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Tailoring a Bacteriochlorin Building Block with Cationic, Amphipathic, or Lipophilic Substituents

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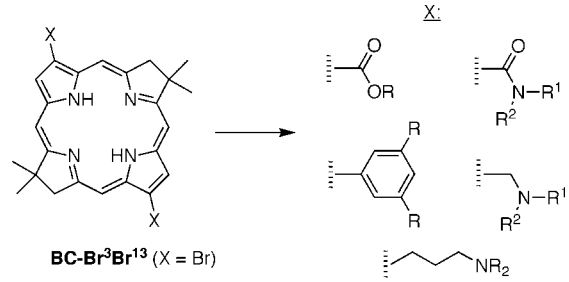

BC-Br^{3}Br^{13} (X = Br)

Bacteriochlorins are attractive candidates for photodynamic therapy (PDT) of diverse medical indications owing to their strong absorption in the near-infrared (NIR) region, but their use has been stymied by lack of access to stable, synthetically malleable molecules. To overcome these limitations, a synthetic free base 3,13-dibromobacteriochlorin (**BC-Br^{3}Br^{13}**) has been exploited as a building block in the synthesis of diverse bacteriochlorins via Pd-mediated coupling reactions (Sonogashira, Suzuki, and reductive carbonylation). Each bacteriochlorin is stable to adventitious dehydrogenation by virtue of the presence of a geminal dimethyl group in each pyrroline ring. The target bacteriochlorins bear cationic, lipophilic, or amphipathic substituents at the 3- and 13- (β-pyrrolic) positions. A dicarboxybacteriochlorin was converted to amide derivatives via the intermediate diacid chloride. A diformylbacteriochlorin was subjected to reductive amination to give aminomethyl derivatives. A set of 3,5-disubstituted aryl groups bearing lipophilic or amphipathic groups was introduced via Suzuki coupling. Altogether 22 free base bacteriochlorins have been prepared. Eight aminoalkylbacteriochlorins were quaternized with methyl iodide at two or four amine sites per molecule, which resulted in water solubility. Each bacteriochlorin exhibits a Q_y absorption band in the range of 720−772 nm. The ability to introduce a wide variety of peripheral functional groups makes these bacteriochlorins attractive candidates for diverse applications in photomedicine including PDT in the NIR region.

Introduction

Photodynamic therapy (PDT) is an emerging approach for treatment of a wide variety of medical indications ranging from solid tumors to microbial infections.[1–7] The essence of PDT entails illumination of a photosensitizer in the presence of oxygen, which yields singlet O_2 and/or other reactive oxygen species to kill target cells. This tripartite approach relies on delivery of both light and the photosensitizer to the affected tissue. The delivery of the photosensitizer to the target tissue can be achieved by active targeting methods (e.g., conjugates with antibodies or receptor ligands) or by passive means owing to the nature of the substituents appended to the photosensitizer.[8,9] Upon delivery in vivo, the ability to excite the photosensitizer depends on the wavelength of light employed; in soft tissue, wavelengths in the NIR region (700−900 nm) afford the deepest

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penetration.[10] Thus, an ideal photosensitizer would absorb light in the same NIR spectral region.

A large number of compounds with PDT activity are now available.[2,6,11,12] Extensive studies with tetrapyrrole macrocycles have been carried out, largely with porphyrins and to a lesser extent chlorins[8,13] despite the lack of absorption in the NIR region of either type of macrocycle. Such studies have revealed the types of peripheral substituents that are suitable for passive targeting of tetrapyrrole macrocycles. The presence of cationic (ammonium) substituents results in uptake by many types of bacteria more avidly than by mammalian cells;[1,4,5,14] examples include the dicationic porphyrin XF73,[15,16] which exhibits antimicrobial PDT at the 5 nM level, and the polycationic product[17,18] obtained with the polylysine conjugate of chlorin e_6 (Chart 1). A variety of substituents have been employed with chlorins to achieve passive targeting of tumors as well as rapid systemic clearance; representative examples include phenolic substituents (Foscan[19] and analogue[20]), alkyl carboxylic acids (the water-soluble aspartyl derivative of chlorin e_6),[21] and lipophilic groups (Photochlor).[22]

To obtain photosensitizers with NIR absorption, more recent work has focused on bacteriochlorins, which absorb strongly in the 700−800 nm region.[23] The primary source of bacteriochlorins has stemmed from derivatives of the bacterial photosynthetic pigment bacteriochlorophyll *a*.[24] Two such derivatives (WST 9[25−28] and WST 11[29,30]) are shown in Chart 2. Two significant problems with derivatives of the bacteriochlorophylls include limited synthetic malleability owing to the presence of a nearly full complement of substituents about the perimeter of the macrocycle[24] and susceptibility to adventitious dehydrogenation (yielding the chlorin or porphyrin, which lack the NIR absorption).[28,31,32] By contrast with the latter limitation, tolyporphin A,[33,34] one of a series of bacteriochlorin pigments[35] from the Pacific alga *Tolypothrix nodosa*, is a stable compound

CHART 1

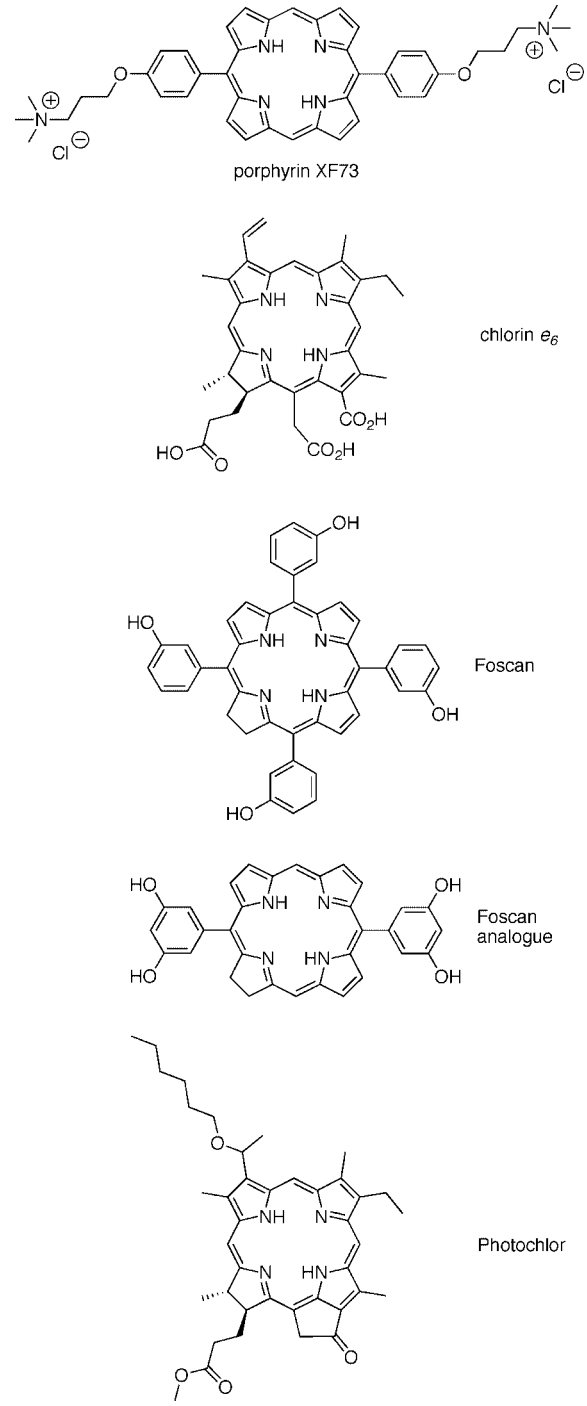

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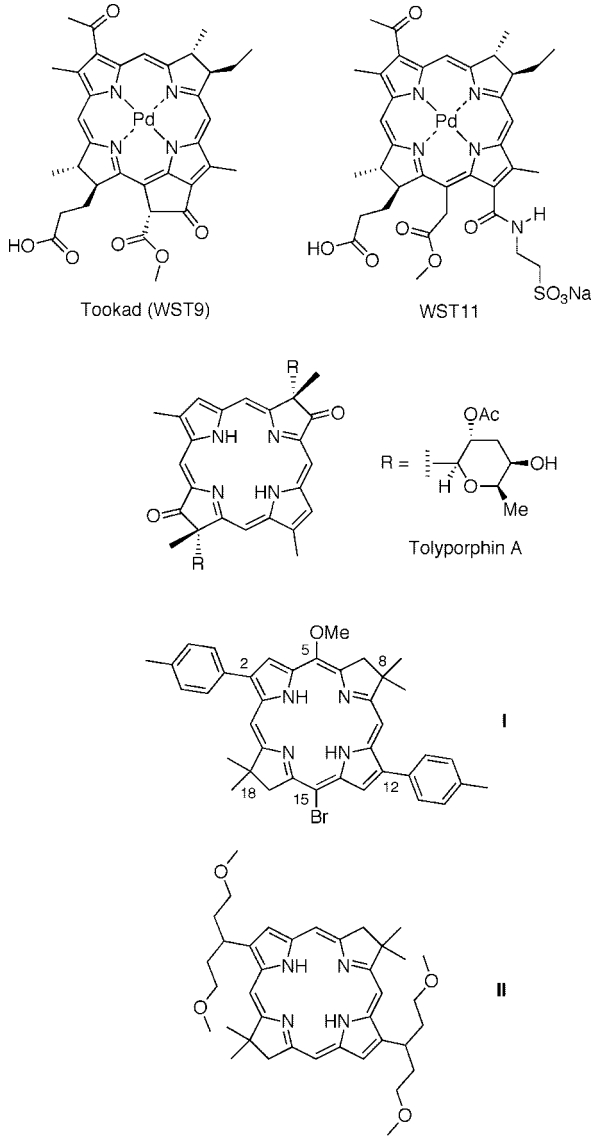
CHART 2



owing to the presence of a geminal dialkyl group in each pyrroline ring. Tolyporphin A has been examined as a photosensitizer;[36] however, the preparation of derivatives thereof has apparently not been reported, and the total synthesis of such compounds is arduous.[37,38]

We recently developed a de novo synthetic pathway to bacteriochlorins[39] that contain a geminal dimethyl group in each pyrroline ring. As with the tolyporphins, this structural attribute blocks adventitious dehydrogenation and thereby affords a stable macrocycle. This synthetic route has afforded a 5-methoxy-2,12-di-*p*-tolylbacteriochlorin, which undergoes bromination selectively at the 15-position.[40] The resulting 15-bromobacteriochlorin (**I**) has been derivatized via a variety of Pd-mediated coupling reactions; however, the 2,12-di-*p*-tolyl groups result in a hydrophobic, crystalline product that is unsuited for most PDT applications. The same route has been exploited to prepare a bacteriochlorin (**II**) bearing branched alkyl ("swallowtail") rather than *p*-tolyl groups at the 2- and 12-positions; although lipophilic and attractive for selected PDT studies, the synthesis of the swallowtail precursor to the bacteriochlorin was quite lengthy.[41] Extension of this synthetic route has recently afforded a 3,13-dibromobacteriochlorin, **BC-Br^{3}Br^{13}**, which lacks the 5-methoxy and 2,12-di-*p*-tolyl groups and is a valuable building block for transformation into bacteriochlorin derivatives.[42] We examined the functionalization of the 3- and 13-positions by Sonogashira, Stille, and Suzuki coupling reactions as a means to tune the position of the long-wavelength absorption band.[42] The substituents introduced included formyl, vinyl, phenylethynyl, and acetyl groups; the position of the long-wavelength absorption band could be shifted from 713 nm (no β-pyrrolic or meso substituents) to 771 nm (3,13-diformyl substituents). All of the resulting bacteriochlorins were soluble in organic solvents such as toluene.

In this paper, we describe the derivatization of **BC-Br^{3}Br^{13}** with groups of a systematic range of polarity for passive targeting in PDT. The paper is divided into three parts. Part I describes the introduction of diverse aminoalkyl groups, which upon quaternization have yielded cationic substituents. The resulting bacteriochlorins are soluble in water. Part II describes the preparation of diverse arylboronic acids bearing substituents to impart amphipathic or lipophilic character, and their introduction via Suzuki coupling to the bacteriochlorin nucleus. Part III compares the absorption spectral properties of the bacteriochlorins. Taken together, these studies establish the foundation for tailoring stable bacteriochlorins with diverse substituents for use in PDT applications ranging from microbial infections to oncological indications.

Results and Discussion

I. Cationic Bacteriochlorins. A simple approach that we first investigated entailed conversion of dibromobacteriochlorin **BC-Br^{3}Br^{13}** to the corresponding dicyanobacteriochlorin, which we envisaged could be further derivatized in a number of ways. Treatment of **BC-Br^{3}Br^{13}** to conditions for cyanation of aryl bromides [$Zn(CN)_2$ in the presence of $Pd(PPh_3)_4$ in DMF at 100 °C][43] afforded the zinc chelate of the 3,13-dicyanobacteriochlorin (**ZnBC-1**) in 89% yield (Scheme 1). The formation of the zinc chelate was unexpected, given the frequent difficulties in metalating bacteriochlorins,[44] but not unprecedented.[29,45] Attempted transformation of the dicyano moieties of **ZnBC-1** by reduction with LAH failed to give the corresponding methylamine, and hydrolysis of **ZnBC-1** with MeOH and HCl resulted only in demetalation to give the free base dicyanobacteriochlorin **BC-1**. The zinc chelate **ZnBC-1** also was deliber-

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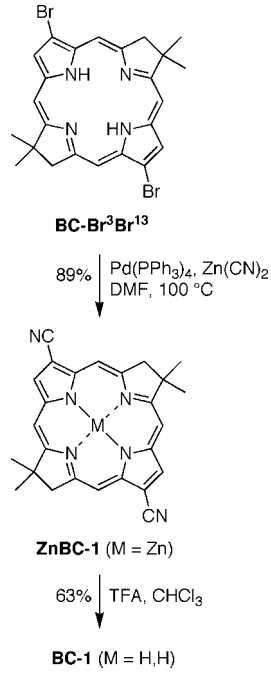
SCHEME 1

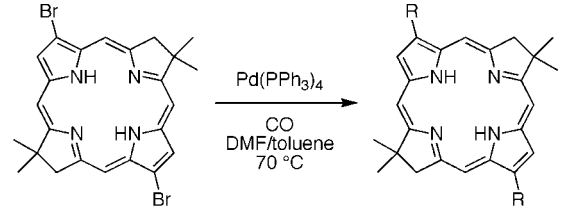


ately demetalated with TFA in $CHCl_3$ to give the free base bacteriochlorin **BC-1**. The difficulty in manipulating the cyano group prompted examination of other more malleable one-carbon functional groups.

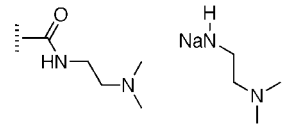
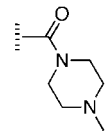
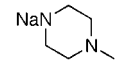
A. Carbonylation. Pd-mediated CO-insertion with heterocyclic halides followed by treatment with a variety of nucleophiles has afforded diverse substituted heterocycles,[46,47] and has been used with bromochlorins to give formylchlorins.[48] This methodology was applied to **BC-Br^{3}Br^{13}** with different nucleophiles (hydride donor, water, alcohol, amine) to obtain the corresponding bacteriochlorin bearing dialdehyde, diacid, diester, and diamide groups. The CO-insertion reaction with a catalytic amount of palladium reagent gave multiple products and predominantly the unreacted **BC-Br^{3}Br^{13}**. By contrast, the use of stoichiometric amounts of the palladium reagent led in each case to the desired compound in good yields.

Thus, reaction of **BC-Br^{3}Br^{13}** with $Pd(PPh_3)_4$ in toluene/DMF at 70 °C under an atmosphere of CO for 2 h and subsequent treatment with Bu_3SnH afforded diformylbacteriochlorin **BC-2** in 60% yield along with the 3-formyl-13-desbromobacteriochlorin in 25% yield (Table 1, entry 1). The diformylbacteriochlorin **BC-2** is a known compound that was previously prepared in very small quantity by oxidative cleavage of the corresponding divinylbacteriochlorin.[42] The same Pd-mediated carbonyl insertion conditions were employed followed by quenching with different nucleophiles to obtain the desired substituted bacteriochlorins. Quenching with NaOH afforded the diacid **BC-3** (entry 2), while use of sodium methoxide in methanol gave diester **BC-4** (entry 3). Upon quenching with the sodium salt of an amine, the amide **BC-5** or **BC-6** was obtained (Table 1, entries 4 and 5). Although the synthesis of amides **BC-5** and **BC-6** was straightforward by this method, the yields were not high, and an additional bacteriochlorin side product having two CO-insertions, a known side reaction under these conditions,[47] was observed. The similarity of this byproduct to the target compound rendered purification somewhat difficult, hence the conversion of diacid **BC-3** to the corresponding diacid chloride was investigated as a means of preparing amides.

TABLE 1. Pd-Mediated Carbonylation



BC-Br^{3}Br^{13}

Entry	R^3, R^{13}	Reagent	Product	Yield
1		Bu_3SnH	**BC-2**	60%[a]
2		NaOH	**BC-3**	76%
3		NaOMe	**BC-4**	72%
4			**BC-5**	53%
5			**BC-6**	47%

[a] The 3-formyl-13-desbromobacteriochlorin also was isolated (25% yield).

B. Acid Chloride Derivatization. The formation of the bacteriochlorin diacid chloride was performed by adding excess oxalyl chloride to a green suspension of the diacid **BC-3** in CH_2Cl_2 at room temperature under an inert atmosphere. After being stirred for 6 h at room temperature, the suspension gave rise to a clear pink solution (λ_{max} of the Q_x and Q_y bands at 554 and 787 nm, versus 518 and 748 nm for the diacid), signaling formation of the diacid chloride. The volatile components were removed under reduced pressure, and the product was dried under high vacuum. The crude diacid chloride was dissolved in 1,2-dichloroethane and then treated with excess *N*-methylpiperazine to obtain bacteriochlorin-diamide **BC-6** in 53% yield.

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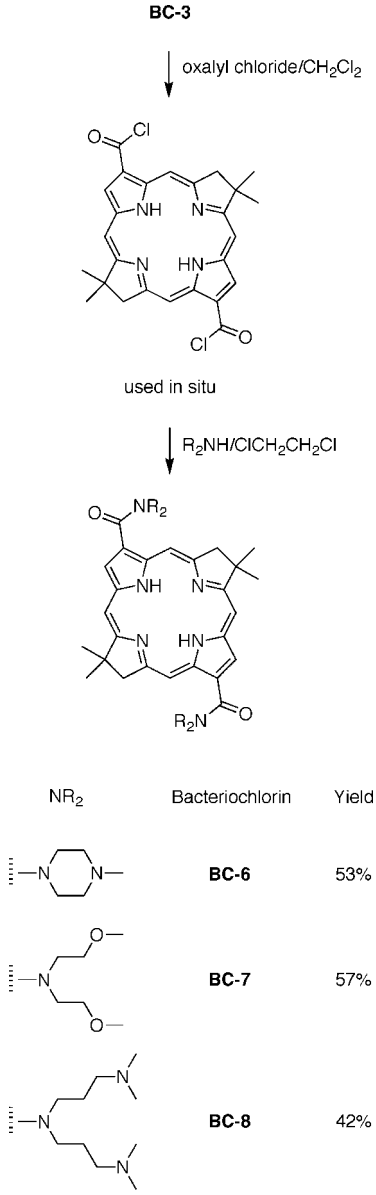
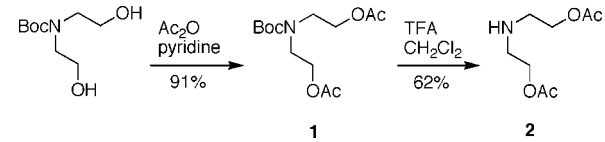
SCHEME 2



Although the yield of **BC-6** via the acid chloride was comparable to that upon direct carboxamide formation (47%, vide supra), the purification of the bacteriochlorin-diamide obtained via the acid chloride was simpler. Similar treatment of the crude diacid chloride with bis(2-methoxyethyl)amine or bis(3-dimethylaminopropyl)amine afforded bacteriochlorin-diamide **BC-7** or **BC-8** in 57% or 42% yield, respectively (Scheme 2). It is worth mentioning that addition of pyridine during the amide formation step led to the decomposition of the diacid chloride; on the other hand, use of excess amine in each coupling reaction afforded smooth formation of the target bacteriochlorin-diamide.

C. Reductive Amination. Conversion of the diformylbacteriochlorin **BC-2** to aminomethyl derivatives was examined via reductive amination, a process previously demonstrated with an aminophenylporphyrin[49] and a formylphenylbacteriochlorin[40] under mild conditions in dilute solution at room temperature.

SCHEME 3



One of the desired amines for reductive amination was synthesized as shown in Scheme 3. Reaction[50] of the Boc derivative of diethanolamine[51] with acetic anhydride gave the diacetate **1**. Exposure of the latter to TFA resulted in the diacetate of diethanolamine (**2**), a known compound previously prepared as the hydrochloride salt by an alternative route.[52]

Reductive amination was carried out at modest concentrations with sodium triacetoxyborohydride[53] in 1,2-dichloroethane containing acetic acid. Reductive amination of **BC-2** with dimethylamine, 1-methylpiperazine, or bis(3-dimethylaminopropyl)amine afforded **BC-9**, **BC-10**, or **BC-11**, respectively. Attempted purification of crude **BC-9**, **BC-10**, and **BC-11** with silica gel column chromatography proved difficult due to the high polarity of the products, and resulted in loss of a large amount of product. Hence, the crude bacteriochlorin products, which were quite clean, were used without chromatographic purification. Each bacteriochlorin was examined by ^{1}H NMR spectroscopy, mass spectrometry (LD-MS[54] or ESI-MS), and absorption spectroscopy. Each bacteriochlorin gave the expected characterization data, including a parent molecule ion (with the exception of **BC-11** where loss of one dialkylamino unit was observed). ^{1}H NMR spectroscopy of each crude product showed no starting material **BC-2**, and the product was estimated to be approximately 90% pure on the basis of NMR integration. Each crude product was sufficiently pure for subsequent quaternization (vide infra). Similar reductive amination of **BC-2** with **2** afforded the acetoxy-protected diethanolamine-bacteriochlorin. Deprotection of the latter in MeOH with K_2CO_3 afforded tetrahydroxy-bacteriochlorin **BC-12** in 33% yield following silica column chromatography (Scheme 4).

D. Sonogashira Coupling. A complementary approach for introducing a tertiary amine group into the bacteriochlorin side chain was investigated via Sonogashira coupling. Thus, reaction of **BC-Br^{3}Br^{13}** with 3-dimethylamino-1-propyne in the presence of $Pd(PPh_3)_2Cl_2$ and CuI in triethylamine at 60 °C for 43 h afforded diethynylbacteriochlorin **BC-13** in 67% yield. While such conditions[55] would typically give the copper chelate of a porphyrin or chlorin,[56,57] no copper insertion into the bacteriochlorin was observed. The alkynes in **BC-13** were reduced to the fully saturated alkyl moieties by catalytic hydrogenation to obtain dialkylbacteriochlorin **BC-14** in 83% yield (Scheme 5).

E. Quaternization. To achieve water solubility and to explore the utility of the bacteriochlorins in antimicrobial

(49) (a) Lindsey, J. S.; Mauzerall, D. C. *J. Am. Chem. Soc.* **1982**, *104*, 4498–4450. (b) Lindsey, J. S.; Delaney, J. K.; Mauzerall, D. C.; Linschitz, H. *J. Am. Chem. Soc.* **1988**, *110*, 3610–3621.

(50) Mori, M.; Tonogaki, K.; Kinoshita, A. *Org. Synth.* **2005**, *81*, 1–13.

(51) Ochiai, H.; Ohtani, T.; Ishida, A.; Kusumi, K.; Kato, M.; Kohno, H.; Odagaki, Y.; Kishikawa, K.; Yamamoto, S.; Takeda, H.; Obata, T.; Nakai, H.; Toda, M. *Bioorg. Med. Chem.* **2004**, *12*, 4645–4665.

(52) Dimo, I.; Bonnemain, B.; Hardouin, M. J.-C.; Lautrou, J. EP 118347, 1984.

(53) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849–3862.

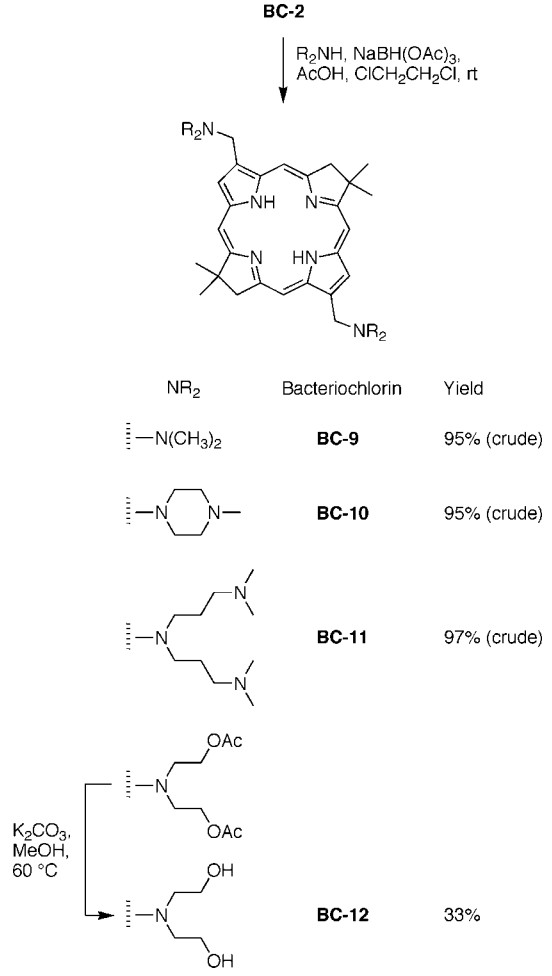
(54) Srinivasan, N.; Haney, C. A.; Lindsey, J. S.; Zhang, W.; Chait, B. T. *J. Porphyrins Phthalocyanines* **1999**, *3*, 283–291.

(55) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467–4470. (b) Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, 627–630.

(56) Wagner, R. W.; Johnson, T. E.; Li, F.; Lindsey, J. S. *J. Org. Chem.* **1995**, *60*, 5266–5273.

(57) Taniguchi, M.; Kim, M. N.; Ra, D.; Lindsey, J. S. *J. Org. Chem.* **2005**, *70*, 275–285.

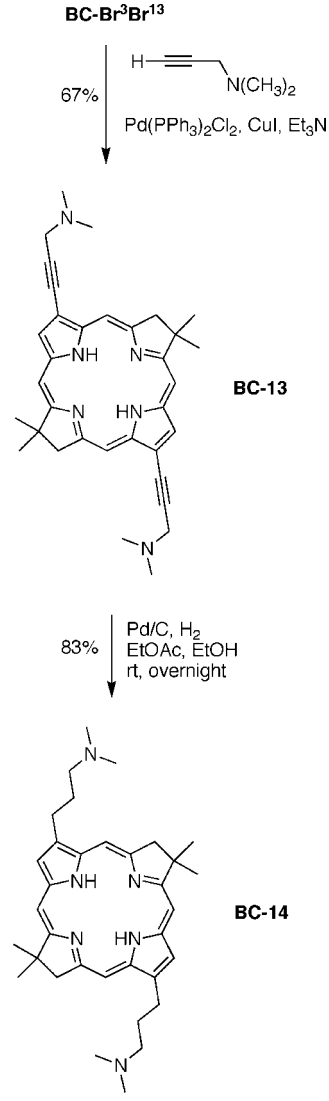
SCHEME 4



PDT,[1,4,5] the amine-containing bacteriochlorins were subjected to conditions for quaternization.[58] Thus, the overnight reaction of bacteriochlorin **BC-5** with excess methyl iodide in $CHCl_3$ at room temperature resulted in precipitation of the corresponding diiodide salt **BC-5′**. Similarly, bacteriochlorins **BC-6**, **BC-8**, **BC-9**, **BC-10**, **BC-11**, **BC-13**, and **BC-14** were converted to the corresponding diiodide or tetraiodide salt in excellent yield. **BC-10** and **BC-11** apparently underwent methylation only at the distal nitrogen(s) on each side chain, affording bacteriochlorins **BC-10′** and **BC-11′**, which contain a total of two and four positive charges, respectively. Evidence in support of this interpretation stems from ^{1}H NMR spectroscopy. In **BC-10**, a singlet at 2.34 ppm (6 protons) is attributed to the *N*-methyl group, whereas in **BC-10′**, the singlet appears at 3.19 ppm and integrates for 12 protons. Similarly for **BC-11** and **BC-11′**, the *N*-methyl peak resonates at 2.21 (24 protons) and 3.10 ppm (36 protons), respectively. More complex spectra would be expected if the proximal nitrogens were methylated preferentially, and a greater number of charges if both distal and proximal nitrogens were quaternized. The eight cationic bacteriochlorins obtained in this manner are shown in Chart 3. It deserves emphasis that the pyrrolic or pyrrolinic nitrogens did not methylate under these conditions. Moreover, the bacteriochlorins employed in crude form (**BC-9**, **BC-10**, and **BC-11**) gave the corresponding quaternary salts that were clean by ^{1}H NMR spectroscopy.

(58) Okada, E.; Tone, H.; Tsukushi, N.; Otsuki, Y.; Takeuchi, H.; Hojo, M. *Heterocycles* **1997**, *45*, 339–345.

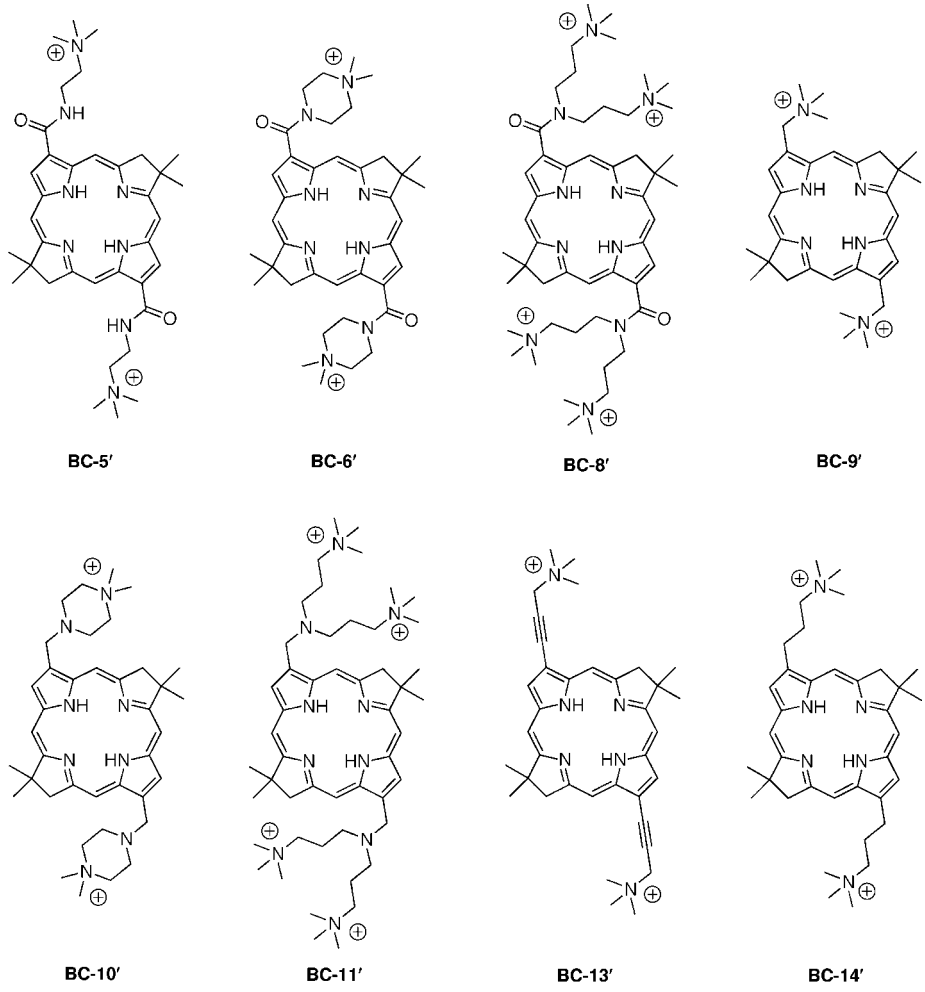
SCHEME 5



Each cationic bacteriochlorin was purified by washing the crude precipitate with organic solvents such as ether and CH_2Cl_2/hexanes. The cationic bacteriochlorins were characterized by ESI-MS, and by ^{1}H NMR spectroscopy in methanol-d_4 or DMSO-d_6. Absorption spectra were collected in water. Each cationic bacteriochlorin was readily soluble in water, giving rapid dissolution at room temperature and homogeneous solutions of at least 100 μm concentrations. The absorption spectra were characteristic of bacteriochlorins,[23] with relatively little change from those of the neutral bacteriochlorin precursors (vide infra). Although the cationic bacteriochlorins were soluble at modest concentration in water, higher quality ^{1}H NMR spectra typically were obtained in polar organic solvents than in water. To further examine water solubility, an aqueous solution of bacteriochlorin **BC-9′** or **BC-10′** was prepared ($\sim$1 mM, from $\sim$1 μmol bacteriochlorin in 1 mL of deionized water) at room temperature. After standing for 1 week, bacteriochlorin **BC-9′** showed no precipitation, whereas **BC-10′** showed a small amount of precipitation. Both bacteriochlorins were recovered intact with no noticeable degradation.

All of the cationic bacteriochlorins shown in Chart 3 have some structural resemblance to the dicationic porphyrin XF73, which is one of the most potent antibacterial PDT agents (Chart

CHART 3



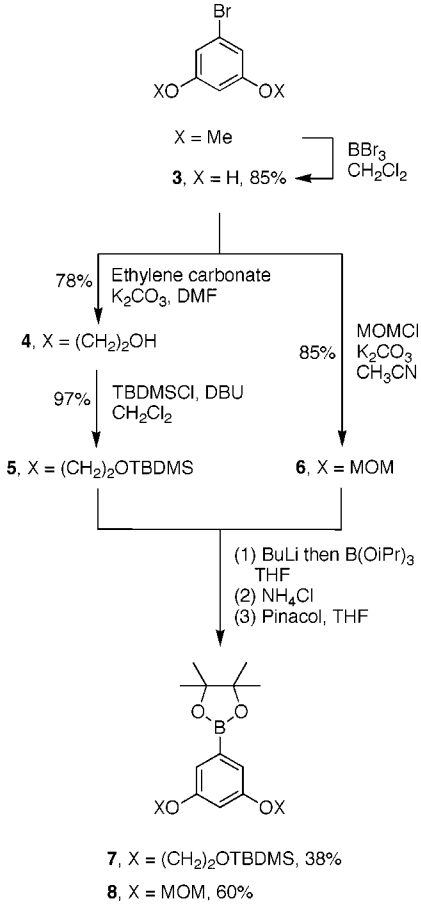
1),[15,16] yet are of comparable if not smaller size, lack the aryl moieties, and absorb in the NIR as desired for in vivo PDT applications. The eight bacteriochlorins provide a set of compounds for examination of structure−activity relationships while maintaining the NIR absorption. Several comparisons can be made: (i) side-chain linkages — **BC-6′** and **BC-8′** contain amide substituents and have as counterparts the methylene analogues **BC-10′** and **BC-11′**; (ii) structural rigidity — **BC-6′** is a structurally rigid analogue of **BC-5′**, and **BC-13′** is a structurally rigid analogue of **BC-14′**; (iii) number of positive charges — **BC-8′** and **BC-11′** contain four cationic groups whereas the six other bacteriochlorins contain only two cationic groups; and (iv) location of charge — **BC-9′** and analogue **BC-14′** contain methylammonium versus propylammonium substituents, which place the charge close to or more remote from the macrocycle, respectively.

II. Amphipathic or Lipophilic Bacteriochlorins. A complementary design was sought to obtain amphipathic or lipophilic bacteriochlorins. We turned to the introduction of 3,5-disubstituted aryl moieties to the bacteriochlorin nucleus via Suzuki coupling. The nature of the substituents at the 3- and 5-positions can be varied to tailor the hydrophobicity. This design approach required the preparation of 3,5-disubstituted arylboronic acids and esters, where two distinct types of substituents were employed: alkoxy groups and alkylaminocarbonyl groups.

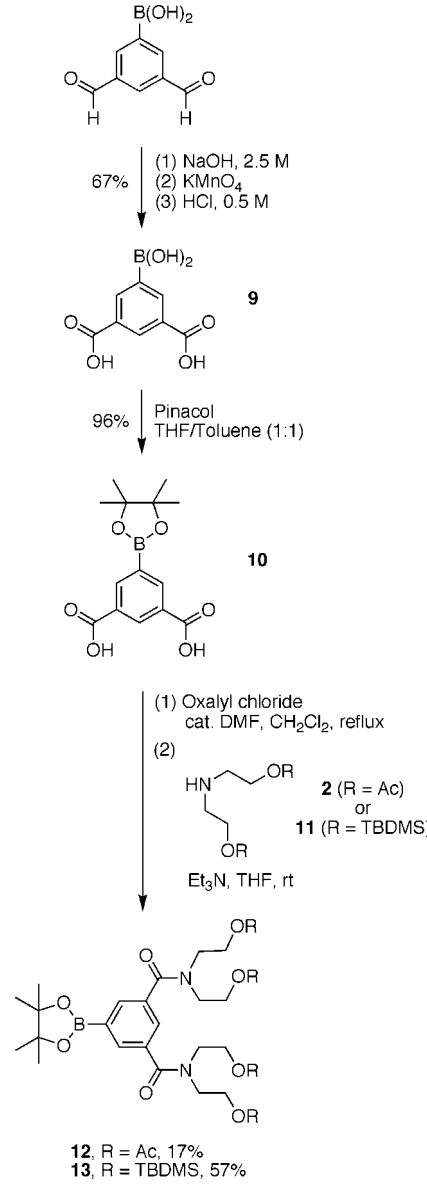
A. Arylboronic Acids and Esters. The two types of 3,5-substituents required distinct synthetic pathways to obtain the corresponding boronic acid derivatives. The first pathway relied on 5-bromoresorcinol (**3**),[59] which was alkylated to give the bis(hydroxyethyl) ether (and its TBDMS derivative) as well as the MOM-protected derivative (Scheme 6). 5-Bromoresorcinol was obtained by demethylation of 3,5-dimethoxy-1-bromobenzene with BBr_3. Treatment of **3** and K_2CO_3 with 2 equiv of ethylene carbonate in DMF (following a procedure for the preparation of a bis(hydroxyethyl ether) of resorcinol[60]) afforded 1-bromo-3,5-bis(2-hydroxyethoxy)benzene (**4**). Protection[61] of the diol **4** with *tert*-butylchlorodimethylsilane in the presence of DBU gave **5**. On the other hand, treatment[62] of **3** with chloromethyl methyl ether afforded the MOM-protected **6**. Metalation of **5** or **6** with BuLi, quenching with $B(OiPr)_3$, and treatment of the resulting boronic acid species with pinacol afford arylboronic ester **7** or **8**, respectively.

(59) Dol, G. C.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Eur. J. Org. Chem.* **1998**, 359–364.
(60) Summer, C. E., Jr.; Hitch, B. J.; Bernard, B. L. WO 9116292, 1991.
(61) Kim, S.; Chang, H. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3669–3670.
(62) Weyermann, P.; Diederich, F.; Gisselbrecht, J.-P.; Boudon, C.; Gross, M. *Helv. Chim. Acta* **2002**, *85*, 571–598.

SCHEME 6



SCHEME 7



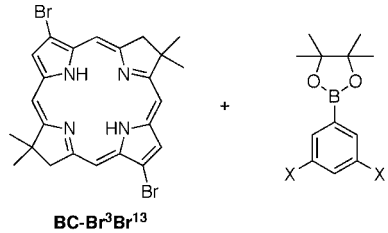
The second pathway entailed introduction of amides at the 3,5-positions of the arylboronic acid (Scheme 7). Oxidation[63] of 3,5-diformylphenylboronic acid in aqueous NaOH solution containing $KMnO_4$ followed by acidification afforded crude 5-boronoisophthalic acid (**9**), a known compound prepared previously by a different route,[64] which upon treatment with pinacol afforded crude 3,5-dicarboxyphenyldioxaborolane **10**. Conversion of the latter to the diacid chloride by reaction with oxalyl chloride in dichloromethane with a catalytic amount of DMF afforded a versatile intermediate for acylation. Treatment of the diacid chloride with dialkylamine **2** or bis(2-(*tert*-butyldimethylsilyloxy)ethyl)amine (**11**)[65] in THF containing triethylamine gave the tertiary amide **12** or **13**, respectively. Compounds **12** and **13** gave satisfactory characterization data, including elemental analysis data for **13**, which was obtained as a solid (**12** was an oil and was not so characterized).

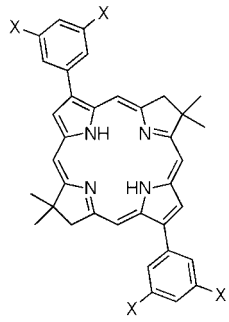
B. Suzuki Coupling. Suzuki coupling of **BC-Br^{3}Br^{13}** with the arylboronic acid derivatives was carried out under similar conditions used previously with porphyrins,[66] chlorins,[57] and bacteriochlorins.[40,42] The conditions are quite standard for Suzuki reactions [$Pd(PPh_3)_4$ in DMF/toluene (2:1) containing K_2CO_3 at 90 °C] except for the modest concentration of the bromo-porphyrinic substrate and the boronic ester, which in this case are approximately 3 and 9 mM, respectively. Thus, reaction of **BC-Br^{3}Br^{13}** with dioxaborolane **7**, **8**, or **13** gave **BC-15**, **BC-16**, or **BC-17**, respectively (Table 2). In the case of the dioxaborolane **12**, the instability of the acetyl protective groups with K_2CO_3 caused us to carry out the reaction with K_3PO_4 to afford **BC-18**. **BC-19** was obtained via a Suzuki coupling reaction with the boronic acid **9** in a mixture of ethanol/water.

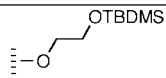
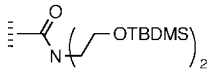
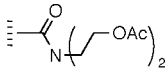
C. Side-Chain Manipulation. Several members of the set of diarylbacteriochlorins were subjected to manipulation of the side chains to obtain amphipathic products. The deprotection of the four TBDMS groups of **BC-15** was achieved with TBAF in anhydrous media[67] to afford the tetrakis(hydroxyethoxy)bacteriochlorin **BC-20**. Cleavage of the MOM groups of **BC-16** was carried out in a mixture of 10% HCl in MeOH to afford the bacteriochlorin **BC-21** bearing four phenolic OH groups. The phenol moieties of the latter were alkylated with methyl

(63) de Filippis, A.; Morin, C.; Thimon, C. *Synth. Commun.* **2001**, *32*, 2669–2676.
(64) Wang, Q.-C.; Ma, X.; Qu, D.-H.; Tian, H. *Chem.-Eur. J.* **2006**, *12*, 1088–1096.
(65) Grote Gansey, M. H. B.; Steemers, F. J.; Verboom, W.; Reinhoudt, D. N. *Synthesis* **1997**, 643–648.
(66) (a) Zhou, X.; Zhou, Z.-Y.; Mak, T. C. W.; Chan, K. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2519–2520. (b) Yu, L.; Lindsey, J. S. *Tetrahedron* **2001**, *57*, 9285–9298.
(67) Kolb, H. C.; Ley, S. V.; Slawin, A. M. Z.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2735–2762.

TABLE 2. Suzuki Coupling





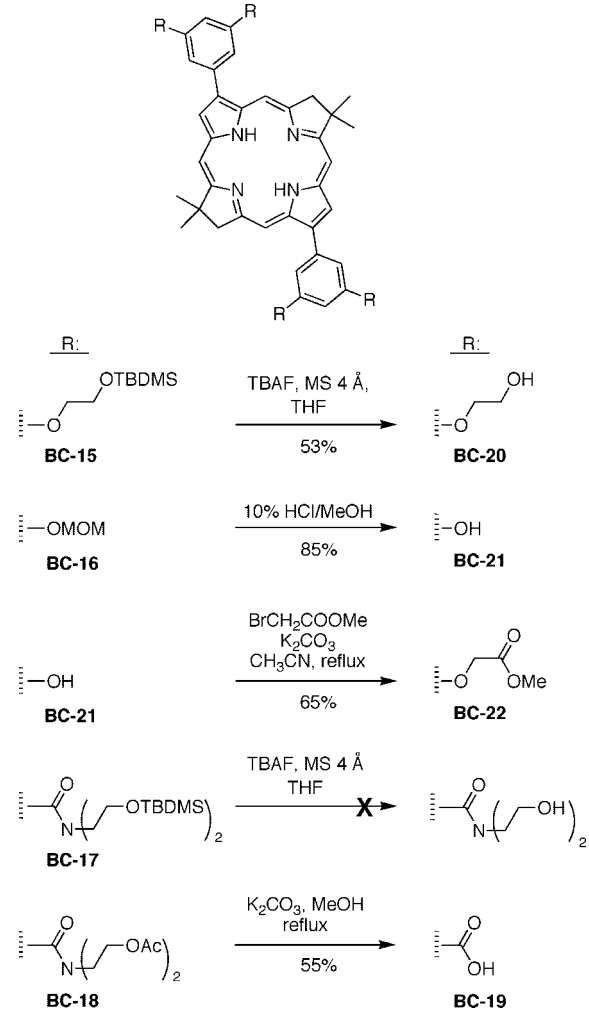
Entry	Ligand	X	Product	Yield
1	**7**		**BC-15**	53%
2	**8**		**BC-16**	61%
3	**13**		**BC-17**	56%
4[a]	**12**		**BC-18**	49%
5[b]	**9**[c]		**BC-19**	47%

[a] K_3PO_4 used in place of K_2CO_3. [b] EtOH/H_2O (1:1) used in place of DMF/toluene (2:1). [c] Boronic acid.

bromoacetate to give bacteriochlorin-tetraester **BC-22**. On the other hand, attempted cleavage of the eight TBDMS groups of **BC-17** (using similar conditions as those for **BC-15**) did not afford the expected tetrahydroxy-bacteriochlorin. An alternative route to obtain the same target bacteriochlorin envisaged cleavage of the eight acetyl groups of **BC-18**. However, treatment of **BC-18** in the presence of K_2CO_3 and MeOH gave hydrolysis of the amide, thereby yielding the bacteriochlorin-tetraacid **BC-19** as the major product (Scheme 8). Purification of **BC-19** was achieved by reversed-phase chromatography with water as the eluant.

The eight diarylbacteriochlorins **BC-15** to **BC-22** encompass a range of polarity that extends from rather lipophilic (**BC-15**, **BC-16**, **BC-22**) to more amphipathic (**BC-17**, **BC-18**, **BC-20**, **BC-21**) to quite polar (**BC-19**). Bacteriochlorin **BC-21** closely resembles the Foscan analogue (Chart 1) yet contains the

SCHEME 8



bacteriochlorin rather than chlorin chromophore, thereby affording absorption in the NIR rather than the red spectral region.

III. Spectral Properties. The bacteriochlorins prepared herein exhibit characteristic bacteriochlorin absorption spectra,[23] with near-UV bands and a long-wavelength band in the NIR region of comparable intensity. The long-wavelength (Q_y) absorption band for the 22 neutral (noncationic) bacteriochlorins appeared in the range of 720−772 nm. The fwhm of the Q_y band was 13−24 nm. The spectra are tabulated in Table 3; representative spectra for the neutral bacteriochlorins in CH_2Cl_2 are shown in Figure 1. The Q_y band of the free base bacteriochlorins (neutral bacteriochlorins in CH_2Cl_2) shifted bathochromically in the following trend as a consequence of the nature of the 3,13-substituents: alkyl (720 nm, **BC-14**) or aminomethyl (722 nm, **BC-9**) < bromo (729 nm, **BC-Br^{3}Br^{13}**) < 3° amide (732 nm, **BC-6**) < aryl (736 nm, **BC-15**) < 2° amide (744 nm, **BC-5**) < cyano (749 nm, **BC-1**) or ethynyl (749 nm, **BC-13**) < methoxycarbonyl (754 nm, **BC-4**) < formyl (772 nm, **BC-2**). The zinc chelate of the dicyanobacteriochlorin (**ZnBC-1**) absorbs at 761 nm, indicating a 12-nm bathochromic shift upon metalation of the free base bacteriochlorin **BC-1**. For the diarylbacteriochlorins, the location of the Q_y band (736−739 nm) was insensitive to the nature of the substituents (alkoxy, carboxy, aminocarbonyl) at the 3- and 5-positions of the aryl ring. Taken together, these data represent a significant expansion concerning the effects of substituents on the spectral properties

TABLE 3. Absorption Spectral Features of 3,13-Disubstituted Bacteriochlorins

bacteriochlorin	Q_y (nm)[a]	fwhm (nm)[a]	substituent
BC-Br^{3}Br^{13}	729	15	bromo
ZnBC-1	761	16	cyano
BC-1	749	14	cyano
BC-2	772	22	formyl
BC-3	748[b]	18[b]	carboxy
BC-4	754	18	methoxycarbonyl
BC-5	744	22	2° amide
BC-6	732	21	3° amide
BC-7	730	20	3° amide
BC-8	730	18	3° amide
BC-9	722	14	aminomethyl
BC-10	722	13	aminomethyl
BC-11	722	18	aminomethyl
BC-12	724	16	aminomethyl
BC-13	749	15	ethynyl
BC-14	720	14	alkyl
BC-15	736	20	3,5-dialkoxyphenyl
BC-16	737	21	3,5-dialkoxyphenyl
BC-17	738	21	3,5-diacylphenyl
BC-18	739	24	3,5-diacylphenyl
BC-19	734[c]	21[c]	3,5-dicarboxyphenyl
BC-20	736	20	3,5-dialkoxyphenyl
BC-21	737	22	3,5-dihydroxyphenyl
BC-22	737	21	3,5-dialkoxyphenyl
BC-5′	746[d]	27[d]	2° amide
BC-6′	736[d]	23[d]	3° amide
BC-8′	734[d]	20[d]	3° amide
BC-9′	733[d]	16[d]	aminomethyl
BC-10′	726[d]	16[d]	aminomethyl
BC-11′	726[d]	18[d]	aminomethyl
BC-13′	753[d]	18[d]	ethynyl
BC-14′	722[d]	17[d]	alkyl

[a] All data were obtained in CH_2Cl_2 at room temperature unless noted otherwise. [b] In THF. [c] In methanol. [d] In water.

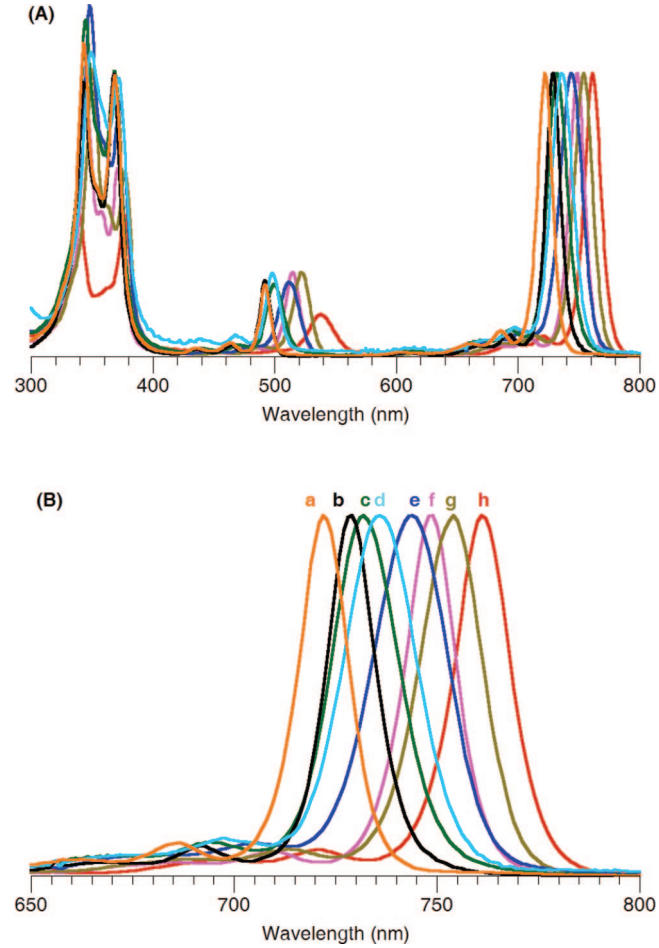


FIGURE 1. Absorption spectra in CH_2Cl_2 at room temperature of bacteriochlorins (normalized at the Q_y bands). (A) Entire spectra and (B) expansion of the Q_y region. The labels and the colors in the graph are as follows: **BC-9** (a, orange, 722 nm), **BC-Br^{3}Br^{13}** (b, black, 729 nm), **BC-6** (c, green, 732 nm), **BC-15** (d, light blue, 736 nm), **BC-5** (e, dark blue, 744 nm), **BC-1** (f, pink, 749 nm), **BC-4** (g, light brown, 754 nm), and **ZnBC-1** (h, red, 761 nm).

of bacteriochlorins,[68–70] and are consistent with those for prior bacteriochlorins where comparisons can be made.[42]

The cationic bacteriochlorins exhibited absorption spectra in water that closely resembled those of the neutral precursor bacteriochlorins in organic media. The Q_y absorption band remained quite sharp (fwhm = 16−27 nm) even in water, and was typically characterized by a bathochromic shift of 2−4 nm for the quaternized bacteriochlorins in water versus the neutral bacteriochlorins in CH_2Cl_2. One exception was **BC-9′**, which exhibited a bathochromic shift of 11 nm versus that of **BC-9**. In **BC-9′**, the positively charged nitrogen is separated from the bacteriochlorin π-system by only a single methylene group.

Outlook

A dibromobacteriochlorin bearing a stabilizing geminal dimethyl group in each pyrroline ring provides a versatile scaffold for synthetic elaboration via Pd-mediated coupling reactions. The Pd-coupling reactions enabled the attachment of cyano, formyl, carboxy, methoxycarbonyl, alkylaminocarbonyl, ethynyl, and aryl moieties onto the bacteriochlorin nucleus. The formyl moiety enabled derivatization via reductive amination, whereas the carboxy group was converted to the acid chloride to facilitate amide formation. The aryl moieties employed herein contained substituents (alkoxy, alkylaminocarbonyl, and carboxy groups) at the 3- and 5-positions, which provided further sites for structural modification. The quaternization of aminoalkyl moieties introduced 2 or 4 cationic moieties and thereby imparted water solubility. This extensive level of alteration of the local environment of the bacteriochlorin can be accomplished while retaining the absorption spectral features characteristic of bacteriochlorins. The ability to introduce diverse functional groups and structural motifs enables the local environment of the synthetic bacteriochlorin to be tailored across a very broad range of polarity, from hydrophilic to amphipathic to lipophilic, which represents a desirable attribute for the development of novel NIR-active compounds for applications in photomedicine.

Experimental Section

***tert*-Butyl Bis(2-acetoxyethyl)carbamate (1).** Following a reported procedure for acylation,[50] a solution of *tert*-butyl bis(2-hydroxyethyl)carbamate (1.03 g, 5.00 mmol) in pyridine (10 mL) at 0 °C was treated dropwise with acetic anhydride (1.88 mL, 20.0 mmol). The reaction mixture was stirred overnight at room temperature and then concentrated under vacuum. The resulting residue was subjected to column chromatography [silica, hexanes → hexanes/ethyl acetate (1:1)] to afford a colorless oil (1.32 g,

(68) Pandey, R. K.; Constantine, S.; Tsuchida, T.; Zheng, G.; Medforth, C. J.; Aoudia, M.; Kozyrev, A. N.; Rodgers, M. A. J.; Kato, H.; Smith, K. M.; Dougherty, T. J. *J. Med. Chem.* **1997**, *40*, 2770–2779.
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91%): ^{1}H NMR δ 1.46 (s, 9H), 2.06 (s, 3H), 2.07 (s, 3H), 3.48 (t, J = 5.8 Hz, 2H), 3.52 (t, J = 5.8 Hz, 2H), 4.16 (t, J = 5.7 Hz, 2H), 4.20 (t, J = 5.7 Hz, 2H); ^{13}C NMR δ 20.8, 28.2, 46.8, 46.9, 62.3, 62.6, 80.1, 155.1, 170.8. ESI-MS obsd 312.1417, calcd 312.1417 [(M + Na)$^+$, M = $C_{13}H_{23}NO_6$].

2-[(2-Acetoxyethyl)amino]ethyl Acetate (2). A solution of **1** (1.16 g, 4.00 mmol) in CH_2Cl_2 (20 mL) was treated with TFA (5.96 mL, 80.0 mmol). The reaction mixture was stirred for 30 min at room temperature, and then treated with a saturated aqueous solution of K_3PO_4. The organic layer was separated, found to contain 61 mg of impure compound, and discarded. The aqueous layer was extracted three times with ethyl acetate. The combined ethyl acetate extract was dried over Na_2SO_4 and concentrated under vacuum. The resulting colorless oil quickly turned brown and was used without further purification (470 mg, 62%): ^{1}H NMR δ 2.07 (s, 6H), 3.10 (t, J = 4.8 Hz, 4H), 4.27 (t, J = 4.8 Hz, 4H), 5.25 (br s, 1H); ^{13}C NMR 20.7, 47.3, 61.6, 170.9; ESI-MS obsd 190.1077, calcd 190.1073 [(M + H)$^+$, M = $C_8H_{15}NO_4$].

1-Bromo-3,5-bis(2-hydroxyethoxy)benzene (4). A solution of **3** (0.645 g, 3.41 mmol) in anhydrous DMF (10 mL) was treated with K_2CO_3 (1.41 g, 10.2 mmol). The mixture was stirred for 30 min, and then ethylene carbonate (0.601 g, 6.82 mmol) was added. The mixture was stirred for 3 h at reflux, and then solvent was removed under vacuum. Water (10 mL) was added, the mixture was stirred at 0 °C, and the solid was collected by filtration. The filtered material was subjected overnight to high vacuum to give the title compound (0.740 g, 78%): ^{1}H NMR (acetone-d_6) δ 3.86 (m, 4H), 4.00 (t, J = 5.9 Hz, 2H), 4.07 (t, J = 4.6 Hz, 4H), 6.50 (t, J = 1.8 Hz, 1H), 6.70 (d, J = 1.8 Hz, 2H); ^{13}C NMR (acetone-d_6) δ 61.0, 61.1, 71.0, 101.5, 111.1, 123.2, 161.9; ESI-MS obsd 277.0069, calcd 277.0069 [(M + H)$^+$, M = $C_{10}H_{13}O_4{}^{79}Br$]. Colorless needles were obtained upon crystallization in hot toluene: mp 78 °C. Anal. Calcd for $C_{10}H_{13}BrO_4$: C, 43.34; H, 4.73. Found: C, 43.64; H, 4.72.

1-Bromo-3,5-bis[2-(*tert*-butyldimethylsilyloxy)ethoxy]benzene (5). A solution of **4** (0.277 g, 1.00 mmol) in anhydrous CH_2Cl_2 (5 mL) was treated with DBU (329 μL, 2.20 mmol) and *tert*-butylchlorodimethylsilane (0.332 g, 2.20 mmol). The reaction mixture was stirred for 20 min at room temperature, and then concentrated under vacuum. The resulting residue was subjected to column chromatography [silica, hexanes/ethyl acetate (95:5)] to afford a white solid (0.490 g, 97%): mp 36 °C; ^{1}H NMR δ 0.10 (s, 12H), 0.91 (s, 18H), 3.95 (t, J = 4.5 Hz, 4H), 3.98 (t, J = 4.5 Hz, 4H), 6.40 (t, J = 2.0 Hz, 1H), 6.67 (d, J = 2.0 Hz, 2H); ^{13}C NMR δ −5.2, 18.4, 25.9, 61.8, 69.6, 100.9, 110.5, 122.8, 160.5; ESI-MS obsd 505.1802, calcd 505.1799 [(M + H)$^+$, M = $C_{22}H_{41}O_4Si_2{}^{79}Br$]. Anal. Calcd for $C_{22}H_{41}BrO_4Si_2$: C, 52.26; H, 8.17. Found: C, 52.09; H, 8.31.

1-Bromo-3,5-bis(methoxymethoxy)benzene (6). A solution of **3** (0.378 g, 2.00 mmol) in anhydrous acetonitrile (5 mL) was cooled to 0 °C in an ice bath and treated with K_2CO_3 (2.21 g, 16.0 mmol). The mixture was stirred for 30 min, and then MOM-Cl (607 μL, 8.0 mmol) was added. The mixture was stirred overnight at room temperature, whereupon the solvent was removed under vacuum. Water (10 mL) was added to the residue, and the mixture was extracted with ethyl acetate (3 × 50 mL). The resulting residue was subjected to column chromatography [silica, hexanes/ethyl acetate (95:5)] to afford a colorless oil (0.551 g, 85%): ^{1}H NMR δ 3.47 (s, 6H), 5.13 (s, 4H), 6.66 (s, 1H), 6.88 (s, 2H); ^{13}C NMR δ 56.1, 94.4, 103.9, 113.1, 122.7, 158.7; ESI-MS obsd 277.0069, calcd 277.0069 [(M + H)$^+$, M = $C_{10}H_{13}O_4{}^{79}Br$].

2-(3,5-Bis[2-(*tert*-butyldimethylsilyloxy)ethoxy]phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (7). A solution of **5** (0.506 g, 1.00 mmol) in anhydrous THF (5 mL) was cooled to −78 °C. *n*-Butyllithium (640 μL, 2.5 M in hexanes, 1.6 mmol) was added dropwise, the mixture was stirred 1 h at −78 °C, and then triisopropylborate (722 μL, 5.00 mmol) was added. The mixture was stirred for 2 h at −78 °C, and then allowed to warm overnight to room temperature. A saturated solution of aqueous NH_4Cl was added, and the mixture was stirred for 1 h. Ethyl acetate was added, and the organic layer was separated, dried over Na_2SO_4, and concentrated under reduced pressure. The crude mixture was dissolved in a mixture of THF/toluene (40 mL, 1:1), to which pinacol (0.118 g, 1.00 mmol) was added. The crude mixture was warmed in a hot water bath and concentrated under vacuum. A mixture of THF/toluene (40 mL, 1:1) was added, and the mixture again was concentrated under vacuum. Dichloromethane was added, and the mixture was washed with water (5 × 20 mL). The resulting residue was subjected to column chromatography [silica, hexanes/ethyl acetate (4:1)] to afford a white solid (0.209 g, 38%): mp 55 °C; ^{1}H NMR δ 0.10 (s, 12H), 0.91 (s, 18H), 1.33 (s, 12H), 3.95 (t, J = 5.1 Hz, 4H), 4.05 (t, J = 5.1 Hz, 4H), 6.59 (t, J = 2.0 Hz, 1H), 6.94 (d, J = 2.0 Hz, 2H); ^{13}C NMR δ −5.2, 18.4, 24.8, 25.9, 62.0, 69.3, 83.8, 105.8, 112.3, 159.6; ESI-MS obsd 553.3550, calcd 553.3546 [(M + H)$^+$, M = $C_{28}H_{53}BO_6Si_2$]. Anal. Calcd for $C_{28}H_{53}BO_6Si_2$: C, 60.85; H, 9.67. Found: C, 61.06; H, 9.89.

2-(3,5-Bis(methoxymethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (8). A solution of TMEDA (343 μL, 2.30 mmol) in anhydrous THF (10 mL) at −78 °C was treated with *n*-butyllithium (924 μL, 2.5 M in hexanes, 2.30 mmol). After stirring for 30 min at −78 °C, a solution of **6** (0.400 g, 1.44 mmol) in anhydrous THF (10 mL) was added dropwise, and the mixture was stirred for 1 h at −78 °C. Triisopropylborate (1.04 mL, 7.20 mmol) was added. The mixture was stirred for 2 h at −78 °C, and then allowed to warm overnight to room temperature. A saturated solution of aqueous NH_4Cl was added, and the mixture was stirred for 1 h. Ethyl acetate was added, and the organic layer was separated, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting crude material was dissolved in a mixture of THF/toluene (40 mL, 1:1), and pinacol (1.20 g, 14.4 mmol) was added. The crude mixture was concentrated under vacuum. A mixture of THF/toluene (40 mL, 1:1) was added, and again the mixture was concentrated under vacuum. Dichloromethane was added, and the mixture was washed with water (5 × 20 mL). Drying of the residue and crystallization from diethyl ether at −20 °C provided a colorless solid (0.278 g, 60%): mp 46 °C; ^{1}H NMR δ 1.33 (s, 12H), 3.48 (s, 6H), 5.18 (s, 4H), 6.82 (t, J = 2.2 Hz, 1H), 7.12 (d, J = 2.2 Hz, 2H); ^{13}C NMR δ 24.8, 56.0, 83.9, 94.3, 108.3, 115.3, 157.8; ESI-MS obsd 325.1822, calcd 325.1816 [(M + H)$^+$, M = $C_{16}H_{25}BO_6$]. Anal. Calcd for $C_{16}H_{25}BO_6$: C, 59.28; H, 7.77. Found: C, 59.54; H, 7.87.

5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)isophthalic Acid (10). A solution of 3,5-diformylphenylboronic acid (1.00 g, 5.60 mmol) in aqueous sodium hydroxide (9 mL of a 2.5 M solution) was treated with a freshly prepared solution of potassium permanganate (414 mg, 2.62 mmol) in water (15 mL). This addition was repeated twice at 1 h intervals. After the solution was stirred overnight, ethanol (5 mL) was added and the mixture was stirred at 50 °C for 10 min. After cooling and filtration on Celite, the filtrate was acidified to pH 2.5 with 0.5 M hydrochloric acid. Filtration of the resulting precipitate gave 5-boronoisophthalic acid (**9**) as a white powder (0.793 g, 67%): mp >300 °C; ^{1}H NMR (DMSO-d_6) 8.42 (br s, 2H), 8.50 (s, 1H), 8.61 (s, 2H), 13.18 (br s, 2H); ^{13}C NMR (DMSO-d_6) 130.3, 131.5, 139.1, 166.9; ESI-MS obsd 211.0410, calcd 211.0408 [(M + H)$^+$, M = $C_{10}H_7BO_6$]. The compound did not give satisfactory elemental analysis without assuming the presence of a hemihydrate (Anal. Calcd for $2C_8H_7BO_6 \cdot H_2O$: C, 43.88; H, 3.68. Found: C, 43.82; H, 3.64) yet was sufficiently pure for boronate ester formation. A mixture of crude **9** (0.210 g, 1.00 mmol) and pinacol (0.118 g, 1.00 mmol) was treated with a mixture of THF/toluene (40 mL, 1:1). The crude mixture was concentrated to dryness under vacuum. This procedure (solvents addition/evaporation) was repeated twice. Crystallization of the white powder in diethyl ether afforded white crystals (0.280 g, 96%): mp >300 °C; ^{1}H NMR (DMSO-d_6) δ 1.32 (s, 12H), 8.42 (d, J = 1.8 Hz, 2H), 8.56 (t, J = 1.8 Hz, 1H), 13.34 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 24.6, 84.3, 130.8, 132.6, 138.8, 166.4; ESI-MS obsd 293.1198, calcd 293.1190 [(M + H)$^+$, M = $C_{14}H_{17}BO_6$]. The title compound

so obtained did not quite give a satisfactory elemental analysis (Anal. Calcd for $C_{14}H_{17}BO_6$: C, 57.57; H, 5.87. Found: C, 58.01; H, 5.98) yet was sufficiently pure for conversion to the acid chloride and subsequent amidation.

***N*¹,*N*¹,*N*³,*N*³-Tetrakis[2-(acetoxy)ethyl]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isophthalamide (12).** A suspension of **10** (0.200 g, 0.684 mmol) in anhydrous CH_2Cl_2 (20 mL) was treated with 10 μL of anhydrous DMF, and the mixture was cooled to 0 °C. Then oxalyl chloride (294 μL, 3.42 mmol) was added dropwise. The mixture was refluxed for 6 h, and then the solvent was removed under vacuum. The residue was dried under high vacuum. The crude mixture was dissolved in anhydrous THF (10 mL), and this solution was added dropwise to a solution of **2** (0.259 g, 1.37 mmol) and triethylamine (475 μL, 3.42 mmol) in anhydrous THF (20 mL) at 0 °C. The mixture was stirred for 1 h at 0 °C, and then allowed to warm overnight to room temperature. The solvent was removed under vacuum. Water (10 mL) was added to the residue, and the mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic extract was dried over Na_2SO_4 and concentrated under vacuum. The resulting residue was subjected to column chromatography [silica, hexanes/ethyl acetate (4:1)] to afford a colorless oil (76 mg, 17%): ^{1}H NMR δ 1.33 (s, 12H), 2.09 (s, 12H), 3.59 (br s, 4H), 3.79 (br s, 4H), 4.11 (br s, 4H), 4.36 (br s, 4H), 7.48 (t, J = 1.7 Hz, 1H), 7.87 (d, J = 1.7 Hz, 2H); ^{13}C NMR δ 20.7, 24.8, 44.4, 48.6, 61.2, 61.9, 84.3, 127.4, 133.8, 135.9, 170.7, 171.6; ESI-MS obsd 635.2980, calcd 635.2981 [(M + H)$^+$, M = $C_{30}H_{43}BN_2O_{12}$].

***N*¹,*N*¹,*N*³,*N*³-Tetrakis[2-(*tert*-butyldimethylsilyloxy)ethyl]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isophthalamide (13).** A suspension of **10** (0.292 g, 1.00 mmol) in anhydrous CH_2Cl_2 (20 mL) was treated with 10 μL of anhydrous DMF, and the mixture was cooled to 0 °C. Then oxalyl chloride (430. μL, 5.00 mmol) was added dropwise. The mixture was refluxed for 6 h, and then the solvent was removed under vacuum. The residue was dried under high vacuum. The crude mixture was dissolved in anhydrous THF (10 mL), and this solution was added dropwise to a solution of **11** (0.667 g, 2.00 mmol) and triethylamine (694 μL, 5.00 mmol) in anhydrous THF (20 mL) at 0 °C. The mixture was stirred for 1 h at 0 °C, and then allowed to warm overnight to room temperature. The solvent was removed under vacuum. Water (10 mL) was added to the residue, and the mixture was extracted with ethyl acetate (3 × 50 mL). The organic extract was dried over Na_2SO_4 and concentrated under vacuum. The resulting residue was subjected to column chromatography [silica, hexanes/ethyl acetate (4:1)] to afford a colorless oil that slowly solidified upon cooling to give a colorless solid (0.531 g, 57%): mp 73 °C; ^{1}H NMR δ −0.03 (s, 12H), 0.06 (s, 12H), 0.82 (s, 18H), 0.89 (s, 18H), 1.28 (s, 12H), 3.43 (t, J = 5.7 Hz, 4H), 3.60 (t, J = 5.7 Hz, 4H), 3.66 (t, J = 5.7 Hz, 4H), 3.85 (t, J = 5.7 Hz, 4H), 7.44 (t, J = 1.7 Hz, 1H), 7.81 (d, J = 1.7 Hz, 2H); ^{13}C NMR δ −5.5, −5.4, 18.2, 24.8, 25.9, 48.0, 52.2, 60.9, 61.1, 84.0, 127.4, 133.7, 136.5, 171.4; ESI-MS obsd 923.6027, calcd 923.6018 [(M + H)$^+$, M = $C_{46}H_{91}BN_2O_8Si_4$]. Anal. Calcd for $C_{46}H_{91}BN_2O_8Si_4$: C, 59.83; H, 9.93; N, 3.03. Found: C, 59.55; H, 9.93; N, 3.03.

Zn(II)-3,13-Dicyano-8,8,18,18-tetramethylbacteriochlorin (Zn-BC-1). Following a general procedure for cyanation of aryl bromides,[43] a mixture of **BC-Br³Br¹³** (70.0 mg, 0.133 mmol), $Zn(CN)_2$ (77.0 mg, 0.656 mmol), and $Pd(PPh_3)_4$ (35 mg, 0.030 mmol) was heated to 100 °C in DMF (12 mL) in a Schlenk flask under anaerobic conditions. After 3 h, the reaction mixture was allowed to cool to room temperature and filtered through a pad of Celite, then the flask and Celite were rinsed with ethyl acetate (30 mL × 3). The filtrate was concentrated, and the resulting red-pink solid was chromatographed [silica, hexanes/CH_2Cl_2/ethyl acetate (3:1:1 → 1:1:1)] to afford a pink-purple solid (57 mg, 89%): ^{1}H NMR ($CDCl_3$/CD_3OD, (9:1)) δ 1.86 (s, 12H), 4.32 (s, 4H), 8.41 (s, 2H), 8.70 (s, 2H), 8.93 (s, 2H); LD-MS obsd 482.1; ESI-MS obsd 482.1189, calcd 482.1197 ($C_{26}H_{22}N_6Zn$); λ_{abs} (CH_2Cl_2) 339, 377, 538, 761 nm.

3,13-Dicyano-8,8,18,18-tetramethylbacteriochlorin (BC-1). A mixture of **ZnBC-1** (7.0 mg, 0.015 mmol) in $CHCl_3$ (1 mL) was treated with TFA (23 μL, 0.31 mmol). The resulting red solution was stirred at room temperature, and the progress of the reaction was monitored by TLC and absorption spectroscopy. After 4 h, the reaction mixture was diluted with CH_2Cl_2 (30 mL) and saturated aqueous $NaHCO_3$ solution (20 mL) was added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (20 mL). The combined organic extract was washed with water (30 mL) and brine (30 mL), dried (Na_2SO_4), and filtered. The filtrate was concentrated to afford a green solid. The crude product was dissolved in a minimum amount of CH_2Cl_2 and chromatographed [silica, hexanes/CH_2Cl_2/ethyl acetate (8:1:1 → 1:1:1)] to obtain the first band (green, the title compound; 4.0 mg, 63%) and the second band (pink, the starting material; 2.5 mg). Data for the title compound: ^{1}H NMR δ −1.65 (br s, 2H), 1.94 (s, 12H), 4.43 (s, 4H), 8.67 (s, 2H), 8.98 (s, 2H), 9.03 (s, 2H); LD-MS obsd 420.7; ESI-MS obsd 421.2123, calcd 421.2135 [(M + H)$^+$, M = $C_{26}H_{24}N_6$]; λ_{abs} (CH_2Cl_2) 346, 371, 515, 749 nm.

3,13-Diformyl-8,8,18,18-tetramethylbacteriochlorin (BC-2). Following a procedure for reductive carbonylation,[48] a mixture of **BC-Br³Br¹³** (104 mg, 0.200 mmol) and $Pd(PPh_3)_4$ (463 mg, 0.400 mmol) was dried under vacuum for 1 h. The reaction flask was filled with CO gas, and anhydrous DMF/toluene [10 mL, (1:1)] was added. CO gas was bubbled through the stirred reaction mixture for 2 h at 70 °C. After 2 h, the reaction mixture was treated with Bu_3SnH (107 μL, 0.400 mmol), and then stirred for 10 min. The reaction mixture was then cooled to room temperature and filtered through a short Celite column, which was eluted with ethyl acetate. The filtrate was concentrated and subjected to column chromatography [silica, CH_2Cl_2]. The 3-formyl-13-desbromobacteriochlorin (20 mg, 25%) eluted first, followed by the expected title compound (50 mg, 60%): ^{1}H NMR δ −1.17 (br s, 2H), 1.95 (s, 12H), 4.42 (s, 4H), 8.65 (s, 2H), 9.12 (s, 2H), 9.58 (s, 2H), 11.14 (s, 2H); LD-MS obsd 426.8; ESI-MS obsd 427.2124, calcd 427.2128 [(M + H)$^+$, M = $C_{26}H_{26}N_4O_2$]; λ_{abs} (CH_2Cl_2) 362, 537, 772 nm. Data for 3-formyl-8,8,18,18-tetramethylbacteriochlorin: ^{1}H NMR δ −0.66 (br s, 1 H), −0.42 (br s, 1 H), 1.86 (s, 12 H), 4.21 (s, 2 H), 4.25 (s, 2 H), 8.30 (s, 1 H), 8.38 (s, 1 H), 8.40 (s, 1 H), 8.54 (m, 2 H), 8.79 (d, J = 1.65 Hz, 1 H), 9.32 (s, 1 H), 11.09 (s, 1 H); ESI-MS obsd 399.2181, calcd 399.2179 [(M + H)$^+$, M = $C_{25}H_{26}N_4O$]; λ_{abs} (CH_2Cl_2) 315, 515, 731 nm.

3,13-Dicarboxy-8,8,18,18-tetramethylbacteriochlorin (BC-3). Following a procedure for Pd-mediated CO insertion in chlorins,[48] a mixture of **BC-Br³Br¹³** (21 mg, 0.040 mmol) and $Pd(PPh_3)_4$ (91 mg, 0.080 mmol) was dried in a Schlenk flask for 1 h. A mixture of DMF and toluene (2 mL each, degassed for 10 min) was added to the flask, and CO gas was bubbled through the reaction mixture for 2 h at 70 °C. The initially green mixture turned pink red. The bubbling of CO was stopped, and aqueous NaOH (0.50 mL, 2 M) was introduced to the flask through a syringe. The reaction mixture was allowed to cool to room temperature in 30 min. Water (10 mL), 2 M aqueous NaOH (2 mL), and CH_2Cl_2 (10 mL) were added. The layers were separated. The organic layer was extracted with H_2O (5 mL) and 2 M aqueous NaOH (2 mL). The combined aqueous layer was washed with CH_2Cl_2 (3 × 20 mL). The aqueous layer was carefully acidified to pH 5 with 2 M aqueous HCl to precipitate the product. The solid was collected upon centrifugation and dried under high vacuum to obtain a pink red solid (14 mg, 76%): ^{1}H NMR (THF-d_8) δ −1.52 (br s, 2H), 1.95 (s, 12H), 4.46 (s, 4H), 8.80 (s, 2H), 9.25 (s, 2H), 9.86 (s, 2H), 11.75 (br s, 2H); LD-MS obsd 458.8; ESI-MS obsd 458.1946, calcd 458.1948 ($C_{26}H_{26}N_4O_4$); λ_{abs} (THF) 348, 375, 518, 748 nm.

3,13-Bis(methoxycarbonyl)-8,8,18,18-tetramethylbacteriochlorin (BC-4). The carbonylation was performed with 10.5 mg (0.0200 mmol) of **BC-Br³Br¹³** following the above procedure for **BC-3**. After 2 h at 70 °C, the reaction mixture was quenched with excess NaOMe (22 mg, 0.50 mmol) in MeOH (1 mL) to obtain a purple solid (7.0 mg, 72%): ^{1}H NMR δ −1.46 (br s, 2H), 1.92 (s, 12H),

4.25 (s, 6H), 4.41 (s, 4H), 8.61 (s, 2H), 9.17 (s, 2H), 9.72 (s, 2H); ESI-MS obsd 487.2327, calcd 487.2339 [$(M + H)^+$, M = $C_{28}H_{30}N_4O_4$]; λ_{abs} (CH_2Cl_2) 350, 377, 522, 754 nm.

3,13-Bis[(2-(dimethylamino)ethylamino)carbonyl]-8,8,18,18-tetramethylbacteriochlorin (BC-5). The carbonylation was performed with 21 mg (0.040 mmol) of **BC-Br^{3}Br^{13}** following the above procedure for **BC-3**. After 2 h at 70 °C, the bubbling of CO gas was stopped and the sodium salt of *N*,*N*-dimethylaminoethylamine in *N*,*N*-dimethylaminoethylamine (0.5 mL) [freshly prepared by adding *N*,*N*-dimethylaminoethylamine (1.0 mL, 9.2 mmol) to NaH (20 mg, 0.83 mmol, 95%) under an inert atmosphere] was introduced via syringe. The heat was turned off and the reaction mixture was allowed to cool to room temperature in 30 min. CH_2Cl_2 (20 mL) was added, and the reaction mixture was filtered through a pad of Celite, which was rinsed with CH_2Cl_2 until the filtrate was colorless. The filtrate was treated with saturated aqueous NH_4Cl (30 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (30 mL). The combined organic extract was washed with H_2O (40 mL) and brine (40 mL), dried (Na_2SO_4), and filtered. The filtrate was concentrated to afford a green solid. The crude product was dissolved in a minimum amount of CH_2Cl_2 and chromatographed [silica, eluant composition: 95 mL of CH_2Cl_2 containing 3 mL of MeOH and 2 mL of MeOH that was saturated with NH_3] to obtain a green solid (12.6 mg, 53%): ^{1}H NMR δ −1.64 (br s, 2H), 1.90 (s, 12H), 2.43 (s, 12H), 2.77 (t, J = 6 Hz, 4H), 3.86(t, J = 6 Hz, 4H), 4.40 (s, 4H), 7.50 (br s, 2H), 8.61 (s, 2H), 8.89 (s, 2H), 9.75 (s, 2H); LD-MS obsd 599.7; ESI-MS obsd 300.1948, calcd 300.1944 [$(M + 2H)^{2+}$, M = $C_{34}H_{46}N_8O_2$]; λ_{abs} (CH_2Cl_2) 348, 373, 512, 744 nm.

3,13-Bis[(2-(trimethylammonio)ethylamino)carbonyl]-8,8,18,18-tetramethylbacteriochlorin Diiodide (BC-5′). Following a standard procedure for amine quaternization,[58] a solution of **BC-5** (7.0 mg, 0.012 mmol) in $CHCl_3$ (1 mL, stabilized with EtOH) was treated with MeI (30 μL, 0.48 mmol, 40 equiv) under argon. The mixture was stirred at room temperature for 24 h. At this time a solid had settled on the walls and bottom of the vial. Excess methyl iodide and solvent were removed under reduced pressure at ambient temperature. Purification of the crude product was achieved by adding anhydrous diethyl ether to the crude product (5.0 mL). The mixture was sonicated for 2 min in a benchtop sonication bath. The mixture was centrifuged and the supernatant was removed, leaving the desired product as a solid. The resulting solid was dried under high vacuum to afford a pink-red solid (7.5 mg, 71%): ^{1}H NMR (CD_3OD) δ 1.98 (s, 12H), 3.42 (s, 18H), 3.88 (t, J = 6.4 Hz, 4H), 4.20 (t, J = 6.4 Hz, 4H), 4.45 (s, 4H), 8.80 (s, 2H), 9.15 (s, 2H), 9.69 (s, 2H); ESI-MS obsd 314.2106, calcd 314.2101 (M^{2+}, M = $C_{36}H_{52}N_8O_2$]; λ_{abs} (H_2O) 346, 371, 513, 746 nm. An alternative purification procedure was as follows: The crude product was dissolved in a minimum amount of MeOH (∼1 mL) and diethyl ether (∼15 mL) was added. The resulting precipitate was filtered and washed with CH_2Cl_2/hexanes [2 mL (1:2), then 2 mL (2:1)].

3,13-Bis(4-methylpiperazin-1-ylcarbonyl)-8,8,18,18-tetramethylbacteriochlorin (BC-6). Method A: The carbonyl insertion reaction was performed with 21 mg (0.040 mmol) of **BC-Br^{3}Br^{13}** following a procedure similar to that described above for **BC-5**. After 2 h at 70 °C, the reaction mixture was quenched with the sodium salt of *N*-methylpiperazine in *N*-methylpiperazine (0.5 mL) to obtain the title compound as a green solid (11.8 mg, 47%): ^{1}H NMR δ −1.95 (br s, 2H), 1.93 (s, 12H), 2.40 (s, 6H), 2.45 (m, 4H), 2.75 (m, 4H), 3.79 (m, 4H), 4.18 (m, 4H), 4.40 (s, 4H), 8.63 (s, 2H), 8.69 (s, 2H), 8.95 (s, 2H); LD-MS obsd 622.8; ESI-MS obsd 623.3807, calcd 623.3816 [$(M + H)^+$, M = $C_{36}H_{46}N_8O_2$]; λ_{abs} (CH_2Cl_2) 345, 368, 500, 732 nm. **Method B:** The diacid **BC-3** (10. mg, 0.022 mmol) in a 10-mL round-bottomed flask under inert atmosphere was suspended in CH_2Cl_2 (4.0 mL). To this green suspension were added DMF (10 μL) and oxalyl chloride (20 μL), and the resulting mixture was stirred at room temperature for 6 h. The reaction mixture became a clear pink solution and the absorption spectrum showed a shift of the Q_x and Q_y bands to 554 and 787 nm, respectively, indicating the formation of diacid chloride. The reaction mixture was concentrated under reduced pressure and dried under high vacuum. The resulting solid was dissolved in 1,2-dichloroethane (4 mL) and then treated with *N*-methylpiperazine (200 μL) at room temperature. The stirring was continued overnight. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and H_2O (20 mL) was added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (30 mL). The combined organic extract was washed with H_2O (40 mL) and brine (40 mL), dried (Na_2SO_4), and filtered. The filtrate was concentrated to obtain a green solid. The crude product was dissolved in a minimum amount of CH_2Cl_2 and chromatographed [silica, CH_2Cl_2/MeOH (97:3 → 90:10)] to obtain the title compound as a green solid (7.2 mg, 53%). The data were consistent with those for a sample obtained by Method A.

3,13-Bis(*N*,*N*-dimethylaminomethyl)-8,8,18,18-tetramethylbacteriochlorin (BC-9). A solution of **BC-2** (5.7 mg, 0.012 mmol) in 1,2-dichloroethane (1.0 mL) was treated with molecular sieves 4 Å (two or three beads) and dimethylamine (60 μL, 0.12 mmol, 2.0 M in THF). The mixture was stirred at room temperature under argon for 5 min before adding $NaBH(OAc)_3$ (10. mg, 0.048 mmol) all at once, followed by glacial acetic acid (1.4 μL, 0.024 mmol). The reaction was complete after 4 h as determined by TLC (silica, CH_2Cl_2). After 4 h, the mixture was quenched by the addition of saturated aqueous $NaHCO_3$ (2 mL) and ethyl acetate. The organic layer was separated, dried (Na_2SO_4), and concentrated to yield a green solid (6 mg, ∼90% pure, ∼95% yield): ^{1}H NMR δ −2.26 (br s, 2H), 1.96 (s, 12H), 2.59 (s, 12H), 4.48 (s, 4H), 4.67 (s, 4H), 8.63 (s, 2H), 8.66 (s, 2H), 8.92 (s, 2H); ESI-MS obsd 243.1741, calcd 243.1729 [$(M + 2H)^{2+}$, M = $C_{30}H_{40}N_6$]; λ_{abs} (CH_2Cl_2) 343, 369, 492, 722 nm.

3,13-Bis[bis(2-hydroxyethyl)aminomethyl]-8,8,18,18-tetramethylbacteriochlorin (BC-12). Following the procedure described for the preparation of **BC-9**, reductive amination of **BC-2** (5.0 mg, 0.012 mmol) with **2** (45 mg, 0.24 mmol) at 36 °C for 16 h gave a green solid. TLC analysis showed the disappearance of **BC-2**. LD-MS analysis of the crude product showed a dominant peak at *m*/*z* 772.5 (calcd 772.4, $C_{42}H_{56}N_6O_8$). The crude product was deprotected by dissolution in MeOH (10 mL) and treatment with K_2CO_3 (260 mg, 0.48 mmol). After the mixture was stirred at 60 °C for 1 h, the deprotection was complete as determined by TLC (silica, CH_2Cl_2). The mixture was quenched by the addition of water and ethyl acetate. The organic layer was separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic extract was dried (Na_2SO_4) and concentrated to yield a green solid. The crude mixture was subjected to column chromatography [silica, ethyl acetate/methanol (9:1 → 4:1)], and the fractions containing the desired product were combined and concentrated. The resulting product was dissolved in a minimum amount of CH_2Cl_2 (∼0.5 mL), and hexanes (∼10 mL) was added. The resulting precipitate was collected to yield a green solid (2.4 mg, 33%): ^{1}H NMR δ −2.21 (br s, 2H), 1.91 (s, 2H), 1.93 (s, 2H), 1.95 (s, 12H), 3.09 (t, J = 5.13 Hz, 8H), 3.80 (t, J = 5.13 Hz, 8H), 4.46 (s, 4H), 4.97 (s, 4H), 8.63 (s, 2H), 8.68 (s, 2H), 8.89 (s, 2H); ESI-MS obsd 604.3730, calcd 604.3731 ($C_{34}H_{48}N_6O_4$); λ_{abs} (CH_2Cl_2) 343, 369, 494, 724 nm.

3,13-Bis(3-(*N*,*N*-dimethylamino)prop-1-ynyl)-8,8,18,18-tetramethylbacteriochlorin (BC-13). Following a general procedure for Sonogashira coupling,[55] a mixture of **BC-Br^{3}Br^{13}** (21 mg, 0.040 mmol), $PdCl_2(PPh_3)_2$ (3.2 mg, 0.0045 mmol), CuI (1.0 mg, 0.0052 mmol), and 3-dimethylamino-1-propyne (50. μL, 0.46 mmol) in triethylamine (2 mL) was heated to 60 °C for 43 h in a Schlenk flask under anaerobic conditions. The reaction was complete as monitored by TLC. The reaction mixture was allowed to cool to room temperature. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and filtered through a pad of Celite. The flask and the solids were rinsed with CH_2Cl_2 (3 × 10 mL). The filtrate was concentrated and chromatographed [silica, CH_2Cl_2/MeOH (97:3 → 95:5)] to obtain a green solid (14.2 mg, 67%): ^{1}H NMR δ −1.99

(br s, 2H), 1.92 (s, 12H), 2.63 (s, 12H), 3.88 (s, 4H), 4.42 (s, 4H), 8.56 (s, 2H), 8.72 (s, 2H), 8.97 (s, 2H); LD-MS obsd 533.3; ESI-MS obsd 267.1736, calcd 267.1729 [$(M + 2H)^{2+}$, $M = C_{34}H_{40}N_6$]; λ_{abs} (CH_2Cl_2) 348, 375, 505, 749 nm. The reaction under the copper-free Sonogashira conditions[49] gave a poor yield and multiple products.

3,13-Bis(3-*N*,*N*-dimethylaminopropyl)-8,8,18,18-tetramethylbacteriochlorin (BC-14). A mixture of **BC-13** (5.5 mg, 0.010 mmol) and Pd/C (3.0 mg, 10% Pd on carbon, 0.0030 mmol) under an inert atmosphere was treated with ethyl acetate and ethanol (1 mL each). The mixture was stirred at room temperature under a H_2 balloon for 20 h. The mixture was filtered through a pad of Celite and rinsed with ethyl acetate and ethanol until the filtrate was colorless. The filtrate was concentrated and chromatographed [silica, CH_2Cl_2/MeOH/conc. NH_4OH (94:5:1 → 92:7:1)] to obtain a green solid (4.5 mg, 83%): ^{1}H NMR δ −2.42 (br s, 2H), 1.94 (s, 12H), 2.34 (s, 12H), 2.44 (m, 4H), 2.62 (m, 4H), 3.87 (t, J = 10 Hz, 4H), 4.45 (s, 4H), 8.52 (s, 2H), 8.60 (s, 2H), 8.79 (s, 2H); LD-MS obsd 541.5; ESI-MS obsd 541.3997, calcd 541.4013 [$(M + H)^+$, $M = C_{34}H_{48}N_6$]; λ_{abs} (CH_2Cl_2) 343, 369, 490, 720 nm.

3,13-Bis[3,5-bis(2-(*tert*-butyldimethylsilyloxy)ethoxy)phenyl]-8,8,18,18-tetramethylbacteriochlorin (BC-15). A mixture of **BC-Br^{3}Br^{13}** (10. mg, 0.019 mmol), $Pd(PPh_3)_4$ (6.6 mg, 0.0057 mmol, 30 mol %), anhydrous K_2CO_3 (15.0 mg, 0.110 mmol), and **7** (31 mg, 0.057 mmol) was dried in a Schlenk flask for 15 min. Toluene (4 mL) and DMF (2 mL) were added, and the mixture was degassed by 2 "freeze−pump−thaw" cycles. The mixture was placed in a preheated oil bath and heated overnight at 90 °C. After cooling to room temperature, the suspension was filtered through Celite. The filtrate was concentrated under vacuum. The resulting residue was subjected to column chromatography [silica, hexanes/ethyl acetate (7:3)] to afford a green solid (12.2 mg, 53%): ^{1}H NMR δ −2.02 (s, 2H), 0.17 (s, 24H), 0.96 (s, 36H), 1.98 (s, 12H), 4.10 (t, J = 5.0 Hz, 8H), 4.26 (t, J = 5.0 Hz, 8H), 4.43 (s, 4H), 6.74 (s, 2H), 7.34 (s, 4H), 8.71 (s, 2H), 8.78 (s, 2H), 8.97 (s, 2H); ^{13}C NMR δ −5.1, 18.5, 26.0, 31.0, 45.9, 51.7, 62.1, 69.6, 96.4, 97.6, 100.6, 110.1, 120.6, 133.2, 134.8, 135.6, 138.5, 158.4, 160.3, 170.0; LD-MS obsd 1219.9; ESI-MS obsd 1219.7121, calcd 1219.7160 [$(M + H)^+$, $M = C_{68}H_{106}N_4O_8Si_4$]; λ_{abs} (CH_2Cl_2) 349, 372, 498, 736 nm.

3,13-Bis[3,5-bis(methoxymethoxy)phenyl]-8,8,18,18-tetramethylbacteriochlorin (BC-16). A mixture of **BC-Br^{3}Br^{13}** (20. mg, 0.038 mmol), $Pd(PPh_3)_4$ (13.2 mg, 0.0114 mmol, 30 mol %), anhydrous K_2CO_3 (31.0 mg, 0.228 mmol), and **8** (37.0 mg, 0.114 mmol) was dried in a Schlenk flask for 15 min. Toluene (4 mL) and DMF (2 mL) were added, and the mixture was degassed by 2 "freeze−pump−thaw" cycles. The mixture was placed in a preheated oil bath and heated overnight at 90 °C. After cooling to room temperature, the suspension was filtered over Celite. The filtrate was concentrated under vacuum. The resulting residue was subjected to column chromatography [silica, hexanes/ethyl acetate (7:3)] to afford a green solid (17.6 mg, 61%): ^{1}H NMR δ −1.99 (s, 2H), 1.97 (s, 12H), 3.63 (s, 12H), 4.43 (s, 4H), 5.39 (s, 8H), 7.01 (s, 2H), 7.56 (s, 4H), 8.71 (s, 2H), 8.80 (s, 2H), 9.00 (s, 2H); ^{13}C NMR δ 31.04, 45.9, 51.7, 56.2, 94.8, 96.5, 97.6, 103.7, 112.8, 120.6, 133.1, 134.8, 135.1, 138.7, 158.5, 158.6, 170.0; LD-MS obsd 763.7; ESI-MS obsd 762.3626, calcd 762.3623 ($C_{44}H_{50}N_4O_8$); λ_{abs} (CH_2Cl_2) 350, 373, 499, 737 nm.

3,13-Bis[3,5-(bis(2-(*tert*-butyldimethylsilyloxy)ethyl)aminocarbonyl)phenyl]-8,8,18,18-tetramethylbacteriochlorin (BC-17). A mixture of **BC-Br^{3}Br^{13}** (15.0 mg, 0.0285 mmol), $Pd(PPh_3)_4$ (10. mg, 0.0085 mmol, 30 mol %), anhydrous K_2CO_3 (24.0 mg, 0.171 mmol), and **13** (79.0 mg, 0.0855 mmol) was dried in a Schlenk flask for 15 min. Toluene (4 mL) and DMF (2 mL) were added, whereupon the mixture was degassed by 2 "freeze−pump−thaw" cycles. The mixture was placed in a preheated oil bath and heated overnight at 90 °C. After cooling to room temperature, the suspension was filtered over Celite. The filtrate was concentrated under vacuum. The resulting residue was subjected to column chromatography [silica, hexanes/ethyl acetate (3:1)] to afford a green solid (31.3 mg, 56%): ^{1}H NMR δ −1.98 (s, 2H), −0.08 (s, 24H), 0.10 (s, 24H), 0.76 (s, 36H), 0.90 (s, 36H), 1.98 (s, 12H), 3.75 (br s, 16H), 3.81 (br t, J = 5.6 Hz, 8H), 3.98 (br t, J = 5.6 Hz, 8H), 4.43 (s, 4H), 7.66 (s, 2H), 8.23 (s, 4H), 8.70 (s, 2H), 8.79 (s, 2H), 8.86 (s, 2H); ^{13}C NMR δ −5.4, 18.2, 25.8, 31.0, 45.9, 48.2, 51.7, 52.4, 61.3, 96.7, 97.5, 121.2, 124.2, 130.2, 133.1, 134.0, 134.9, 137.3, 137.9, 158.8, 170.3, 171.4; LD-MS obsd 1962.1; ESI-MS obsd 980.6088, calcd 980.6099 [$(M + 2H)^{2+}$, $M = C_{104}H_{182}N_8O_{12}Si_8$]; λ_{abs} (CH_2Cl_2) 355, 372, 499, 738 nm.

3,13-Bis[3,5-(bis(2-(acetoxy)ethyl)aminocarbonyl)phenyl]-8,8,18,18-tetramethylbacteriochlorin (BC-18). A mixture of **BC-Br^{3}Br^{13}** (10. mg, 0.019 mmol), $Pd(PPh_3)_4$ (6.6 mg, 0.0057 mmol, 30 mol %), anhydrous K_3PO_4 (40.0 mg, 0.190 mmol), and **12** (36.0 mg, 0.0570 mmol) was dried in a Schlenk flask for 15 min. Toluene (2 mL) and DMF (3 mL) were added, and the mixture was degassed by 2 "freeze−pump−thaw" cycles. The mixture was placed in a preheated oil bath and heated overnight at 90 °C. After cooling to room temperature, the suspension was filtered over Celite. The filtrate was concentrated under vacuum. The resulting residue was subjected to column chromatography [silica, CH_2Cl_2/MeOH (97:3)] to afford a green solid (13 mg, 49%): ^{1}H NMR −1.93 (s, 2H), 1.86 (br s, 12H), 1.98 (s, 12H), 2.09 (br s, 12H), 3.83 (br s, 8H), 3.91 (br s, 8H), 4.23 (br s, 8H), 4.44 (s, 4H), 4.47 (br s, 8H), 7.66 (t, J = 1.4 Hz, 2H), 8.25 (d, J = 1.4 Hz, 4H), 8.73 (s, 2H), 8.84 (d, J = 1.9 Hz, 2H), 8.88 (s, 2H); LD-MS obsd 1384.5; ESI-MS obsd 1383.6022, calcd 1383.6031 [$(M + H)^+$, $M = C_{72}H_{86}N_8O_{20}$]; λ_{abs} (CH_2Cl_2) 356, 372, 500, 739 nm.

3,13-Bis(3,5-dicarboxyphenyl)-8,8,18,18-tetramethylbacteriochlorin (BC-19). A mixture of **BC-Br^{3}Br^{13}** (10. mg, 0.019 mmol), $Pd(PPh_3)_4$ (6.6 mg, 0.0060 mmol, 30 mol %), anhydrous K_2CO_3 (21 mg, 0.15 mmol), and **9** (16 mg, 0.076 mmol) was dried in a Schlenk flask for 15 min. Ethanol (3 mL) and water (3 mL) were added, and the mixture was degassed by 2 "freeze−pump−thaw" cycles. The mixture was placed in a preheated oil bath and heated overnight at 90 °C. After cooling to room temperature, ethanol was removed under vacuum, and the resulting aqueous suspension was filtered through Celite. The filtrate was concentrated under vacuum. The resulting residue was subjected to reversed-phase column chromatography [C-18 silica, water] to afford after freeze-drying a green solid (6.2 mg, 47%): ^{1}H NMR (CD_3OD) δ 2.02 (s, 12H), 4.52 (s, 4H), 8.84 (s, 2H), 8.85 (s, 2H), 8.89 (d, J = 1.6 Hz, 4H), 8.97 (s, 2H), 9.10 (s, 2H); ^{13}C NMR (CD_3OD) δ 31.4, 46.9, 52.6, 97.6, 98.7, 122.0, 130.4, 134.4, 134.5, 136.3, 136.9, 139.9, 160.1, 171.4, 175.4; ESI-MS obsd 698.2363, calcd 698.2371 ($C_{40}H_{34}N_4O_8$); λ_{abs} (H_2O) 347, 366, 500, 737 nm; λ_{abs} (methanol) 350, 368, 497, 734 nm.

3,13-Bis[3,5-bis(2-hydroxyethoxy)phenyl]-8,8,18,18-tetramethylbacteriochlorin (BC-20). Following a reported procedure,[67] a solution of **BC-15** (12 mg, 0.0098 mmol) in anhydrous THF (5 mL) was treated with molecular sieves 4 Å (20 mg) and TBAF (118 μL, 1 M in THF, 0.110 mmol). After 30 min, the suspension was diluted with ethyl acetate (10 mL) and poured into saturated aqueous NH_4Cl (10 mL). The aqueous layer was extracted with ethyl acetate, and the organic extract was dried over Na_2SO_4 and concentrated under vacuum. The resulting residue was subjected to column chromatography [silica, ethyl acetate/MeOH (98:2 to 96:4)] to afford a green solid (4.0 mg, 53%): ^{1}H NMR δ −2.00 (s, 2H), 1.98 (s, 12H), 2.15 (br s, 4H), 4.10 (br s, 8H), 4.32 (br t, J = 4.0 Hz, 8H), 4.45 (s, 4H), 6.78 (s, 2H), 7.32 (s, 4H), 8.71 (s, 2H), 8.78 (s, 2H), 8.95 (s, 2H); LD-MS obsd 762.8; ESI-MS obsd 762.3634, calcd 762.3623 ($C_{44}H_{50}N_4O_8$); λ_{abs} (CH_2Cl_2) 349, 372, 498, 736 nm.

3,13-Bis(3,5-dihydroxyphenyl)-8,8,18,18-tetramethylbacteriochlorin (BC-21). A sample of **BC-16** (17.5 mg, 0.0229 mmol) was treated with a solution of 10% HCl in MeOH (10 mL), and the mixture was refluxed for 30 min. After the mixture was allowed to cool to room temperature, the solution was neutralized by addition of saturated aqueous $NaHCO_3$. The resulting mixture was extracted

with ethyl acetate. The organic extract was washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated under vacuum. The resulting residue was subjected to column chromatography [silica, hexanes/ethyl acetate (1:9)] to afford a green solid (11.4 mg, 85%): ^{1}H NMR (acetone-d_6) δ −1.97 (s, 2H), 1.98 (s, 12H), 4.48 (s, 4H), 6.66 (s, 2H), 7.25 (s, 4H), 8.65 (br s, 4H), 8.90 (s, 2H), 8.92 (s, 2H), 9.02 (s, 2H); ^{13}C NMR (acetone-d_6) δ 31.2, 46.6, 52.2, 97.5, 98.4, 102.8, 110.5, 121.5, 133.9, 135.8, 136.8, 139.2, 159.3, 159.9, 170.9; LD-MS obsd 586.7; ESI-MS obsd 586.2579, calcd 586.2574 ($C_{36}H_{34}N_4O_4$); λ_{abs} (CH_2Cl_2) 350, 373, 499, 737 nm.

3,13-Bis[3,5-bis(methoxycarbonylmethoxy)phenyl]-8,8,18,18-tetramethylbacteriochlorin (BC-22). A solution of **BC-21** (6.4 mg, 0.011 mmol) in anhydrous acetonitrile (5 mL) was treated with anhydrous K_2CO_3 (9.0 mg, 0.065 mmol). After the solution was stirred for 30 min at room temperature, methyl bromoacetate (6.2 μL, 0.065 mmol) was added, and the resulting mixture was refluxed overnight. After the mixture was cooled to room temperature, water was added and the resulting mixture was extracted with ethyl acetate. The organic extract was washed (brine), dried (Na_2SO_4), and concentrated under vacuum. The resulting residue was subjected to column chromatography [silica, hexanes/ethyl acetate (1:9)] to afford a green solid (6.2 mg, 65%): ^{1}H NMR δ −2.00 (s, 2H), 1.98 (s, 12H), 3.89 (s, 12H), 4.44 (s, 4H), 4.85 (s, 8H), 6.76 (s, 2H), 7.37 (s, 4H), 8.71 (s, 2H), 8.76 (s, 2H), 8.92 (s, 2H); ^{13}C NMR δ 31.0, 45.9, 51.7, 52.5, 65.6, 96.6, 97.6, 101.0, 110.9, 120.7, 133.1, 134.8, 134.9, 139.0, 158.7, 159.2, 169.3, 170.2; LD-MS obsd 875.2; ESI-MS obsd 874.3410, calcd 874.3419 ($C_{48}H_{50}N_4O_{12}$); λ_{abs} (CH_2Cl_2) 351, 372, 498, 737 nm.

Attempted Deprotection of BC-18. A solution of **BC-18** (9.0 mg, 0.0065 mmol) in MeOH (8 mL) and H_2O (2 mL) was treated with K_2CO_3 (14. mg, 0.10 mmol). The mixture was stirred overnight at room temperature without any change, and then heated for 6 h at 60 °C. After the solution was cooled to room temperature, solvents were removed under vacuum. The resulting residue was subjected to reversed-phase column chromatography [C-18 silica, water] to afford after freeze-drying the unexpected product **BC-19** (2.5 mg, 55%).

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Supporting Information Available: Experimental section including characterization data for 11 bacteriochlorins prepared by reductive amination or quaternization, and spectral data for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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