NJC

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Journal:	*New Journal of Chemistry*
Manuscript ID	NJ-ART-12-2021-005852.R1
Article Type:	Paper
Date Submitted by the Author:	02-Feb-2022
Complete List of Authors:	Jing, Haoyu; North Carolina State University, Chemistry Wang, Pengzhi; North Carolina State University, Chemistry Chen, Boyang; North Carolina State University, Chemistry Jiang, Jianbing; University of Cincinnati, Chemistry Vairaprakash, Pothiappan; SASTRA University, School of Chemical and Biotechnology Liu, Sijia; North Carolina State University, Chemistry Rong, Jie; North Carolina State University, Chemistry Chen, Chih-Yuan; NC State University, Chemistry Nalaoh, Phattananawee; Vidyasirimedhi Institute of Science and Technology, Department of Materials Science and Engineering Lindsey, Jonathan; North Carolina State University, Chemistry

Synthesis of Bacteriochlorins Bearing Diverse β-Substituents

Haoyu Jing,[a] Pengzhi Wang,[a] Boyang Chen,[a] Jianbing Jiang,[a] Pothiappan Vairaprakash,[a] Sijia Liu,[a] Jie Rong,[a] Chih-Yuan Chen,[a] Phattananawee Nalaoh,[b] and Jonathan S. Lindsey [a,*]

[a]Department of Chemistry
North Carolina State University
Raleigh, North Carolina 27695-8204

[b]Department of Materials Science and Engineering
School of Molecular Science and Engineering
Vidyasirimedhi Institute of Science and Technology
Wangchan, Rayong, 21210, Thailand

e-mail: jlindsey@ncsu.edu
Tel: +1-919-515-6406

Abstract

Synthetic bacteriochlorins, analogues of native bacteriochlorophylls, provide absorption in the near-infrared spectral region and hence are valuable for fundamental studies in photochemistry and applications ranging from solar energy conversion to photomedicine. The full realization of such opportunities hinges on access to synthetically malleable bacteriochlorins. Here, two established routes that rely on self-condensation of a dihydrodipyrrin-acetal or dihydrodipyrrin-carboxaldehyde have been exploited to prepare 6 bacteriochlorins (2 new, 4 known in improved fashion). Each bacteriochlorin contains a gem-dimethyl group in the reduced, pyrroline ring to ensure stability toward adventitious dehydrogenation. These and related synthetic bacteriochlorins have been derivatized to tailor the perimeter of the macrocycle with diverse groups, affording 9 additional new bacteriochlorins and 4 known bacteriochlorins. By direct installation and/or derivatization, the scope of attached entities in this collection includes alkyl, amino, aryl, bromo, carboethoxy, oxo, phenylethynyl, and pyridyl. The bacteriochlorins are suited for surface bioconjugation, water-solubilization, vibrational studies, and elaboration into multichromophore arrays. Altogether the synthesis of 25 new compounds (11 bacteriochlorins, 14 precursors) is described.

Introduction

Bacteriochlorophylls are Nature's near-infrared (NIR) absorbers and provide the basis for light-harvesting and electron-transfer processes in anoxygenic photosynthetic bacteria.[1] The fundamental chromophore of a bacteriochlorophyll is a bacteriochlorin. Another class of bacteriochlorins found in Nature appears in the cyanobacterium *Tolypothrix nodosa*;[2] such compounds are referred to as tolyporphins and are not believed to participate in photosynthetic processes. Tolyporphins pale in importance compared with bacteriochlorophylls, yet their existence highlights the molecular possibilities afforded by the bacteriochlorin system.[3] The chief bacteriochlorophylls are denoted *a*, *b*, and *g*,[1] whereas the tolyporphins include 14 bacteriochlorin members (A–J, L–O).[4] The structures of bacteriochlorophyll *a* and tolyporphin A are shown in Chart 1. Total syntheses of bacteriochlorophylls and tolyporphins are not yet available.[5] A longstanding objective in tetrapyrrole science has been to gain access to synthetic analogues of the native pigments so as to (1) probe the fundamental properties of the macrocycles, and (2) exploit the structures in diverse applications ranging across energy sciences and photomedicine.

There are essentially four distinct approaches to prepare bacteriochlorins:[6-10] (1) hydrogenation of a porphyrin or chlorin at the appropriate β-pyrrolic positions;[8,11,12] (2) cycloaddition of a reactant with a porphyrin or chlorin at the β-pyrrolic positions;[6,8] (3) semisynthetic modification of a natural bacteriochlorin (e.g., bacteriochlorophyll *a* or tolyporphin A);[10] and (4) *de novo* synthesis of non-natural bacteriochlorins. Each method has advantages and limitations. Kishi and coworkers developed a *de novo* synthesis of an *O,O*-diacetyl derivative of tolyporphin A.[5,13,14] Our focus over the past two decades has been to develop *de novo* synthetic routes to non-natural bacteriochlorins from commercially available, small-molecule precursors.[15] The molecular design employed for the latter includes a geminal-dimethyl group in each reduced (pyrroline) ring. The rationale for the gem-dimethyl group is to "secure the chromophore" from

the deleterious effects of molecular oxygen. Bacteriochlorins prepared by hydrogenation of a porphyrin, for example, undergo dehydrogenation to afford the intermediate chlorin, and ultimately the starting porphyrin, on routine handling in an aerobic environment. Such dehydrogenation is precluded in the gem-dimethyl-substituted bacteriochlorins. A further advantage of the *de novo* synthesis is, in principle, complete control over the nature and pattern of substituents about the perimeter of the macrocycle, which is not possible by hydrogenation, cycloaddition, or semisynthesis.

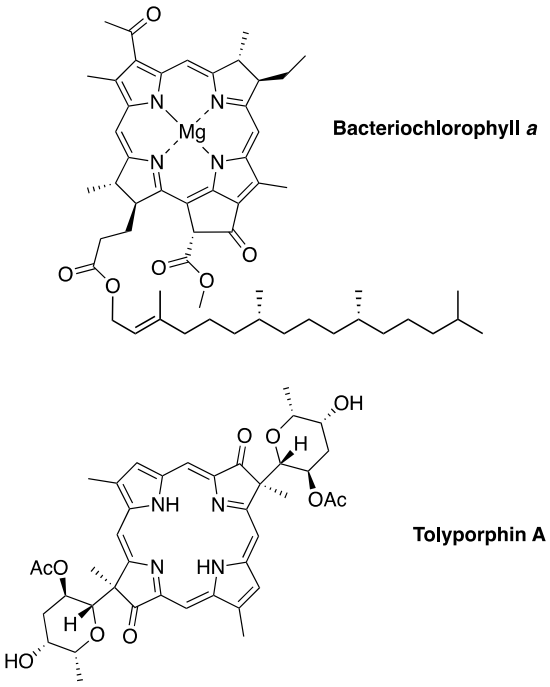


Chart 1. Native bacteriochlorins.

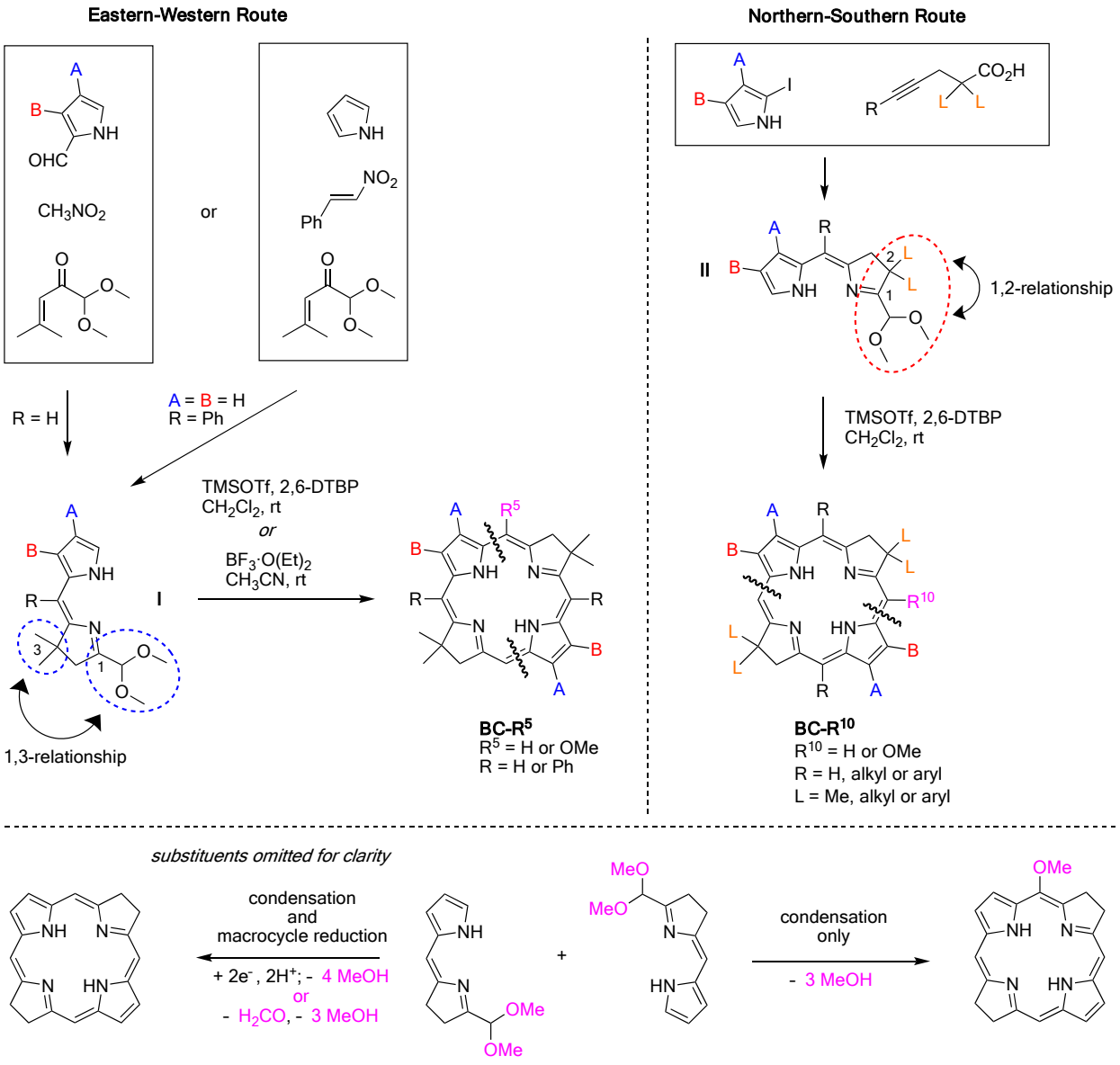
On the other hand, the design malleability afforded by the *de novo* routes comes with a stiff price, namely a substantial effort in laboratory synthesis. To date, several hundred bacteriochlorins have been prepared by *de novo* synthesis encompassing a wide range of structures and features yet all built around a common gem-dimethyl core motif. Still, numerous molecular designs remain unexplored, and access to many known designs could benefit from refined syntheses. In this paper, we report the use of existing routes for bacteriochlorin formation to gain access to molecular

designs suitable for surface attachment, bioconjugation, vibrational studies, and elaboration into multichromophore arrays. Altogether, the preparation of 19 bacteriochlorins is reported, of which 11 are new and 8 are known; the latter are prepared via refined or new approaches. Many bacteriochlorins constitute building blocks that can be further elaborated. Together, the work provides insights into the introduction of diverse entities (e.g., alkyl, amino, aryl, bromo, carboethoxy, ethynyl, hydroxy, oxo, phenylethynyl, and pyridyl) via suitably derivatized precursors or by elaboration of a bacteriochlorin scaffold.

Results

Bacteriochlorin Synthesis – Reconnaissance

Two general routes to construct bacteriochlorin macrocycles in a *de novo* manner rely on the head-to-tail self-condensation of two dihydrodipyrrin-acetal molecules. The two routes, an Eastern-Western route[15-19] and a Northern-Southern route,[20,21] differ in (1) the structure of the dihydrodipyrrin-acetal, and (2) the synthetic route for constructing the dihydrodipyrrin-acetals (Scheme 1). The latter route is less developed. In the Eastern-Western route, condensation and addition processes are chiefly used to construct the dihydrodipyrrin-acetal, wherein the dimethyl acetal substituent and the gem-dimethyl group are positioned in a 1,3-relationship. In the Northern-Southern route, Pd-mediated joining in the first step followed by Petasis methenylation, Paal-Knorr reaction, Riley oxidation, and acetal formation lead to a dihydrodipyrrin-acetal wherein the dimethyl acetal substituent and the gem-dimethyl group are positioned in a 1,2-relationship. The methods of construction of the dihydrodipyrrin-acetals impose limitations in the available nature and pattern of substituents.



Scheme 1. Eastern-Western and Northern-Southern routes to bacteriochlorins (top). Conversion of dihydrodipyrrin-acetals to the 5-methoxy or 5-unsubstituted bacteriochlorin (bottom).

The self-condensation of a dihydrodipyrrin-acetal, regardless of location of the gem-dimethyl substituent, results in loss of the methoxy groups of the dimethyl acetal unit. In a strict condensation process, three molecules of methanol are expelled and one remains at the 5-position of the bacteriochlorin.[15,17] In some cases, four molecules are lost and the resulting bacteriochlorin lacks any methoxy group. The use of trimethylsilyl triflate (TMSOTf) in the presence of the proton scavenger 2,6-di-*tert*-butylpyridine (2,6-DTBP)[22] in CH_2Cl_2 typically affords the 5-

methoxybacteriochlorin (**BC-R^5**, R^5 = methoxy, Scheme 1), whereas acids such as $BF_3{\cdot}O(Et)_2$ in CH_3CN typically afford a mixture of the 5-methoxy and 5-unsubstituted bacteriochlorins.[16] The mechanistic origin of the 5-unsubstituted bacteriochlorin is unknown. Both structures have attractions and drawbacks (depending on the presence of other substituents): the 5-methoxy group can direct electrophilic bromination selectively to the distal-like 15-position,[23] whereas such selectivity is often missing with the 5-unsubstituted bacteriochlorin; however, the 5-methoxy group also shifts the long-wavelength absorption band hypsochromically by ~5–20 nm versus that of the 5-unsubstituted bacteriochlorin, which may be undesired.

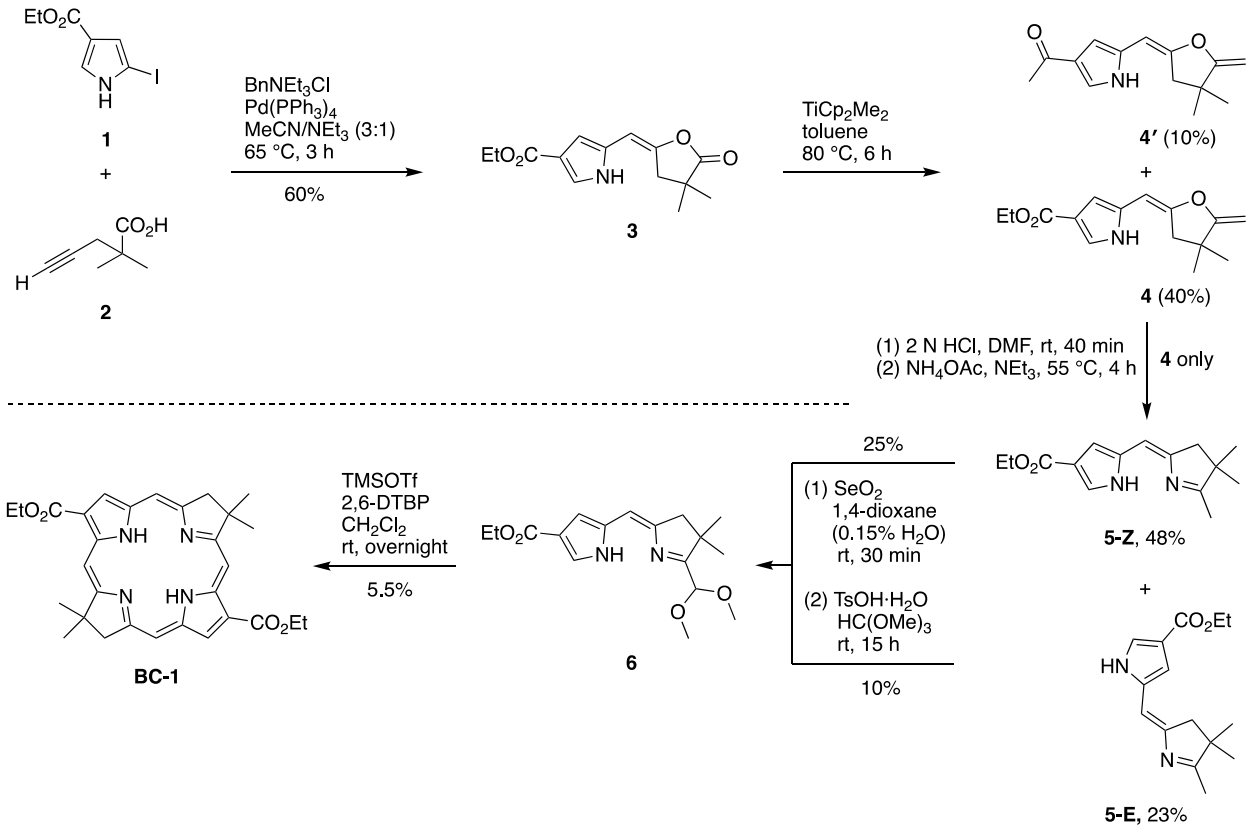
Numerous gem-dimethyl-substituted bacteriochlorins bearing substituents at the β-pyrrolic positions have been prepared.[16,24-36] The placement of auxochromes at the β-pyrrolic positions enables tuning of the position of the long-wavelength (Q_y) absorption band, and the focus on the 3,13-positions stems from facile substitution of the site in the initial pyrrole precursor (e.g., substituent A in the Eastern-Western route, Scheme 1) destined for location at the 3,13-position. For subsequent elaboration of the bacteriochlorins, the presence of β-pyrrolic substituents may be limiting (Chart 2): (a) in 3,13-disubstituted bacteriochlorins, the 3,13-substituents can hinder the adjacent meso-(5,15) and 2,12-positions, whereas the 10,20-positions are hindered by the gem-dimethyl groups at the adjacent (8,8,18,18) positions; and (b) in 2,12-disubstituted bacteriochlorins, the 10,20-positions are hindered by two flanking substituents, the 3,13-positions are hindered by only the flanking 2,12-substituents, but the 5,15-positions are unhindered. We considered that bacteriochlorins bearing electron-withdrawing groups at the 2,12-positions might provide selective electrophilic substitution at the 5- or 5,15-positions (i.e., bromination, see companion paper[37]). The synthesis of such bacteriochlorins is described below.

Chart 2. Steric effects of substituents in gem-dimethyl-substituted bacteriochlorins are shown for selected sites. The pairwise 2,12- 3,13-, 5,15-, 7,17-, 8,18-, and 10,20-positions are equivalent by symmetry.

Bacteriochlorins Bearing Bromo/Carboalkoxy Groups at the β-Pyrrole Positions

A candidate bacteriochlorin bearing 2,12-dicarboethoxy substituents (**BC-1**) was previously synthesized via the Northern-Southern route (Scheme 2).[20] The self-condensation proceeded in low yield (6%) and only a small amount of **BC-1** was obtained (1.3 mg), which prompted attempts to improve the route. In the Northern-Southern route,[20] Jacobi reaction[38-42] of iodopyrrole **1**[20] and pentynoic acid **2**[20] has afforded the lactone-pyrrole **3** at small (727 mg)[20] and somewhat larger (6 g)[43] scale. Here, the Tebbe olefination of **3** afforded ene-ether pyrrole **4** in 60% yield (versus 48% previously[20]) in one case, while in a separate case the yield of **4** was 40%, and byproduct (**4′**) derived from further methenylation at the pyrrole carboethoxy group was also obtained. Acidic hydrolysis of **4** followed by Paal-Knorr type reaction with NH_4OAc and NEt_3 afforded two dihydrodipyrrins (**5-Z** and **5-E**). Previously, **5-Z** was isolated (40% yield) and carried forward on the path to the bacteriochlorin;[20] alternatively, the mixture of isomers was treated with dibutylboron triflate to make the dialkylboron complex of **5-Z**,[43] a boron-dipyrrinato (BODIPY) homologue. Here, the two isomers were separated by column chromatography, which was straightforward due to the difference in polarity, and isolated in yields of 29% (**5-Z**) and 52% (**5-**

E). On standing exposed to a weak acid, some equilibration of the two isomers apparently occurred. For example, treatment of the crude product (following workup of the Paal-Knorr reaction in ethyl acetate) with saturated aqueous KH_2PO_4 solution for 24 h at room temperature gave **5-Z** in 48% yield and **5-E** in 23% yield.



Scheme 2. Northern-Southern route to a bacteriochlorin-2,12-diester.

Identification of the dihydrodipyrrins (**5-Z** and **5-E**) was achieved by ^{1}H NMR spectroscopy (Figure 1A). For **5-Z**, the N-H proton (labeled "a") resonates downfield at 11.2 ppm due to intramolecular hydrogen bonding, while that of **5-E**, which lacks intramolecular hydrogen bonding, appears in the vicinity of 9 ppm (Figure 1A). The meso-proton (labeled "d") of **5-Z** resonates downfield at ~6.5 ppm versus that of **5-E** at ~5.8 ppm. The β-proton (labeled "c") of the pyrrole ring, which is not directly connected to the pyrroline ring, also resonates further downfield ($\Delta\delta$ = 0.1 ppm) for **5-Z** versus **5-E**. Not unexpectedly, the α-proton (labeled "b") of the pyrrole

ring resonated at the same chemical shift (~7.4 ppm) in each isomer. A single-crystal X-ray structure determination of **5-E** confirmed the assigned stereochemistry (Figure 1B). Two dihydrodipyrrin molecules occupy the unit cell. In each case, both the pyrrole and pyrroline nitrogen atoms are positioned on the convex face of the dihydrodipyrrin, flanking the meso C–H. Further discussion of the crystal structure is provided in the Electronic Supplementary Information. While rotation about the pyrrole–ene carbon-carbon single bond can give distinct conformers, and conformation in a crystal does not necessarily reflect conformations in solution, the configuration of the assigned structure for **5-E** is unambiguous.

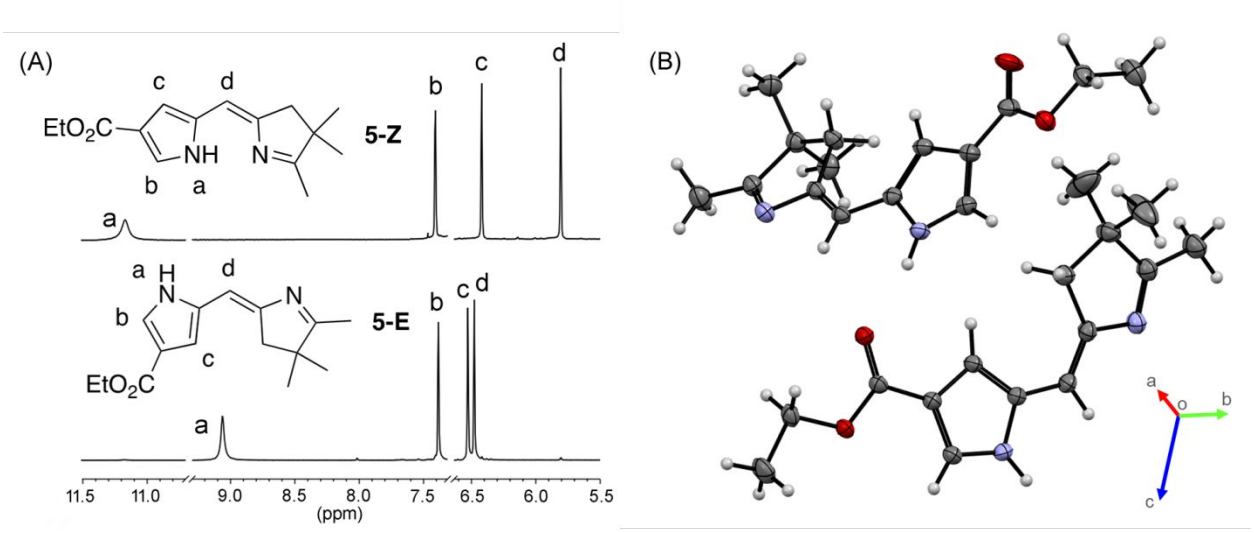


Figure 1. Panel A: ^{1}H NMR spectra of **5-Z** and **5-E** isomers (in $CDCl_3$ at room temperature). Panel B: ORTEP diagrams of two molecules of dihydrodipyrrin **5-E** in the single-crystal X-ray structure. Ellipsoids are at the 50% probability level.

A short study of the ratio of the two dihydrodipyrrins **5-Z** and **5-E** under various acidic conditions was carried out. A sample of pure **5-E** was dissolved in *N,N*-dimethylformamide (DMF) and 1 equivalent of acid was added. After standing for 12–72 h, the mixture was quenched by the addition of water and extracted with ethyl acetate, then concentrated to dryness, dissolved in $CDCl_3$, and examined by ^{1}H NMR spectroscopy. The results for six acids at room temperature (entries 1–10) and with $TsOH{\cdot}H_2O$ at 40 °C (entries 11–13) are shown in Table 1. There were no

acids examined that afforded solely the *Z* or *E* isomer, although certain acids tended to favor the *Z* isomer (entries 2–4). Prolonged treatment appeared to result in decomposition preferentially of the *Z* isomer. Given the inevitable workup process, the observed ratios may not reflect equilibrium compositions in the solutions studied.

Table 1. Survey of acid-catalyzed interconversions of **5-Z** and **5-E**.

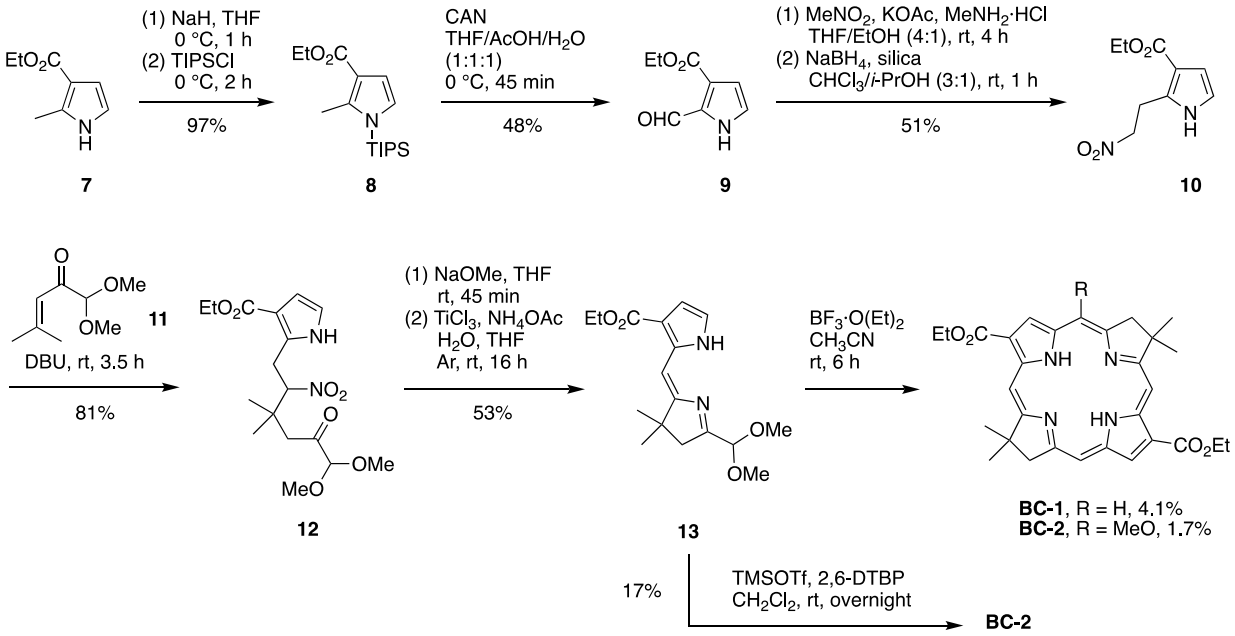
Entry	Acid[a]	Temperature	Time	Ratio of **5-Z** to **5-E**[b]
1[c]	Saturated aqueous KH_2PO_4 (50 μL)	r.t.	24 h	2.2:1
2[c]	Acetic Acid	r.t.	24 h	3.3:1
3[c]	$TsOH·H_2O$	r.t.	24 h	3.3:1
4[c]	2N aqueous HCl	r.t.	24 h	2.9:1
5[c]	LiOTf	r.t.	24 h	1.4:1
7[d]	2N aqueous HCl	r.t.	48 h	1:2
8[d]	2N aqueous HCl	r.t.	72 h	1:3
9[d]	$TsOH·H_2O$	r.t.	12 h	1:4
10[d]	$TsOH·H_2O$	r.t.	32 h	3.3:1 (25%:6%)[e]
11[d]	$TsOH·H_2O$	40 °C	12 h	1:6.5
12[d]	$TsOH·H_2O$	40 °C	24 h	1:1
13[d]	$TsOH·H_2O$	40 °C	36 h	1:4

[a]One equivalent of acid was added for entries 2–13. [b]The ratio was determined by the ^1H NMR spectrum of reaction mixture (quenched by water and extracted with ethyl acetate). [c]A sample of 13 mg of **5-E** was dissolved in 0.5 mL (0.1 M) of DMF. [d]A sample of 130 mg of **5-E** was dissolved in 5 mL (0.1 M) of DMF. [e]Isolated yield.

Riley oxidation[44] of **5-Z** followed by treatment of the crude mixture with $HC(OMe)_3$ under acidic conditions afforded dihydrodipyrrin-acetal **6** in 25% yield (Scheme 2). The similar reaction of **5-E** also afforded **6**, but only in 10% yield. In each case **6** was obtained as the *Z* isomer to the exclusion of any *E* isomer. The results suggest that the mixture of *E* and *Z* isomers could be taken forward as a mixture and subjected to Riley oxidation and acetal formation. The low yields

observed for the Riley oxidation are in the range typical for dihydrodipyrrins.[44] The self-condensation of **6** under the reported conditions[16] of TMSOTf and 2,6-DTBP in CH_2Cl_2 at room temperature gave **BC-1** in 5.5% yield, which was consistent with the previous result (Scheme 2).[20] While the low yield was dissatisfying, and obtaining a sizeable quantity of the iodopyrrole (**1**) in pure form was challenging (despite the presence of the stabilizing and essential ester group[45]), the bacteriochlorin is stable and could be readily isolated. To obtain a sizeable quantity of **BC-1**, we turned to use the Eastern-Western route.

The Eastern-Western route[16] was employed beginning with commercially available compound **7**, which was protected as the *N*-triisopropylsilyl (TIPS) derivative **8** (Scheme 3). The oxidation of TIPS-protected pyrrole **8** by ceric ammonium nitrate (CAN) afforded aldehyde **9**. The pyrrole-aldehyde **9** was converted to dihydrodipyrrin–acetal **13** in three steps via the standard intermediates **10** and **12** with use of the Michael acceptor[17] **11**. A suitable crystal of **12** for single-crystal X-ray diffraction analysis was obtained following column chromatography. The crystal structure of **12**, a racemic compound, presented the monoclinic crystal system with space group of $P2_1/n$ ($Z' = 4$), as described in the ESI. The unit cell contained two *R* and two *S* enantiomers, where chirality arises from the configuration of the nitro-substituted carbon (Figure 2). While ^{1}H NMR spectroscopic analysis routinely affords a characteristic ABX pattern of the methylene protons on the carbon adjacent to the stereogenic center, structural analysis of such pyrrole–nitrohexanones has previously been reported for only four compounds,[46-48] although 2-(2-nitroethyl)pyrroles are growing in importance.[49]



Scheme 3. Eastern-Western route to a bacteriochlorin-2,12-diester.

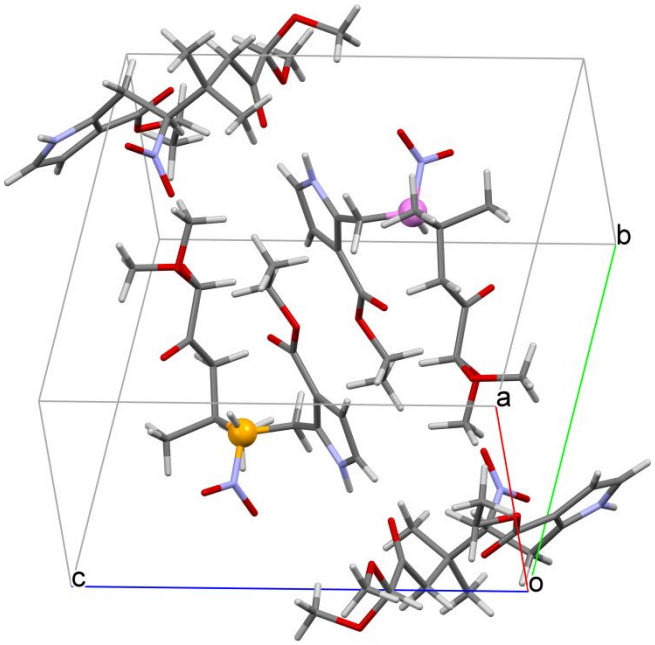
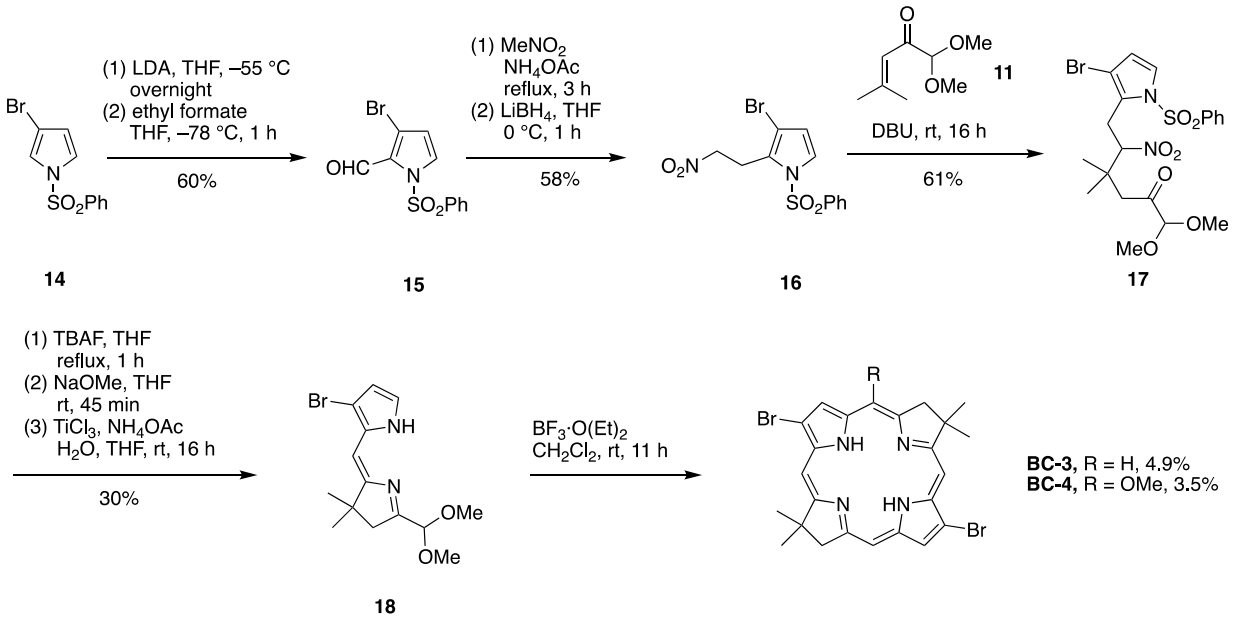


Figure 2. The unit cell in the crystal structure of **12** with *R* and *S* configurations of the C5 position of two of the enantiomers shown in pink and amber, respectively.

To our surprise, the standard self-condensation conditions[15] afforded 5-unsubstituted **BC-1** only in 4.1% yield and was accompanied by 5-methoxybacteriochlorin **BC-2** in 1.7% yield. While the origin of the low yield of self-condensation of **13** (compared to other dihydrodipyrrins bearing electron-withdrawing groups[16]) is unclear, this route was employed to obtain ~25 mg of

the desired bacteriochlorin **BC-1**. The overall yield of **BC-1** was 0.28% from the Northern-Southern route versus 0.41% from the Eastern-Western route starting from the initial pyrroles. In both routes, the bottleneck is the macrocycle formation step. One further limiting factor of the Northern-Southern route is the difficulty in obtaining a sizeable quantity of the iodopyrrole (**1**) in pure form. In contrast, the starting compound (pyrrole **7**) of the Eastern-Western route is commercially available, and the route entails fewer reactions that use organometallic reagents.

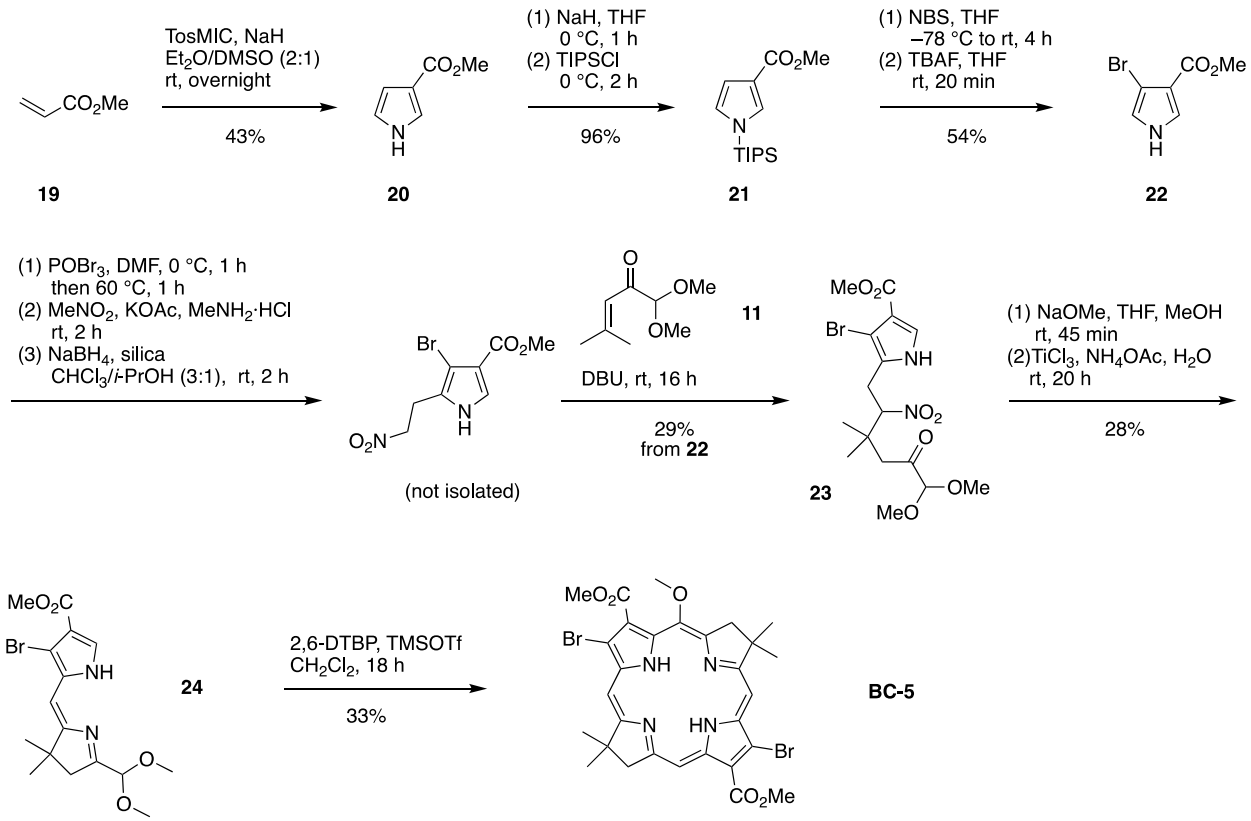
The synthesis of the versatile scaffold 2,12-dibromobacteriochlorin **BC-3** began with the 3-brominated phenylsulfonyl-protected pyrrole **14**.[50] The deprotonation of **14** using LDA followed by selective formylation[51] gave pyrrole-aldehyde **15**. The pyrrole-aldehyde **15** underwent Henry reaction[52] with nitromethane followed by reduction of the vinyl group with $LiBH_4$ in a standard procedure[53] to give **16**, which upon Michael addition with **11** gave the nitrohexanone pyrrole **17**. The latter was treated with tetrabutylammonium fluoride (TBAF) to remove the phenylsulfonyl group, then to the conditions for McMurry cyclization to give the dihydrodipyrrin-acetal **18**. The self-condensation of 7-bromo substituted dihydrodipyrrin-acetal **18** using $BF_3{\cdot}O(Et)_2$ in dichloromethane afforded the 5-unsubstituted bacteriochlorin **BC-3** and 5-methoxybacteriochlorin **BC-4** in 4.9% and 3.5% yield, respectively (Scheme 4). The yield of **BC-3** decreased to only 1.7% if the reaction time was extended to 14 hours. The reaction of **18** with catalysis by $BF_3{\cdot}O(Et)_2$ in CH_3CN gave only a trace amount (observable by absorption spectroscopy) of the 2,12-dibromobacteriochlorin **BC-3**; by contrast, the self-condensation of an 8-bromo substituted dihydrodipyrrin-acetal under the same catalysis conditions gave the 5-unsubstituted 3,13-dibromobacteriochlorin in 15% yield.[24] The reactivity of dihydrodipyrrin-acetals bearing a given substituent but at different positions (8- versus 7-) can vary significantly.[54]



Scheme 4. Synthesis of 2,12-dibromobacteriochlorins.

The synthesis of a 2,12-dibromobacteriochlorin bearing 3,13-dicarbomethoxy groups (**BC-5**) is shown in Scheme 5. The bacteriochlorin is known[55] but was prepared here in a modified route. The van Leusen synthesis[56] using methyl acrylate (**19**) and *p*-tosylmethylisocyanide (TosMIC) gave in 43% yield the corresponding pyrrole **20**, a known compound[57] prepared here in 100-times larger scale. Subsequent TIPS installation afforded pyrrole **21** in 96% yield. Treatment[46] with *N*-bromosuccinimide (NBS) at –78 °C followed by cleavage of the TIPS group by addition of TBAF afforded the target pyrrole **22** in 54% yield, affording >20 g in two batches. Single-crystal X-ray analysis validated the expected substituent pattern of pyrrole **22** (see the ESI), which was prepared previously by lithiation of 3,4-dibromopyrrole followed by reaction with dimethyl carbonate.[55] Vilsmeier formylation of **22** with $POBr_3$ in DMF at 0 °C followed by 60 °C afford the formylpyrrole, which was obtained by recrystallization with CH_2Cl_2/hexanes and used without further purification.[55] The remainder of the synthesis was as reported previously,[55] although streamlined here. Thus, Henry reaction of **22** using KOAc/$MeNH_2$·HCl buffer in EtOH followed by reduction using $NaBH_4$ afforded the nitroethyl-pyrrole without chromatographic

purification. The resulting product was used directly in the subsequent Michael addition with **11** in neat 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The excess **11** could be removed by bulb-to-bulb distillation, and the undistilled residue was passed through a silica pad. The filtrate was collected and proved to be pure enough (by TLC analysis) for the next step. The yield of **23** was 29% (from **22**) in this streamlined manner versus 36% previously with isolation of intermediates.[55] Reductive cyclization of pyrrole **23** with $TiCl_3$ in NH_4OAc buffer solution generated dihydrodipyrrin **24** in 28% yield. Self-condensation of **24** under 2,6-DTBP/TMSOTf in CH_2Cl_2 gave the corresponding bacteriochlorin **BC-5** in 33% yield.

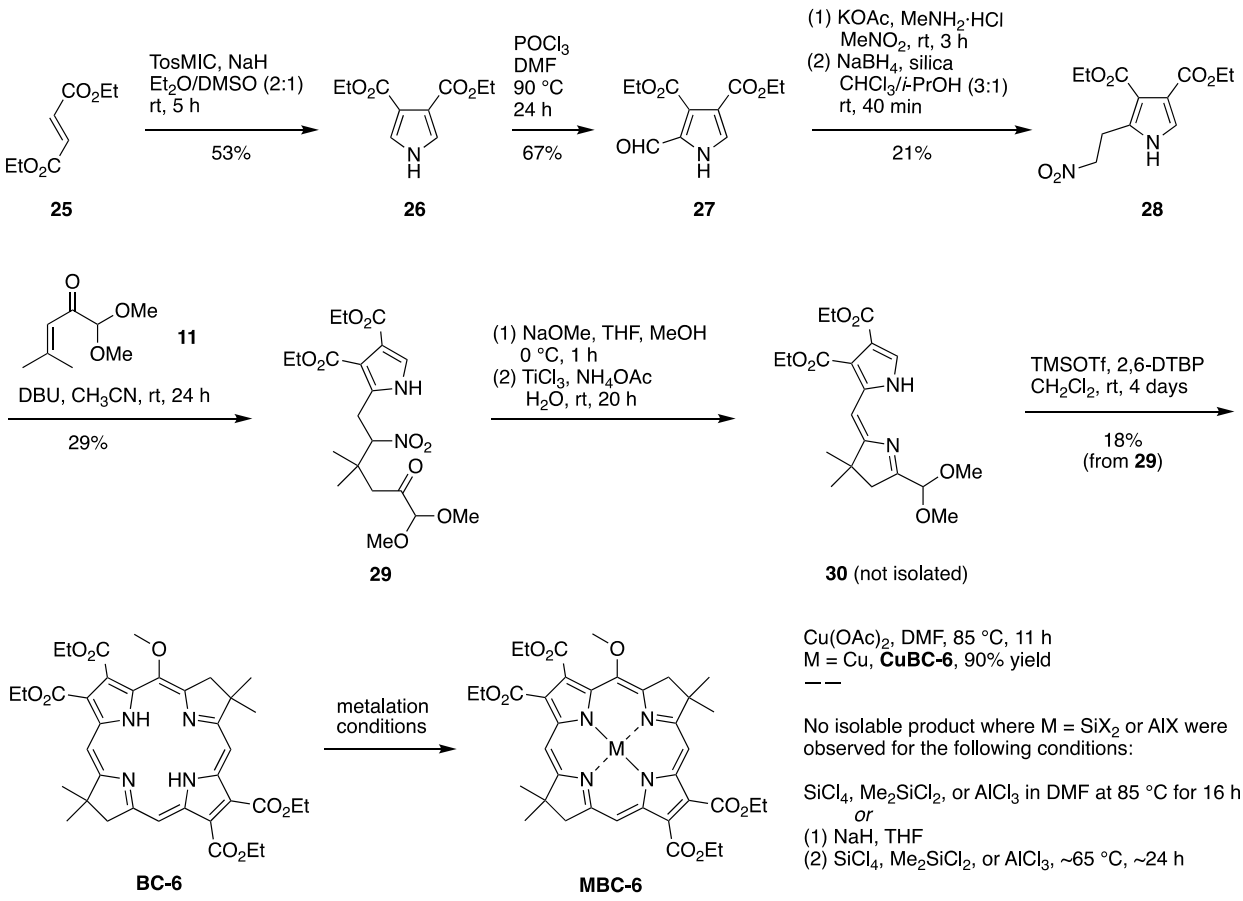


Scheme 5. Streamlined synthesis of a 2,12-dibromo-3,13-dicarbomethoxybacteriochlorin.

Bacteriochlorins **BC-3**, **BC-4**, and **BC-5** each contain two β-bromine atoms and are well suited as chromophore building blocks for subsequent synthetic elaboration. Bacteriochlorin **BC-3** is used in the companion paper to create wavelength-tuned building blocks,[37] **BC-4** has been

employed to create a water-soluble bioconjugatable bacteriochlorin,[55] and **BC-5** is used herein (*vide infra*) in the synthesis of a tetraethynyl-bacteriochlorin building block.

An analogous 2,3,12,13-tetracarboethoxybacteriochlorin (**BC-6**) lacking bromine atoms was prepared in similar manner. van Leusen reaction[56] of diethyl fumarate (**25**) and TosMIC in Et_2O/DMSO (2:1) gave pyrrole **26** in 53% yield at a >90-fold larger scale than previously[57] reported. Subsequent formylation of **26** with $POCl_3$/DMF at 90 °C and at ~3-fold larger scale[16] afforded pyrrole-aldehyde **27** in 67% yield, with recovery of 27% of starting material **26**. Carrying out the formylation reaction at higher temperature (130 °C), with excess $POCl_3$, or at longer time (2 days) still resulted in 20% to 30% of unreacted starting material in each case. Surprisingly, the 2,5-diformylpyrrole was never observed even when >4.0 equiv of Vilsmeier reagent was used. Moreover, the yield decreased to ~20% when 5 M NaOH or saturated aqueous sodium acetate solution was used to quench the reaction rather than saturated aqueous LiCl solution. The subsequent Henry reaction at 20 mmol scale in KOAc/$MeNH_2$·HCl and reduction with $NaBH_4$ afforded 2-(2-nitroethyl)pyrrole **28** in 21% yield. Michael addition with **11** in acetonitrile containing DBU[58] gave nitrohexanone-pyrrole **29** in 29% yield. Reductive cyclization of **29** gave dihydrodipyrrin-acetal **30**. The crude compound **30** was used in the next step by treatment with TMSOTf and 2,6-DTBP for 4 days, whereupon bacteriochlorin **BC-6** was obtained in 18% yield from **29** (Scheme 6).



Scheme 6. Synthesis and metalation studies of a bacteriochlorin-tetraester.

The absorption spectra of 5-methoxybacteriochlorins bearing diester (**BC-2**), dibromo (**BC-4**), dibromodiester (**BC-5**), and tetraester (**BC-6**) substituents are shown in Figure 3. Each shows the characteristic bacteriochlorin absorption spectrum, with strong bands in the near-ultraviolet (B bands) and a strong absorption in the NIR (Q_y band). The latter spans 724–758 nm. The synthetic bacteriochlorins are generally characterized by a molar absorption coefficient of 120,000 $M^{-1}cm^{-1}$ for the Q_y band,[15] and are displayed here in normalized fashion.

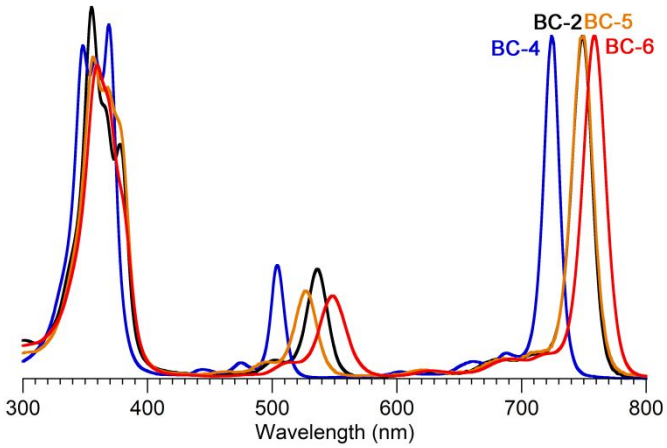
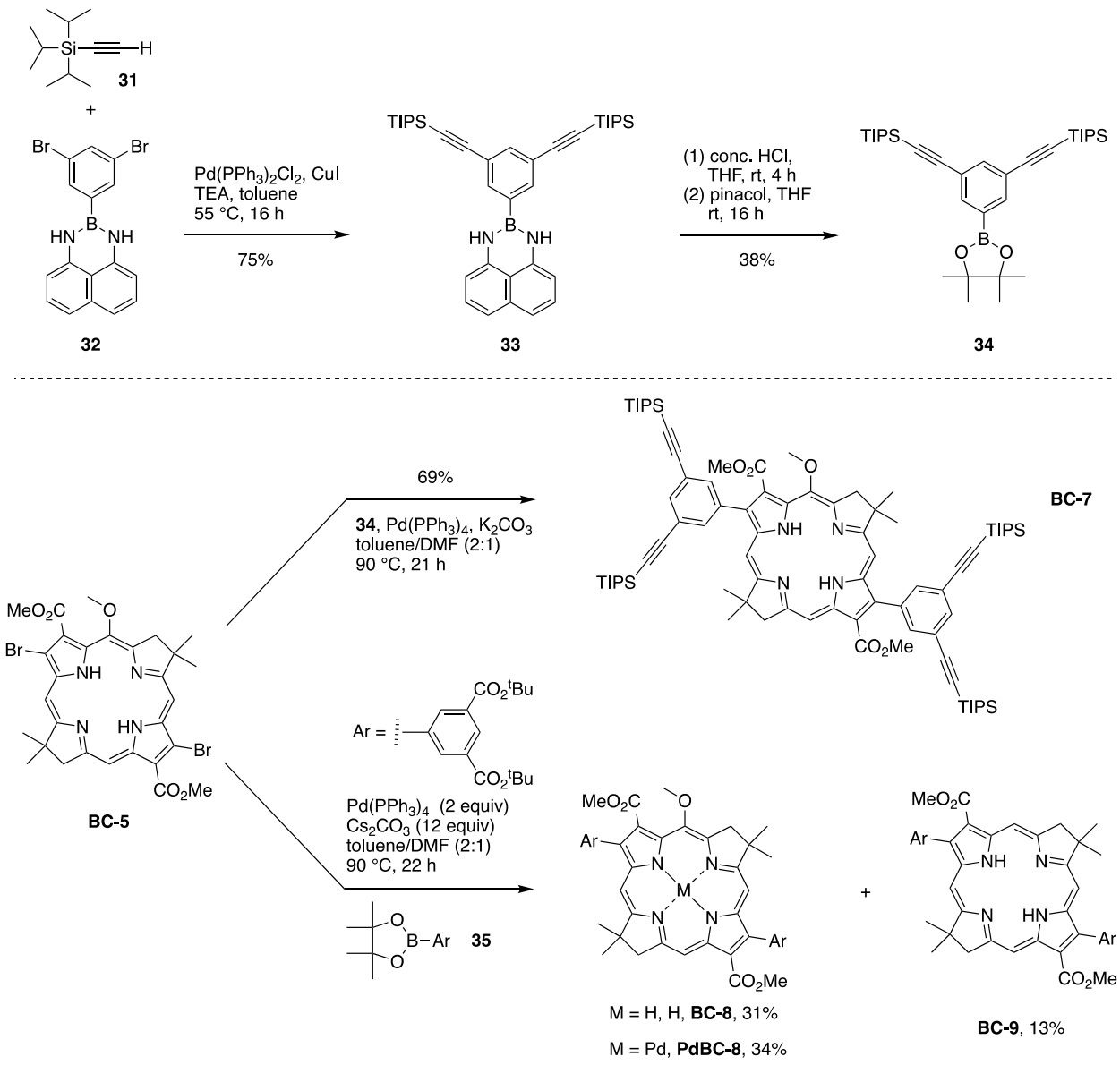


Figure 3. Absorption spectra (normalized at the Q_y bands) of bacteriochlorins in CH_2Cl_2 at room temperature.

The metalation of free base bacteriochlorins has proved far more difficult than with free base porphyrins. Among the gem-dimethyl-substituted bacteriochlorins, the only metals that have been successfully introduced and afford a photoactive metallobacteriochlorin are Zn(II), Mg(II), and In(III).[59,60] A broader range of metals has been inserted with other bacteriochlorins.[61,62] The metalation of bacteriochlorins becomes progressively more facile with increasing number of carbonyl substituents at the perimeter of the macrocycle.[60] Treatment of **BC-6** with copper acetate in DMF at 85 °C gave the copper chelate **CuBC-6**, which exhibited the Q_y band at 787 nm. The bathochromic shift upon metalation of bacteriochlorins is well known.[63] The copper chelate is desired for vibrational studies,[64,65] perhaps photoacoustic imaging, and as the ^{64}Cu isotopologue, for positron emission tomography.[66-68] On the other hand, attempts to introduce Si(IV) or Al(III), which are known to afford photoactive metalloporphyrins[69] and also have labile apical ligands enabling introduction of substituents bound to the metal and positioned above the macrocycle,[70] were not successful using $SiCl_4$, Cl_2SiMe_2, or $AlCl_3$ in DMF at 85 °C for 16 h, or with the same metalation agents under more forcing conditions[60] that utilize NaH in THF (see the ESI). In these cases, the free base bacteriochlorin **BC-6** was unreacted.

Modification of β-substituents on bacteriochlorins

A complementary strategy to tailor bacteriochlorins relies on late-stage derivatization at sites where halogens are pre-installed about the perimeter of the macrocycle, as illustrated here in several examples. A porphyrin that bears a 3,5-diethynylphenyl group at each of the four meso-positions has proved to be a valuable module in the construction of 3-dimensional multichromophore arrays.[71] Here, we pursued installation of two 3,5-diethynylphenyl groups on a bacteriochlorin. The Sonogashira reaction[72,73] of TIPS-acetylene (**31**) with 2-(3,5-dibromophenyl)-1,3,2-diazaborinane **32**[74] gave **33** in 75% yield (Scheme 7). Compound **32**, while commercially available, was prepared here by straightforward reaction of 1,8-diaminonaphthalene and 3,5-dibromobenzeneboronic acid.[74] Compound **33** was characterized by single-crystal X-ray diffraction (see ESI). To our knowledge, structural characterization of analogues thereof has not been reported. Treatment of **33** with concentrated HCl (12 M) followed by pinacol at room temperature[75] gave borolane **34** in 38% yield. The Suzuki coupling reaction[76] of **34** with 2,12-dibromobacteriochlorin **BC-5** gave the tetraethynylbacteriochlorin **BC-7** in 69% yield. The absorption spectra of starting and product bacteriochlorins were nearly identical, with the Q_y band located at 749 nm[55] and 754 nm, respectively.



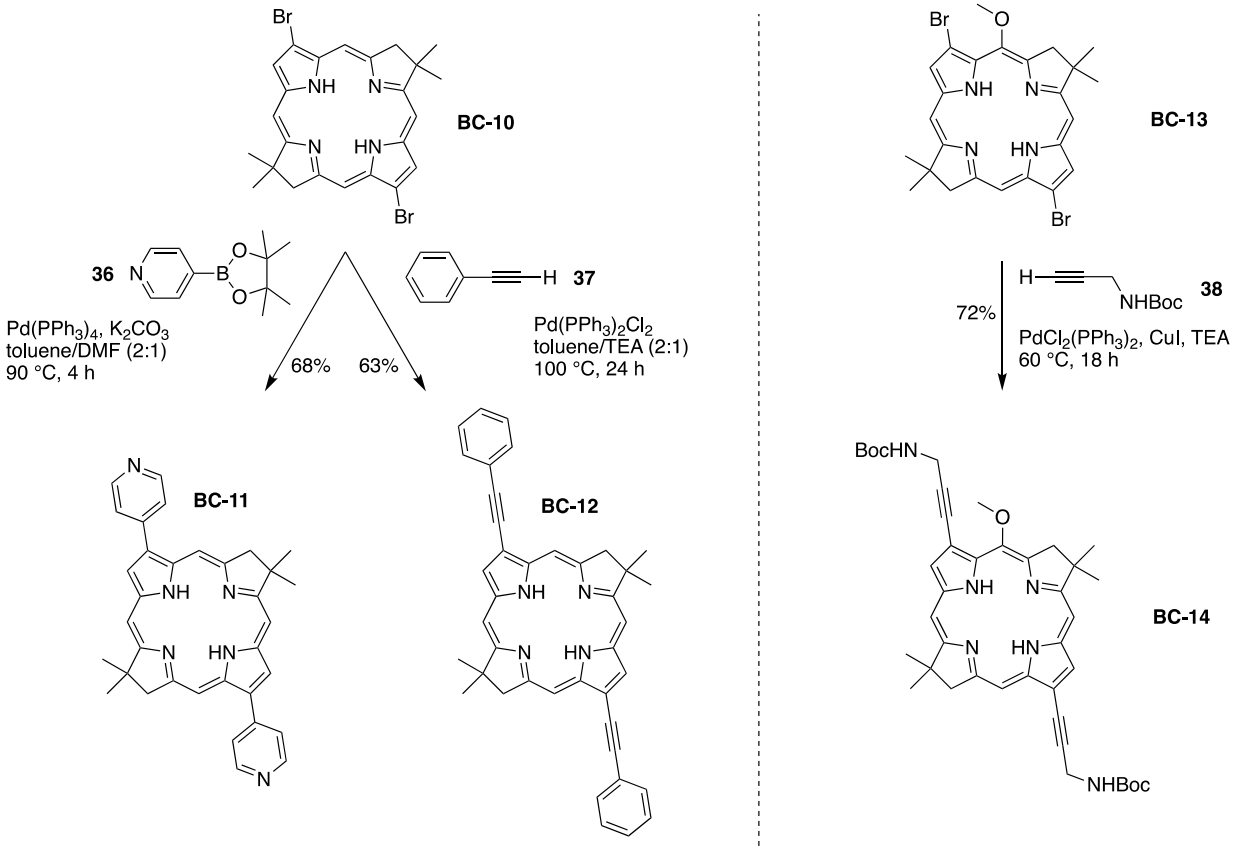
Scheme 7. Unexpected result of Suzuki coupling.

The coupling reaction of dibromobacteriochlorin **BC-5** and borolane **35**[55] was carried out in an effort to achieve both Suzuki coupling and desmethoxylation, as a prelude to attempted formation of the water-soluble bacteriochlorin-bis(imide). The route to the bacteriochlorin-bis(imide) requires the intermediacy of a bacteriochlorin bearing 5,15-dibromo-3,13-dicarboalkoxy groups,[77] hence the necessity to remove the 5-methoxy group. Desmethoxylation of analogues of **BC-5** has been observed in Pd-coupling reactions when the reaction was carried

out in the presence of excess base,[78] or during attempted base-mediated Pd insertion reactions.[60] Here, the Suzuki coupling reaction of 2,12-dibromo-5-methoxybacteriochlorin **BC-5** and **35** under standard conditions[79] gave three bacteriochlorins each bearing 2,12-diaryl groups: the bacteriochlorin with the 5-methoxy group intact (**BC-8**, 31%), the palladium(II) chelate thereof (**PdBC-8**, 34%), and the desired 5-desmethoxybacteriochlorin (**BC-9**, 13%) (Scheme 7). The synthesis of bacteriochlorin **BC-8** is known and was achieved previously in 33% yield (small scale, 12 equiv of K_2CO_3) or 85% yield (larger scale, 3 equiv of Cs_2CO_3).[55] As a control experiment, application of the same excess-base conditions[78] to 5-methoxy-8,8,18,18-tetramethylbacteriochlorin gave no observed desmethoxylation or Pd-insertion, implying the importance of the 3,13-dicarbonyl substituents for desmethoxylation.

A 5-methoxy-3,13-di-*p*-pyridylbacteriochlorin was synthesized previously in trace amount (< 1 mg, estimated 0.7%) by acid-catalyzed condensation of the corresponding pyridyl-substituted dihyrodipyrrin-acetal.[16] Here, 3,13-dibromobacteriochlorin **BC-10**[24] and 4,4,5,5-tetramethyl-2-(4-pyridyl)-1,3,2-borolane (**36**) were subjected to Suzuki coupling to afford the corresponding 3,13-di-*p*-pyridylbacteriochlorin (**BC-11**) in 68% yield (Scheme 8). Analogous reaction with phenylacetylene gave the 3,13-bis(2-phenylethynyl)bacteriochlorin (**BC-12**) in 63% yield. Bacteriochlorins **BC-10** and **BC-12** were characterized by single-crystal X-ray diffraction (Figure 4). The late-stage derivatization approach is clearly superior for installation of pyridyl substituents. An analogous 3,13-dibromo-5-methoxybacteriochlorin (**BC-13**)[16] was treated to Sonogashira coupling[72,73] with *N*-Boc-protected propargylamine (**38**) to afford the corresponding diethynylbacteriochlorin **BC-14**. The ethynyl units cause a significant bathochromic shift of the Q_y band to deeper in the NIR region (743 and 762 nm, versus 713 and 709 for the 3,13-diunsubstituted analogues[16,24]). The ability to install amines at the periphery of the bacteriochlorin

macrocycle affords NIR-photoactive chromophores for potential use in photodynamic therapy or photodynamic inactivation.[80]



Scheme 8. Coupling reactions of 3,13-dibromobacteriochlorins.

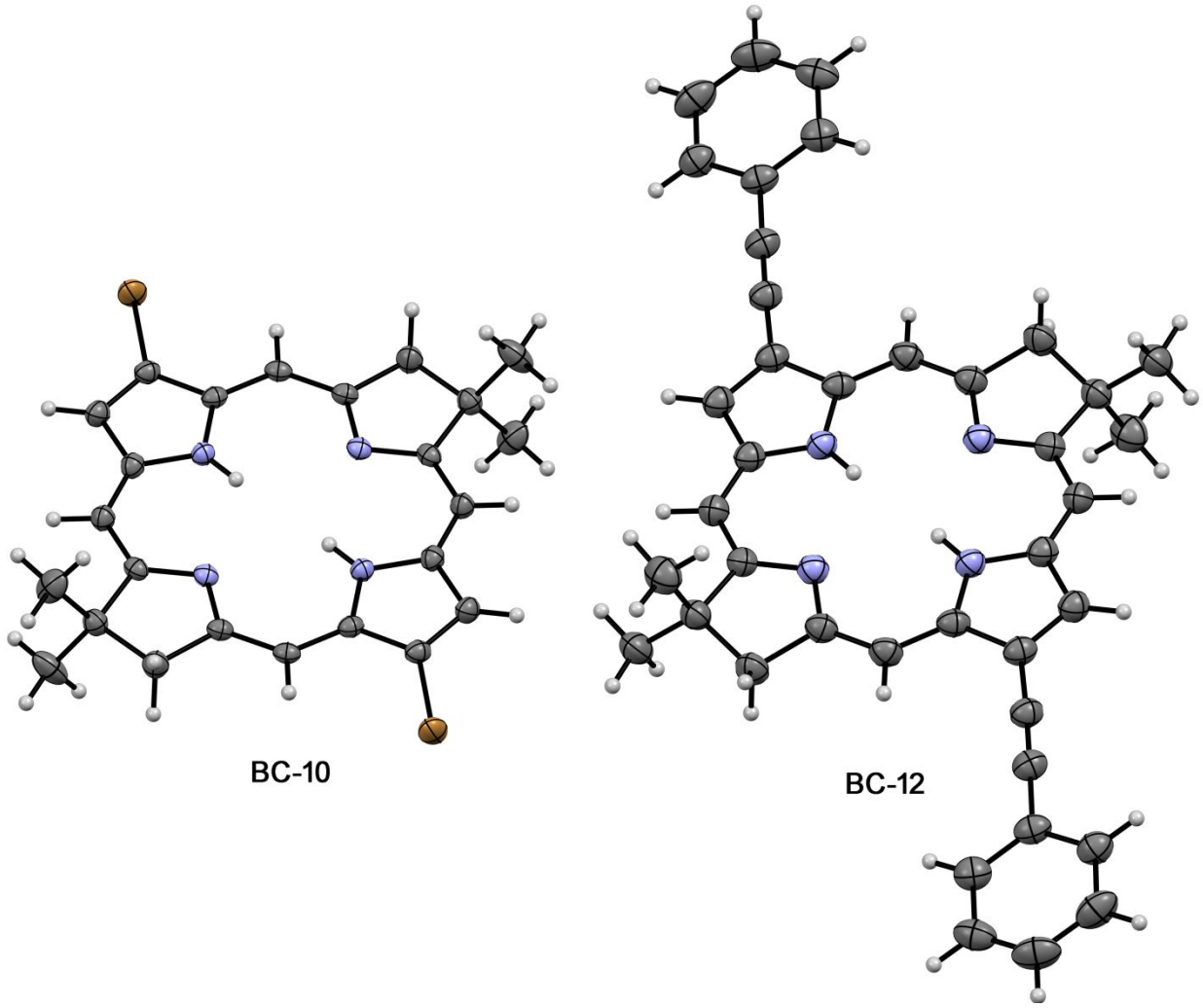
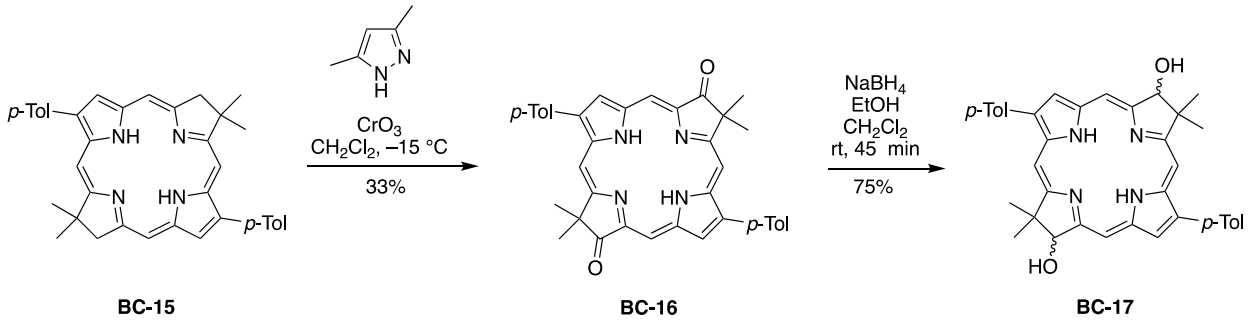


Figure 4. ORTEP diagrams of bacteriochlorin **BC-10** (showing the 3,13-dibromo atoms) and bacteriochlorin **BC-12** (showing the 3,13-bis(phenylethynyl) groups). Ellipsoids are displayed at the 50% probability level.

Synthesis and reaction of dioxobacteriochlorins

The naturally occurring tolyporphin A is a 7,17-dioxobacteriochlorin (Chart 1), as are analogues tolyporphins B–J and L–O. The presence of the two oxo groups along the x-axis, which is perpendicular to the y-axis and thus perpendicular to the transition dipole moment giving rise to the long-wavelength absorption band, causes a hypsochromic shift of the Q_y absorption band. We recently developed a sensitive fluorescence assay for the detection of dioxobacteriochlorin-type

tolyporphins in the presence of chlorophyll *a* by reduction of the respective ketones.[81] In so doing, the Q_y band of the tolyporphins shifted bathochromically whereas that of chlorophyll *a* shifted hypsochromically; the latter shift stems from the removal of a potent auxochrome (the 13-ketone) aligned along the y-axis. A model system for the development of the assay was provided by the synthetic dioxobacteriochlorin prepared as shown in Scheme 9, given the known sensitivity of the methylene unit flanking the gem-dimethyl group.[77,82] Thus, treatment of 2,12-di-*p*-tolylbacteriochlorin **BC-15**[15] with CrO_3 in the presence of 3,5-dimethylpyrazole[13,14,83] (the same reagent used in the synthesis of tolyporphin A *O,O*-diacetate) afforded the corresponding 7,17-dioxobacteriochlorin **BC-16** (19.2 mg, 33%), which was prepared previously (2.4 mg, 41%)[77] and only partially characterized. Reduction of the two ketones of **BC-16** with $NaBH_4$ (a known procedure with chlorophylls[84]) gave the 7,17-dihydroxybacteriochlorin compound **BC-17**. Each hydroxy group is benzylic in nature, and a mixture of four stereoisomers is expected.



Scheme 9. Synthesis and reduction of a 7,17-dioxobacteriochlorin.

The absorption spectra of the parent bacteriochlorin **BC-15**, dioxobacteriochlorin **BC-16**, and dihydroxybacteriochlorin **BC-17** are shown in Figure 5, along with that of tolyporphin A. The bathochromic shift upon reduction of **BC-16** is 43 nm (694 versus 737 nm, respectively). The fluorescence properties (λ_{em}, Φ_f) of the three bacteriochlorins (in toluene) are as follows: 697 nm, 0.16 (**BC-16**); 742 nm, 0.20 (**BC-17**); and 744 nm, 0.14 (**BC-15**). The absorption and fluorescence properties and trends are consistent with prior studies (in toluene) of dioxobacteriochlorins

containing[77] or lacking[82] the 2,12-di-*p*-tolyl groups, as well as that of tolyporphin A (681 nm, 0.14).[85]

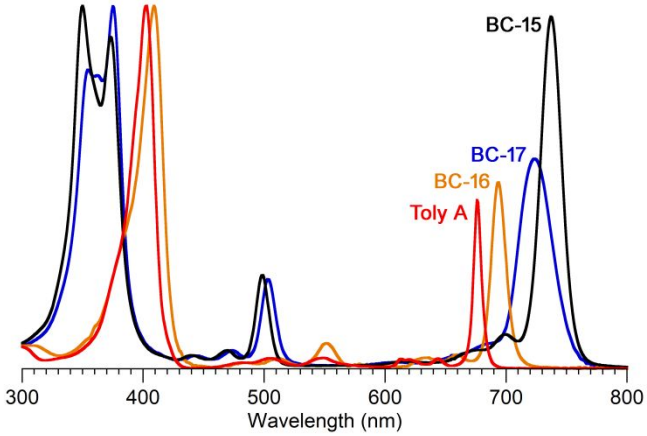


Figure 5. Absorption spectra of **BC-15** (black), **BC-16** (orange), and **BC-17** (blue) in toluene, and tolyporphin A (red) in methanol (normalized at the B band).

Outlook

Synthetic bacteriochlorins are mimics of native bacteriochlorophylls, Nature's NIR absorbers in anoxygenic photosynthesis, yet with appropriate tailoring can be designed for specific non-native applications. Here, five dihydrodipyrrin-acetals/carboxaldehydes were prepared for conversion to the corresponding bacteriochlorins. Four utilized the Eastern-Western route whereas one employed the Northern-Southern route. Both routes proceed via acid-catalyzed condensation and joining of two dihydrodipyrrin-acetals/carboxaldehydes, affording bacteriochlorins equipped with identical substituents on the opposite pyrrolic units. The condensations typically proceed in low yield, which highlights the importance of continued focus on new and improved methods; still, the routes at present generally provide sufficient bacteriochlorin product for exploration of molecular designs and studies of physicochemical properties. The present work reports the synthesis of 11 new bacteriochlorin building blocks and derivatives. Three examples are salient:

- The requirement for acidic conditions in the dihydrodipyrrin self-condensation can limit the types of peripheral substituents on bacteriochlorins. One workaround is to synthesize a dibromobacteriochlorin and then carry out a Pd-mediated coupling reaction to install the desired acid-sensitive functional units. The 3,13-di-*p*-pyridylbacteriochlorin (**BC-11**) was only obtained previously in trace quantities by acid-catalyzed condensation of the corresponding dihydrodipyrrin-acetal,[16] but here was obtained smoothly upon Suzuki coupling with the 3,13-dibromobacteriochlorin and the pyridyl-borolane.
- A bacteriochlorin bearing four ethynyl groups (**BC-7**) was prepared by Suzuki coupling of the parent dibromobacteriochlorin and the 3,5-bis(TIPS-ethynyl)phenyl-borolane. The resulting tetraethynyl-bacteriochlorin constitutes a chromophore building block amenable for construction of 3-dimensional light-harvesting architectures, as has been done with a tetraethynyl-porphyrin analogue.[71]
- The introduction of 7,17-dioxo moieties (**BC-16**) imparts a hypsochromic shift of ~30 nm, whereas reduction of the dioxo groups to hydroxymethylene groups (**BC-17**) relieves the hypsochromic shift. The resulting shift has been employed in a fluorescence assay for naturally occurring dioxobacteriochlorins.[81]

In summary, the ability to tailor the bacteriochlorin by condensation of diverse dihydrodipyrrin-acetals or by derivatization of bacteriochlorins provides flexibility in pursuit of target molecular designs. The present paper concerns pairwise installation of substituents at the β-pyrrole or β-pyrroline sites. The companion paper[37] concerns derivatization of bacteriochlorins at a single meso-site to create and elaborate NIR-active molecular building blocks.

Experimental Section

General methods

Silica (40 μm average particle size) was used for column chromatography. All solvents were reagent grade and were used as received unless noted otherwise. THF was freshly distilled from sodium/benzophenone. All other solvents (anhydrous or reagent-grade) were employed as received from commercial suppliers. Electrospray ionization mass spectrometry (ESI-MS) data generally enable accurate mass measurements, were obtained in the positive-ion mode (unless noted otherwise) and are reported for the molecular ion or protonated molecular ion. Commercial compounds were used as received. ^{1}H NMR and ^{13}C NMR spectra were collected at room temperature in $CDCl_3$ unless noted otherwise and using instruments as indicated for each compound. Matrix-assisted laser desorption ionization mass spectrometry (MALDI-MS) was performed routinely using the matrix α-cyano-4-hydroxycinnamic acid unless noted otherwise.

Single crystal X-ray diffraction analyses

5-E: Data were obtained using a Bruker D8 Venture diffractometer at 100 K (Cu Kα = 1.5418 Å). The structural refinement and graphics were calculated and generated using APEX3, SAINT, SHELXT, and SHELXlE software.

12 and **33**: Data were obtained using a Bruker D8 Venture diffractometer at 110 K (Mo Kα = 0.7107 Å). The structural refinement and graphics were calculated and generated using APEX4, PLATON, OLEX2, and MERCURY3 software.

22: Data were obtained using a Bruker-Nonius X8 Kappa Apex2 diffractometer at 100 K (Mo Kα = 0.7107 Å). The structural refinement and graphics were calculated and generated using APEX3, SAINT, XS, SHELXT, and SHELXlE software.

BC-10 and **BC-12**: Data were obtained using a Bruker-Nonius X8 Apex2 diffractometer at 173 K (Mo Kα = 0.7107 Å). The structural refinement and graphics were calculated and generated using APEX2, SAINT, SIR92, XL, and NRCVAX software.

Non-commercial compounds

The compounds 4-carboethoxy-2-iodopyrrole (**1**),[20] 2,2-dimethylpent-4-ynoic acid (**2**),[20] 4-carboethoxy-(*E*)-2-[(4,4-dimethyl-5-oxodihydrofuran-2(3*H*)-ylidene)methyl]pyrrole (**3**),[43] 1,1-dimethoxy-4-methylpent-3-en-2-one (**11**),[17] 3-bromo-1-phenylsulfonylpyrrole (**14**),[50] 3,5-dibromophenylborolane (**32**),[74] 2-(3,5-bis(*tert*-butoxycarbonyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**35**),[55] and several bacteriochlorins (**BC-10**,[24] **BC-13**,[16] **BC-15**[15]) were prepared following literature procedures.

Synthetic procedures

4-Carboethoxy-(*E*)-2-[(4,4-dimethyl-5-methylenedihydrofuran-2(3*H*)-ylidene)methyl]pyrrole (4). Following a reported procedure[20] with some modification, a solution of $TiCp_2Cl_2$ (12.0 g, 48.2 mmol) in toluene (125 mL) under an argon atmosphere was treated dropwise with MeLi (67 mL of 1.6 M solution in Et_2O, 0.11 mol) over 15 min at 0 °C. After 1 h at 0 °C, the reaction was quenched by the addition of saturated aqueous NH_4Cl solution. The organic layer was washed with water and brine, dried (Na_2SO_4), and filtered. The filtrate was treated with lactone-pyrrole **3** (2.50 g, 9.50 mmol) and additional $TiCp_2Cl_2$ (150 mg, 0.603 mmol).

The mixture was heated to 80 °C in the dark for 6 h and then allowed to cool to room temperature, whereupon $NaHCO_3$ (600 mg), MeOH (12.5 mL) and H_2O (120 μL) were added. The mixture was then stirred at 40 °C for 12 h. The reaction mixture was filtered through Celite. The filtrate was concentrated, dissolved in ethyl acetate and filtered through Celite again to remove a brownish solid. The filtrate was concentrated and chromatographed [silica, hexanes/ethyl acetate (4:1 to 3:1) with 1% of NEt_3] to afford a yellow-brown solid (1.55 g, 60%): mp 113–115 °C; ^{1}H NMR (500 MHz) δ 1.25 (s, 6H), 1.34 (t, J = 7.2 Hz, 3H), 2.68 (d, J = 1.8 Hz, 2H), 4.00 (d, J = 2.4 Hz, 1H), 4.29 (q, J = 7.2 Hz, 2H), 4.37 (d, J = 2.4 Hz, 1H), 5.84–5.86 (m, 1H), 6.29–6.33 (m, 1H), 7.32 (dd, J = 3.0, 1.6 Hz, 1H), 8.97 (br, 1H); ^{13}C NMR (150 MHz) δ 14.5, 27.9, 40.1, 42.5, 59.8, 80.7, 92.1, 105.5, 117.6, 122.3, 129.5, 154.8, 165.1, 169.4; ESI-MS obsd 262.1433, calcd 262.1438 [$(M + H)^+$, M = $C_{15}H_{20}NO_3$].

4-Acetyl-(*E*)-2-[(4,4-dimethyl-5-methylenedihydrofuran-2(3*H*)-ylidene)methyl]pyrrole (4′). In another case, a sample of lactone-pyrrole **3** (3.00 g, 11.4 mmol) was treated in the same way as in the preparation of **4** but using a different batch of $TiCp_2Cl_2$. The crude mixture was chromatographed [silica, hexanes/ethyl acetate (4:1 to 1:1) with 1% of NEt_3] to afford a yellow-brown solid (**4**, 1.21 g, 40%) as the major product and an orange-brown solid as the title compound (0.27 g, 10%) as a minor product: mp 133–135 °C; ^{1}H NMR (600 MHz) δ 1.26 (s, 6H), 2.42 (s, 3H), 2.71 (d, J = 2.0 Hz, 2H), 4.02 (d, J = 2.5 Hz, 1H), 4.39 (d, J = 2.5 Hz, 1H), 5.82–5.84 (m, 1H), 6.33–6.35 (m, 1H), 7.33 (dd, J = 3.0, 1.6 Hz, 1H), 8.54 (br, 1H); ^{13}C NMR (150 MHz) δ 27.0, 27.9,40.0, 42.7, 80.9, 91.9, 104.2, 122.7, 127.3, 130.4, 155.3, 169.4, 193.7; ESI-MS obsd 232.1332, calcd 232.1332 [$(M + H)^+$, M = $C_{14}H_{17}NO_2$].

8-Carboethoxy-2,3-dihydro-1,2,2-trimethyldipyrrin (5-Z and **5-E).** Following a reported procedure,[20] a solution of **4** (120 mg, 11.4 mmol) in DMF (5.5 mL) was treated with 2 M HCl (0.3 mL). After 40 min, NH_4OAc (0.72 g, 9.4 mmol) and NEt_3 (1.2 mL, 8.9 mmol) were added, and the resulting mixture was stirred at 55 °C for 4 h. Then the reaction was quenched by the addition of 20 mL of saturated KH_2PO_4 aqueous solution. Ethyl acetate (30 mL) was added. The organic layer was separated and treated with 1 mL of saturated KH_2PO_4 aqueous solution. The resulting mixture was allowed to stand under ambient conditions (at room temperature; not deaerated) for 24 h, conditions that allow sizeable conversion of the *E* isomer to the *Z* isomer. Then the mixture was dried (Na_2SO_4) and concentrated. Column chromatography [silica, hexanes/ethyl acetate (4:1)] afforded a light-yellow solid [**5-Z**, 58 mg, 48%, R_f = 0.32 on silica TLC, hexanes/ethyl acetate (4:1)]. Further elution with ethyl acetate afforded a brown solid (**5-E**, 28 mg, 23%, R_f = 0.37 on silica TLC, ethyl acetate). Data for **5-Z**: mp 77–79 °C; ^{1}H NMR (600 MHz) δ 1.20 (s, 6H), 1.36 (t, J = 7.2 Hz, 3H), 2.16 (s, 3H), 2.58 (d, J = 1.8 Hz, 2H), 4.29 (q, J = 7.2 Hz, 2H), 5.83 (s, 1H), 6.43–6.45 (m, 1H), 7.42–7.44 (m, 1H), 11.20 (br, 1H); ^{13}C NMR (150 MHz) δ 14.5, 15.6, 25.6, 43.9, 48.4, 59.5, 105.5, 108.0, 116.2, 124.0, 132.0, 150.2, 165.3, 187.3; λ_{abs} (CH_2Cl_2) 319 nm; ESI-MS obsd 261.1598, calcd 261.1596 [$(M + H)^+$, M = $C_{15}H_{20}N_2O_2$]. Data for **5-E**: mp 138–140 °C; ^{1}H NMR (600 MHz) δ 1.23 (s, 6H), 1.35 (t, J = 7.2 Hz, 3H), 2.10 (s, 3H), 2.68 (d, J = 2.3 Hz, 2H), 4.30 (q, J = 7.2 Hz, 2H), 6.44–6.46 (m, 1H), 6.53 (s, 1H), 7.37–7.40 (m, 1H), 8.60 (br, 1H); ^{13}C NMR (150 MHz) δ 14.5, 15.2, 26.1, 43.6, 50.4, 59.8, 107.6, 108.0, 117.9, 123.1, 131.0, 154.0, 165.0, 186.4; λ_{abs} (CH_2Cl_2) 305 nm; ESI-MS obsd 261.1598, calcd 261.1596 [$(M + H)^+$, M = $C_{15}H_{20}N_2O_2$].

8-Carboethoxy-2,3-dihydro-1-(1,1-dimethoxymethyl)-2,2-dimethyldipyrrin (6). Following a reported procedure[20] with modification, a solution of **5-Z** (253 mg, 0.972 mmol) in anhydrous 1,4-dioxane (20.0 mL) was treated with SeO_2 (209 mg, 1.88 mmol) and water (30 μL). The reaction mixture was stirred at room temperature for 30 min. Ethyl acetate and saturated aqueous $NaHCO_3$ solution were then added. The organic layer was washed (brine), dried, and

concentrated. The crude product was passed through a short silica pad and eluted with ethyl acetate to remove selenium species. The eluant was concentrated, dissolved in $HC(OMe)_3$ (15.0 mL), and treated with $TsOH \cdot H_2O$ (60.0 mg, 0.315 mmol). After 12 h with stirring at room temperature, the reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ solution and then extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and concentrated. Column chromatography [silica, hexanes/ethyl acetate (4:1)] afforded a brown oil (74 mg, 25%): ^{1}H NMR (500 MHz) δ 1.20 (s, 6H), 1.26 (t, J = 7.2 Hz, 3H), 2.52 (d, J = 1.8 Hz, 2H), 3.38 (s, 6H), 4.20 (q, J = 7.2 Hz, 2H), 5.03 (s, 1H), 5.88 (s, 1H), 6.38–6.42 (m, 1H), 7.34–7.38 (m, 1H), 10.90 (br, 1H); ^{13}C NMR (125 MHz) δ 14.5, 25.9, 45.6, 48.2, 54.4, 59.6, 102.1, 108.7, 109.2, 116.4, 124.7, 131.6, 149.2, 165.2, 181.9; ESI-MS obsd 321.1811, calcd 321.1809 [$(M + H)^+$, M = $C_{15}H_{20}N_2O_2$]. The characterization data matched those reported previously; the starting material here was scaled up from 109 mg[20] to 253 mg.

Following the same procedure, a solution of **5-E** (330 mg, 1.26 mmol) in anhydrous 1,4-dioxane (25.0 mL) was treated with SeO_2 (270 mg, 2.43 mmol) and water (40 μL). The resulting intermediate was dissolved in $HC(OMe)_3$ (20.0 mL) and treated with $TsOH \cdot H_2O$ (80.0 mg, 0.421 mmol). Similar work up afforded **6** (40 mg) as a brown oil in 10% yield.

3-Carboethoxy-2-methyl-1-(triisopropylsilyl)pyrrole (8). A suspension of NaH (60% in mineral oil, 2.23 g, 56 mmol) in freshly distilled THF (75 mL) was cooled in an ice bath, to which **7** (7.00 g, 45.7 mmol) was added slowly to avoid vigorous reaction. The mixture was stirred at 0 °C for 1 h. Triisopropylsilyl chloride (9.60 g, 49.8 mmol) was added dropwise at 0 °C. The resulting mixture was further stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. Column chromatography [silica, hexanes/ethyl acetate (10:1)] afforded a light yellow oil that slowly solidified at room temperature (13.70 g, 97%): mp 40–41 °C; ^{1}H NMR (600 MHz) δ1.12 (s, 9H), 1.13 (s, 9H), 1.34 (t, J = 7.2 Hz, 3H), 1.55 (sept, J = 7.5 Hz, 2H), 2.62 (s, 3H), 4.26 (q, J = 7.2 Hz, 2H), 6.61 (d, J = 3.1 Hz, 1H), 6.64 (d, J = 3.1 Hz, 1H); ^{13}C NMR (150 MHz) δ 12.3, 13.0, 14.4, 14.5, 17.7, 18.1, 59.2, 111.3, 115.3, 123.7, 141.1, 165.8; ESI-MS obsd 310.2197, calcd 310.2197 [$(M + H)^+$, M = $C_{17}H_{31}NO_2Si$].

3-Carboethoxy-2-formylpyrrole (9). A solution of **8** (12.50 g, 40.40 mmol) in THF/acetic acid/water (420 mL, a 1:1:1 mixture) in an ice bath was treated with ceric ammonium nitrate (88.00 g, 160.5 mmol). The resulting solution was stirred at 0 °C for 45 min. The reaction mixture was poured into ice and extracted with ethyl acetate. The organic layer was washed with saturated aqueous $NaHCO_3$ solution and brine, dried (Na_2SO_4), and concentrated. Column chromatography [silica, hexanes/ethyl acetate (6:1 to 3:1)] afforded an orange solid (3.22 g, 48%): mp 116–118 °C; ^{1}H NMR (600 MHz) δ 1.40 (t, J = 7.2 Hz, 3H), 4.38 (q, J = 7.2 Hz, 2H), 6.77–6.79 (m, 1H), 7.02–7.04 (m, 1H), 9.82 (br, 1H), 10.23 (s, 1H); ^{13}C NMR (150 MHz) δ14.3, 60.8, 113.7, 122.7, 123.7, 132.8, 163.5, 181.8; ESI-MS obsd 168.0655, calcd 168.0655 [$(M + H)^+$, M = $C_8H_9NO_3$].

3-Carboethoxy-2-(2-nitroethyl)pyrrole (10). Following a general procedure[16] with modification, a mixture of **9** (2.58 g, 15.5 mmol), potassium acetate (1.52 g, 15.5 mmol), and methylamine hydrochloride (0.99 g, 14.7 mmol) in freshly distilled THF/anhydrous ethanol (85 mL, 4:1) was treated with nitromethane (7.6 mL, 0.14 mol) and stirred at room temperature for 4 h. The resulting solution was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The resulting orange solid was dried under high vacuum and then dissolved in dry $CHCl_3$/*i*-propanol (3:1, 240 mL). Silica (15.20 g) and $NaBH_4$ (1.13 g, 29.8 mmol) were added, and the mixture was stirred at room temperature

for 1 h. The reaction mixture was filtered, and the filtrate was concentrated and dissolved in CH_2Cl_2. The resulting solution was washed (water, brine), dried (Na_2SO_4), and concentrated. Column chromatography [silica, hexanes/ethyl acetate (4:1)] afforded a yellow solid (1.65 g, 51%): mp 72–74 °C; ^{1}H NMR (600 MHz) δ 1.35 (t, J = 7.2 Hz, 3H), 3.59 (t, J = 6.1 Hz, 2H), 4.28 (q, J = 7.2 Hz, 2H), 4.71 (t, J = 6.1 Hz, 2H), 6.57–6.59 (m, 1H), 6.61–6.63 (m, 1H), 8.56 (br, 1H); ^{13}C NMR (150 MHz) δ 14.4, 25.0, 59.8, 74.5, 110.8, 112.9, 117.2, 133.0, 165.1; ESI-MS obsd 213.0872, calcd 213.0870 [$(M + H)^+$, M = $C_9H_{12}N_2O_4$].

3-Carboethoxy-2-(1,1-dimethoxy-4,4-dimethyl-5-nitro-2-oxohexan-6-yl)pyrrole (12). Following a general procedure[16] with modification, a mixture of **10** (1.44 g, 6.79 mmol) and **11** (3.28 g, 20.7 mmol) was treated with DBU (3.20 g, 21.0 mmol) followed by ethyl acetate (2 mL). The resulting solution was stirred at room temperature for 3.5 h. A saturated solution of cold aqueous NH_4Cl was added. The mixture was extracted with ethyl acetate, and the organic layer was washed with brine, dried (Na_2SO_4), and concentrated. Column chromatography [silica, hexanes/ethyl acetate (4:1)] afforded an off-white solid (2.04 g, 81%): mp 84–85 °C; ^{1}H NMR (600 MHz) δ 1.19 (s, 3H), 1.31 (s, 3H), 1.36 (t, J = 7.1 Hz, 3H), 2.66, 2.72 (AB, ^2J = 18.6 Hz, 2H), 3.33 (ABX, ^3J = 11.6 Hz, ^2J = 14.7 Hz, 1H), 3.42 (s, 3H), 3.43 (s, 3H), 3.79 (ABX, ^3J = 1.5 Hz, ^2J = 14.7 Hz, 1H), 4.25–4.32 (m, 2H), 4.40 (s, 1H), 5.18 (ABX, ^3J = 2.4 Hz, ^2J = 11.7 Hz, 1H), 6.54-6.57 (m, 2H), 8.29 (br, 1H); ^{13}C NMR (150 MHz) δ 14.6, 23.7, 24.1, 26.2, 36.6, 44.6, 54.96, 55.00, 59.7, 94.7, 104.5, 110.8, 113.0, 117.3, 132.6, 165.0, 203.1; ESI-MS obsd 371.1813, calcd 371.1813 [$(M + H)^+$, M = $C_{17}H_{26}N_2O_7$].

7-Carboethoxy-2,3-dihydro-1-(1,1-dimethoxymethyl)-3,3-dimethyldipyrrin (13). Following a general procedure[16] with modification, in a first flask, a solution of **12** (830 mg, 2.24 mmol) in freshly distilled THF (20 mL) was treated with NaOMe (983 mg, 18.2 mmol). The mixture was stirred and deaerated by bubbling argon through the solution for 45 min. In a second flask purged with argon, $TiCl_3$ (19.0 mL, 12 wt % in HCl solution, 18 mmol), water (100 mL), and NH_4OAc (58.1 g, 0.754 mol) were combined under argon, and the mixture was deaerated by bubbling argon for 45 min. Then, the first flask mixture was transferred to the buffered $TiCl_3$ mixture quickly. The resulting mixture was stirred at room temperature for 16 h under argon. The reaction mixture was then poured over a pad of Celite and eluted with ethyl acetate. The eluant was neutralized with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and concentrated. Column chromatography [silica, hexanes/ethyl acetate (3:1)] afforded a light yellow oil that slowly solidified at −20 °C to give a light yellow solid (375 mg, 53%): mp 70–72 °C; ^{1}H NMR (600 MHz) δ 1.25 (s, 6H), 1.37 (t, J = 7.2 Hz, 3H), 2.65 (s, 2H), 3.46 (s, 6H), 4.30 (q, J = 7.2 Hz, 2H), 5.03 (s, 1H) 6.57–6.60 (m, 1H), 6.72–6.75 (m, 1H), 6.90 (s, 1H), 11.11 (br, 1H); ^{13}C NMR (150 MHz) δ 14.5, 29.0, 40.5, 48.4, 54.6, 59.4, 102.5, 105.9, 110.4, 112.5, 118.5, 135.0, 163.6, 165.4, 176.8; ESI-MS obsd 321.1810, calcd 321.1809 [$(M + H)^+$, M = $C_{17}H_{24}N_2O_4$].

3-Bromo-2-formyl-1-phenylsulfonylpyrrole (15). Following a general procedure[51] with modification, a solution of **14** (13.45 g, 47.00 mmol) in freshly distilled THF (128 mL) was treated with LDA solution (38.4 mL, 2.0 M in THF/heptane/ethylbenzene, 76.8 mmol) at −78 °C. Then the solution was stirred overnight in a cooling bath at −55 °C and then chilled again to −78 °C. A solution of ethyl formate (38.0 mL, 470 mmol) in freshly distilled THF (95 mL) was cooled at −78 °C and poured into the pyrrole-lithium solution in one batch. (The addition of ethyl formate should be finished in one batch rather than dropwise, otherwise the resulting reactive aldehyde would likely dimerize with the unreacted pyrrole-lithium.) The resulting mixture was stirred at −78 °C for 1 h. Then saturated aqueous NH_4Cl solution was added to quench the reaction. The product was extracted with ethyl acetate, and the extract was washed with brine, dried (Na_2SO_4), and

concentrated. Column chromatography [silica, hexanes/ethyl acetate (8:1 to 4:1)] recovered 2.20 g of starting material and afforded the title compound as an orange solid (8.80 g, 60%): mp 67–69 °C; ^{1}H NMR (500 MHz) δ 6.49 (d, J = 3.3 Hz, 1H), 7.52–7.58 (m, 2H), 7.64–7.69 (m, 1H), 7.72 (d, J = 3.3 Hz, 1H), 7.97–8.01 (m, 2H), 9.82 (s, 1H); ^{13}C NMR (125 MHz) δ 115.6, 116.3, 128.15, 128.23, 129.30, 129.33, 134.7, 137.6, 177.5; ESI-MS obsd 313.9482, calcd 313.9481 [(M + H)$^+$, M = $C_{11}H_8BrNO_3S$]. The characterization data matched those previously reported.[51]

3-Bromo-2-(2-nitroethyl)-1-phenylsulfonylpyrrole (16). Following a general procedure[53] with modification, a solution of **15** (2.95 g, 9.39 mmol) in nitromethane (60 mL) was treated with ammonium acetate (0.93 g, 12 mmol). The resulting solution was refluxed for 3.5 h and then allowed to cool to room temperature. The mixture was concentrated and passed through a short column [silica, hexanes/ethyl acetate (3:1)]. The eluant was concentrated and dried under high vacuum to give an orange solid. Then the orange solid was dissolved in freshly distilled THF (50 mL) and treated with $LiBH_4$ (90%, 310 mg, 12.8 mmol) at 0 °C for 1 h. Then saturated aqueous NH_4Cl solution was added to quench the reaction. The product was extracted with ethyl acetate, and the extract was washed with brine, dried (Na_2SO_4), and concentrated. Column chromatography [silica, hexanes/ethyl acetate (4:1)] afforded a light yellow oil (1.94 g, 58%): ^{1}H NMR (500 MHz) δ 3.40–3.48 (m, 2H), 4.47–4.55 (m, 2H), 6.34 (d, J = 3.6 Hz, 1H), 7.34 (d, J = 3.6 Hz, 1H), 7.54–7.61 (m, 2H), 7.65–7.71 (m, 1H), 7.78–7.83 (m, 2H); ^{13}C NMR (125 MHz) δ 24.1, 22.7, 105.5, 114.8, 123.2, 125.1, 126.8, 129.9, 134.7, 138.2; ESI-MS obsd 356.9546, calcd 356.9550 [(M - H)$^-$, M = $C_{12}H_{11}BrN_2O_4S$].

3-Bromo-2-(1,1-dimethoxy-4,4-dimethyl-5-nitro-2-oxohexan-6-yl)-1-phenylsulfonylpyrrole (17). Following a general procedure[16] with modification, a mixture of **16** (1.94 g, 5.40 mmol) and **11** (2.07 g, 13.1 mmol) was treated with DBU (2.10 g, 13.8 mmol) followed by ethyl acetate (2 mL). The resulting solution was stirred at room temperature for 16 h. A saturated solution of cold aqueous NH_4Cl was added. The mixture was extracted with ethyl acetate, and the organic layer was washed with brine, dried (Na_2SO_4), and concentrated. Column chromatography [silica, hexanes/ethyl acetate (4:1 to 2:1)] afforded a brown solid (1.70 g, 61%): mp 87–90 °C; ^{1}H NMR (500 MHz) δ 1.23 (s, 3H), 1.28 (s, 3H), 2.66, 2.76 (AB, ^2J = 18.6 Hz, 2H), 3.12 (ABX, ^3J = 2.9 Hz, ^2J = 15.4 Hz, 1H), 3.41 (s, 3H), 3.43 (s, 3H), 3.79 (ABX, ^3J = 11.4 Hz, ^2J = 15.4 Hz, 1H), 4.37 (s, 1H), 5.31 (ABX, ^3J = 3.7 Hz, ^2J = 11.2 Hz, 1H), 6.28 (d, J = 3.7 Hz, 1H), 7.27 (d, J = 3.3 Hz, 1H), 7.52–7.58 (m, 2H), 7.63–7.68 (m, 1H), 7.71–7.75 (m, 2H);^{13}C NMR (125 MHz) δ 23.6, 23.8, 25.7, 36.6, 44.2, 55.00, 55.02, 60.4, 93.0, 104.6, 106.7, 115.9, 124.2, 126.46, 126.5, 129.8, 134.4, 138.4, 203.1; ESI-MS obsd 539.0440, calcd 539.0458 [(M + Na)$^+$, M = $C_{20}H_{25}BrN_2O_7S$].

7-Bromo-2,3-dihydro-1-(1,1-dimethoxymethyl)-3,3-dimethyldipyrrin (18). Following a general procedure[24] with modification, a sample of **17** (1.60 g, 3.09 mmol) in freshly distilled THF (25 mL) was treated with TBAF (1.0 M solution in THF, 3.6 mL). The resulting mixture was refluxed for 1 h and then allowed to cool to room temperature. Then saturated aqueous $NaHCO_3$ solution was added. The resulting mixture was stirred for another 3 h at room temperature. The product was extracted with ethyl acetate, and the extract was washed with brine, dried (Na_2SO_4), and concentrated. The mixture was concentrated and passed through a short column [silica, hexanes/ethyl acetate (3:1 to 1:1)]. The eluant was concentrated and dried under high vacuum to afford a brown oil. Then the crude deprotected intermediate was dissolved in freshly distilled THF (25.0 mL) and treated with NaOMe (839 mg, 15.5 mmol). The mixture was stirred and deaerated by bubbling argon through the solution for 30 min. In a second flask purged with argon, $TiCl_3$ (20.0 mL, 12 wt % in HCl solution, 19 mmol), water (120 mL), and NH_4OAc (25.4 g, 0.330 mol) were combined under argon, and the mixture was deaerated by bubbling argon for 45 min. Then,

the first flask mixture was transferred quickly to the buffered $TiCl_3$ mixture. The resulting mixture was stirred at room temperature for 16 h under argon. The reaction mixture was then poured over a pad of Celite and eluted with ethyl acetate. The eluant was neutralized with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and concentrated. Column chromatography [silica, hexanes/ethyl acetate (4:1 to 2:1)] afforded a yellow solid (300 mg, 30%): mp 100–102 °C; ^{1}H NMR (500 MHz) δ 1.23 (s, 6H), 2.62 (s, 2H), 3.44 (s, 6H), 5.01 (s, 1H), 5.93 (s, 1H), 6.18 (t, J = 2.9 Hz, 1H), 6.78 (t, J = 2.9Hz, 1H), 10.74 (br, 1H); ^{13}C NMR (175 MHz) δ 29.1, 40.3, 48.4, 54.5, 96.9, 102.6, 104.7, 111.0, 119.2, 128.3, 160.9, 175.2; ESI-MS obsd 327.0707, calcd 327.0703 [$(M + H)^+$, M = $C_{14}H_{19}BrN_2O_2$].

3-Carbomethoxypyrrole (20). Following a reported procedure[57] with some modification, a mixture of **19** (20 mL, 0.22 mol) and TosMIC (43.6 g, 0.22 mol) in anhydrous THF (220 mL) was transferred to a suspension of NaH (18.0 g, 60% dispersion in mineral oil, 1.1 mol) in anhydrous THF (150 mL) via a dropping funnel under argon over 1 h. The mixture started to reflux due to the exothermic reaction and turned brown. Then the mixture was stirred overnight. Water (400 mL) was added slowly, and the mixture was extracted with ethyl acetate (400 mL × 3). The organic layer was dried (Na_2SO_4) and concentrated to a dark solid. Purification by chromatography [silica, hexanes/ethyl acetate (2:1)] afforded a yellow solid (11.7 g, 43%): mp 86–90 °C (lit.[57] 87–89 °C); ^{1}H NMR (400 MHz) δ 3.82 (s, 3H), 6.65 (s, 1H), 6.75–6.77 (m, 1H), 7.42–7.43 (m, 1H), 8.96 (br, 1H); ^{13}C{^{1}H} NMR (100 MHz) δ 51.2, 109.5, 115.7, 119.2, 123.9, 166.2; ESI-MS obsd 126.0552, calcd 126.0550 [$(M + H)^+$, M = $C_6H_7NO_2$].

3-Carbomethoxy-1-(triisopropylsilyl)pyrrole (21). A suspension of NaH (4.05 g, 60% dispersion in mineral oil, 0.10 mol) in anhydrous THF (50 mL) was slowly treated with a solution of **20** (11.5 g, 92.0 mmol) in anhydrous THF (100 mL) at 0 °C under argon. The mixture was stirred for 1 h at 0 °C. Triisopropylsilyl chloride (20.7 mL, 96.6 mmol) was added dropwise to the mixture at 0 °C. The resulting mixture was stirred for 1.5 h at 0 °C. Ice water (250 mL) was added slowly, and the mixture was extracted with diethyl ether. The extract was dried (Na_2SO_4), concentrated to a dark oil, and chromatographed [silica, hexanes to hexanes/ethyl acetate (9:1)] to afford a pale-yellow liquid (24.6 g, 96%): ^{1}H NMR (400 MHz) δ 1.10 (d, J = 7.5 Hz, 18H), 1.41–1.52 (m, 3H), 3.81 (s, 3H), 6.68–6.76 (m, 2H), 7.42 (dd, J = 2.1, 1.4 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz) δ 11.5, 17.6, 50.9, 111.5, 118.2, 124.9, 129.9, 185.4; ESI-MS obsd 282.1884, calcd 282.1888 [$(M + H)^+$, M = $C_{15}H_{27}NO_2Si$].

3-Bromo-4-carbomethoxypyrrole (22). Following a standard procedure[46] with modification, a solution of **21** (24.2 g, 86.1 mmol) in THF (ACS grade, 250 mL) was cooled to −78 °C. A solution of NBS (15.3 g, 86.1 mmol) in THF was slowly added by a dropping funnel over 10 min. The mixture was stirred at –78 °C for 1.5 h. Then the flask was allowed to warm to room temperature with continued stirring at room temperature. The reaction process was monitored by TLC and ^{1}H NMR spectroscopy. After 4 h, the solvent was removed, and the residue was dissolved in ethyl acetate. The organic layer was washed with water, dried (Na_2SO_4) and concentrated. The residue was chromatographed [silica, hexanes/ethyl acetate (10:1)] to collect the crude product [R_f = 0.47, hexanes/ethyl acetate (10:1)], which was directly used in the next step. The crude product (28.3 g) was dissolved in THF (ACS grade, 300 mL) under argon and then was treated with TBAF (118.2 mL, 120 mmol, 1 M in THF). The color changed from yellow to pink. The reaction progress was monitored by TLC. After 30 min, all starting material was consumed, and the mixture was diluted by the addition of ethyl acetate. The organic layer was washed with water, dried (Na_2SO_4), and concentrated. The residue was chromatographed [silica, hexanes/ethyl acetate (3:1)] to afford a white solid (9.4 g, 54%): mp 95–98 °C (lit.[55] 96–98 °C);

^{1}H NMR (400 MHz, THF-d_8) δ 3.71 (s, 3H), 6.81 (d, J = 2.3 Hz, 1H), 7.37 (dd, J = 3.4, 2.3 Hz, 1H), 10.95 (br, 1H); ^{13}C{^{1}H} NMR (100 MHz, THF-d_8) δ 49.6, 96.3, 114.0, 120.3, 124.8, 162.8; ESI-MS obsd 203.9657, calcd 203.9655 [(M + H)$^+$, M = $C_6H_6BrNO_2$].

3-Bromo-4-carbomethoxy-2-(1,1-dimethoxy-4,4-dimethyl-5-nitro-2-oxohexan-6-yl)pyrrole (23). A solution of anhydrous DMF (16 mL) was treated with $POBr_3$ (15.5 g, 54.0 mmol) at 0 °C under argon and stirred for 15 min. A solution of **22** (9.13 g, 45.0 mmol) in anhydrous DMF (178 mL) was bubbled with argon for 10 min. Then the freshly prepared Vilsmeier reagent was added dropwise into the solution of **22** at 0 °C under argon. The mixture was then stirred for 1 h at 60 °C in an oil bath and then allowed to cool to room temperature. The reaction mixture was cooled to 0 °C and treated with saturated aqueous sodium acetate (300 mL). The resulting mixture was stirred for 2 h and then allowed to warm to room temperature. The mixture was extracted with CH_2Cl_2 (300 mL × 2). The organic layer was washed with water and saturated brine, dried (Na_2SO_4), and concentrated. The product was obtained by recrystallization (CH_2Cl_2/hexanes) as a white solid (6.73 g). A mixture of the resulting white solid (6.73 g, 29.1 mmol), methylamine hydrochloride (3.93 g, 58.2 mmol) and potassium acetate (5.71 g, 58.2 mmol) in absolute ethanol (38 mL) was treated with nitromethane (4.6 mL) at room temperature under argon. The resulting mixture was stirred for 2 h, whereupon water was added. The resulting precipitate was separated by filtration, washed with water, and dried under high vacuum to afford a yellow solid. The yellow solid was dissolved in $CHCl_3$/*i*-propanol (380 mL, 3:1, v/v). Silica (38 g) and $NaBH_4$ (1.42 g, 37.5 mmol) were slowly added, and the resulting reaction mixture was stirred for 3 h under argon at room temperature. Then, the reaction mixture was filtered, and the filtrate was collected and concentrated. The resulting crude solid was dissolved in a minimal amount of CH_2Cl_2 and washed with water. The aqueous phase was removed, and the organic phase was dried (Na_2SO_4) and concentrated to afford a brown solid (~2.3 g). A mixture of the resulting brown solid (2.3 g, 8.33 mmol) and freshly prepared **11** (2.64 g, 16.7 mmol) was treated with DBU (6.23 mL, 41.7 mmol) at room temperature under argon. The resulting reaction mixture was stirred for 16 h whereupon cold aqueous saturated NH_4Cl solution was added. The reaction mixture was extracted with ethyl acetate. The extract was dried (Na_2SO_4) and concentrated to a dark oil. The excess **11** was removed by bulb-to-bulb distillation, and the undistilled residue was passed through a silica pad with elution by ethyl acetate/CH_2Cl_2 (1:9 to 1:4). The filtrate was concentrated to afford a yellow oil (5.6 g, 29%): ^{1}H NMR (400 MHz): δ 1.12 (s, 3H), 1.25 (s, 3H), 2.57–2.74 (m, 2H), 3.13 (ABX, ^3J = 15.3 Hz, ^2J = 2.9 Hz, 1H), 3.29 (ABX, ^3J = 15.4 Hz, ^2J = 11.5 Hz, 1H), 3.40 (s, 3H), 3.41 (s, 3H), 3.79 (s, 3H), 4.36 (s, 1H), 5.18 (dd, J = 11.4, 2.8 Hz, 1H), 7.31 (d, J = 3.4 Hz, 1H), 9.13 (br, 1H); ^{13}C{^{1}H} NMR (100 MHz): δ 23.8, 24.2, 25.4, 36.5, 44.7, 51.1, 55.1, 93.3, 97.3, 104.6, 114.6, 124.5, 126.1, 163.7, 203.4; ESI-MS obsd 435.0756, calcd 435.0761 [(M + H)$^+$, M = $C_{16}H_{23}BrN_2O_7$].

7-Bromo-8-carbomethoxy-2,3-dihydro-1-(1,1-dimethoxymethyl)-3,3-dimethyldipyrrin (24). In a first flask, a solution of **23** (1.36 g, 3.13 mmol) in anhydrous THF/methanol (110 mL, 10:1) was bubbled with argon for 10 min, and then was treated with NaOMe (1.26 g, 23.3 mmol) and stirred for 45 min. In a second flask, a solution of NH_4OAc (95.6 g, 1.24 mol) in deionized water (100 mL) was bubbled for 15 min, and then was treated with $TiCl_3$ (19.7 mL, 25 mmol, 20% w/v solution in 2N HCl). The suspension was stirred for 30 min at room temperature under argon. The solution in the first flask containing the nitronate anion of **23** was transferred via a cannula to the buffered $TiCl_3$ solution in the second flask. The resulting brown mixture was stirred for 1 h under argon, and then the flask was sealed to react for 19 h. The reaction mixture was slowly poured into a stirred mixture of saturated aqueous $NaHCO_3$ (400 mL) and ethyl acetate (250 mL). The mixture was stirred vigorously at room temperature for 30 min.

The combined mixture was extracted with ethyl acetate (400 mL×2) and washed with saturated aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4) and concentrated. The residue was chromatographed [silica, CH_2Cl_2] to afford a pale-yellow oil (336 mg, 28%): ^{1}H NMR (300 MHz): δ 1.24 (s, 6H), 1.67 (s, 1H), 2.64 (d, J = 0.7 Hz, 2H), 3.44 (s, 6H), 3.82 (d, J = 0.5 Hz, 3H), 5.03 (s, 1H), 5.98 (s, 1H), 7.44–7.53 (m, 1H), 11.21 (br, 1H); ^{13}C{^{1}H} NMR (75 MHz): δ 29.0, 40.5, 48.5, 51.0, 54.5, 97.0, 102.3, 104.2, 109.8, 114.3, 125.2, 130.5, 162.7, 164.0, 176.7; ESI-MS obsd 385.0760, calcd 385.0758 [$(M + H)^+$, M = $C_{16}H_{21}BrN_2O_4$].

3,4-Dicarboethoxypyrrole (26). Following a reported procedure[16] with some modification, a suspension of NaH (4.4g, 60% dispersion in mineral oil, 0.11 mol) in anhydrous diethyl ether (100 mL) was added dropwise to a mixture of **25** (15.0 mL, 91.7 mmol) and TosMIC (17.9 g, 188 mmol) in diethyl ether/DMSO (420 mL, 2:1, v/v) via a dropping funnel under argon over 1.5 h, whereupon the mixture turned from yellow to brown. Then the reaction mixture was stirred vigorously at room temperature for 3.5 h under argon. Water (250 mL) was added slowly and the mixture was stirred for 20 min. The mixture was extracted with ethyl acetate (400 mL × 3), washed with water and brine, dried (Na_2SO_4) and concentrated to brown solid. The resulting solid was washed with *n*-hexane and chromatographed [silica, CH_2Cl_2/ethyl acetate (3:1 to 1:2)] to afford a pale-yellow solid (10.2 g, 53%): mp 135–144 °C; ^{1}H NMR (400 MHz) δ 1.33 (t, J = 7.1 Hz, 6H), 4.29 (q, J = 7.1 Hz, 4H), 7.38 (dd, J = 2.9, 0.6 Hz, 2H), 9.92 (br, 1H); ^{13}C{^{1}H} NMR (100 MHz) δ 14.3, 60.2, 115.8, 125.9, 164.1; ESI-MS obsd 212.0920, calcd 212.0917 [$(M + H)^+$, M = $C_{10}H_{13}NO_4$].

3,4-Dicarboethoxy-2-formylpyrrole (27). Following a reported procedure[16] with slight modification, a solution of **26** (7.80 g, 37.0 mmol) in anhydrous DMF (80 mL) was treated with $POCl_3$ (5.1 mL, 56 mmol) under argon at 0 °C. The mixture was stirred for 20 min and then heated to 90 °C. Then the reaction mixture was stirred for 24 h under argon. After allowing to cool to room temperature, a biphasic solution of CH_2Cl_2/saturated aqueous sodium acetate (500 mL, 1:1, v/v) was added, and the resulting mixture was stirred for 1 h at room temperature. The organic layer was separated and washed with saturated aqueous lithium chloride (300 mL × 3). The organic layer was dried over Na_2SO_4 and concentrated. The residue was chromatographed [silica, hexanes/ethyl acetate (4:1 to 1:2)] to afford a pale-yellow solid (5.9 g, 67%): mp 61–64 °C; ^{1}H NMR (400 MHz) δ 1.35 (t, J = 7.1 Hz, 3H), 1.40 (t, J = 7.1 Hz, 3H), 4.32 (q, J = 7.1 Hz, 2H), 4.43 (q, J = 7.1 Hz, 2H), 7.59–7.70 (m, 1H), 9.90 (s, 1H), 10.88 (br, 1H); ^{13}C{^{1}H} NMR (100 MHz) δ 14.1, 14.2, 60.8, 61.8, 118.2, 124.4, 129.0, 132.4, 162.8, 163.3, 181.0; ESI-MS obsd 240.0868, calcd 240.0867 [$(M + H)^+$, M = $C_{11}H_{13}NO_5$]. Further elution with ethyl acetate afforded starting material **26** (2.0 g, 26%).

3,4-Dicarboethoxy-2-(2-nitroethyl)pyrrole (28). Following a reported procedure[16] with some modification, a mixture of **27** (4.70 g, 19.7 mmol), potassium acetate (2.13 g, 21.7 mmol) and methylamine hydrochloride (1.47 g, 21.7 mmol) dissolved in nitromethane (70 mL) under argon. The reaction mixture was stirred at room temperature and monitored by TLC. After 3 h, brine (100 mL) was added, and the mixture was extracted with ethyl acetate, dried (Na_2SO_4) and concentrated. The residue was further dried under high vacuum to afford a brown solid. The crude solid (8.8 g) was dissolved in $CHCl_3$/*i*-propanol (380 mL, 3:1, v/v), whereupon silica (36 g) was added. The mixture was stirred vigorously at room temperature under argon for 40 min. The silica was filtered, and the filter cake was washed with CH_2Cl_2. The filtrate was concentrated and chromatographed [silica, CH_2Cl_2/ethyl acetate (4:1)] to afford a white solid (1.2 g, 21%): mp 160–165 °C; ^{1}H NMR (300 MHz) δ 1.32 (t, J = 7.1 Hz, 3H), 1.34 (t, J = 7.2 Hz, 3H), 3.44–3.51 (m, 2H), 4.27 (q, J = 7.2 Hz, 4H), 4.30 (q, J = 7.2 Hz, 2H), 4.68–4.75 (m, 2H), 7.21 (d, J = 2.9 Hz,

1H), 9.01 (br, 1H); $^{13}C\{^1H\}$ NMR (75 MHz) δ 14.2, 14.3, 24.7, 60.5, 60.6, 74.5, 113.2, 117.2, 123.3, 133.6, 164.0, 164.5; ESI-MS obsd 283.0934, calcd 283.0936 [$(M + H)^+$, M = $C_{12}H_{16}N_2O_6$].

3,4-Dicarboethoxy-2-(1,1-dimethoxy-4,4-dimethyl-5-nitro-2-oxohexan-6-yl)pyrrole (29). Following a reported procedure[58] with some modification, a solution of **28** (700 mg, 2.46 mmol) and Michael acceptor (**11**, 1.00 g, 6.33 mmol) in anhydrous acetonitrile (25 mL) was slowly treated with DBU (1.35 mL, 9.04 mmol) under argon. The reaction process was monitored by TLC, and after 3 h, another 1.35 mL of DBU was added. The mixture was stirred for 21 h at room temperature under argon. Cold saturated aqueous ammonium chloride (30 mL) was added, and the mixture was extracted with ethyl acetate (30 mL × 3), dried (Na_2SO_4) and concentrated to a dark oil. The resulting oil was chromatographed [silica, CH_2Cl_2/ethyl acetate (6:1 to 4:1)] to afford a pale-yellow oil (312 mg, 29%): ^1H NMR (300 MHz) δ 1.15 (s, 3H), 1.27 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H), 1.35 (t, J = 7.2 Hz, 3H), 2.59–2.78 (m, 2H), 3.33 (dd, J = 14.8, 11.5 Hz, 1H), 3.42 (s, 3H), 3.43 (s, 3H), 3.55 (dd, J = 14.9 Hz, 2.5 Hz, 1H), 4.22–4.37 (m, 4H), 4.39 (s, 1H), 5.22 (dd, J = 11.5, 2.5 Hz, 1H), 7.14 (d, J = 2.9 Hz, 1H), 8.70 (s, 1H); $^{13}C\{^1H\}$ NMR (75 MHz) δ 14.3, 14.3, 23.8, 24.1, 25.9, 36.6, 44.7, 55.0, 55.1, 60.4, 60.5, 94.4, 104.5, 113.4, 117.2, 123.2, 133.1, 164.0, 164.5, 203.2; ESI-MS obsd 443.2025, calcd 443.2024 [$(M + H)^+$, M = $C_{12}H_{16}N_2O_6$].

2-(3,5-Bis(2-(triisopropylsilyl)ethynyl)phenyl-2,3-dihydro-1*H*-naphtho[1,8-de]-1,3,2-diazaborine (33). Following a standard procedure,[72] a Schlenk flask containing triisopropylsilylacetylene (**31**, 0.585 g, 3.21 mmol), **32** (0.320 g, 0.796 mmol), and CuI (8.1 mg, 44 μmol) was deaerated by three vacuum-purge cycles with argon. Then deaerated toluene/TEA (6 mL, 5:1) was added to the flask under a stream of argon. The Schlenk flask was deaerated by three freeze-pump-thaw cycles. $Pd(PPh_3)_2Cl_2$ (28 mg, 40 μmol) was added to the flask and followed by three additional freeze-pump-thaw cycles. The resulting mixture was heated to 55 °C and stirred for 20 h. The reaction mixture was allowed to cool to room temperature, and then concentrated and purified by chromatography [silica, hexanes/CH_2Cl_2 (10:1 to 1:1)] to afford a white solid (360 mg, 75%): mp 179–180 °C; ^1H NMR (600 MHz) δ 1.15 (d, J = 1.6 Hz, 36H), 6.01 (s, 2H), 6.44 (dd, J = 7.3, 1.0 Hz, 2H), 7.07 (dd, J = 8.3, 1.0 Hz, 2H), 7.14 (dd, J = 8.3, 7.3 Hz, 2H), 7.65–7.63 (m, 3H), the 2° proton of each TIPS group was not observed; ^{13}C NMR (150 MHz) δ 11.31, 11.33, 18.6, 18.7, 91.8, 106.0, 106.2, 118.1, 119.9, 123.8, 127.6, 134.6, 136.3, 136.7, 140.7; MALDI-MS obsd 604.4, calcd 604.384 [$(M)^+$, M = $C_{38}H_{53}BN_2Si_2$].

2-(3,5-Bis(2-(triisopropylsilyl)ethynyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (34). A solution of **33** (0.908 g, 1.50 mmol) in anhydrous THF (39 mL) was treated with hydrochloric acid (25 mL, 12 M) at room temperature for 4 h. The reaction mixture was filtered, and the filtrate was concentrated. The resulting solid was dissolved in CH_2Cl_2, washed with hydrochloric acid (20 mL, 2M) and saturated aqueous $NaHCO_3$ (20 mL), dried (Na_2SO_4) and concentrated. Following a standard procedure,[75] the resulting solid was dissolved in anhydrous THF (9.1 mL), treated with pinacol (0.273 g, 2.31 mmol), and stirred at room temperature for 40 h. (Note that isolation and storage of the intermediate boronic acid resulted in undesired formation of the boronic acid trimer, but combining the two steps prevented such trimerization.) The reaction mixture was concentrated, diluted with CH_2Cl_2, washed with brine (20 mL), dried (Na_2SO_4), concentrated, and purified by chromatography [silica, hexanes/CH_2Cl_2 (10:1 to 1:1)] to afford a white solid (334.1 mg, 38%): mp 153–155 °C; ^1H NMR (600 MHz) δ 1.12 (s, 36H), 1.35 (s, 12H), 7.63 (t, J = 1.7 Hz, 1H), 7.82 (d, J = 1.7 Hz, 2H), the 2° proton of each TIPS group was not observed; ^{13}C NMR (150 MHz) δ 11.3, 18.7, 24.8, 84.2, 91.1, 106.0, 123.3, 137.79, 137.85; MALDI-MS obsd 587.3, calcd 587.380 [$(M + Na)^+$, M = $C_{34}H_{57}BO_2Si_2$].

2,12-Dicarboethoxy-8,8,18,18-tetramethylbacteriochlorin (BC-1) via the Northern-Southern route. Following a general procedure,[20] a solution of **6** (100 mg, 312 μmol) in anhydrous CH_2Cl_2 (18.5 mL) was treated with 2,6-DTBP (1.43 mL, 6.28 mmol) followed by TMSOTf (300 μL, 1.65 mmol). The reaction mixture was stirred overnight under an argon atmosphere at room temperature, and then diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4) and concentrated. Column chromatography [silica, hexanes/CH_2Cl_2 (1:1) to CH_2Cl_2] afforded a green-purple solid (5.5 mg, 5.5%). The characterization data (by absorption, ^{1}H NMR and ^{13}C NMR spectroscopy) matched those obtained previously via the same route.[20]

2,12-Dicarboethoxy-8,8,18,18-tetramethylbacteriochlorin (BC-1) via the Eastern-Western route. Following a general procedure[16] with modification, a solution of **13** (203 mg, 0.633 mmol, 18 mM) in anhydrous CH_3CN (35 mL) was treated with $BF_3{\cdot}O(Et)_2$ (610 μL, 4.91 mmol, 140 mM). The reaction mixture was stirred at room temperature for 6 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2, and concentrated. Column chromatography [silica, hexanes/CH_2Cl_2 (1:1) to CH_2Cl_2] gave two bands. The first green-purple band afforded the title compound as a green-purple solid (6.7 mg, 4.1%). The second purple band afforded 5-methoxybacteriochlorin **BC-2** as a dark purple solid (3.0 mg, 1.7%). Data for the title compound: ^{1}H NMR (600 MHz) δ –1.45 (s, 2H), 1.70 (t, J = 7.2 Hz, 6H), 1.97 (s, 12H), 4.39 (s, 4H), 4.76 (q, J = 7.2 Hz, 4H), 8.75 (s, 2H), 9.17 (s, 2H), 9.70 (s, 2H); ^{13}C NMR (150 MHz) δ 14.7, 31.0, 46.7, 51.2, 60.9, 97.3, 100.5, 122.3, 125.7, 133.2, 136.0, 159.9, 165.6, 173.0; ESI-MS obsd 515.2646, calcd 515. 2653 [$(M + H)^+$, M = $C_{30}H_{34}N_4O_4$]; λ_{abs} (CH_2Cl_2) 351, 378, 521, 753 nm.

Data for **2,12-Dicarboethoxy-5-methoxy-8,8,18,18-tetramethylbacteriochlorin (BC-2).** ^{1}H NMR (600 MHz) δ –1.30 (s, 1H), –1.19 (s, 1H), 1.70 (t, J = 7.2 Hz, 3H), 1.71 (t, J = 7.2 Hz, 3H), 1.95 (s, 6H), 1.96 (s, 6H), 4.32 (s, 2H), 4.33 (s, 2H), 4.46 (s, 3H), 4.72-4.78 (m, 4H), 8.61 (s, 1H), 9.14 (s, 1H), 9.34 (s, 1H), 9.63 (s, 1H), 9.67 (s, 1H); ^{13}C NMR (150 MHz) δ 14.7, 14.8, 30.3, 30.9, 31.0, 45.8, 46.1, 47.1, 51.5, 60.8, 61.0, 65.3, 97.4, 97.7, 99.7, 120.4, 120.8, 123.8, 124.7, 126.9, 129.1, 134.7, 135.7, 136.1, 136.4, 154.8, 161.7, 165.3, 165.8, 172.2, 172.4; ESI-MS obsd 544.2675, calcd 544.2680 [$(M)^+$, M = $C_{31}H_{36}N_4O_5$]; λ_{abs} (CH_2Cl_2) 355, 378, 536, 749 nm.

Synthesis of **BC-2** using 2,6-DTBP/TMSOTf. Following a general procedure[16] with modification, a solution of **13** (32 mg, 0.10 mmol, 18 mM) in anhydrous CH_2Cl_2 (5.5 mL) was treated with 2,6-DTBP (450 μL, 2.04 mmol) followed by TMSOTf (90 μL, 0.50 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was poured into saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2, and concentrated. Column chromatography [silica, hexanes/CH_2Cl_2 (1:1) to CH_2Cl_2] afforded **BC-2** as a dark purple solid (4.6 mg, 17%).

2,12-Dibromo-8,8,18,18-tetramethylbacteriochlorin (BC-3). Following a general procedure[16] with modification, a solution of **18** (200 mg, 0.611 mmol, 18 mM) in anhydrous CH_2Cl_2 (34 mL) was treated with $BF_3{\cdot}O(Et)_2$ (500 μL, 4.05 mmol). The reaction mixture was stirred at room temperature for 11 h. The reaction mixture was quenched by the addition of triethylamine (1.0 mL) and then concentrated. Column chromatography [silica, hexanes/CH_2Cl_2 (1:0 to 1:1)] gave two green bands. The first green band afforded the title compound as a green solid (7.8 mg, 4.9%). The second green band afforded 5-methoxybacteriochlorin **BC-4** as a dark green solid (6.0 mg, 3.5%). Data for the title compound: ^{1}H NMR (700 MHz) δ –2.16 (s, 2H), 1.98 (s, 12H), 4.42 (s, 4H), 8.71 (s, 2H), 8.74 (d, J = 2.2 Hz, 2H), 8.78 (s, 2H);^{13}C NMR (175 MHz) δ 31.1, 46.1, 51.4, 94.9, 98.8, 122.8, 133.5, 134.1, 158.8, 170.8; ESI-MS obsd 526.0369, calcd 526.0362 [$(M)^+$, M = $C_{24}H_{24}Br_2N_4$]; λ_{abs} (CH_2Cl_2) 343, 368, 492, 728 nm.

Data for **2,12-Dibromo-5-methoxy-8,8,18,18-tetramethylbacteriochlorin (BC-4).** ^{1}H NMR (700 MHz) δ –2.04 (s, 1H), –1.93 (s, 1H), 1.95 (s, 6H), 1.97 (s, 6H), 4.36 (s, 2H), 4.37 (s, 2H), 4.44 (s, 3H), 8.57 (s, 1H), 8.69 (d, J = 2.1 Hz, 1H), 8.708 (s, 1H), 8.710 (s, 1H), 8.93 (d, J = 2.3 Hz, 1H); ^{13}C NMR (175 MHz) δ 31.0, 31.1, 45.7, 46.0, 47.4, 51.7, 65.1, 95.1, 95.2, 97.9, 109.4, 113.1, 118.7, 123.6, 129.8, 132.7, 134.1, 135.0, 135.5, 153.7, 160.5, 170.0, 173.3; ESI-MS obsd 556.0470, calcd 556.0468 [$(M)^+$, M = $C_{25}H_{26}Br_2N_4O$]; λ_{abs} (CH_2Cl_2) 348, 359, 369, 504, 724 nm. The characterization data matched those obtained from an alternative route.[55]

2,12-Dibromo-3,13-dicarbomethoxy-5-methoxy-8,8,18,18-tetramethylbacteriochlorin (BC-5). A solution of **24** (464 mg, 1.21 mmol) in anhydrous CH_2Cl_2 (64 mL) was treated with 2,6-DTBP (4.60 g, 24.2 mmol) and TMSOTf (1.09 mL, 6.04 mmol) under argon. The reaction mixture was stirred for 18 h at room temperature. The reaction mixture was washed with saturated aqueous $NaHCO_3$ solution, and the organic phase was dried and concentrated. The residue was chromatographed [silica, hexanes to hexanes/CH_2Cl_2 (1:1)] to afford a dark purple solid (128 mg, 33%): ^{1}H NMR (500 MHz): δ –1.52 (s, 1H), –1.24 (s, 1H), 1.93 (s, 6H), 1.94 (s, 6H), 4.23 (s, 3H), 4.31 (s, 3H), 4.32 (m, 5H), 4.37 (s, 2H), 8.65 (s, 1H), 8.85 (s, 1H), 9.53 (s, 1H); ^{13}C{^{1}H} NMR (125 MHz): δ 30.8, 31.0, 45.7, 46.0, 47.8, 51.6, 52.3, 53.4, 64.5, 95.5, 97.7, 98.5, 110.2, 115.2, 120.1, 126.5, 128.3, 131.8, 133.4, 135.0, 135.1, 157.3, 161.9, 165.1, 167.2, 169.8, 173.3; ESI-MS obsd 673.0640, calcd 637.0656 [$(M + H)^+$, M = $C_{29}H_{30}Br_2N_4O_5$]; λ_{abs} (CH_2Cl_2) 356, 368, 527, 750 nm.

2,3,12,13-Tetracarboethoxy-5-methoxy-8,8,18,18-tetramethylbacteriochlorin (BC-6). Following a general procedure[16] with modification, in a first flask, a solution of **29** (305 mg, 0.689 mmol) in anhydrous THF (23 mL) and methanol (1.8 mL) was bubbled for 15 min with argon, and then was treated with NaOMe (280 mg, 5.18 mmol). The mixture was stirred for 45 min under argon whereupon the color changed from yellow to orange. In a second flask, a solution of NH_4OAc (21.3 g, 276 mmol) in deionized water (25 mL) was bubbled for 30 min with argon, and then treated with $TiCl_3$ (4.38 mL, 20% w/v solution in 2N HCl, 5.5 mmol). The mixture was stirred for 20 min where the color changed from transparent to dark green. The first flask mixture was transferred via cannula to the buffered $TiCl_3$ mixture. The resulting mixture was stirred for 20 h at room temperature under argon. Then the mixture was poured into a 1 L beaker containing saturated aqueous $NaHCO_3$ (150 mL), and the resulting mixture was stirred vigorously for 20 min. The aqueous mixture was extracted with ethyl acetate, dried (Na_2SO_4), and concentrated to a yellow oil. The oil was passed through a silica pad (CH_2Cl_2) to afford a pale-yellow oil (compound **30**, 73 mg): ESI-MS obsd 393.2020, calcd 393.2020 [$(M + H)^+$, M = $C_{20}H_{30}N_2O_6$]. TLC analysis indicated the resulting oil was sufficiently pure for subsequent reaction; hence, the entire quantity was dissolved in anhydrous CH_2Cl_2 (10.3 mL) under argon and then treated with 2,6-DTBP (711 mg, 3.72 mmol) and TMSOTf (168 μL, 0.926 mmol). The resulting red reaction mixture was stirred for 4 days (and monitored by absorption spectroscopy) whereupon the mixture turned purple. Then, the reaction mixture was concentrated and chromatographed [silica, CH_2Cl_2 to CH_2Cl_2/ethyl acetate (4:1)] to afford a purple solid (42 mg, 18%): ^{1}H NMR (400 MHz) δ –1.09 (s, 1H), –0.88 (s, 1H), 1.61–1.69 (m, 12H), 1.91 (s, 6H), 1.92 (s, 6H), 4.22 (s, 3H), 4.29 (s, 2H), 4.31 (s, 2H), 4.69–4.82 (m, 8H), 9.07 (s, 1H), 9.13 (s, 1H), 9.66 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz) δ 14.3, 14.5, 30.7, 30.8, 45.9, 46.0, 47.4, 51.4, 61.3, 61.8, 61.9, 62.1, 64.3, 97.9, 98.5, 98.7, 118.2, 124.8, 124.9, 127.1, 128.2, 133.2, 133.7, 135.2, 136.7, 156.8, 163.3, 164.4, 165.4, 165.6, 167.8, 171.7, 174.2; ESI-MS obsd 689.3178, calcd 689.3181 [$(M + H)^+$, M = $C_{37}H_{44}N_4O_9$]; λ_{abs} (CH_2Cl_2) 357, 548, 758 nm.

Cu(II)-2,3,12,13-Tetracarboethoxy-5-methoxy-8,8,18,18-tetramethylbacteriochlorin (CuBC-6). Following a reported procedure[60] with some modification, a solution of **BC-6** (1.0 mg, 1.5 μmol) in anhydrous DMF (350 μL) was treated with copper(II) acetate (11.8 mg, 65.0 μmol) under an argon atmosphere. The reaction mixture was stirred at 85 °C for 11 h. The mixture was allowed to cool to room temperature. TLC analysis [silica, CH_2Cl_2/ethyl acetate (4:1)] showed only one spot. The Q_y band shifted from 758 nm to 782 nm in the absorption spectrum. The disappearance of fluorescence showed that the reaction was completed. The reaction mixture was washed with brine and water. The organic layer was dried (Na_2SO_4) and concentrated to afford a purple solid (0.9 mg, 90%): MALDI-MS obsd 749.1; ESI-MS obsd 750.2321, calcd 750.2328 [$(M + H)^+$, M = $C_{37}H_{42}CuN_4O_9$]; λ_{abs} (DMF) 349, 383, 576, 782 nm.

2,12-(3,5-Bis(2-(triisopropylsilyl)ethynyl)phenyl)-5-methoxy-3,13-dicarbomethoxy-8,8,18,18-tetramethylbacteriochlorin (BC-7). Following a standard procedure[55] with modification, a Schlenk flask containing samples of **BC-5** (49.7 mg, 73.7 μmol), **34** (209 mg, 371 μmol), and K_2CO_3 (124 mg, 897 μmol) was deaerated by three vacuum-purge cycles with argon. Then deaerated toluene/TEA (7.5 mL, 2:1) was added to the flask under a stream of argon. The Schlenk flask was deaerated by three freeze-pump-thaw cycles. $Pd(PPh_3)_4$ (52.4 mg, 45.3 μmol) was added to the flask under a stream of argon. The resulting mixture was heated to 90 °C and stirred for 21 h. The crude mixture was allowed to cool to room temperature, diluted with CH_2Cl_2, washed with brine, and purified by a first chromatography [silica, hexane/ethyl acetate (15:1)] followed by a second chromatography [silica, hexanes/CH_2Cl_2 (1:2)] to afford a purple solid (70.7 mg, 69%): ^{1}H NMR (500 MHz) δ –1.49 (s, 1H), –1.19 (s, 1H), 1.17 (dd, J = 3.8, 2.0 Hz, 72H), 1.47 (s, 4H), 1.82 (s, 6H), 1.85 (s, 6H), 4.05 (s, 3H), 4.18 (s, 3H), 4.25 (s, 3H), 4.43 (s, 2H), 4.40 (d, J = 3.2 Hz, 2H), 7.80 (t, J = 1.5 Hz, 1H), 7.83 (t, J = 1.5 Hz, 1H), 8.01 (d, J = 1.5 Hz, 2H), 8.16 (d, J = 1.5 Hz, 2H), 8.43 (s, 1H), 8.55 (s, 1H), 9.60 (s, 1H); ^{13}C NMR (125 MHz) δ 11.32, 11.33, 18.7, 30.6, 30.7, 45.7, 46.1, 51.7, 52.9, 64.4, 76.8, 77.0, 77.3, 91.6, 92.0, 98.3, 106.0, 106.2, 123.4, 124.5, 128.2, 135.0, 135.1, 135.5, 135.9, 148.1, 148.3, 156.9, 161.7, 166.4, 168.6; MALDI-MS obsd 1388.603, calcd 1388.834 [$(M)^+$, M = $C_{85}H_{120}N_4O_5Si_4$]; λ_{abs} (CH_2Cl_2) 377, 533, 755 nm.

2,12-Bis[3,5-bis(*tert*-butoxycarbonyl)phenyl]-3,13-dicarbomethoxy-8,8,18,18-tetramethylbacteriochlorin (BC-9). Following a general procedure,[79] a mixture of **BC-5** (50 mg, 0.074 mmol), borolane **35** (180 mg, 0.440 mmol), $Pd(PPh_3)_4$ (171 mg, 0.148 mmol), and anhydrous Cs_2CO_3 (289 mg, 0.888 mmol) was deaerated under vacuum in a Schlenk flask for 1 h. Toluene/DMF [7.4 mL, (2:1), deaerated by bubbling argon] was added, and the reaction mixture was deaerated by four freeze–pump–thaw cycles. The reaction mixture was heated at 90 °C for 22 h. After allowing to cool to room temperature, the solvent was evaporated. The crude reaction mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The organic layer was separated, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (silica, CH_2Cl_2) to afford the following compounds in the elution order of the title compound, which lacks the 5-methoxy group (10.1 mg, 13%); the 5-methoxybacteriochlorin **BC-8** (24.4 mg, 31%); and the palladium(II) chelate of the 5-methoxybacteriochlorin **PdBC-8** (30.0 mg, 34%). Each compound was isolated as a purple solid. Data for the title compound: ^{1}H NMR (400 MHz) δ –1.05 (s, 2H), 1.67 (s, 36H), 1.83 (s, 12H), 4.04 (s, 6H), 4.43 (s, 4H), 8.36 (s, 2H), 8.90 (t, J = 1.6 Hz, 2H), 9.69 (s, 2H); ^{13}C NMR (100 MHz) δ 28.4, 28.5, 29.9, 31.0, 46.2, 51.9, 52.1, 82.0, 97.3, 99.7, 119.9, 130.1, 132.0, 132.3, 134.1, 134.9, 135.9, 136.7, 137.0, 162.1, 165.4, 166.4, 172.7; ESI-MS obsd 1038.49719, calcd 1038.49902 [$(M)^+$, M = $C_{60}H_{70}N_4O_{12}$]; λ_{abs} (CH_2Cl_2) 360, 528, 772 nm.

Data for **2,12-bis[3,5-bis(*tert*-butoxycarbonyl)phenyl]-3,13-dicarbomethoxy-5-methoxy-8,8,18,18-tetramethylbacteriochlorin (BC-8)**: The characterization data (by absorption, ^{1}H NMR, and ^{13}C NMR spectroscopy) matched those obtained in an alternative route.[55]

Data for **Pd(II)-2,12-Bis[3,5-bis(*tert*-butoxycarbonyl)phenyl]-3,13-dicarbomethoxy-5-methoxy-8,8,18,18-tetramethylbacteriochlorin (PdBC-8)**: ^{1}H NMR (500 MHz) δ1.657 (s, 18H), 1.664 (s, 18H), 1.78 (s, 6H), 1.84 (s, 6H), 3.97 (s, 3H), 4.09 (s, 3H), 4.15 (s, 3H), 4.39 (s, 2H), 4.43 (s, 2H), 8.22 (s, 1H), 8.40 (s, 1H), 8.66 (d, J = 1.6 Hz, 2H), 8.80 (d, J = 1.6 Hz, 2H), 8.82–8.83 (m, 1H), 8.84–8.85 (m, 1H), 9.65 (s, 1H); ^{13}C NMR (125 MHz) δ28.3, 30.0, 30.1, 44.9, 45.4, 46.2, 50.2, 51.6, 52.8, 64.1, 81.68, 81.71, 98.4, 100.3, 100.9, 121.7, 127.2, 129.5, 129.8, 131.9, 132.4, 133.0, 134.8, 135.4, 135.7, 135.9, 136.3, 136.5, 137.0, 137.1, 137.6, 140.2, 143.9, 147.8, 157.1, 159.2, 164.9, 165.2, 166.1, 168.9; ESI-MS obsd 1172.3984, calcd 1172.3969 [$(M)^+$, M = $C_{61}H_{70}N_4O_{13}Pd$]; λ_{abs} (CH_2Cl_2) 338, 380, 531, 755 nm.

8,8,18,18-Tetramethyl-3,13-di-4-pyridylbacteriochlorin (BC-11). A mixture of **BC-10** (15 mg, 0.029 mmol), $Pd(PPh_3)_4$ (9.9 mg, 8.6 μmol), anhydrous K_2CO_3 (23.3 mg, 0.169 mmol), and **36** (18.0 mg, 0.088 mmol) was dried in a Schlenk flask for 15 min. Toluene/DMF (4.5 mL, 2:1) was added, and the mixture was deaerated by three freeze-pump-thaw cycles. The mixture was placed in a preheated oil bath at 90 °C for 4 h. After allowing to cool to room temperature, the mixture was poured into water and extracted with CH_2Cl_2. The organic phase was treated with THF/hexanes [(1:1), 2 mL]. The resulting mixture was sonicated for 2 min (benchtop sonication bath) and centrifuged. The supernatant was then removed. The solid was treated with THF/hexanes [(1:1), 2 mL] and then the process of sonication and centrifugation was repeated. This cycle was performed four more times. The title compound was obtained as a green solid (10 mg, 68%): ^{1}H NMR (300 MHz) δ –1.83 (s, 2H), 1.99 (s, 12H), 4.46 (s, 4H), 8.12–8.14 (m, 4H), 8.75 (s, 2H), 8.88 (d, J = 2.2 Hz, 2H), 8.92 (s, 2H), 8.97–8.99 (m, 4H); LD-MS 524.6; ESI-MS obsd 525.2765, calcd 525.2761 [$(M + H)^+$, M = $C_{34}H_{32}N_6$]; λ_{abs} (CH_2Cl_2) 357, 503, 742 nm.

3,13-Bis(2-phenylethynyl)-8,8,18,18-tetramethylbacteriochlorin (BC-12). Following a general procedure,[30] samples of **BC-10** (36.4 mg, 68.9 μmol) and phenylacetylene (**37**, 38.0 μL, 346 μmol) were placed into a 25 mL Schlenk flask and dissolved in toluene/TEA (15 mL, 2:1). The resulting mixture was deaerated by three freeze-pump-thaw cycles under argon. Then $Pd(PPh_3)_2Cl_2$ (25.4 mg, 36.1 μmol) was added, and the reaction mixture was stirred at 100 °C. After 6 h, another batch of **37** (38.0 μL, 346 μmol) was added to the mixture. After another 18 h, the mixture was allowed to cool to room temperature and then diluted with CH_2Cl_2. The organic layer was washed (aqueous $NaHCO_3$), separated, dried (Na_2SO_4), and filtered. The filtrate was concentrated and chromatographed [silica, hexanes/CH_2Cl_2 (2:1)] to afford a dark green solid (24.7 mg, 63%): ^{1}H NMR (600 MHz) δ –1.81 (s, 2H), 1.96 (s, 12H), 4.47 (s, 4H), 7.44–7.46 (m, 2H), 7.50–7.52 (m, 4H), 7.90 (d, J = 6.8 Hz, 4H), 8.60 (s, 2H), 8.81 (d, J = 1.9 Hz, 2H), 9.06 (s, 2H); ^{13}C NMR (150 MHz) δ 28.5, 42.3, 52.3, 52.4, 54.0, 83.4, 118.1, 119.5, 122.1, 122.2, 123.6, 124.9, 126.1, 127.3, 127.6, 128.0, 128.3, 128.4, 129.2, 129.3, 130.7, 130.9, 159.8, 166.9, 167.2; ESI-MS obsd 527.2706, calcd 569.2711 [$(M-H)^-$, M = $C_{40}H_{33}N_4$]; λ_{abs} (CH_2Cl_2) 366, 480, 511, 762 nm.

3,13-Bis[3-(*N*-*tert*-butoxycarbonyl)aminoprop-1-ynyl]-5-methoxy-8,8,18,18-tetramethylbacteriochlorin (BC-14). Following a general procedure,[79] samples of **BC-13** (22 mg, 40 μmol), **38** (62 mg, 0.40 mmol), $PdCl_2(PPh_3)_2$ (5.6 mg, 8.0 μmol) and TEA (2.0 mL, deaerated by bubbling with argon for 45 min) were added to a Schlenk flask and deaerated by three freeze-pump-thaw cycles. The reaction mixture was stirred at 60 °C for 18 h. The reaction mixture was allowed to cool to room temperature, then concentrated to dryness, diluted with CH_2Cl_2, and washed with saturated aqueous $NaHCO_3$. The organic layer was separated, dried (Na_2SO_4), and

concentrated. Column chromatography [silica, CH_2Cl_2/TEA (99:1 to 49:1)] afforded a green solid (20 mg, 72%): ^{1}H NMR (300 MHz) δ –1.86 (s, 1H), –1.66 (s, 1H), 1.56 (s, 9H), 1.57 (s, 9H), 1.92 (s, 12H), 4.38–4.41 (m, 7H), 4.57 (br, 4H), 5.12 (br, 2H), 8.49 (s, 1H), 8.50 (s, 1H), 8.68 (d, J = 1.5 Hz, 1H), 8.70 (d, J = 1.5 Hz, 1H), 8.80 (s, 1H); ^{13}C NMR (100 MHz) δ 28.7, 31.0, 31.2, 45.7, 45.9, 51.9, 64.7, 78.3, 80.7, 89.6, 92.8, 96.5, 97.3, 97.6, 111.9, 116.5, 125.0, 125.8, 131.4, 134.3, 135.6, 135.9, 138.4, 154.8, 161.4, 170.0, 170.6; MALDI-MS (POPOP[86] matrix) obsd 708.1287; ESI-MS obsd 706.3841, calcd 706.3837 [$(M)^+$, M = $C_{41}H_{50}N_6O_5$]; λ_{abs} (CH_2Cl_2) 354, 365, 376, 518, 743 nm.

7,17-Dioxo-8,8,18,18-tetramethyl-2,12-di-*p*-tolylbacteriochlorin (BC-16). Following the procedure used in the synthesis of tolyporphin A *O,O*-diacetate[13,14] and also in a small-scale synthesis of the title compound,[77] a 10 mM solution of the CrO_3-3,5-dimethylpyrazole complex in CH_2Cl_2 was prepared by suspension of CrO_3 (300 mg, 3.00 mmol) in anhydrous CH_2Cl_2 (300 mL) at –15 °C, to which 3,5-dimethylpyrazole (289 mg, 3.00 mmol) was added in one portion followed by stirring at –15 °C for 1 h.[83] Following a reported procedure[77] but at larger scale, a solution of **BC-15** (55.1 mg, 100 μmol) in anhydrous CH_2Cl_2 (30 mL) was titrated with the 10 mM solution of CrO_3-3,5-dimethylpyrazole complex in CH_2Cl_2 at –15 °C, and the progress of the reaction was monitored by TLC and absorption spectroscopy. After addition of 140 mL of 10 mM CrO_3-3,5-dimethylpyrazole complex in CH_2Cl_2 (1.4 mmol), the oxidation was complete. The reaction mixture was washed with water (200 mL) and brine (200 mL), dried, concentrated to dryness, and then purified by chromatography [silica, hexanes/CH_2Cl_2 (3:1 to 1:1)] to afford a purple solid (19.2 mg, 33%): ^{1}H NMR (500 MHz) δ –2.39 (s, 2H), 2.01 (s, 12H), 2.66 (s, 6H), 7.63–7.69 (m, 4H), 8.13–8.20 (m, 4H), 9.20 (d, J = 2.2 Hz, 2H), 9.30 (s, 2H), 9.79 (s, 2H); ^{13}C NMR (125 MHz) δ 21.5, 23.7, 49.9, 97.2, 97.6, 124.9, 130.2, 131.2, 132.5, 135.3, 136.1, 138.3, 140.2, 146.0, 166.0; ESI-MS obsd 579.2744, calcd 579.2755 [$(M + H)^+$, M = $C_{38}H_{34}N_4O_2$]; MALDI-MS obsd 578.404 $(M)^+$; λ_{abs} (toluene) 409, 552, 694 nm; λ_{em} (toluene, λ_{exc} = 409 nm) 697 nm; Φ_f (toluene) = 0.16.[77]

7,17-Dihydroxy-8,8,18,18-tetramethyl-2,12-di-*p*-tolylbacteriochlorin (BC-17). Following a general procedure,[84] a suspension of **BC-16** (2.0 mg, 3.5 μmol) in EtOH/CH_2Cl_2 (1:1, 2.0 mL) was treated with $NaBH_4$ (13.2 mg, 350 μmol) at room temperature for 45 min. The reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with saturated $NaHCO_3$ aqueous solution (20 mL) and brine (20 mL), and dried. The mixture was then concentrated to dryness and purified by chromatography [silica, CH_2Cl_2/MeOH (1:0 to 20:1)] to afford a green solid (1.5 mg, 75%): ^{1}H NMR (500 MHz, THF-d_8) δ –1.97–1.91 (m, 2H), 1.75–1.80 (m, 6H), 1.91–1.96 (m, 6H), 2.58 (s, 6H), 6.05–6.08 (m, 2H), 7.60–7.56 (m, 4H), 8.12–8.17 (m, 4H), 8.87–8.89 (m, 2H), 8.93–8.96 (m, 2H), 9.10–9.12 (m, 2H), 10.84 (s, 2H); ^{13}C NMR (125 MHz, THF-d_8) δ 20.4, 22.1, 22.2, 27.5, 49.7, 70.6, 85.3, 95.8, 98.7, 98.8, 112.6, 120.4, 129.6, 130.8, 133.8, 134.0, 134.7, 136.1, 136.9; ESI-MS obsd 583.3040, calcd 583.3068 [$(M + H)^+$, M = $C_{38}H_{38}N_4O_2$]; MALDI-MS obsd 582.345 $(M)^+$; λ_{abs} (toluene) 355, 362, 375, 724 nm; λ_{em} (toluene, λ_{exc} = 503 nm) 742 nm; Φ_f = 0.20 (toluene). For comparison, the spectral parameters of **BC-15** are as follows:[15] λ_{abs} (toluene) 351, 374, 499, 737 nm; λ_{em} (toluene, λ_{exc} = 503 nm) 744 nm; Φ_f = 0.14 (toluene).

Electronic Supplementary Information. Studies of metalation of **BC-6**; and single-crystal X-ray data. CCDC 2120134 (**5-E**), 2125374 (**12**), 2119912 (**22**), 2125378 (**33**), 2120866 (**BC-10**), and 2120288 (**BC-12**).

Notes

The authors declare no competing financial interests.

Acknowledgments

This work was supported by a grant from the Chemical Sciences, Geosciences and Biosciences Division, Office of Basic Energy Sciences, of the U. S. Department of Energy (DE-FG02-05ER15661) and by Vidyasirimedhi Institute of Science and Technology (VISTEC). All mass spectrometry, NMR, and X-ray structural data were obtained in the Molecular Education, Technology, and Research Innovation Center (METRIC) at NC State University, except for **12** and **33**, for which the X-ray structural data were obtained at VISTEC. We thank NC Biotechnology Center for partial funding for the D8Venture X-ray instrument (2019-IDG-1010). We thank Drs. Paul D. Boyle, Roger D. Sommer, and Masahiko Taniguchi for X-ray analyses.

Corresponding Author

E-mail: jlindsey@ncsu.edu. Phone: 919-515-6406.

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