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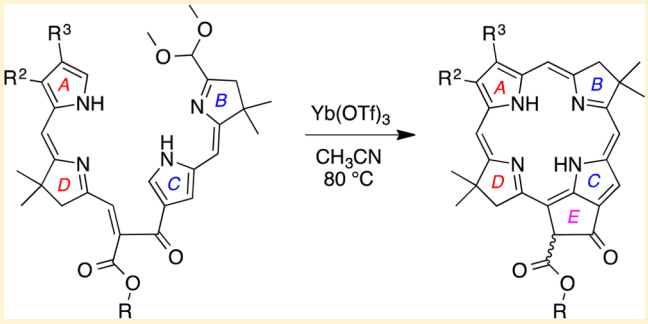
Construction of the Bacteriochlorin Macrocycle with Concomitant Nazarov Cyclization To Form the Annulated Isocyclic Ring: Analogues of Bacteriochlorophyll *a*

Shaofei Zhang and Jonathan S. Lindsey*

Department of Chemistry, North Carolina State University, Raleigh, North Carolina 27695-8204, United States

Supporting Information

ABSTRACT: Bacteriochlorophylls contain a bacteriochlorin macrocycle bearing an annulated fifth ring. The fifth ring, termed the isocyclic ring or ring E, is equipped with 13^1-oxo and 13^2-carbomethoxy substituents. Herein, a general route to stable, synthetic bacteriochlorophyll analogues is described. Knoevenagel condensation (~40 mM, rt, CH_2Cl_2, piperidine/AcOH/molecular sieves) of a dihydrodipyrrin−carboxaldehyde (AD half) and a dihydrodipyrrin substituted with a β-ketoester (BC half) forms a propenone bearing the two halves (a hydrobilin analogue). Subsequent treatment (0.2 mM) with acid ($Yb(OTf)_3$, CH_3CN, 80 °C) promotes a double ring-closure process: (i) condensation between the α-position of pyrrole ring A and the α-acetal unit attached to pyrroline ring B forms the bacteriochlorin macrocycle, and (ii) Nazarov cyclization of the β-(propenoyl)-substituted ring C forms the isocyclic ring (E). Five new bacteriochlorins bearing various substituents (alkyl/alkyl, aryl, and alkyl/ester) at positions 2 and 3 (β-pyrrole sites, ring A) and 13^2 carboalkoxy groups (R = Me or Et) were constructed in 37−61% yield from the hydrobilin analogues. The BC half and AD half are available in five and eight steps, respectively, from the corresponding pyrrole-2-carboxaldehyde and unsaturated ketone. The bacteriochlorins exhibit absorption spectra typical of bacteriopheophytins (free base bacteriochlorophylls), with a strong near-infrared absorption band (707−751 nm).



INTRODUCTION

Bacteriochlorins are attractive candidates for a variety of photophysical studies owing to their strong absorption in the near-infrared (NIR) spectral region.[1,2] The core chromophore of bacteriochlorophylls *a*, *b*, and *g*, the chief light-harvesting pigments in anoxygenic photosynthetic bacteria, is a bacteriochlorin (Scheme 1). Bacteriochlorins are members of the tetrapyrrole family and contain alternating pyrrole and pyrroline rings. Bacteriochlorophylls also contain a fifth, annulated ring (the "isocyclic" ring, or ring E) that spans positions 13 and 15; the ring is equipped with an integral keto group that lies coplanar with the organic π-system. In addition, an auxochrome is present at the 3-position, distal to the coplanar keto group of the isocyclic ring. Bacteriochlorophyll *b* differs from bacteriochlorophyll *a* in the presence of an exocyclic ethylidene group in ring B, whereas bacteriochlorophyll *g* contains the exocyclic ethylidene group in ring B as well as a 3-vinyl group and farnesyl (or other hydrocarbon) rather than phytol as the esterifying unit at the 17^3-position.

To access synthetically malleable analogues of bacteriochlorophylls, we have been developing a de novo synthesis of bacteriochlorins (**I**). The route relies on the self-condensation of a dihydrodipyrrin−acetal (**II-acetal**)[3,4] or dihydrodipyrrin−carboxaldehyde (**II-CHO**)[5] (Scheme 1). A *gem*-dimethyl group is positioned in each pyrroline ring to block any adventitious (aerobic) dehydrogenation leading to the more unsaturated chlorin or porphyrin. Incorporation of the *gem*-dimethyl group has proved synthetically more expedient than the *trans*-dialkyl (or alkyl/alkylidene) configuration of the natural macrocycles.[6] An alternative route (not shown) employs a Northern−Southern self-condensation of a dihydrodipyrrin−acetal similar to that in the Eastern−Western route.[7] Regardless, a chief limitation of both de novo syntheses originates with the dimerization process—whatever substituents are present on the pyrrole unit of the dihydrodipyrrin species are conveyed to the two pyrroles of the bacteriochlorin.

Rational approaches to bacteriochlorins with nonidentical substituents on the two pyrrole units have been severely limited (Scheme 2): (1) Sonogashira coupling of a 3,13-dibromo-5-methoxybacteriochlorin (**I-a**) proceeds selectively at the unhindered 13-position, after which more forcing Pd-mediated conditions could be employed to install diverse substituents at the 3-position en route to the differentially substituted bacteriochlorin (**I-b**).[8] (2) A 3,13-diacetyl-5-methoxybacteriochlorin (**I-c**) underwent 15-bromination (**I-d**), setting up Pd-mediated α-arylation to close the annulated 5-membered ring spanning positions 13 and 15, thereby forming the bacterio-13^1-

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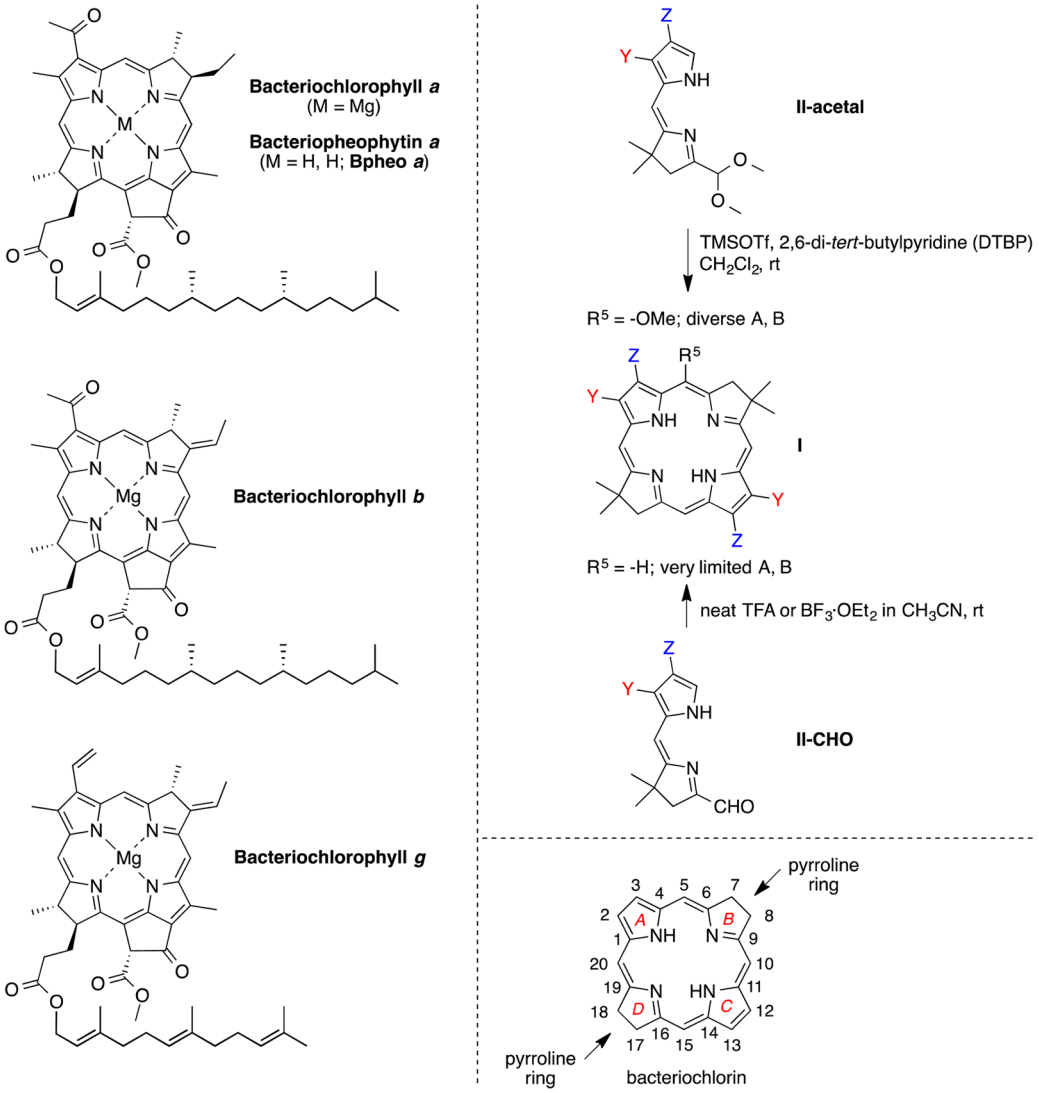
Scheme 1. Bacteriochlorophylls and Self-Condensations To Form Bacteriochlorins



oxophorbine (**I-e**). To date, **I-e** is the only bacterio-13^1-oxophorbine prepared by de novo synthesis. (3) A route to tolyporphin A diacetate,[9−11] a derivative of a naturally occurring dioxobacteriochlorin (not shown), is ingenious yet inordinately lengthy for our purposes. An alternative approach toward bacteriochlorins entails derivatization of porphyrins or chlorins.[12]

In contrast with these synthetic limitations, bacteriochlorophylls *a*, *b*, and *g* contain distinct substituents in rings A−C as well as the isocyclic ring (E) bearing a carbomethoxy group at the 13^2-position (Scheme 1). The synthesis shown in Scheme 2 (right panel) affords the 13^1-oxobacteriophorbine macrocycle but lacking the 13^2-carbomethoxy group. The resulting macrocycles are akin to bacteriopyropheophorbides (Chart 1), which are the natural bacteriochlorophyll derivatives obtained upon demetalation and pyrolytic loss of the 13^2-carbomethoxy substituent. The functional role of the 13^2-carbomethoxy group remains unclear, whereas the coplanar keto group (13-position) is known to cause a bathochromic shift of the long-wavelength absorption band and to interact via hydrogen bonding with protein sites.[1] Note that the term isocyclic ring is typically used regardless of the presence or absence of the 13^2-carbomethoxy group, as well as vast other modifications to the native structure.[13,14] To date, names for tetrapyrrole macrocycles bearing isocyclic rings derive from those of the natural compounds.[15]

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

In this paper, we describe a rational route to bacteriochlorin macrocycles that incorporate the *β*-ketoester-containing isocyclic ring as well as diverse substituents at the 2- and 3-positions. The route relies on directed joining of two distinct dihydrodipyrrins (BC and AD halves) by mild Knoevenagel

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Scheme 2. Rational Routes to Unsymmetrically Substituted Bacteriochlorins

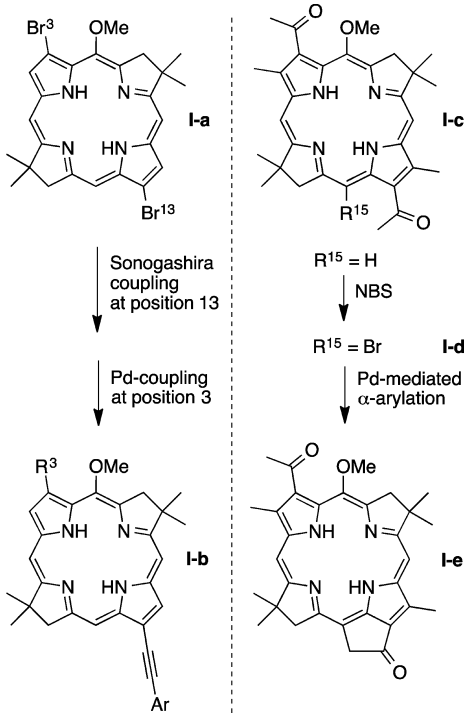
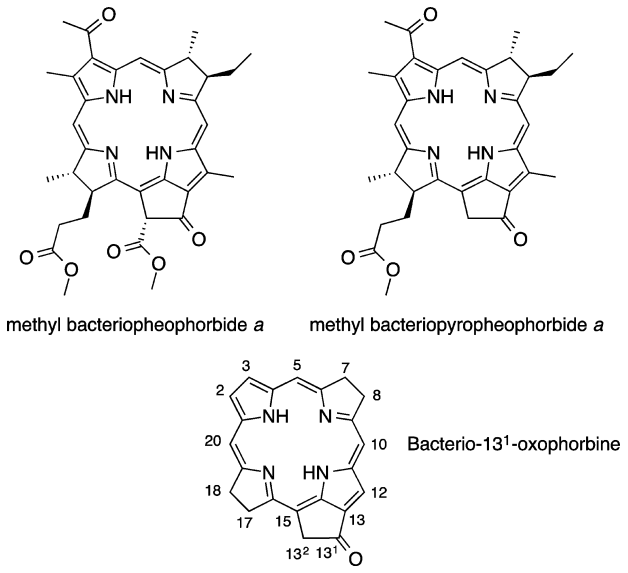


Chart 1. Bacteriopheophytin Derivatives and Bacterio-13^1-oxophorbine

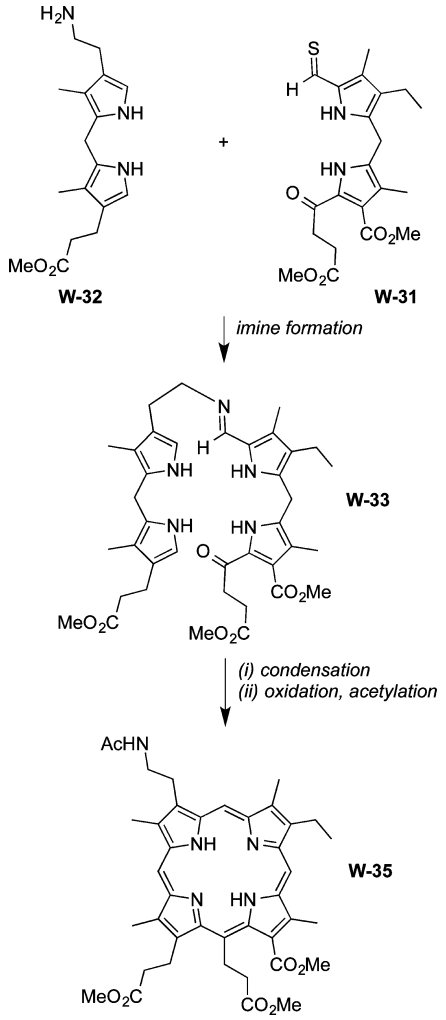


condensation followed by one-flask, mild acid-mediated electrophilic aromatic substitution and Nazarov cyclization to form the macrocycle along with the isocyclic ring. We describe the routes to the BC and AD halves, studies of the conditions for conversion to the bacteriochlorins, and application to the synthesis of five new bacteriochlorins. The static absorption and fluorescence spectroscopic properties of the new bacteriochlorins are reported and compared with those of the natural bacteriopheophytin *a* (**Bpheo *a***).

RESULTS

I. Reconnaissance. After several years of study (for an earlier attempt, see ref 16), two precedents proved enlightening for developing a directed synthesis of unsymmetrically substituted bacteriochlorins. The first precedent was Woodward's pioneering synthesis of chlorin e_6 trimethyl ester, a precursor of chlorophyll, which relies on directed joining of an AD half and a BC half to form an unsymmetric porphyrin (Scheme 3).[17−19] Acid-catalyzed condensation of a dipyrromethane−thioaldehyde (**W-31**, Woodward numbering[19]) and a dipyrromethane−amine (**W-32**) gave a Schiff's base (**W-33**). Intramolecular condensation of the juxtaposed rings A and B in **W-33** generated a single bilene-*b* salt; subsequent condensation between rings C and D under more forcing acidic conditions deftly closed the macrocycle and, upon dehydrogenation and acetylation, afforded the desired porphyrin (**W-35**) in 50% overall yield. In our case, to prepare an unsymmetric bacteriochlorin, dihydrodipyrrins would be the constituents instead of dipyrromethanes. Also required is a unit at the *β*-pyrrole position of one dihydrodipyrrin to direct intermolecular joining of the BC and AD halves followed by an intramolecular joining of the resulting linear intermediate to close the macrocycle.

Scheme 3. Macrocycle Formation in Woodward's Approach to Chlorophyll



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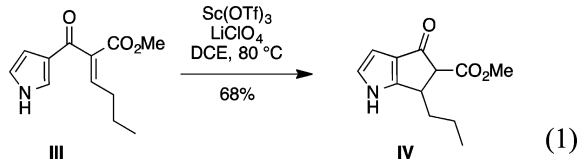
The second precedent emerged from studies of the Nazarov cyclization with heteroaromatic compounds.[20] Examples of Nazarov cyclization with pyrroles bearing appended propenoyl substituents have emerged only in the past decade. In the first two reports, Knight and co-workers employed an *N*-protected pyrrole and a propenoic acid,[21] whereas Frontier and co-workers[22] employed an unprotected pyrrole bearing a propenoyl substituent at the β-position. The latter appeared ideal for our case. Under a catalytic amount of $Sc(OTf)_3$ (10 mol %) and in the presence of $LiClO_4$ for 1.25 h, β-(propenoyl)pyrrole **III** underwent ring closure at the α-position in 68% yield (eq 1).[22] The resulting annulated pyrrole **IV** bears



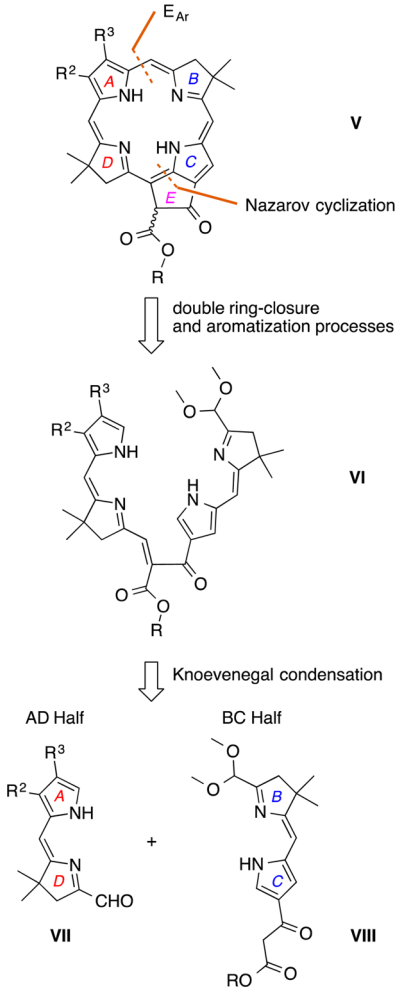
(1)

the same structural motif as in the isocyclic ring of bacteriochlorophylls *a*, *b*, and *g*. The Nazarov cyclization of unprotected β-(propenoyl)pyrroles also was reported to proceed with other catalysts and to be tolerant of various substituents.[23,24] The Nazarov substrate **III** could be easily prepared via Knoevenagel condensation of the β-ketoester–pyrrole and butanal.[22]

The resulting retrosynthetic analysis for the preparation of unsymmetrical annulated bacteriochlorins is outlined in Scheme 4. First, the bacteriochlorin macrocycle (**V**) is created upon the double ring-closure process of a linear tetrapyrrole (**VI**) containing two dihydropyrrins linked via a propenoyl unit: (i) electrophilic aromatic substitution of the acetal unit and the open pyrrole α-position joins rings A and B; (ii) Nazarov cyclization joins rings C and D, thereby constructing the isocyclic ring (E). The oxidation state of the linear tetrapyrrole remains unchanged during the overall double ring-closure and aromatization processes. Second, the linear tetrapyrrole (**VI**) is prepared by Knoevenagel condensation of the AD half (**VII**) and BC half (**VIII**). The conditions for Knoevenagel condensation must be compatible with sensitive functionalities (e.g., the open pyrrole α-position and the acetal unit) and occur specifically between the β-ketoester and the carboxaldehyde group.

II. Synthesis. *1. AD and BC Halves.* The synthesis of the BC halves began with the known *N*-tosyl-protected bromopyrrole **1**.[25] Following a reported procedure[26] with modification to use cobalt carbonyl as a source of carbon monoxide, carbonylation of **1** with a potassium monoalkyl malonate gave the densely functionalized methyl β-ketoester **2a** in 80% yield and the ethyl β-ketoester **2b** in 56% yield (Scheme 5). We were pleased to find that this Pd-catalyzed carbonylation could be carried out on a bromopyrrole, although more than a catalytic amount of $Pd(OAc)_2$ (0.5 molar equiv) and a longer reaction time (48 h) were required for completion of the reaction. The remainder of the synthesis followed established procedures for dihydrodipyrrins lacking the β-ketoester.[25] Cleavage of the tosyl group by refluxing in THF containing TBAF gave the free pyrrole **3a** or **3b** in 70% or 64% yield, respectively. Each of the latter was treated with NaOMe followed by a buffered aqueous–organic solution of $TiCl_3$ at room temperature for 16 h to afford BC half **4a** or **4b** in 45% or 36% yield. Both BC halves were readily prepared in 200 mg quantities.

Scheme 4. Retrosynthetic Analysis



Four AD halves were sought (Chart 2). The synthesis of AD halves[4,5] generally begins with the desired β-substituted pyrrole-2-carboxaldehyde. For the case where the pyrrole bears two electron-releasing substituents at the β-positions (e.g., **5-MeMe**), a stabilizing ester substituent at the 5-position is required.[5] AD halves **5-T** and **5-MeMe** are known compounds,[5] whereas the synthesis of **5-Ar** and **5-EtEs** is reported herein.

The synthesis of **5-Ar** proceeds in well practiced fashion[4] as shown in Scheme 6. Wittig reaction of *p*-bromobenzaldehyde with (carbethoxymethylene)triphenylphosphorane afforded cinnamate **6**, which upon van Leusen reaction with TosMIC and subsequent saponification and decarboxylation gave the 3-arylpyrrole **7**. Vilsmeier formylation of the latter gave regioselectively the 2-formylpyrrole **8** in 77% yield. Conversion to the 2-(2-nitroethyl) derivative **9-Ar** proceeded via Henry reaction with nitromethane and subsequent reduction with $NaBH_4$.

The completion of the AD half syntheses is shown in Scheme 7. The key steps involve (i) Michael addition between 2-(2-nitroethyl)pyrroles (**9-Ar**, **9-EtEs**[4]) and mesityl oxide to form the nitrohexanone–pyrroles (**10-Ar**, **10-EtEs**); (ii) reductive ring closure to give the 1-methyldihydrodipyrrins (**11-Ar**, **11-EtEs**); and (iii) SeO_2 oxidation to convert the 1-methyl group to the 1-formyl group and thereby afford the desired dihydrodipyrrin–carboxaldehydes (**5-Ar**, **5-EtEs**). Compounds

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Scheme 5. Preparation of BC Halves

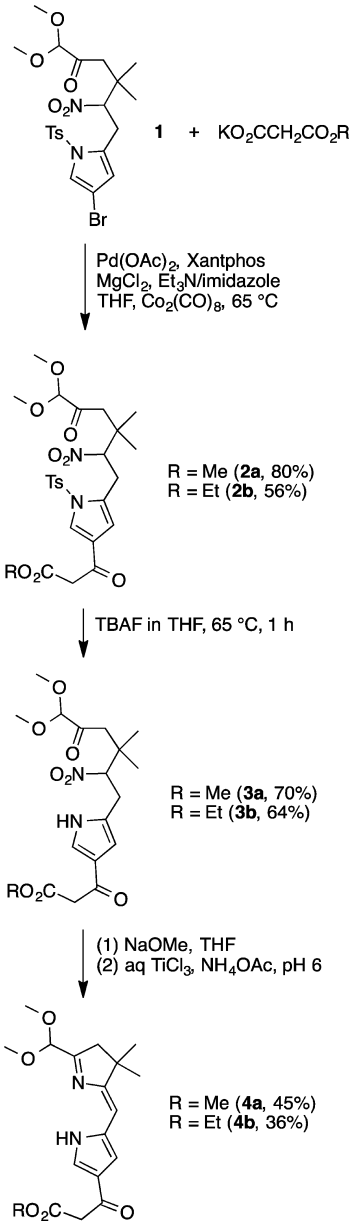
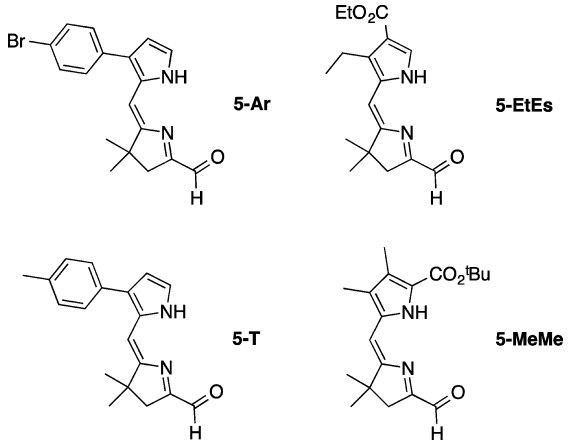
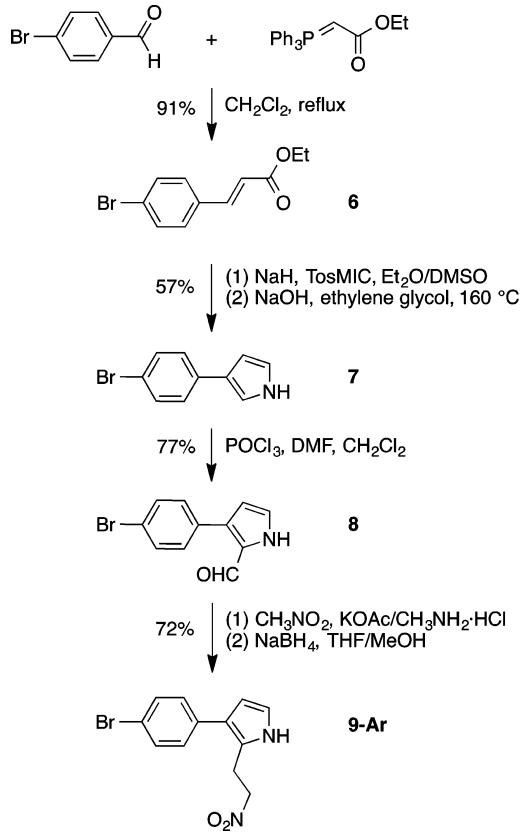


Chart 2. Target AD Halves



Scheme 6. Precursors of an AD Half



5-Ar and **5-EtEs** exhibit absorption spectra (λ_{abs} in CH_2Cl_2 = 470, 451 nm, respectively) similar to those of the known dihydrodipyrrin−carboxaldehydes **5-Ar** and **5-T**.[5] The dihydrodipyrrin−carboxaldehydes generally are unstable to acidic conditions and should be prepared immediately prior to use.

2. Conditions for Bacteriochlorin Formation. The formation of the bacteriochlorin entails a two-step approach as illustrated for the dihydrodipyrrins **5-T** and **4a** in Scheme 8. For the first (intermolecular) step, Knoevenagel condensation of the two dihydrodipyrrins, a catalytic amount of piperidine and acetic acid (1:1) in CH_2Cl_2 containing molecular sieves (3 Å powder) at room temperature for 20 h was found to produce the target hydrobilin **12-T** in 61% yield. The conditions are quite mild, with a near-neutral catalyst combination (see the Experimental Section) and modest concentrations (**4a**, 41 mM; **5-T**, 48 mM). Both the α-unsubstituted pyrrole and the acetal group survived the reaction conditions. The linear intermediate **12-T** was obtained following chromatography as a dark red oil and exhibits the absorption spectrum shown in Figure 1. ^{1}H NMR spectroscopy of **12-T** gave two peaks (δ 7.65 and 7.39 ppm) characteristic of the α-olefinic proton and the α-pyrrolic proton. We know of no other molecules resembling **12-T** for spectroscopic comparisons; perhaps the closest would be a 10-oxobiladiene-*ac*,[27] yet **12-T** is a vinylogous relative and also contains two pyrroline rings.

For the second (intramolecular) step, the double ring-closure process of the hydrobilin intermediate, the requirement for acid catalysis engendered several considerations: (1) Frontier and co-workers found that $Sc(OTf)_3$, $In(OTf)_3$, and $Hf(OTf)_4$ are more effective catalysts in the Nazarov cyclization.[22] (2) Our previous studies on the self-condensation of dihydrodipyrrin−acetals identified Lewis acids suitable for the condensation

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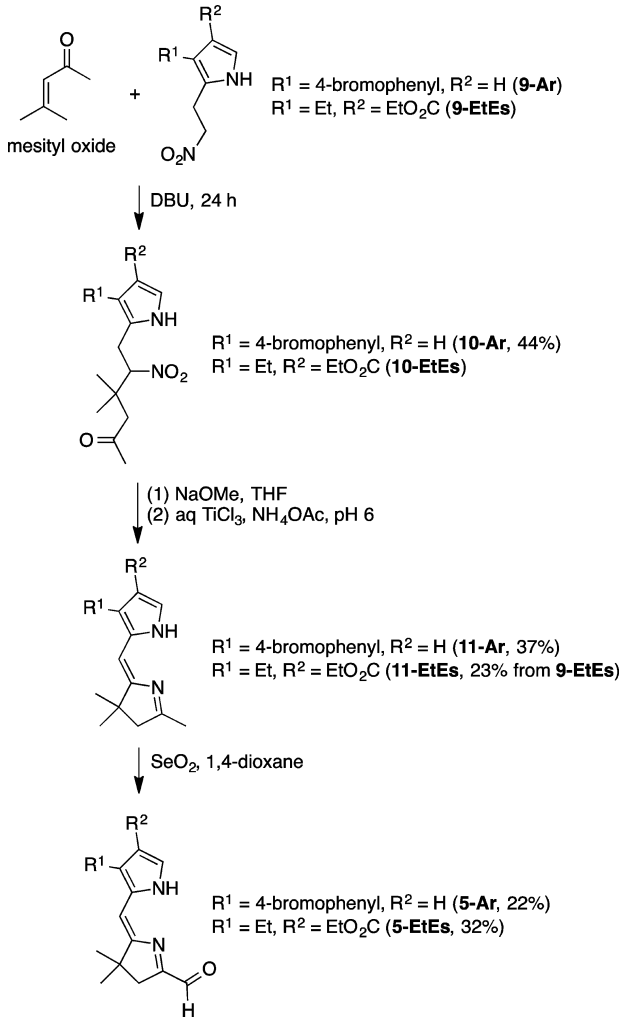
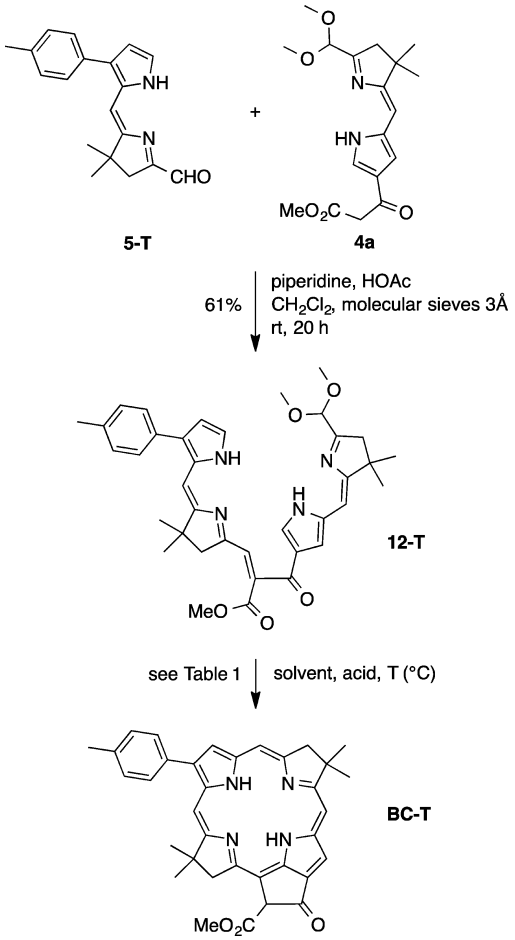
Scheme 7. Synthesis of AD Halves



Scheme 8. De Novo Route to Bacteriopheophytin Analogues



between pyrrole and acetal units (e.g., $BF_3{\cdot}OEt_2$ in CH_3CN,[3] TMSOTf/DTBP (2,6-di-*tert*-butylpyridine) in CH_2Cl_2[4]). (3) $Yb(OTf)_3$ and $Sc(OTf)_3$ were especially efficient in catalyzing pyrrole–acetal condensations, although tetradehydrocorrin-type macrocycles were obtained rather than bacteriochlorins.[16,28]

Six acids were examined for the double ring-closure process of **12-T** (Table 1, entries 1–6). The reaction was conducted with 0.2 mM **12-T** and 2 mM acid with the indicated solvent or temperature. The reactions were followed by UV–vis absorption spectroscopy and typically were complete in 20 h. The yield was calculated using the measured molar absorption coefficient for **BC-T** of 5.0×10^4 M^{-1} cm^{-1} at the Q_y band (λ_{Qy} = 722 nm in toluene). Among the acids examined, $Hf(OTf)_4$ (entry 1), TMSOTf/DTBP (entry 2), or $BF_3{\cdot}OEt_2$ (entry 3), which are all effective catalysts in the de novo synthesis strategy,[3,4] did not afford a peak characteristic of bacteriochlorins. On the other hand, $Sc(OTf)_3$ and $Yb(OTf)_3$ gave **BC-T** in 10% yield (entry 4) and 14% yield (entry 5), respectively. With $In(OTf)_3$, the corresponding indium bacteriochlorin (λ_{Qy} = 746 nm in toluene) was produced instead of the free base bacteriochlorin (entry 6). Indium-chelated bacteriochlorins (lacking the isocyclic ring) have been formed previously upon indium catalysis of the self-condensation of a dihydrodipyrrin–acetal.[29]

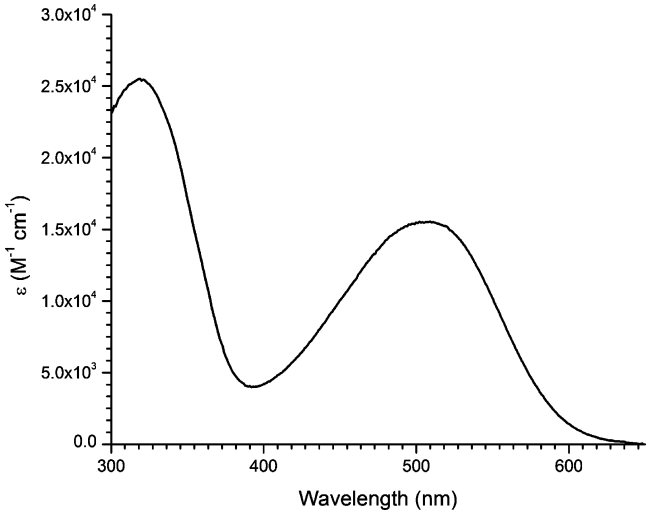


Figure 1. Absorption spectrum of **12-T** in CH_2Cl_2 at room temperature. The peak absorption in the visible region is at ~505 nm.

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

The effect of temperature and solvent on bacteriochlorin formation was examined with $Yb(OTf)_3$ as catalyst. The yield

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Table 1. Conditions for Bacteriochlorin (BC-T) Formation from 12-T

entry	Lewis acid	solvent[a]	temp (°C)	yield[b] (%)
1	$Hf(OTf)_4$	DCE	50	0[c]
2	TMSOTf/DTBP	CH_2Cl_2	20	0[c]
3	$BF_3{\cdot}OEt_2$	CH_3CN	20	*d*
4	$Sc(OTf)_3$	DCE	50	9.6
5	$Yb(OTf)_3$	DCE	50	14
6	$In(OTf)_3$	DCE	50	7.6[e]
7	$Yb(OTf)_3$	DCE	20	13
8	$Yb(OTf)_3$	DCE	35	14
9	$Yb(OTf)_3$	DCE	65	16
10	$Yb(OTf)_3$	DCE	80	20
11	$Yb(OTf)_3$	CH_3NO_2	80	0[c]
12	$Yb(OTf)_3$	toluene	80	5.6
13	$Yb(OTf)_3$	CH_3CN	80	46
14	$Yb(OTf)_3$	CH_2Cl_2	40	13

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

of bacteriochlorin in 1,2-dichloroethane increased with reaction temperature (20−80 °C, entries 7−10). When the temperature was maintained at 80 °C, no bacteriochlorin was obtained in nitromethane (entry 11), while the yield was very low in toluene (5.6%, entry 12). The reaction proceeded efficiently in acetonitrile at 80 °C (46%, entry 13) and moderately well in dichloromethane at 40 °C (13%, entry 14).

Frontier and co-workers[22] identified $LiClO_4$ as an effective catalyst for the Nazarov cyclization. Here, reaction in the presence of 10 equiv of $LiClO_4$ did not affect the yield, whereas excess $LiClO_4$ (100 equiv) led to a lower yield. In summary, the reaction of **12-T** in dilute solution with $Yb(OTf)_3$ in acetonitrile at 80 °C gave the best results for bacteriochlorin formation.

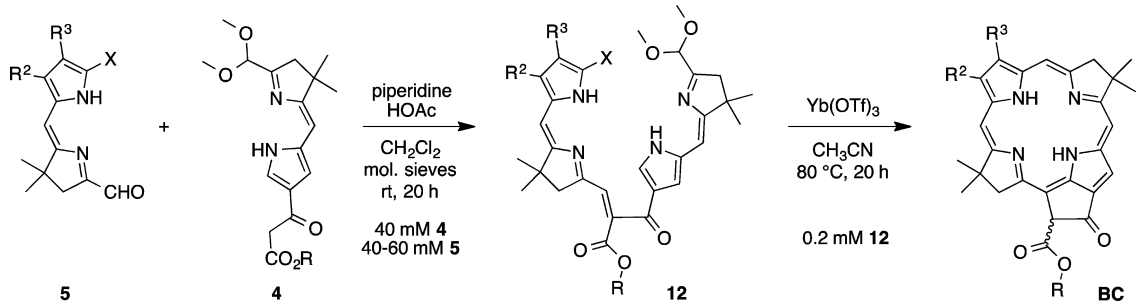
3. Scope of Reaction. The reaction using the refined catalysis conditions was carried out with 20 mg of the hydrobilin **12-T**, and the resulting bacteriochlorin was purified by chromatography. To our delight, the yield of isolated bacteriochlorin **BC-T** reached 56% (9.5 mg). Other hydrobilins of type **12** were prepared by reaction with various AD halves and BC half **4a** or **4b** in the same manner as for **12-T** (Table 2). BC halves **4a** and **4b** differ only in the nature of the carboalkoxy substituent (methyl, ethyl). The Knoevenagel reaction was carried out with 1−1.5 equiv of the dihydrodipyrrin−carboxaldehyde (AD half, **5**) relative to the BC half (**4a**, **4b**), whereupon the hydrobilins (**12**) were obtained in yields ranging from 57−71%.

With the hydrobilins **12** in hand, conversion to the bacteriochlorins was pursued by application of the refined reaction conditions. First, the reaction conditions are compatible with a bromoaryl substituent to give **BC-Ar** (61% yield, entry 1). Second, a bacteriochlorin (**BC-MeMe**) with two electron-donating groups was obtained in 37% yield. In addition to the pyrrole−acetal condensation and Nazarov cyclization, cleavage of the *tert*-butyl ester occurred in this process, albeit with a lower overall yield compared with the other examples. The presence of the *tert*-butyl ester was essential to stabilize the very electron-rich dihydrodipyrrin unit.[5] Third, a bacteriochlorin (**BC-EtEs**) with an electron-withdrawing group at the *β*-pyrrole position (−CO_2Et) was prepared in good yield (57%). Finally, starting with BC half **4b**, a bacteriochlorin with a 13^2-carbethoxy group (**BC-Ar/Et**, where the "/Et" designates the 13^2-ester substituent) was obtained, indicating the possibility of more elaborate modification at this site of the macrocycle.

III. Characterization. *1. Structures.* The dihydrodipyrrins typically were purified by silica gel chromatography. While the isolated dihydrodipyrrins examined herein are relatively stable, limiting the duration of exposure to silica gel was important. The dihydrodipyrrins obtained in this manner were characterized (by TLC, ^{1}H and ^{13}C NMR spectroscopy, and accurate-mass ESI-MS) and used successfully in bacteriochlorin formation.

All new bacteriochlorins were characterized by ^{1}H NMR and ^{13}C NMR spectroscopy, accurate-mass ESI-MS, and static absorption and fluorescence spectroscopy. A single-crystal X-ray structure was obtained for bacteriochlorin **BC-Ar** (see the Supporting Information). In general, the ^{1}H NMR spectra of

Table 2. Investigation of the Scope of Bacteriochlorin Formation



	compounds				substituents				yield (%)	
entry	**5**	**4**	**12**	**BC**	R^2	R^3	X	R	**12**	**BC**
1	**5-T**	**4a**	**12-T**	**BC-T**	*p*-tolyl	H	H	Me	61	56
2	**5-Ar**	**4a**	**12-Ar**	**BC-Ar**	*p*-Br-phenyl	H	H	Me	68	61
3	**5-MeMe**	**4a**	**12-MeMe**	**BC-MeMe**	Me	Me	$CO_2{}^tBu$	Me	71	37
4	**5-EtEs**	**4a**	**12-EtEs**	**BC-EtEs**	Et	CO_2Et	H	Me	61	57
5	**5-Ar**	**4b**	**12-Ar/Et**	**BC-Ar/Et**	*p*-Br-phenyl	H	H	Et	57	48

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the bacteriochlorins were complex due to the nonequivalent A, B, C, and D rings as well as the presence of the additional E ring. The structure and ^{1}H NMR spectrum of **BC-MeMe** are illustrative: (1) The four distinct protons around the perimeter of the bacteriochlorin (meso-protons at the 5-, 10-, and 20-positions and one β-pyrrolic proton) give rise to four singlets in the region δ 7.62−7.97 ppm. (2) The proton at the 13^2-position resonates as a singlet at δ 5.64 ppm, which is comparable to that of the 13^2-H in **Bpheo *a*** (δ 6.08 ppm[30]). (3) The presence of a stereocenter at the 13^2-position causes the pyrroline CH_2 protons (ring D, position 17: δ 3.62−3.74 ppm) flanking the isocyclic ring (E) to be split into an AB pattern, while the pyrroline CH_2 protons distal to the stereocenter resonate as an apparent singlet (ring B, position 7: δ 3.97 ppm). (4) The two methyl groups of a *gem*-dimethyl unit are similarly inequivalent, and those at the 18-position resonate as two singlets (1.72 and 1.80 ppm). (5) The N−H protons give rise to two broad upfield peaks (1.16 and 1.62 ppm). No peaks upfield of 0 ppm were observed.

Comparing the ^{1}H NMR spectra of **BC-MeMe**, **BC-EtEs**, and **Bpheo *a*** [30] yields the following observations: (1) The chemical shifts of the peripheral protons of **BC-MeMe** (with two electron-donating groups) are in the range of 7.63−7.97 ppm, while those of **BC-EtEs** (with one electron-withdrawing group) are in the range of 8.20−9.16 ppm; the latter are more similar to those of **Bpheo *a*** (8.39−8.96 ppm). (2) The N−H protons in **BC-EtEs** resonate at −0.07 and 1.59 ppm, compared to those in **BC-MeMe** (δ1.16, 1.62 ppm) and **Bpheo *a*** (δ −0.99, 0.44 ppm).[30]

2. Absorption and Fluorescence Spectra. Figure 2 shows the absorption spectra and fluorescence emission spectra of four synthetic, isocyclic ring-containing bacteriochlorins (**BC-MeMe**, **BC-T**, **BC-Ar**, and **BC-EtEs**) in toluene. The spectral data shown in Table 3 include the position and the relative intensity of the characteristic absorption bands, the full-width at half-maximum (fwhm) value of the long-wavelength absorption band (Q_y), and the ratio of the intensity of the Q_y to B_y band (I_{Qy}/I_{By} ratio). For comparison, the table also includes spectral data for **BPheo *a*** [31] and the benchmark[5] **Me$_4$-BC**. The molar absorption coefficient of **BC-T** in toluene (5.0×10^4 M^{-1} cm^{-1}, determined using ∼6 mg of **BC-T**) is close to that reported for **BPheo *a*** (42−49 mM^{-1} cm^{-1} in acetone−methanol (7:2, v/v) and 63−73 mM^{-1} cm^{-1} in ether).[32] The spectrum of **BC-Ar/Et** matches almost identically that of **BC-Ar** and is not shown in Figure 2; for comparison, the spectra of **BC-Ar/Et**, **Me$_4$-BC**, and **Bpheo *a*** are provided in the Supporting Information.

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

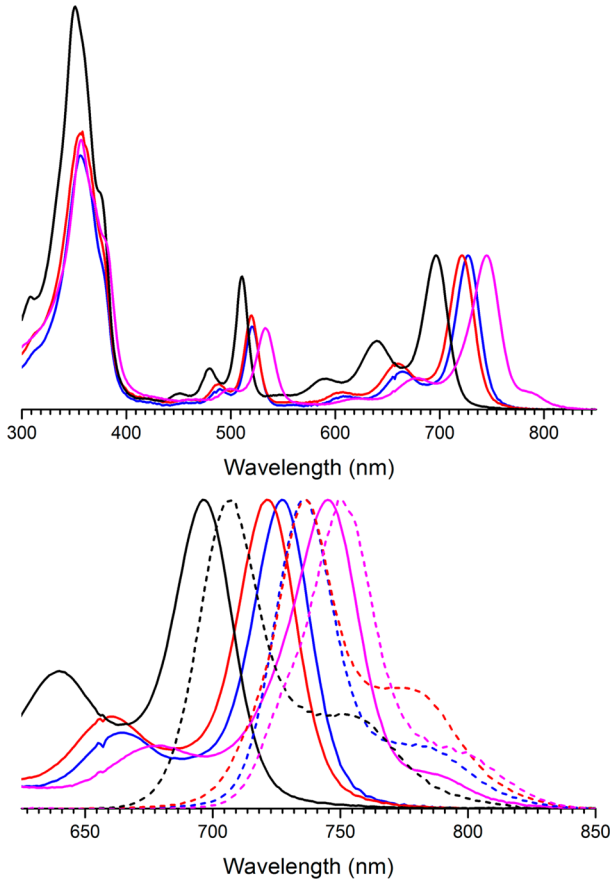

Figure 2. Absorption (solid line) and fluorescence spectra (dashed line; λ_{ex} at the Q_x band near 520 nm) in toluene at room temperature of bacteriochlorins (normalized at the Q_y bands). The colors in the graph are as follows: **BC-MeMe** (black), **BC-T** (red), **BC-Ar** (blue), and **BC-EtEs** (purple).

The fluorescence emission spectra of the four synthetic bacteriochlorins (**BC-MeMe**, **BC-T**, **BC-Ar**, and **BC-EtEs**) in toluene at room temperature are shown in Figure 2. In each case, the $Q_y(0,0)$ emission band is shifted 6−15 nm to longer wavelength than the $Q_y(0,0)$ absorption band, to be compared with a Stokes shift for **Me$_4$-BC** of ∼2 nm. The comparatively large Stokes shift of the isocyclic ring-containing bacteriochlorins indicates more substantial structural changes or solvent interactions upon photoexcitation. The fwhm of the $Q_y(0,0)$ emission band is in the range of 26−32 nm.

DISCUSSION

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

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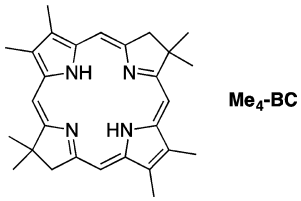
Table 3. Spectral Characteristics of Bacteriochlorins[a]

	absorption in nm (relative intensity[b])					flu	fwhm (nm)		intensity ratios		
compd	B(0,0)[c]	$Q_x(1,0)$	$Q_x(0,0)$	$Q_y(1,0)$	$Q_y(0,0)$	$Q_y(0,0)$ in nm	$Q_y(0,0)$ abs	Q_y em	I_{Qy}/I_B	$I_{Qx(0,0)}/I_{Qx(1,0)}$	$I_{Qy(0,0)}/I_{Qx(0,0)}$
BC-T	356	489	520	660	721	736	29	26	0.55	3.4	1.6
	(1.8)	(0.18)	(0.62)	(0.31)	(1.0)						
BC-Ar	356	490	521	664	727	737	27	29	0.62	3.8	1.9
	(1.6)	(0.14)	(0.54)	(0.25)	(1.0)						
BC-MeMe	351	480	511	640	696	707	29	31	0.38	3.1	1.1
	(2.6)	(0.28)	(0.87)	(0.45)	(1.0)						
BC-EtEs	357	501	533	680	745	751	33	32	0.58	3.8	1.9
	(1.7)	(0.14)	(0.53)	(0.21)	(1.0)						
BC-Ar/Et	357	490	521	665	728	737	28	28	0.62	4.1	1.9
	(1.6)	(0.13)	(0.53)	(0.24)	(1.0)						
BPheo *a*[d]	356	492	524	681	749	768[e]	31	27[e]	0.63	4.6	2.0
	(1.6)	(0.11)	(0.51)	(0.18)	(1.0)						
Me_4-BC[f]	346, 374	462	490	685	721	723	11.9	15.5	0.97	1.9	5.3
	(1.0, 1.1)	(0.10)	(0.19)	(0.10)	(1.0)						

[a]Obtained in toluene at room temperature. [b]Relative intensity of the indicated peak versus that of the $Q_y(0,0)$ band. [c]Mixture of the $B_x(0,0)$ and $B_y(0,0)$ absorption bands. [d]Absorption data (in diethyl ether) from ref 33. [e]Fluorescence data (in toluene) from ref 31. [f]Data from ref 5.

Chart 3. Benchmark Bacteriochlorin



Me_4-BC

Installation of the Isocyclic Ring. A handful of approaches for installation of a fifth ring spanning positions 13 and 15 in tetrapyrrole macrocycles has been developed over the years (Scheme 9). Fischer dehydrated (hydroxymethylcarbonyl)porphyrin **A** in concd H_2SO_4 to give the porphyrin bearing the isocyclic ring (**B**).[34] Lash condensed dipyrromethane $\mathbf{C}^1$ and dipyrromethane $\mathbf{C}^2$ bearing an annulated oxocyclopentanyl ring[35] to form **D** (which lacks the 13^1-oxo group).[36] Both **B** and **D** are porphyrins. Fischer also converted chlorin e_6 trimethyl ester (**E**) via Dieckmann cyclization to methyl pheophorbide *a* (**F**),[37,38] a chlorin degradation product of chlorophyll *a*. Smith extended Kenner's thallium-photochemical route[39−42] for conversion of the β-ketoester-substituted chlorin **G** to methyl pheophorbide *a* (**F**).[43] A more recent method entails 15-bromination and Pd-mediated α-arylation (Scheme 2), which has been applied to *gem*-dimethyl stabilized chlorins and bacteriochlorins but requires bromination of the macrocycle and lacks provisions for incorporation of the 13^2-carboalkoxy group.[44−47] To our knowledge, only the method shown in Scheme 2 has been applied with bacteriochlorins. The formation of the isocyclic ring concomitantly with macrocycle construction described herein affords considerable simplicity, and does so while enabling distinct substituents in the two halves of the bacteriochlorin.

Features of the Nazarov Cyclization. Nazarov cyclization is a classical synthetic method for producing a cyclic ketone.[20] While known for some time with a variety of substrates, in 2006, Song, Knight, and Whatton reported the first example involving a pyrrole.[21] The reaction was carried out with an *N*-tosylpyrrole and a propenoic acid in the presence of trifluoroacetic anhydride, affording the corresponding annulated α-acylpyrrole. In the same year, Frontier and co-workers reported examples of both α-(propenoyl)pyrroles and β-(propenoyl)pyrroles without any *N*-protection (eq 1).[22] While >50 examples of Nazarov cyclization have since been reported with α-(propenoyl)pyrroles,[48−57] to our knowledge there are only three prior examples of analogous β-substituted pyrroles.[22−24] Moreover, regardless of pyrrole substitution position, most such examples stem from model studies rather than as integral to total syntheses. Examples of the latter include synthesis of (±)-roseophilin.[49,50,52,54,56]

The Nazarov reaction process also can be regarded as an intramolecular Michael addition (5-*endo*-*trig*)[58] of the pyrrole with the appended propenoyl substituent. Intermolecular examples of such pyrrole *C*-alkylations date to as early as 1951 and were typically carried out with either activated reactants or somewhat forcing conditions.[59−66] Research in the past 15 years has shifted to unactivated reactants and implementation with mild Lewis acid catalysts and/or enantioselective catalysts (for a comprehensive set of references, see the Supporting Information; for a partial review, see ref 67).

The Nazarov cyclization is regarded to proceed via a 4π-electrocyclization of a pentadienyl cation derived from a divinylketone species;[20] here, the pyrrole moiety provides one of the "vinyl" units. The resulting conrotatory ring closure creates two stereocenters. Here, one of the stereocenters is lost upon elimination, leading to the aromatic, 18π-electron bacteriochlorin chromophore. The remaining stereocenter is at the 13^2-position, whereupon the resulting bacteriochlorin is racemic. The carboalkoxy group at the 13^2-position in (bacterio)chlorophylls is susceptible to epimerization given the presence of the β-keto group.[13,14] While the *trans*-configuration (13^2- relative to the 17-position) is typically more stable, macrocycles with the *cis*-configuration of the two groups have been considered as possible minority pigments in selected photosynthetic systems.[68] The mole fraction of the *cis*-isomer was found to range from 0.12−0.25 over a set of eight chlorophylls, bacteriochlorophylls, and analogues.[69] Accordingly, the natural tetrapyrroles bearing an isocyclic ring often exist as diastereomeric mixtures owing to unavoidable epimerization of the 13^2-carbomethoxy group. Thus, while the synthetic bacteriochlorins obtained herein are racemic, even

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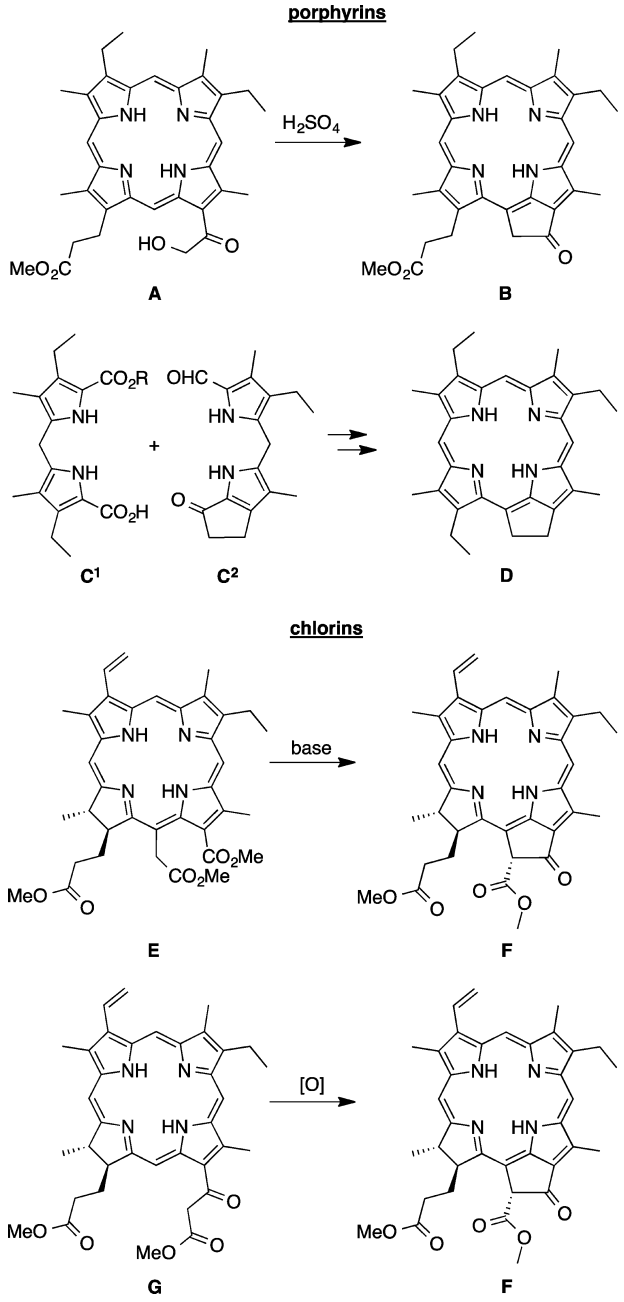
Scheme 9. Routes for Installation of the Isocyclic Ring

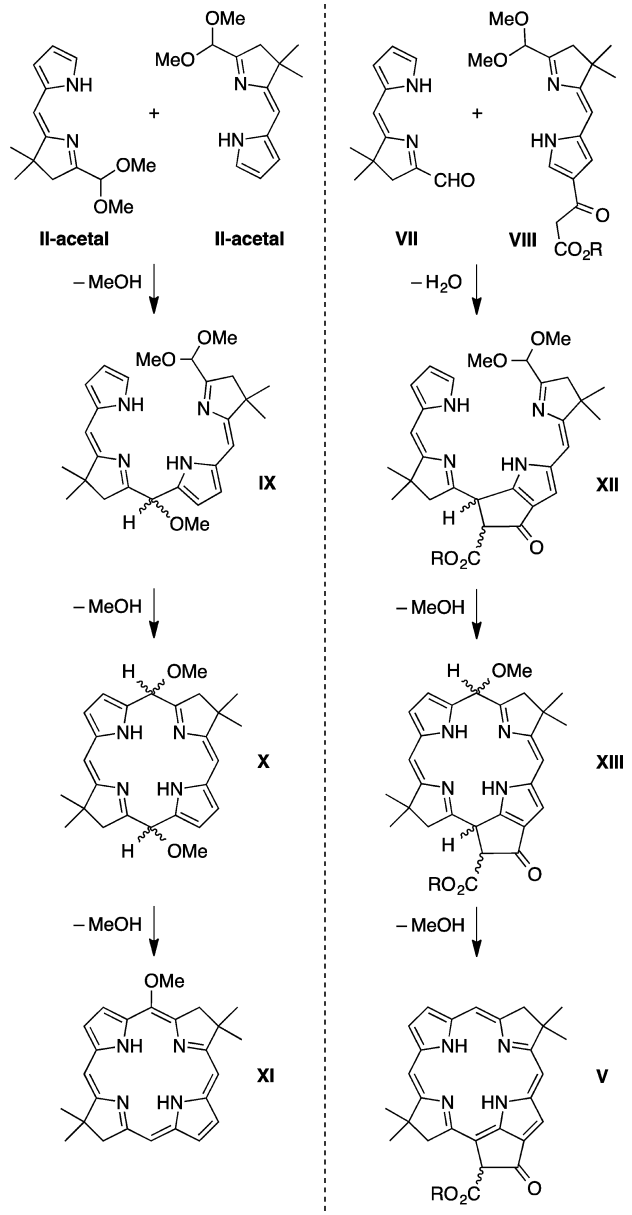


an asymmetric synthesis is likely to yield products that spontaneously racemize owing to the intrinsic features of the β-ketoester.

Comparison of Routes. The Eastern−Western (or Northern−Southern) route to bacteriochlorins is concise, but installation of the isocyclic ring requires 15-bromination followed by Pd-mediated α-arylation. Even then, the isocyclic ring lacks the 13^2-carbomethoxy group. The synthesis described herein entails preparation of BC and AD components, joining of these two halves to form a hydrobilin intermediate under conditions wherein neither half undergoes self-condensation leading to a symmetrical bacteriochlorin, and the one-flask double ring-closure process of the hydrobilin to form the bacteriochlorin macrocycle along with the isocyclic ring (E). In this manner, a Pd-mediated coupling is still required (attachment of the β-ketoester to the pyrrole of the BC half), but bromination of the bacteriochlorin is not required. Hence, halogens can be installed on the AD half (e.g., **5-Ar**) for subsequent exploitation following formation of the macrocycle (e.g., **BC-Ar**, **BC-Ar/Et**).

A direct comparison of two routes for constructing the bacteriochlorin macrocycle is provided in Scheme 10. The self-

Scheme 10. Comparison of Bacteriochlorin Syntheses



condensation of two dihydrodipyrrin−acetal molecules (**II-acetal**) results in successive elimination of two molecules of methanol, whereupon a 5,15-dihydro-5,15-dimethoxybacteriochlorin (**X**) is obtained. Elimination of a third molecule of methanol affords the 5-methoxybacteriochlorin (**XI**).[70] The presence of the 5-methoxy group provides a convenient directive entity for 15-bromination,[71] but otherwise may be undesired. By contrast, for purposes of comparison the reaction of AD (**VII**) and BC (**VIII**) halves can be envisaged as proceeding via Nazarov cyclization following the Knoevenagel condensation (**XII**). Subsequent cyclization and elimination of one molecule of methanol affords the 5,15-dihydro-5-

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methoxybacteriochlorin (**XIII**). Elimination of the second molecule of methanol aromatizes the macrocycle to give bacteriochlorin **V**. The difference in 5-position substitution patterns of **V** versus **XI** originates early in the reaction process: two carbon−carbon bonds are formed upon Knoevenagel condensation and Nazarov cyclization (giving **XII**) versus only one upon electrophilic aromatic substitution (giving **IX**). Side-by-side comparison of intermediates **X** (5,15-dimethoxy) and **XIII** (5-methoxy) illustrates that while aromatization is likely similar in the two syntheses, requisite elimination of only one molecule of methanol leaves one methoxy group remaining in **XI**, whereas none is left in the isocyclic ring (E)-containing bacteriochlorin **V**.

Synthetic Attributes. There are now four distinct routes for de novo construction of the bacteriochlorin chromophore (excluding derivatization of porphyrins or chlorins). The routes include (1) the Kishi synthesis of tolyporphin A diacetate and analogues;[9−11] (2) the Eastern−Western synthesis shown in Scheme 1; (3) a Northern−Southern route;[7] and (4) the directed AD + BC route described herein. Only the latter enables simultaneous construction of the macrocycle and the isocyclic ring. The utility of a general route to bacteriochlorins with distinct substituents in the various A−D rings is outlined in the Introduction. Because the present route enables such capabilities yet also constructs the isocyclic ring (E), further applications and extensions can be envisaged, of which five are described here.

First, the preparation of bacteriochlorins with progressive extent of substitution ranging from the fully unsubstituted to the fully decorated analogue of **BPheo *a*** is essential for understanding the molecular origins of bacteriochlorophyll photophysics.[5] The present route appears ideal for preparing more elaborate analogues along this progression.

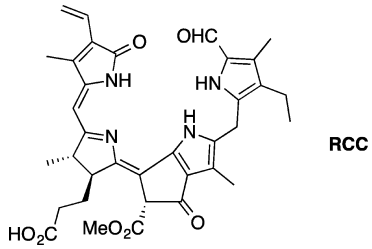
Second, the Nazarov cyclization is compatible with other heterocycles;[20] hence, core-modified ring-C analogues should be accessible.

Third, the new route might enable synthetic access to the natural macrocycles themselves. The synthesis of chlorophylls would require one enantiopure dipyrrin and one dipyrromethane rather than two dihydrodipyrrins yet would offer a fundamental alternative to the route devised by Woodward and co-workers.[17−19] The synthesis of bacteriochlorophylls, which has never been reported, would require two enantiopure dihydrodipyrrins.

Fourth, the isocyclic ring has been the site of extensive derivatization chemistry over the years, including reactions at each of the sites (13^1 oxo, 13^2 methylene, 13^2-carboalkoxy) as well as allomerization and splitting of the ring (by scission of the 13^1−13^2 C−C bond).[13,14] While widely exploited with chlorophylls, analogous chemistry with bacteriochlorophylls has been less investigated owing to the lability of the natural macrocycles.[72] The stability of the macrocycles prepared herein should provide an entrée into diverse derivatives by reactions in the isocyclic ring.

Finally, very little is known about the in vivo degradation of bacteriochlorophylls, in contrast with the results from the intensive study of the enzymatic degradation of chlorophylls in senescent plants. Kräutler and co-workers have identified and characterized a variety of "phyllobilin" species such as the red chlorophyll catabolite (**RCC**) shown in Chart 4.[73−75] The structure of the phyllobilins closely resembles that of the Nazarov intermediate **XII** shown in Scheme 9. To our knowledge, phyllobilins have not been the target of reported synthetic studies, and hence knowledge of reactivity and photochemical features depends on isolation of species along the slippery slope of enzymatic catabolism. Whether analogous phyllobilins derive from anoxygenic photosynthetic bacteria remains to be determined. For both types of hydroporphyrins, the synthesis of putative intermediates could prove vital.

Chart 4. Chlorophyll Catabolite



EXPERIMENTAL SECTION

General Methods. ^{1}H NMR and ^{13}C NMR spectra were collected at room temperature in $CDCl_3$. Absorption spectra were obtained in toluene at room temperature unless noted otherwise. Electrospray ionization mass spectrometry (ESI-MS) data, obtained via ion trap mass analyzer, are reported for the molecular ion or protonated molecular ion. THF used in all reactions was freshly distilled from Na/benzophenone ketyl. Molecular sieves (3 Å, powder) were heated (>100 °C) overnight prior to use. All commercially available compounds were used as received. Noncommercially available compounds including **1**,[25] **5-T**,[5] **5-MeMe**,[5] and **9-EtEs**[4] were prepared as described in the literature. The dihydrodipyrrin−carboxaldehyde and dihydrodipyrrin−acetal compounds were chromatographed by gravity flow with short columns (~12 cm in length) to limit duration of exposure to silica gel.

6-[4-(3-Methoxy-3-oxopropanoyl)-*N*-tosylpyrrol-2-yl]-1,1-dimethoxy-4,4-dimethyl-5-nitrohexan-2-one (2a). A mixture of **1** (1.34 g, 2.50 mmol), methylpotassium malonate (585 mg, 3.80 mmol), Xantphos (725 mg, 1.30 mmol), $MgCl_2$ (357 mg, 3.80 mmol), and imidazole (330 mg, 5.00 mmol) was placed in a 50 mL Schlenk flask, which was charged with argon. THF (25.0 mL) was added followed by Et_3N (520 μL, 3.80 mmol). The mixture was degassed by three freeze−pump−thaw cycles. Then $Pd(OAc)_2$ (280 mg, 1.30 mmol) and $Co_2(CO)_8$ (430 mg, 1.30 mmol) were added. The flask was sealed immediately and heated at 65 °C for 48 h, with reaction progress monitored by TLC analysis. If the reaction was not complete, $Pd(OAc)_2$ (140 mg, 0.65 mmol) and $Co_2(CO)_8$ (215 mg, 0.65 mmol) were added, and the reaction was continued for another 24 h. The reaction mixture was diluted with ethyl acetate and filtered through a Celite pad. The filtrate was washed with brine and water, dried (Na_2SO_4), concentrated and chromatographed (silica, ethyl acetate) to give a light-yellow solid (1.10 g, 80%): mp 138−140 °C; ^{1}H NMR (300 MHz) δ 1.14 (s, 3H), 1.23 (s, 3H), 2.45 (s, 3H), 2.57−2.73 (AB, ^2J = 18.6 Hz, 2H), 3.11−3.17 (ABX, ^2J = 16.0 Hz, 1H), 3.35−3.45 (ABX, ^2J = 16.0 Hz, ^3J = 12.3 Hz, 1H), 3.42 (s, 6H), 3.73 (s, 3H), 3.75 (s, 2H), 4.37 (s, 1H), 5.21−5.26 (ABX, ^2J = 12.0 Hz, ^3J = 2.1 Hz, 1H), 6.42 (d, J = 1.5 Hz, 1H), 7.37−7.40 (d, J = 8.2 Hz, 2H), 7.70−7.73 (d, J = 8.2 Hz, 2H), 7.93 (d, J = 1.8 Hz, 1H); ^{13}C NMR (75 MHz) δ 21.8, 23.8, 24.0, 26.3, 36.4, 44.5, 46.6, 52.5, 55.1, 92.8, 104.7, 112.5, 126.1, 127.1, 128.0, 130.7, 130.9, 134.8, 146.5, 167.5, 186.5, 203.1; ESI-MS m/z $[M + H]^+$ calcd for $C_{25}H_{33}N_2O_{10}S$ 553.1850, found 553.1846.

6-[4-(3-Ethoxy-3-oxopropanoyl)-*N*-tosylpyrrol-2-yl]-1,1-dimethoxy-4,4-dimethyl-5-nitrohexan-2-one (2b). A mixture of **1** (267 mg, 0.500 mmol), ethylpotassium malonate (128 mg, 0.750 mmol), $Pd(OAc)_2$ (56.0 mg, 0.250 mmol), Xantphos (145 mg, 0.250 mmol), $MgCl_2$ (71.4 mg, 0.750 mmol), and imidazole (66.0 mg, 1.00 mmol) was placed in a 10 mL Schlenk tube, which was charged with argon. THF (4.0 mL) was added followed by Et_3N (104 μL, 0.750 mmol) and $Co_2(CO)_8$ (86.0 mg, 0.250 mmol). The tube was sealed immediately and heated at 65 °C for 48 h. The reaction mixture was

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diluted with ethyl acetate and filtered through a Celite pad. The filtrate was washed with brine and water, dried (Na_2SO_4), concentrated, and chromatographed (silica, ethyl acetate) to give a light-yellow oil (160 mg, 56%): ^{1}H NMR (400 MHz) δ 1.14 (s, 3H), 1.23 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H), 2.46 (s, 3H), 2.57−2.72 (AB, ^2J = 18.8 Hz, 2H), 3.12−3.17 (ABX, ^2J = 16.4 Hz, 1H), 3.35−3.40 (ABX, ^2J = 16.4 Hz, ^3J = 12.4 Hz, 1H), 3.42 (s, 3H), 3.43 (s, 3H), 3.72 (d, J = 0.8 Hz, 2H), 4.16−4.22 (q, J = 7.2 Hz, 2H), 4.36 (s, 1H), 5.21−5.24 (ABX, ^2J = 12.4 Hz, ^3J = 1.6 Hz, 1H), 6.42 (d, J = 2.0 Hz, 1H), 7.37−7.40 (d, J = 8.8 Hz, 2H), 7.69−7.72 (d, J = 8.8 Hz, 2H), 7.91 (d, J = 1.6 Hz, 1H); ^{13}C NMR (75 MHz) δ 14.3, 22.0, 24.0, 24.3, 26.5, 36.6, 44.7, 47.1, 55.35, 55.38, 61.8, 93.1, 104.9, 112.7, 126.3, 127.3, 128.1, 130.8, 131.1, 135.0, 146.6, 167.3, 168.8, 203.3; ESI-MS m/z [M + H]$^+$ calcd for $C_{26}H_{35}N_2O_{10}S$ 567.2003, found 567.2007.

6-[4-(3-Methoxy-3-oxopropanoyl)pyrrol-2-yl]-1,1-dimethoxy-4,4-dimethyl-5-nitrohexan-2-one (3a). Following a standard procedure,[2S] a sample of **2a** (1.10 g, 2.00 mmol) was treated with TBAF (1.0 M in THF, 2.0 mL, 2.0 mmol) in a 20 mL flask and heated to 65 °C for 1 h. The mixture was allowed to cool to room temperature, quenched by the addition of saturated aqueous $NaHCO_3$ solution, and then extracted with ethyl acetate. The organic extract was washed (brine and water), dried (Na_2SO_4), concentrated, and chromatographed [silica, hexanes/ethyl acetate (1:1)] to give a yellow oil (566 mg, 70%): ^{1}H NMR (300 MHz) δ 1.13 (s, 3H), 1.21 (s, 3H), 2.57−2.76 (AB, ^2J = 18.6 Hz, 2H), 2.99−3.05 (ABX, ^2J = 15.6 Hz, ^3J = 2.4 Hz, 1H), 3.29−3.37 (ABX, ^2J = 15.6 Hz, ^3J = 12.0 Hz, 1H), 3.43 (s, 3H), 3.43 (s, 3H), 3.72 (s, 3H), 3.75 (s, 2H), 4.37 (s, 1H), 5.15−5.20 (ABX, ^2J = 11.7 Hz, ^3J = 2.7 Hz, 1H), 6.40 (m, 1H), 7.33−7.35 (m, 1H), 9.14 (br, 1H); ^{13}C NMR (100 MHz) δ 24.2, 24.3, 26.5, 36.6, 45.1, 46.6, 52.5, 55.3, 94.2, 104.7, 107.8, 124.8, 125.3, 128.8, 168.6, 187.3, 203.9; ESI-MS m/z [M + H]$^+$ calcd for $C_{18}H_{27}N_2O_8$ 399.1762, found 399.1755.

6-[4-(3-Ethoxy-3-oxopropanoyl)pyrrol-2-yl]-1,1-dimethoxy-4,4-dimethyl-5-nitrohexan-2-one (3b). Following a standard procedure,[2S] a sample of **2b** (160 mg, 0.283 mmol) was treated with TBAF (1.0 M in THF, 0.34 mL, 0.34 mmol) in a 20 mL flask and heated to 65 °C for 1 h. The mixture was allowed to cool to room temperature, quenched by the addition of saturated aqueous $NaHCO_3$ solution, and then extracted with ethyl acetate. The organic extract was washed (brine and water), dried (Na_2SO_4), concentrated, and chromatographed [silica, hexanes/ethyl acetate (1:1), then ethyl acetate] to give a yellow oil (75 mg, 64%): ^{1}H NMR (300 MHz) δ 1.20 (s, 3H), 1.21 (s, 3H), 1.24 (t, J = 6.9 Hz, 3H), 2.56−2.75 (AB, ^2J = 18.6 Hz, 2H), 2.98−3.04 (ABX, ^2J = 15.3 Hz, ^3J = 2.4 Hz, 1H), 3.28−3.37 (ABX, ^2J = 15.3 Hz, ^3J = 11.7 Hz, 1H), 3.42 (s, 3H), 3.43 (s, 3H), 3.72 (s, 2H), 4.14−4.21 (q, J = 6.9 Hz, 2H), 4.36 (s, 1H), 5.14−5.19 (ABX, ^2J = 12.0 Hz, ^3J = 2.4 Hz, 1H), 6.39 (m, 1H), 7.32 (m, 1H), 9.06 (br, 1H); ^{13}C NMR (100 MHz) δ 14.3, 24.3, 26.6, 36.7, 45.3, 46.9, 55.4, 61.6, 94.3, 104.7, 107.8, 125.1, 125.4, 129.0, 168.5, 187.9, 204.0; ESI-MS m/z [M + H]$^+$ calcd for $C_{19}H_{29}N_2O_8$ 413.1918, found 413.1918.

2,3-Dihydro-1-(1,1-dimethoxymethyl)-8-(3-methoxy-3-oxopropanoyl)-3,3-dimethyldipyrrin (4a). Following a standard procedure,[4] a solution of **3a** (566 mg, 1.42 mmol) in THF (14.0 mL) was treated with $NaOCH_3$ (307 mg, 5.68 mmol) in a 20 mL flask under argon at 0 °C. The mixture was stirred at room temperature for 45 min. In a 250 mL flask, NH_4OAc (11.1 g, 142 mmol) in distilled THF (36.0 mL) was bubbled with argon for 15 min before a solution of $TiCl_3$ (12 wt % in 2 N HCl, 14.0 mL, 11.4 mmol) was added. The mixture was stirred for another 15 min. Then the mixture in the first flask was transferred via cannula to the buffered $TiCl_3$ solution in the second flask. The resulting mixture was stirred for 20 h at room temperature under argon. The reaction mixture was poured into saturated aqueous $NaHCO_3$ solution, filtered through a Celite pad (the filter cake was washed with ethyl acetate), and extracted with ethyl acetate. The organic extract was combined, washed (brine/water), dried (Na_2SO_4), concentrated, and chromatographed [silica, CH_2Cl_2, then CH_2Cl_2/ethyl acetate (1:1)] to give a yellow oil (223 mg, 45%): ^{1}H NMR (300 MHz) δ 1.22 (s, 6H), 2.64 (s, 2H), 3.46 (s, 6H), 3.73 (s, 3H), 3.77 (s, 2H), 5.04 (s, 1H), 5.84 (s, 1H), 6.53 (m, 1H), 7.50 (m, 1H), 11.20 (br, 1H); ^{13}C NMR (75 MHz) δ 29.0, 40.3, 46.8, 48.4, 52.4, 54.7, 102.5, 106.4, 108.4, 125.1, 125.6, 132.7, 162.2, 168.6, 176.2, 187.1; ESI-MS m/z [M + H]$^+$ calcd for $C_{18}H_{25}N_2O_5$ 349.1758, found 349.1758.

8-(3-Ethoxy-3-oxopropanoyl)-2,3-dihydro-1-(1,1-dimethoxymethyl)-3,3-dimethyldipyrrin (4b). Following a standard procedure,[4] a solution of **3b** (75 mg, 0.18 mmol) in THF (1.8 mL) and MeOH (50. μL) was treated with $NaOCH_3$ (39 mg, 0.73 mmol) in a 20 mL flask under argon at 0 °C. The mixture was stirred at 0 °C for 45 min. In a 100 mL flask, NH_4OAc (1.42 g, 18.2 mmol) in distilled THF (18 mL) was bubbled with argon for 15 min before a solution of $TiCl_3$ (12 wt % in 2 N HCl, 1.8 mL, 1.46 mmol) was added. The mixture was stirred for another 15 min. Then the mixture in the first flask was transferred via cannula to the buffered $TiCl_3$ solution in the second flask. The resulting mixture was stirred at room temperature under argon for 20 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate. The organic extract was combined, washed (brine/water), dried (Na_2SO_4), concentrated, and chromatographed [silica, CH_2Cl_2, then CH_2Cl_2/ethyl acetate (1:1)] to give a yellow oil (24 mg, 36%): ^{1}H NMR (300 MHz) δ 1.22 (s, 6H), 1.26 (t, J = 7.2 Hz, 3H), 2.64 (s, 2H), 3.46 (s, 6H), 3.77 (s, 2H), 4.16−4.23 (q, J = 7.2 Hz, 2H), 5.03 (s, 1H), 5.84 (s, 1H), 6.53 (m, 1H), 7.50 (m, 1H), 11.18 (br, 1H); ^{13}C NMR (75 MHz) δ 14.4, 29.2, 40.4, 47.3, 48.6, 54.8, 61.5, 102.6, 106.6, 108.6, 125.3, 125.6, 132.8, 162.2, 168.3, 176.3, 187.4; ESI-MS m/z [M + H]$^+$ calcd for $C_{19}H_{27}N_2O_5$ 363.1916, found 363.1915.

7-(4-Bromophenyl)-1-formyl-2,3-dihydro-3,3-dimethyldipyrrin (5-Ar). Following a standard procedure,[5] a solution of **11-Ar** (300 mg, 0.87 mmol) in 1,4-dioxane (17.4 mL) was treated with SeO_2 (288 mg, 2.60 mmol) under argon. The progress of the reaction was monitored by absorption spectroscopy. After 90 min, ethyl acetate (200 mL) was added. The organic layer was washed [aqueous $NaHCO_3$ solution (200 mL); water/brine (2 × 200 mL)], dried, concentrated and chromatographed [silica, hexanes/ethyl acetate (3:1)] to afford a red solid (67 mg, 22%): ^{1}H NMR (400 MHz) δ 1.22 (s, 6H), 2.72 (s, 2H), 6.29 (s, 1H), 6.33 (m, 1H), 7.00 (m, 1H), 7.29−7.31 (d, J = 8.8 Hz, 2H), 7.53−7.55 (d, J = 8.8 Hz, 2H), 9.99 (s, 1H), 10.81 (br, 1H); ^{13}C NMR (100 MHz) δ 29.2, 41.2, 46.1, 109.9, 112.4, 120.4, 122.1, 127.2, 127.7, 130.4, 131.8, 135.3, 161.2, 169.3, 190.1; ESI-MS m/z [M + H]$^+$ calcd for $C_{18}H_{18}BrN_2O$ 357.0597, found 357.0592; λ_{abs} in CH_2Cl_2 = 470 nm.

8-Carbethoxy-7-ethyl-1-formyl-2,3-dihydro-3,3-dimethyldipyrrin (5-EtEs). Following a standard procedure,[5] a solution of **11-EtEs** (100 mg, 0.33 mmol) in 1,4-dioxane (6.6 mL) was treated with SeO_2 (111 mg, 1.0 mmol) under argon. Progress of the reaction was monitored by absorption spectroscopy. After 90 min, ethyl acetate (100 mL) was added. The organic layer was washed with aqueous $NaHCO_3$ solution (100 mL) and brine (2 × 100 mL), dried, concentrated, and chromatographed [silica, hexanes/ethyl acetate (3:1)] to afford a red solid (32 mg, 32%): ^{1}H NMR (400 MHz) δ 1.20 (t, J = 7.2 Hz, 3H), 1.27 (s, 6H), 1.36 (t, J = 6.8 Hz, 3H), 2.73 (s, 2H), 2.84−2.89 (q, J = 7.2 Hz, 2H), 4.26−4.32 (q, J = 6.8 Hz, 2H), 6.18 (s, 1H), 7.53 (d, J = 3.2 Hz, 1H), 9.98 (s, 1H), 10.82 (br, 1H); ^{13}C NMR (100 MHz) δ 14.6, 16.5, 18.2, 29.3, 41.1, 46.1, 59.6, 111.1, 115.0, 127.4, 128.3, 130.4, 160.7, 165.0, 169.4, 190.0; ESI-MS m/z [M + H]$^+$ calcd for $C_{17}H_{23}N_2O_3$ 303.1703, found 303.1699; λ_{abs} in CH_2Cl_2 = 451 nm.

Ethyl 3-(4-Bromophenyl)prop-2-enoate (6). Following a standard procedure,[4] a solution of 4-bromobenzaldehyde (17.4 g, 94.0 mmol) and (carbethoxymethylene)triphenylphosphorane (35.8 g, 103 mmol) in CH_2Cl_2 (120 mL) was refluxed for 20 h. The reaction mixture was allowed to cool to room temperature and then concentrated. The residue was diluted with Et_2O and filtered. The filtrate was washed with brine, dried (Na_2SO_4), concentrated, and chromatographed [silica, hexanes/ethyl acetate (2:1)] to give a colorless oil (21.9 g, 91%): ^{1}H NMR (400 MHz) δ 1.33 (t, J = 7.2 Hz, 3H), 4.26 (q, J = 7.2 Hz, 2H), 6.41 (d, J = 16.0 Hz, 1H), 7.37 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 8.8 Hz, 2H), 7.60 (d, J = 16.0 Hz, 1H); ^{13}C NMR (100 MHz) δ 14.4, 60.7, 119.0, 124.5, 129.5, 132.2, 133.4, 143.2,

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166.8; ESI-MS m/z $[M + H]^+$ calcd for $C_{11}H_{12}BrO_2$ 255.0015, found 255.0011.

3-(4-Bromophenyl)pyrrole (7). Following a standard procedure,[4] a suspension of **6** (21.9 g, 85.8 mmol) and TosMIC (16.7 g, 85.8 mmol) in dry ether/DMSO (2:1, 150 mL) was added dropwise to a suspension of NaH (60% in mineral oil, 5.16 g, 129 mmol) in dry ether (70 mL) under argon. The mixture was stirred at room temperature for 5 h. Water (200 mL) was added. The aqueous phase was extracted with ethyl acetate (2 × 200 mL). The organic layer was separated, dried (Na_2SO_4), and concentrated to a brown solid. The brown solid was dissolved in ethylene glycol (200 mL) in a 500 mL flask and bubbled with argon for 10 min. Powdered NaOH (17.2 g, 430 mmol) was added. The flask was heated to 160 °C in an oil bath. After 2.5 h, the reaction mixture was allowed to cool to room temperature, whereupon brine (200 mL) was added. The resulting mixture was extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4), concentrated, and recrystallized (hot ethanol) to afford a yellow solid (10.9 g, 57%): mp 142−143 °C; ^{1}H NMR (400 MHz) δ 6.49 (m, 1H), 6.81 (m, 1H), 7.04 (m, 1H), 7.37−7.39 (d, J = 8.4 Hz, 2H), 7.42−7.44 (d, J = 8.4 Hz, 2H), 8.24 (br, 1H); ^{13}C NMR (100 MHz) δ 106.5, 114.8, 119.0, 119.3, 123.9, 126.9, 131.7, 134.9; ESI-MS m/z $[M + H]^+$ calcd for $C_{10}H_9BrN$ 221.9913, found 221.9910.

3-(4-Bromophenyl)-2-formylpyrrole (8). Following a standard procedure,[4] a solution of **7** (10.9 g, 49.0 mmol) in DMF (15.2 mL, 196 mmol) and CH_2Cl_2 (200 mL) at 0 °C under argon was treated dropwise with $POCl_3$ (5.5 mL, 58.8 mmol). After 1 h, the ice bath was removed and the mixture was stirred overnight. Then, the reaction mixture was cooled to 0 °C again, whereupon 2.0 M aqueous NaOH solution (350 mL) was added. The mixture was extracted with CH_2Cl_2. The organic extract was washed with brine, dried (Na_2SO_4), concentrated, and chromatographed [silica, CH_2Cl_2] to give a yellow solid (9.44 g, 77%): mp 163−164 °C; ^{1}H NMR (400 MHz) δ 6.43 (m, 1H), 7.17 (m, 1H), 7.35−7.37 (d, J = 8.0 Hz, 2H), 7.56−7.58 (d, J = 8.0 Hz, 2H), 9.59 (s, 1H), 10.41 (br, 1H); ^{13}C NMR (100 MHz) δ 111.6, 122.2, 126.3, 128.8, 130.8, 132.0, 132.8, 136.2, 179.7; ESI-MS m/z $[M + H]^+$ calcd for $C_{11}H_9BrNO$ 249.9862, found 249.9863.

3-(4-Bromophenyl)-2-(2-nitroethyl)pyrrole (9-Ar). Following a standard procedure,[4] a mixture of pyrrole **8** (9.44 g, 37.8 mmol), potassium acetate (4.08 g, 41.6 mmol), methylamine hydrochloride (2.87 g, 41.6 mmol), and nitromethane (75 mL) was stirred at room temperature under argon. The progress of the reaction was monitored via TLC analysis. After 2 h, brine was added. The resulting mixture was extracted with ethyl acetate. The organic extract was washed with brine and water, dried (Na_2SO_4), and concentrated to afford an orange solid. The crude solid was dissolved in anhydrous THF/MeOH (166 mL, 9:1) under argon at 0 °C. The mixture was stirred vigorously and treated with $NaBH_4$ (2.51 g, 66.4 mmol) in one portion. Stirring was continued for 1 h at 0 °C and then for 2 h at room temperature. The reaction mixture was neutralized to pH 7 with acetic acid. Water was added followed by extraction with ethyl acetate. The organic extract was washed with brine and water, dried (Na_2SO_4), concentrated, and chromatographed [silica, hexanes/ethyl acetate (1:1)] to give a yellow solid (8.01 g, 72%): mp 93−94 °C; ^{1}H NMR (400 MHz) δ 3.42 (t, J = 6.6 Hz, 2H), 4.54 (t, J = 6.6 Hz, 2H), 6.26 (m, 1H), 6.74 (m, 1H), 7.19−7.21 (d, J = 8.0 Hz, 2H), 7.49−7.51 (d, J = 8.0 Hz, 2H), 8.33 (br, 1H); ^{13}C NMR (100 MHz) δ 24.2, 75.0, 109.4, 117.9, 119.9, 122.0, 122.2, 129.6, 131.8, 135.2; ESI-MS m/z $[M + H]^+$ calcd for $C_{12}H_{12}BrN_2O_2$ 295.0077, found 295.0078.

6-[3-(4-Bromophenyl)pyrrol-2-yl]-4,4-dimethyl-5-nitrohexan-2-one (10-Ar). Following a standard procedure,[5] a mixture of **9-Ar** (8.01 g, 27.1 mmol) and mesityl oxide (6.2 mL, 54.2 mmol) was treated with DBU (8.1 mL, 54 mmol) at room temperature. After 16 h, water was added, and the mixture was extracted with ethyl acetate (2 × 100 mL). The organic layer was washed thoroughly with brine and water, dried (Na_2SO_4), concentrated, and chromatographed [silica, hexanes/ethyl acetate (3:1)] to give a brown oil (4.63 g, 44%): ^{1}H NMR (300 MHz) δ 1.08 (s, 3H), 1.19 (s, 3H), 2.11 (s, 3H), 2.34−2.59 (AB, ^2J = 18.0 Hz, 2H), 3.12−3.18 (ABX, ^2J = 15.6 Hz, ^3J = 2.7 Hz, 1H), 3.35−3.44 (ABX, ^2J = 15.6 Hz, ^3J = 11.4 Hz, 1H), 5.19−5.23 (ABX, ^2J = 11.4 Hz, ^3J = 2.4 Hz, 1H), 6.21−6.22 (m, 1H), 6.68−6.70 (m, 1H), 7.20−7.22 (d, ^2J = 8.4 Hz, 2H), 7.49−7.52 (d, ^2J = 8.4 Hz, 2H), 8.20 (br, 1H); ^{13}C NMR (100 MHz) δ 24.2, 24.5, 25.2, 31.9, 37.1, 51.5, 94.4, 109.4, 118.1, 120.1, 122.5, 122.7, 130.1, 120.2, 131.7, 131.8, 125.6, 206.9; ESI-MS m/z $[M + H]^+$ calcd for $C_{18}H_{22}BrN_2O_3$ 393.0808, found 393.0808.

7-(4-Bromophenyl)-2,3-dihydro-1,3,3-trimethyldipyrrin (11-Ar). Following a standard procedure,[5] a solution of **10-Ar** (4.63 g, 11.8 mmol) in distilled THF (22 mL) and dry methanol (1.0 mL) under argon was treated with NaOMe (1.91 g, 35.4 mmol), and the mixture was stirred for 45 min at room temperature. In a second flask, $TiCl_3$ (20 wt % in 3% HCl solution, 60. mL), THF (160 mL), and NH_4OAc (45 g) were combined under argon, and the mixture was degassed by bubbling with argon for 45 min. The solution in the first flask containing the nitronate anion was transferred via a cannula to the buffered $TiCl_3$ mixture in the second flask. The resulting mixture was stirred at room temperature for 16 h under argon. The reaction mixture was poured over a pad of Celite and eluted with ethyl acetate. The eluant was washed with aqueous $NaHCO_3$ solution. The organic phase was dried (Na_2SO_4), concentrated and chromatographed [silica, hexanes/ethyl acetate (1:1)] to afford a light yellow solid (1.50 g, 37%): mp 119−121 °C; ^{1}H NMR (400 MHz) δ 1.19 (s, 6H), 2.23 (s, 3H), 2.52 (s, 2H), 5.89 (s, 1H), 6.26 (m, 1H), 6.85 (m, 1H), 7.31−7.33 (d, J = 8.0 Hz, 2H), 7.49−7.51 (d, J = 8.0 Hz, 2H), 11.10 (br, 1H); ^{13}C NMR (100 MHz) δ 20.8, 29.2, 41.3, 53.8, 102.4, 108.7, 118.6, 119.2, 122.1, 127.6, 130.2, 131.2, 136.3, 162.0, 177.3; ESI-MS m/z $[M + H]^+$ calcd $C_{18}H_{20}BrN_2$ 343.0804, found 343.0807.

8-Carbethoxy-7-ethyl-1,3,3-trimethyl-2,3-dihydrodipyrrin (11-EtEs). Following a standard procedure,[5] a mixture of **9-EtEs** (5.1 g, 21 mmol) and mesityl oxide (4.1 g, 42 mmol) was treated with DBU (10 mL, 64 mmol) at room temperature. After 16 h, water was added, and then the mixture was extracted with ethyl acetate (2 × 100 mL). The organic layer was washed thoroughly with brine and water, dried (Na_2SO_4), and concentrated. The resulting brown oil was dried overnight under high vacuum to give a crude material (4.2 g) that was used directly in the next step. In a first flask, a solution of the crude material in distilled THF (20 mL) and dry methanol (1.0 mL) under argon was treated with NaOMe (2.0 g, 37 mmol), and the mixture was stirred for 45 min at room temperature. In a second flask, $TiCl_3$ (20 wt % in 3% HCl solution, 63 mL, 100 mmol), THF (160 mL), and NH_4OAc (47 g, 620 mmol) were combined under argon, and the mixture was degassed by bubbling with argon for 45 min. The solution in the first flask containing the nitronate anion was transferred via cannula to the buffered $TiCl_3$ mixture in the second flask. The resulting mixture was stirred at room temperature for 16 h under argon. The reaction mixture was poured over a pad of Celite and eluted with ethyl acetate. The eluant was washed with aqueous $NaHCO_3$ solution. The organic phase was dried (Na_2SO_4), concentrated, and chromatographed [silica, hexanes/ethyl acetate (3:1)] to afford a yellow oil (1.4 g, 23%): ^{1}H NMR (400 MHz) δ 1.16 (t, J = 7.6 Hz, 3H), 1.22 (s, 6H), 1.34 (t, J = 7.0 Hz, 3H), 2.21 (s, 3H), 2.52 (s, 2H), 2.78−2.83 (q, J = 7.6 Hz, 2H), 4.24−4.29 (q, J = 7.0 Hz, 2H), 5.71 (s, 1H), 7.40 (d, J = 3.2 Hz, 1H), 11.15 (br, 1H); ^{13}C NMR (100 MHz) δ 14.6, 16.4, 18.1, 20.8, 29.3, 41.3, 53.9, 59.2, 101.4, 114.0, 124.5, 125.1, 128.6, 161.3, 165.7, 177.1; ESI-MS m/z $[M + H]^+$ calcd for $C_{17}H_{25}N_2O_2$ 289.1911, found 289.1907.

2-Carbomethoxy-3-(2,3-dihydro-3,3-dimethyl-7-*p*-tolyldipyrrin-1-yl)-1-[2,3-dihydro-1-(1,1-dimethoxymethyl)-3,3-dimethyldipyrrin-8-yl]prop-2-en-1-one (12-T). Samples of **4a** (17 mg, 49 μmol), **5-T** (17 mg, 58 μmol, 1.2 equiv), and dried molecular sieves 3 Å (17 mg, powder form) were placed in a 20 mL vial under argon. A solution of piperidine/acetic acid in CH_2Cl_2 (15 mM/15 mM, 1.2 mL, 18 μmol/18 μmol) was added, and the mixture was stirred at room temperature for 20 h. The mixture was filtered through a Celite pad. The filtrate was concentrated and chromatographed [silica, hexanes/ethyl acetate (3:1 then 1:1)] to give an orange-red gum (19 mg, 61%): ^{1}H NMR (400 MHz) δ 1.07 (s, 6H), 1.22 (s, 6H), 2.37 (s, 3H), 2.56 (s, 2H), 2.64 (s, 2H), 3.44 (s, 6H), 3.78 (s, 3H), 5.00 (s, 1H), 5.85 (s, 1H), 6.12 (s, 1H), 6.27 (m, 1H), 6.57 (s, 1H), 6.91 (m, 1H), 7.19−7.21 (d, J = 7.6 Hz, 2H), 7.30−7.32 (d, J = 7.6 Hz, 2H), 7.39 (s, 1H), 7.65 (s, 1H), 10.68 (br, 1H), 11.27 (br, 1H); ^{13}C NMR (100 MHz) δ

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21.3, 29.07, 29.09, 40.4, 41.8, 48.5, 50.4, 52.9, 54.7, 102.4, 106.4, 108.2, 108.8, 109.4, 121.0, 126.0, 126.5, 126.9, 127.4, 128.7, 129.3, 129.4, 133.3, 133.9, 134.9, 135.6, 138.0, 161.0, 162.5, 165.7, 167.3, 176.6, 188.5; ESI-MS m/z $[M + H]^+$ calcd for $C_{37}H_{43}N_4O_5$ 623.3228, found 623.3224; λ_{abs} (CH_2Cl_2) 319 nm (ε 2.6 × 10^4 M^{-1} cm^{-1}), 505 nm (ε 1.6 × 10^4 M^{-1} cm^{-1}). Note that addition of piperidine and acetic acid (15 mM each) in water afforded a pH = 6.7, reflecting the near-neutral conditions of this combination of reagents for the Knoevenagel condensation.

3-[7-(4-Bromophenyl)-2,3-dihydro-3,3-dimethylpyrrin-1-yl]-2-carbomethoxy-1-[2,3-dihydro-1-(1,1-dimethoxymethyl)-3,3-dimethyldipyrrin-8-yl]prop-2-en-1-one (12-Ar). Reaction of **4a** (31 mg, 90 μmol) and **5-Ar** (32 mg, 90 μmol) under the general procedure for **12-T** followed by chromatography [silica, hexanes/ethyl acetate (3:1 then 1:1)] gave an orange-red gum (38 mg, 68%): ^{1}H NMR (400 MHz) δ 1.08 (s, 6H), 1.22 (s, 6H), 2.57 (s, 2H), 2.64 (s, 2H), 3.44 (s, 6H), 3.79 (s, 3H), 5.01 (s, 1H), 5.85 (s, 1H), 6.03 (s, 1H), 6.25 (m, 1H), 6.56 (s, 1H), 6.92 (m, 1H), 7.25−7.28 (d, J = 8.4 Hz, 2H), 7.39 (s, 1H), 7.48−7.50 (d, J = 8.4 Hz, 2H), 7.64 (s, 1H), 10.70 (br, 1H), 11.27 (br, 1H); ^{13}C NMR (100 MHz) δ 29.1, 40.4, 41.7, 48.6, 50.5, 53.0, 54.7, 102.4, 106.4, 108.1, 108.2, 109.2, 119.8, 121.1, 125.0, 125.9, 126.8, 127.6, 130.3, 131.7, 133.3, 134.6, 135.8, 138.4, 161.6, 162.6, 165.6, 167.9, 176.6, 188.4; ESI-MS m/z $[M + H]^+$ calcd for $C_{36}H_{40}BrN_4O_5$ 687.2177, found 687.2168.

2-Carbomethoxy-3-(2,3-dihydro-3,3,7,8-tetramethyldipyrrin-1-yl)-1-[2,3-dihydro-1-(1,1-dimethoxymethyl)-3,3-dimethyldipyrrin-8-yl]prop-2-en-1-one (12-MeMe). Reaction of **4a** (35 mg, 100 μmol) and **5-MeMe** (41 mg, 120 μmol, 1.2 equiv) under the general procedure for **12-T** followed by chromatography [silica, hexanes/ethyl acetate (3:1 then 1:1)] gave an orange-red gum (47 mg, 71%): ^{1}H NMR (400 MHz) δ 1.08 (s, 6H), 1.22 (s, 6H), 1.63 (s, 9H), 2.03 (s, 3H), 2.25 (s, 3H), 2.51 (s, 2H), 2.64 (s, 2H), 3.44 (s, 6H), 3.78 (s, 3H), 5.01 (s, 1H), 5.85 (s, 1H), 5.88 (s, 1H), 6.54 (s, 1H), 7.36 (s, 1H), 7.73 (s, 1H), 11.02 (br, 1H), 11.29 (br, 1H); ^{13}C NMR (100 MHz) δ 9.0, 10.6, 28.6, 29.06, 29.09, 40.4, 42.2, 48.5, 49.6, 52.9, 54.7, 80.3, 102.4, 106.4, 106.8, 108.2, 121.0, 121.6, 126.3, 127.2, 130.4, 133.5, 135.9, 139.1, 161.0, 162.6, 162.9, 165.5, 170.1, 176.7, 188.1; ESI-MS m/z $[M + H]^+$ calcd for $C_{37}H_{49}N_4O_7$ 661.3596, found 661.3590.

2-Carbomethoxy-3-(8-carbethoxy-7-ethyl-2,3-dihydro-3,3-dimethyldipyrrin-1-yl)-1-[2,3-dihydro-1-(1,1-dimethoxymethyl)-3,3-dimethyldipyrrin-8-yl]prop-2-en-1-one (12-EtEs). Reaction of **4a** (25 mg, 71 μmol) and **5-EtEs** (32 mg, 106 μmol, 1.5 equiv) under the general procedure for **12-T** followed by chromatography [silica, hexanes/ethyl acetate (3:1 then 1:1)] gave an orange-red gum (27 mg, 61%): ^{1}H NMR (400 MHz) 1.12 (s, 6H), 1.14 (t, J = 7.2 Hz, 3H), 1.22 (s, 6H), 1.35 (t, J = 7.0 Hz, 3H), 2.58 (s, 2H), 2.64 (s, 2H), 2.76−2.82 (q, J = 7.2 Hz, 2H), 3.44 (s, 6H), 3.78 (s, 3H), 4.25−4.30 (q, J = 7.0 Hz, 2H), 5.01 (s, 1H), 5.86 (s, 1H), 5.89 (s, 1H), 6.55 (s, 1H), 7.39 (s, 1H), 7.45 (d, J = 3.2 Hz, 1H), 7.60 (s, 1H), 10.60 (br, 1H), 11.28 (br, 1H); ^{13}C NMR (100 MHz) δ 14.6, 16.5, 18.1, 29.1, 29.2, 40.4, 41.6, 48.5, 50.7, 53.0, 54.7, 59.4, 102.4, 106.4, 106.9, 108.1, 114.3, 125.8, 126.8, 128.2, 128.7, 133.3, 134.3, 138.4, 160.9, 162.6, 165.4, 165.5, 167.8, 176.6, 188.5; ESI-MS m/z $[M + H]^+$ calcd for $C_{35}H_{45}N_4O_7$ 633.3283, found 633.3268.

3-[7-(4-Bromophenyl)-2,3-dihydro-3,3-dimethylpyrrin-1-yl]-2-carbethoxy-1-[2,3-dihydro-1-(1,1-dimethoxymethyl)-3,3-dimethyldipyrrin-8-yl]prop-2-en-1-one (12-Ar/Et). Reaction of **4b** (31 mg, 84 μmol) and **1-Ar** (36 mg, 100 μmol, 1.2 equiv) under the general procedure for **12-T** followed by chromatography [silica, hexanes/ethyl acetate (3:1 then 1:1)] gave an orange-red gum (33 mg, 57%): ^{1}H NMR (300 MHz) δ 1.08 (s, 6H), 1.22 (s, 6H), 1.25 (t, J = 7.2 Hz, 3H), 2.57 (s, 2H), 2.64 (s, 2H), 3.43 (s, 6H), 4.22−4.29 (q, J = 7.2 Hz, 2H), 5.00 (s, 1H), 5.84 (s, 1H), 6.03 (s, 1H), 6.24 (m, 1H), 6.56 (m, 1H), 6.91 (m, 1H), 7.25−7.28 (d, J = 8.4 Hz, 2H), 7.38 (m, 1H), 7.48−7.51 (d, J = 8.4 Hz, 2H), 7.61 (s, 1H), 10.71 (br, 1H), 11.24 (br, 1H); ^{13}C NMR (100 MHz) δ 14.26, 14.32, 29.1, 40.4, 41.7, 48.6, 50.6, 54.7, 62.0, 102.5, 106.5, 108.0, 108.2, 109.2, 119.8, 121.1, 124.9, 126.0, 126.7, 127.6, 130.3, 131.7, 133.2, 134.2, 135.9, 139.0, 161.6, 162.5, 165.0, 168.1, 176.6, 188.4; ESI-MS m/z $[M + H]^+$ calcd for $C_{37}H_{42}BrN_4O_5$ 701.2333, found 701.2334.

13^2-Carbomethoxy-8,8,18,18-tetramethyl-2-*p*-tolylbacterio-13^1-oxophorbine (BC-T). A solution of **12-T** (19 mg, 30 μmol) in acetonitrile (ACS grade, 150 mL) was degassed by bubbling with argon for 20 min. Yb(OTf)$_3$ (186 mg, 0.300 mmol) was added in one portion under argon. The reaction mixture was immediately heated to 80 °C and stirred under argon for 20 h, during which time the solution changed from orange-red to dark green. Then, the reaction mixture was allowed to cool to room temperature, whereupon excess Et_3N (0.5 mL) was added. The reaction mixture was concentrated and chromatographed [silica, hexanes/ethyl acetate (3:1 then 1:1)] to afford a blue-green solid (9.5 mg, 56%): ^{1}H NMR (400 MHz) δ 0.52 (br, 1H), 1.72 (s, 3H), 1.82 (s, 9H), 2.03 (br, 1H), 2.58 (s, 3H), 3.76−3.88 (AB, J = 16.8 Hz, 2H), 3.83 (s, 3H), 4.09 (s, 2H), 5.79 (s, 1H), 7.52−7.54 (d, J = 7.8 Hz, 2H), 7.91−7.93 (d, J = 7.8 Hz, 2H), 8.08 (s, 1H), 8.11 (m, 2H), 8.21 (s, 1H), 8.34 (d, J = 1.6 Hz, 1H); ^{13}C NMR (100 MHz) δ 21.6, 29.7, 30.1, 30.9, 31.0, 43.9, 45.6, 49.0, 52.9, 53.3, 64.7, 95.1, 98.2, 100.2, 106.0, 108.1, 126.3, 128.6, 130.1, 130.5, 131.8, 138.7, 140.1, 140.3, 141.9, 142.3, 149.8, 152.2, 165.5, 169.4, 169.8, 177.3, 188.6; ESI-MS m/z $[M + H]^+$ calcd for $C_{35}H_{35}N_4O_3$ 559.2704, found 559.2702; λ_{abs} 356, 489, 520, 660, 721 nm.

2-(4-Bromophenyl)-13^2-carbomethoxy-8,8,18,18-tetramethylbacterio-13^1-oxophorbine (BC-Ar). Reaction of **12-Ar** (18 mg, 26 μmol) under the general procedure for **BC-T** followed by chromatography [silica, hexanes/ethyl acetate (3:1 then 3:2)] gave a blue-green solid (10.5 mg, 61%): ^{1}H NMR (400 MHz) δ 0.31 (br, 1H), 1.73 (s, 3H), 1.78 (br, 1H), 1.82 (s, 3H), 1.83 (s, 6H), 3.79−3.91 (AB, J = 16.8 Hz, 2H), 3.84 (s, 3H), 4.14 (s, 2H), 5.83 (s, 1H), 7.85−7.87 (d, J = 8.4 Hz, 2H), 7.88−7.90 (d, J = 8.4 Hz, 2H), 8.07 (s, 1H), 8.17 (s, 1H), 8.19 (s, 1H), 8.27 (s, 1H), 8.40 (d, J = 1.6 Hz, 1H); ^{13}C NMR (100 MHz) δ 29.8, 30.2, 31.0, 31.1, 44.0, 45.8, 48.9, 52.9, 53.2, 64.7, 94.8, 98.6, 100.4, 106.5, 108.3, 123.2, 126.5, 128.9, 132.1, 132.5, 133.7, 139.7, 140.2, 141.5, 149.7, 152.5, 165.2, 169.6, 169.8, 177.0, 188.6; ESI-MS m/z $[M + H]^+$ calcd for $C_{34}H_{32}BrN_4O_3$ 623.1652, found 623.1647; λ_{abs} 356, 490, 521, 664, 727 nm.

13^2-Carbomethoxy-2,3,8,8,18,18-hexamethylbacterio-13^1-oxophorbine (BC-MeMe). Reaction of **12-MeMe** (23 mg, 35 μmol) under the general procedure for **BC-T** followed by chromatography [silica, hexanes/ethyl acetate (3:1 then 1:1)] gave a blue solid (6.7 mg, 37%): ^{1}H NMR (400 MHz) δ 1.16 (br, 1H), 1.62 (br, 1H), 1.72 (s, 3H), 1.75 (s, 6H), 1.80 (s, 3H), 2.93 (s, 3H), 2.95 (s, 3H), 3.62−3.74 (AB, J = 16.8 Hz, 2H), 3.82 (s, 3H), 3.97 (s, 2H), 5.64 (s, 1H), 7.63 (s, 1H), 7.74 (s, 1H), 7.85 (s, 1H), 7.97 (s, 1H); ^{13}C NMR (100 MHz) δ 10.9, 29.6, 29.9, 30.8, 30.9, 43.3, 45.1, 49.0, 52.8, 53.7, 64.4, 91.5, 94.3, 100.0, 104.6, 107.9, 127.7, 133.8, 134.2, 139.7, 142.4, 144.7, 150.6, 151.6, 166.3, 168.5, 169.9, 177.9, 188.5; ESI-MS m/z $[M + H]^+$ calcd for $C_{30}H_{33}N_4O_3$ 497.2547, found 497.2548; λ_{abs} 351, 480, 511, 640, 696 nm.

3-Carbethoxy-2-ethyl-13^2-carbomethoxy-8,8,18,18-tetramethylbacterio-13^1-oxophorbine (BC-EtEs). Reaction of **12-EtEs** (13 mg, 21 μmol) under the general procedure for **BC-T** followed by chromatography [silica, hexanes/ethyl acetate (4:1 then 2:1)] gave a purple solid (6.6 mg, 57%): ^{1}H NMR (400 MHz) δ − 0.07 (br, 1H), 1.59 (br, 1H), 1.66−1.69 (t, J = 7.6 Hz, 3H), 1.67−1.71 (t, J = 7.6 Hz, 3H), 1.81 (s, 3H), 1.83 (s, 6H), 1.91 (s, 3H), 3.81−3.91 (AB, J = 16.2 Hz, 2H), 3.84 (s, 3H), 3.91−3.98 (q, J = 7.6 Hz, 2H), 4.20 (s, 2H), 4.71−4.78 (q, J = 7.6 Hz, 2H), 5.85 (s, 1H), 8.20 (s, 1H), 8.23 (s, 1H), 8.30 (s, 1H), 9.16 (s, 1H); ^{13}C NMR (100 MHz) δ 14.7, 17.1, 20.8, 30.1, 30.4, 31.0, 31.1, 44.0, 45.9, 48.8, 52.9, 53.7, 61.5, 64.7, 94.0, 98.0, 100.4, 107.0, 108.6, 124.0, 129.3, 138.3, 139.5, 140.6, 148.1, 149.6, 153.1, 165.5, 165.8, 169.7, 170.4, 176.0, 188.6; ESI-MS m/z $[M + H]^+$ calcd for $C_{33}H_{37}N_4O_5$ 569.2758, found 569.2753; λ_{abs} 357, 501, 533, 680, 745 nm.

2-(4-Bromophenyl)-13^2-carbethoxy-8,8,18,18-tetramethylbacterio-13^1-oxophorbine (BC-Ar/Et). Reaction of **12-Ar/Et** (16 mg, 23 μmol) under the general procedure for **BC-T** followed by chromatography [silica, hexanes/ethyl acetate (3:1)] gave a blue-green solid (7.1 mg, 48%): ^{1}H NMR (400 MHz) δ 0.27 (br, 1H), 1.23−1.27 (t, J = 6.8 Hz, 3H), 1.73 (br, 1H), 1.75 (s, 3H), 1.81 (s, 3H), 1.83 (s, 6H), 3.81−3.92 (AB, J = 16.8 Hz, 2H), 4.14 (s, 2H), 4.29−4.34 (q, J = 6.8 Hz, 2H), 5.80 (s, 1H), 7.85−7.87 (d, J = 8.0 Hz, 2H), 7.89−7.91

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(d, J = 8.0 Hz, 2H), 8.08 (s, 1H), 8.18 (s, 1H), 8.20 (s, 1H), 8.27 (s, 1H), 8.40 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz) δ 14.4, 30.0, 30.1, 31.0, 31.3, 44.1, 45.8, 48.9, 53.3, 61.8, 65.0, 94.8, 98.6, 100.4, 106.6, 108.5, 123.2, 126.4, 129.1, 132.1, 132.5, 133.8, 139.7, 140.1, 140.2, 141.4, 149.7, 152.5, 165.1, 169.3, 169.6, 176.8, 188.8; ESI-MS m/z $[M]^+$ calcd for $C_{35}H_{33}BrN_4O_3$ 636.1652, found 636.1652; λ_{abs} 357, 489, 521, 665, 728 nm.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02878.

Nomenclature of the linear tetrapyrroles; absorption spectral data for three bacteriochlorins; X-ray data for **BC-Ar**; list of 27 references for Michael reactions with pyrroles; and characterization data for all new compounds (PDF)

X-ray data for **BC-Ar** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jlindsey@ncsu.edu.

ORCID

Jonathan S. Lindsey: 0000-0002-4872-2040

Notes

The authors declare the following competing financial interest(s): J.S.L. is a cofounder of NIRvana Sciences, which has licensed technology described herein. Also, the two coauthors have filed a patent application on 11/30/2016 on the same technology.

X-ray crystallographic data for compound **BC-Ar** have been deposited with the Cambridge Crystallographic Data Centre (CCDC 1528392).

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