbonyl-1-formyl-2,3-dihydro-3,3,7,9-tetramethyldipyrpin (7b). A solution of 6b (50 mg, 0.18 mmol) in 1,4-dioxane (5.0 mL) was treated with SeO_2 (60. mg, 0.54 mmol) under argon and stirred at room temperature. The progress of the reaction was monitored by absorption spectroscopy. After 15 min, the reaction mixture was dilute with ethyl acetate, washed with water and brine, dried (Na_2SO_4) and concentrated. Chromatography [silica, CH_2Cl_2] gave a red-orange solid (36 mg, 66%): 1H NMR (400 MHz) \(\delta\) 1.25 (s, 6H), 1.37 (t, \(J = 6.8\) Hz, 3H), 2.35 (s, 3H), 2.57 (s, 3H), 2.72 (s, 2H), 4.29 (q, \(J = 6.8\) Hz, 2H), 6.16 (s, 1H), 9.97 (s, 1H), 10.57 (br, 1H); 13C NMR (100 MHz) \(\delta\) 11.3, 14.6, 14.8, 29.3, 41.1, 45.9, 59.4, 111.2, 112.2, 125.0, 126.4, 139.6, 159.7, 166.0, 168.5, 189.9; ESI-MS obsd 303.1699, calcd 303.1703 [(M + H)^+, M = C_{17}H_{22}N_{2}O_{3}]; \lambda_{\text{abs}} (\text{CH}_2\text{Cl}_2) 473 nm.
8-Ethoxycarbonyl-1-formyl-2,3-dihydro-3,3-dimethyl-7-(p-tolyl)dipyrrin (7c). Following a general procedure,$^{13}$ a solution of dihydrodipyrrin 6c (123 mg, 0.350 mmol) in 1,4-dioxane (7.0 mL) was treated with SeO$_2$ (117 mg, 1.05 mmol) under argon and stirred at room temperature for 60 min. Ethyl acetate (50 mL) was added, and the mixture was washed with saturated aqueous NaHCO$_3$ solution, water and brine. The organic layer was dried (Na$_2$SO$_4$), concentrated and chromatographed [silica, hexanes/ethyl acetate (4:1)] to afford a yellow oil (50.1 mg, 39%): $^1$H NMR (300 MHz) $\delta$ 1.17 (s, 6H), 1.21 (t, $J = 7.2$ Hz, 3H), 2.41 (s, 3H), 2.71 (s, 2H), 4.17 (q, $J = 7.2$ Hz, 2H), 6.08 (s, 1H), 7.23–7.29 (m, 4H), 7.63 (d, $J = 3.0$ Hz, 1H), 10.0 (s, 1H), 11.1 (br, 1H); $^{13}$C NMR (100 MHz) $\delta$ 14.3, 21.4, 29.1, 41.1, 46.1, 59.6, 112.4, 115.2, 127.3, 128.4, 129.4, 130.8, 136.9, 161.7, 164.5, 165.8, 189.9; ESI-MS obsd 351.2075, calcd 351.2067 [(M + H)$^+$, M = C$_{22}$H$_{24}$N$_2$O$_3$]; $\lambda_{abs}$ (CH$_2$Cl$_2$) 451 nm.

9-Ethoxycarbonyl-2,3-dihydro-1-(1,1-dimethoxymethyl)-3,3,7,8-tetramethyldipyrrin (8a). Following a standard procedure,$^{14}$ a solution of 6a (104 mg, 0.361 mmol) in 1,4-dioxane (10.0 mL) was treated with SeO$_2$ (120. mg, 1.08 mmol) under argon and stirred at room temperature. The progress of the reaction was monitored by absorption spectroscopy. After 15 min, the reaction mixture was dilute with ethyl acetate, washed with water and brine, dried (Na$_2$SO$_4$) and concentrated to an orange-red solid (crude 7a). The residue was dissolved in trimethyl orthoformate (5.0 mL) and then TsOH·H$_2$O (205 mg, 1.08 mmol) was added at room temperature. After 1 h, the reaction mixture was diluted with ethyl acetate and quenched by the addition of saturated aqueous NaHCO$_3$ solution. The separated organic phase was washed with water, dried (Na$_2$SO$_4$), concentrated and chromatographed [silica, CH$_2$Cl$_2$, then hexanes/ethyl acetate (1:1)] to afford an orange-yellow oil (80 mg, 64%): $^1$H NMR (300 MHz) $\delta$ 1.23 (s, 6H), 1.37 (t, $J = 7.2$ Hz, 3H), 2.04 (s,
3H), 2.27 (s, 3H), 2.64 (s, 2H), 3.49 (s, 6H), 4.30 (q, J = 7.2 Hz, 2H), 5.01 (s, 1H), 5.83 (s, 1H), 10.90 (br, 1H); $^{13}$C NMR (100 MHz) δ 8.9, 10.5, 14.7, 29.2, 40.6, 48.1, 55.2, 59.7, 103.3, 104.3, 119.1, 119.4, 126.8, 130.8, 161.8, 162.6, 176.1; ESI-MS obsd 349.21218, calcd 349.21128 [(M + H)$^+$, M = C$_{19}$H$_{28}$N$_2$O$_4$].

8-Ethoxycarbonyl-2,3-dihydro-1-(1,1-dimethoxymethyl)-3,3,7,9-tetramethyldipyrrin (8b). Following a standard procedure,$^{14}$ a solution of 6b (207 mg, 0.720 mmol) in 1,4-dioxane (15 mL) was treated with SeO$_2$ (240 mg, 2.16 mmol) and stirred at room temperature. The progress of the reaction was monitored by absorption spectroscopy. After 15 min, the reaction mixture was dilute with ethyl acetate, washed with brine and water, dried and concentrated to give an orange-red solid. The resulting residue (crude 7b) was dissolved in trimethyl orthoformate (7.2 mL), and TsOH·H$_2$O (415 mg, 2.16 mmol) was added at room temperature under argon. After 1 h, the reaction mixture was diluted with ethyl acetate, washed with water, dried (Na$_2$SO$_4$), and concentrated. Column chromatography [silica, hexanes/ethyl acetate (3:1)] afforded a yellow oil (130 mg, 52%): $^1$H NMR (400 MHz) δ 1.22 (s, 6H), 1.35 (t, 3H), 2.30 (s, 3H), 2.53 (s, 3H), 2.62 (s, 2H), 3.47 (s, 6H), 4.27 (q, 2H), 5.02 (s, 1H), 5.84 (s, 1H), 10.7 (br, 1H); $^{13}$C NMR (100 MHz) δ 11.1, 14.55, 14.60, 29.2, 40.4, 48.3, 54.6, 59.0, 102.7, 104.4, 111.1, 120.3, 125.9, 136.8, 158.9, 166.4, 173.9; ESI-MS obsd 349.2113, calcd 349.2122 [(M + H)$^+$, M = C$_{19}$H$_{28}$N$_2$O$_4$].

2-Formyl-4-methylthiopyrrole (10). A solution of 9 (7.1 g, 63 mmol) in CH$_2$Cl$_2$ (120 mL) and DMF (7.1 mL, 94 mL) was treated dropwise with POCl$_3$ (8.7 mL, 94 mmol) under argon at 0 °C. After 1 h, the ice bath was removed, and the reaction mixture was allowed to warm to room temperature. The reaction mixture was stirred for 20 h before being cooled to 0 °C again, whereupon 2.0 M NaOH (50 mL) was added. The reaction
mixture was extracted with CH$_2$Cl$_2$ (3 x 50 mL). The organic extract was washed (brine), dried (Na$_2$SO$_4$), concentrated and chromatographed [silica, CH$_2$Cl$_2$/ethyl acetate (9:1)] to afford a dark red solid (4.5 g, 51%): mp 96–98 °C; $^1$H NMR (300 MHz) $\delta$ 2.520 (s, 3H), 6.28 (m, 1H), 6.96 (m, 1H), 9.36 (s, 1H); $^{13}$C NMR (75 Hz) $\delta$ 17.7, 112.9, 123.6, 133.9, 136.9, 178.1; ESI-MS obsd 142.0323, calcd 142.0321 [(M + H)$^+$, M = C$_6$H$_8$NO$_2$S].

2-(2-Nitroethyl)-4-methylthiopyrrole (11). A solution of 10 (4.70 g, 33.3 mmol), potassium acetate (3.91 g, 40.0 mmol) and methylamine hydrochloride (2.75 g, 40.0 mmol) in absolute ethanol (40 mL) was treated with nitromethane (5.5 mL, 100 mmol). The mixture was stirred for 4 h and monitored by TLC analysis [silica, CH$_2$Cl$_2$/ethyl acetate (3:1)]. Then, water was added. The mixture was extracted with CH$_2$Cl$_2$. The organic phase was dried and concentrated to give a red solid. The crude solid was dissolved in a mixture of CHCl$_3$ (75 mL) and 2-propanol (24 mL), to which silica (23 g) was then added. The mixture was stirred vigorously, and NaBH$_4$ (1.90 g, 50.0 mmol) was added in several batches. After 1 h, the mixture was filtered. The filter cake was washed with CH$_2$Cl$_2$. The filtrate was concentrated and chromatographed (silica, CH$_2$Cl$_2$) to afford an orange-red oil (2.59 g, 42%): $^1$H NMR (300 MHz) $\delta$ 2.32 (s, 3H), 3.28 (t, $J = 6.6$ Hz 2H), 4.59 (t, $J = 6.6$ Hz, 2H), 5.97 (m, 1H), 6.25 (m, 1H), 8.16 (br, 1H); $^{13}$C NMR (100 MHz) $\delta$ 21.6, 25.6, 75.0, 108.5, 115.5, 121.4, 128.4; ESI-MS obsd 187.0541, calcd 187.0536 [(M + H)$^+$, M = C$_7$H$_{10}$N$_2$O$_2$S].

1,1-Dimethoxy-4,4-dimethyl-5-nitro-6-(4-methylthiopyrrol-2-yl)hexan-2-one (13). A mixture of 11 (2.59 g, 13.9 mmol) and 12 (4.39 g, 27.8 mmol) was treated with DBU (4.3 mL, 28 mmol) at room temperature. After 16 h, the reaction mixture was diluted with ethyl acetate and washed with water. The organic layer was dried (Na$_2$SO$_4$), concentrated and chromatographed [silica, hexanes/ethyl acetate (3:1)] to give a red oil (2.28 g, 48%): $^1$H
NMR (300 MHz) δ 1.14 (s, 3H), 1.22 (s, 3H), 2.29 (s, 3H), 2.65 (AB, $^2J = 18.9$ Hz, 2H), 2.98 (ABX, $^2J = 15.6$ Hz, $^3J = 2.4$ Hz, 1H), 3.32 (ABX, $^2J = 15.6$ Hz, $^3J = 12.0$ Hz, 1H), 3.43 (s, 3H), 3.44 (s, 3H), 4.37 (s, 1H), 5.14 (ABX, $^2J = 2.4$ Hz, $^2J = 12.0$ Hz, 1H), 5.93 (m, 1H), 6.20 (m, 1H), 8.10 (br, 1H); $^{13}$C NMR (100 MHz) δ 21.8, 24.4, 27.0, 36.6, 45.1, 55.4, 94.5, 104.9, 109.1, 115.7, 121.4, 128.6, 203.7; ESI-MS obsd 345.1473, calcd 345.1479 [(M + H)$^+$, M = C$_{15}$H$_{24}$N$_2$O$_5$S].

2,3-Dihydro-1-(1,1-dimethoxymethyl)-3,3-dimethyl-9-methylthiodipyrrin (14). In a first flask, a solution of 13 (2.28 g, 6.63 mmol) in anhydrous THF (50 mL) under argon was treated with NaOMe (1.79 g, 33.1 mmol). The mixture was bubbled with argon for 10 min and stirred for 1 h at room temperature. In a second flask, TiCl$_3$ (20 wt% TiCl$_3$ in 3 wt% HCl, 21 mL, 33 mmol) and water (264 mL) was combined. The solution was bubbled with argon for 10 min, NH$_4$OAc (51 g, 0.66 mol) was slowly added to buffer the solution to pH 6.0, and then THF (18 mL) was added under argon. After 30 min, the solution in the first flask was transferred via a cannula to the solution in the second flask. The resulting mixture was stirred at room temperature for 14 h under argon. Then saturated aqueous NaHCO$_3$ (500 mL) was added. The mixture was extracted with ethyl acetate. The organic layer was dried (Na$_2$SO$_4$), concentrated and chromatographed [alumina, hexanes/ethyl acetate (3:1)] to give a yellow oil (0.28 g, 14%): $^1$H NMR (300 MHz) δ 1.20 (s, 6H), 2.39 (s, 3H), 2.62 (s, 2H), 3.48 (s, 6H), 5.04 (s, 1H), 5.80 (s, 1H), 6.11 (m, 1H), 6.25 (m, 1H), 10.58 (br, 1H); $^{13}$C NMR (100 MHz) δ 21.5, 29.3, 40.3, 48.2, 55.1, 103.1, 107.1, 110.7, 114.8, 123.3, 132.8, 160.5, 174.9; ESI-MS obsd 295.1477, calcd 295.1475 [(M + H)$^+$, M = C$_{15}$H$_{22}$N$_2$O$_5$S].

9-Bromo-1-formyl-2,3-dihydro-7-(4-iodophenyl)-3,3-dimethylidipyrrin (16). A solution of 15 (30. mg, 0.074 mmol) in THF (7.4 mL) was treated with NBS (13 mg, 0.074
mmol) in one portion at –78 °C under argon. The reaction mixture was stirred at –78 °C for 1 h. Then hexanes/Et$_3$N (20 mL, 99:1) was added. The dry ice/acetone bath was removed and water (50 mL) was added. After the mixture warmed to room temperature, ethyl acetate was added. The organic extract was washed (brine and water), dried (Na$_2$SO$_4$), concentrated and chromatographed [silica, hexane/CH$_2$Cl$_2$ (3:1)] to give an orange-red solid (16 mg, 45%):

$^1$H NMR (300 MHz) $\delta$ 1.21 (s, 6H), 2.73 (s, 2H), 6.18 (s, 1H), 6.27 (d, $J = 3.0$ Hz, 1H), 7.11 (d, $J = 8.7$ Hz, 2H), 7.74 (d, $J = 8.7$ Hz, 2H), 10.02 (s, 1H), 10.80 (br, 1H); ESI-MS obsd 482.9568, calcd 482.9564 [(M + H)$^+$, M = C$_{18}$H$_{17}$N$_2$OBr].

1-(N-tert-butyl)methanimine-8-ethoxycarbonyl-2,3-dihydro-3,3-dimethyl-7-(p-tolyl)dipyrrin (17). A solution of 7c (22 mg, 0.060 mmol) in dichloromethane (6.0 mL) was treated with tert-BuNH$_2$ (25 µL, 0.24 mmol) under argon. The resulting mixture was stirred at room temperature and monitored by absorption spectroscopy. After 2 h, the mixture was concentrated to afforded a brownish yellow solid (16 mg, 63%): mp 165–166 °C; $^1$H NMR (300 MHz) $\delta$ 1.16 (s, 6H), 1.20 (t, $J = 7.2$ Hz, 3H), 1.30 (s, 9H), 2.40 (s, 3H), 2.81 (s, 2H), 4.17 (q, $J = 7.2$ Hz, 2H), 5.86 (s, 1H), 7.19–7.30 (m, 4H), 7.56 (d, $J = 3.0$ Hz, 1H), 8.28 (s, 1H), 11.25 (br, 1H); $^{13}$C NMR (100 MHz) $\delta$ 14.4, 21.4, 21.5, 29.1, 29.6, 40.3, 48.0, 58.9, 59.4, 106.6, 114.7 125.4, 125.8, 128.4, 129.8, 130.8, 131.4, 136.2, 153.5, 162.7, 165.0, 173.9; ESI-MS obsd 420.2658, calcd 420.2645 [(M + H)$^+$, M = C$_{26}$H$_{33}$N$_3$O$_2$]; $\lambda_{abs}$ (CH$_2$Cl$_2$) 406 nm.

1H,22H,24H-7,8,17,18-tetrahydro-1,3,3,13,13-pentamethyl-7-p-tolyl-18-methylthiocorrin (TDC-1). A solution of 18 (11 mg, 0.040 mmol) and 14 (12 mg, 0.040 mmol) in CH$_2$Cl$_2$ (40 mL) was treated with Yb(OTf)$_3$ (124 mg, 0.200 mmol) under argon at room temperature and kept stirring for 3 h. Then, saturated aqueous NaHCO$_3$ solution (50
mL) was added. The organic extract was washed with brine and water, dried (Na$_2$SO$_4$), concentrated, and chromatographed [silica, hexanes/ethyl acetate (3:1)] to give a dark green solid (10.1 mg, 50%): $^1$H NMR (400 MHz) δ 1.05 (s, 3H), 1.23 (s, 3H), 1.27 (s, 3H), 1.40 (s, 3H), 1.67 (s, 3H), 2.00 (d, $J = 12.8$ Hz, 1H), 2.33 (s, 3H), 2.43 (s, 2H), 2.51 (d, $J = 12.8$ Hz, 1H), 2.69 (d, $J = 17.6$ Hz, 1H), 2.76 (d, $J = 17.6$ Hz, 1H), 5.54 (s, 1H), 5.56 (s, 1H), 5.80 (s, 1H), 6.14 (m, 1H), 6.85 (m, 1H), 7.29 (d, $J = 8.0$ Hz, 2H), 7.40 (d, $J = 8.0$ Hz, 2H), 10.88 (br, 1H), 11.61 (br, 1H); $^{13}$C NMR (100 MHz) δ 21.6, 21.9, 27.3, 29.0, 29.3, 29.9, 30.0, 40.6, 49.4, 49.9, 52.4, 72.1, 94.1, 95.6, 102.2, 106.8, 110.4, 127.1, 128.6, 129.8, 130.3, 139.0, 143.7, 148.3, 148.5, 149.4, 163.6, 170.5, 179.7; ESI-MS obsd 509.2732, calcd 509.2733 [(M + H)$^+$, M = C$_{32}$H$_{36}$N$_4$S].

7,10,13-Tris(p-bromophenyl)-2,3,17,18-tetrahydro-1,3,3,17,17,19-hexamethylbiladiene-ac (23). A solution of 4-bromobenzaldehyde (5.3 mg, 0.029 mmol) and dihydrodipyrrin 21 (20. mg, 0.058 mmol) in CH$_2$Cl$_2$ (3.0 mL) was treated with Ga(OTf)$_3$ (45 mg, 0.087 mmol) and stirred at room temperature for 20 h. Saturated aqueous NaHCO$_3$ solution was added, whereupon the mixture was extracted with CH$_2$Cl$_2$. The combined organic extract was combined, washed with brine, dried (Na$_2$SO$_4$) and concentrated to a magenta solid (22 mg, 88%), which was characterized and used in the next step without further purification: $^1$H NMR (300 MHz) δ 1.14 (s, 12H), 1.98 (s, 6H), 2.44 (s, 4H), 5.51 (s, 1H), 5.84 (s, 2H), 6.09 (d, $J = 3.0$ Hz, 2H), 7.27–7.31 (m, 6H), 7.44–7.50 (m, 6H), 10.93 (br, 2H); $^{13}$C NMR (75 MHz) δ 20.6, 21.9, 29.2, 41.3, 44.1, 53.8, 102.2, 107.6, 119.1, 120.9, 122.6, 126.9, 130.0, 130.7, 131.5, 131.8, 133.0, 136.3, 141.3, 161.7, 177.1. The compound was easily oxidized and gave $m/z$ of the corresponding oxidized product (–2H): ESI-MS obsd 849.0779, calcd 849.0798 [(M + H)$^+$, M = C$_{43}$H$_{39}$Br$_3$N$_4$].
7,10,13-Tris(p-bromophenyl)-1,3,3,17,17,19-hexamethyl-7,8,12,13-tetradehydrocorrin nickel chloride (Ni-TDC-2). Biladiene 23 (22 mg, 0.026 mmol), nickel acetate tetrahydrate (30. mg, 0.12 mmol) and sodium acetate (30. mg, 0.36 mmol) were dissolved in methanol (3.0 mL) and heated to reflux for 30 min. The solution quickly turned to an indigo color. The resulting solution was concentrated, poured into water and extracted with CH$_2$Cl$_2$. The combined extract was dried (Na$_2$SO$_4$), concentrated to dryness, and chromatographed on alumina. The column was eluted with CH$_2$Cl$_2$ until the eluate was colorless and then with methanol/CH$_2$Cl$_2$ (1:10). The indigo-colored fraction was collected, shaken with aq HCl solution (20 mL, 0.5 M), dried (Na$_2$SO$_4$) and concentrated. The residue was crystallized (CH$_2$Cl$_2$-hexanes) as dark blue needles (20. mg, 82%): $^1$H NMR (700 MHz) δ 1.56 (s, 12H), 1.63 (s, 6H), 2.44 (AB, $J = 10.4$ Hz, 1H), 2.64 (AB, $J = 10.4$ Hz, 1H), 6.86 (s, 2H), 7.30 (s, 2H), 7.42 (m, 6H), 7.71 (m, 6H); $^{13}$C NMR (175 MHz) δ 29.0, 29.2, 29.8, 32.1, 44.6, 51.9, 85.1, 103.6, 123.6, 124.3, 130.7, 131.2, 131.9, 132.3, 132.6, 133.8, 134.7, 148.9, 154.9, 156.4, 173.3; MALDI-MS obsd 905.5; ESI-MS obsd 904.9973, calcd 904.9995 [M$^+$, M = C$_{43}$H$_{38}$Br$_3$N$_4$Ni]; $\lambda_{\text{abs}}$(CH$_2$Cl$_2$) 349, 601 nm.

Chloroiridium(III)-13-ethoxycarbonyl-8,8,18,18-tetramethyl-2,12-di-p-tolylbacteriochlorin (In-BC-1). Method A: A solution of dihydrodipyrrins 18 (7.0 mg, 0.025 mmol) and 8c (10. mg, 0.025 mmol) in CH$_2$Cl$_2$ (2.5 mL) was treated with Bi(OTf)$_3$ (33 mg, 0.050 mmol). After stirring for 20 min at room temperature, the reaction mixture was quenched by the addition of Et$_3$N (0.06 mmol, 8 μL) and then concentrated. The resulting crude product was dissolved in CH$_2$Cl$_2$ (2.5 mL), and the stock solution was distributed among five microvials. The solution in each vial was concentrated to a solid. The resulting solids were dissolved in the indicated solvent. Then each solution was treated with InCl$_3$ (11
mg, 0.050 mmol) and TMPi (9 µL, 0.05 mmol) and each reaction mixture was stirred at the indicated temperature. The progress of each microreaction was monitored by absorption spectroscopy. After 1.5 h, each microreaction mixture was diluted with CH₂Cl₂. Water was added to each microvial, and the organic extract was separated, washed with brine, dried (Na₂SO₄), concentrated and chromatographed [silica, CH₂Cl₂/ethyl acetate (4:1)] to give the indium bacteriochlorin. The bacteriochlorin yields were determined spectroscopically (Table 3.1). The highest yield was obtained for the reaction carried out in toluene (8%, determined by absorption spectroscopy).

**Method B:** A solution of 17 (25 mg, 0.060 mmol) and 2 (17 mg, 0.060 mmol) in CH₂Cl₂ (6.0 mL) was treated with Bi(OTf)₃ (79 mg, 0.12 mmol). After stirring for 15 min at room temperature, the reaction mixture was quenched by the addition of TMPi (0.10 mL, 0.60 mmol) and then concentrated to a brown solid. The residue was dissolved in toluene (6.0 mL) and treated with InCl₃ (133 mg, 0.60 mmol) and TMPi (0.10 mL, 0.60 mmol). The reaction mixture was stirred at 80 °C. Absorption spectroscopy of the reaction mixture showed the formation of the indium bacteriochlorin. After 2 h, the reaction mixture was diluted with ethyl acetate (50 mL). The organic extract was washed with brine and water, dried (Na₂SO₄), concentrated and chromatographed [silica, hexanes/ethyl acetate (3:2 to 1:1)] to afford a pink solid (1 mg, 2%).

**In-BC-1:** ¹H NMR (400 MHz) δ 1.28 (t, J = 7.2 Hz, 3H), 1.76 (s, 3H), 1.78 (s, 3H), 1.94 (s, 3H), 2.06 (s, 3H), 2.60 (s, 6H), 4.31–4.61 (m, 6H), 7.47 (d, J = 8.0 Hz, 2H), 7.56 (d, J = 8.0 Hz, 2H), 7.76 (d, J = 8.0 Hz, 2H), 7.99 (d, J = 8.0 Hz, 2H), 8.43 (s, 1H), 8.62 (s, 1H), 8.67 (s, 1H), 8.69 (s, 1H), 9.68 (s, 1H); MALDI-MS found 769.8; ESI-MS obsd 769.1810, calcd 769.1806 [(M-H)−, M = C₄₁H₄₀ClInN₄O₂]; ESI-MS obsd 735.2175, calcd 735.2185
[(M-Cl)+, M = C_{41}H_{40}ClIInN_{4}O_{2}]; \lambda_{\text{abs}} (\text{toluene}) 353, 391, 550, 773 nm; \lambda_{\text{em}} (\lambda_{\text{exe}} = 550 \text{ nm}) 789 \text{ nm}.

**Chloroindium(III)-12-(4-iodophenyl)-8,8,18,18-tetramethyl-2-p-tolylbacteriochlorin (In-BC-2).** A solution of 2 (3.1 mg, 0.011 mmol) and 16 (5.3 mg, 0.011 mmol) in CH_{2}Cl_{2} (1.1 mL) was treated with TsOH·H_{2}O (10. mg, 0.055 mmol). After stirring for 50 min at room temperature, the reaction mixture was quenched by the addition of TMPi (19 \mu L, 0.11 mmol) and then concentrated. The resulting residue was dissolved in toluene (1.1 mL) and treated with InCl_{3} (24 mg, 0.11 mmol) and TMPi (19 \mu L, 0.11 mmol). The reaction mixture was stirred at 90 °C. The reaction progress was monitored by absorption spectroscopy. After 2 h, the reaction mixture was diluted with ethyl acetate. The organic extract was washed with brine and water, dried (Na_{2}SO_{4}), concentrated and chromatographed [silica, CH_{2}Cl_{2} then CH_{2}Cl_{2}/ethyl acetate (4:1)] to afford a pink solid (1%, yield determined spectroscopically): \textsuperscript{1}H NMR (400 MHz) \delta 1.82 (s, 3H), 1.84 (s, 3H), 2.07 (s, 3H), 2.08 (s, 3H), 2.60 (s, 3H), 4.43 (AB, \textsuperscript{2}J = 16.8 Hz, \textsuperscript{3}J = 4.4 Hz, 2H), 4.64 (AB, \textsuperscript{2}J = 18.0 Hz, 2H), 7.57 (d, J = 8.4 Hz, 2H), 7.87 (d, J = 8.4 Hz, 2H), 8.03 (d, J = 8.4 Hz, 2H), 8.08 (d, J = 8.4 Hz, 2H), 8.73 (s, 1H), 8.75 (s, 1H), 8.77 (m, 2H), 8.78 (s, 1H), 8.82 (s, 1H); MALDI-MS obsd 812.4; ESI-MS obsd 810.0476, calcd 810.0472 [M\textsuperscript{+}, M = C_{37}H_{33}ClIIn_{4}]; obsd 775.0780, calcd 775.0783 [(M-Cl)+, M = C_{37}H_{33}ClIIn_{4}]; \lambda_{\text{abs}} (\text{toluene}) 350, 389, 539, 765 nm; \lambda_{\text{em}} (\lambda_{\text{exe}} = 539 \text{ nm}) 775 nm.

**Copper(II)-12-(4-bromophenyl)-2,3,8,8,18,18-hexamethylbacteriochlorin (Cu-BC-1).** A mixture of dihydrodipyrrin–acetal 8a (20. mg, 0.057 mmol) and dihydrodipyrrin 21 (20. mg, 0.057 mmol) in CH_{2}Cl_{2} (6 mL) was treated with Cu(OTf)\textsubscript{2} (50. mg, 0.14 mmol) at room temperature under argon for 90 min. Then saturated aqueous NaHCO\textsubscript{3} solution was
added to the reaction mixture, which was then extracted with CH₂Cl₂. The combined organic extract was washed with brine and water, dried (Na₂SO₄) and concentrated to a red purple gum with the following characterization data: MALDI-MS obsd 689.2; ESI-MS obsd 688.1469, calcd 688.1462 [M⁺, M = C₃₅H₃₈BrCuN₄O₂]; λ<sub>abs</sub> (CH₂Cl₂) 540 nm. The residue was dissolved in ethylene glycol (6.0 mL) and treated with powdered NaOH (228 mg, 5.70 mmol). The mixture was degassed by bubbling with argon, then heated to 160 °C under argon, and stirred for 1 h. The mixture was allowed to cool to room temperature, then diluted with ethyl acetate (100 mL) and washed thoroughly with brine and water. The resulting organic phase was dried (Na₂SO₄), concentrated and chromatographed [silica, hexanes/CH₂Cl₂ (1:1)] to give a green solid (2%, yield determined by absorption spectroscopy): MALDI-MS obsd 612.9; ESI-MS obsd 613.1012, calcd 613.1022 [M⁺, M = C₃₂H₃₁BrCuN₄]; λ<sub>abs</sub> (toluene) 337, 385, 511, 744 nm.

**Copper(II)-12-(4-bromophenyl)-3-ethoxycarbonyl-2,8,8,18,18-pentamethyl-7,17-dioxobacteriochlorin (Cu-OxoBC).** A mixture of dihydridopyrrin–acetal 8b (20 mg, 0.057 mmol) and dihydridopyrrin 21 (20 mg, 0.057 mmol) in CH₂Cl₂ (6 mL) was treated with Cu(OTf)₂ (25 mg, 0.068 mmol) at room temperature under argon for 90 min. Then saturated aqueous NaHCO₃ solution was added to the reaction mixture, which was then extracted with CH₂Cl₂. The combined organic extract was washed with brine and water, dried (Na₂SO₄) and concentrated to a red purple solid with the following characterization data: MALDI-MS obsd 689.2; ESI-MS obsd 688.1444, calcd 688.1469 [M⁺, M = C₃₅H₃₈BrCuN₄O₂]; λ<sub>abs</sub> (CH₂Cl₂) ~550 nm. The residue was dissolved in DMF (10 mL) and treated with anhydrous CuCl₂ (115 mg, 0.858 mmol). The mixture was degassed by bubbling argon for 10 min and then heated to 120 °C for 20 h under argon. The mixture was allowed to cool to room
temperature and then diluted with ethyl acetate (100 mL) and washed thoroughly with water (4 × 100 mL). The organic phase was dried (Na$_2$SO$_4$), concentrated and chromatographed [silica, hexanes/ethyl acetate (4:1 then 3:1)] to give a green solid (2% yield, determined by absorption spectroscopy): MALDI-MS obsd 700.1; ESI-MS obsd 718.0836, calcd 718.0846 [(M + H$_2$O)$^+$, M = C$_{34}$H$_{29}$BrCuN$_4$O$_4$]; ESI-MS obsd 698.0602, calcd 698.0595 [(M - H)$^-$, M = C$_{34}$H$_{29}$BrCuN$_4$O$_4$]; $\lambda_{\text{abs}}$ (toluene) 388, 434, 528, 711 nm.

**Screening method of In-BC-1.** For $n$ microreactions a solution of 17 (0.005$n$ mmol) and 2 (0.005$n$ mmol) in anhydrous CH$_2$Cl$_2$ ($n$ mL) was treated with 2 molar equiv of Bi(OTf)$_3$. After 20 min the reaction mixture was neutralized with TMPi (2.2 molar equiv) and concentrated to a solid. The crude solid was dissolved in 0.5$n$ mL of CH$_3$CN, and the bulk solution was distributed among the $n$ reaction microvials (0.5 mL each) with 0.005 mmol theoretical amount of linear putative intermediate in each vial. Then TMPi (10 molar equiv) and a metal salt (10 molar equiv) were added, and the microreaction contents were stirred at reflux. Reactions were monitored by UV-spectroscopy assuming $\varepsilon = 100,000$ M$^{-1}$ cm$^{-1}$ [50 $\mu$L of sample from reaction mixture was added to 0.9 mL of toluene/EtOH (3:1)], and by LD-MS analysis with 4 time points (30 min, 1 h, 2 h and overnight).
References


Chapter IV

Construction of the Bacteriochlorin Macrocycle with Concomitant Nazarov Cyclization to Form the Annulated Isocyclic Ring – Analogues of Bacteriochlorophyll a

Preamble

The full contents of this chapter have been published (Zhang, S.; Lindsey, J. S. J. Org. Chem., 2017, 82, 2489–2504).

Introduction

Bacteriochlorins are attractive candidates for a variety of photophysical studies owing to their strong absorption in the near infrared (NIR) spectral region.\(^1,2\) The core chromophore of bacteriochlorophylls \(a\), \(b\) and \(g\), the chief light-harvesting pigments in anoxygenic photosynthetic bacteria, is a bacteriochlorin (Scheme 4.1). Bacteriochlorins are members of the tetrapyrrole family and contain alternating pyrrole and pyrroline rings. Bacteriochlorophylls also contain a fifth, annulated ring (the ‘isocyclic’ ring, or ring E) that spans positions 13 and 15; the ring is equipped with an integral keto group that lies coplanar with the organic \(\pi\)-system. In addition, an auxochrome is present at the 3-position, distal to the coplanar keto group of the isocyclic ring. Bacteriochlorophyll \(b\) differs from bacteriochlorophyll \(a\) in the presence of an exocyclic ethyldiene group in ring B, whereas bacteriochlorophyll \(g\) contains the exocyclic ethyldiene group in ring B as well as a 3-vinyl group and farnesyl (or other hydrocarbon) rather than phytol as the esterifying unit at the 17\(^3\)-position.
To access synthetically malleable analogues of bacteriochlorophylls, we have been developing a \textit{de novo} synthesis of bacteriochlorins (I). The route relies on the self-condensation of a dihydrodipyrrin–acetal (II-acetal)$^{3,4}$ or dihydrodipyrrin–carboxaldehyde (II-CHO)$^5$ (Scheme 4.1). A gem-dimethyl group is positioned in each pyrroline ring to block any adventitious (aerobic) dehydrogenation leading to the more unsaturated chlorin or porphyrin. Incorporation of the gem-dimethyl group has proved synthetically more expedient than the \textit{trans}-dialkyl (or alkyl/alkylidene) configuration of the natural macrocycles.$^6$ An alternative route (not shown) employs a Northern-Southern self-condensation of a dihydrodipyrrin–acetal similar to that in the Eastern-Western route.$^7$ Regardless, a chief limitation of both \textit{de novo} syntheses originates with the dimerization process – whatever substituents are present on the pyrrole unit of the dihydrodipyrrin species are conveyed to the two pyrroles of the bacteriochlorin.
Rational approaches to bacteriochlorins with nonidentical substituents on the two pyrrole units have been severely limited (Scheme 4.2): (1) Sonogashira coupling of a 3,13-dibromo-5-methoxybacteriochlorin (I-a) proceeds selectively at the unhindered 13-position, after which more forcing Pd-mediated conditions could be employed to install diverse substituents at the 3-position en route to the differentially substituted bacteriochlorin (I-b).
(2) A 3,13-diacetyl-5-methoxybacteriochlorin (I-c) underwent 15-bromination (I-d), setting up Pd-mediated α-arylation to close the annulated 5-membered ring spanning positions 13 and 15, thereby forming the bacterio-13\(^1\)-oxophorbine (I-e). To date, I-e is the only bacterio-13\(^1\)-oxophorbine prepared by *de novo* synthesis. (3) A route to tolyporphin A diacetate,\(^9\)-\(^11\) a derivative of a naturally occurring dioxobacteriochlorin (not shown), is ingenious yet inordinately lengthy for our purposes. An alternative approach toward bacteriochlorins entails derivatization of porphyrins or chlorins.\(^12\)

![Scheme 4.2. Rational Routes to Unsymmetrically Substituted Bacteriochlorins](image)

By contrast with these synthetic limitations, bacteriochlorophylls *a*, *b* and *g* contain distinct substituents in rings A–C, as well as the isocyclic ring (E) bearing a carbomethoxy group at the 13\(^2\)-position (Scheme 4.1). The synthesis shown in Scheme 4.2 (right panel)
affords the $13^1$-oxobacteriophorbine macrocycle but lacking the $13^2$-carbomethoxy group. The resulting macrocycles are akin to bacteriopyropheophorbides (Figure 4.1), which are the natural bacteriochlorophyll derivatives obtained upon demetalation and pyrolytic loss of the $13^2$-carbomethoxy substituent. The functional role of the $13^2$-carbomethoxy group remains unclear, whereas the coplanar keto group (13-position) is known to cause a bathochromic shift of the long-wavelength absorption band and to interact via hydrogen bonding with protein sites. Note that the term isocyclic ring is typically used regardless of the presence or absence of the $13^2$-carbomethoxy group, as well as vast other modifications to the native structure. To date, names for tetrapyrrole macrocycles bearing isocyclic rings derive from those of the natural compounds.

![Figure 4.1. Bacteriopheophytin derivatives and bacterio-$13^1$-oxophorbine.](image)

The synthesis of bacteriochlorins that are unsymmetrically substituted with diverse groups in the pyrrole (A, C) and pyrroline (B, D) rings remains an unmet challenge. Access to such macrocycles would open a number of scientific opportunities, of which the following
are representative: (1) incorporation of distinct auxochromes for wavelength-tuning; (2) introduction of a single tether (for bioconjugation or surface attachment) and/or a single water-solubilizing group; (3) site-selective incorporation of single isotopes (e.g., $^{13}$C or $^{15}$N) for vibronic studies; (4) introduction of distinct substituents on opposite sides of the macrocycle to engender self-assembly; and (5) incorporation of the resulting tailored macrocycles as building blocks in the construction of multi-pigment arrays for studies of light-harvesting and energy transduction.

In this paper, we describe a rational route to bacteriochlorin macrocycles that incorporates the $\beta$-ketoester-containing isocyclic ring as well as diverse substituents at the 2- and 3-positions. The route relies on directed joining of two distinct dihydrodipyrrins (BC and AD halves) by mild Knoevenagel condensation followed by one-flask, mild acid-mediated electrophilic aromatic substitution and Nazarov cyclization to form the macrocycle along with the isocyclic ring. We describe the routes to the BC and AD halves, studies of the conditions for conversion to the bacteriochlorins, and application to the synthesis of five new bacteriochlorins. The static absorption and fluorescence spectroscopic properties of the new bacteriochlorins are reported and compared with those of the natural bacteriopheophytin $a$ (Bpheo $a$).

**Results**

**I. Reconnaissance.** After several years of study (for an earlier attempt, see reference 16), two precedents proved enlightening for developing a directed synthesis of unsymmetrically substituted bacteriochlorins. The first precedent was Woodward’s pioneering synthesis of chlorin $e_6$ trimethyl ester, a precursor of chlorophyll, which relies on
directed joining of an AD half and a BC half to form an unsymmetric porphyrin (Scheme 4.3).\textsuperscript{17-19} Acid-catalyzed condensation of a dipyrrromethane–thioaldehyde (W-31, Woodward numbering\textsuperscript{19}) and a dipyrrromethane–amine (W-32) gave a Schiff’s base (W-33). Intramolecular condensation of the juxtaposed rings A and B in W-33 generated a single bilene-\textit{b} salt; subsequent condensation between rings C and D under more forcing acidic conditions deftly closed the macrocycle and, upon dehydrogenation and acetylation, afforded the desired porphyrin (W-35) in 50% overall yield. In our case, to prepare an unsymmetric bacteriochlorin, dihydrodipyrrins would be the constituents instead of dipyrrromethanes. Also required is a unit at the \( \beta \)-pyrrole position of one dihydrodipyrrin to direct intermolecular joining of the BC and AD halves followed by an intramolecular joining of the resulting linear intermediate to close the macrocycle.
The second precedent emerged from studies of the Nazarov cyclization with heteroaromatic compounds. Examples of Nazarov cyclization with pyrroles bearing appended propenoyl substituents have emerged only in the past decade. In the first two reports, Knight and coworkers employed an $N$-protected pyrrole and a propenoic acid whereas Frontier and co-workers employed an unprotected pyrrole bearing a propenoyl substituent at the $\beta$-position. The latter appeared ideal for our case. Under a catalytic
amount of Sc(OTf)_3 (10 mol%) and in the presence of LiClO_4 for 1.25 h, \( \beta \)-(propenoyl)pyrrole \( \text{III} \) underwent ring closure at the \( \alpha \)-position in 68% yield (eq. 1).\(^{22}\) The resulting annulated pyrrole \( \text{IV} \) bears the same structural motif as in the isocyclic ring of bacteriochlorophylls \( a, b \) and \( g \). The Nazarov cyclization of unprotected \( \beta \)-(propenoyl)pyrroles also was reported to proceed with other catalysts and to be tolerant of various substituents.\(^{23,24}\) The Nazarov substrate \( \text{III} \) could be easily prepared via Knoevenagel condensation of the \( \beta \)-ketoester–pyrrole and butanal.\(^{22}\)

![Chemical Structure](image)

(1)

The resulting retrosynthetic analysis for the preparation of unsymmetrical annulated bacteriochlorins is outlined in Scheme 4.4. First, the bacteriochlorin macrocycle (\( \text{V} \)) is created upon double ring-closure of a linear tetrapyrrole (\( \text{VI} \)) containing two dihydropyrrins linked via a propenoyl unit: (i) electrophilic aromatic substitution of the acetal unit and the open pyrrole \( \alpha \)-position joins rings A and B; (ii) Nazarov cyclization joins rings C and D thereby constructing the isocyclic ring (E). The oxidation state of the linear tetrapyrrrole remains unchanged during the overall double ring-closure and aromatization processes. Second, the linear tetrapyrrrole (\( \text{VI} \)) is prepared by Knoevenagel condensation of the AD half (\( \text{VII} \)) and BC half (\( \text{VIII} \)). The conditions for Knoevenagel condensation must be compatible with sensitive functionalities (e.g., the open pyrrole \( \alpha \)-position and the acetal unit) and occur specifically between the \( \beta \)-ketoester and the carboxaldehyde group.
II. Synthesis. 1. AD and BC Halves. The synthesis of the BC halves began with the known N-tosyl protected bromopyrrole 1.\textsuperscript{25} Following a reported procedure\textsuperscript{26} with modification to use cobalt carbonyl as a source of carbon monoxide, carbonylation of 1 with a potassium monoalkyl malonate gave the densely functionalized methyl $\beta$-ketoester 2a in 80% yield and the ethyl $\beta$-ketoester 2b in 56% yield (Scheme 4.5). We were pleased to find that
this Pd-catalyzed carbonylation could be carried out on a bromopyrrole, although more than a catalytic amount of Pd(OAc)$_2$ (0.5 molar equivalent) and a longer reaction time (48 h) were required for completion of the reaction. The remainder of the synthesis followed established procedures for dihydridopyrrins lacking the β-ketoester.$^{25}$ Cleavage of the tosyl group by refluxing in THF containing TBAF gave the free pyrrole 3a or 3b in 70% or 64% yield, respectively. Each of the latter was treated with NaOMe followed by a buffered aqueous–organic solution of TiCl$_3$ at room temperature for 16 h to afford BC half 4a or 4b in 45% or 36% yield. Both BC halves were readily prepared in 200-mg quantity.
Scheme 4.5. Preparation of BC Halves

Four AD halves were sought (Figure 4.2). The synthesis of AD halves generally begins with the desired $\beta$-substituted pyrrole-2-carboxaldehyde. For the case where the pyrrole bears two electron-releasing substituents at the $\beta$-positions (e.g., 5-MeMe), a
stabilizing ester substituent at the 5-position is required.\textsuperscript{5} AD halves 5-T and 5-MeMe are known compounds,\textsuperscript{5} whereas the synthesis of 5-Ar and 5-EtEs is reported herein.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure42.png}
\caption{Target AD halves.}
\end{figure}

The synthesis of 5-Ar proceeds in well practiced fashion\textsuperscript{4} as is shown in Scheme 4.6. Wittig reaction of \textit{p}-bromobenzaldehyde with (carboethoxymethylene)triphenylphosphorane afforded cinnamate 6, which upon van Leusen reaction with TosMIC and subsequent saponification and decarboxylation gave the 3-arylpurrole 7. Vilsmeier formylation of the latter gave regioselectively the 2-formylpyrrole 8 in 77\% yield. Conversion to the 2-(2-nitroethyl) derivative 9-Ar proceeded via Henry reaction with nitromethane and subsequent reduction with NaBH\textsubscript{4}.
Scheme 4.6. Precursors of an AD Half

The completion of the AD half syntheses is shown in Scheme 4.7. The key steps involve (i) Michael addition between 2-(2-nitroethyl)pyrroles (9-Ar, 9-EtEs)4 and mesityl oxide to form the nitrohexanone–pyrroles (10-Ar, 10-EtEs); (ii) reductive ring closure to give the 1-methyldihydropyrrins (11-Ar, 11-EtEs); and (iii) SeO₂ oxidation to convert the 1-methyl group to the 1-formyl group and thereby afford the desired dihydropyrrin–carboxaldehydes (5-Ar, 5-EtEs). Compounds 5-Ar and 5-EtEs exhibit absorption spectra (λₘₐₓ in CH₂Cl₂ = 470, 451 nm, respectively) similar to those of the known dihydropyrrin–carboxaldehydes 5-Ar and 5-T.5 The dihydropyrrin–carboxaldehydes generally are unstable to acidic conditions and should be prepared immediately prior to use.
2. Conditions for Bacteriochlorin Formation. The formation of the bacteriochlorin entails a two-step approach as illustrated for the dihydrodipyrrins 5-T and 4a in Scheme 4.8. For the first (intermolecular) step – Knoevenagel condensation of the two dihydrodipyrrins – a catalytic amount of piperidine and acetic acid (1:1) in CH₂Cl₂ containing molecular sieves (3Å powder) at room temperature for 20 h was found to produce the target bilin 12-T in 61% yield. The conditions are quite mild, with a near-neutral catalyst.
combination (see Experimental section) and modest concentrations (4a, 41 mM; 5-T, 48 mM). Both the α-unsubstituted pyrrole and the acetal group survived the reaction conditions. The linear intermediate 12-T was obtained following chromatography as a dark red oil, and exhibits the absorption spectrum shown in Figure 4.3. $^1$H NMR spectroscopy of 12-T gave two peaks (δ 7.65 and 7.39 ppm) characteristic of the α-olefinic proton and the α-pyrrolic proton. We know of no other molecules resembling 12-T for spectroscopic comparisons; perhaps the closest would be a 10-oxobiladiene-ac,$^{27}$ yet 12-T is a vinylogous relative and also contains two pyrroline rings.

Scheme 4.8. De novo Route to Bacteriopheophytin Analogues
For the second (intramolecular) step – the double ring-closure of the bilin intermediate – the requirement for acid catalysis engendered several considerations: (1) Frontier and co-workers found that Sc(OTf)$_3$, In(OTf)$_3$ and Hf(OTf)$_4$ are more effective catalysts in the Nazarov cyclization.\textsuperscript{22} (2) Our previous studies on the self-condensation of dihydridopyrinn–acetals identified Lewis acids suitable for the condensation between pyrrole and acetal units (e.g., BF$_3$·OEt$_2$ in CH$_3$CN,\textsuperscript{3} TMSOTf/DTBP (2,6-di-tert-butylpyridine) in CH$_2$Cl$_2$\textsuperscript{4}). (3) Yb(OTf)$_3$ and Sc(OTf)$_3$ were especially efficient in catalyzing pyrrole–acetal condensations, although tetrahydrocorrin-type macrocycles were obtained rather than bacteriochlorins.\textsuperscript{16,28}

Six acids were examined for the double ring-closure of 12-T (Table 4.1, entries 1–6). The reaction was conducted with 0.2 mM 12-T and 2 mM acid with the indicated solvent or temperature. The reactions were followed by UV-Vis absorption spectroscopy, and typically were complete in 20 h. The yield was calculated using the measured molar absorption
coefficient for $\text{BC-T}$ of $5.0 \times 10^4 \text{M}^{-1}\text{cm}^{-1}$ at the $Q_y$ band ($\lambda_{Q_y} = 722$ nm in toluene). Among the acids examined, Hf(OTf)$_4$ (entry 1), TMSOTf/DTBP (entry 2) or BF$_3$·OEt$_2$ (entry 3), which are all effective catalysts in the *de novo* synthesis strategy,$^{3,4}$ did not afford a peak characteristic of bacteriochlorins. On the other hand, Sc(OTf)$_3$ and Yb(OTf)$_3$ gave $\text{BC-T}$ in 10% yield (entry 4) and 14% yield (entry 5), respectively. With In(OTf)$_3$, the corresponding indium bacteriochlorin ($\lambda_{Q_y} = 746$ nm in toluene) was produced instead of the free base bacteriochlorin (entry 6). Indium-chelated bacteriochlorins (lacking the isocyclic ring) have been formed previously upon indium catalysis of the self-condensation of a dihydrodipyrrin–acetal.$^{29}$

All the condensations were carried out in dilute solution (0.2 mM of bilin 12-T) to avoid intermolecular side-reactions. Reactions at a higher concentration (10 mM) led to only a trace amount of an unknown bacteriochlorin ($\lambda_{Q_y} = 743$ nm in toluene).

The effect of temperature and solvent on bacteriochlorin formation was examined with Yb(OTf)$_3$ as catalyst. The yield of bacteriochlorin in 1,2-dichloroethane increased with reaction temperature (20–80 °C, entries 7–10). Maintaining the temperature at 80 °C, no bacteriochlorin was obtained in nitromethane (entry 11) while the yield was very low in toluene (5.6%, entry 12). The reaction proceeded efficiently in acetonitrile at 80 °C (46%, entry 13) and moderately well in dichloromethane at 40 °C (13%, entry 14).

Frontier and co-workers$^{22}$ identified LiClO$_4$ as an effective catalyst for the Nazarov cyclization. Here, reaction in the presence of 10 equiv of LiClO$_4$ did not affect the yield, whereas excess LiClO$_4$ (100 equiv) led to a lower yield. In summary, the reaction of 12-T in dilute solution with Yb(OTf)$_3$ in acetonitrile at 80 °C gave the best results for bacteriochlorin formation.
Table 4.1. Conditions for Bacteriochlorin (BC-T) Formation from 12-T

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid</th>
<th>Solvent(^a)</th>
<th>Temperature</th>
<th>Yield (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hf(OTf)(_4)</td>
<td>DCE</td>
<td>50</td>
<td>0(^c)</td>
</tr>
<tr>
<td>2</td>
<td>TMSOTf/DTBP</td>
<td>CH(_2)Cl(_2)</td>
<td>20</td>
<td>0(^c)</td>
</tr>
<tr>
<td>3</td>
<td>BF(_3)·OEt(_2)</td>
<td>CH(_3)CN</td>
<td>20</td>
<td>--(^d)</td>
</tr>
<tr>
<td>4</td>
<td>Sc(OTf)(_3)</td>
<td>DCE</td>
<td>50</td>
<td>9.6</td>
</tr>
<tr>
<td>5</td>
<td>Yb(OTf)(_3)</td>
<td>DCE</td>
<td>50</td>
<td>14</td>
</tr>
<tr>
<td>6</td>
<td>In(OTf)(_3)</td>
<td>DCE</td>
<td>50</td>
<td>7.6(^e)</td>
</tr>
<tr>
<td>7</td>
<td>Yb(OTf)(_3)</td>
<td>DCE</td>
<td>20</td>
<td>13</td>
</tr>
<tr>
<td>8</td>
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</tr>
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<td>16</td>
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<td>20</td>
</tr>
<tr>
<td>11</td>
<td>Yb(OTf)(_3)</td>
<td>CH(_3)NO(_2)</td>
<td>80</td>
<td>0(^c)</td>
</tr>
<tr>
<td>12</td>
<td>Yb(OTf)(_3)</td>
<td>Toluene</td>
<td>80</td>
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</tr>
<tr>
<td>13</td>
<td>Yb(OTf)(_3)</td>
<td>CH(_3)CN</td>
<td>80</td>
<td>46</td>
</tr>
<tr>
<td>14</td>
<td>Yb(OTf)(_3)</td>
<td>CH(_2)Cl(_2)</td>
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<td>13</td>
</tr>
</tbody>
</table>

\(^a\)DCE = 1,2-dichloroethane. \(^b\)Yields were determined on the basis of the absorption spectrum. \(^c\)No absorption peak was detected >700 nm. \(^d\)The desired bacteriochlorin (\(\lambda_{Qy} = 722\) nm) was not detected. A trace amount of unknown bacteriochlorin (\(\lambda_{Qy} = 750\) nm) was observed with a yield <2%. \(^e\)Yield of the corresponding indium bacteriochlorin.

3. Scope of Reaction. The reaction using the refined catalysis conditions was carried out with 20 mg of the bilin 12-T, and the resulting bacteriochlorin was purified by chromatography. To our delight, the yield of isolated bacteriochlorin BC-T reached 56% (9.5 mg). Other bilins of type 12 were prepared by reaction with various AD halves and BC half 4a or 4b in the same manner as for 12-T (Table 4.2). BC halves 4a and 4b differ only in the nature of the carboalkoxy substituent (methyl, ethyl). The Knoevenagel reaction was carried out with 1–1.5 equiv of the dihydrodipyrrin–carboxaldehyde (AD half, 5) relative to
the BC half (4a, 4b), whereupon the bilins (12) were obtained in yields ranging from 57–71%.
**Table 4.2. Investigation of the Scope of Bacteriochlorin Formation**

![Chemical structures and reactions]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compounds</th>
<th>Substituents</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>4</td>
<td>12</td>
<td>BC</td>
</tr>
<tr>
<td>1</td>
<td>5-T 4a</td>
<td>12-T</td>
<td>BC-T</td>
</tr>
<tr>
<td>2</td>
<td>5-Ar 4a</td>
<td>12-Ar</td>
<td>BC-Ar</td>
</tr>
<tr>
<td>3</td>
<td>5-MeMe 4a</td>
<td>12-MeMe</td>
<td>BC-MeMe</td>
</tr>
<tr>
<td>4</td>
<td>5-EtEs 4a</td>
<td>12-EtEs</td>
<td>BC-EtEs</td>
</tr>
<tr>
<td>5</td>
<td>5-Ar 4b</td>
<td>12-Ar/Et</td>
<td>BC-Ar/Et</td>
</tr>
</tbody>
</table>
With the bilins 12 in hand, conversion to the bacteriochlorins was pursued by application of the refined reaction conditions. First, the reaction conditions are compatible with a bromoaryl substituent to give BC-Ar (61% yield, entry 1). Second, a bacteriochlorin (BC-MeMe) with two electron-donating groups was obtained in 37% yield. In addition to the pyrrole–acetal condensation and Nazarov cyclization, cleavage of the tert-butyl ester occurred in this process, albeit with a relative lower overall yield compared with the other examples. The presence of the tert-butyl ester was essential to stabilize the very electron-rich dihydrodipyrrin unit. Third, a bacteriochlorin (BC-EtEs) with an electron-withdrawing group at the β-pyrrole position (-CO₂Me) was prepared in good yield (57%). Finally, starting with BC half 4b, a bacteriochlorin with a 13²-carboethoxy group (BC-Ar/Et, where the “/Et” designates the 13²-ester substituent) was obtained, indicating the possibility of more elaborate modification at this site of the macrocycle.

III. Characterization. 1. Structures. The dihydrodipyrrins typically were purified by silica gel chromatography. While the isolated dihydrodipyrrins examined herein are relatively stable, limiting the duration of exposure to silica gel was important. The dihydrodipyrrins obtained in this manner were characterized (by TLC, ¹H and ¹³C NMR spectroscopy, and accurate-mass ESI-MS) and used successfully in bacteriochlorin formation. All new bacteriochlorins were characterized by ¹H NMR and ¹³C NMR spectroscopy, accurate-mass ESI-MS, and static absorption and fluorescence spectroscopy. A single-crystal X-ray structure was obtained for bacteriochlorin BC-Ar (Figure 4.4, CCDC# 1528392). In general, the ¹H NMR spectra of the bacteriochlorins were complex due to the non-equivalent A, B, C and D rings as well as the presence of the additional E ring. The structure and ¹H NMR spectrum of BC-MeMe are illustrative: (1) The four distinct protons
around the perimeter of the bacteriochlorin (meso-protons at the 5-, 10-, and 20-positions, and one β-pyrrolic proton) give rise to four singlets in the region δ 7.62–7.97 ppm. (2) The proton at the 13\(^2\)-position resonates as a singlet at δ 5.64 ppm, which is comparable to that of the 13\(^2\)-H in Bpheo \(a\) (δ 6.08 ppm\(^{30}\)). (3) The presence of a stereocenter at the 13\(^2\)-position causes the pyrroline CH\(_2\) protons (ring D, position 17: δ 3.62–3.74 ppm) flanking the isocyclic ring (E) to be split into an AB pattern, while the pyrroline CH\(_2\) protons distal to the stereocenter resonate as an apparent singlet (ring B, position 7: δ 3.97 ppm). (4) The two methyl groups of a gem-dimethyl unit are similarly inequivalent, and those at the 18-position resonate as two singlets (1.72 and 1.80 ppm). (5) The N-H protons give rise to two broad upfield peaks (1.16 and 1.62 ppm). No peaks upfield of 0 ppm were observed.

![Figure 4.4. ORTEP drawing of BC-Ar.](image)

**Figure 4.4.** ORTEP drawing of BC-Ar. Ellipsoids are at the 50% probability level, and hydrogen atoms are omitted for clarity. The conjugated macrocycle is slightly bent out of plane, while the torsion angle of the four nitrogens (N1-N2-N1’-N2’) is 4.68°.
Comparing the $^1$H NMR spectra of BC-MeMe, BC-EtEs and Bpheo $^a$ yields the following observations: (1) The chemical shifts of the peripheral protons of BC-MeMe (with two electron-donating groups) are in the range of 7.63–7.97 ppm, while those of BC-EtEs (with one electron-withdrawing group) are in the range of 8.20–9.16 ppm; the latter are more similar to those of Bpheo $a$ (8.39–8.96 ppm). (2) The N-H protons in BC-EtEs resonate at –0.07 and 1.59 ppm, compared to those in BC-MeMe ($\delta$ 1.16, 1.62 ppm) and Bpheo $a$ ($\delta$ –0.99, 0.44 ppm).$^{30}$

2. Absorption and Fluorescence Spectra. Figure 4.5 shows the absorption spectra and fluorescence emission spectra of four synthetic, isocyclic ring-containing bacteriochlorins (BC-MeMe, BC-T, BC-Ar, and BC-EtEs) in toluene. The spectral data shown in Table 4.3 include the position and the relative intensity of the characteristic absorption bands, the full-width at half-maximum (fwhm) value of the long-wavelength absorption band ($Q_y$), and the ratio of the intensity of the $Q_y$ to $B_y$ band ($I_{Qy}/I_{By}$ ratio). For comparison, the table also includes spectral data for Bpheo $a$ and the benchmark $^5$ Me$_4$-BC. The molar absorption coefficient of BC-T in toluene ($5.0 \times 10^4$ M$^{-1}$cm$^{-1}$, determined using ~6 mg of BC-T) is close to that reported for Bpheo $a$ (42–49 mM$^{-1}$cm$^{-1}$ in acetone-methanol (7:2, v/v) and 63–73 mM$^{-1}$cm$^{-1}$ in ether).$^{32}$ The spectrum of BC-Ar/Et matches almost identically that of BC-Ar and is not shown in Figure 4.5.
Figure 4.5. Absorption (solid line) and fluorescence spectra (dashed line; $\lambda_{ex}$ at the Q$_x$ band near 520 nm) in toluene at room temperature of bacteriochlorins (normalized at the Q$_y$ bands). The colors in the graph are as follows: BC-MeMe (black), BC-T (red), BC-Ar (blue) and BC-EtEs (purple).

The spectrum of each bacteriochlorin contains three main absorption bands termed the B band (a mixture of B$_x$ and B$_y$ transitions), Q$_x$ band and Q$_y$ band. The spectral features resemble those of Bpheo a, but differ to some degree from those of bacteriochlorins lacking the isocyclic ring. In comparison with the 2,3,12,13-tetramethylbacteriochlorin (Me$_4$-BC, Figure 4.6), which lacks the isocyclic ring, the following features are noteworthy: (1) The $I_{Qy}/I_{By}$ ratio is much lower (0.38–0.62 vs. 0.97), indicating a relatively lower intensity of the
Q_y band. (2) The $I_{Q_y(0,0)}/I_{Q_x(0,0)}$ ratio is much lower (1.1−2.0 vs. 5.3), indicating a relatively greater intensity of the Q_x band. (3) The $I_{Q_x(0,0)}/I_{Q_x(1,0)}$ ratio also is greater (3.1−4.1 vs. 1.9). (4) The fwhm of the Q_y(0,0) band is in the range of 27−33 nm, which is slightly broader than reported for bacteriochlorins lacking the isocyclic ring (11−25 nm).^{31}

![Figure 4.6. A benchmark bacteriochlorin](image)

The fluorescence emission spectra of the four synthetic bacteriochlorins (BC-MeMe, BC-T, BC-Ar, and BC-EtEs) in toluene at room temperature are shown in Figure 4.3. In each case, the Q_y(0,0) emission band is shifted 6−15 nm to longer wavelength than the Q_y(0,0) absorption band, to be compared with a Stokes shift for Me_4-BC of ~2 nm. The comparatively large Stokes shift of the isocyclic ring-containing bacteriochlorins indicates more substantial structural changes or solvent interactions upon photoexcitation. The fwhm of Q_y(0,0) emission band is in the range of 26−32 nm.
Table 4.3. Spectral Characteristics of Bacteriochlorins

<table>
<thead>
<tr>
<th>Compound</th>
<th>Absorption in nm (relative intensity)</th>
<th>Flu</th>
<th>Fwhm (nm)</th>
<th>Intensity ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B(0,0)</td>
<td>Qₓ(1,0)</td>
<td>Qₓ(0,0)</td>
<td>Qᵧ(1,0)</td>
</tr>
<tr>
<td>BC-T</td>
<td>356 (1.8)</td>
<td>489 (0.18)</td>
<td>520 (0.62)</td>
<td>660 (0.31)</td>
</tr>
<tr>
<td>BC-Ar</td>
<td>356 (1.6)</td>
<td>490 (0.14)</td>
<td>521 (0.54)</td>
<td>664 (0.25)</td>
</tr>
<tr>
<td>BC-MeMe</td>
<td>351 (2.6)</td>
<td>480 (0.28)</td>
<td>511 (0.87)</td>
<td>640 (0.45)</td>
</tr>
<tr>
<td>BC-EtEs</td>
<td>357 (1.7)</td>
<td>501 (0.14)</td>
<td>533 (0.53)</td>
<td>680 (0.21)</td>
</tr>
<tr>
<td>BC-Ar/Et</td>
<td>357 (1.6)</td>
<td>490 (0.13)</td>
<td>521 (0.53)</td>
<td>665 (0.24)</td>
</tr>
<tr>
<td>BPheo a</td>
<td>356 (1.6)</td>
<td>492 (0.11)</td>
<td>524 (0.51)</td>
<td>681 (0.18)</td>
</tr>
<tr>
<td>Me₄-BC</td>
<td>346, 374 (1.0, 1.1)</td>
<td>462 (0.10)</td>
<td>490 (0.19)</td>
<td>685 (0.10)</td>
</tr>
</tbody>
</table>

*a Obtained in toluene at room temperature. *b Relative intensity of the indicated peak versus that of the Qᵧ(0,0) band. *c Mixture of the Bₓ(0,0) and Bᵧ(0,0) absorption bands. *d Absorption data (in diethyl ether) from reference 33. *e Fluorescence data (in toluene) from reference 31. *f Data from reference 5.
Discussion

The development of new routes to bacteriochlorins remains a pressing need given the importance of such molecules in harvesting NIR light. The route described herein constitutes a new approach for macrocycle construction that concomitantly forms the isocyclic ring while maintaining a gem-dimethyl group in each pyrroline ring. The gem-dimethyl motif secures the macrocycle from adventitious dehydrogenation processes that are likely in an aerobic environment. In this section, we first compare methods for installation of the isocyclic ring. We then describe features (including stereochemistry) of the Nazarov cyclization in the context of the new route to bacteriochlorins, followed by a side-by-side evaluation with a prior de novo route to bacteriochlorins from dihydrodipyrrin halves. The final section sketches synthetic possibilities of the new route.

Installation of the Isocyclic Ring. A handful of approaches for installation of a fifth ring spanning positions 13 and 15 has been developed over the years (Scheme 4.9). Fischer dehydrated (hydroxymethylcarbonyl)porphyrin A in conc. H₂SO₄ to give the porphyrin bearing the isocyclic ring (B).³⁴ Lash condensed dipyrromethane C¹ and dipyrromethane C² bearing an annulated oxocyclopentanyll ring³⁵ to form D (which lacks the 1₃³⁻oxo group).³⁶ Both B and D are porphyrins. Fischer also converted chlorin e₆ trimethyl ester (E) via Dieckmann cyclization to methyl pheophorbide a (F),³⁷,³⁸ a chlorin degradation product of chlorophyll a. Smith extended Kenner’s thallium-photochemical route³⁹-⁴² for conversion of the β-ketoester-substituted chlorin G to methyl pheophorbide a (F).⁴³ A more recent method entails 15-bromination and Pd-mediated α-arylation (Scheme 4.2), which has been applied to gem-dimethyl stabilized chlorins and bacteriochlorins but requires bromination of the macrocycle, and lacks provisions for incorporation of the 1₃²-carboalkoxy group.⁴⁴-⁴⁷ To our
knowledge, no methods other than those shown in Schemes 4.2 and 4.9 have been developed previously for use with bacteriochlorins. The formation of the isocyclic ring concomitantly with macrocycle construction affords considerable simplicity, and does so while enabling distinct substituents in the two halves of the bacteriochlorin.

Scheme 4.9. Routes for Installation of the Isocyclic Ring
Features of the Nazarov Cyclization. Nazarov cyclization is a classical synthetic method for producing a cyclic ketone. While known for some time with a variety of substrates, in 2006 Song, Knight and Whatton reported the first example involving a pyrrole. The reaction was carried out with an N-tosylpyrrole and a propenoic acid in the presence of trifluoroacetic anhydride, affording the corresponding annulated α-acylpyrrole. In the same year, Frontier and co-workers reported examples of both α-(propenoyl)pyrroles and β-(propenoyl)pyrroles without any N-protection (eq 1). While >50 examples of Nazarov cyclization have since been reported with α-(propenoyl)pyrroles, to our knowledge there are only three prior examples of analogous β-substituted pyrroles. Moreover, regardless of pyrrole substitution position, most such examples stem from model studies rather than as integral to total syntheses. Examples of the latter include synthesis of (±)-Roseophilin.

The Nazarov reaction process also can be regarded as an intramolecular Michael addition (5-endo-trig) of the pyrrole with the appended propenoyl substituent. Intermolecular examples of such pyrrole C-alkylations date to as early as 1951 and were typically carried out with either activated reactants or somewhat forcing conditions. Research in the past 15 years has shifted to unactivated reactants and implementation with mild Lewis acid catalysts and/or enantioselective catalysts.

The Nazarov cyclization is regarded to proceed via a 4π-electrocyclization of a pentadienyl cation derived from a divinylketone species; here, the pyrrole moiety provides one of the “vinyl” units. The resulting conrotatory ring closure creates two stereocenters. Here, one of the stereocenters is lost upon elimination leading to the aromatic, 18π-electron bacteriochlorin chromophore. The remaining stereocenter is at the 132-position, whereupon
the resulting bacteriochlorin is racemic. The carboalkoxy group at the \(13^2\)-position in (bacterio)chlorophylls is susceptible to epimerization given the presence of the \(\beta\)-keto group.\(^{13,14}\) While the \textit{trans}-configuration (\(13^2\)-relative to the 17-position) is typically more stable, macrocycles with the \textit{cis}-configuration of the two groups have been considered as possible minority pigments in selected photosynthetic systems.\(^6\) The mole fraction of the \textit{cis}-isomer was found to range from 0.12–0.25 over a set of 8 chlorophylls, bacteriochlorophylls and analogues.\(^6\) Accordingly, the natural tetrapyrroles bearing an isocyclic ring often exist as diastereomeric mixtures owing to unavoidable epimerization of the \(13^2\)-carbomethoxy group. Thus, while the synthetic bacteriochlorins obtained herein are racemic, even an asymmetric synthesis is likely to yield products that spontaneously racemize owing to the intrinsic features of the \(\beta\)-ketoester.

**Comparison of Routes.** The Eastern-Western (or Northern-Southern) route to bacteriochlorins is concise, but installation of the isocyclic ring requires 15-bromination followed by Pd-mediated \(\alpha\)-arylation. Even then, the isocyclic ring lacks the \(13^2\)-carbomethoxy group. The synthesis described herein entails preparation of BC and AD components, joining of these two halves to form a bilin intermediate under conditions wherein neither half undergoes self-condensation leading to a symmetrical bacteriochlorin, and one-flask double ring-closure of the bilin to form the bacteriochlorin macrocycle along with the isocyclic ring (E). In this manner, a Pd-mediated coupling is still required (attachment of the \(\beta\)-ketoester to the pyrrole of the BC half), but bromination of the bacteriochlorin is not required. Hence, halogens can be installed on the AD half (e.g., 5-Ar) for subsequent exploitation following formation of the macrocycle (e.g., BC-Ar, BC-Ar/Et).
A direct comparison of two routes for constructing the bacteriochlorin macrocycle is provided in Scheme 4.10. The self-condensation of two dihydrodipyrrin–acetal molecules (II-acetal) results in successive elimination of two molecules of methanol, whereupon a 5,15-dihydro-5,15-dimethoxybacteriochlorin (X) is obtained. Elimination of a third molecule of methanol affords the 5-methoxybacteriochlorin (XI). The presence of the 5-methoxy group provides a convenient directive entity for 15-bromination, but otherwise may be undesired. By contrast, for purposes of comparison the reaction of AD (VII) and BC (VIII) halves can be envisaged as proceeding via Nazarov cyclization following the Knoevenagel condensation (XII). Subsequent cyclization and elimination of one molecule of methanol affords the 5,15-dihydro-5-methoxybacteriochlorin (XIII). Elimination of the second molecule of methanol aromatizes the macrocycle to give bacteriochlorin V. The difference in 5-position substitution patterns of V versus XI originates early in the reaction process: two carbon-carbon bonds are formed upon Knoevenagel condensation and Nazarov cyclization (giving XII) versus only one upon electrophilic aromatic substitution (giving XI). Side-by-side comparison of intermediates X (5,15-dimethoxy) and XIII (5-methoxy) illustrates that while aromatization is likely similar in the two syntheses, requisite elimination of only one molecule of methanol leaves one methoxy group remaining in XI, whereas none is left in the isocyclic ring (E)-containing bacteriochlorin V.
Scheme 4.10. Comparison of Bacteriochlorin Syntheses

**Synthetic Attributes.** There are now four distinct routes for *de novo* construction of the bacteriochlorin chromophore (excluding derivatization of porphyrins or chlorins). The routes include (1) the Kishi synthesis of tollyporphin A diacetate and analogues;\(^9-11\) (2) the
Eastern-Western synthesis shown in Scheme 4.1; (3) a Northern-Southern route; and (4) the directed AD + BC route described herein. Only the latter enables simultaneous construction of the macrocycle and the isocyclic ring. The utility of a general route to bacteriochlorins with distinct substituents in the various A–D rings is outlined in the Introduction. Because the present route enables such capabilities yet also constructs the isocyclic ring (E), further applications and extensions can be envisaged, of which five are described here.

First, the preparation of bacteriochlorins with progressive extent of substitution ranging from the fully unsubstituted to the fully decorated analogue of BPheo a is essential for understanding the molecular origins of bacteriochlorophyll photophysics. The present route appears ideal for preparing more elaborate analogues along this progression.

Second, the Nazarov cyclization is compatible with other heterocycles, hence core-modified ring-C analogues should be accessible.

Third, the new route might enable synthetic access to the natural macrocycles themselves. The synthesis of chlorophylls would require one enantiopure dipyrrin and one dipyrrromethane rather than two dihydrodipyrrins, yet would offer a fundamental alternative to the route devised by Woodward and co-workers. The synthesis of bacteriochlorophylls, which has never been reported, would require two enantiopure dihydrodipyrrins.

Fourth, the isocyclic ring has been the site of extensive derivatization chemistry over the years, including reactions at each of the sites (131 oxo, 132 methylene, 132-carboalkoxy) as well as allomerization and splitting of the ring (by scission of the 131–132 C–C bond). While widely exploited with chlorophylls, analogous chemistry with bacteriochlorophylls has been less investigated owing to the lability of the natural macrocycles. The stability of the
macrocycles prepared herein should provide an entrée into diverse derivatives by reactions in the isocyclic ring.

Finally, very little is known about the *in vivo* degradation of bacteriochlorophylls, by contrast with the results from the intensive study of the enzymatic degradation of chlorophylls in senescent plants. Kräutler and co-workers have identified and characterized a variety of “phyllobilin” species such as the red chlorophyll catabolite (RCC) shown in Figure 4.7. The structure of the phyllobilins closely resembles that of the Nazarov intermediate XII shown in Scheme 4.9. To our knowledge, phyllobilins have not been the target of reported synthetic studies, and hence knowledge of reactivity and photochemical features depends on isolation of species along the slippery slope of enzymatic catabolism. Whether analogous phyllobilins derive from anoxygenic photosynthetic bacteria remains to be determined. For both types of hydroporphyrins, the synthesis of putative intermediates could prove vital.

![Figure 4.7. A chlorophyll catabolite](image)
Experimental Section

General Methods. ¹H NMR and ¹³C NMR spectra were collected at room temperature in CDCl₃. Absorption spectra were obtained in toluene at room temperature unless noted otherwise. Electrospray ionization mass spectrometry (ESI-MS) data, obtained via ion trap mass analyzer, are reported for the molecular ion or protonated molecular ion. THF used in all reactions was freshly distilled from Na/benzophenone ketyl. Molecular sieves (3Å, powder) were heated (>100 °C) overnight prior to use. All commercially available compounds were used as received. Non-commercially available compounds including 1,²⁵ 5-T,⁵ 5-MeMe,⁵ and 9-EtEs⁴ were prepared as described in the literature. The dihydrodipyrrin–carboxaldehyde and dihydrodipyrrin–acetal compounds were chromatographed by gravity flow with short columns (~12 cm in length) to limit duration of exposure to silica gel.

6-[4-(3-Methoxy-3-oxopropanoyl)-N-tosylpyrrol-2-yl]-1,1-dimethoxy-4,4-dimethyl-5-nitrohexan-2-one (2a). A mixture of 1 (1.34 g, 2.50 mmol), methyl potassium malonate (585 mg, 3.80 mmol), Xantphos (725 mg, 1.30 mmol), MgCl₂ (357 mg, 3.80 mmol) and imidazole (330 mg, 5.00 mmol) was placed in a 50-mL Schlenk flask and charged with argon. THF (25.0 mL) was added followed by Et₃N (520 μL, 3.80 mmol). The mixture was degassed by three freeze-pump-thaw cycles. Then, Pd(OAc)₂ (280 mg, 1.30 mmol) and Co₂(CO)₈ (430 mg, 1.30 mmol) were added. The flask was sealed immediately and heated at 65 °C for 48 h, with reaction progress monitored by TLC analysis. If the reaction was not complete, Pd(OAc)₂ (140 mg, 0.65 mmol) and Co₂(CO)₈ (215 mg, 0.65 mmol) were added, and the reaction was continued for another 24 h. The reaction mixture was diluted with ethyl acetate and filtered through a Celite pad. The filtrate was washed with brine and water, dried
(Na$_2$SO$_4$), concentrated and chromatographed (silica, ethyl acetate) to give a light-yellow solid (1.10 g, 80%): $^1$H NMR (300 MHz) $\delta$ 1.14 (s, 3H), 1.23 (s, 3H), 2.45 (s, 3H), 2.57–2.73 (AB, $^2J = 18.6$ Hz, 2H), 3.11–3.17 (ABX, $^2J = 16.0$ Hz, 1H), 3.35–3.45 (ABX, $^2J = 16.0$ Hz, $^3J = 12.3$ Hz, 1H), 3.42 (s, 6H), 3.73 (s, 3H), 3.75 (s, 2H), 4.37 (s, 1H), 5.21–5.26 (ABX, $^2J = 12.0$ Hz, $^3J = 2.1$ Hz, 1H), 6.42 (d, $J = 1.5$ Hz, 1H), 7.37–7.40 (d, $J = 8.2$ Hz, 2H), 7.70–7.73 (d, $J = 8.2$ Hz, 2H), 7.93 (d, $J = 1.8$ Hz, 1H); $^{13}$C NMR (75 MHz) $\delta$ 21.8, 23.8, 24.0, 26.3, 36.4, 44.5, 46.6, 52.5, 55.1, 92.8, 104.7, 112.5, 126.1, 127.1, 128.0, 130.7, 130.9, 134.8, 146.5, 167.5, 186.5, 203.1; ESI-MS $m/z$: [M+H]$^+$ calcd for C$_{25}$H$_{33}$N$_2$O$_{10}$S 553.1850; found 553.1846.

6-[4-(3-Ethoxy-3-oxopropanoyl)-N-tosylpyrrol-2-yl]-1,1-dimethoxy-4,4-dimethyl-5-nitrohexan-2-one (2b). A mixture of 1 (267 mg, 0.500 mmol), ethyl potassium malonate (128 mg, 0.750 mmol), Pd(OAc)$_2$ (56.0 mg, 0.250 mmol), Xantphos (145 mg, 0.250 mmol), MgCl$_2$ (71.4 mg, 0.750 mmol) and imidazole (66.0 mg, 1.00 mmol) was placed in a 10-mL Schlenk tube and charged with argon. THF (4.0 mL) was added followed by Et$_3$N (104 $\mu$L, 0.750 mmol) and Co$_2$(CO)$_8$ (86.0 mg, 0.250 mmol). The tube was sealed immediately and heated at 65 °C for 48 h. The reaction mixture was diluted with ethyl acetate and filtered through a Celite pad. The filtrate was washed with brine and water, dried (Na$_2$SO$_4$), concentrated and chromatographed (silica, ethyl acetate) to give a light-yellow oil (160 mg, 56%): $^1$H NMR (400 MHz) $\delta$ 1.14 (s, 3H), 1.23 (s, 3H), 1.26 (t, $J = 7.2$ Hz, 3H), 2.46 (s, 3H), 2.57–2.72 (AB, $^2J = 18.8$ Hz, 2H), 3.12–3.17 (ABX, $^2J = 16.4$ Hz, 1H), 3.35–3.40 (ABX, $^2J = 16.4$ Hz, $^3J = 12.4$ Hz, 1H), 3.42 (s, 3H), 3.43 (s, 3H), 3.72 (d, $J = 0.8$ Hz, 2H), 4.16–4.22 (q, $J = 7.2$ Hz, 2H), 4.36 (s, 1H), 5.21–5.24 (ABX, $^2J = 12.4$ Hz, $^3J = 1.6$ Hz, 1H), 6.42 (d, $J = 2.0$ Hz, 1H), 7.37–7.40 (d, $J = 8.8$ Hz, 2H), 7.69–7.72 (d, $J = 8.8$ Hz, 2H), 7.91 (d, $J = 1.6$ Hz, 3H), 8.17 (d, $J = 8.8$ Hz, 2H), 8.32 (d, $J = 5.4$ Hz, 1H). $^{13}$C NMR (75 MHz) $\delta$ 21.7, 23.8, 24.0, 26.3, 36.4, 44.5, 46.6, 52.5, 55.1, 92.8, 104.7, 112.5, 126.1, 127.1, 128.0, 130.7, 130.9, 134.8, 136.5, 146.5, 167.5, 186.5, 203.1; ESI-MS $m/z$: [M+H]$^+$ calcd for C$_{25}$H$_{33}$N$_2$O$_{10}$S 553.1850; found 553.1846.
Hz, 1H); $^{13}$C NMR (75 MHz) $\delta$ 14.3, 22.0, 24.0, 24.3, 26.5, 36.6, 44.7, 47.1, 55.35, 55.38, 61.8, 93.1, 104.9, 112.7, 126.3, 127.3, 128.1, 130.8, 131.1, 135.0, 146.6, 167.3, 168.8, 203.3; ESI-MS m/z: [M+H]$^+$ calcd for C$_{26}$H$_{35}$N$_2$O$_{10}$S 567.2003; found 567.2007.

6-[4-(3-Methoxy-3-oxopropanoyl)pyrrol-2-yl]-1,1-dimethoxy-4,4-dimethyl-5-nitrohexan-2-one (3a). Following a standard procedure, a sample of 2a (1.10 g, 2.00 mmol) was treated with TBAF (1.0 M in THF, 2.0 mL, 2.0 mmol) in a 20-mL flask and heated to 65 °C for 1 h. The mixture was allowed to cool to room temperature, quenched by addition of saturated aqueous NaHCO$_3$ solution and then extracted with ethyl acetate. The organic extract was washed (brine and water), dried (Na$_2$SO$_4$), concentrated and chromatographed [silica, hexanes/ethyl acetate (1:1)] to give a yellow oil (566 mg, 70%): $^1$H NMR (300 MHz) $\delta$ 1.13 (s, 3H), 1.21 (s, 3H), 2.57–2.76 (AB, $^2J = 18.6$ Hz, 2H), 2.99–3.05 (ABX, $^2J = 15.6$ Hz, $^3J = 2.4$ Hz, 1H), 3.29–3.37 (ABX, $^2J = 15.6$ Hz, $^3J = 12.0$ Hz, 1H), 3.43 (s, 3H), 3.43 (s, 3H), 3.72 (s, 3H), 3.75 (s, 2H), 4.37 (s, 1H), 5.15–5.20 (ABX, $^2J = 11.7$ Hz, $^3J = 2.7$ Hz, 1H), 6.40 (m, 1H), 7.33–7.35 (m, 1H), 9.14 (br, 1H); $^{13}$C NMR (100 MHz) $\delta$ 24.2, 24.3, 26.5, 36.6, 45.1, 46.6, 52.5, 55.3, 94.2, 104.7, 107.8, 124.8, 125.3, 128.8, 168.6, 187.3, 203.9; ESI-MS m/z: [M+H]$^+$ calcd for C$_{18}$H$_{27}$N$_2$O$_8$ 399.1762; found 399.1755.

6-[4-(3-Ethoxy-3-oxopropanoyl)pyrrol-2-yl]-1,1-dimethoxy-4,4-dimethyl-5-nitrohexan-2-one (3b). Following a standard procedure, a sample 2b (160 mg, 0.283 mmol) was treated with TBAF (1.0 M in THF, 0.34 mL, 0.34 mmol) in a 20-mL flask and heated to 65 °C for 1 h. The mixture was allowed to cool to room temperature, quenched by addition of saturated aqueous NaHCO$_3$ solution and then extracted with ethyl acetate. The organic extract was washed (brine and water), dried (Na$_2$SO$_4$), concentrated and chromatographed [silica, hexanes/ethyl acetate (1:1), then ethyl acetate] to give a yellow oil
(75 mg, 64%): $^1$H NMR (300 MHz) $\delta$ 1.20 (s, 3H), 1.21 (s, 3H), 1.24 (t, $J$ = 6.9 Hz, 3H), 2.56–2.75 (AB, $^2J$ = 18.6 Hz, 2H), 2.98–3.04 (ABX, $^2J$ = 15.3 Hz, $^3J$ = 2.4 Hz, 1H), 3.28–3.37 (ABX, $^2J$ = 15.3 Hz, $^3J$ = 11.7 Hz, 1H), 3.42 (s, 3H), 3.43 (s, 3H), 3.72 (s, 2H), 4.14–4.21 (q, $J$ = 6.9 Hz, 2H), 4.36 (s, 1H), 5.14–5.19 (ABX, $^2J$ = 12.0 Hz, $^3J$ = 2.4 Hz, 1H), 6.39 (m, 1H), 7.32 (m, 1H), 9.06 (br, 1H); $^{13}$C NMR (100 MHz) $\delta$ 14.3, 24.3, 26.6, 36.7, 45.3, 46.9, 55.4, 61.6, 94.3, 104.7, 107.8, 125.1, 125.4, 129.0, 168.5, 187.9, 204.0; ESI-MS m/z: [M+H]$^+$ calcd for C$_{19}$H$_{29}$N$_2$O$_8$ 413.1918; found 413.1918.

2,3-Dihydro-1-(1,1-dimethoxymethyl)-8-(3-methoxy-3-oxopropanoyl)-3,3-dimethylidipyrrin (4a). Following a standard procedure,$^4$ a solution of 3a (566 mg, 1.42 mmol) in THF (14.0 mL) was treated with NaOCH$_3$ (307 mg, 5.68 mmol) in a 20-mL flask under argon at 0 °C. The mixture was stirred at room temperature for 45 min. In a 250-mL flask, NH$_4$OAc (11.1 g, 142 mmol) in distilled THF (36.0 mL) was bubbled with argon for 15 min before a solution of TiCl$_3$ (12 wt% in 2 N HCl, 14.0 mL, 11.4 mmol) was added. The mixture was stirred for another 15 min. Then the mixture in the first flask was transferred via cannula to the buffered TiCl$_3$ solution in the second flask. The resulting mixture was stirred for 20 h at room temperature under argon. The reaction mixture was poured into saturated aqueous NaHCO$_3$ solution, filtered through a Celite pad (the filter cake was washed with ethyl acetate) and extracted with ethyl acetate. The organic extract was combined, washed (brine/water), dried (Na$_2$SO$_4$), concentrated and chromatographed [silica, CH$_2$Cl$_2$, then CH$_2$Cl$_2$/ethyl acetate (1:1)] to give a yellow oil (223 mg, 45%): $^1$H NMR (300 MHz) $\delta$ 1.22 (s, 6H), 2.64 (s, 2H), 3.46 (s, 6H), 3.73 (s, 3H), 3.77 (s, 2H), 5.04 (s, 1H), 5.84 (s, 1H), 6.53 (m, 1H), 7.50 (m, 1H), 11.20 (br, 1H); $^{13}$C NMR (75 MHz) $\delta$ 29.0, 40.3, 46.8, 48.4, 52.4,
8-(3-Ethoxy-3-oxopropanoyl)-2,3-dihydro-1-(1,1-dimethoxymethyl)-3,3-dimethyldipyrpin (4b). Following a standard procedure,\(^4\) a solution of 3b (75 mg, 0.18 mmol) in THF (1.8 mL) and MeOH (50. \(\mu\)L) was treated with NaOCH\(_3\) (39 mg, 0.73 mmol) in a 20-mL flask under argon at 0 °C. The mixture was stirred at 0 °C for 45 min. In a 100-mL flask, \(\text{NH}_4\text{OAc}\) (1.42 g, 18.2 mmol) in distilled THF (18 mL) was bubbled with argon for 15 min before a solution of TiCl\(_3\) (12 wt% in 2 N HCl, 1.8 mL, 1.46 mmol) was added. The mixture was stirred for another 15 min. Then the mixture in the first flask was transferred via cannula to the buffered TiCl\(_3\) solution in the second flask. The resulting mixture was stirred at room temperature under argon for 20 h. The reaction mixture was poured into saturated aqueous NaHCO\(_3\) solution and extracted with ethyl acetate. The organic extract was combined, washed (brine/water), dried (Na\(_2\)SO\(_4\)), concentrated and chromatographed [silica, CH\(_2\)Cl\(_2\), then CH\(_2\)Cl\(_2\)/ethyl acetate (1:1)] to give a yellow oil (24 mg, 36%): \(^1\)H NMR (300 MHz) \(\delta\) 1.22 (s, 6H), 1.26 (t, \(J = 7.2\) Hz, 3H), 2.64 (s, 2H), 3.46 (s, 6H), 3.77 (s, 2H), 4.16–4.23 (q, \(J = 7.2\) Hz, 2H), 5.03 (s, 1H), 5.84 (s, 1H), 6.53 (m, 1H), 7.50 (m, 1H), 11.18 (br, 1H); \(^13\)C NMR (75 MHz) \(\delta\) 14.4, 29.2, 40.4, 47.3, 48.6, 54.8, 61.5, 102.6, 106.6, 108.6, 125.3, 125.6, 132.8, 162.2, 168.3, 176.3, 187.4; ESI-MS \(m/z\): [M+H]\(^+\) calcd for C\(_{19}\)H\(_{27}\)N\(_2\)O\(_5\) 363.1916; found 363.1915.

7-(4-Bromophenyl)-1-formyl-2,3-dihydro-3,3-dimethyldipyrpin (5-Ar). Following a standard procedure,\(^5\) a solution of 11-Ar (300 mg, 0.87 mmol) in 1,4-dioxane (17.4 mL) was treated with SeO\(_2\) (288 mg, 2.60 mmol) under argon. Progress of the reaction was monitored by absorption spectroscopy. After 90 min, ethyl acetate (200 mL) was added.
The organic layer was washed [aqueous NaHCO$_3$ solution (200 mL); water/brine (2 × 200 mL)], dried, concentrated and chromatographed [silica, hexanes/ethyl acetate (3:1)] to afford a red solid (67 mg, 22%): $^1$H NMR (400 MHz) $\delta$ 1.22 (s, 6H), 2.72 (s, 2H), 6.29 (s, 1H), 6.33 (m, 1H), 7.00 (m, 1H), 7.29–7.31 (d, $J = 8.8$ Hz, 2H), 7.53–7.55 (d, $J = 8.8$ Hz, 2H), 9.99 (s, 1H), 10.81 (br, 1H); $^{13}$C NMR (100 MHz) $\delta$ 29.2, 41.2, 46.1, 109.9, 112.4, 120.4, 122.1, 127.2, 127.7, 130.4, 131.8, 135.3, 161.2, 169.3, 190.1; ESI-MS m/z: [M+H]$^+$ calcd for C$_{18}$H$_{18}$BrN$_2$O 357.0597; found 357.0592. $\lambda_{\text{abs}}$ in CH$_2$Cl$_2$ = 470 nm.

8-Carboethoxy-7-ethyl-1-formyl-2,3-dihydro-3,3-dimethylidipyrrin (5-EtEs).

Following a standard procedure,$^5$ a solution of 11-EtEs (100 mg, 0.33 mmol) in 1,4-dioxane (6.6 mL) was treated with SeO$_2$ (111 mg, 1.0 mmol) under argon. Progress of the reaction was monitored by absorption spectroscopy. After 90 min, ethyl acetate (100 mL) was added. The organic layer was washed with aqueous NaHCO$_3$ solution (100 mL), brine (2 × 100 mL), dried, concentrated and chromatographed [silica, hexanes/ethyl acetate (3:1)] to afford a red solid (32 mg, 32%): $^1$H NMR (400 MHz) $\delta$ 1.20 (t, $J = 7.2$ Hz, 3H), 1.27 (s, 6H), 1.36 (t, $J = 6.8$ Hz, 3H), 2.73 (s, 2H), 2.84–2.89 (q, $J = 7.2$ Hz, 2H), 4.26–4.32 (q, $J = 6.8$ Hz, 2H), 6.18 (s, 1H), 7.53 (d, $J = 3.2$ Hz, 1H), 9.98 (s, 1H), 10.82 (br, 1H); $^{13}$C NMR (100 MHz) $\delta$ 14.6, 16.5, 18.2, 29.3, 41.1, 46.1, 59.6, 111.1, 115.0, 127.4, 128.3, 130.4, 160.7, 165.0, 169.4, 190.0; ESI-MS m/z: [M+H]$^+$ calcd for C$_{17}$H$_{23}$N$_2$O$_3$ 303.1703; found 303.1699. $\lambda_{\text{abs}}$ in CH$_2$Cl$_2$ = 451 nm.

Ethyl 3-(4-bromophenyl)prop-2-enoate (6). Following a standard procedure,$^4$ a solution of 4-bromobenzaldehyde (17.4 g, 94.0 mmol) and (carbethoxymethylene)triphenylphosphorane (35.8 g, 103 mmol) in CH$_2$Cl$_2$ (120 mL) was refluxed for 20 h. The reaction mixture was allowed to cool to room temperature and then
concentrated. The residue was diluted with Et₂O and filtered. The filtrate was washed with brine, dried (Na₂SO₄), concentrated and chromatographed [silica, hexanes/ethyl acetate (2:1)] to give a colorless oil (21.9 g, 91%): ¹H NMR (400 MHz) δ 1.33 (t, J = 7.2 Hz, 3H), 4.26 (q, J = 7.2 Hz, 2H), 6.41 (d, J = 16.0 Hz, 1H), 7.37 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 8.8 Hz, 2H), 7.60 (d, J = 16.0 Hz, 1H); ¹³C NMR (100 MHz) δ 14.4, 60.7, 119.0, 124.5, 129.5, 132.2, 133.4, 143.2, 166.8; ESI-MS m/z: [M+H]⁺ calcd for C₁₁H₁₂BrO₂ 255.0015; found 255.0011.

3-(4-Bromophenyl)pyrrole (7). Following a standard procedure,⁴ a suspension of 6 (21.9 g, 85.8 mmol) and TosMIC (16.7 g, 85.8 mmol) in dry ether/DMSO (2:1, 150 mL) was added dropwise to a suspension of NaH (60% in mineral oil, 5.16 g, 129 mmol) in dry ether (70 mL) under argon. The mixture was stirred at room temperature for 5 h. Water (200 mL) was added. The aqueous phase was extracted with ethyl acetate (2 × 200 mL). The organic layer was separated, dried (Na₂SO₄) and concentrated to a brown solid. The brown solid was dissolved in ethylene glycol (200 mL) in a 500 mL flask and bubbled with argon for 10 min. Powdered NaOH (17.2 g, 430 mmol) was added. The flask was heated to 160 °C in an oil bath. After 2.5 h, the reaction mixture was allowed to cool to room temperature, whereupon brine (200 mL) was added. The resulting mixture was extracted with CH₂Cl₂. The organic extract was dried (Na₂SO₄), concentrated and recrystallized (hot ethanol) to afford a yellow solid (10.9 g, 57%): mp 142–143 °C; ¹H NMR (400 MHz) δ 6.49 (m, 1H), 6.81 (m, 1H), 7.04 (m, 1H), 7.37–7.39 (d, J = 8.4 Hz, 2H), 7.42–7.44 (d, J = 8.4 Hz, 2H), 8.24 (br, 1H); ¹³C NMR (100 MHz) δ 106.5, 114.8, 119.0, 119.3, 123.9, 126.9, 131.7, 134.9; ESI-MS m/z: [M+H]⁺ calcd for C₁₀H₉BrN 221.9913; found 221.9910.

3-(4-Bromophenyl)-2-formylpyrrole (8). Following a standard procedure,⁴ a solution of 7 (10.9 g, 49.0 mmol) in DMF (15.2 mL, 196 mmol) and CH₂Cl₂ (200 mL) at
0 °C under argon was treated dropwise with POCl₃ (5.5 mL, 58.8 mmol). After 1 h, the ice bath was removed and the mixture was stirred overnight. Then, the reaction mixture was cooled to 0 °C again, whereupon 2.0 M aqueous NaOH solution (350 mL) was added. The mixture was extracted with CH₂Cl₂. The organic extract was washed with brine, dried (Na₂SO₄), concentrated and chromatographed [silica, CH₂Cl₂] to give a yellow solid (9.44 g, 77%): mp 163−164 °C; ¹H NMR (400 MHz) δ 6.43 (m, 1H), 7.17 (m, 1H), 7.35−7.37 (d, J = 8.0 Hz, 2H), 7.56−7.58 (d, J = 8.0 Hz, 2H), 9.59 (s, 1H), 10.41 (br, 1H); ¹³C NMR (100 MHz) δ 111.6, 122.2, 126.3, 128.8, 130.8, 132.0, 132.8, 136.2, 179.7; ESI-MS m/z: [M+H]+ calcd for C₁₁H₉BrNO 249.9862; found 249.9863.

3-(4-Bromophenyl)-2-(2-nitroethyl)pyrrole (9-Ar). Following a standard procedure,⁴ a mixture of pyrrole 8 (9.44 g, 37.8 mmol), potassium acetate (4.08 g, 41.6 mmol), methylamine hydrochloride (2.87 g, 41.6 mmol), and nitromethane (75 mL) was stirred at room temperature under argon. The progress of the reaction was monitored via TLC analysis. After 2 h, brine was added. The resulting mixture was extracted with ethyl acetate. The organic extract was washed with brine and water, dried (Na₂SO₄) and concentrated to afford an orange solid. The crude solid was dissolved in anhydrous THF/MeOH (166 mL, 9:1) under argon at 0 °C. The mixture was stirred vigorously and treated with NaBH₄ (2.51 g, 66.4 mmol) in one portion. Stirring was continued for 1 h at 0 °C, then for 2 h at room temperature. The reaction mixture was neutralized to pH 7 with acetic acid. Water was added followed by extraction with ethyl acetate. The organic extract was washed with brine and water, dried (Na₂SO₄), concentrated and chromatographed [silica, hexanes/ethyl acetate (1:1)] to give a yellow solid (8.01 g, 72%): mp 93−94 °C; ¹H NMR (400 MHz) δ 3.42 (t, J = 6.6 Hz, 2H), 4.54 (t, J = 6.6 Hz, 2H), 6.26 (m, 1H), 6.74 (m, 1H),
7.19–7.21 (d, \( J = 8.0 \) Hz, 2H), 7.49–7.51 (d, \( J = 8.0 \) Hz, 2H), 8.33 (br, 1H); \(^{13}\)C NMR (100 MHz) \( \delta \) 24.2, 75.0, 109.4, 117.9, 119.9, 122.0, 122.2, 129.6, 131.8, 135.2; ESI-MS \( m/z \): \([\text{M+H}]^+\) calcd for C\(_{12}\)H\(_{12}\)BrN\(_2\)O\(_2\) 295.0077; found 295.0078.

**6-[3-(4-Bromophenyl)pyrrol-2-yl]-4,4-dimethyl-5-nitrohexan-2-one** (10-Ar).

Following a standard procedure,\(^5\) a mixture of 9-Ar (8.01 g, 27.1 mmol) and mesityl oxide (6.2 mL, 54.2 mmol) was treated with DBU (8.1 mL, 54 mmol) at room temperature. After 16 h, water was added, and the mixture was extracted with ethyl acetate (2 \( \times \) 100 mL). The organic layer was washed thoroughly with brine and water, dried (Na\(_2\)SO\(_4\)), concentrated, and chromatographed [silica, hexanes/ethyl acetate (3:1)] to give a brown oil (4.63 g, 44%): \(^1\)H NMR (300 MHz) \( \delta \) 1.08 (s, 3H), 1.19 (s, 3H), 2.11 (s, 3H), 2.34–2.59 (AB, \( ^2J = 18.0 \) Hz, 2H), 3.12–3.18 (ABX, \( ^2J = 15.6 \) Hz, \( ^3J = 2.7 \) Hz, 1H), 3.35–3.44 (ABX, \( ^2J = 15.6 \) Hz, \( ^3J = 11.4 \) Hz, 1H), 5.19–5.23 (ABX, \( ^2J = 11.4 \) Hz, \( ^3J = 2.4 \) Hz, 1H), 6.21–6.22 (m, 1H), 6.68–6.70 (m, 1H), 7.20–7.22 (d, \( ^2J = 8.4 \) Hz, 2H), 7.49–7.52 (d, \( ^2J = 8.4 \) Hz, 2H), 8.20 (br, 1H); \(^{13}\)C NMR (100 MHz) \( \delta \) 24.2, 24.5, 25.2, 31.9, 37.1, 51.5, 94.4, 109.4, 118.1, 120.1, 122.5, 122.7, 130.1, 120.2, 131.7, 131.8, 125.6, 206.9; ESI-MS \( m/z \): \([\text{M+H}]^+\) calcd for C\(_{18}\)H\(_{22}\)BrN\(_2\)O\(_3\) 393.0808; found 393.0808.

**7-(4-Bromophenyl)-2,3-dihydro-1,3,3-trimethylidipyrren** (11-Ar). Following a standard procedure,\(^5\) a solution of 10-Ar (4.63 g, 11.8 mmol) in distilled THF (22 mL) and dry methanol (1.0 mL) under argon was treated with NaOMe (1.91 g, 35.4 mmol), and the mixture was stirred for 45 min at room temperature. In a second flask, TiCl\(_3\) (20 wt% in 3% HCl solution, 60. mL), THF (160 mL) and NH\(_4\)OAc (45 g) were combined under argon, and the mixture was degassed by bubbling with argon for 45 min. The solution in the first flask containing the nitronate anion was transferred via a cannula to the buffered TiCl\(_3\) mixture in
The resulting mixture was stirred at room temperature for 16 h under argon. The reaction mixture was poured over a pad of Celite and eluted with ethyl acetate. The eluant was washed with aqueous NaHCO₃ solution. The organic phase was dried (Na₂SO₄), concentrated and chromatographed [silica, hexanes/ethyl acetate (1:1)] to afford a light yellow solid (1.50 g, 37%): mp 119–121 °C; ¹H NMR (400 MHz) δ 1.19 (s, 6H), 2.23 (s, 3H), 2.52 (s, 2H), 5.89 (s, 1H), 6.26 (m, 1H), 6.85 (m, 1H), 7.31–7.33 (d, J = 8.0 Hz, 2H), 7.49–7.51 (d, J = 8.0 Hz, 2H), 11.10 (br, 1H); ¹³C NMR (100 MHz) δ 20.8, 29.2, 41.3, 53.8, 102.4, 108.7, 118.6, 119.2, 122.1, 127.6, 130.2, 131.2, 136.3, 162.0, 177.3; ESI-MS m/z: [M+H]+ calcd C₁₈H₂₀BrN₂ 343.0804; found 343.0807.

8-Carboethoxy-7-ethyl-1,3,3-trimethyl-2,3-dihydodipyrrin (11-EtEs). Following a standard procedure,⁵ a mixture of 9-EtEs (5.1 g, 21 mmol) and mesityl oxide (4.1 g, 42 mmol) was treated with DBU (10 mL, 64 mmol) at room temperature. After 16 h, water was added, then the mixture was extracted with ethyl acetate (2 × 100 mL). The organic layer was washed thoroughly with brine and water, dried (Na₂SO₄) and concentrated. The resulting brown oil was dried overnight under high vacuum to give a crude material (4.2 g) that was used directly in the next step. In a first flask, a solution of the crude material in distilled THF (20 mL) and dry methanol (1.0 mL) under argon was treated with NaOMe (2.0 g, 37 mmol), and the mixture was stirred for 45 min at room temperature. In a second flask, TiCl₃ (20 wt% in 3% HCl solution, 63 mL, 100 mmol), THF (160 mL) and NH₄OAc (47 g, 620 mmol) were combined under argon, and the mixture was degassed by bubbling with argon for 45 min. The solution in the first flask containing the nitronate anion was transferred via cannula to the buffered TiCl₃ mixture in the second flask. The resulting mixture was stirred at room temperature for 16 h under argon. The reaction mixture was
poured over a pad of Celite and eluted with ethyl acetate. The eluant was washed with aqueous NaHCO₃ solution. The organic phase was dried (Na₂SO₄), concentrated and chromatographed [silica, hexanes/ethyl acetate (3:1)] to afford a yellow oil (1.4 g, 23%): ¹H NMR (400 MHz) δ 1.16 (t, J = 7.6 Hz, 3H), 1.22 (s, 6H), 1.34 (t, J = 7.0 Hz, 3H), 2.21 (s, 3H), 2.52 (s, 2H), 2.78–2.83 (q, J = 7.6 Hz, 2H), 4.24–4.29 (q, J = 7.0 Hz, 2H), 5.71 (s, 1H), 7.40 (d, J = 3.2 Hz, 1H), 11.15 (br, 1H); ¹³C NMR (100 MHz) δ 14.6, 16.4, 18.1, 20.8, 29.3, 41.3, 53.9, 59.2, 101.4, 114.0, 124.5, 125.1, 128.6, 161.3, 165.7, 177.1; ESI-MS m/z: [M+H]+ calcd for C₁₇H₂₅N₂O₂ 289.1911; found 289.1907.

2-Carbomethoxy-3-(2,3-dihydro-3,3-dimethyl-7-p-tolylidipyrrin-1-yl)-1-[2,3-dihydro-1-(1,1-dimethoxymethyl)-3,3-dimethylidpyrrin-8-yl]-prop-2-en-1-one (12-T).

Samples of 4a (17 mg, 49 µmol), 5-T (17 mg, 58 µmol, 1.2 equiv) and dried molecular sieves 3Å (17 mg, powder form) were placed in a 20-mL vial under argon. A solution of piperidine/acetic acid in CH₂Cl₂ (15 mM/15 mM, 1.2 mL, 18 µmol/18 µmol) was added, and the mixture was stirred at room temperature for 20 h. The mixture was filtered through a Celite pad. The filtrate was concentrated and chromatographed [silica, hexanes/ethyl acetate (3:1 then 1:1)] to give an orange-red gum (19 mg, 61%): ¹H NMR (400 MHz) δ 1.07 (s, 6H), 1.22 (s, 6H), 2.37 (s, 3H), 2.56 (s, 2H), 2.64 (s, 2H), 3.44 (s, 6H), 3.78 (s, 3H), 5.00 (s, 1H), 5.85 (s, 1H), 6.12 (s, 1H), 6.27 (m, 1H), 6.57 (s, 1H), 6.91 (m, 1H), 7.19–7.21 (d, J = 7.6 Hz, 2H), 7.30–7.32 (d, J = 7.6 Hz, 2H), 7.39 (s, 1H), 7.65 (s, 1H), 10.68 (br, 1H), 11.27 (br, 1H); ¹³C NMR (100 MHz) δ 21.3, 29.07, 29.09, 40.4, 41.8, 48.5, 50.4, 52.9, 54.7, 102.4, 106.4, 108.2, 108.8, 109.4, 121.0, 126.0, 126.5, 126.9, 127.4, 128.7, 129.3, 129.4, 133.3, 133.9, 134.9, 135.6, 138.0, 161.0, 162.5, 165.7, 167.3, 176.6, 188.5; ESI-MS m/z: [M+H]+ calcd for C₃₇H₄₅N₄O₅ 623.3228; found 623.3224. λₘₐₓ(CH₂Cl₂) 319 nm (ε 2.6 x 10⁴ M⁻¹cm⁻¹), 505 nm
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(ε 1.6 x 10^4 M⁻¹ cm⁻¹). Note that addition of piperidine and acetic acid (15 mM each) in water afforded a pH = 6.7, reflecting the near-neutral conditions of this combination of reagents for the Knoevenagel condensation.

3-[7-(4-Bromophenyl)-2,3-dihydro-3,3-dimethylpyrrin-1-yl]-2-carboxethoxy-1-[2,3-dihydro-1-(1,1-dimethoxymethyl)-3,3-dimethyldipyrin-8-yl]-prop-2-en-1-one (12-Ar). Reaction of 4a (31 mg, 90 µmol) and 5-Ar (32 mg, 90 µmol) under the general procedure for 12-T followed by chromatography [silica, hexanes/ethyl acetate (3:1 then 1:1)] gave an orange-red gum (38 mg, 68%): ¹H NMR (400 MHz) δ 1.08 (s, 6H), 1.22 (s, 6H), 2.57 (s, 2H), 2.64 (s, 2H), 3.44 (s, 6H), 3.79 (s, 3H), 5.01 (s, 1H), 5.85 (s, 1H), 6.03 (s, 1H), 6.25 (m, 1H), 6.56 (s, 1H), 6.92 (m, 1H), 7.25–7.28 (d, J = 8.4 Hz, 2H), 7.39 (s, 1H), 7.48–7.50 (d, J = 8.4 Hz, 2H), 7.64 (s, 1H), 10.70 (br, 1H), 11.27 (br, 1H); ¹³C NMR (100 MHz) δ 29.1, 40.4, 41.7, 48.6, 50.5, 53.0, 54.7, 102.4, 106.4, 108.1, 108.2, 109.2, 119.8, 121.1, 125.0, 125.9, 126.8, 127.6, 130.3, 131.7, 133.3, 134.6, 135.8, 138.4, 161.6, 162.6, 165.6, 167.9, 176.6, 188.4; ESI-MS m/z: [M+H]⁺ calcd for C₃₆H₄₀BrN₄O₅ 687.2177; found 687.2168.

2-Carbomethoxy-3-(2,3-dihydro-3,3,7,8-tetramethyldipyrin-1-yl)-1-[2,3-dihydro-1-(1,1-dimethoxymethyl)-3,3-dimethyldipyrin-8-yl]-prop-2-en-1-one (12-MeMe). Reaction of 4a (35 mg, 100 µmol) and 5-MeMe (41 mg, 120 µmol, 1.2 equiv) under the general procedure for 12-T followed by chromatography [silica, hexanes/ethyl acetate (3:1 then 1:1)] gave an orange-red gum (47 mg, 71%): ¹H NMR (400 MHz) δ 1.08 (s, 6H), 1.22 (s, 6H), 1.63 (s, 9H), 2.03 (s, 3H), 2.25 (s, 3H), 2.51 (s, 2H), 2.64 (s, 2H), 3.44 (s, 6H), 3.78 (s, 3H), 5.01 (s, 1H), 5.85 (s, 1H), 5.88 (s, 1H), 6.54 (s, 1H), 7.36 (s, 1H), 7.73 (s, 1H), 11.02 (br, 1H), 11.29 (br, 1H); ¹³C NMR (100 MHz) δ 9.0, 10.6, 28.6, 29.06, 29.09,
2-Carbomethoxy-3-(8-carboethoxy-7-ethyl-2,3-dihydro-3,3-dimethyldipyrrin-1-yl)-1-[2,3-dihydro-1-(1,1-dimethoxymethyl)-3,3-dimethyldipyrrin-8-yl]-prop-2-en-1-one (12-EtEs). Reaction of 4a (25 mg, 71 µmol) and 5-EtEs (32 mg, 106 µmol, 1.5 equiv) under the general procedure for 12-T followed by chromatography [silica, hexanes/ethyl acetate (3:1 then 1:1)] gave an orange-red gum (27 mg, 61%): $^1$H NMR (400 MHz) $\delta$ 1.12 (s, 6H), 1.14 (t, $J = 7.2$ Hz, 3H), 1.22 (s, 6H), 1.35 (t, $J = 7.0$ Hz, 3H), 2.58 (s, 2H), 2.64 (s, 2H), 2.76–2.82 (q, $J = 7.2$ Hz, 2H), 3.44 (s, 6H), 3.78 (s, 3H), 4.25–4.30 (q, $J = 7.0$ Hz, 2H), 5.01 (s, 1H), 5.86 (s, 1H), 5.89 (s, 1H), 6.55 (s, 1H), 7.39 (s, 1H), 7.45 (d, $J = 3.2$ Hz, 1H), 7.60 (s, 1H), 10.60 (br, 1H), 11.28 (br, 1H); $^{13}$C NMR (100 MHz) $\delta$ 14.6, 16.5, 18.1, 29.1, 29.2, 40.4, 41.6, 48.5, 50.7, 53.0, 54.7, 59.4, 102.4, 106.4, 106.9, 108.1, 114.3, 125.8, 126.8, 128.2, 128.7, 133.3, 134.3, 138.4, 160.9, 162.6, 165.4, 165.5, 167.8, 176.6, 188.5; ESI-MS $m/z$: [M+H]$^+$ calcd for C$_{37}$H$_{49}$N$_4$O$_7$ 661.3596; found 661.3590.

3-[7-(4-Bromophenyl)-2,3-dihydro-3,3-dimethypyrin-1-yl]-2-carboethoxy-1-[2,3-dihydro-1-(1,1-dimethoxymethyl)-3,3-dimethyldipyrrin-8-yl]-prop-2-en-1-one (12-Ar/Et). Reaction of 4b (31 mg, 84 µmol) and 1-Ar (36 mg, 100 µmol, 1.2 equiv) under the general procedure for 12-T followed by chromatography [silica, hexanes/ethyl acetate (3:1 then 1:1)] gave an orange-red gum (33 mg, 57%): $^1$H NMR (300 MHz) $\delta$ 1.08 (s, 6H), 1.22 (s, 6H), 1.25 (t, $J = 7.2$ Hz, 3H), 2.57 (s, 2H), 2.64 (s, 2H), 3.43 (s, 6H), 4.22–4.29 (q, $J = 7.2$ Hz, 2H), 5.00 (s, 1H), 5.84 (s, 1H), 6.03 (s, 1H), 6.24 (m, 1H), 6.56 (m, 1H), 6.91 (m, 1H), 7.25–7.28 (d, $J = 8.4$ Hz, 2H), 7.38 (m, 1H), 7.48–7.51 (d, $J = 8.4$ Hz, 2H), 7.61 (s, 1H),
13\textsuperscript{2}-Carbomethoxy-8,8,18,18-tetramethyl-2-\textit{p}-tolylbacterio-13\textsuperscript{1}-oxophorbine (BC-T). A solution of 12-T (19 mg, 30 μmol) in acetonitrile (ACS grade, 150 mL) was degassed by bubbling with argon for 20 min. Yb(OT\textsubscript{f})\textsubscript{3} (186 mg, 0.300 mmol) was added in one portion under argon. The reaction mixture was immediately heated to 80 °C and stirred under argon for 20 h, during which the solution changed from orange-red to dark green. Then, the reaction mixture was allowed to cool to room temperature whereupon excess Et\textsubscript{3}N (0.5 mL) was added. The reaction mixture was concentrated and chromatographed [silica, hexanes/ethyl acetate (3:1 then 1:1)] to afford a blue-green solid (9.5 mg, 56%): \textsuperscript{1}H NMR (400 MHz) \(\delta\) 0.52 (br, 1H), 1.72 (s, 3H), 1.82 (s, 9H), 2.03 (br, 1H), 2.58 (s, 3H), 3.76–3.88 (AB, \(J = 16.8\) Hz, 2H), 3.83 (s, 3H), 4.09 (s, 2H), 5.79 (s, 1H), 7.52–7.54 (d, \(J = 7.8\) Hz, 2H), 7.91–7.93 (d, \(J = 7.8\) Hz, 2H), 8.08 (s, 1H), 8.11 (m, 2H), 8.21 (s, 1H), 8.34 (d, \(J = 1.6\) Hz, 1H); \textsuperscript{13}C NMR (100 MHz) \(\delta\) 21.6, 29.7, 30.1, 30.9, 31.0, 43.9, 45.6, 49.0, 52.9, 53.3, 64.7, 95.1, 98.2, 100.2, 106.0, 108.1, 126.3, 128.6, 130.1, 130.5, 131.8, 138.7, 140.1, 140.3, 141.9, 142.3, 149.8, 152.2, 165.5, 169.4, 169.8, 177.3, 188.6; ESI-MS \(m/z\): [M+H]\textsuperscript{+} calcd for C\textsubscript{37}H\textsubscript{43}BrN\textsubscript{4}O\textsubscript{5} 701.2333; found 701.2334; \(\lambda_{\text{abs}}\) 356, 489, 520, 660, 721 nm.

2-(4-Bromophenyl)-13\textsuperscript{2}-carbomethoxy-8,8,18,18-tetramethylbacterio-13\textsuperscript{1}-oxophorbine (BC-Ar). Reaction of 12-Ar (18 mg, 26 μmol) under the general procedure for BC-T followed by chromatography [silica, hexanes/ethyl acetate (3:1 then 3:2)] gave a blue-green solid (10.5 mg, 61%): \textsuperscript{1}H NMR (400 MHz) \(\delta\) 0.31 (br, 1H), 1.73 (s, 3H), 1.78 (br,
1H), 1.82 (s, 3H), 1.83 (s, 6H), 3.79–3.91 (AB, J = 16.8 Hz, 2H), 3.84 (s, 3H), 4.14 (s, 2H),
5.83 (s, 1H), 7.85–7.87 (d, J = 8.4 Hz, 2H), 7.88–7.90 (d, J = 8.4 Hz, 2H), 8.07 (s, 1H), 8.17
(s, 1H), 8.19 (s, 1H), 8.27 (s, 1H), 8.40 (d, J = 1.6 Hz, 1H); 13C NMR (100 MHz) δ 29.8,
30.2, 31.0, 31.1, 44.0, 45.8, 48.9, 52.9, 53.2, 64.7, 94.8, 98.6, 100.4, 106.5, 108.3, 123.2,
126.5, 128.9, 132.1, 132.5, 133.7, 139.7, 140.2, 141.5, 149.7, 152.5, 165.2, 169.6, 169.8,
177.0, 188.6; ESI-MS m/z: [M+H]+ calcd for C34H32BrN4O3 623.1652; found 623.1647; λabs
356, 490, 521, 664, 727 nm.

132-Carboxemethoxy-2,3,8,8,18,18-hexamethylbacterio-131-oxophorbine (BC-MeMe). Reaction of 12-MeMe (23 mg, 35 µmol) under the general procedure for BC-T followed by chromatography [silica, hexanes/ethyl acetate (3:1 then 1:1)] gave a blue solid (6.7 mg, 37%): 1H NMR (400 MHz) δ 1.16 (br, 1H), 1.62 (br, 1H), 1.72 (s, 3H), 1.75 (s, 6H),
1.80 (s, 3H), 2.93 (s, 3H), 2.95 (s, 3H), 3.62–3.74 (AB, J = 16.8 Hz, 2H), 3.82 (s, 3H), 3.97
(s, 2H), 5.64 (s, 1H), 7.63 (s, 1H), 7.74 (s, 1H), 7.85 (s, 1H), 7.97 (s, 1H); 13C NMR (100 MHz) δ 10.9, 29.6, 29.9, 30.8, 30.9, 43.3, 45.1, 49.0, 52.8, 53.7, 64.4, 91.5, 94.3, 100.0,
104.6, 107.9, 127.7, 133.8, 134.2, 139.7, 142.4, 144.7, 150.6, 151.6, 166.3, 168.5, 169.9,
177.9, 188.5; ESI-MS m/z: [M+H]+ calcd for C30H33N4O3 497.2547; found 497.2548; λabs
351, 480, 511, 640, 696 nm.

3-Carboxethoxy-2-ethyl-132-carboxemethoxy-8,8,18,18-tetramethylbacterio-131-
oxophorbine (BC-EtEs). Reaction of 12-EtEs (13 mg, 21 µmol) under the general procedure for BC-T followed by chromatography [silica, hexanes/ethyl acetate (4:1 then 2:1)] gave a purple solid (6.6 mg, 57%): 1H NMR (400 MHz) δ –0.07 (br, 1H), 1.59 (br, 1H),
1.66–1.69 (t, J = 7.6 Hz, 3H), 1.67–1.71 (t, J = 7.6 Hz, 3H), 1.81 (s, 3H), 1.83 (s, 6H), 1.91
(s, 3H), 3.81–3.91 (AB, J = 16.2 Hz, 2H), 3.84 (s, 3H), 3.91–3.98 (q, J = 7.6 Hz, 2H), 4.20 (s,
2H), 4.71–4.78 (q, \( J = 7.6 \) Hz, 2H), 5.85 (s, 1H), 8.20 (s, 1H), 8.23 (s, 1H), 8.30 (s, 1H), 9.16 (s, 1H); \(^{13}\)C NMR (100 MHz) \( \delta \) 14.7, 17.1, 20.8, 30.1, 30.4, 31.0, 31.1, 44.0, 45.9, 48.8, 52.9, 53.7, 61.5, 64.7, 94.0, 98.0, 100.4, 107.0, 108.6, 124.0, 129.3, 138.3, 139.5, 140.6, 148.1, 149.6, 153.1, 165.5, 165.8, 169.7, 170.4, 176.0, 188.6; ESI-MS \( m/z \): \([M+H]^+\) calcd for C\(_{33}\)H\(_{37}\)N\(_4\)O\(_5\) 569.2758; found 569.2753; \( \lambda_{\text{abs}} \) 357, 501, 533, 680, 745 nm.

\begin{align*}
\text{2-((4-Bromophenyl)-13\(^2\)-carboethoxy-8,8,18,18-tetramethylbacterio-13\(^1\)-oxophorbine (BC-Ar/Et).} \\
\text{Reaction of 12-Ar/Et (16 mg, 23 \( \mu \)mol) under the general procedure for BC-T followed by chromatography [silica, hexanes/ethyl acetate (3:1)] gave a blue-green solid (7.1 mg, 48%):} \\
\text{\(^1\)H NMR (400 MHz) \( \delta \) 0.27 (br, 1H), 1.23–1.27 (t, \( J = 6.8 \) Hz, 3H), 1.73 (br, 1H), 1.75 (s, 3H), 1.81 (s, 3H), 1.83 (s, 6H), 3.81–3.92 (AB, \( J = 16.8 \) Hz, 2H), 4.14 (s, 2H), 4.29–4.34 (q, \( J = 6.8 \) Hz, 2H), 5.80 (s, 1H), 7.85–7.87 (d, \( J = 8.0 \) Hz, 2H), 7.89–7.91 (d, \( J = 8.0 \) Hz, 2H), 8.08 (s, 1H), 8.18 (s, 1H), 8.20 (s, 1H), 8.27 (s, 1H), 8.40 (d, \( J = 2.0 \) Hz, 1H);} \\
\text{\(^{13}\)C NMR (100 MHz) \( \delta \) 14.4, 30.0, 30.1, 31.0, 31.3, 44.1, 45.8, 48.9, 53.3, 61.8, 65.0, 94.8, 98.6, 100.4, 106.6, 108.5, 123.2, 126.4, 129.1, 132.1, 132.5, 133.8, 139.7, 140.1, 140.2, 141.4, 149.7, 152.5, 165.1, 169.3, 169.6, 176.8, 188.8; ESI-MS \( m/z \): [M]^+ calcd for C\(_{35}\)H\(_{33}\)BrN\(_4\)O\(_3\) 636.1652; found 636.1652; \( \lambda_{\text{abs}} \) 357, 489, 521, 665, 728 nm.}
\end{align*}

\text{X-ray Analysis.} Diffusion of hexanes into a chloroform solution of the bacteriochlorin of BC-Ar afforded a single-crystal suitable for X-ray diffraction analysis. The crystal was examined by X-ray diffraction using a Bruker-Nonius X8 Apex2 CCD diffractometer at 100 K. The frame integration was performed using SAINT+.\(^{76}\) The resulting raw data were scaled and absorption-corrected by multiscan averaging of symmetry equivalent data using SADABS.\(^{77}\) The structures were solved using direct methods from SIR92\(^{78}\) and refined using the NRCVAX\(^{79}\) crystallographic suite. The structure was refined
using the SHELXL program from the SHELX2013\textsuperscript{80} package, and graphic plots were produced using Mercury 3.5.
References


