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Regioselective 15-Bromination and Functionalization of a Stable Synthetic Bacteriochlorin

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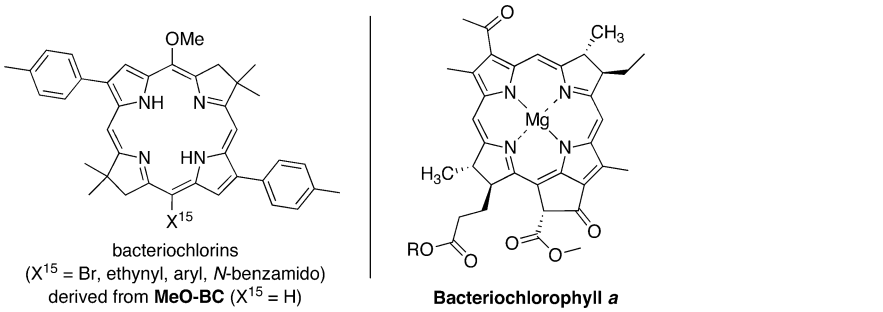
Received April 15, 2007



5-Methoxy-8,8,18,18-tetramethyl-2,12-di-*p*-tolylbacteriochlorin (**MeO-BC**) undergoes regioselective electrophilic bromination with NBS to give the 15-bromo analogue (**MeO-BC-Br^{15}**) in 85% yield. By contrast, the bacteriochlorin lacking the 5-methoxy group (8,8,18,18-tetramethyl-2,12-di-*p*-tolylbacteriochlorin, **H-BC**) gives a mixture of two monobromo- and two dibromobacteriochlorins. Deuterium exchange of both bacteriochlorins (**H-BC** and **MeO-BC**) in acidic media (TFA-*d*) occurs preferentially at the β-pyrrole positions (3, 13) > unhindered meso-positions (5, 15 for **H-BC**; 15 for **MeO-BC)** > hindered meso-positions (10, 20). The 15-bromo-5-methoxybacteriochlorin **MeO-BC-Br^{15}** was subjected to three types of Pd-mediated coupling reactions (Suzuki, Sonogashira, Hartwig−Buchwald) to give six bacteriochlorins bearing functional groups at the 15-position (49% to 85% yield). The groups include 4-(*tert*-butoxycarbonylmethoxy)phenyl, 4-pyridyl, 3,5-diformylphenyl, phenylethynyl, TIPS-ethynyl, and *N*-benzamido. The presence of the 15-ethynyl moiety shifts the position of the long-wavelength Q_y band from 732 nm to ~753 nm. The ability to introduce a range of groups at a specific site enables synthetic bacteriochlorins to be tailored for a variety of applications.

Introduction

We recently developed a concise rational synthesis of stable bacteriochlorins.[1] The bacteriochlorins are stable to adventitious oxidation by virtue of the presence of a geminal dimethyl group in each of the two reduced, pyrroline rings. The synthetic bacteriochlorins exhibit the characteristic absorption features of naturally occurring bacteriochlorins, namely strong absorption in the near-UV and the near-IR spectral regions. To our knowledge, the only other bacteriochlorins bearing geminal-dialkyl groups in both pyrroline rings include members of the tolyporphin family of natural products,[2] of which tolyporphin A has been the target of a lengthy total synthesis by Kishi,[3] and synthetic bacteriochlorins derived from β-alkyl-substituted porphyrins by vicinal dihydroxylation followed by pinacol rearrangement.[4] Routes to bacteriochlorins that lack this stabilizing structural motif include the derivatization of naturally occurring chlorophylls, manipulation of naturally occurring bacteriochlorophylls, and reduction of synthetic porphyrins or chlorins.[5]

The access to stable bacteriochlorins holds promise for a number of applications where strong absorption in the near-IR

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10.1021/jo070785s CCC: $37.00
Published on Web 06/13/2007

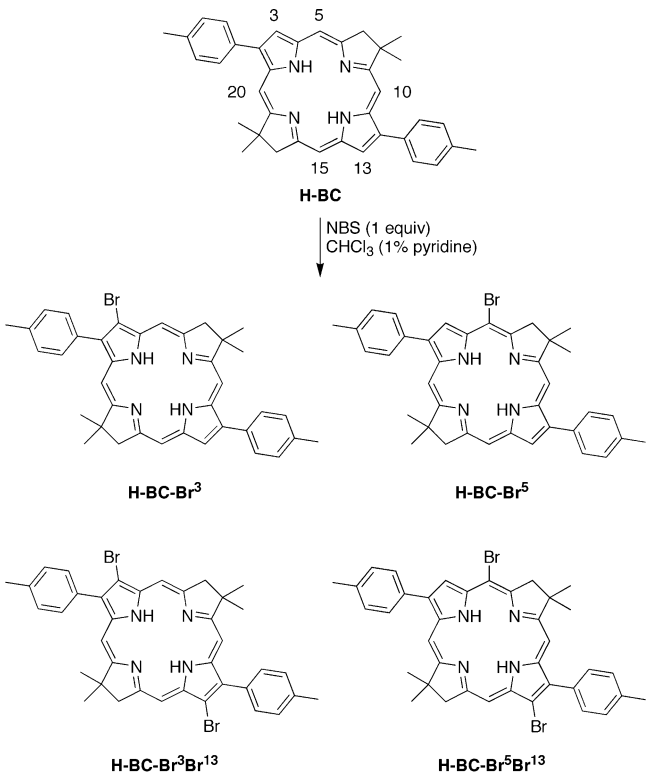
spectral region is essential. In photomedical applications, photosensitizers and optical imaging agents are desired that strongly absorb near-IR light, which affords deep penetration in soft tissue.[6] In diagnostics applications, compounds with sharp, wavelength-tunable absorption/emission bands in the near-IR would be useful as fluorescent markers.[7] In artificial photosynthesis, molecular absorbers that capture the large fraction of sunlight that is in the near-IR are essential contributors to the overall solar-conversion efficiency.[8] All such applications share a common design requirement for the ability to tailor the substituents at the perimeter of the macrocycle, such as introducing groups to modify solubility or enable conjugation to biological targeting agents, a surface, or another chromophore.

The few bacteriochlorins that have been used in photomedicine generally are naturally occurring bacteriochlorins themselves (e.g., tolyporphins)[9] or derivatives therefrom, particularly from bacteriochlorophyll *a*.[10] Relatively few synthetic modifications have been carried out with naturally occurring bacteriochlorins such as bacteriochlorophyll *a*, owing to the presence of a full complement of β-pyrrolic substituents and limited stability of the bacteriochlorin toward oxidation and other side reactions.[11] In this paper, we report the regioselective bromination of a bacteriochlorin and use of the resulting bromobacteriochlorin as a versatile building block in the synthesis of a variety of tailored bacteriochlorins.

Results and Discussion

1. Halogenation of Bacteriochlorins. Two synthetic bacteriochlorins (**H-BC**, **MeO-BC**)[1] were available for studies of halogenation. The bromination or iodination was performed according to literature procedures that have been employed for porphyrins or chlorins.[12−15] The bromination of **H-BC** (5-substituent = H) with NBS (1 equiv) in $CHCl_3$ (1% pyridine) was examined. The reaction was complete at room temperature within 10 min. ^{1}H NMR spectroscopy of the crude reaction mixture showed the presence of the following components: **H-BC-Br^3** (32%), **H-BC-Br^5** (21%), **H-BC-Br^{3}Br^{13}** (11%), **H-BC-Br^{5}Br^{13}** (4%), and unreacted **H-BC** (32%) (Scheme 1). The crude reaction mixture was separated into two fractions: the first fraction consisted of a mixture of the two dibromobacteriochlorins, whereas the second fraction consisted of the two monobromobacteriochlorins. Further purification was unsuccessful; however, NOESY spectra of each fraction gave a clear view of the substitution pattern (see the Supporting Information for detailed ^{1}H NMR spectra and NOESY experiments).

SCHEME 1



There are three possible monobromobacteriochlorins (and nine possible dibromobacteriochlorins) given the presence of three distinct sites for bromination: (i) the β (3 or 13)-position flanking each *p*-tolyl group, (ii) the unhindered meso (5 or 15)-position, and (iii) the sterically hindered meso (10 or 20)-position. The fewer number of products stems from bromination solely at the β-position and unhindered meso-position, with no bromination of the sterically hindered meso-position. The β-positions were more than twice as reactive as the unhindered meso-positions, as measured by the total bromination at the

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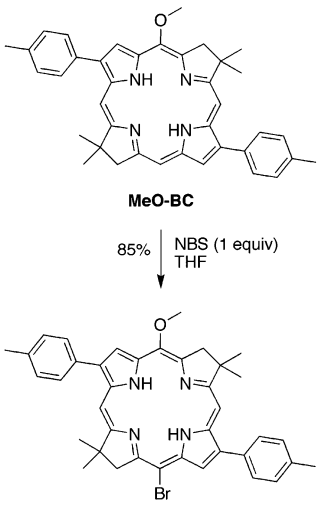
TABLE 1. ^{1}H NMR Chemical Shifts for Bacteriochlorins with Bromo Substituents[a]

position	H-BC δ	H-BC-Br^5 δ ($\Delta\delta$)	H-BC-Br^3 δ ($\Delta\delta$)	H-BC-Br^{5}Br^{13} δ ($\Delta\delta$)	H-BC-Br^{3}Br^{13} δ ($\Delta\delta$)	MeO-BC δ	MeO-BC-Br^{15} δ ($\Delta\delta$)
5	8.82		8.99 (+**0.17**)		8.98 (+**0.16**)		
10	8.86	8.73 (−0.13)	8.83 (−0.03)	8.52 (−**0.34**)	8.62 (−**0.24**)	8.78	8.82 (+0.04)
15	8.82	8.70 (−0.12)	8.78 (−0.04)	8.92 (+0.10)	8.98 (+**0.16**)	8.68	
20	8.86	8.81 (−0.05)	8.62 (−**0.24**)	8.83 (−0.03)	8.62 (−**0.24**)	8.81	8.77 (−0.04)
3	8.73	9.04 (+**0.31**)		9.06 (+**0.33**)		8.94	8.98 (+0.04)
13	8.73	8.70 (−0.03)	8.71 (−0.02)			8.63	9.04 (+**0.41**)
2a	8.13	8.11 (−0.02)	8.02 (−**0.11**)	8.10 (−0.03)	8.01 (−**0.12**)	8.14	8.11 (−0.03)
12a	8.13	8.08 (−0.05)	8.10 (−0.03)	7.98 (−**0.15**)	8.01 (−**0.12**)	8.10	8.10 (0)

[a] In $CDCl_3$ at 298 K. Significant shifts ($\Delta\delta$) are shown in bold.

former (58%) versus the latter (25%) sites. All further attempts with variation of reaction conditions and halogenating agent (including Br_2/pyridine, NIS, or I_2/$(CF_3CO_2)_2IC_6H_5$/pyridine) failed to give regioselective monobromination (see the Supporting Information), and difficult separation of the resulting mixtures limited the utility of this approach.

By contrast to the poor regioselectivity upon halogenation of **H-BC**, treatment of the 5-methoxybacteriochlorin (**MeO-BC**) with NBS in THF at room temperature for 30 min cleanly afforded the corresponding 15-bromobacteriochlorin (**MeO-BC-Br^{15}**) in 85% yield (eq 1). In some cases a trace of a



(1)

β-bromobacteriochlorin (putative 13-bromo derivative) was observed in the crude reaction mixture. Iodination of **MeO-BC** also was examined, but the expected 15-iodo product was not obtained. The 15-position is the least hindered of the three open meso sites (10, 15, 20) in **MeO-BC**; however, the regioselectivity of bromination of **MeO-BC** versus **H-BC**, particularly the preference for 15- versus 13-bromination, must stem in part from an electronic effect of the 5-methoxy substituent.

The resonances in the ^{1}H NMR spectra of the bromobacteriochlorins are assigned and summarized in Table 1. The resonances from the protons adjacent to the bromine atom exhibit characteristic shifts depending on the location at the perimeter of the macrocycle. Introduction of a bromine atom at the meso-position of a bacteriochlorin (**H-BC** or **MeO-BC**) causes the resonances from the adjacent β-protons (H^3 or H^{13}) to shift downfield (~0.3 ppm for **H-BC-Br^5**, **H-BC-Br^{5}Br^{13}**, and **MeO-BC-Br^{15}**). This result matches well with a previous ^{1}H NMR spectroscopic study of analogous meso-bromo-substituted chlorins, wherein a downfield shift (0.32 ppm) was observed of the β-pyrrolic proton adjacent to the meso-bromo substituent.[16] Introduction of a bromine atom at the β-position causes the resonances from adjacent meso-protons (H^5 or H^{15}) to shift downfield (~0.16 ppm for **H-BC-Br^3** or **H-BC-Br^{3}Br^{13}**). In addition, the resonances from the adjacent *p*-tolyl protons (H^{2a} or H^{12a}) are shifted upfield (~0.1 ppm) versus that of **H-BC**. The latter observation is useful to confirm the presence of β-bromo substitution in the crude mixture of bromobacteriochlorins, as well as to clarify the substitution pattern for more highly substituted bacteriochlorins.

2. Deuteration of Bacteriochlorins. Deuteration has long been employed to evaluate the reactivity of porphyrinic macrocycles toward electrophilic attack.[17] Woodward first reported that chlorins possessing no meso substituents and a partial or full complement of β-substituents undergo deuteration preferentially at the meso sites (15- and 20-positions) flanking the pyrroline ring rather than the meso sites (5, 10) distal to the pyrroline ring.[18] More recent studies of fully unsubstituted chlorins showed that the meso positions flanking the pyrroline ring (15- and 20-position) are the most reactive (among four meso sites and six β-pyrrolic sites) toward deuteration in acidic media.[15] To our knowledge, no study of the deuteration of bacteriochlorins has been reported.

In preparation for a study of bacteriochlorin deuteration, the resonances from the meso- and the β-protons of **H-BC** and **MeO-BC** were assigned by NOESY spectra (in TFA-*d* at 25 °C). Unlike chlorins, which gave selective meso- versus β-substitution,[15] a considerable amount of deuteration occurred at the β-positions in TFA-*d* during the course of preliminary spectral measurements (~8 h at 25 °C). Indeed, ^{1}H NMR spectroscopic examination in $CDCl_3$ of the isolated bacteriochlorin product in each case identified the deuterated product to be **H-BC-D^{3}D^{13}** (~70% deuterated, partial deuteration at the 5- and 15-positions) or **MeO-BC-D^{3}D^{13}** (~60% deuterated, partial deuteration at the 15-position) (Scheme 2).

It should be noted that the treatment of a free base bacteriochlorin with a strong acid affords the corresponding dication. Indeed, **H-BC** (or **MeO-BC**) in TFA solution promptly underwent protonation to form the putative **H-BC-2H^{2+}** (or **MeO-BC-2H^{2+}**). A small aliquot of the TFA solution was diluted

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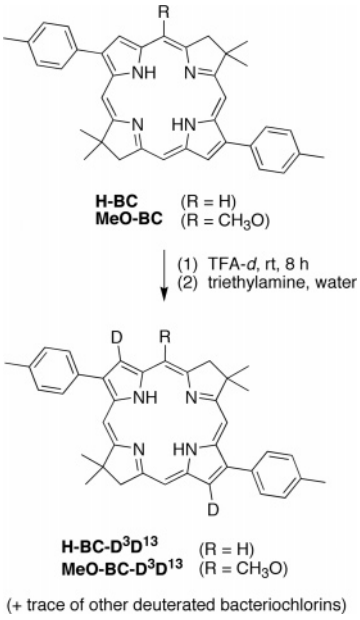
SCHEME 2



with toluene and examined by absorption spectroscopy. The bacteriochlorin dication exhibits a bathochromically shifted Q_y band [**H-BC**, 737 nm (ϵ 130 000 M^{-1} cm^{-1});[1] **H-BC-2H**$^{2+}$, 796 nm (ϵ 95 000 M^{-1} cm^{-1}); **MeO-BC**, 732 nm (ϵ 120 000 M^{-1} cm^{-1});[1] **MeO-BC-2H**$^{2+}$, 789 nm (ϵ 85 000 M^{-1} cm^{-1})] (Figure 1). Identical spectra were obtained upon use of TFA-*d*. In each case the spectrum of the free base bacteriochlorin was reobtained upon neutralization with triethylamine, indicating the reversibility of protonation and deprotonation.

The kinetics of the deuterium exchange process of the bacteriochlorins (**H-BC** and **MeO-BC**) in neat TFA-*d* at 50 °C was measured by ^{1}H NMR spectroscopy. For example, dissolution of **H-BC** in neat TFA-*d* at 50 °C resulted in a steady decrease over 1 h in the intensity of the resonance from H^3 (8.67 ppm). By contrast, the intensity of the resonance from H^5 (8.92 ppm) declined slowly whereas that of H^{10} (8.84 ppm) did not show any change. Partial decomposition of the bacteriochlorin was observed after 3 h; thus, the data up to 2 h were used for kinetic studies. The data obtained obeyed first-order rate expressions quite closely, thereby enabling calculation of rate constants *k*. The data are summarized in Table 2.

The key observations from the kinetic study are as follows: (1) The rate constant for deuteration of **MeO-BC** increased in order of 10- and 20- < 15- < 13- < 3-position. (2) The rate constant for deuteration of **H-BC** increased in order of 10-, 20- < 5-, 15- ≪ 3-, 13-positions. (3) The rate constants for deuteration of the meso-positions of bacteriochlorins were slightly less than that for the corresponding meso-positions (flanking the pyrroline ring; $k_{15} = 13 \times 10^{-5}$ s^{-1}; $k_{20} = 4.7 \times 10^{-5}$ s^{-1}) of a fully unsubstituted chlorin (**H$_2$C**) under identical conditions,[15] with no detectable β-deuteration.

The deuteration results were surprising in two regards. First, the predominance of β-substitution versus meso-substitution was unexpected, because chlorins undergo selective meso-substitution. It remains to be determined to what extent the rapid rate of β-deuteration of the bacteriochlorins stems from the adjacent *p*-tolyl groups. An effect of substituents in directing deuteration in porphyrins was recently described.[19] Second, the product profiles were quite different upon deuteration and bromination of the bacteriochlorins. Many possible mechanistic explanations

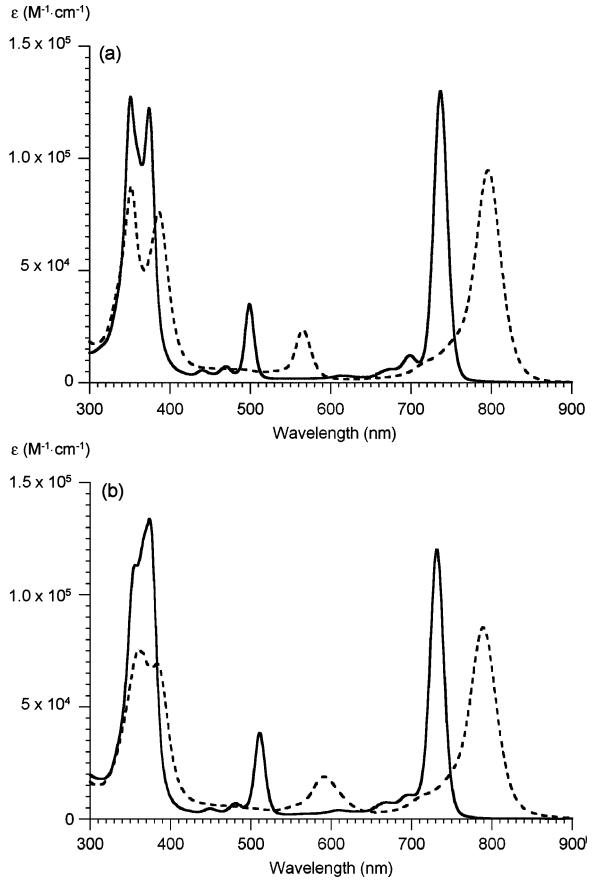


FIGURE 1. Absorption spectra (normalized) in toluene containing TFA at room temperature: (a) **H-BC** (solid trace, λ_{Q_y} 737 nm) and **H-BC-2H**$^{2+}$ (dashed trace, λ_{Q_y} 796 nm) and (b) **MeO-BC** (solid trace, λ_{Q_y} 732 nm) and **MeO-BC-2H**$^{2+}$ (dashed trace, λ_{Q_y} 789 nm).

TABLE 2. Rate Constants for Deuterium Exchange of Bacteriochlorin Protons[a]

	rate constant k ($\times 10^{-5}$) in s^{-1}	
	H-BC	**MeO-BC**
β-positions		
3	75	53
13		23
meso-positions		
5	2	–
15		6
10	–[b]	<2
20		–[b]

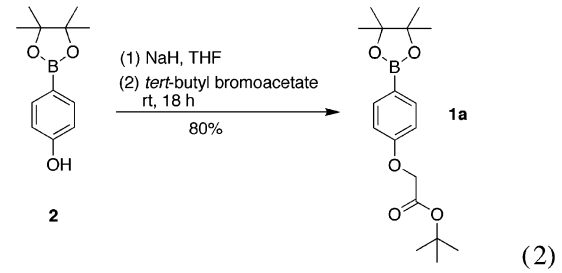
[a] Pseudo-first-order rate constants measured in TFA-*d* at 50 °C. [b] Not observed.

can be suggested for the different regiochemical outcome of the two reactions. One explanation concerns the different reactants present under the two reaction conditions (strong acid versus neutral media). The presumed reactant that undergoes deuterium exchange is the bacteriochlorin dication whereas the reactant that undergoes bromination is the neutral, free base bacteriochlorin.

3. Substitution at the 15-Position: (a) Suzuki Reaction. The Suzuki coupling of **MeO-BC-Br**[15] and dioxaborolanes **1a**−**c** was carried out under standard conditions for use with

(19) Zhu, Y.; Silverman, R. B. *J. Org. Chem.* **2007**, *72*, 233−239.

porphyrinic compounds.[14,20,21] The boronic acid moiety was employed as the dioxaborolane derivative to improve the reaction yield and facilitate purification.[22] The dioxaborolane-containing reactants **1a** and **1c** for Suzuki coupling were synthesized, whereas **1b** was available commercially. Thus, phenol **2**[23] was treated with NaH in THF followed by condensation with *tert*-butyl bromoacetate to give compound **1a** in 80% yield (eq 2). The treatment of 3,5-diformylphenylboronic acid with pinacol in dry THF at room temperature[21] afforded the corresponding dialkyl boronate **1c** in 77% yield (eq 3). The



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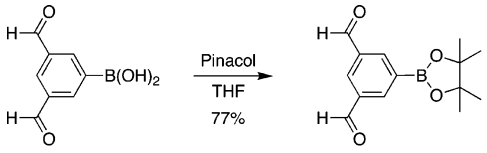


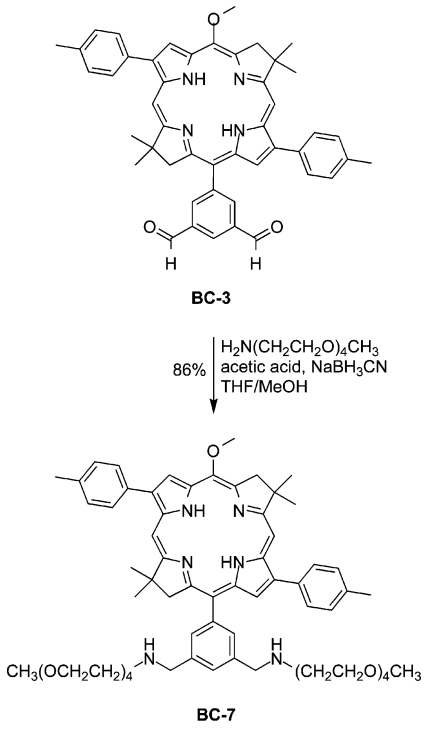
(3)

Suzuki coupling reactions were carried out in toluene/DMF (2:1) at 90 °C for 18 h with modest concentrations of **MeO-BC-Br**[15] (10 mM) and **1a**−**c** (20−40 mM) in the presence of $Pd(PPh_3)_4$ (30 mol %) and K_2CO_3 (8 molar equiv). In so doing, the corresponding bacteriochlorins **BC-1**−**BC-3** were obtained in 67% to 85% yield (Table 3, entries 1−3).

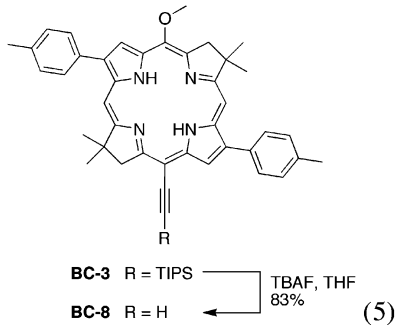
(b) Sonogashira Reaction. The Sonogashira coupling of **MeO-BC-Br**[15] and phenylethyne (**1d**) or 2-(triisopropylsilyl)-ethyne (**1e**) was carried out under standard conditions for use with porphyrinic substrates [2.4 mM **MeO-BC-Br**[15], 7.2 mM ethyne, 0.36 mM $Pd_2(dba)_3$, and 3.1 mM P(*o*-tol)$_3$ in toluene/TEA (5:1) at 60 °C].[24] These conditions afforded reaction under mild conditions, in dilute solution where porphyrinic compounds are soluble, and in the absence of any copper reagents that might insert into the bacteriochlorin core. Under these conditions, the 15-(phenylethynyl)bacteriochlorin **BC-4** and 15-[2-(triisopropylsilyl)ethynyl]bacteriochlorin **BC-5** were obtained in 49% and 59% yield, respectively (Table 3, entries 4 and 5).

(c) Hartwig−**Buchwald Reaction.** The Hartwig−Buchwald reaction of **MeO-BC-Br**[15] and benzamide (**1f**) was carried out under conditions that have been used previously for the amidation of porphyrins.[25] The coupling of **MeO-BC-Br**[15] and benzamide was carried out with use of modest concentrations (5 and 20 mM, respectively) in the presence of $Pd_2(dba)_3$, Cs_2CO_3, and a phosphine ligand in THF. When DPEphos[26] was employed, the yield of **BC-6** was 14%. The use of Xantphos[27] rather than DPEphos gave **BC-6** in 57% isolated yield (Table 3, entry 6).

4. Derivatization of Substituents at the 15-Position. The 3,5-diformylphenylbacteriochlorin **BC-3** was treated to reductive amination[28] with a short oligoethylene glycol moiety bearing a single amino group (eq 4). The reaction was carried out with



BC-3 and 3,6,9,12-tetraoxatridecylamine in 1:5 ratio in a dilute solution (2 mM **BC-3**) in MeOH/THF (1:9) at room temperature for 3 h. Workup including chromatography afforded the bis-aminated bacteriochlorin product **BC-7** in 86% yield (purity ~95%). In addition, the TIPS group of **BC-5** was removed upon treatment with TBAF in THF affording **BC-8** in 83% yield (eq 5).



(5)

5. Bacteriochlorin NMR Spectra. The ^{1}H NMR spectra of the substituted bacterichlorins were readily interpreted. Two points merit comment: (1) The resonance from each β-pyrrole

(20) (a) Shultz, D. A.; Gwaltney, K. P.; Lee, H. *J. Org. Chem.* **1998**, *63*, 769−774. (b) Hyslop, A. G.; Kellett, M. A.; Iovine, P. M.; Therien, M. J. *J. Am. Chem. Soc.* **1998**, *120*, 12676−12677. (c) Zhou, X.; Chan, K. S. *J. Org. Chem.* **1998**, *63*, 99−104.

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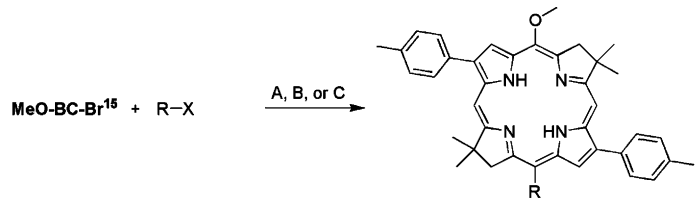
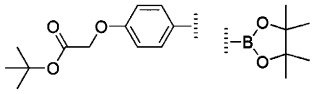
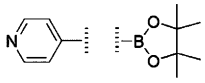
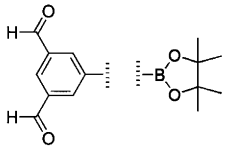
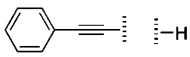
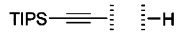
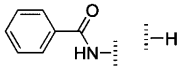
TABLE 3. Pd-Mediated Substitution[a] of MeO-BC-Br[15]



Entry	R-X	R	X	Condition	Product	Yield (%)
1	**1a**			A	**BC-1**	67
2	**1b**			A	**BC-2**	85
3	**1c**			A	**BC-3**	81
4	**1d**			B	**BC-4**	49
5	**1e**			B	**BC-5**	59
6	**1f**			C	**BC-6**	57

[a] Conditions: (A) $Pd(PPh_3)_4$, K_2CO_3, toluene/DMF (2:1), Ar, 90 °C, 18 h; (B) $Pd_2(dba)_3$, P(*o*-tol)$_3$, toluene/TEA (5:1), Ar, 60 °C, 18 h; (C) Cs_2CO_3, $Pd_2(dba)_3$, Xantphos, THF, reflux, Ar, 18 h.

proton (H^3, H^{13}) in each bacteriochlorin examined herein (including **H-BC**, **MeO-BC**, bromobacteriochlorins, and 5-methoxy-15-substituted bacteriochlorins) appears as a doublet ($J \approx 2$ Hz). Such splitting is attributed to coupling with the pyrrolic NH proton. Analogous splitting is observed in free base porphyrins at low temperature, where N−H tautomerization processes are very slow. Such tautomerization processes in bacteriochlorins are energetically less favorable owing to the presence of the two pyrroline rings, and hence are observed at room temperature.[29] A similar observation and interpretation was reported for 5,10,15,20-tetraphenylbacteriochlorin.[30] Further supporting evidence stems from ^{1}H NMR studies of metal chelates of **H-BC**, wherein the splitting disappears and the β-pyrrole proton (H^3, H^{13}) resonates as a singlet (unpublished data). (2) The resonance from each meso-proton (H^{10}, H^{20}) appears as a singlet. The presence of only four protons at the perimeter of the macrocycle (H^3, H^{10}, H^{13}, and H^{20}) renders the ^{1}H NMR spectra of the 5,15-disubstituted bacteriochlorins exceptionally simple. Moreover, the chemical shift of H^{13} depends on the nature of the 15-substituent whereas that of H^3 (and H^{10} and H^{20}) is relatively unchanged (see the Supporting Information).

6. Bacteriochlorin Absorption Spectra. The features of the absorption spectrum of the bacteriochlorin **MeO-BC** as well as **BC-1** to **BC-8** are summarized in Table 4. The absorption spectra of two bacteriochlorins are shown in Figure 2. The key points of interest include the effects of substituents on (1) the extent of absorption in the red or near-IR region, which can be assessed by the position of the long-wavelength (Q_y) absorption maximum (λ_{Q_y}) and the ratio of the intensity of the Q_y versus the B band (I_{Q_y}/I_B), and (2) the sharpness of the long-wavelength absorption band, which can be assessed by the full-width at half-maximum (fwhm) of the band.[16,31,32] Increased absorption

TABLE 4. Absorption Spectral Features of Bacteriochlorins[a]

Compound	15-substituent	λ (nm)			I_{Q_y}/I_B[b]
		B	Q_x	Q_y (fwhm)[c]	
MeO-BC	−H	374	511	732 (20)	0.91
BC-1	−aryl	378	519	735 (20)	0.81
BC-2	−aryl	378	518	736 (20)	0.87
BC-3	−aryl	376	520	738 (20)	0.97
BC-4	−≡−Ph	387	551	754 (19)	0.94
BC-5	−≡−TIPS	385	540	753 (20)	0.99
BC-6	−NHCOPh	374	513	737 (21)	0.92
BC-7	−aryl	377	519	735 (20)	0.81
BC-8	−≡−H	383	533	750 (20)	1.00

[a] Absorption spectra were recorded in toluene at room temperature. [b] Ratio of the intensities of the Q_y and B bands. [c] Full-width at half-maximum in nm.

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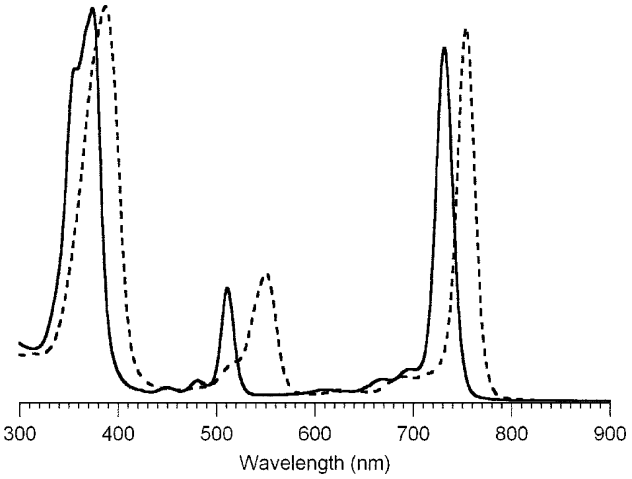

FIGURE 2. Absorption spectra (normalized) in toluene at room temperature of **MeO-BC** (solid line, λ_{Q_y} 732 nm) and **BC-4** (dashed line, λ_{Q_y} 754 nm).

in the red or near-IR region is of interest for a variety of photochemical applications. In this regard, the presence of the 15-*N*-benzamido group (**BC-6**) or a 15-aryl group (**BC-1**, **BC-2**, **BC-3**, and **BC-7**) causes a bathochromic shift of the Q_y band by 3−6 nm, whereas a 15-ethynyl substituent (**BC-4**, **BC-5**, and **BC-8**) causes a bathochromic shift of the Q_y band by 18−22 nm. Relatively little change in the I_{Q_y}/I_B ratio occurs among the substituents examined herein versus that of **MeO-BC** ($I_{Q_y}/I_B = 0.91$), although a slight relative increase in the Q_y band intensity occurs upon 15-ethynyl substitution. In all cases, the long-wavelength band remains quite sharp, with fwhm ∼20 nm. In one case where fluorescence was examined, excitation of the 15-phenylethynylbacteriochlorin (**BC-4**) at 551 nm (Q_x band) resulted in emission at 761 nm with a fluorescence quantum yield (Φ_f) of 0.16, which compares well with that of **MeO-BC** ($\Phi_f = 0.18$) and **H-BC** ($\Phi_f = 0.14$).[1]

7. Outlook. The 5-methoxybacteriochlorin **MeO-BC** can be tailored with a variety of groups in a selective manner by regioselective bromination followed by Pd-mediated coupling. The introduction of an aryl or *N*-benzamido group causes hardly any change in absorption features, whereas the introduction of an ethynyl group shifts the long-wavelength band bathochromically by ∼20 nm. Such facile tailoring should open the door to a number of applications where strong near-IR absorption is required.

Experimental Section

15-Bromination: 5-Bromo-15-methoxy-8,8,18,18-tetramethyl-2,12-bis(4-methylphenyl)bacteriochlorin (MeO-BC-Br[15]). A solution of **MeO-BC**[1] (127 mg, 219 μmol, 2.0 mM) in THF (110 mL) was treated with NBS (38.9 mg, 219 μmol, 2.0 mM) at room temperature for 15 min. TLC analysis [silica, hexanes/CH_2Cl_2 (1:1)] showed only one spot. The reaction mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4) and filtered. The filtrate was concentrated. The residue was chromatographed [silica, hexanes/CH_2Cl_2 (1:1)] to afford a black green solid (122 mg, 85%): ^{1}H NMR δ −2.00 (br, 1H), −1.80 (br, 1H), 1.91 (s, 6H), 1.92 (s, 6H), 2.61 (s, 6H), 4.38−4.42 (br, 2H), 4.49 (s, 3H), 4.48−4.52 (br, 2H), 7.56−7.62 (m, 4H), 8.08−8.14 (m, 4H), 8.77 (s, 1H), 8.82 (s, 1H), 8.98 (d, J = 2.0 Hz, 1H), 9.04 (d, J = 2.0 Hz, 1H); λ_{abs} (CH_2Cl_2) 377, 523, 735 nm; LD-MS obsd 658.5 and 660.5; FAB-MS obsd 658.2328, calcd 658.2307 ($C_{39}H_{39}BrN_4O$).

***tert*-Butyl [4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-phenoxy]acetate (1a).** A solution of **2**[23] (220 mg, 1.00 mmol) in dry THF (20 mL) was treated with NaH (48.2 mg, 2.00 mmol) at room temperature for 10 min. *tert*-Butyl bromoacetate (220 μL, 1.50 mmol) was added, and the mixture was stirred at room temperature for 18 h. TLC analysis [silica, hexanes/ethyl acetate (5:1)] showed only one spot. The reaction mixture was diluted with ethyl acetate and washed with brine. The organic layer was separated, dried (Na_2SO_4), concentrated, and chromatographed [silica, hexanes/ethyl acetate (5:1)] to afford a colorless solid (268 mg, 80%): mp 90−91 °C; ^{1}H NMR δ 1.33 (s, 12H), 1.48 (s, 9H), 4.53 (s, 2H), 6.85−6.90 (m, 2H), 7.73−7.78 (m, 2H); ^{13}C NMR δ 25.1, 28.2, 65.6, 82.6, 83.8, 114.1, 136.7, 160.6, 168.0. Anal. Calcd for $C_{18}H_{27}BO_5$: C, 64.69; H, 8.14. Found: C, 64.75; H, 8.22. Compound **1a**, prepared via a different route, has been described previously with limited characterization data.[33]

3,5-Diformyl(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (1c). A solution of 3,5-diformylphenylboronic acid (178 mg, 1.00 mmol) in dry THF (10 mL) was treated with pinacol (142 mg, 1.20 mmol) at room temperature for 18 h. The reaction mixture became yellow, and TLC analysis (silica, CH_2Cl_2) showed only one spot. The reaction mixture was concentrated to a light yellow oil. Trituration with hexanes gave a solid, which was filtered and dried to give a colorless solid (200 mg, 77%): mp 89−91 °C; ^{1}H NMR δ 1.39 (s, 12H), 8.46−8.47 (m, 1H), 8.55−8.56 (m, 2H), 10.14 (s, 2H); ^{13}C NMR δ 25.1, 85.0, 132.4, 136.6, 141.6, 191.50, 191.51 (the resonance of the 4° carbon, which is close to the oxygen atom, is overlapped by that of residual $CHCl_3$). Anal. Calcd for $C_{14}H_{17}BO_4$: C, 64.65; H, 6.59. Found: C, 64.69; H, 6.65.

Suzuki Coupling: 15-[4-(*tert*-Butoxycarbonylmethoxy)phenyl]-5-methoxy-8,8,18,18-tetramethyl-2,12-bis(4-methylphenyl)-bacteriochlorin (BC-1). A mixture of **MeO-BC-Br[15]** (26.3 mg, 40.0 μmol, 10 mM), **1a** (40.1 mg, 120 μmol), $Pd(PPh_3)_4$ (13.9 mg, 12.0 μmol), and K_2CO_3 (66.3 mg, 480 μmol) was placed into a 10 mL Schlenk flask, which was then pump-purged three times with argon. Toluene/DMF [4 mL (2:1)] was added, and the reaction mixture was stirred at 90 °C. After 18 h, the mixture was concentrated to dryness and diluted with CH_2Cl_2. The organic layer was washed with aqueous $NaHCO_3$, separated, dried (Na_2SO_4), and filtered. The filtrate was concentrated and chromatographed [silica, hexanes/CH_2Cl_2 (1:2)] to afford a green solid (21.2 mg, 67%): ^{1}H NMR δ −1.84 (br, 1H), −1.62 (br, 1H), 1.59 (s, 9H), 1.81 (s, 6H), 1.91 (s, 6H), 2.57 (s, 3H), 2.61 (s, 3H), 4.00 (s, 2H), 4.39 (s, 2H), 4.50 (s, 3H), 4.74 (s, 2H), 7.17−7.20 (m, 2H), 7.49−7.53 (m, 2H), 7.57−7.60 (m, 2H), 7.74−7.79 (m, 2H), 7.97−8.01 (m, 2H), 8.12−8.17 (m, 2H), 8.16 (d, J = 1.6 Hz, 1H), 8.81 (s, 1H), 8.82 (s, 1H), 8.94 (d, J = 1.6 Hz, 1H); λ_{abs} (toluene) 378, 519, 735 nm; LD-MS obsd 787.0; FAB-MS obsd 786.4156, calcd 786.4145 ($C_{51}H_{54}N_4O_4$).

5-Methoxy-15-(4-pyridyl)-8,8,18,18-tetramethyl-2,12-bis(4-methylphenyl)bacteriochlorin (BC-2). A mixture of **MeO-BC-Br[15]** (26.3 mg, 40.0 μmol, 10 mM), **1b** (53.5 mg, 160 μmol), $Pd(PPh_3)_4$ (13.9 mg, 12.0 μmol), and K_2CO_3 (88.5 mg, 640 μmol) was heated in toluene/DMF [4 mL (2:1)] at 90 °C for 18 h, whereupon TLC analysis [silica, CH_2Cl_2/ethyl acetate (10:1)] showed two main spots (the bacteriochlorin debromination byproduct **MeO-BC**, and the desired product). Standard workup including chromatography [silica, CH_2Cl_2/ethyl acetate (10:1)] afforded a green solid (22.3 mg, 85%): ^{1}H NMR δ −1.92 (br, 1H), −1.65 (br, 1H), 1.83 (s, 6H), 1.92 (s, 6H), 2.57 (s, 3H), 2.61 (s, 3H), 3.99

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(s, 2H), 4.41 (s, 2H), 4.51 (s, 3H), 7.49−7.55 (m, 2H), 7.57−7.61 (m, 2H), 7.82−7.85 (m, 2H), 7.96−8.00 (m, 2H), 8.09 (d, $J = 2.0$ Hz, 1H), 8.12−8.16 (m, 2H), 8.84 (s, 1H), 8.86 (s, 1H), 8.92−8.96 (m, 2H), 8.98 (d, $J = 2.0$ Hz, 1H); λ_{abs} (toluene) 378, 518, 736 nm; LD-MS obsd 658.0; FAB-MS obsd 657.3494, calcd 657.3468 ($C_{44}H_{43}N_5O$).

15-(3,5-Diformylphenyl)-5-methoxy-8,8,18,18-tetramethyl-2,-12-bis(4-methylphenyl)bacteriochlorin (BC-3). A mixture of **MeO-BC-Br**[15] (26.4 mg, 40.0 μmol, 10 mM), **1c** (20.8 mg, 80.0 μmol), $Pd(PPh_3)_4$ (13.8 mg, 12.0 μmol), and K_2CO_3 (44.2 mg, 160 μmol) was heated in toluene/DMF [4 mL (2:1)] at 90 °C for 18 h, whereupon TLC analysis [silica, hexanes/CH_2Cl_2 (1:1)] showed three main spots: **MeO-BC-Br**[15], **MeO-BC**, and product. Standard workup including chromatography [silica, hexanes/CH_2Cl_2 (1:1) followed by CH_2Cl_2] afforded a black solid (23.1 mg, 81%): ^{1}H NMR δ −1.92 (br, 1H), −1.61 (br, 1H), 1.83 (s, 6H), 1.93 (s, 6H), 2.56 (s, 3H), 2.61 (s, 3H), 3.96 (s, 2H), 4.42 (s, 2H), 4.52 (s, 3H), 7.48−7.52 (m, 2H), 7.57−7.61 (m, 2H), 7.94 (d, $J = 2.0$ Hz, 1H), 7.93−7.98 (m, 2H), 8.12−8.17 (m, 2H), 8.66 (d, $J = 1.5$ Hz, 2H), 8.68 (d, $J = 1.5$ Hz, 1H), 8.84 (s, 1H), 8.87 (s, 1H), 9.00 (d, $J = 2.0$ Hz, 1H), 10.33 (s, 2H); λ_{abs} (toluene) 376, 520, 738 nm; LD-MS obsd 712.8; FAB-MS obsd 712.3433, calcd 712.3413 ($C_{47}H_{44}N_4O_3$).

Sonogashira Coupling: 5-Methoxy-8,8,18,18-tetramethyl-2,-12-bis(4-methylphenyl)-15-(2-phenylethynyl)bacteriochlorin (BC-4). A mixture of **MeO-BC-Br**[15] (23 mg, 36 μmol, 2.4 mM), phenylacetylene (12 μL, 0.11 mmol, 7.2 mM), $Pd_2(dba)_3$ (4.9 mg, 5.3 μmol, 0.36 mM), and P(*o*-tol)$_3$ (14 mg, 46 μmol, 3.1 mM) was placed into a 100 mL Schlenk flask, which was then pump-purged three times with argon. Toluene/TEA [15 mL (5:1)] was added, and the reaction mixture was stirred at 60 °C. After 7 h, phenylacetylene (12 μL, 0.11 mmol, 7.2 mM), $Pd_2(dba)_3$ (4.9 mg, 5.3 μmol, 0.36 mM), and P(*o*-tol)$_3$ (14 mg, 46 μmol, 3.1 mM) were added. After 16 h, the mixture was concentrated to dryness. TLC analysis [silica, hexanes/THF (17:3)] showed three main spots (starting material, product and an unknown compound). Purification entailed removal of palladium reagents by silica-pad filtration [hexanes/CH_2Cl_2 (1:1)] followed by three additional chromatography columns [silica, hexanes/THF (17:3); silica, hexanes/$CHCl_3$ (1:1); silica, hexanes/CH_2Cl_2 (1:1)], which afforded a black solid (11 mg, 49%): ^{1}H NMR δ −1.49 (br, 1H), −1.28 (br, 1H), 1.90 (s, 6H), 1.92 (s, 6H), 2.61 (s, 6H), 4.35 (s, 2H), 4.48 (s, 3H), 4.62 (s, 2H), 7.43−7.45 (m, 1H), 7.49−7.53 (m, 2H), 7.56−7.61 (m, 4H), 7.88−7.90 (m, 2H), 8.09−8.14 (m, 4H), 8.75 (s, 1H), 8.77 (s, 1H), 8.90 (d, $J = 2.0$ Hz, 1H), 9.15 (d, $J = 2.0$ Hz, 1H); λ_{abs} (toluene) 387, 551, 754 nm; λ_{em} (λ_{exc} 551 nm) 761 nm, $\Phi_f = 0.16$; LD-MS obsd 680.7; FAB-MS obsd 680.3516, calcd 680.3515 ($C_{47}H_{44}N_4O$).

5-Methoxy-8,8,18,18-tetramethyl-2,12-bis(4-methylphenyl)-15-[2-(triisopropylsilyl)ethynyl]bacteriochlorin (BC-5). A mixture of **MeO-BC-Br**[15] (26 mg, 40 μmol, 2.5 mM), (triisopropylsilyl)-acetylene (27 μL, 120 μmol), $Pd_2(dba)_3$ (11 mg, 12 μmol), and P(*o*-tol)$_3$ (16 mg, 52 μmol) was heated in toluene/TEA [16 mL (5:1)] at 60 °C for 16 h. Standard workup including chromatography [silica, hexanes/CH_2Cl_2 (2:1)] afforded a red-black solid (18 mg, 59%): ^{1}H NMR δ −1.58 (br, 1H), −1.37 (br, 1H), 1.37−1.39 (m, 21H), 1.89 (s, 12H), 2.60 (s, 3H), 2.61 (s, 3H), 4.34 (s, 2H), 4.47 (s, 3H), 4.52 (s, 2H), 7.56−7.62 (m, 4H), 8.08−8.14 (m, 4H), 8.76 (s, 1H), 8.77 (s, 1H), 8.89 (d, $J = 2.0$ Hz, 1H), 9.10 (d, $J = 2.0$ Hz, 1H); λ_{abs} (toluene) 385, 540, 753 nm; LD-MS obsd 760.8; FAB-MS obsd 760.4567, calcd 760.4536 ($C_{50}H_{60}N_4OSi$).

Hartwig−Buchwald Coupling: 15-(*N*-Benzamido)-5-methoxy-8,8,18,18-tetramethyl-2,12-bis(4-methylphenyl)bacteriochlorin (BC-6). A mixture of **MeO-BC-Br**[15] (26 mg, 40 μmol, 5 mM), benzamide (19 mg, 80 μmol), $Pd_2(dba)_3$ (3.6 mg, 4.0 μmol), Xantphos (4.8 mg, 8.0 μmol), and Cs_2CO_3 (104 mg, 320 μmol) was placed into a 10 mL Schlenk flask, which was then pump-purged three times with argon. Distilled THF (8 mL) was added, and the reaction mixture was stirred at reflux. After 18 h, the mixture was concentrated to dryness and diluted with CH_2Cl_2. The organic layer was washed with water, separated, dried (Na_2SO_4), and filtered. The filtrate was concentrated and chromatographed [silica, hexanes/ethyl acetate (3:1) followed by CH_2Cl_2/ethyl acetate (10:1)] to afford a black solid (13 mg, 46%): ^{1}H NMR (THF-d_8 + DMSO-d_6) δ −1.95 (br, 1H), −1.81 (br, 1H), 1.84 (s, 6H), 1.89 (s, 6H), 2.54 (s, 3H), 2.57 (s, 3H), 4.31 (s, 2H), 4.40 (s, 2H), 4.49 (s, 3H), 7.58−7.63 (m, 4H), 7.68−7.74 (m, 3H), 8.06−8.10 (m, 2H), 8.15−8.19 (m, 2H), 8.40−8.44 (m, 2H), 8.80 (s, 1H), 8.81 (s, 1H), 8.82 (d, $J = 2.0$ Hz, 1H), 9.03 (d, $J = 2.0$ Hz, 1H), 11.5 (s, 1H); λ_{abs} (toluene) 374, 513, 737 nm; LD-MS obsd 699.6; FAB-MS obsd 699.3562, calcd 699.3573 ($C_{46}H_{45}N_5O_2$).

5-Methoxy-8,8,18,18-tetramethyl-2,12-bis(4-methylphenyl)-15-[3,5-bis(5,8,11,14-tetraoxa-2-azapentadecyl)phenyl]bacteriochlorin (BC-7). A solution of **BC-3** (7.1 mg, 10 μmol) and 3,6,9,12-tetraoxatridecylamine (10 mg, 50 μmol) in THF/MeOH (5 mL, 9:1) was treated with acetic acid (3.0 mg, 50 μmol) and $NaBH_3CN$ (2.8 mg, 40 μmol). The reaction mixture was stirred at room temperature for 4 h. The crude mixture was concentrated, diluted in CH_2Cl_2, and washed with water. The organic layer was separated, dried (Na_2SO_4), and concentrated. The residue was chromatographed [silica, MeOH/DMF (1:1)]. The collected eluate was concentrated under high vacuum, diluted with CH_2Cl_2, and washed with water. The organic layer was separated, dried (Na_2SO_4), and concentrated to afford a red-black solid (9.4 mg, 86%): ^{1}H NMR δ −1.86 (br, 1H), −1.63 (br, 1H), 1.81 (s, 6H), 1.92 (s, 6H), 2.56 (s, 3H), 2.61 (s, 3H), 2.95−2.97 (m, 4H), 3.22 (s, 3H), 3.25 (s, 3H), 3.35−3.67 (m, 24H), 3.99 (s, 2H), 4.03 (s, 4H), 4.21−4.22 (m, 4H), 4.40 (s, 2H), 4.51 (s, 3H), 7.48−7.61 (m, 6H), 7.67−7.73 (m, 3H), 7.96−8.00 (m, 2H), 8.12−8.17 (m, 3H), 8.80 (s, 1H), 8.83 (s, 1H), 8.95 (d, $J = 2.0$ Hz, 1H); λ_{abs} (toluene) 377, 519, 735 nm; LD-MS obsd 1094.5; FAB-MS obsd 1095.6556, calcd 1095.6535 [$(M + H)^+$, $M = C_{65}H_{86}N_6O_9$].

5-Ethynyl-15-methoxy-8,8,18,18-tetramethyl-2,12-bis(4-methylphenyl)bacteriochlorin (BC-8). A solution of **BC-5** (14 mg, 19 μmol) in THF (1.9 mL) was treated with TBAF/THF (1.0 M, 56 μL, 56 mmol) in an ice bath for 15 min. The reaction mixture was concentrated, diluted with CH_2Cl_2, and washed with aqueous $NaHCO_3$. The organic layer was separated, dried (Na_2SO_4), concentrated, and chromatographed [silica, hexanes/CH_2Cl_2 (2:1)] to afford a green solid (9.3 mg, 83%): ^{1}H NMR δ −1.64 (br, 1H), −1.41 (br, 1H), 1.90 (s, 12H), 2.61 (s, 6H), 3.92 (s, 1H), 4.35 (s, 2H), 4.48 (s, 3H), 4.54 (s, 2H), 7.56−7.60 (m, 4H), 8.08−8.12 (m, 4H), 8.77 (s, 1H), 8.80 (s, 1H), 8.90 (d, $J = 2.0$ Hz, 1H), 9.09 (d, $J = 2.0$ Hz, 1H); λ_{abs} (toluene) 383, 533, 750 nm; LD-MS obsd 604.8; FAB-MS obsd 604.3227, calcd 604.3202 ($C_{41}H_{40}N_4O$).

Acknowledgment. This research was supported by the NIH (GM-36238). Mass spectra were obtained at the Mass Spectrometry Laboratory for Biotechnology at North Carolina State University. Partial funding for the facility was obtained from the North Carolina Biotechnology Center and the National Science Foundation.

Supporting Information Available: Spectral data (absorption, ^{1}H NMR, LD-MS) for all new bacteriochlorins including spectral assignments; description of deuteration experiments and data, and additional information concerning experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

JO070785S