

ABSTRACT

MENEELY, KELLY ROSE. Synthesis of Substituted Bacteriochlorins. (Under the Direction of Dr. Jonathan S. Lindsey.)

The objective of this work is two-fold: first, to find new conditions to improve the condensation reactions leading to the macrocycles 3,13-dibromo-5-methoxybacteriochlorin (BC-Br³OMe⁵Br¹³) and 3,13-dibromobacteriochlorin (BC-Br³Br¹³), and second, to functionalize the valuable BC-Br³OMe⁵Br¹³ building block. This work improves upon past condensation methods, which afforded low yields of bacteriochlorin with an inseparable chlorin product during formation of BC-Br³Br¹³, and provided no access to BC-Br³OMe⁵Br¹³.

Through microscale optimization of conditions, solvents, concentrations, Lewis acids, and additives, BC-Br³OMe⁵Br¹³ and BC-Br³Br¹³ were isolated in 42% and 30% yield, respectively.

Several derivatizations including diacetylation of BC-Br³OMe⁵Br¹³ was achieved in 70% yield, followed by bromination at the β -position in 22% yield. Stille coupling of BC-Br³OMe⁵Br¹³ to introduce a formyl group was performed in 30% yield. Two TIPS-ethynyl groups were also installed on BC-Br³OMe⁵Br¹³ in 4.7% yield.

Synthesis of Substituted Bacteriochlorins

by
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DEDICATION

This work is dedicated to my husband, Andy Meneely
(who appreciates this accomplishment despite not understanding any chemistry).

BIOGRAPHY

Kelly Rose Meneely was born on January 20, 1984. Her parents are Karen Mahoney, Tim Urness, and step-father, Blaise Mahoney. She is the eldest of five children: Sean, Ryan, Molly and Erin Urness. She was recently married to Andrew Meneely in December 2008.

Kelly is a person of many interests. She works hard and always aspires to be a better person, employee, and friend. She's frequently seen with a Starbucks[®] extra-hot peppermint mocha (no whip), and enjoys NCIS and knitting.

She obtained her high school diploma from Burlington High School in Burlington, Wisconsin in 2002. Through her experiences in her high school chemistry classes she was inspired to pursue a Bachelor's degree in Chemistry, which she obtained from Calvin College in Grand Rapids, Michigan in 2006. It was here that she discovered her love of Organic Chemistry. She enjoyed her experiences in several internships and summer research programs at Calvin, Zeeland Chemicals, and Pfizer. She accepted an offer to attend NCSU in Fall 2006, and began working for Dr. Jonathan Lindsey in Spring 2007. From here, she plans to use her talents to better the lives of others whether in the pharmaceutical industry, teaching, or elsewhere.

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Chapter I: Introduction

Porphyrins, chlorins, and bacteriochlorins are intensely colored pigments known for centuries and involved in various biological processes such as photosynthesis, gene regulation, hormone synthesis, oxygen transport, and iron metabolism.¹ The diversity of porphyrins and hydroporphyrins in nature and their potential for synthetic versatility make porphyrins useful for applications such as light harvesting, photodynamic therapy (PDT), and solar cells.² Synthetic bacteriochlorins may be significantly more useful than naturally occurring bacteriochlorins due to their greater stability, wavelength tunability, and versatility owing to vast substituent combinations. Additionally, naturally occurring bacteriochlorins are prone to adventitious dehydrogenation, readily undergoing conversion to chlorins and/or porphyrins.²

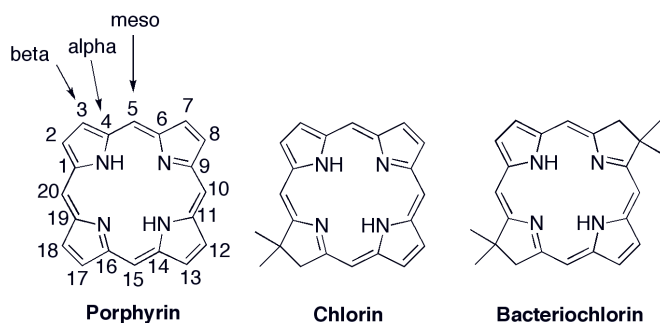


Figure I.1 – Hydroporphyrins

This work focuses on bacteriochlorins, particularly in achieving stable versatile bacteriochlorins while maintaining the spectroscopic and photochemical features of the

natural products. The previous method³ for the condensation to 2,12-di-*p*-tolyl-8,8,18,18-tetramethylbacteriochlorin (**H-BC**) afforded modest yields but when applied to the formation of dibromo-8,8,18,18-tetramethylbacteriochlorin (**BC-Br³Br¹³**) afforded low yields and various inseparable products. The primary goal of this work, therefore, was optimizing a new method for formation of **BC-Br³Br¹³** and the methoxy version 3,13-dibromo-5-methoxy-8,8,18,18-tetramethylbacteriochlorin (**BC-Br³OMe⁵Br¹³**). The secondary goal was to further derivatize **BC-Br³OMe⁵Br¹³**.

Chapter I contains background information about porphyrins, chlorins, and bacteriochlorins along with the motivation for the work in each chapter. Chapter II contains the results of the condensation study of bacteriochlorin macrocycle formation (**BC-Br³Br¹³** and **BC-Br³OMe⁵Br¹³**). Chapter III describes the scale-up procedure and characterization of **BC-Br³OMe⁵Br¹³** and Chapter IV describes several derivatizations of **BC-Br³OMe⁵Br¹³**. This work is an important contribution to synthetic bacteriochlorin research in two ways: identification of new conditions for bacteriochlorin condensations and discovery of knowledge about reactivity, structure, and spectroscopic properties of bacteriochlorins. The spectral properties of the new compounds will also be analyzed by our collaborators.

I.A. Background and Motivation^{1,4}

1. Structure: Porphyrinic macrocycles are a class of aromatic compounds structurally comprised of four pyrrolic units joined at the α -pyrrole positions by methine bridges. Each macrocycle contains eight β -positions (2, 3, 7, 8, 12, 13, 17, and 18) and four

meso-positions (5, 10, 15, and 20) that can be substituted. Porphyrins are fully unsaturated macrocycles, chlorins are saturated at the β -positions of one pyrrole (positions 7 and 8), and bacteriochlorins are saturated at the β -positions of two pyrroles opposite one another (positions 7, 8, 17, and 18).

2. Spectroscopic Information:⁴ The number of double bonds that a porphyrinic macrocycle contains impacts the spectral properties of the molecule by producing wavelength shifts in the absorption bands. In the series: porphyrin, chlorin, bacteriochlorin, the number of double bonds decreases but the Q_y band shifts to longer wavelength and increases in intensity. (Chart I.1)

Porphyrinic macrocycles have sharp absorbance bands ranging from the near UV region to the near IR region, depending on the saturation and the substituents. Chart I.1 illustrates the difference between the porphyrin, chlorin, and bacteriochlorin aromatic systems and their resulting absorbance spectra. In the visible range, the porphyrin Soret band appears at ~ 420 nm, while the chlorin Soret and Q_y bands appear at ~ 420 and 650 nm, respectively. The bacteriochlorin B_y , B_x , Q_x , and Q_y bands are present in the visible spectrum at ~ 360 (B_y and B_x), 580, and 750 nm, respectively. For bacteriochlorins, the Q_y band is typically the most intense absorption band. Bacteriochlorins, in particular, are good candidates for many photomedical applications because the saturation at carbons 7-8 and 17-18 (two fewer π bonds) shifts the Q_y band wavelength into the near-IR.² The best prospect for a potent therapeutic drug candidate is a compound with a Q_y band absorbance between

700-900 nm; at this range, absorption and autofluorescence of biological tissues is diminished, allowing for deeper skin penetration.²

3. Bacteriochlorophyll *a*: Bacteriochlorins received their name from the naturally occurring bacteriochlorophylls *a*, *b*, and *g*, which are present in phototrophic bacteria.^{1,2,4} The structure of bacteriochlorophyll *a* is shown in Figure I.2. One class of synthetic bacteriochlorins has geminal dimethyl groups instead of the *trans*-alkyl groups since *trans*-alkyl groups are much more synthetically challenging and because the geminal methyl groups help prevent oxidation of the saturated rings.²

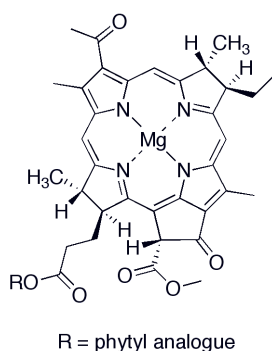


Figure I.2 - Bacteriochlorophyll *a*

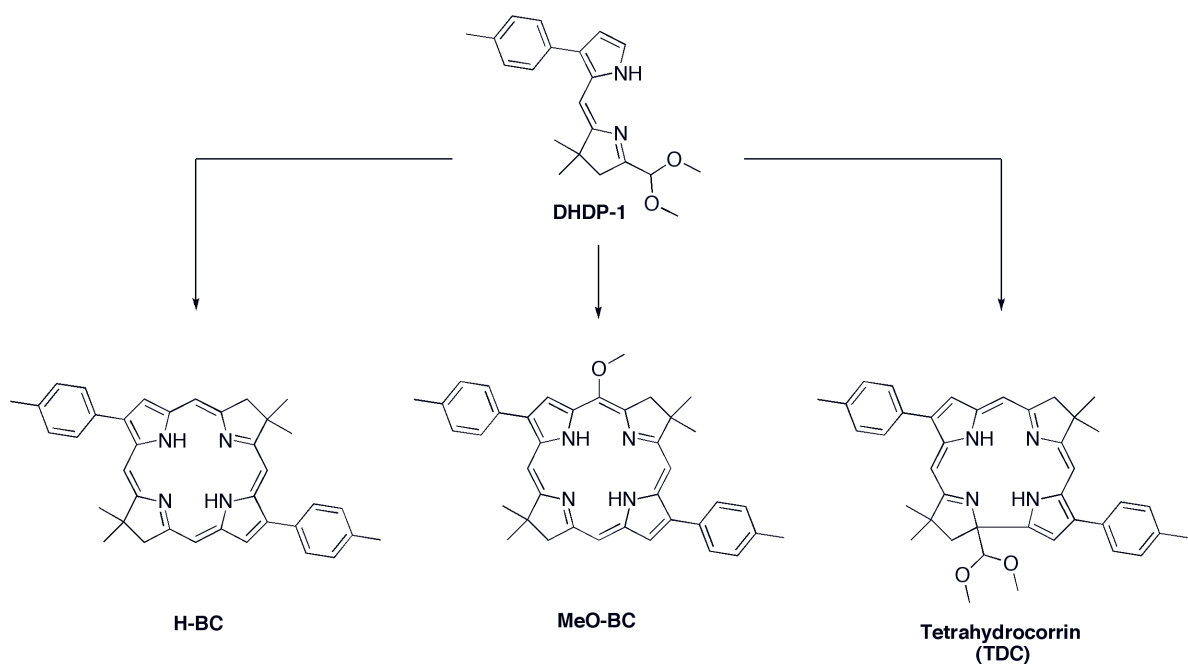
Bacteriochlorophyll *a* contains several distinctive structural features, including a magnesium coordinated cation, an acetyl group, and an exocyclic five-membered ring (figure I.2). The macrocycle is fully β -substituted but lacks *meso*-substituents at positions 5, 10, and 20. Some characteristic spectral features of bacteriochlorophyll *a* are the strong bathochromic shift in comparison to bacteriochlorins that do not contain an exocyclic ring and/or metal coordination. The Q_y absorbance is in the near-IR (>800 nm) for bacteriochlorophyll derivatives.⁵ Under both acidic and basic conditions, the exocyclic ring is unstable while the

rest of the structure readily undergoes oxidation to the corresponding chlorin or porphyrin. One of the goals of bacteriochlorin research in the Lindsey group is to develop a diverse synthetic methodology that can be used to make bacteriochlorins that are stable and malleable for diverse applications.

4. Bacteriochlorin Synthesis: Bacteriochlorins are the least explored of the three main porphyrinic macrocycles, primarily due to various synthetic challenges and the prior lack of versatile synthetic routes. Three primary categories of bacteriochlorin preparation are (1) derivatization of pre-existing naturally occurring bacteriochlorins through substitutions,⁶⁻⁸ (2) oxidation, reduction, and cycloadditions^{9,10} of existing porphyrins or chlorins, and (3) a *de novo* route to porphyrinic macrocycles, as embraced by Kishi^{9,11} and Lindsey.^{2,3,10} Each synthesis begins with a small molecule (such as a pyrrole derivative) and involves building the macrocycle from commercially available starting materials. The substituents are installed throughout the synthesis rather than after the macrocycle formation is complete. The *de novo* route can be lengthy and synthetically challenging, but affords products that are manipulated with control. Many products can be synthesized from simple precursors using these methods. Another benefit of the *de novo* synthesis is the installation of geminal methyl groups (positions 8, 8, 18, and 18) leaving four saturated β -positions (positions 7, 7, 17, and 17). Geminal dimethyl installation prevents adventitious oxidation, thereby creating a more stable molecule without changing the electronic features to a large degree.

Over the last several years, two major bacteriochlorin syntheses were reported. The synthesis yielded two 2,12-di-*p*-tolylbacteriochlorins³ (**H-BC** and **MeO-BC**, Scheme I.1) and 3,13-dibromobacteriochlorin (**BC-Br³Br¹³**).^{2,10} Each synthesis relies on the self-condensation of two dihydrodipyrin molecules to give the corresponding bacteriochlorin plus two other products (Scheme I.1). The product distribution of **H-BC**, **MeO-BC**, and a B,D-tetradehydrocorrins (**TDC**, a contracted macrocycle) can be altered based on various conditions laid out in Chapter II. Each DHDP is a stable bacteriochlorin precursor, which facilitates installation of various groups corresponding to positions 2, 3, 12, and 13 on the macrocycle. The geminal dimethyl groups add stability to the molecule.

The synthesis of **H-BC** was tailored by investigating the role of solvents, concentrations of reactants, and types of Lewis acids to selectively afford each bacteriochlorin product without formation of **TDC**.³



Scheme I.1 - Three macrocycles from the self-condensation of DHDP-1³

BC-Br³Br¹³ is formed using the same condensation conditions ($\text{BF}_3 \cdot \text{OEt}_2 / \text{CH}_3\text{CN}$) but the route affords a nearly inseparable chlorin product in addition to the target bacteriochlorin. A new method, therefore, would make the synthesis cleaner and higher yielding.

5. Dibromobacteriochlorins: The route to the dibromobacteriochlorins precursor, 8-bromo-1-(1,1-dimethoxymethyl)-3,3-dimethyl-2,3-dihydrodipyrrole (DHDP-Br) is well-established.¹⁰ The synthesis begins with the commercially available pyrrole-2-carboxaldehyde and through a series of seven linear steps, DHDP-Br is formed. The bottleneck of the dibromobacteriochlorin synthesis is that the self-condensation of two molecules of DHDP-Br proceeds in low yield, in small scale, and with multiple products.

Although the mechanisms of formation of **BC-Br³Br¹³** and **BC-Br³OMe⁵Br¹³** are not completely understood, the former involves a condensation and a 2 e⁻, 2H⁺ reduction while the latter is the product of only a condensation.³ The reductant, however, is unknown. By analyzing condensations under varying conditions, more information can be gleaned about the actual mechanistic routes.

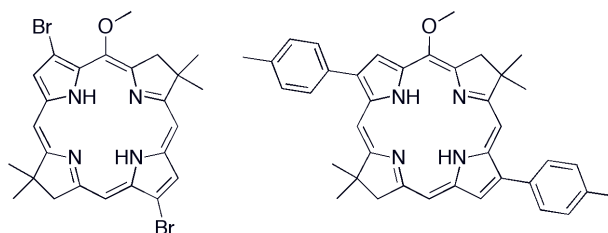


Figure I.3 - BC-Br³OMe⁵Br¹³ (left) and MeO-BC (right)³

BC-Br³OMe⁵Br¹³ derivatives have the potential for efficacy in medicinal applications, particularly if the methoxy substituent can be used as a bioconjugatable handle. In addition, if a difference in reactivity of the two bromides (positions 3 and 13) is observed, selective derivatizations are a possibility.

6. Substituted Bacteriochlorins: Various substituted bacteriochlorins aid our understanding of wavelength tunability and the relationship between porphyrin, chlorin, and bacteriochlorin reactivity. Many substitutions have been performed on porphyrins, chlorins, and bacteriochlorins (**H-BC**, **MeO-BC** and **BC-Br³Br¹³**) via Pd couplings, but the impact of the methoxy group on reactivity under Pd coupling conditions is unknown. Examining the

role of various categories of substituents provides insight into the effect of each substituent on the position and intensity of the Q_y band.

7. Bacteriooxophorbines: Oxophorbines have recently been a research focus,¹² but until now, a *de novo* route to bacteriooxophorbines has not been achieved.

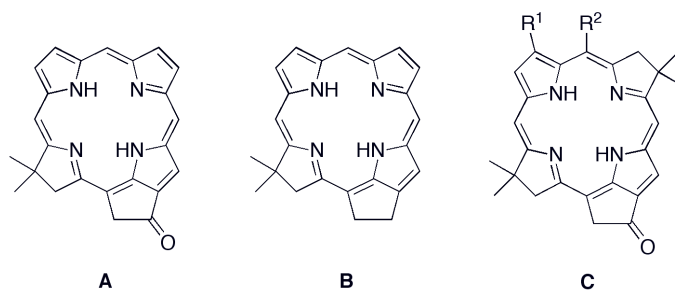


Figure I.4 - (A) An oxophorbine, (B) a phorbine, and (C) a proposed bacteriooxophorbine

The isocyclic ring of a phorbine is made of two carbons attached to position 13 and position 15 of the macrocycle, forming a fused five-membered ring. Oxophorbines are phorbines with a carbonyl in place of one of the carbons in the isocyclic ring.¹² Oxophorbines are attractive due to the resulting red-shifted Q_y band, which extends the range of bacteriochlorin absorption.

I.B. Summary

The spectral properties of bacteriochlorins make them viable candidates for many spectral, medical, and technological applications.² While major inroads made the dihydrodipyrin precursor to dibromobacteriochlorins accessible, the condensation reaction remains challenging due to low yields, inseparable products, and lack of scalability. Improvements in the self-condensation reaction would make large-scale syntheses of **BC-Br³Br¹³** and **BC-Br³OMe⁵Br¹³** more practical and less expensive as well as provide a reasonable route to other 3,13-substituted bacteriochlorins.

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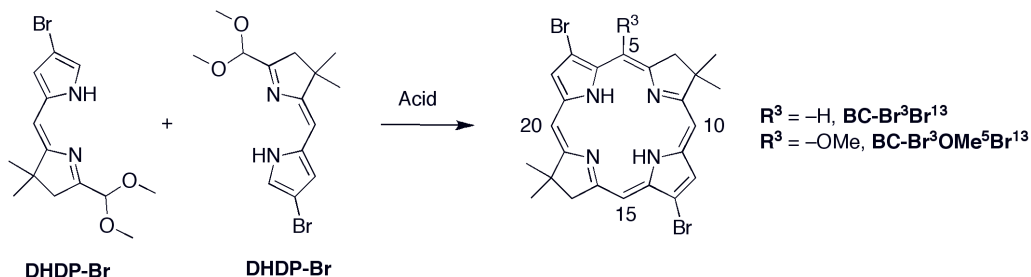
Chapter II: Survey of Lewis Acid Mediated Self-Condensations to Bacteriochlorins

II.A. Objectives

The overall goal of this work is to optimize the existing Lewis acid-mediated bacteriochlorin self-condensation of **DHDP-Br** (Scheme II.1) to form exclusively **BC-Br³OMe⁵Br¹³** or **BC-Br³Br¹³** in a controlled, scalable, and versatile manner. The 3,13-dibromobacteriochlorin synthesis has been improved at nearly every step for higher yielding and faster reactions. The bacteriochlorin self-condensation reaction, however, has proven challenging. Previously, Lewis acid screenings were performed for condensation of a dipyrromethane-1-carbinol to give porphyrins,¹ where Lewis acids can be used in catalytic amounts to afford relatively high yields of different porphyrins. Bacteriochlorins, however, require multiple equivalents of Lewis acid and afford more than one product in low yields. In addition, there is a need for a set of generalized DHDP condensation conditions to bacteriochlorins. Bromo-substituted bacteriochlorins can be derivatized after macrocycle formation to afford many new products. In this study, various mild acids were investigated in a similar manner to the previous porphyrin studies as just one of the conditions used for tuning the reactions to produce exclusively **BC-Br³Br¹³** or **BC-Br³OMe⁵Br¹³**.

Under the BF₃·OEt₂/CH₃CN conditions developed for the conversion of **DHDP-1** to **H-BC**,² the condensation of **DHDP-Br** to **HBC-Br₂** afforded a low yield (19%) with multiple side products. By replacing the *p*-tolyl groups at the β-positions (2 and 12) with Br

atoms (3 and 13), multiple products of similar polarities (**BC-Br³Br¹³**, **BC-Br³OMe⁵Br¹³**, and a chlorin) were formed, making separation laborious.



Scheme II.1 - Condensation to dibromobacteriochlorin

The specific goals of this project were to: (1) develop a general reaction affording 3,13-dibromobacteriochlorins in synthetically useful yields that are effective in various conditions such as in the presence of electron-donating, electron-withdrawing, and acid-sensitive groups, and (2) find individual condensation conditions specific to the formation of **BC-Br³Br¹³** and the previously inaccessible **BC-Br³OMe⁵Br¹³**. It should be noted that while **TDC** was also observed in most reactions discussed in this chapter, **TDC** was not the focus of this study and its presence is not discussed. In addition, all yields reported are spectroscopic yields assuming molar extinction coefficients of: $\epsilon_{\text{Qy}} = 130,000 \text{ M}^{-1}\text{cm}^{-1}$ (**BC-Br³Br¹³**) and $\epsilon_{\text{Qy}} = 120,000 \text{ M}^{-1}\text{cm}^{-1}$ (**BC-Br³OMe⁵Br¹³**).

II.B. Results and Discussion

1. Overview: A selection of Lewis acids, additives, solvents, concentrations, and temperatures were investigated to establish a set of conditions, which exclusively forms **BC-**

Br³Br¹³ or **BC-Br³OMe⁵Br¹³** in high yields (> 20%). The self-condensation of **DHDP-Br** to the corresponding dibromobacteriochlorin (Scheme II.1) was examined on a small scale (~10 mg **DHDP-Br**) under varying conditions.

2. Lewis Acid Study: Seventeen Lewis acids were selected based on the Lewis acids that gave the best yields for 2,12-di-*p*-tolylbacteriochlorin formation,² as well as other literature references pertaining to Lewis acid catalyzed acetal hydrolysis^{3,4} and Mukaiyama reactions.^{5,6} Preliminary studies were performed in anhydrous CH₂Cl₂ at fixed dihydrodipyrin concentrations. The reactions were monitored using TLC analysis and absorption spectroscopy. Reaction mixtures that turned dark green/black typically had the best yields, while reactions that failed completely (yielding only starting material) were typically clear, yellow, or pale orange. The results can be summarized in four categories and are listed in Table II.1: (1) Lewis acids that yielded no reaction and only starting material: Ti(O*i*Pr)₄ and trimethylsilyl chloride (TMSCl). (2) Reactions that afforded no product but starting material was consumed: AgOTf, Zn(OTf)₂, AuCl₃, iodotrimethylsilane (TMIS), and triisopropylsilyl chloride (TIPSCl). (3) Reactions that afforded trace amounts of **BC-Br³Br¹³** and/or **BC-Br³OMe⁵Br¹³**: trimethylsilyl trifluoromethanesulfonate (TMSOTf), TiCl₃, MgBr₂, In(OTf)₃, Sc(OTf)₃, Ga(OTf)₃, Al(OTf)₃, TIPSOTf, and BiCl₃. (4) Reactions that afforded synthetically useful yields of bacteriochlorin: Bi(OTf)₃ (**BC-Br³Br¹³**, 31%) and Hf(OTf)₄ (**BC-Br³Br¹³**, 7%). Chart II.1 contains three normalized absorption spectra of (a) pure **BC-Br³Br¹³**, (b) pure **BC-Br³OMe⁵Br¹³**, and (c) a “typical” mixture of **BC-Br³Br¹³** and **BC-Br³OMe⁵Br¹³**. Note the broader Q_y band in (c).

Table II.1 - Lewis acid study

Entry	DHDP-Br conc. (mM)	Lewis acid	Lewis Acid conc. (mM)	Yield ^a of BC-Br ³ Br ¹³ (%)	Yield of BC-Br ³ OMe ⁵ Br ¹³ (%)
Ref ^b	18 (DHDP-1)	BF ₃ ·OEt ₂	140	21	1.5
1	19	Bi(OTf) ₃	84	31	Trace
2	10	Hf(OTf) ₄	77	7	Trace
3	19	TMSOTf	76	Trace	0
4	19	Ti(OiPr) ₄	110	0	0
5	19	TiCl ₃	82	0	Trace
6	17	MgBr ₂	90	Trace	Trace
7	17	In(OTf) ₃	73	0	0
8	17	AgOTf	85	0	0
9	17	Zn(OTf) ₂	88	0	0
10	17	AuCl ₃	95	0	0
12	17	In(OTf) ₃	80	0	Trace
13	15	Sc(OTf) ₃	66	0	Trace
14	15	Ga(OTf) ₃	66	Trace	Trace
15	15	Al(OTf) ₃	77	0	Trace
16	15	TMSCl	75	0 ^c	0 ^c
17	15	TMIS	75	0	0
18	15	TIPSOTf	75	Trace	0
19	15	TIPSCl	75	0	0
20	15	Bi(OTf) ₃	75	33 ^d	Trace
21	15	BiCl ₃	75	Trace	0

^aSpectroscopic Yield was determined to be the actual measured absorption (measured as the integration of the Q_y band) of the reaction mixture solution of (known concentration and a known aliquot used) divided by a theoretical yield and multiplying by 100

$[(A_{\text{actual}}/A_{\text{theoretical}})*100]$. Theoretical value: Absorption = $[\text{mM of entire reaction solution/mL used to dilute reaction mixture}*(\text{uL of stock solution used for absorption measurement}/\text{total uL of solution used for absorption measurement})*\text{extinction coefficient}]$. ^bReference reaction developed for formation of **H-BC**.⁷ ^cStarting material present. ^dCrude yield.

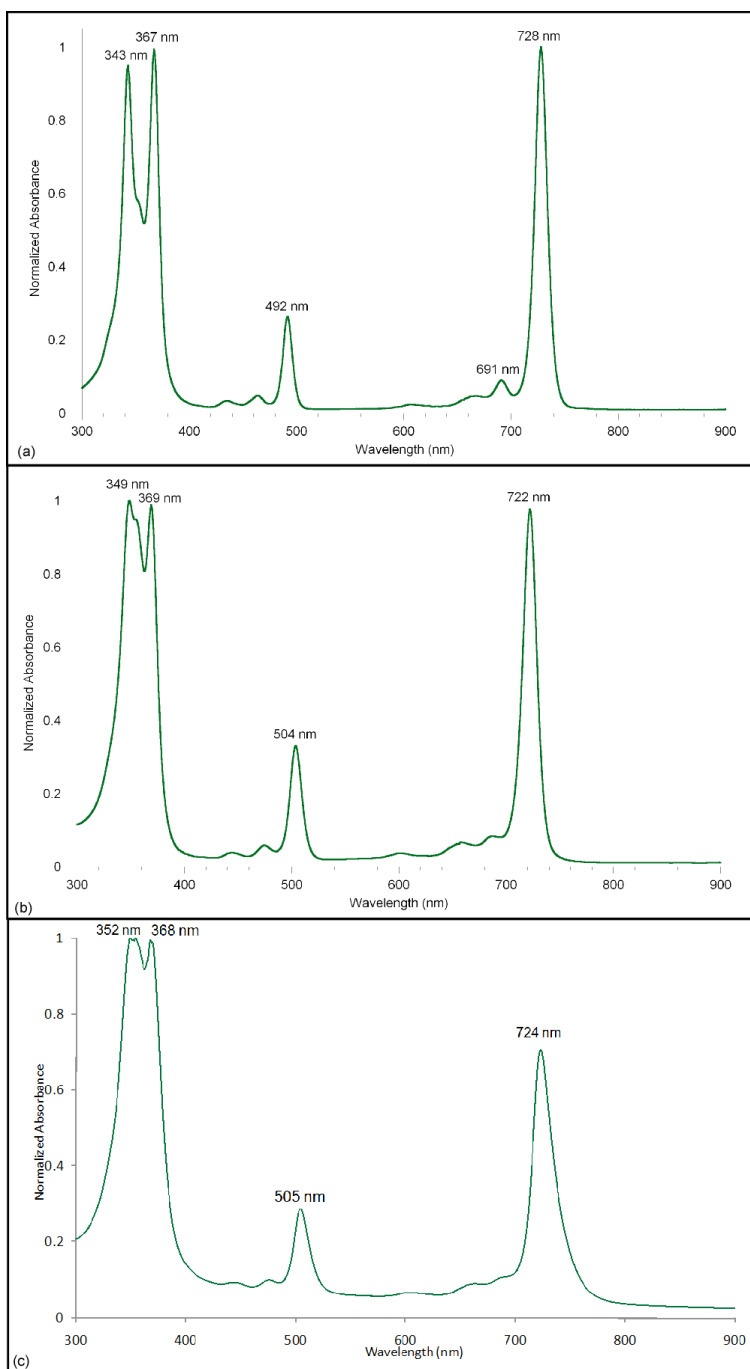


Chart II.1 - Normalized absorption spectra of $\text{BC-Br}^3\text{Br}^{13}$ and $\text{BC-Br}^3\text{OMe}^5\text{Br}^{13}$: (a) pure $\text{BC-Br}^3\text{Br}^{13}$, (b) pure $\text{BC-Br}^3\text{OMe}^5\text{Br}^{13}$, and (c) a mixture of $\text{BC-Br}^3\text{Br}^{13}$ and $\text{BC-Br}^3\text{OMe}^5\text{Br}^{13}$

Four Lewis acids were chosen for further investigations: Bi(OTf)₃, TMSOTf, TMIS, and BiCl₃. Bi(OTf)₃ was chosen because it afforded the highest yield of **BC-Br³Br¹³**, while BiCl₃ was chosen as an inexpensive alternative to Bi(OTf)₃. The reasons for TMSOTf and TMIS selection are discussed in the following section.

3. Study of Additives: Some Lewis acid mediated reactions perform better with a co-reactant or an additive such as an amine base, particularly TMSOTf.^{3,5,6} Two possible reasons for the necessity of an additive are: (1) the amine attacks the activated acetal, creating an unstable pyridinium salt^{3a} and (2) a double activation (nucleophilic and electrophilic) of the starting materials occurs.^{3c} There is no evidence for or against these hypotheses in this particular case as no reaction intermediates were isolated. Most of the additive (amine) study was focused on the Lewis acid, TMSOTf, due to literature findings. Results for TMIS, BiCl₃, and Bi(OTf)₃, however, are also listed in Table II.2.

Condensation reactions using TMSOTf alone afforded trace amounts of **BC-Br³Br¹³**. The reactivity of TMSOTf was enhanced by the addition of various bases to produce a maximum of 32% of **BC-Br³OMe⁵Br¹³** (*Note: this is a different product than that achieved without base.*)^{3,5,6} Seven amines were chosen for the additive survey using TMSOTf as the Lewis acid: 2,6-di-*tert*-butylpyridine (2,6-DTBP), 2,6-lutidine, diisopropylethylamine, DBU, 2,3,5-collidine, imidazole, and dicyclohexylmethylamine. 2,6-DTBP afforded 32% (spectroscopic) yield and 2,6-lutidine afforded a trace amount of **BC-Br³OMe⁵Br¹³**. Diisopropylethylamine, DBU, 2,3,5-collidine, imidazole, or dicyclohexylmethylamine,

however, did not improve the yield of bacteriochlorin. 2,6-DTBP was used as an additive for other Lewis acids that previously afforded trace amounts of **BC-Br³OMe⁵Br¹³**, but the only significant increase in yield was shown with TMIS. TMIS produced comparable results to TMSOTf, however, TMSOTf remained the focus based on the sensitivity of TMIS to light and the greater affordability of TMSOTf.

BiCl₃ was used in conjunction with additives in the hope of achieving similar results as for Bi(OTf)₃, as suggested by the literature.^{4,5} BiCl₃ is an inexpensive alternative to Bi(OTf)₃. Using BiCl₃ with a base/additive (2,6-DTBP, imidazole, 2,3,5-collidine, NaI, or TMSOTf) did not afford any significant improvement in bacteriochlorin yields.

Molecular sieves were investigated as an alternate means of facilitating condensation. Two reactions, one “control” reaction with **DHDP-Br** and no Lewis acid, and one reaction with **DHDP-Br** and TMSOTf were investigated. The control reaction (activated molecular sieves only) resulted in no product formation, while the reaction of TMSOTf and activated molecular sieves afforded only trace amounts of **BC-Br³OMe⁵Br¹³**. No further exploration was done with molecular sieves.

Table II.2 – Study of additives

Entry	DHDP-Br conc. (mM)	Lewis acid (75 mM)	Additive (750 mM)	Yield ^a of BC- Br³Br¹³ (%)	Yield of BC- Br³OMe⁵Br¹³ (%)
1	15	TMSOTf	2,6-DTBP	0	32
2	15	TMSOTf	Diisopropylethylamine	0 ^b	0 ^b
3	15	TMSOTf	2,6-lutidine	0	Trace

Table II.2 (Continued)

4	15	TMSOTf	DBU	0 ^b	0 ^b
5	15	TMSOTf	2,3,5-collidine	0 ^c	Trace
6	15	TMSOTf	Imidazole	0 ^b	0 ^b
7	15	TMSOTf	2,6-lutidine	0 ^b	0 ^b
8	15	TMSOTf	Dicyclohexylmethylamine	0 ^c	0 ^c
9	15	TMSOTf	4 Å mol sieves (150 mg per 0.03 mmol)	0	Trace
10	10	TMIS	2,6-DTBP	0	30 ^d
11	10	TIPSOTf	2,6-DTBP	0 ^b	0 ^b
12	10	TiCl ₃	2,6-DTBP	Trace	0
13	10	TiCl ₄	2,6-DTBP	Trace ^b	0 ^b
14	15	BiCl ₃	Imidazole	0 ^c	0 ^c
15	15	BiCl ₃	2,6-lutidine	0 ^c	0 ^c
16	15	BiCl ₃	2,6-DTBP	0 ^c	0 ^c
17	15	BiCl ₃	2,3,5-collidine	0 ^c	0 ^c
18	15	BiCl ₃	TMSOTf	0 ^c	0 ^c
19	15	BiCl ₃	TMSOTf (75 mM)	0 ^c	0 ^c
20	15	BiCl ₃	NaI (225 mM)	0 ^c	0 ^c

^aSpectroscopic Yield was determined to be the actual measured absorption (measured as the integration of the Q_y band) of the reaction mixture solution of (known concentration and a known aliquot used) divided by a theoretical yield and multiplying by 100 [(A_{actual}/A_{theoretical})*100]. Theoretical value: Absorption = [mM of entire reaction solution/mL used to dilute reaction mixture]*(uL of stock solution used for absorption measurement/total uL of solution used for absorption measurement)*extinction coefficient]. ^bStarting material present. ^cNo significant macrocyclic product observed. ^dCrude yield.

4. Solvent Study: After the best Lewis acids/additive combinations were determined [Bi(OTf)₃, TMSOTf (with 2,6-DTBP), and TMIS (with 2,6-DTBP)], these reagent combinations (12 reactions) were carried out in CH₃CN, anhydrous CH₂Cl₂, anhydrous toluene, and anhydrous CH₃NO₂. The best acid/base/solvent combinations are as follows: Bi(OTf)₃ in anhydrous CH₂Cl₂, 31% yield of **BC-Br³Br¹³** (Table II.3, entry 1); TMSOTf (with 2,6-DTBP) in anhydrous CH₂Cl₂, 32% yield of **BC-Br³OMe⁵Br¹³** (entry 2); iodotrimethylsilane (TMIS) (with 2,6-DTBP) in anhydrous CH₃CN, 30% yield of **BC-Br³OMe⁵Br¹³** (entry 13). The non-polar aprotic solvent, toluene, did not facilitate good yields of the condensation in the presence of the three Lewis acids, although color changes were observed for both Bi(OTf)₃ and TMSOTf/2,6-DTBP. Reactions in CH₂Cl₂ and CH₃CN typically displayed rapid color changes and the best yields (Table II.3). Dichloroethane was also investigated for Bi(OTf)₃ and TMSOTf. Bi(OTf)₃ and TMSOTf (with 2,6-DTBP) in CH₂Cl₂ are listed for comparison.

Table II.3 - Solvent study

Entry	Lewis acid ^a	Additive (750 mM)	Solvent	Yield ^b of BC-Br³Br¹³ (%)	Yield BC-Br³OMe⁵Br¹³ (%)
1	Bi(OTf) ₃	--	CH ₂ Cl ₂	31	Trace
2	TMSOTf	2,6-DTBP	CH ₂ Cl ₂	Trace	32
3	TMSOTf	2,6-DTBP	Toluene	0	Trace
4	TMIS	2,6-DTBP	Toluene	0	Trace
5	Bi(OTf) ₃	--	Toluene	7 ^c	0
6	TMSOTf	2,6-DTBP	CH ₃ CN ^d	0	10 ^c

Table II.3 (Continued)

7	TMIS	2,6-DTBP	CH ₃ CN ^d	0	13 ^c
8	Bi(OTf) ₃	--	CH ₃ CN ^d	14 ^c	0
9	TMSOTf	2,6-DTBP	CH ₃ NO ₂	Trace	0
10	TMIS	2,6-DTBP	CH ₃ NO ₂	0	23.5 ^c
11	Bi(OTf) ₃	--	CH ₃ NO ₂	10	0
12	TMSOTf	2,6-DTBP	CH ₃ CN	0	8.4 ^c
13	TMIS	2,6-DTBP	CH ₃ CN	0	29.7
14	Bi(OTf) ₃	--	CH ₃ CN	Trace	0
15	Bi(OTf) ₃	--	ClCH ₂ CH ₂ Cl	Trace	0
16	TMSOTf	2,6-DTBP	ClCH ₂ CH ₂ Cl	Trace	35

^aLewis acid concentration: 75 mM. ^bSpectroscopic Yield was determined to be the actual measured absorption (measured as the integration of the Q_y band) of the reaction mixture solution of (known concentration and a known aliquot used) divided by a theoretical yield and multiplying by 100 [(A_{actual}/A_{theoretical})*100]. Theoretical value: Absorption = [mM of entire reaction solution/mL used to dilute reaction mixture]*(uL of stock solution used for absorption measurement/total uL of solution used for absorption measurement)*extinction coefficient]. ^cCrude yield. ^dNon-anhydrous solvent.

5. Concentration Study: In an effort to optimize the condensations of **DHDP-Br** to give **BC-Br³Br¹³** or **BC-Br³OMe⁵Br¹³**, a series of reactions were run at various concentrations of **DHDP-Br**, Lewis acid, and amine and are summarized in Table II.4. The yields reported in Table II.4 are lower than expected but results were used comparatively (see section 7).

Table II.4 – Bi(OTf)₃ concentration study

Entry	DHDP-Br (mM)	Lewis acid (mM)	Yield ^a of BC-Br ³ Br ¹³ (%)	Yield BC-Br ³ OMe ⁵ Br ¹³ (%)
1	15	75	15.9	0
2	15	15	Trace	Trace
3	15	3	0	Trace
4	135	675	0	0
5 ^b	45	225	5.8	0
6 ^b	30	300	11.9	0
7 ^c	3	3	3.6	0

^aSpectroscopic Yield was determined to be the actual measured absorption (measured as the integration of the Q_y band) of the reaction mixture solution of (known concentration and a known aliquot used) divided by a theoretical yield and multiplying by 100 [(A_{actual}/A_{theoretical})*100]. Theoretical value: Absorption = [mM of entire reaction solution/mL used to dilute reaction mixture)*(uL of stock solution used for absorption measurement/total uL of solution used for absorption measurement)*extinction coefficient]. ^bReaction was run with 150 mg of 4 Å mol sieves per 0.03 mmol. ^cReaction was run in a sealed 20 mL (10 mL of solvent) scintillation vial.

Reactions with a lower concentration (3 mM, entry 7) of **DHDP-Br** afforded lower yields (3.6% BC-Br³Br¹³) than those run at 10-15 mM. Reaction mixtures with a high concentration (675 mM) of Bi(OTf)₃, however, were difficult to stir and afforded no product (entry 4). When ≤ 3 equivalents of Bi(OTf)₃ was used, **BC-Br³OMe⁵Br¹³** (entry 3) was formed in only a trace amount.

The concentration of the amine (2,6-DTBP) was investigated at 50, 10, and 2 equivalents (750, 150, 30 mM) relative to **DHDP-Br** and with a **DHDP-Br** concentration of 15 mM. Ten equivalents of 2,6-DTBP gave the highest yield (Table II.5). Entry 1, while a

higher yield than entry 2, contains a considerable amount of both bacteriochlorins. A five-fold decrease in concentration of 2,6-DTBP drastically diminished the cost of the reaction to give **BC-Br³OMe⁵Br¹³**.

Table II.5 – TMSOTf/2,6-DTBP concentration study

Entry ^a	DHDP-Br (mM)	TMSOTf (mM)	2,6-DTBP concentration	Yield ^b of BC-Br³Br¹³ (%)	Yield of BC-Br³OMe⁵Br¹³ (%)
1	15	75	750 mM		33 ^c
2	15	75	150 mM	Trace	22
3	15	75	30 mM	Trace	11
4	15	150	150 mM		23 ^c
5	15	150	300 mM		17.5 ^c
6	15	750	0 mM	Trace	0

^aAll yields reported here are crude yields. ^bSpectroscopic Yield was determined to be the actual measured absorption (measured as the integration of the Q_y band) of the reaction mixture solution of (known concentration and a known aliquot used) divided by a theoretical yield and multiplying by 100 [(A_{actual}/A_{theoretical})*100]. Theoretical value: Absorption = [mM of entire reaction solution/mL used to dilute reaction mixture]*(uL of stock solution used for absorption measurement/total uL of solution used for absorption measurement)*extinction coefficient]. ^cYield reflects the presence of both bacteriochlorins (products not separated).

6. Temperature Study: In addition to the studies above, TMSOTf/2,6-DTBP in anhydrous 1,2-dichloroethane (DCE) was examined at different temperatures: (a) –78°C to room temperature (RT) for 30 min followed by stirring overnight at RT (entry 2), (b) at 84 °C for four hours followed by stirring overnight at RT (entry 1), and (c) at room temperature (entry 3). The yields (by absorption spectroscopy) were: trace, 14% (crude), and 35% yield

of **BC-Br³OMe⁵Br¹³**, respectively. Assuming no solvent effects, the result of this temperature test indicates the importance of the first 15-30 min of the reaction. Another reaction was run in anhydrous CH₂Cl₂ at 0°C for the first two hours and stirred overnight at RT, giving **BC-Br³OMe⁵Br¹³** in 42% yield.

Table II.6 – Temperature study

Entry	Lewis acid ^a	Additive (750 mM)	Solvent	Temperature	Yield ^b
1	TMSOTf	2,6-DTBP	ClCH ₂ CH ₂ Cl	84°C 4 h, overnight, RT	14% ^c - BC-Br³OMe⁵Br¹³
2	TMSOTf	2,6-DTBP	ClCH ₂ CH ₂ Cl	-78°C – RT 30 min; overnight, RT	Trace - BC-Br³OMe⁵Br¹³
3	TMSOTf	2,6-DTBP	ClCH ₂ CH ₂ Cl	RT	35% - BC-Br³OMe⁵Br¹³
4	Bi(OTf) ₃	--	CH ₂ Cl ₂	0°C	<5% - BC-Br³Br¹³
5	TMSOTf	2,6-DTBP	CH ₂ Cl ₂	0°C – RT	42% - BC-Br³OMe⁵Br¹³

^aLewis acid concentration: 75 mM. ^bSpectroscopic Yield was determined to be the actual measured absorption (measured as the integration of the Q_y band) of the reaction mixture solution of (known concentration and a known aliquot used) divided by a theoretical yield and multiplying by 100 [(A_{actual}/A_{theoretical})*100]. Theoretical value: Absorption = [mM of entire reaction solution/mL used to dilute reaction mixture]*(uL of stock solution used for absorption measurement/total uL of solution used for absorption measurement)*extinction coefficient]. ^cCrude yield.

7. Workup Conditions: Several reaction mixtures from the preceding sections afforded unusually low yields. While investigating the possible factors in sections 2–6, the biggest discrepancy in the yields tabulated arose from quenching the reaction with triethylamine (TEA). A color change in the crude bacteriochlorin reaction mixture is often, but not always, apparent when TEA is added. If a color change is observed, it is generally a

transition from black to dark green. No change was observed in the intensity of absorption due to TEA addition. The result of no TEA addition is most apparent during purification. When purifications are performed without TEA addition, the reaction mixture remains dark and polar at the top of the column and only a small amount of product elutes. While some of the reactions in sections 2–6 may have low yields due to workup, yields were always treated comparatively and reactions were not repeated.

After considering the effect and potential consequences of adding TEA, a more reasonable practice is to quench reactions with solid NaHCO_3 followed by filtering. Using NaHCO_3 allows the reaction to be quenched without adding any other organics to the mixture. A saturated solution of NaHCO_3 can also be used but the separation is more time consuming.

II.C. Summary

Several major achievements arose from this project. (1) Two distinct methods for formation of $\text{BC-Br}^3\text{OMe}^5\text{Br}^{13}$ and $\text{BC-Br}^3\text{Br}^{13}$ were developed, and varying the type of Lewis acid controlled the product distribution. Each method affords synthetically useful yields. (2) Yields were optimized by varying the temperature, solvents, additives, and concentration of starting materials. (3) The condensation methods eliminate formation of chlorin byproduct and trace amounts of other byproducts are easy to separate.

Ultimately, through investigation of temperature, solvent, concentration, Lewis acid, and additive effects, separate reactions afforded $\text{BC-Br}^3\text{OMe}^5\text{Br}^{13}$ or $\text{BC-Br}^3\text{Br}^{13}$ in 42% or

30%, isolated yield, respectively. The best conditions involve relatively mild Lewis acids. The requirement for so many equivalents of acid and additive for the self-condensation reaction is unknown. Also unknown is why different Lewis acids afford different products and why only one amine (2,6-DTBP) works in useful yield for formation of **BC-Br³OMe⁵Br¹³** and why formation of **BC-Br³B¹³** does not require an additive. New studies will need to be developed to probe the answers to the remaining important mechanistic questions.

II.D. Experimental Section

II.D.1 General Procedure for Acid Survey: Each reaction was performed in an oven-dried 3 mL microreaction vial, fitted with a Teflon seal, and purged with argon until the vial was cooled to RT. Reactions were performed at a concentration of 10-15 mM (0.025 to 0.030 mmol) with 5 equivalents of Lewis acid and 50 equivalents of amine (if added). Most reactions were performed at RT. In the case of no base, the Lewis acid was added first and then a stock solution of the starting material (**DHDP-Br**) was added via syringe and stirred. In the cases where base was added, the base was added first, then the stock solution of starting material, followed by the Lewis acid. After ~15 min of stirring, each reaction was checked by TLC analysis and absorption spectroscopy for the presence of **BC-Br³B¹³** ($\lambda_{Qy} = 722$ nm), **BC-Br³OMe⁵Br¹³** ($\lambda_{Qy} = 728$ nm), starting material ($\lambda_{Qy} = \sim 338$ nm), or any intermediates. Most reactions were allowed to stir for 24 h, while a few with low yields were allowed to stir for 48 h. The reactions were followed by observing color change, as well as

by TLC analysis [CH_2Cl_2 /hexanes (1:1)] and absorption spectroscopy. Toward the end of the study, crude yields were taken to determine if the yield was sufficient to warrant purification. If the yield was below 15%, or both products were present to a large extent, the product was not separated and only a crude yield is reported. Single column purification was performed [silica, hexanes/ CH_2Cl_2 (1:1)] when one bacteriochlorin was present. A second column [silica, hexanes] was performed to separate **BC-Br³Br¹³** and **BC-Br³OMe⁵Br¹³** when both products were present in more than trace amounts.

II.D.2 General Acid-Only Procedure: Each reaction was performed in an oven-dried 3 mL microreaction vial fitted with a Teflon seal, and purged with argon until the vial was cooled to RT. Reactions were performed at a concentration of 10-15 mM (0.025 to 0.030 mmol) with 5 equivalents of Lewis acid in most cases. (An increase in the number of acid equivalents and/or an increase/decrease in concentration did not improve the yield of bacteriochlorin, nor did decreasing the equivalents of acid afford a comparable yield.) Most reactions were stirred at RT. After 24 h, each reaction was checked by absorption spectroscopy for the presence of **BC-Br³Br¹³** ($\lambda_{\text{Qy}} = 722 \text{ nm}$), **BC-Br³OMe⁵Br¹³** ($\lambda_{\text{Qy}} = 728 \text{ nm}$), starting material ($\lambda_{\text{Qy}} = \sim 338 \text{ nm}$), or any intermediates. A few reactions with low yields were allowed to stir for 48 h. The reactions were followed by observing color changes, as well as with TLC analysis and absorption spectroscopy. Reactions that were dark green or black in color tended to have better yields. Toward the end of the study, crude yields were taken to determine if the yield was sufficient to warrant purification. If the yield

was below 15%, or if both products were present to a large extent, the product was not separated and only a crude yield is reported. Single column purification was performed [silica, hexanes/CH₂Cl₂ (1:1)] when one bacteriochlorin was present. A second column [silica, hexanes] was performed to separate **BC-Br³Br¹³** from **BC-Br³OMe⁵Br¹³** when both products were present in more than trace amounts.

II.D.3 General Acid Plus Additive Procedure: Each reaction was performed in an oven-dried 3 mL microreaction vial fitted with a Teflon seal, and purged with argon until the vial was cooled to RT. Reactions were kept at a concentration of 10-15 mM (0.025 to 0.030 mmol) with 5 equivalents of Lewis acid in most cases. Most reactions were stirred at RT. In the cases where base was added, the base was added first, then the stock solution of starting material, followed by the Lewis acid. After 24 h of stirring at RT, each reaction was checked by absorption spectroscopy for the presence of **BC-Br³Br¹³** (722 nm), **BC-Br³OMe⁵Br¹³** (728 nm), starting material (~338 nm), or any intermediates. A few reactions with low yields were allowed to stir for 48 h. The reactions were followed by observing color changes, as well as by TLC analysis and absorption spectroscopy. Reactions that were dark green or black in color tended to afford better yields. Toward the end of the study, crude yields were taken to determine if the yield was sufficient to warrant purification. If the yield was below ~15%, or both products were present to a large extent, the products were not separated and only a crude yield is reported. Single column purification was performed [silica, hexanes/CH₂Cl₂ (1:1)] when one bacteriochlorin was present. A second column [silica,

hexanes] was performed to separate **BC-Br³Br¹³** from **BC-Br³OMe⁵Br¹³** when both products were present in more than trace amounts.

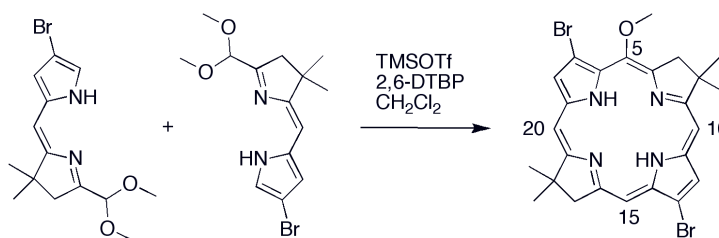
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Chapter III: Scale-Up Procedure for Formation of $\text{BC-Br}^3\text{OMe}^5\text{Br}^{13}$

III.A. Objectives

To verify the versatility of the route to $\text{BC-Br}^3\text{OMe}^5\text{Br}^{13}$, the condensation of DHDP-Br to $\text{BC-Br}^3\text{OMe}^5\text{Br}^{13}$ was performed on the gram scale (Scheme III.1). Previously, this reaction was performed on the 10, 100, 200, and 300 mg scales, affording a maximum of 42% (spectroscopic) yield and only a trace of $\text{BC-Br}^3\text{Br}^{13}$.¹ This overnight condensation reaction afforded green crystals after a relatively quick column purification and washing with hexanes.



Scheme III.1 - Formation of $\text{BC-Br}^3\text{OMe}^5\text{Br}^{13}$

III.B. Results and Discussion

1. Synthesis: The resulting procedure for the scale-up of $\text{BC-Br}^3\text{OMe}^5\text{Br}^{13}$ is as follows: to an oven dried 250 mL round bottomed flask, DHDP-Br (1.15 g, 3.50 mmol, 15.0 mM) and anhydrous CH_2Cl_2 (233 mL) were added under an argon atmosphere. A sample of 2,6-DTBP (7.73 mL, 35.0 mmol, 150 mM) was added via syringe. The reaction was stirred vigorously at 0°C for 15 min before adding TMSOTf (3.10 mL, 17.5 mmol, 75.0 mM) via

syringe. Immediately after addition, the reaction mixture changed from brown to green and darkened. The reaction was allowed to stir overnight and was quenched with saturated aqueous NaHCO_3 (instead of TEA). Purification [silica, hexanes/ CH_2Cl_2 (1:1)] was performed with HPLC-grade solvents. During purification, **BC-Br³Br¹³** (pale green) eluted first followed by **BC-Br³OMe⁵Br¹³** (dark green). 2,6-DTBP eluted with **BC-Br³Br¹³** and was removed by treatment overnight in a high vacuum oven at $T = 40\text{ }^\circ\text{C}$. (Heating on a high vacuum evaporator is not sufficient to remove the high boiling amine.) The resulting sample of **BC-Br³OMe⁵Br¹³** was dried overnight followed by washing with HPLC-grade hexanes to remove residual grease. In this manner, the title compound was isolated in 27% yield (260 mg).

2. ¹H and ¹³C NMR Spectroscopy: The ¹H NMR spectrum of **BC-Br³OMe⁵Br¹³** provides exhibits a singlet at 4.3 ppm ($\text{CH}_3\text{O}-$) as well as three peaks between 8.4 and 8.8 ppm (five meso- and β -protons). The ¹H NMR signal at 4.35 ppm was determined to be the methyl due to integration indicating 3H's.

3. NOESY and TOCSY: NOESY revealed interactions between β and meso protons as well as between the geminal dimethyl groups (8, 8, 18, 18) and both meso and aliphatic protons (7, 7, 17, 17). TOCSY displayed interactions between the meso and aliphatic protons as well as between the β protons and the NH protons. Finally, the interaction between 15 and

17 was verified. No interaction between the methoxy methyl group and any other proton was observed. Correlations are shown in figure III.1 and assignments are shown in Chart III.1.

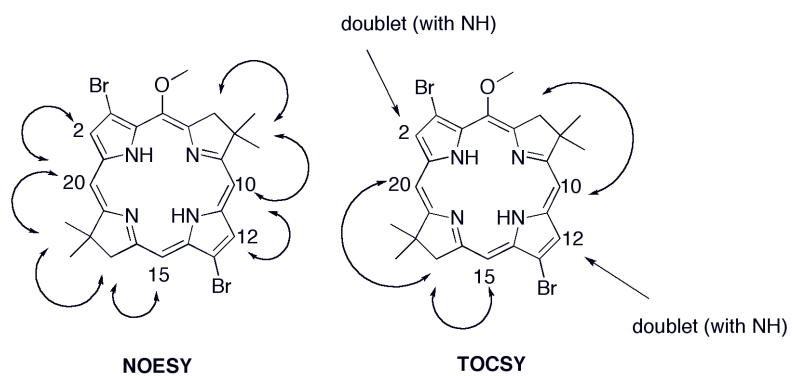


Figure III.1 - NOESY and TOCSY ^1H correlations

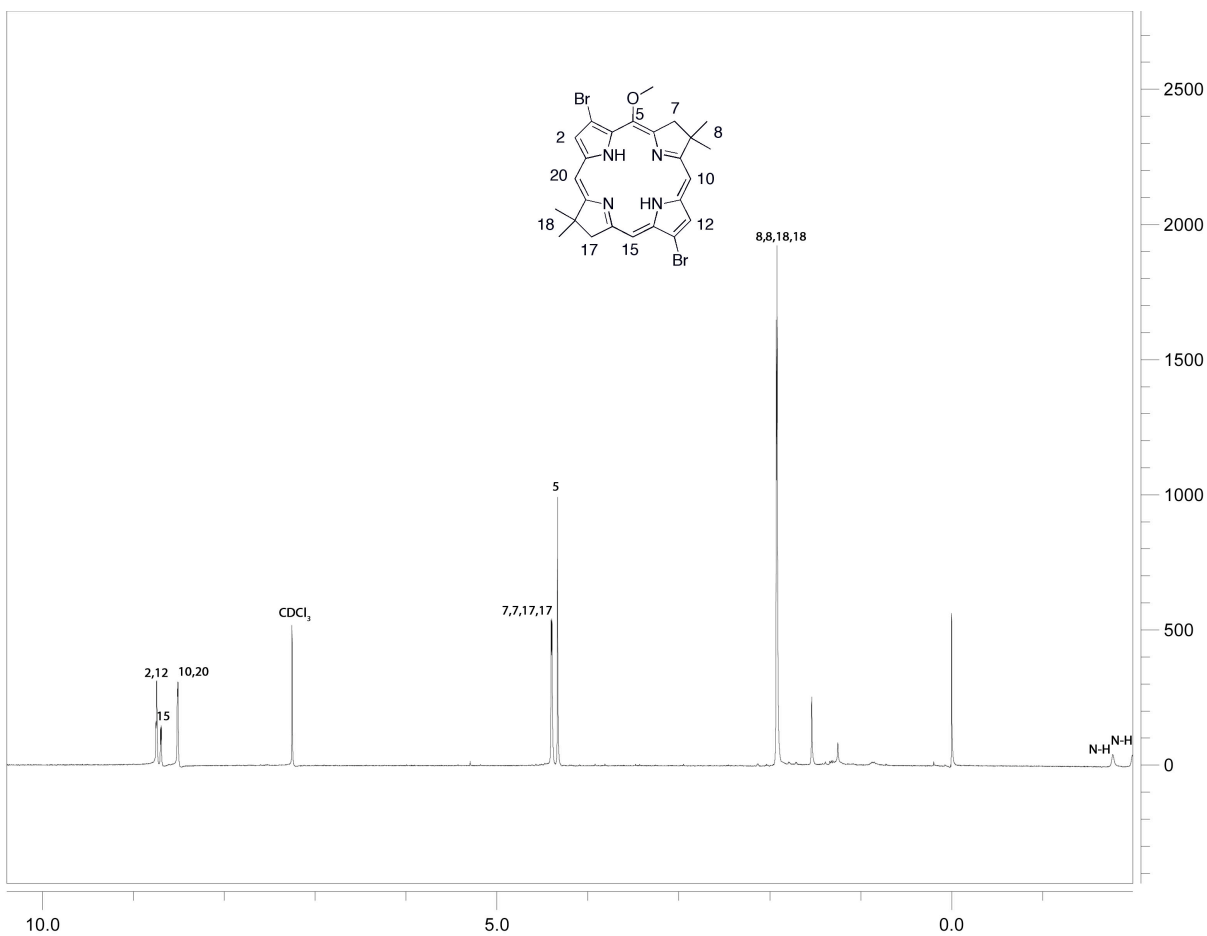


Chart III.1 - Assigned ^1H NMR spectrum of $\text{BC-Br}^3\text{OMe}^5\text{Br}^{13}$

4. Absorption and Emission Spectroscopy: The spectra below were acquired in toluene. The absorbance of $\text{BC-Br}^3\text{OMe}^5\text{Br}^{13}$ ($\lambda_{\text{Qy}} = 722$ nm) is blue-shifted compared to that of $\text{BC-Br}^3\text{Br}^{13}$ ($\lambda_{\text{Qy}} = 728$ nm). The emission spectrum displayed a 6-nm Stokes shift ($\lambda_{\text{em}} = 728$ nm).

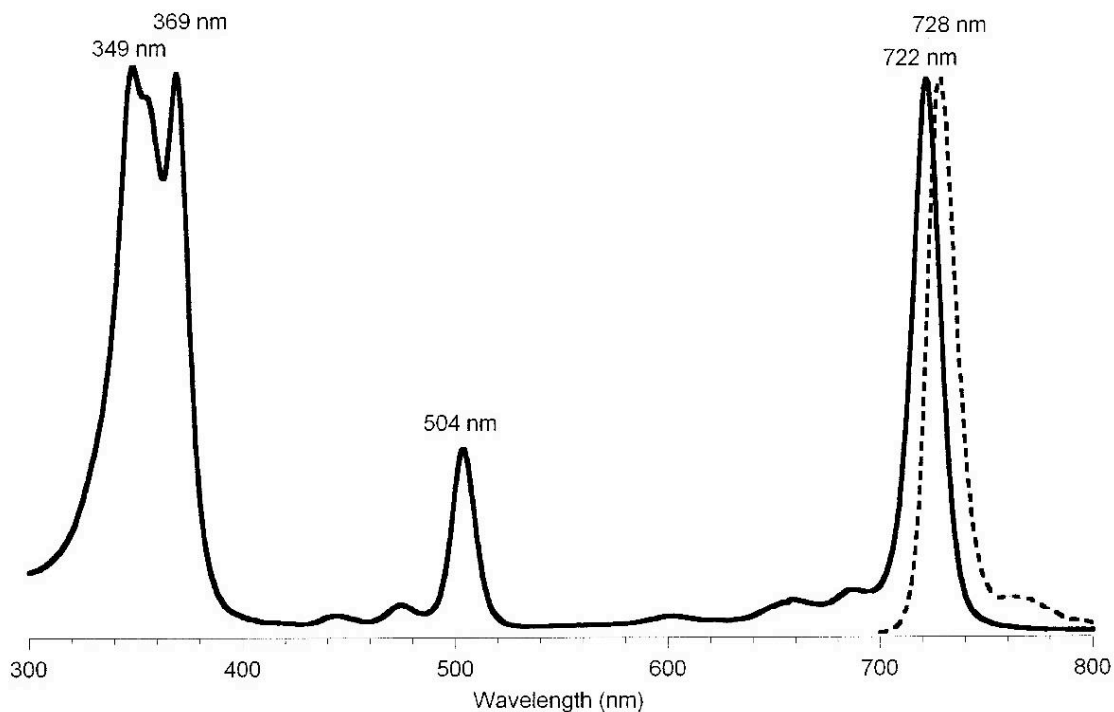


Chart III.2 – Normalized absorption and emission spectra of BC-Br³OMe⁵Br¹³ in toluene

5. Mass Spectrometry: The mass spectrum of BC-Br³OMe⁵Br¹³ is consistent with the proposed formula C₂₅H₂₆Br₂N₄O. ESI-MS obsd 556.04495, calcd 556.04734 (C₂₅H₂₆Br₂N₄O).

III.C. Summary

The reaction proceeded smoothly in excellent yield (260 mg, 27%) and workup was performed in a straightforward manner. A benefit of this reaction is the scalability and the yield of product formation without chlorine formation and only a minimal amount of BC-

Br³Br¹³, which is readily separable. In addition, through 2-D NMR studies the protons signals were assigned. The discrepancy in yields between small and large scale could be due to a discrepancy between spectroscopic and gravimetric yield calculations, combined with a general decrease in yield from scaling the reaction.

III.D. Experimental Section

3,13-Dibromo-5-methoxy-8,8,18,18-tetramethylbacteriochlorin (BC-Br³OMe⁵Br¹³). [*As described in III.B.1*] The reaction was run in an oven dried 250 mL round bottomed flask. A sample of **DHDP-Br** (1.15 g, 3.50 mmol, 15.0 mM) was placed in the flask and anhydrous CH₂Cl₂ (233 mL) was added under an argon atmosphere. A sample of 2,6-DTBP (7.73 mL, 35.0 mmol, 150 mM) was added via syringe. The reaction was stirred vigorously at 0°C for 15 min before adding TMSOTf (3.10 mL, 17.5 mmol, 75.0 mM) via syringe. The reaction changed from brown to green/black shortly after TMSOTf addition. The reaction was allowed to stir overnight, keeping the reaction at 0 °C for 2 h, after which the reaction was allowed to warm to room temperature. The reaction was quenched after 18 h with saturated aqueous NaHCO₃ (200 mL). The mixture was diluted with CH₂Cl₂ (100 mL), and the organic layer was extracted with HPLC-grade CH₂Cl₂. The organic layer was washed (brine), dried (Na₂SO₄), and concentrated. The crude mixture was concentrated under high vacuum (50 °C) to remove the remaining 2,6-DTBP, although not all could be removed after ~30 min. The crude mixture was dissolved in a minimal amount of HPLC-grade CH₂Cl₂ and purified through a silica column [hexanes/CH₂Cl₂ (1:1); HPLC-

grade solvents] to afford green crystals upon drying. To remove residual grease from the product, the sample was washed several times with HPLC-grade hexanes and dried overnight under high vacuum to afford 260 mg (27%) of product. Most of the 2,6-DTBP was present in the **BC-Br³Br¹³** fraction (with some trace **BC-Br³OMe⁵Br¹³**) isolated from the column. This was removed by high vacuum evaporation and in a high vacuum oven (10 mg, <1% total weight). ¹H NMR (300 MHz, CDCl₃) δ -1.90 (br, 1H), -1.78 (br, 1H), 1.90 (d, $J = 1.66$ Hz, 12H), 4.35 (s, 3H), 4.4 (d, $J = 20.90$ Hz, 4H), 8.5 (d, $J = 1.92$ Hz, 2H), 8.7 (d, $J = 2.47$ Hz, 1H), 8.75 (d, $J = 2.47$ Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 30.786, 31.014, 45.550, 45.785, 47.271, 51.700, 64.409, 96.211, 96.863, 105.128, 112.218, 124.176, 124.624, 126.535, 133.845, 134.694, 135.467, 154.341, 161.067, 169.522, 170.265; ESI-MS obsd 556.04495, calcd 556.04734 (C₂₅H₂₆Br₂N₄O); λ_{abs} (toluene) = 722 nm (**BC-Br³OMe⁵Br¹³**); λ_{em} (toluene) = 728 nm (**BC-Br³Br¹³**).

III.E. References

- (1) Ptaszek, M.; Meneely, K. R.; Lindsey, J. S. (*Unpublished observations.*)

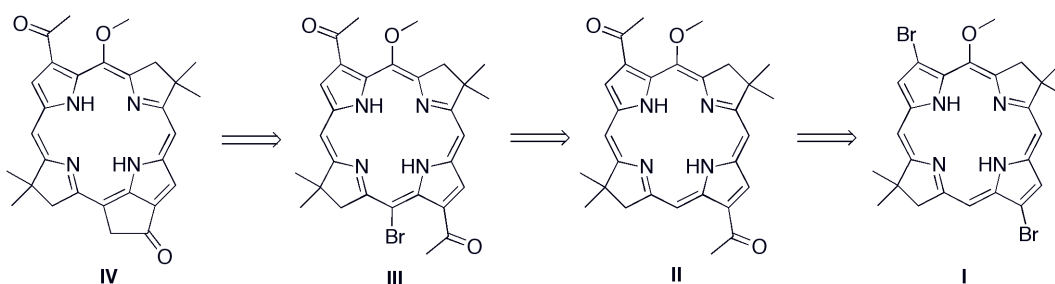
Chapter IV: Derivatization of $\text{BC-Br}^3\text{OMe}^5\text{Br}^{13}$

IV.A. Objectives and Methods

$\text{BC-Br}^3\text{OMe}^5\text{Br}^{13}$ is a useful scaffold for derivatizations. Several compounds were synthesized to establish benchmarks for reactivity and electronic properties. There were two main goals of this project. (1) The primary goal was to functionalize $\text{BC-Br}^3\text{OMe}^5\text{Br}^{13}$ by installing a five-membered carbonyl-containing exocyclic ring between positions 13 and 15 to create a 3-acetyl-5-methoxy-8,8,18,18-tetramethylbacteriooxophorbine (**IV**) (Scheme IV.1). Both acetyl groups and the exocyclic ring of oxophorbines produce a characteristic bathochromic shift, pushing the Q_y absorbance band further into the near-IR.¹ (2) The second goal was to install acetyl, formyl, and TIPS-ethynyl groups at the 3 and 13 positions of $\text{BC-Br}^3\text{OMe}^5\text{Br}^{13}$. 3,13-diformyl and 3,13-diacetylbacteriochlorins have previously been synthesized in good yield.^{2,3} Chlorins have also been derivatized with acetyl, formyl, and ethynyl-TIPS groups and positions 3 and 13.^{1,4,5} The ultimate goals of all the above reactions were to examine the effect of substituents on the electronic properties (such as absorption, emission, and energy transfer) of the macrocycle so the bacteriochlorins spectroscopic properties can be tuned for fundamental studies and efficacy in various medical and technological applications.

A three-step derivatization strategy was selected for $\text{BC-Br}^3\text{OMe}^5\text{Br}^{13}$. Scheme IV.1 illustrates the proposed route. In the first step, $\text{BC-Br}^3\text{OMe}^5\text{Br}^{13}$ is diacetylated via Pd-mediated Stille coupling. Pd couplings are generally facile at the β -positions of

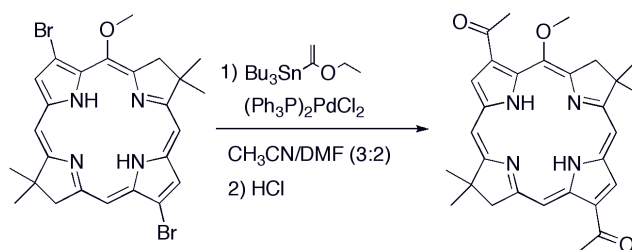
bacteriochlorins and proceed relatively quickly in moderate to good yields.^{2,3} The second step was 15-bromination with NBS. Chlorins readily undergo favorable 15-bromination,^{6,7} therefore the same effect was expected for bacteriochlorins. The third step was a Pd-mediated cyclization to close the isocyclic ring.¹ This ring formation has a precedent in chlorin chemistry and the reaction was expected to be successful. The resulting bacteriooxophorbine would be valuable for a wide variety of studies.



Scheme IV.1 – Retrosynthetic analysis of 3-acetyl-5-methoxybacteriooxophorbine from BC-Br³OMe⁵Br¹³

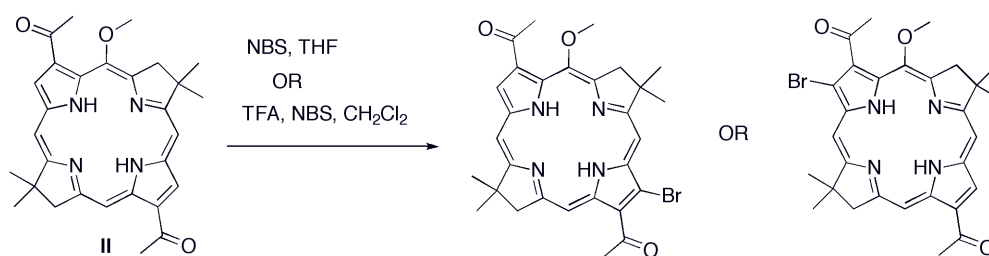
IV.B. Results and Discussion

1. Acetylation: Two acetyl groups were installed with a Stille coupling reaction. 3,13-Diacetyl-5-methoxy-8,8,18,18-tetramethylbacteriochlorin (BC-Ac³OMe⁵Ac¹³) was isolated as the major product in 70% yield along with several other unidentified products and a small amount of monoacetyl-5-methoxybacteriochlorin (Scheme IV.2).²



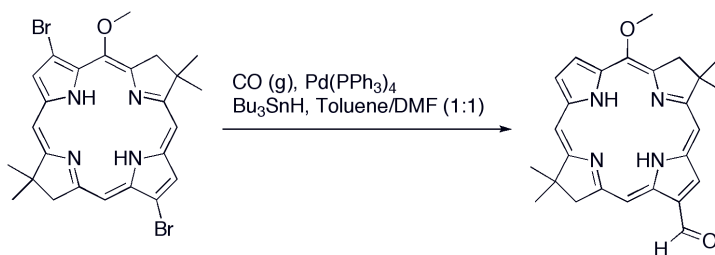
Scheme IV.2 - Acetylation of BC-Br³OMe⁵Br¹³

2. Bromination: The bromination of **BC-Ac³OMe⁵Ac¹³** was carried out under both neutral^{1,4,6} and acidic conditions.⁷ Interestingly, no 15-bromo product was isolated. Instead, a β -Br product (2 or 12) was isolated (22% yield, neutral conditions; trace yield, acidic conditions) in addition to several other unidentified products. These results were surprising considering the ability to brominate **BC-Br³OMe⁵Br¹³** at the 15-position.⁶ 2-D NMR experiments (NOESY, gHMBC, gHSQC) provided inconclusive results as to the position of the bromination. A single crystal structure is necessary for accurate characterization. This result provides insight into the greater reactivity of the β -pyrrole site versus 15-position for bromo-substitution.



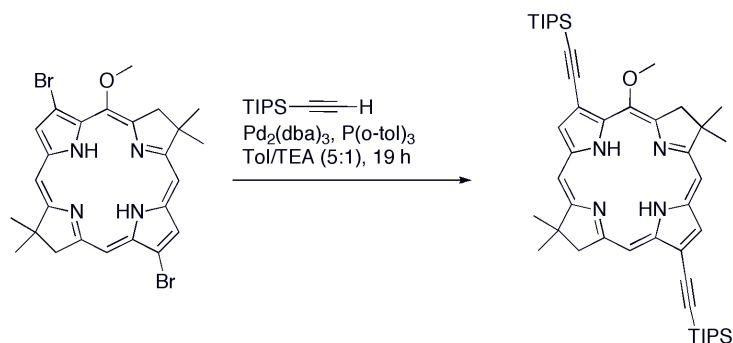
Scheme IV.3 - Bromination of BC-Ac³OMe⁵Ac¹³

3. Formylation: A formylation reaction was performed under the same conditions as those used to synthesize 3,13-diformylbacteriochlorin.² The formylation reaction is straightforward in principle; however, due to unknown reasons, the reaction produced multiple products, including a trace amount of 5-methoxy-8,8,18,18-tetramethylbacteriochlorin (debrominated product) in addition to the main product, a mono-formylbacteriochlorin (30% yield). The mono-formylbacteriochlorin structure was solved using NOESY NMR and determined to be 13-formyl-5-methoxybacteriochlorin (Scheme IV.4).



Scheme IV.4 - Formylation of BC-Br³OMe⁵Br¹³

4. Sonogashira Coupling: A Sonogashira coupling reaction modeled after the reaction similar to that performed on a chlorin,^{4,5} was done with **BC-Br³OMe⁵Br¹³**. The reaction afforded two main products, 3,13-bis(triisopropylsilylethynyl)-5-methoxybacteriochlorin (4.7% yield) and an unknown compound with $\lambda_{Qy} = 735$ nm. Many other impurities were isolated but structures were not determined. The title compound has a long wavelength absorption band $\lambda_{Qy} = 747$ nm. (Scheme IV.5)



Scheme IV.5 – TIPS-ethynyl substitution via Sonogashira coupling

5. Related Work: The spectral properties of derivatives of **BC-Br³OMe⁵Br¹³** are compared with selected analogues derived from **BC-Br³Br¹³** in table IV.1. The 3,13-diacetyl analogues have a 26 nm difference in absorbance wavelength (blue-shifted for the 5-methoxy compound). The 13-formyl analogues, however, have only a 1 nm red-shift in the presence of the 5-methoxy group. Further comparisons are not yet possible.

Table IV.1 – Absorption features of 5-H- vs. 5-MeO Bacteriochlorins

Compound	BC-Br³Br¹³ derivative	BC-Br³OMe⁵Br¹³ derivative
	Absorbance (nm)	Absorbance (nm)
3,13-dibromo	728	722
3,13-diacetyl	768	742
13-formyl	731	732
3,13-TIPS-ethynyl	--	747
3,13-phenylethynyl	763	--

IV.C. Summary

Neutral conditions for 15-bromination afforded a mono- β -brominated (2 or 12) product. The results indicated β -substitution rather than a *meso*-substitution, although the precise location of the bromo-substitution (2 or 12) could not be determined. Acidic conditions were investigated and afforded a small amount of mono- β -bromination at either position 2 or 12. Accordingly, the bacteriooxophorbine could not be accessed through this route.

Diacetylation was successful based on the NMR and MS evidence and the product was isolated in 70% yield. The yield was better than that of the acetylation for **BC-Br³Br¹³**, which resulted in 55% yield.²

Conditions for diformylation afforded a trace amount of unidentified products as well as a mono-formylated product (30%). The result was similar for **BC-Br³Br¹³** but in that case, the 3,13-diformylbacteriochlorin was the major product (60%) and monoformylated product was the minor product (25%).²

Conditions for TIPS-ethynyl installation afforded two main products and many side products. The yield of this reaction has been much higher on the chlorin analogue.^{4,5} The result, therefore, was surprising and while this coupling has not been performed on **BC-Br³Br¹³**, the analogous phenylethynyl reaction afforded a 30% yield.³

Each bacteriochlorin compound provides new and valuable spectroscopic information. The effect of the methoxy group compared to no substituent is apparent in the position of the long-wavelength absorption band. The 15-position is unreactive towards

bromination (in the case of **BC-Ac³OMe⁵Ac¹³**). This surprising reactivity requires further exploration. Bacteriochlorins have important roles in nature and there is an opportunity for use of synthetic bacteriochlorins in biological and technological applications.

IV.D. Experimental Section

HPLC-grade solvents were used for column purifications and washing of final compounds. ¹H NMR and ¹³C NMR spectra were collected at 300 MHz and 75 MHz, respectively.

3,13-Diacetyl-5-methoxy-8,8,18,18-tetramethylbacteriochlorin (I). Compound **I** was synthesized following a known procedure³ for the analogue lacking the 5-methoxy group. To a 5 mL oven-dried Schlenk flask, **BC-Br³OMe⁵Br¹³** (28 mg, 0.050 mmol, 0.010 M) and (Ph₃P)₂PdCl₂ (14 mg, 0.020 mmol, 0.0040 M) were added and the flask was pump-purged. CH₃CN (3 mL) and DMF (2 mL) were added and the flask was freeze-pump-thawed. The mixture was quickly treated with tributyl(1-ethoxyvinyl)tin (90 mg, 0.25 mmol, 0.050 M) under a stream of argon. The reaction was heated to reflux for 3 h and checked by TLC analysis [CH₂Cl₂/hexanes (1:1)]. The reaction was quenched with 10% HCl (~0.5 mL). The mixture was diluted with ethyl acetate and neutralized with saturated aqueous NaHCO₃. *(If not neutralized, the acid plus the heat used to remove the DMF causes cleavage of the methoxy group.)* The organic layer was separated and washed (water and brine), dried Na₂SO₄, and concentrated. Column purification was performed: silica [CH₂Cl₂ →

CH₂Cl₂/ethyl acetate (1:1)]. After two columns, the oily pink/purple product was isolated in 70% yield (17 mg). By ESI-MS and ¹H and ¹³C NMR spectroscopy, the evidence was consistent with the title compound accompanied by some mono-acetylchlorin product. After washing with hexanes, a solid pink/purple product was obtained and used immediately for the neutral bromination reaction: ¹H NMR (CDCl₃) δ -1.67 (s, 1H), -1.32 (s, 1H), 1.93 (d, *J* = 27.23 Hz, 12H), 3.08 (s, 3H), 3.16 (s, 3H), 4.18 (s, 3H), 4.38 (d, *J* = 11.55 Hz, 4H), 8.54 (s, 1H), 8.64 (dd, *J* = 4.95 Hz, 2H), 9.08 (d, 1H), 9.77 (s, 1H); ¹³C NMR (CDCl₃) δ 29.85, 30.99, 31.24, 33.15, 45.49, 46.09, 48.17, 51.62, 64.87, 97.58, 99.50, 99.80, 121.23, 125.65, 128.28, 129.07, 132.98, 135.10, 135.64, 135.68, 135.87, 157.20, 162.42, 169.14, 172.81, 196.95, 202.38; ESI-MS obsd 485.25401; calcd 485.25527 [(M + H)⁺, M = C₂₉H₃₂N₄O₃]; λ_{abs} [CH₂Cl₂/ethanol, (3:1)] = 742 nm.

Neutral Conditions for β-Bromo-3,13-diacetyl-5-methoxy-8,8,18,18-tetramethylbacteriochlorin. A reported procedure was followed for bromination under neutral conditions.^{5,6} To a 5 mL oven-dried Schlenk flask, **1** (17 mg, 0.035 mmol, 2.0 mM) and distilled THF (17.6 mL) were added. Recrystallized NBS (6.25 mg, 0.035 mmol) was added via syringe from a stock solution (0.1 M) of NBS in distilled THF. The reaction was allowed to stir vigorously for 1 h at RT and checked by TLC analysis [CH₂Cl₂/ethyl acetate (1:1)] and absorption spectroscopy. The reaction mixture was concentrated and purified by column chromatography [silica, CH₂Cl₂]. The pink solid (5.0 mg, 22% yield) was isolated and characterized: ¹H NMR (CDCl₃) δ -1.69 (s, 1H), -1.36 (s, 1H), 1.94 (d, *J* = 2.20 Hz,

12H), 3.01 (s, 3H), 3.17 (s, 3H), 4.15 (s, 3H), 4.37 (d, $J = 18.43$ Hz, 4H), 8.65 (d, $J = 5.77$ Hz, 1H), 9.09 (d, $J = 1.93$ Hz, 2H), 9.774 (s, 1H); ESI-MS obsd 563.16451, calcd 563.16578 [(M + H)⁺, M = C₂₉H₃₁BrN₄O₃]; λ_{abs} [CH₂Cl₂/ethanol, (3:1)] = 744 nm.

Acidic Conditions for β -Bromo-3,13-diacetyl-5-methoxy-8,8,18,18-tetramethylbacteriochlorin. A reported procedure was followed for bromination under acidic conditions.⁷ To a 50 mL round bottom flask, 3,13-diacetyl-5-methoxybacteriochlorin (19 mg, 0.040 mmol, 2.5 mM) and CH₂Cl₂/TFA (10:1, 14.40 mL : 1.5 mL) were added. The mixture was treated with recrystallized NBS (0.40 mmol, 0.40 mL, 0.10 M stock solution in CH₂Cl₂), and the mixture was stirred under argon for 30 min at RT. After ~30 min of stirring, a small sample of the reaction mixture was quenched with saturated aqueous NaHCO₃, extracted with ethyl acetate, and checked by absorption spectroscopy and TLC analysis [CH₂Cl₂/ethyl acetate (1:1)]. A 4 nm blue shift of the Q_y band was noted (738 nm versus 734 nm for starting reaction mixture) and the reaction was quenched after ~1 h with saturated aqueous NaHCO₃ (~175 mL). The organic layer was washed with brine (~125 mL), dried with Na₂SO₄, and concentrated. The product was identified by absorption spectroscopy. Only a trace amount of the β -bromo product and 2.9 mg of the starting material were isolated, therefore clean ¹H NMR spectroscopic results were not obtained. ESI-MS was not performed due to the lack of viability of the route. Data for the title compound: ¹H NMR (CDCl₃) δ -1.69 (s, 1H), -1.36 (s, 1H), 1.94 (s, 12H), 3.0 (s, 3H), 3.17

(s, 3H), 4.15 (s, 3H), 4.37 (d, $J = 18.43$ Hz, 4H), 8.65 (d, $J = 5.77$ Hz, 1H), 9.10 (s, 2H), 9.77 (s, 1H); λ_{abs} [CH₂Cl₂/ethanol, (3:1)] = 744 nm.

13-Formyl-5-methoxy-8,8,18,18-tetramethylbacteriochlorin. Following a procedure for formylation² of **BC-Br³Br¹³**, **BC-Br³OMe⁵Br¹³** (56 mg, 0.10 mmol, 20.0 mM) and Pd(PPh₃)₄ (230 mg, 0.20 mmol) were placed in an oven dried 5 mL flask. The flask was placed under high vacuum for 1 h. The flask was fitted with a reflux condenser and filled with CO (g). DMF (2.5 mL) and toluene (2.5 mL) were combined in a scintillation (20 mL) vial and bubbled with CO (g) for several minutes. The mixture of solvents was transferred to the flask, and CO (g) was bubbled through the flask with vigorous stirring for 2 h at 65 °C. The reaction was treated with Bu₃SnH (58.2 mg, 0.2 mmol). The reaction mixture was stirred for 10 min, whereupon a color change (green to purple) was noted. The reaction mixture was cooled and filtered through a celite pad (ethyl acetate). The filtrate was concentrated and purified three times by chromatography [silica, CH₂Cl₂; silica, hexanes → hexanes/ CH₂Cl₂ (1:1), silica, hexanes/CH₂Cl₂ (1:1)]. A polar decomposition product was observed on top of the column and 13-formyl-5-methoxy-8,8,18,18-tetramethylbacteriochlorin was isolated in 30% yield (12.9 mg); ¹H NMR (CDCl₃) δ -1.28 (s, 1H), -0.88 (s, 1H), 1.92 (d, $J = 3.85$ Hz, 12H), 4.34 (d, $J = 6.60$ Hz, 4H), 4.43 (s, 3H), 8.44 (s, 1H), 8.55 (s, 1H), 8.64 (dd, $J = 1.65, 1.92, 4.82$ Hz, 1H), 8.93 (dd, $J = 1.93, 2.2, 4.27$ Hz, 2H), 9.39 (s, 1H), 11.12 (s, 1H); ¹³C NMR (CDCl₃) δ 31.67, 31.41, 44.57, 46.80, 49.03, 50.64, 65.89, 96.04, 97.47, 100.22, 122.20, 122.45, 125.12, 126.25, 132.07, 134.35, 134.58,

135.42, 140.59, 160.01, 160.17, 167.37, 175.47, 188.29; ESI-MS obsd 429.22758, calcd 429.22905 [(M + H)⁺, M = C₂₆H₂₈N₄O₂]; λ_{abs} [CH₂Cl₂/ethanol, (3:1)] = 732 nm.

5-Methoxy-8,8,18,18-tetramethyl-3,13-bis[2-(trimethylsilyl)ethynyl]bacteriochlorin. Following a procedure for Sonogashira coupling for 3,13-dibromochlorins,⁴ **BC-Br³OMe⁵Br¹³** (55.8 mg, 0.10 mmol, 2.0 mM), Pd₂(dba)₃ (28 mg, 0.015 mmol), and P(*o*-tol)₃ (74 mg, 0.12 mmol) were placed in an oven dried 100 mL Schlenk flask. The flask was pump-purged with argon and anhydrous solvents (toluene/TEA (5:1), 50 mL) were added. The flask was freeze-pump-thawed and the mixture was treated with TIPS-acetylene (55 mg, 0.30 mmol). The reaction mixture was submitted to vigorous stirring for ~19 h at 55 °C. The reaction was checked by absorption spectroscopy. The reaction mixture was cooled, concentrated, and purified [silica, hexanes → hexanes/CH₂Cl₂ (1:1)]. The first spot ($\lambda_{\text{Qy}} = 747$ nm) and the second spot ($\lambda_{\text{Qy}} = 735$ nm) were isolated. The product with absorption of $\lambda_{\text{Qy}} = 747$ nm is the title compound while the product with absorption of $\lambda_{\text{Qy}} = 735$ nm is unknown. Data for the title compound: ¹H NMR (CDCl₃) δ -1.84 (s, 1H), -1.63 (s, 1H), 1.34 (m, 42H), 1.92, (d, *J* = 1.65 Hz, 12H), 4.38 (d, *J* = 7.42 Hz, 4H), 4.42 (s, 3H), 8.47 (d, *J* = 3.57 Hz, 2H) 8.73 (d, *J* = 1.93 Hz, 1H), 8.77 (d, *J* = 2.48 Hz, 1H), 8.84 (s, 1H); ESI-MS obsd 761.49723, calcd 761.50099 [(M + H)⁺, M = C₄₇H₆₈N₄OSi₂]; λ_{abs} [CH₂Cl₂/ethanol, (3:1)] = 747 nm.

IV.E. References

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