Synthesis and Spectral Properties of meso-Arylbacteriochlorins, Including Insights into Essential Motifs of their Hydrodipyrrin Precursors

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Academic Editor: Augusto C. Tomé
Received: 13 March 2017; Accepted: 11 April 2017; Published: 14 April 2017

Abstract: Synthetic bacteriochlorins—analogue of bacteriochlorophylls, Nature’s near-infrared absorbers—are attractive for diverse photochemical studies. meso-Arylbacteriochlorins have been prepared by the self-condensation of a dihydrodipyrrin–carbinol or dihydrodipyrrin–acetal following an Eastern-Western (E-W) or Northern-Southern (N-S) joining process. The bacteriochlorins bear a gem-dimethyl group in each pyrroline ring to ensure stability toward oxidation. The two routes differ in the location of the gem-dimethyl group at the respective 3- or 2-position in the dihydrodipyrrin, and the method of synthesis of the dihydrodipyrrin. Treatment of a known 3,3-dimethyldihydrodipyrrin-1-carboxaldehyde with an aryl Grignard reagent afforded the dihydrodipyrrin-1-(aryl)carbinol, and upon subsequent acetylation, the corresponding dihydrodipyrrin-1-methyl acetate (dihydrodipyrrin–acetate). Self-condensation of the dihydrodipyrrin–acetate gave a meso-diarylbacteriochlorin (E-W route). A 2,2-dimethyl-5-aryldihydrodipyrrin-1-(aryl)carbinol underwent self-condensation to give a trans-A2B2-type meso-tetraarylbacteriochlorin (N-S route). In each case, the aromatization process entails a 2e−/2H+ (aerobic) dehydrogenative oxidation following the dihydrodipyrrin self-condensation. Comparison of a tetrahydrodipyrrin–acetal (0%) versus a dihydrodipyrrin–acetal (41%) in bacteriochlorin formation and results with various 1-substituted dihydrodipyrrins revealed the importance of resonance stabilization of the reactive hydrodipyrrin intermediate. Altogether 10 new dihydrodipyrrins and five new bacteriochlorins have been prepared. The bacteriochlorins exhibit characteristic bacteriochlorophyll-like absorption spectra, including a Qy band in the region 726–743 nm.

Keywords: self-condensation; bacteriochlorophyll; near-infrared; tetrahydrodipyrrin; dihydrodipyrrin; absorption; fluorescence; oxocarbenium ion; resonance; oxidation

1. Introduction

Bacteriochlorophyll a is the core pigment in the natural light-harvesting processes and electron-transfer reactions of anoxygenic phototrophic bacteria (Figure 1) [1]. Bacteriochlorophyll a features a strong long-wavelength absorption band in the near-infrared (NIR) region [1]. The spectroscopic properties of bacteriochlorophyll a stem from the tetrahydroporphyrin macrocycle, termed a bacteriochlorin [2]. Synthetic bacteriochlorins are attractive due to their strong NIR absorption, resembling that of bacteriochlorophyll a, yet also require amenability to tailoring to meet the molecular design objectives for various photochemical applications ranging from artificial photosynthesis to photomedicine.
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Figure 1. Bacteriochlorophyll a, tolyporphin A, and synthetic bacteriochlorins.

A longstanding approach to prepare synthetic bacteriochlorins entails hydrogenation of a porphyrin [3,4]; one prominent example is provided by meso-tetraphenylbacteriochlorin [5,6] (Figure 1). While porphyrin hydrogenation is easily implemented, limitations of this approach include: (1) susceptibility of the tetrahydroporphyrin to adventitious dehydrogenation leading to the corresponding chlorin and porphyrin; (2) incompatibility with placement of auxochromes at the β-pyrrole positions for wavelength tuning; and (3) positional isomers if distinct patterns of meso-aryl groups are employed. Other methods for preparing bacteriochlorins include derivatization of porphyrins [7,8] yielding compounds such as I and II, or semisynthesis typically beginning with chlorophyll a or bacteriochlorophyll a [9,10]. Bacteriochlorophylls have not yet succumbed to total synthesis [11,12], but tolyporphin A diacetate, a derivative of one member of a family of dioxobacteriochlorins (Figure 1) isolated from a cyanobacterial culture [13,14], has been prepared in an elegant yet very lengthy synthesis [15–17].

As a compromise between the simplicity of porphyrin hydrogenation and the complexity of natural bacteriochlorin total synthesis, we have been developing de novo synthetic routes to stable, tailorable bacteriochlorins [18–20]. Such bacteriochlorins contain a gem-dimethyl group in each pyrroline ring to protect the macrocycle from adventitious oxidation. Two routes rely on the self-condensation of a dihydridopyrinn–acetal, either in an “Eastern-Western” (E-W) [18] or “Northern-Southern” (N-S) fashion, defined by the respective 3- versus 2-position of the gem-dimethyl group in the pyrroline ring of the dihydridopyrinn–acetal (compare III and IV, Scheme 1) [19]. The routes along with creative extensions by others [21–28] have enabled preparation of >100 bacteriochlorins with specific substituent patterns for diverse applications [29–36].
The E-W and N-S routes both afford stable, gem-dimethyl-substituted bacteriochlorins yet differ in the method of preparation of the respective dihydrodipyrrin–acetals: the N-S route enables facile incorporation of alkyl or aryl substituents at the meso-position of the dihydrodipyrrin whereas such groups are not easily incorporated in the E-W route. In both routes, the 1-methyl position appears available for incorporation of an aryl group, but chemistry to introduce such groups has heretofore not been accomplished [33]. Regardless of synthetic issues, a key consideration is the nature of the reactive intermediates in the self-condensation leading to the bacteriochlorin. The reaction of 1 under the standard mild conditions (TMSOTf and 2,6-di-tert-butylpyridine (DTBP) in CH₂Cl₂ at room temperature) afforded bacteriochlorin in 41% yield [37] (consistent with 30%–46% under other conditions [18,31]). The oxocarbenium ion 1a is a likely species in the head-to-tail dimerization process (Scheme 2) [33,38], although the extent to which the pyrrole participates in resonance-stabilization of the 1-oxocarbenium ion 1b has remained unclear. Attempts to employ a dihydrodipyrrin bearing a single alkoxy substituent at the 1-methyl position (2, R = Me; 3, R = Ph) under identical catalysis conditions (TMSOTf, DTBP in CH₂Cl₂) met with failure to form the bacteriochlorin (0% yield), which we attributed to the inability to form (2,3-i) or adequately stabilize (2,3-ii) the 1° carbenium ion [33]. We felt that incorporation of an electron-rich aryl group at the 1-methyl position would afford stabilization and enable synthesis of the corresponding meso-diarylbacteriochlorin.

In this paper, we describe the synthesis of several new dihydrodipyrrins wherein each is equipped with an aryl group and a single oxygen-containing substituent (hydroxy or acetoxy) at the 1-methyl group rather than the traditional acetal unit (Scheme 2). The dihydrodipyrrins incorporate the gem-dimethyl group at the 3-position for E-W condensations (V) or the 2-position for N-S condensations (VI), respectively. We then report studies concerning the reactivity of the dihydrodipyrrins (under conditions encompassing acids, solvents, and reaction time) for bacteriochlorin formation. One tetrahydrodipyrrin–acetal (compound 4) also has been prepared for comparison with the analogous dihydrodipyrrin–acetal 1 to understand the structural requirements for bacteriochlorin formation. To delineate the spectral effects of meso-aryl substitution, the absorption and fluorescence spectroscopic properties of three new bacteriochlorins (with two or four meso-aryl groups) are reported and compared with those of eight known bacteriochlorins. The fluorescence properties (fluorescence spectrum, fluorescence quantum yield) of four of the latter bacteriochlorins have not been previously examined. Here, the fluorescence properties are reported for the three new and four known synthetic bacteriochlorins.
2. Results

2.1. Reconnaissance

To gain access to meso-diarylbacteriochlorins in an E-W condensation, or meso-tetraarylbacteriochlorins in a N-S condensation, requires introduction of an aryl group at the dihydrodipyrrin 1-methyl site, and hence modification of the acetal (1,1-dimethoxymethyl) unit otherwise present at the 1-position (Scheme 3).

Scheme 3. Retrosynthetic analysis for incorporating meso-aryl groups via the E-W synthesis.
Prior synthetic efforts to install an aryl group for E-W synthesis (V), wherein the aryl group was incorporated at an early stage of the reaction (VII + VIII), were unsuccessful. The failure of the synthesis occurred upon attempted McMurry-type reductive cyclization (conversion of IX → V; Scheme 3); hence the conversion of the target dihydrodipyrrin V to the bacteriochlorin remained untested. Given this backdrop, we turned to examine an approach wherein a dihydrodipyrrin–carboxaldehyde X is treated with an aryl Grignard reagent to introduce the aryl group at the 1-methyl position. The resulting dihydrodipyrrin-1-carbinol (XI) bearing an α-aryl group can then be subjected to self-condensation or further derivatized.

2.2. Synthesis of Dihydrodipyrrin–Carbinols and Dihydrodipyrrin–Acetates

A wide variety of dihydrodipyrrin-carboxaldehydes are now known and could be examined for reaction with an aryl Grignard reagent. Dihydrodipyrrin–carboxaldehyde 5 bears two β-methyl groups and a stabilizing α-ester unit [36]. Treatment of 5 with commercially available p-tolylmagnesium bromide gave the target dihydrodipyrrin–carbinol 6a in 56% yield (Scheme 4). The reaction required 3.5 equiv of Grignard reagent for completion, in part due to the pyrrole NH unit, which is expected to consume one equiv of Grignard reagent. The carbinol 6a was subjected to acylation with acetic anhydride in the presence of DMAP, affording dihydrodipyrrin–acetate 6a-Ac in 92% yield (compound 6a-Ac and analogues; vide infra) is formally a dihydrodipyrrin-1-methyl acetate but is referred to hereafter in shorthand as a dihydrodipyrrin–acetate). The dihydrodipyrrin–acetate 6a-Ac was stable as a solid as well as for several weeks in CDCl₃ solution. Similarly, the reaction of 5 with p-anisylmagnesium bromide gave the dihydrodipyrrin–carbinol 6b in 46% yield, followed by acylation with Ac₂O/DMAP to give dihydrodipyrrin–acetate 6b-Ac in 85% yield. In all cases, workup of the Grignard reaction affording the dihydrodipyrrin–carbinol was achieved by treatment of the cooled reaction mixture with saturated aqueous NH₄Cl.

Scheme 4. Synthesis of dihydrodipyrrin–carbinols and dihydrodipyrrin–acetates.

Dihydrodipyrrin-carboxaldehydes bearing β-substituents other than dialkyl can be handled without the presence of an α-ester substituent. Thus, treatment of dihydrodipyrrin–carboxaldehyde
with p-tolylmagnesium bromide gave dihydrodipyrrin–carbinol 8a in 52% yield, followed by acetylation with Ac₂O/DMAP to form dihydrodipyrrin–acetate 8a-Ac in 85% yield (Scheme 4). Similar reaction of 7 with p-anisylmagnesium bromide followed by acetylation gave dihydrodipyrrin–acetate 8b-Ac. In each case, the modest yield of the dihydrodipyrrin–carbinol may stem in part due to the presence of the corresponding ketone, formed upon oxidation on standing. The corresponding dihydrodipyrrin–acetates were stable in solid form and in solution. The ketone 8a-Ox (a 1-p-toluoyl–dihydrodipyrrin) derived from dihydrodipyrrin–carbinol 8a was isolated and characterized by 1H-NMR spectroscopy, ESI-MS, and absorption spectroscopy; the latter exhibited longer wavelength absorption (451 nm) due to an increase in conjugation compared to 8a (340 nm). In summary, this route to aryl-substituted dihydrodipyrrin–carbinols is admittedly wasteful of the aryl Grignard reagent, but the latter is typically far less valuable than the dihydrodipyrrin–carboxaldehyde. Indeed, the aryl Grignard reagents employed herein were readily obtained in ample quantities from commercially suppliers.

2.3. Synthesis of Meso-Diarylbacteriochlorins (via E-W Route)

The self-condensation of 6a was first surveyed in CH₂CN containing BF₃·O(Et)₂, after which 6a-Ac (18 mM) was examined under a variety of acid catalysis conditions that have proved viable with dihydrodipyrrin–acetals (including BF₃·O(Et)₂ in CH₂CN, TMSOTf and DTBP in CH₂Cl₂, and neat TFA) typically at room temperature open to air (see Appendix A for the results from the survey herein, as well as literature references to the origin and development of these catalysis conditions). The reaction was carried out with exposure to air given the necessity for a 2e⁻/2H⁺ oxidation in bacteriochlorin formation. The reactions were monitored by absorption spectroscopy and laser-desorption mass spectrometry (LD-MS). The yield of diarylbacteriochlorin in crude samples was assessed by absorption spectroscopy of the Qy band (~726 nm, assumed εQy = 120,000 M⁻¹·cm⁻¹ [18]) without isolation (“spectroscopic yield”). The best conditions identified for dihydrodipyrrin–carbinol 6a (140 mM BF₃·O(Et)₂ in CH₂CN at reflux for 2 h exposed to air) afforded meso-di-p-tolylbacteriochlorin B1-T₂ in 4.3% spectroscopic yield (Scheme 5). On the other hand, dihydrodipyrrin–acetate 6a-Ac gave B1-T₂ in 22% spectroscopic yield under the same conditions.

The spectroscopic yield is determined without purification and isolation of the product, a longstanding method in tetrapyrrole chemistry enabled by the intense and characteristic absorption bands of the tetrapyrrole macrocycle. Such bands appear in the near-ultraviolet, visible, and near-infrared region for bacteriochlorins, are typically well-separated from—and more intense than—absorption bands due to impurities; accordingly, the presence and yield of the bacteriochlorin can be assessed even in low yields in the presence of a large quantity of impurities including reaction intermediates and unreacted starting material.

To isolate the bacteriochlorin, the self-condensation of dihydrodipyrrin–acetate 6a-Ac was carried out at ~30-fold increased scale (0.069 mmol, 32 mg), whereupon B1-T₂ was obtained in 16% yield (3.3 mg) (Scheme 5). In this and subsequent examples, the isolated yield is invariably lower than the spectroscopic yield, a phenomenon that is attributed to losses upon purification and handling of small quantities of product. In this regard, the spectroscopic yield provides an unvarnished view of the potential of the chemistry. Unless noted otherwise, the reported yield in each case is the isolated yield. The bacteriochlorin was characterized by 1H-NMR spectroscopy, ESI-MS, LD-MS, and absorption spectroscopy. Bacteriochlorin B1-T₂, which bears four methyl and two p-tolyl groups, is stable as a solid but slowly decomposed upon standing in CDCl₃, despite treatment with K₂CO₃. The similar self-condensation of dihydrodipyrrin–acetate 6b-Ac afforded meso-di-p-anisylbacteriochlorin B1-A₂ in 25% spectroscopic yield. An increase (37% spectroscopic yield) was observed upon prolonging the reaction time to 4 h at reflux, or performing the reaction at room temperature for 24 h (41% spectroscopic yield). Limited solubility thwarted chromatographic purification, and attempts to purify by washing with organic solvents or crystallization also failed to give a pure product. The bacteriochlorin B1-A₂ was characterized by absorption spectroscopy and MALDI-MS (matrix POPOP [39]).
Dihydropyrrin–acetates \(8\text{a-Ac}\) and \(8\text{b-Ac}\) differ from \(6\text{a-Ac}\) and \(6\text{b-Ac}\) in the presence of a pyrrole \(\beta\)-carbethoxy group and the absence of a pyrrole \(\alpha\)-ester substituent. The self-condensation of \(8\text{a-Ac}\) in CH\(_3\)CN containing BF\(_3\)·O(Et)\(_2\) at room temperature for 24 h gave bacteriochlorin in 3% yield by absorption spectroscopy. Under reflux for 4 h, bacteriochlorin was observed in 20% yield (absorption spectrum) and the isolated yield of meso-di-\(p\)-tolylbacteriochlorin \(8\text{b-T2}\) was 12% (Scheme 5). The reactivity of \(8\text{a-Ac}\) is lower than that of dihydropyrrin–acetate \(6\text{a-Ac}\), as longer reaction time was required under reflux, and the reaction at room temperature was sluggish. The self-condensation of \(8\text{b-Ac}\) under BF\(_3\)·O(Et)\(_2\) at room temperature for 24 h gave bacteriochlorin \(8\text{b-A2}\) (16%), and \(8\text{a-Ac}\) gave \(8\text{b-T2}\) (3%) under similar conditions. The self-condensation under reflux for 2 h also gave \(8\text{b-A2}\) (28% spectroscopic yield; 16% isolated yield).

The greater yield in the self-condensation of dihydropyrrin–acetate \(6\text{a-Ac}\) (16%) versus dihydropyrrin–carbinol \(6\text{a}\) (4.3%) prompted examination of other, perhaps better leaving groups. However, attempts at \(O\)-derivatization of \(8\text{a}\) with tosyl chloride, mesyl chloride, trichloroacetic anhydride, trifluoroacetic anhydride, and triflic anhydride in the presence of various bases (DMAP, Et\(_3\)N, pyridine, DBU, NaOH, NaH) did not afford a clean reaction. By contrast, acylation of \(8\text{a}\) with...
acetic anhydride in the presence of DMAP gave a fairly clean reaction and the product was obtained in 85% yield. Two noteworthy points even for reaction with Ac₂O/DMAP are that the reaction time should be short and should be carried out in non-chlorinated solvents, otherwise the oxidized product (e.g., 8a-Ox) predominates.

2.4. Synthesis of a Meso-Tetraarylbacteriochlorin (via the N-S Route)

We turned our attention to the synthesis of a meso-tetraarylbacteriochlorin (B₃-P₂T₂). Access to B₃-P₂T₂ can be achieved in principle by pre-installation of one aryl group at the dihydrodipyrrin meso position, and the other at the α-methyl position. Such an approach requires use of the N-S route. Thus, the Pd-mediated coupling of acid precursor 9 [40] and iodopyrrole 10 [19] gave the lactone–pyrrole 11 in 68% yield. Treatment of the latter with the Petasis reagent afforded 12 in 67% yield. Hydrolysis of 12 and a subsequent Paal-Knorr type ring closure gave dihydrodipyrrin 13 as the major compound, accompanied by a very minor amount of the corresponding E-isomer. Oxidation of 13 with SeO₂ furnished dihydrodipyrrin–carboxaldehyde 14 in 65% yield. Treatment of 14 with p-tolylmagnesium bromide afforded the dihydrodipyrrin–carbinol 15 in 56% yield. Subsequent acetylation with acetic anhydride/DMAP gave the desired dihydrodipyrrin–acetate 15-Ac in 92% yield (Scheme 6).

The self-condensation of 15-Ac following the conditions identified above (r.t. or 80 °C) did not furnish any bacteriochlorin, which prompted examination of a variety of acid catalysts (see Appendix A).
The best conditions identified (p-TsOH·H2O, AcOH, 80 °C, in air) gave tetraaryl bacteriochlorin B3-P2 T2 in up to 2% spectroscopic yield. As an alternative route, dihydrodipyrrin–carbinol 15 was examined for self-condensation but no bacteriochlorin was observed upon use of neat TFA. Upon use of trifluoroacetic anhydride (TFAA), dihydrodipyrrin–carbinol 15 in CH2Cl2 gave the tetraaryl bacteriochlorin B3-P2 T2 in up to 17% spectroscopic yield (see Appendix A) and 13% isolated yield (Scheme 6). The reaction likely proceeds via the dihydrodipyrrin-1-methyl trifluoroacetate intermediate (not shown) formed in situ. Tetraaryl bacteriochlorin B3-P2 T2 was characterized by 1H-NMR spectroscopy, ESI-MS, MALDI-MS and absorption spectroscopy. The absorption and fluorescence properties of the bacteriochlorins are described in the final section.

2.5. A Tetrahydrodipyrrin for Bacteriochlorin Formation

In chlorin synthetic chemistry, tetrahydrodipyrrins—lacking a double bond bridging the pyrrole and pyrroline motifs—have proved superior to dihydrodipyrrins [41]. The origin of the superiority has been regarded to stem from the greater stability upon handling of tetrahydrodipyrrins versus dihydrodipyrrins. Hence, we sought to examine the use of a tetrahydrodipyrrin–acetal for comparison with the dihydrodipyrrin–acetal in conversion to the bacteriochlorin. The synthesis of a tetrahydrodipyrrin–acetal follows the procedure established previously for a tetrahydrodipyrrin–acetal lacking a p-tolyl group [42]. Deprotonation of pyrrole-2-carboxaldehyde 16 [31] with sodium hydride followed by treatment with p-tosyl chloride afforded 17 in 82% yield (Scheme 7). Subsequent nitro–aldol condensation followed by reduction with NaBH4 [43] afforded nitroethylpyrrole 18 in 48% yield. The Michael addition of 18 and α,β-unsaturated ketone 19 [33] in the presence of DBU for 24 h at room temperature afforded 20 in 21% yield. Reductive cyclization of 20 in the presence of zinc dust in ethanolic acetic acid afforded tetrahydrodipyrrin-N-oxide 21 in 42% yield. The use of ammonium formate [43] rather than ethanolic acetic acid was found to lead to the loss of the acetal moiety [42]. Deoxygenation of 21 with TiCl4 and LiAlH4 gave 22 in 82% yield. The p-tosyl group was removed when 22 was treated overnight with TBAF at room temperature, thereby affording 4 in 82% yield. The use of p-tosyl protection may be a significant beneficial factor in the synthesis of 4, particularly in the deoxygenation of the pyrroline-N-oxide (21 → 22); similar deoxygenation of an analogue lacking both the p-tolyl group and p-tosyl protection proceeded in only 8% yield [42] versus 82% here.

With tetrahydrodipyrrin–acetal 4 in hand, comparison with the reaction of dihydrodipyrrin–acetal 1 was examined. The self-condensation conditions (5 equiv of TMSOTf and 20 equiv of DTBP in CH2Cl2) employed [31] for diverse dihydrodipyrrin–acetals were modified to use a lesser amount of reagents (4 equiv of TMSOTf and 8 equiv of DTBP), which emerged from a factorial design study [37]. Application of the latter conditions with dihydrodipyrrin–acetal 1 [18,31] gave the known [18] 5-methoxy-8,8,18,18-tetramethyl-2,12-di-p-tolylbacteriochlorin (B5) in 41% yield [37], whereas tetrahydrodipyrrin–acetal 4 decomposed and gave no B4 or any other bacteriochlorin. The sole difference between 1 and 4 is the presence of a double bond rather than a single bond linking the pyrrole and pyrroline units of the hydrodipyrrin.

2.6. Spectroscopic Properties

The absorption and fluorescence features of the meso-aryl bacteriochlorins are summarized in Table 1. The absorption and fluorescence spectra of meso-di-p-tolylbacteriochlorin B1-T2 displayed in Figure 2 are representative. The fluorescence spectrum of each bacteriochlorin was obtained upon illumination into the Qx band of samples in toluene at room temperature. The Φf value was determined by comparison with 8,8,18,18-tetramethyl-2,12-di-p-tolylbacteriochlorin (B5, Figure 3), which has Φf = 0.14 [18,44].
Table 1. Absorption and Fluorescence Spectral Properties of meso-Arylbacteriochlorins a.

| Compound | $\lambda_{Bx}$ abs (nm) | $\lambda_{Bx}$ abs (nm) | $\lambda_{Qx}$ abs (nm) | $\lambda_{Qy}$ abs (nm) | $\lambda_{Qy}$ ems (nm) | $\Phi_f$ b |
|----------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-----------|
| B1-T2    | 356                     | 382                     | 503                     | 726                     | 729                     | 0.12      |
| B2-T2    | 357                     | 381                     | 516                     | 739                     | 747                     | 0.15      |
| B3-P2-T2 | 362 c                   | 382                     | 533                     | 743                     | 757                     | 0.15      |

a In toluene at room temperature; b Fluorescence quantum yield; c Shoulder.

The characteristic features of diverse synthetic bacteriochlorins include an absorption feature in the near-ultraviolet region (B bands); an absorption band in the green region (Qx band); an absorption band $>700$ nm (Qy band), which is often quite sharp with full-width-at-half maximum (fwhm) of $\sim 20$ nm; a commensurably sharp fluorescence band with small Stokes shift relative to the Qy absorption band; and modest fluorescence quantum yield ($\Phi_f$) in the range 0.05–0.20. The meso-arylbacteriochlorins prepared herein largely display these features.
with the dihydrodipyrrin lacking an aryl group (Scheme 2) is at best tentative—the prior studies of 2 or 3 employed TMSOTf/DTBP and gave 0% yield, whereas the same conditions here with 6a gave ~1% yield, yet self-condensation mediated by BF₃·O(Et)₂ in CH₃CN at reflux with 6a-Ac gave 22% spectroscopic yield (see Appendix A). A more extensive matrix of studies concerning substrates and conditions is required to draw firm conclusions, yet the body of data assembled to date concerning substrates and conditions is required to draw firm conclusions, yet the body of data assembled to date

3. Discussion

New routes to tailored bacteriochlorins are required to fully access the NIR spectral region. meso-Arylbacteriochlorins are of interest in this regard. In this section, we discuss the following features of the chemistry: (1) summation of knowledge concerning the essential motifs in the hydrodipyrrin unit for successful conversion to the bacteriochlorin; (2) comparison with other routes in tetrapyrrole chemistry; (3) necessity for dehydrogenation in the reaction; (4) advantages and limitations of the synthesis; and (5) spectral properties of the meso-aryl bacteriochlorins.

3.1. Essential Motifs

The failure of the tetrahydrodipyrrin–acetal (4) to form a bacteriochlorin, whereas the analogous dihydrodipyrrin–acetal (1) reacts smoothly, suggests the importance of a resonance-stabilized oxocarbenium ion intermediate (Scheme 8). The conjugation of the pyrrole and pyrroline units in the dihydrodipyrrin permits resonance delocalization (1b) whereas such conjugation is absent in the tetrahydrodipyrrin (4a). An alternative interpretation is that the coplanar architecture of the dihydrodipyrrin–acetal permits reaction whereas the tetrahedral carbons in the tetrahydrodipyrrin–acetal do not afford an architecture suitable for macrocyclization. While a possibility, we note that tetrahydrodipyrrins are used as the Western half in successful chlorin–forming reactions [41].

The acetal unit has been the dominant group installed at the dihydrodipyrrin 1-position, and also has been the object of the most extensive refinement, yet other groups also have been explored [33,36]. Here, substitution of the 1-methyl group with both an aryl group and a hydroxy or acetoxy substituent gave rise to the corresponding bacteriochlorin, which is attributed to the stabilization imparted by the aryl group, with p-anisyl superior to p-tolyl for obvious electronic reasons (Scheme 9). A comparison with the dihydrodipyrrin lacking an aryl group (2 or 3, Scheme 2) is at best tentative—the prior studies of 2 or 3 employed TMSOTf/DTBP and gave 0% yield, whereas the same conditions here with 6a gave ~1% yield, yet self-condensation mediated by BF₃·O(Et)₂ in CH₃CN at reflux with 6a-Ac gave 22% spectroscopic yield (see Appendix A). A more extensive matrix of studies concerning substrates and conditions is required to draw firm conclusions, yet the body of data assembled to date
suggests that more extensive resonance stabilization of the intermediate dihydrodipyrrin (versus the tetrahydrodipyrrin) facilitates formation of the corresponding bacteriochlorin.

![Scheme 8. Resonance stabilization in a dihydrodipyrrin but not tetrahydrodipyrrin.](image)

3.2. Comparison of Routes

The dihydrodipyrrin–carbinols and dihydrodipyrrin–acetates employed herein are ostensibly similar to other compounds used in tetrapyrrole syntheses (Scheme 10). A dipyrromethane–carbinol (XII) undergoes self-condensation in the presence of acid to give the porphyrinogen, which upon \(6\text{e}^-/6\text{H}^+\) oxidation (e.g., by 3 DDQ) gives the corresponding \(\text{meso}-\text{trans-}A_2B_2\)-porphyrin [45,46]. Analogous routes have provided access to \(\text{meso}-\text{aryl}tetrabenzoporphyrins\) (not shown) [47]. The Ph.D. thesis of O’Neal (under the guidance of Jacobi) describes the preparation of dihydrodipyrrins (XIII,

![Scheme 9. Putative intermediates en route to bacteriochlorins.](image)
XIV) for examination in routes to meso-trans-AB-bacteriochlorins (e.g., XIII + XIV \(\rightarrow\) XV). One of the dihydrodipyrrins (XIII) bears an \(\alpha\)-acetoxymethyl group, and both contain gem-dimethyl groups at the 2-position, engendering a N-S joining process. While pioneering in terms of dihydrodipyrrin synthetic methodology, to our knowledge a successful route to bacteriochlorins was not achieved [48].

3.3. Dehydrogenation

A dihydrodipyrrin–acetal is at the same oxidation level as the corresponding monomethoxybacteriochlorin. A critical difference between the self-condensation of a dihydrodipyrrin–acetal and a dihydrodipyrrin–acetate is the requirement for dehydrogenation in the latter process: the dihydrodipyrrin–acetal self-condensation proceeds via the trans-dimethoxy-dihydrobacteriochlorin (XVI), which upon elimination of one molecule of methanol affords the monomethoxy-bacteriochlorin directly. In contrast, the dihydrodipyrrin–acetate affords the trans-diaryl-dihydrobacteriochlorin (XVII), which upon subsequent dehydrogenation (2e\(^{-}\)/2H\(^{+}\) oxidation) gives the bacteriochlorin lacking any meso-methoxy groups (Scheme 11).

In chlorin syntheses, reduced precursors (e.g., a tetrahydrodipyrrin or a dihydrodipyrrin; and a dipyrromethane) are employed, whereupon in situ oxidation affords the chlorin macrocycle [41]. In porphyrin syntheses, diverse reaction pathways afford porphyrinogens (i.e., hexahydroporphyrins), which undergo smooth dehydrogenation (6e\(^{-}\)/6H\(^{+}\) oxidation) to give the porphyrin macrocycle [46]. The dihydrobacteriochlorin (XVII) can equally be regarded as a bacteriochlorinogen precursor to the bacteriochlorin, in the same manner as a porphyrinogen is a precursor to the porphyrin. Thus, the use of reduced precursors in and of itself is not expected to cause adverse effects in the reactions of the various dihydrodipyrrin–carbinols and dihydrodipyrrin–acetates examined herein, although we note that in the synthesis of corrins, Eschenmoser emphasized the use of precursors at the same oxidation level as the target corrin macrocycles [49]. To gain a deep understanding of the role of oxidation state in forming bacteriochlorins may require study of a larger set of substrates, isolation of the corresponding hydrobacteriochlorin (i.e., bacteriochlorinogen) intermediates, and examination of the susceptibility of the latter toward dehydrogenation yielding bacteriochlorins.
3.4. Meso-Arylbacteriochlorins

The route described herein provides access to meso-trans-A₂B₂-bacteriochlorins and meso-trans-A₂B₂-bacteriochlorins, albeit with several present limitations. The limitations include (1) low yields of macrocycle formation; (2) requirement to use a Grignard reagent to install the aryl unit; and (3) likely restriction to use of electron-rich aryl units.

An alternative route to trans-A₂-bacteriochlorins entails use of the N-S route. Advantages of the route described herein include the following: (1) use of the E-W route to construct the dihydrodipyrrin–carboxaldehyde on the path to trans-A₂-bacteriochlorins; and (2) use of the N-S route to prepare trans-A₂B₂-bacteriochlorins, which have previously been inaccessible (although see Sutton et al. [50] for meso-trans-AB-bacteriochlorins bearing vic-diols at the pyrrole β-positions; e.g., II in Figure 1). Mono-arylbacteriochlorins have previously been prepared by selective bromination of a 5-methoxybacteriochlorin (from the E-W route) at the 15-position. Subsequent Pd-mediated coupling enabled installation of diverse aryl or other groups [29,32,35], whereas control of bromination was elusive with bacteriochlorins lacking a 5-alkoxy group [29]. Thus, routes to stable, gem-dimethylbacteriochlorins bearing 1, 2 or 4 meso-aryl groups have now been sketched out. The availability of such bacteriochlorins enables spectroscopic comparisons, as described in the next section.

3.5. Spectroscopic Properties

The synthetic meso-arylbacteriochlorins exhibit spectral features characteristic of members of the bacteriochlorophyll family. The meso-arylbacteriochlorins exhibit relatively sharp absorption and fluorescence bands along with Φₜ values in the range 0.1–0.2, all of which are typical of bacteriochlorins that lack aryl substituents. Tetrapyrrrole macrocycles that are highly distorted typically exhibit bathochromically shifted absorption bands accompanied by low Φₜ values [51,52]. The meso-arylbacteriochlorins prepared herein do not fall into the family of highly distorted macrocycles, at least to the extent that the absorption and fluorescence properties are relevant proxies.

The presence of meso-aryl groups does give rise to noticeable shifts in band location and in one case slight broadening (but in no case are gross distortions of the spectra observed). Such effects are delineated here upon comparison against a set of synthetic bacteriochlorins that lack meso-aryl substituents. Here, the spectral properties of three new synthetic bacteriochlorins are compared with those of seven benchmark bacteriochlorins (Figure 4) as well as that of meso-tetraphenylbacteriochlorin (TPBC, Figure 1). The bacteriochlorins in Figure 4 enable incisive comparisons as follows.
(1) Bacteriochlorins B1 [36], B2 [31,44], iso-B2 [19], B3 [19], and B6 [36] contain no meso-aryl groups and serve as benchmarks to gauge the effects of meso-aryl incorporation.

(2) Bacteriochlorins B2 and iso-B2 are positional isomers (due to swapping the positions of the β-ethyl and β-carbethoxy groups).

(3) Bacteriochlorins in the second row (B1-T2, B2-T2, and iso-B2-T2 [19]) differ from the first row (B1, B2, iso-B2) in the presence of two meso-aryl groups.

(4) Bacteriochlorins in the third row (B3, B3-T2 [19], and B3-P2T2) each contain two β-carbethoxy groups but differ in the number (0, 2, 4) of meso-aryl groups.

Figure 4. Ten bacteriochlorins for spectroscopic comparisons; the position of the long-wavelength (Qy) absorption band is included for ease of comparison. New compounds are labeled in red.

The absorption spectra of the 11 bacteriochlorins are summarized in Table 2 in pairwise fashion with the benchmark bacteriochlorin (above) and meso-arylbacteriochlorins (below). As a prelude
to in-depth consideration of the effects of meso-aryl substituents on photophysical properties of bacteriochlorins, the following features warrant comment.

(1) Bacteriochlorin positional isomers B2 and iso-B2 exhibit absorption and fluorescence spectral properties that are nearly identical with each other.

(2) β-Carbethoxy groups are established auxochromes in bacteriochlorins [53]. The presence of two β-carbethoxy groups in B3 (754 nm) causes a bathochromic shift of the Qy absorption band by 41 nm compared to that of the unsubstituted benchmark bacteriochlorin B6 (713 nm).

(3) Aryl groups also serve as auxochromes in bacteriochlorins upon incorporation at the meso- or β-positions. Two β-aryl groups (2,12- or 3,13-diarylbacteriochlorins) cause a bathochromic shift of the Qy absorption band by ~23 nm relative to that of B6 [30], whereas a single meso-aryl group typically causes a bathochromic shift of the Qy absorption band by 3 to 6 nm [29].

| Compound          | λBx (Δb) (nm) | λBx (Δb) (nm) | λQx (Δb) (nm) | λQy (Δb) (nm) | Qy fwhm (Δb) (nm) | ΣQy/ΣT |
|-------------------|---------------|---------------|---------------|---------------|------------------|--------|
| iso-B2            | 355           | 384           | 521           | 760           | 20               | 0.126  |
| iso-B2-T2         | 362 (+7)      | 388 (+4)      | 535 (+14)     | 759 (~1)      | 25 (+5)          | 0.117  |
| B2                | 354           | 383           | 521           | 760           | 20               | 0.136  |
| B2-T2             | 357 (+3)      | 381 (~2)      | 516 (~5)      | 739 (~21)     | 22 (+2)          | 0.106  |
| B1                | 346           | 374           | 490           | 721           | 12               | 0.107  |
| B1-T2             | 356 (+10)     | 382 (+8)      | 503 (+13)     | 726 (+5)      | 14 (+2)          | 0.101  |
| B3                | 352           | 379           | 523           | 754           | 16               | 0.133  |
| B3-T2             | 361 (+1)      | 383           | 543 (+20)     | 759 (+5)      | 16 (+0)          | 0.125  |
| B3-P3-T2          | 362 (+6)      | 382           | 533 (+10)     | 743 (~11)     | 27 (+11)         | 0.100  |
| B6                | 340           | 365           | 489           | 713           | 12               | 0.091  |
| TPBC a            | 355 (+15)     | 378 (+13)     | 522 (+33)     | 742 (+29)     | 15 (+3)          | 0.091  |

a In toluene at room temperature; b Shift compared to the corresponding benchmark bacteriochlorin lacking meso-aryl substituents; c Ratio of the integrated intensities of the Qy band (ΣQy) versus the integrated intensity of the full spectrum (ΣT, 300–900 nm) for spectra plotted in wavenumber (cm⁻¹); d [53]; e [36]; f 373 nm; g Shoulder; h [6].

The absorption spectra of the bacteriochlorins are shown in Figure 5, where (1) spectra of the meso-aryl/bacteriochlorins are plotted in solid lines; and (2) benchmark bacteriochlorins (lacking meso-aryl substituents) are plotted in dotted lines. The y-axis scales (integrated energy, see Materials and Methods) are set equal across the panels A to F to facilitate comparison of integrated absorption intensities. Comparison of the absorption spectra of iso-B2 and iso-B2-T2 highlights the effect of meso-aryl substituents (Figure 5, Panel A):

(1) The position of the Qy absorption band is nearly unchanged, while a hypochromic change is observed together with an increase in the fwhm by 5 nm for iso-B2-T2.

(2) The Bx, Bx, and Qx absorption bands exhibit bathochromic shifts (+7, +4, and +14 nm, respectively) for iso-B2-T2. At odds with this observation, the absorption spectra of B2 and B2-T2 are distinct from each other (Figure 5, Panel B). Compared to the benchmark bacteriochlorin B2, B2-T2 shows a large (21 nm) hypsochromic shift of the Qy absorption band, together with a large hypochromic change (~40% decline), while the fwhm is slightly increased. The positions of the Bx, Bx, and Qx absorption bands of B2 and B2-T2 are relatively unchanged.

(3) The contrasting results for the meso-di-p-tolylbacteriochlorins B2-T2 and iso-B2-T2 are quite surprising, since the two are positional isomers, where the only structural difference is the swapped position of the β-ethyl and β-carbethoxy groups. Reasonable expectations are that the absorption spectra of B2-T2 and iso-B2-T2 should be nearly identical, as shown for their respective non-aryl analogues B2 and iso-B2. The origin of the hypsochromic shift of the Qy...
absorption band due to pairwise juxtaposition of a β-carbethoxy group and a meso-aryl substituent remains unclear.

The effects of meso-aryl substituents on the absorption spectra are further highlighted with additional examples. The absorption spectrum of B1 (which lacks β-carbethoxy groups) is compared with that of the corresponding meso-di-p-tolylbacteriochlorin B1-T2 (Figure 5, Panel C). The B_y, B_x, Q_x, and Q_y absorption bands of B1-T2 exhibit bathochromic shifts (+10, +8, +13, and +5 nm, respectively) compared to those of benchmark bacteriochlorin B1. Similar effects are observed upon comparison of B3 and B3-T2, where the p-tolyl substituents are introduced at distal (non-adjacent) meso-positions relative to the β-carbethoxy groups (Figure 5, Panel D, see dashed and grey solid lines). The Q_x and Q_y absorption bands of B3-T2 exhibit bathochromic shifts (+20 and +5 nm, respectively) compared to those of benchmark bacteriochlorin B3 (but comparison of the B_y, B_x bands is thwarted by the further apparent split into three peaks).
Moving from bacteriochlorin B3-T2 to B3-P2T2, where two additional meso-p-tolyl substituents are present, juxtaposes the β-carbethoxy groups and the meso-p-tolyl substituents. As described above for B2 and B2-T2, such an arrangement causes a significant hypsochromic shift of the Qy absorption band. Indeed, the absorption spectra of B3-T2 and B3-P2T2 exhibit similar trends. Compared to B3-T2, bacteriochlorin B3-P2T2 shows a large (16 nm) hypsochromic shift of the Qy absorption band, together with a large hypochromic change (~50% decline) and an increase in fwhm (by 11 nm).

In summary, two examples now illustrate that the expected auxochromic effect of the β-carbethoxy groups is canceled by the meso-aryl substituents adjacent thereto (Figure 5, Panel B and Panel D). Such effects may accrue from structural and/or electronic factors, the origin of which will require structural studies and density functional theory calculations, as well as further examples.

A final comparison concerns the spectral properties of meso-tetraphenylbacteriochlorin (TPBC). The study of synthetic bacteriochlorins largely originated (ca. 1950s) with the first report of the preparation of meso-tetraphenylbacteriochlorin (TPBC) [54] and was significantly enabled by the subsequent synthetic method of Whitlock and coworkers [6]. The Bγ, Bx, Qx, and Qy absorption bands of TPBC exhibit bathochromic shifts (+15, +13, +33, and +29 nm, respectively) compared to those of benchmark bacteriochlorin B6 (Figure 5, Panel E).

The fluorescence properties of the new meso-arylbacteriochlorins (B1-T2, B2-T2, B3-P2T2) and relevant benchmark bacteriochlorins are summarized in Table 3. The fluorescence properties of known bacteriochlorins iso-B2, iso-B2-T2, B3 and B3-T2 have not been previously reported whereas those of B1 [36] and B2 [44,53] are known. The seven newly reported Φf values here were determined with B5 (Φf = 0.14 [18]) as a common reference standard, which also was used as the standard for B2 [44,53]. The same value for B2 was found upon use of an integrating sphere [36], an approach also employed for B1 [36]. Hence, all of the values reported in Table 3 share a common reference and/or are self-consistent where distinct methods of determination were employed. The fluorescence spectra and yields were typically acquired upon excitation into the Qx band near 500 nm. The fluorescence spectra of nine bacteriochlorins are shown in Figure 6. The major findings are as follows:

1. The difference in position of the Qy fluorescence band versus that of the benchmarks (Δ) corresponds very well to the difference of the Qy absorption band compared to that of benchmarks (Δ), except for that of B3-P2T2. The position of the Qy fluorescence band of B3-P2T2 was unchanged compared to that of benchmark B3, which results in a large Stokes shift (vide infra).

2. The Stokes shift of each benchmark bacteriochlorin lacking meso-aryl substituents is small (<70 cm⁻¹ (<4 nm)). On the other hand, meso-arylbacteriochlorins exhibit larger Stokes shifts (>120 cm⁻¹ (>7 nm)), and B3-P2T2 shows the largest Stokes shift (250 cm⁻¹ (12 nm)).

3. The presence of meso-aryl substituents causes broadening of the fluorescence spectra. Such an effect is most pronounced for B3-P2T2, where the fwhm has almost doubled (34 nm, +16 nm) compared to that of benchmark bacteriochlorin B3 (18 nm).

4. The fluorescence quantum yield (Φf) of meso-arylbacteriochlorins is increased (1.2–1.6 times) compared to that of the benchmarks lacking meso-aryl substituents.

In summary, the meso-arylbacteriochlorins exhibit absorption spectra, fluorescence spectra, and fluorescence quantum yields that are characteristic of exemplary members of the family of natural and synthetic bacteriochlorins, along with spectral shifts and broadening in specific instances.
prepared as described in the literature and confirmed for purity by 1H-NMR spectroscopy. The known, non-commercial compounds or protonated molecular ion. THF used in all reactions was freshly distilled from Na/benzophenone ketyl. The known bacteriochlorins are summarized in Table 3. The fluorescence properties of the new known bacteriochlorins (1) The difference in position of the Qy fluorescence band versus that of the benchmarks (spectra of nine bacteriochlorins are shown in Figure 6. The major findings are as follows: (2) The Stokes shift of each benchmark bacteriochlorin lacking meso-aryl substituents causes broadening of the fluorescence spectra. Such an effect is most pronounced for B3-P (dotted) and B2-T (solid); (3) The presence of -aryl substituents compared to that of the benchmarks lacking -aryl substituents is increased (1.2–1.6 times) which results in a large Stokes shift (18 nm). (4) The fluorescence quantum yield (Φ) of B2-T (solid); (dotted) and B3-P (dotted) and B3-T (grey), and B3-P_T (solid).

Table 3. Fluorescence Spectral Properties of Bacteriochlorins a.

| Compound        | λQy (Δ b) (nm) | fwhm (Δ b) (nm) | Δν (cm⁻¹) c | Φf d |
|-----------------|---------------|----------------|-------------|-----|
| iso-B2          | 764           | 20             | 70          | 0.11|
| iso-B2-T₂       | 766 (+2)      | 25 (+5)        | 120         | 0.15|
| B2 e            | 764           | 21             | 60          | 0.14|
| B2-T₂           | 747 (−17)     | 27 (+6)        | 140         | 0.15|
| B1 f            | 723           | 14             | 40          | 0.10|
| B1-T₂           | 729 (+6)      | 18 (+4)        | 60          | 0.12|
| B3              | 757           | 18             | 50          | 0.12|
| B3-T₂           | 761 (+3)      | 18 (0)         | 35          | 0.16|
| B3-P₂T₂         | 757 (0)       | 34 (+16)       | 250         | 0.15|

a In toluene at room temperature; b Shift compared to the corresponding benchmark bacteriochlorin lacking meso-aryl substituents; c Stokes shift; d Fluorescence quantum yield; e [36]; f [36].

Figure 6. Fluorescence spectra of bacteriochlorins in toluene at room temperature. (A) iso-B2 (dotted) and iso-B2-T₂ (solid); (B) B2 (dotted) and B2-T₂ (solid); (C) B1 (dotted) and B1-T₂ (solid); (D) B3 (dotted), B3-T₂ (grey), and B3-P₂T₂ (solid).

4. Materials and Methods

4.1. General Methods

1H-NMR (300 MHz) and 13C-NMR (75 MHz) spectra were collected at room temperature in CDCl₃ unless noted otherwise. Absorption spectra were obtained in toluene at room temperature unless noted otherwise. Electrospray ionization mass spectrometry (ESI-MS) data are reported for the molecular ion or protonated molecular ion. THF used in all reactions was freshly distilled from Na/benzophenone ketyl. The known, non-commercial compounds 5 [36], 7 [34], 9 [40], 10 [19], 16, [31], and 19 [33] were prepared as described in the literature and confirmed for purity by 1H-NMR spectroscopy.
4.2. Self-Condensation Study

Following the procedure employed previously to gauge suitability of dihydrodipyrrin substrates [33,37], a solution of tetrahydrodipyrrin–acetal 4 (0.014–0.047 mmol, 18 mM) and DTBP (8 mol equiv) in anhydrous CH$_2$Cl$_2$ was treated with TMSOTf (4 molar equiv) at room temperature. The reaction mixture was stirred overnight, then diluted with CH$_2$Cl$_2$ and quenched by the addition of saturated aqueous NaHCO$_3$. After extraction, the organic phase was washed (water, brine), dried (Na$_2$SO$_4$) and concentrated. The crude sample was analyzed for the presence of bacteriochlorin by TLC, LD-MS and absorption spectroscopy.

4.3. Synthesis and Characterization

2,3,4,5-Tetrahydro-1-(dimethoxymethyl)-3,3-dimethyl-7-(4-methylphenyl)dipyrrin (4). Following a reported procedure [42] with some modification, a sample of 22 (200 mg, 0.426 mmol) was treated with TBAF (1.3 mL, 1.3 mmol, 1.0 M in THF) under argon. The reaction mixture was stirred overnight at reflux. Saturated aqueous NaHCO$_3$ was added, and the mixture was extracted with ethyl acetate. The organic extract was washed (brine), dried (Na$_2$SO$_4$), and chromatographed (silica, CH$_2$Cl$_2$/ethyl acetate (4:1)) to afford a yellow oil (118 mg, 82%): $^{1}$H-NMR $\delta$ 0.95 (s, 3H), 1.12 (s, 3H), 1.27 (s, 3H), 2.43, 2.51 (AB, $J$ = 17.4 Hz, 2H), 2.64 (ABX, $J$ = 11.7 Hz, 1H), 2.05 (ABX, $J$ = 2.9 Hz, J = 15.2 Hz, 1H), 3.45 (s, 6H), 3.76–3.79 (m, 1H), 4.87 (s, 1H), 6.28–6.30 (m, 1H), 6.75–6.77 (m, 1H), 7.18 (d, $J$ = 3.0 Hz, 2H), 7.31 (d, $J$ = 8.1 Hz, 2H), 9.95 (br, 1H); $^{13}$C-NMR (100 MHz) $\delta$ 79.7, 103.5, 118.9, 120.3, 125.7, 127.4, 129.5, 130.0, 132.6, 138.8, 142.1, 149.3, 75.7, 79.7, 103.5, 118.9, 120.3, 125.7, 127.4, 129.5, 130.0, 132.6, 138.8, 161.1, 161.9, 170.3, 176.8; ESI-MS obsd 423.2225, calcld. 423.2224 [(M + H)$^+$], M = C$_{21}$H$_{26}$N$_2$O$_2$ [43].

9-tert-Butoxycarbonyl-2,3-dihydro-1-{(hydroxy)(4-methoxyphenyl)methyl}-3,3,7,8-tetramethyldipyrrin (6a). Following a literature procedure ([55]; see Supporting Information therein) with slight modification, a solution of 5 (97 mg, 0.29 mmol) in THF (1.9 mL) at 0 °C was treated with p-tolylimagnesium bromide (1.0 mL, 1.0 mmol, 3.5 equiv, 1.0 M in THF) over the course of 2 min. After 5 min further, the ice bath was removed, and the reaction mixture was stirred for 2 h. The reaction mixture was then cooled to 0 °C, whereupon saturated aqueous NH$_4$Cl (4.0 mL) was added. The mixture was extracted with ethyl acetate. The organic extract was washed with water, dried (Na$_2$SO$_4$), and chromatographed (silica, ethyl acetate/hexanes (1:3)) to give a light brown solid (69 mg, 56%): m.p. 130–132 °C; $^{1}$H-NMR $\delta$ 1.11 (s, 3H), 1.20 (s, 3H), 1.59 (s, 9H), 2.05 (s, 3H), 2.29 (s, 3H), 2.36 (3, 3H), 2.30, 2.45 (AB, $^2J$ = 18.6 Hz, 2H), 3.86 (d, $J$ = 4.2 Hz, 1H), 5.43 (d, $J$ = 4.2 Hz, 1H), 5.81 (s, 1H), 7.18 (d, $J$ = 8.0 Hz, 2H), 7.27 (d, $J$ = 8.0 Hz, 2H), 10.65–10.72 (br, 1H); $^{13}$C-NMR $\delta$ 8.8, 10.2, 21.2, 28.5, 28.85, 28.94, 41.9, 48.8, 74.5, 80.0, 103.3, 119.2, 119.9, 126.7, 126.8, 129.4, 129.5, 136.5, 138.2, 160.7, 160.9, 181.2; ESI-MS obsd 432.2637, calcld. 432.2642 [(M + H)$^+$], M = C$_{26}$H$_{34}$N$_2$O$_3$; $\lambda_{abs}$ (toluene) 360 nm.

1-{(Acetoxy)(4-methoxyphenyl)methyl}-9-tert-butoxycarbonyl-2,3-dihydro-3,3,7,8-tetramethyldipyrrin (6a-Ac). Following a procedure [48] with slight modification, a solution of 6a (22 mg, 52 µmol) in THF (2.1 mL) at room temperature was treated with acetic anhydride (11 mg, 0.11 mmol) and DMAP (13 mg, 0.11 mmol). The reaction mixture was stirred for 2 h. Saturated aqueous NaHCO$_3$ (2 mL) was added, and the mixture was extracted with ethyl acetate. The organic extract was washed with water, dried (Na$_2$SO$_4$), and chromatographed (silica, ethyl acetate/hexanes (1:3)) to give a light brown solid (22 mg, 92%): m.p. 159–161 °C; $^{1}$H-NMR $\delta$ 1.14 (s, 3H), 1.16 (s, 3H), 1.58 (s, 9H), 2.02 (s, 3H), 2.250 (3, 3H), 2.252 (s, 3H), 2.35 (s, 3H), 2.41, 2.55 (AB, $^2J$ = 18.3 Hz, 2H), 5.77 (s, 1H), 6.41 (s, 1H), 7.18 (d, $J$ = 8.1 Hz, 2H), 7.33 (d, $J$ = 8.1 Hz, 2H), 10.90–10.98 (br, 1H); $^{13}$C-NMR $\delta$ 8.8, 10.4, 20.0, 21.2, 28.6, 28.8, 41.1, 49.3, 75.7, 79.7, 103.5, 118.9, 120.3, 125.7, 127.4, 129.5, 130.0, 132.6, 138.8, 161.1, 161.9, 170.3, 176.8; ESI-MS obsd 487.2567, calcld. 487.2567 [(M + Na)$^+$], M = C$_{28}$H$_{36}$N$_2$O$_4$; $\lambda_{abs}$ (toluene) 369 nm.

9-tert-Butoxycarbonyl-2,3-dihydro-1-{(hydroxy)(4-methoxyphenyl)methyl}-3,3,7,8-tetramethyldipyrrin (6b). Following a literature procedure ([55]; see Supporting Information therein) with slight modification, a solution of 5 (80 mg, 0.24 mmol) in THF (1.6 mL) at 0 °C was treated with p-anisylmagnesium bromide
1-(Acetoxy)(4-methylphenyl)methyl-8-carbethoxy-7-ethyl-2,3-dihydro-3,3-dimethyldipyrrin (1).

Following a procedure [48] with slight modification, a solution of 6b (20 mg, 46 µmol) in THF (1.8 mL) at room temperature was treated with acetic anhydride (9.3 mg, 0.092 mmol) and DMAP (11 mg, 0.092 mmol). The reaction mixture was stirred for 2 h. Saturated aqueous NaHCO₃ (2 mL) was added, and the mixture was extracted with ethyl acetate. The organic extract was washed with water, dried (Na₂SO₃), and chromatographed (silica, ethyl acetate/hexanes (1:3)) to give a pale yellow oil (75 mg, 45%): m.p. 120.4, 125.7, 127.7, 129.1, 130.1, 160.1, 161.1, 181.5; ESI-MS obsd 503.2517, calcd. 503.2516 [(M + H)⁺].

8-Carbethoxy-7-ethyl-2,3-dihydro-1-(4-methylbenzoyl)-3,3-dimethyldipyrrin (6b-Ac).

Following a procedure [48] with slight modification, a solution of 6a (20 mg, 0.424 mmol) in THF (4.24 mL) was cooled to 0 °C and treated with p-tolylmagnesium bromide (1.48 mL, 1.48 mmol, 3.5 equiv, 1.0 M in THF) over the course of 5 min. After 10 min further, the ice bath was removed, and the reaction mixture was stirred for 2 h. The reaction mixture was treated with saturated aqueous NaHCO₃ (15 mL) and extracted with ethyl acetate. The organic extract was washed with water, dried (Na₂SO₃), and chromatographed (silica, hexanes/ethyl acetate (3:1)) to give a pale yellow oil (75 mg, 45%): m.p. 29.0, 29.1, 41.6, 48.8, 59.3, 74.6, 80.1, 103.3, 114.3, 119.3, 119.9, 126.8, 128.2, 129.6, 131.7, 159.8, 160.8, 161.1, 181.5; ESI-MS obsd 439.2599, calcd. 439.2591 [(M + H)⁺], M = C₂₆H₃₄N₂O₄].

8-Carbethoxy-7-ethyl-2,3-dihydro-1-(hydroxy)(4-methylphenyl)methyl]-3,3-dimethyldipyrrin (6b). Following a procedure [48] with slight modification, a solution of 6b (20 mg, 46 µmol) in THF (1.8 mL) at room temperature was treated with acetic anhydride (9.3 mg, 0.092 mmol) and DMAP (11 mg, 0.092 mmol). The reaction mixture was stirred for 2 h. Saturated aqueous NaHCO₃ (2 mL) was added, and the mixture was extracted with ethyl acetate. The organic extract was washed with water, dried (Na₂SO₃), and chromatographed (silica, ethyl acetate/hexanes (1:4)) to give a light brown oil (19 mg, 85%): m.p. 1.14 (s, 3H), 1.17 (s, 3H), 1.57 (s, 9H), 2.02 (s, 3H), 2.41, 2.55 (AB, J = 18.0 Hz, 2H), 3.81 (s, 3H), 5.77 (s, 1H), 6.38 (s, 1H), 6.90 (dd, J = 7.2, 2.1 Hz, 2H), 7.37 (dd, J = 7.2, 2.1 Hz, 2H), 10.95 (br, 1H); 13C-NMR δ 8.89, 10.3, 28.6, 28.98, 29.0, 41.9, 48.9, 55.4, 74.3, 79.8, 80.1, 103.3, 114.3, 119.0, 120.4, 125.7, 127.7, 129.1, 130.1, 160.1, 161.2, 162.0, 170.4, 176.9; ESI-MS obsd 439.2599, calcd. 439.2591 [(M + H)⁺], M = C₂₆H₃₄N₂O₄].

8a-Ox. A solution of 8a in CDCl₃ in an NMR tube changed from yellow to orange on standing for 7 days; chromatography (silica, hexanes/ethyl acetate (4:1)) gave a yellow oil. 1H-NMR δ 1.20 (t, J = 6.9 Hz, 3H), 1.31 (s, 6H), 1.35 (t, J = 7.2 Hz, 3H), 2.47 (s, 3H), 2.86 (q, J = 6.9 Hz, 2H), 2.98 (s, 2H), 4.27 (q, J = 7.2 Hz, 2H), 6.14 (s, 1H), 7.31 (d, J = 8.1 Hz, 2H), 7.38 (d, J = 3.6 Hz, 1H), 8.03 (d, J = 8.1 Hz, 2H), 10.65 (br, 1H); ESI-MS obsd 393.2168, calcd. 393.2173 [(M + H)⁺], M = C₂₄H₂₈N₂O₃; λabs (CH₂Cl₂) 451 nm.

1-[(Acetoxy)(4-methylphenyl)methyl]-8-carbethoxy-7-ethyl-2,3-dihydro-3,3-dimethyldipyrrin (8a-Ac). Following a procedure [48] with slight modification, a solution of 8a (70 mg, 0.18 mmol) in THF (7.2 mL) at room temperature was treated with acetic anhydride (38 mg, 0.36 mmol) and DMAP (44 mg, 0.361 mmol). The reaction mixture was stirred for 2 h. The reaction mixture was treated with saturated aqueous NaHCO₃ (15 mL) and extracted with ethyl acetate. The organic extract was washed with water, dried (Na₂SO₃), and chromatographed [silica, hexanes/ethyl acetate (4:1)] to give a light brown oil (67 mg, 85%): 1H-NMR δ 1.16 (t, J = 7.2 Hz, 3H), 1.18 (s, 6H), 1.34 (t, J = 7.2 Hz, 3H), 2.19 (s, 3H), 2.37 (s, 3H), 2.45, 2.57 (AB, J = 18.6 Hz, 2H), 2.80 (q, J = 7.2 Hz, 2H), 4.27 (q, J = 7.2 Hz, 2H), 5.82 (s, 1H), 6.49 (s, 1H), 7.30 (d, J = 7.2 Hz, 2H), 7.38 (d, J = 6.9 Hz, 1H), 8.03 (d, J = 8.1 Hz, 2H), 10.65 (br, 1H); ESI-MS obsd 393.2168, calcd. 393.2173 [(M + H)⁺], M = C₂₄H₂₈N₂O₃; λabs (CH₂Cl₂) 451 nm.
7.20 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 3.0 Hz, 1H), 10.95 (brs, 1H); 13C-NMR δ 14.5, 16.4, 18.0, 21.0, 21.3, 28.9, 29.0, 41.0, 49.3, 59.2, 75.5, 103.8, 114.1, 124.9, 126.1, 127.3, 128.3, 129.6, 133.0, 138.9, 159.8, 165.4, 169.8, 175.5; ESI-MS obsd 340.1548, calcd. 340.1543 [M + H]+, M = C26H32N2O4; λabs (CH2Cl2) 343 nm.

8-Carbethoxy-7-ethyl-2,3-dihydro-1-[(hydroxy)(4-methoxyphenyl)methyl]-3,3-dimethyldipyrrin (8b). Following a literature procedure [55]; see Supporting Information therein) with slight modification, a solution of 7 (52 mg, 0.17 mmol) in THF (1.1 mL) at 0 °C was treated with p-anisylmagnesium bromide (0.60 mL, 0.60 mmol, 3.5 equiv, 1.0 M in THF) over the course of 5 min. After 10 min further, the ice bath was removed, and the reaction mixture was stirred for 2 h. The reaction mixture was then cooled to 0 °C, whereupon saturated aqueous NH4Cl (4.0 mL) was added. The reaction mixture was extracted with ethyl acetate. The organic extract was washed with water, dried (Na2SO4), and chromatographed (silica, hexanes/ethyl acetate (3:2)) to give a red oil (33 mg, 47%): 1H-NMR δ 1.13 (s, 3H), 1.17 (t, J = 7.2 Hz, 2H), 1.20 (s, 3H), 1.35 (t, J = 7.2 Hz, 3H), 2.34, 2.46 (AB, J = 18.6 Hz, 2H), 2.82 (q, J = 7.2 Hz, 2H), 3.71 (br, 1H), 3.81 (s, 3H), 4.28 (q, J = 7.2 Hz, 2H), 5.43 (s, 1H), 5.82 (s, 1H), 6.90 (d, J = 8.7 Hz, 2H), 7.29 (d, J = 8.7 Hz, 2H), 7.43 (d, J = 3.0 Hz, 1H), 10.71 (br, 1H); ESI-MS obsd 411.2271, calcd. 411.2278 [(M + H)]+.

1-[(Acetoxy)(4-methoxyphenyl)methyl]-8-carbethoxy-7-ethyl-2,3-dihydro-3,3-dimethyldipyrrin (8b-Ac). Following a procedure [48] with slight modification, a solution of 8b (20 mg, 49 μmol) in THF (1.9 mL) at room temperature was treated with acetic anhydride (9.5 µL, 100 µmol) at 0 °C for 16 h, whereupon saturated aqueous NaHCO3 (4.0 mL) was added. The resulting solution was heated at 80 °C for 2 h with stirring and then filtered through Celite. The organic layer was washed with water, dried (Na2SO4), and chromatographed (silica, hexanes/ethyl acetate (4:1)) to give a light brown oil (19 mg, 86%): 1H-NMR δ 1.13–1.18 (m, 9H), 1.34 (t, J = 6.9 Hz, 3H), 2.19 (s, 3H), 2.45, 2.57 (AB, J7 = 18.6 Hz, 2H), 2.80 (q, J = 7.2 Hz, 2H), 3.82 (s, 3H), 4.27 (q, J = 6.9 Hz, 2H), 5.82 (s, 1H), 6.47 (s, 1H), 6.92 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 3.0 Hz, 1H), 10.95 (br, 1H); 13C-NMR δ 14.5, 16.4, 18.0, 21.1, 28.9, 29.0, 41.1, 49.4, 55.4, 59.3, 75.2, 103.8, 114.1, 114.3, 124.9, 126.1, 127.9, 128.3, 128.6, 159.8, 160.1, 165.5, 170.0, 175.6; ESI-MS obsd 475.2203, calcd. 475.2203 [(M + Na)+, M = C28H34N2O4; λabs (CH2Cl2) 343 nm.

(E)-Ethyl 5-[(4,4-dimethyl-5-oxodihydrofuran-2(3H)-ylidene)(phenyl)methyl]-1H-pyrrole-3-carboxylate (11). Following a literature procedure [19], in a Schlenk flask, a solution of 9 (2.5 g, 10 mmol) in dry acetonitrile (16.5 mL) was treated with 10 (2.1 g, 8.2 mmol), BnNEt2Cl (2.3 g, 8.2 mmol), and Et3N (10 mL). The mixture was deaerated by freeze–pump–thaw cycles. A sample of PD(PPh3)4 (0.47 g, 0.41 mmol) was then added, and the resulting mixture was further deaerated. The reaction mixture was heated at 80 °C for 16 h, and upon allowing to cool to room temperature, CH2Cl2 and water were added. The organic layer was dried (Na2SO4), concentrated, and chromatographed (silica, hexanes/ethyl acetate (7:3)) to afford a light yellow solid (1.9 g, 68%): m.p. 115–116 °C; 1H-NMR δ 1.35 (t, J = 6.9 Hz, 3H), 1.37 (s, 6H), 3.06 (s, 2H), 4.29 (q, J = 6.9 Hz, 2H), 6.56–6.57 (m, 1H), 7.27–7.37 (m, 6H), 8.17 (brs, 1H); 13C-NMR δ 14.5, 25.1, 39.9, 41.8, 59.9, 109.1, 111.0, 117.3, 123.3, 127.9, 128.6, 129.5, 129.7, 135.1, 145.1, 164.9, 179.6; ESI-MS obsd 340.1548, calcd. 340.1543 [(M + H)+, M = C20H21NO4; λabs (CH2Cl2) 343 nm.

(E)-Ethyl 5-[(4,4-dimethyl-5-methylenedihydrofuran-2(3H)-ylidene)(phenyl)methyl]-1H-pyrrole-3-carboxylate (12). Following a general procedure [19], a solution of TiCp2Cl2 (6.2 g, 25 mmol) in toluene (100 mL) was treated dropwise with a solution of MeLi (1.6 M, 32 mL in Et2O, 50 mmol) at 0 °C under argon. The resulting solution was stirred at 0 °C for 1 h, whereupon saturated aqueous NaHCO3 solution was added. The organic layer was washed (water and brine), dried (Na2SO4) and filtered. The filtrate was treated with lactone 11 (1.7 g, 5.0 mmol) and TiCp2Cl2 (50 mg) in a Schlenk flask under argon. The resulting solution was heated at 80 °C for 16 h. The resulting mixture was allowed to cool to room temperature whereupon MeOH (1.8 mL), NaHCO3 (50 mg) and water (1.0 mL) were added. The resulting mixture was kept at 40 °C with 2 h stirring and then filtered through Celite. The filtrate
was concentrated and chromatographed (silica, hexanes/ethyl acetate (4:1)) to afford a gummy oil (1.1 g, 67%): 1H-NMR δ 1.27 (s, 6H), 1.34 (t, J = 7.2 Hz, 3H), 2.76 (s, 2H), 4.02 (d, J = 2.4 Hz, 1H), 4.24 (q, J = 7.2 Hz, 2H), 4.37 (d, J = 2.4 Hz, 1H), 6.46–6.48 (m, 1H), 7.21–7.36 (m, 6H), 8.53 (brs, 1H); 13C-NMR δ 14.5, 27.5, 39.8, 43.9, 59.8, 81.3, 105.7, 108.7, 116.5, 123.0, 126.8, 128.3, 129.6, 131.5, 136.8, 150.2, 165.3, 169.8; ESI-MS obsd 338.1756, calcd. 338.1751 [(M + H)+, M = C21H22N2O3].

8-Carbethoxy-2,3-dihydro-1,2,2-trimethyl-5-phenyldipyrrin (13). Following a general procedure [19], a solution of 12 (544 mg, 1.60 mmol) in DMF (26.0 mL) was treated with 10% aqueous HCl (2.0 mL). After 30 min, NH4OAc (2.46 g, 32 mmol) and Et3N (4.5 mL, 32 mmol) were added, and the resulting mixture was stirred at 55 °C for 16 h. Then, the reaction mixture was treated with saturated aqueous KH2PO4 solution. Ethyl acetate (100 mL) was added, and the organic layer was washed (water), dried (Na2SO4), concentrated and chromatographed (silica, hexanes/ethyl acetate (4:1)) to afford a yellow solid (401 mg, 74%): m.p. 157–159 °C; 1H-NMR δ 1.13 (s, 6H), 1.28 (t, J = 6.9 Hz, 3H), 2.17 (s, 3H), 2.36 (s, 2H), 4.22 (q, J = 6.9 Hz, 2H), 6.01 (d, J = 2.4 Hz, 1H), 7.28–7.49 (m, 6H), 11.03 (brs, 1H); 13C-NMR δ 14.5, 15.7, 25.7, 48.0, 59.5, 109.4, 116.0, 120.3, 124.2, 127.2, 128.4, 129.7, 131.5, 136.8, 152.0, 165.3, 169.8; ESI-MS obsd 338.1756, calcd. 338.1751 [(M + H)+, M = C21H22N2O3]; λabs (CH2Cl2) 348 nm.

8-Carbethoxy-1-formyl-2,3-dihydro-2,2-dimethyl-5-phenyldipyrrin (14). Following a general procedure [19], a solution of 13 (0.35 g, 1.0 mmol) in 1,4-dioxane (20 mL) was treated with SeO2 (0.33 g, 3.0 mmol) and stirred at room temperature for 60 min. Ethyl acetate and saturated NaHCO3 solution. Ethyl acetate (100 mL) was added, and the organic layer was washed (brine), dried, concentrated and chromatographed (silica, hexanes/ethyl acetate (4:1)) to afford a yellow solid (72 mg, 56%): m.p. 146–148 °C; 1H-NMR δ 1.27 (s, 6H), 1.34 (t, J = 6.9 Hz, 2H), 6.06 (s, 1H), 7.19–7.46 (m, 10H), 11.25 (brs, 1H), 11.42 (brs, 1H); 13C-NMR δ 14.5, 25.7, 45.8, 46.1, 59.9, 113.9, 117.0, 126.7, 128.1, 128.7, 129.1, 130.3, 133.8, 137.9, 148.4, 164.8, 177.0, 190.0; ESI-MS obsd 351.1701 calcd. 351.1703 [(M + H)+, M = C21H23N2O2]; λabs (CH2Cl2) 343 nm.

8-Carbethoxy-1-[(hydroxy)(4-methylphenyl)methyl]-2,3-dihydro-2,2-dimethyl-5-phenyldipyrrin (15). Following a literature procedure [55]; see Supporting Information therein) with slight modification, a solution of 14 (97 mg, 0.29 mmol) in THF (1.9 mL) at 0 °C was treated with p-tolylmagnesium bromide (1.0 mL, 1.0 mmol, 3.5 equiv, 1.0 M in THF) over the course of 5 min. After 5 min further, the ice bath was removed, and the mixture was stirred for 2 h. The reaction mixture was then cooled to 0 °C whereupon saturated aqueous NH4Cl (10.0 mL) was added. The mixture was then extracted with ethyl acetate. The organic layer was washed with water, dried (Na2SO4), and chromatographed (silica, hexanes/ethyl acetate (3:1)) to give a light yellow solid (72 mg, 56%): m.p. 146–148 °C; 1H-NMR δ 0.75 (s, 3H), 1.24 (s, 3H), 1.29 (t, J = 6.9 Hz, 3H), 2.37 (s, 3H), 2.34, 2.46 (AB, 2J = 17.1 Hz, 2H), 3.49 (d, J = 4.8 Hz, 1H), 4.22 (q, J = 6.9 Hz, 2H), 5.52 (d, J = 4.8 Hz, 1H), 6.06 (s, 1H), 7.19–7.46 (m, 10H), 11.25 (brs, 1H); 13C-NMR δ 14.6, 21.3, 26.2, 26.5, 46.1, 47.6, 59.7, 72.0, 110.6, 116.2, 122.5, 124.8, 127.5, 127.6, 128.5, 129.6, 131.4, 137.2, 138.6, 138.7, 146.1, 165.3, 188.5; ESI-MS obsd 443.2341, calcd. 443.2329 [(M + H)+, M = C28H30N2O3]; λabs (CH2Cl2) 343 nm.

1-[(Acetoxy)(4-methylphenyl)methyl]-8-carbethoxy-2,3-dihydro-2,2-dimethyl-5-phenyldipyrrin (15-Ac). Following a procedure [48] with slight modification, a solution of 15 (22 mg, 52 μmol) in THF (2.1 mL) at room temperature was treated with acetic anhydride (11 mg, 0.11 mmol) and DMAP (13 mg, 0.11 mmol). The reaction mixture was stirred for 2 h, and then treated with saturated aqueous NaHCO3 (5 mL). The reaction mixture was extracted with ethyl acetate. The organic extract was washed with water, dried (Na2SO4), and chromatographed (silica, hexanes/ethyl acetate (4:1)) to give a light yellow solid (22 mg, 92%): m.p. 65–67 °C; 1H-NMR δ 0.91 (s, 3H), 1.28 (s, 3H), 1.29 (t, J = 6.9 Hz, 3H), 2.18 (s, 3H), 2.39 (s, 3H), 2.35, 2.45 (AB, 2J = 16.8 Hz, 2H), 4.22 (q, J = 6.9 Hz, 2H), 6.06 (d, J = 1.8 Hz, 1H), 6.53 (s, 1H), 7.23–7.43 (m, 10H), 11.58 (brs, 1H); 13C-NMR δ 14.5, 21.1, 21.3, 26.2, 26.3, 45.3, 48.3, 59.6, 72.6, 110.4, 116.1, 123.0, 124.6, 127.5, 128.3, 128.5, 129.5, 133.4, 134.4, 138.4, 139.2, 146.8, 165.2, 169.9, 183.8; ESI-MS obsd 485.2445, calcd. 485.2435 [(M + H)+, M = C30H32N2O4]; λabs (CH2Cl2) 343 nm.
2-Formyl-3-(4-methylphenyl)-N-p-tosylpyrrole (17). Following a reported procedure [42], a mixture of NaH (1.17 g, 60 wt % in oil, 29 mmol) in THF (90 mL) was treated portionwise with pyrrole 16 (4.20 g, 22.7 mmol) at 0 °C under argon. The reaction mixture was stirred for 20 min at 0 °C, whereupon p-tosyl chloride (6.50 g, 34.1 mmol) was added. The resulting heterogeneous mixture was stirred for 3 h at room temperature. Water and CH₂Cl₂ were added. The organic phase was washed (brine), dried (Na₂SO₄) and concentrated to a pale brown solid. Column chromatography (silica, hexanes/CH₂Cl₂ (1:3)) afforded a pale grey solid (6.34 g, 82%): m.p. 178–180 °C; ¹H-NMR (400 MHz) δ 2.38 (s, 3H), 2.43 (s, 3H), 4.67 (d, J = 3.3 Hz, 1H), 7.21 (d, J = 7.9 Hz, 2H), 7.30 (d, J = 7.9 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 7.82–7.83 (m, 1H), 7.94 (d, J = 8.2 Hz, 2H), 9.62 (s, 1H); ¹³C-NMR (100 MHz) δ 21.3, 21.9, 22.6, 23.0, 26.7, 38.1, 41.9, 55.3, 55.8, 79.9, 97.9, 114.6, 124.1, 125.9, 127.1, 128.9, 129.6, 130.3, 131.5, 132.2, 136.3, 136.4, 136.5, 137.6, 146.2, 147.5, 178.5; ESI-MS obsd 340.1007, calcd. 340.1002 [(M + H)⁺, M = C₁₀H₁₂NO₃S].

3-(4-Methylphenyl)-2-(2-nitroethyl)-N-p-tosylpyrrole (18). Following a reported procedure [43], a mixture of 17 (6.50 g, 18.6 mmol), potassium acetate (2.00 g, 20.4 mmol), methylamine hydrochloride (1.51 g, 22.3 mmol), nitromethane (2.50 mL, 46.6 mmol) and acetic acid (6.30 g, 18.6 mmol), potassium acetate (2.00 g, 20.4 mmol), methylamine hydrochloride (1.51 g, 22.3 mmol) at 0 °C under argon. The reaction mixture was stirred for 20 min at 0 °C. The resulting heterogeneous mixture was stirred for 3 h at room temperature. Saturated aqueous NH₄Cl (3.42 g, 8.90 mmol) and 16 (3.19 g, 20.2 mmol) was treated with DBU (5.20 mL, 26.7 mmol) at room temperature. The reaction mixture was filtered. The filtrate was washed (water, cold ethanol), and then dried under high vacuum for 4 h. The crude product was dissolved in CHCl₃/2-propanol (133 mL, 3:1), treated with silica (22.3 g), and vigorously stirred upon addition of NaBH₄ (1.41 g, 37.1 mmol). The mixture was vigorously stirred for 2 h at room temperature. The progress of the reaction was monitored by ¹H-NMR spectroscopy. The reaction mixture was filtered. The filtrate was washed (water, brine), dried (Na₂SO₄), and concentrated to a brown oil. The oil was chromatographed (silica, hexanes/ethyl acetate (3:1)). The product was recrystallized from hot EtOH and cooled overnight at 1 °C to afford a white solid (3.45 g, 48%): m.p. 115–117 °C; ¹H-NMR δ 2.37 (s, 3H), 2.44 (s, 3H), 3.46 (t, J = 8.0 Hz, 2H), 4.55 (t, J = 8.0 Hz, 2H), 6.35–6.37 (m, 1H), 7.11 (d, J = 7.9 Hz, 2H), 7.18 (d, J = 7.9 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 7.37–7.39 (m, 1H), 7.69 (d, J = 8.1 Hz, 2H); ¹³C-NMR (100 MHz) δ 21.4, 21.9, 24.0, 74.3, 113.9, 123.4, 126.9, 128.4, 129.7, 130.5, 130.9, 131.2, 136.1, 137.6, 145.7; Anal. Calcd. for C₂₀H₂₀N₂O₄S: C, 62.48; H, 5.24; S, 8.34. Found: C, 62.40; H, 5.10; N, 7.21; S, 8.24.

1,1-Dimethoxy-4,4-dimethyl-6-[3-(4-methylphenyl)-N-p-tosylpyrrol-2-yl]-5-nitro-2-hexanone (20). A mixture of 18 (3.42 g, 8.90 mmol) and 19 (3.19 g, 20.2 mmol) was treated with DBU (5.20 mL, 26.7 mmol) at room temperature. The reaction mixture was stirred for 24 h at room temperature. Saturated aqueous NH₄Cl was added, and the mixture was extracted with ethyl acetate. The organic phase was washed (water, brine), dried (Na₂SO₄), and concentrated to a brown oil. A first chromatography (silica, hexanes/ethyl acetate (1:3)) and a second chromatography (silica, CH₂Cl₂) afforded a slightly yellow oil (1.02 g, 21%): m.p. 160–163 °C; ¹H-NMR δ 1.05 (s, 3H), 1.12 (s, 3H), 2.37 (s, 3H), 2.43 (s, 3H), 2.49, 2.59 (AB, J = 18.4 Hz, 2H), 3.28 (ABX, J = 2.9 Hz, J = 15.3 Hz, 1H), 3.34 (s, 3H), 3.38 (s, 3H), 3.62 (ABX, J = 10.9 Hz, J = 15.3 Hz, 1H), 4.31 (s, 1H), 5.10 (ABX, J = 2.9 Hz, J = 10.9 Hz, 1H), 6.26 (d, J = 3.3 Hz, 1H), 7.07 (d, J = 7.8 Hz, 2H), 7.16 (d, J = 7.8 Hz, 2H), 7.30–7.34 (m, 3H), 7.65 (d, J = 8.5 Hz, 2H); ¹³C-NMR (100 MHz) δ 21.4, 21.9, 23.6, 23.9, 25.3, 29.9, 36.6, 44.3, 55.0, 94.3, 104.5, 114.9, 124.2, 124.6, 126.6, 128.9, 129.3, 130.3, 131.5, 132.2, 136.3, 137.2, 145.4, 203.2; ESI-MS obsd 565.1994, calcd. 565.1979 [(M + Na)⁺, M = C₂₈H₃₄N₂O₇S].

2,3,4,5-Tetrahydro-1-(dimethoxymethyl)-3,3-dimethyl-7-(4-methylphenyl)-N¹¹-p-tosylidipyrin N¹₁₀-oxide (21). Following a general procedure [42], a solution of 20 (1.02 g, 1.88 mmol) in AcOH/EtOH (19 mL, 1:1) was treated with zinc dust (3.09 g, 47.6 mmol) at 0 °C. The reaction mixture was vigorously stirred for 1 h at 0 °C, then diluted with ethyl acetate and filtered through Celite. The filtrate was concentrated. The resulting oil was purified by column chromatography (silica, hexanes/ethyl acetate (2:3)) to afford a white solid (400 mg, 42%): m.p. 160–163 °C; ¹H-NMR (400 MHz) δ 0.57 (s, 3H), 0.78 (s, 3H), 2.32 (s, 2H), 2.34 (s, 3H), 2.41 (s, 3H), 3.23 (ABX, J = 11.0 Hz, J = 15.3 Hz, 1H), 3.40 (s, 3H), 3.43 (s, 3H), 3.70 (ABX, J = 4.0 Hz, J = 15.3 Hz, 1H), 4.33–4.37 (m, 1H), 5.43 (s, 1H), 6.33 (d, J = 3.3 Hz, 1H), 7.11–7.15 (m, 4H), 7.27 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 3.3 Hz, 1H), 7.75 (d, J = 8.4 Hz, 2H); ¹³C-NMR (100 MHz) δ 21.4, 21.9, 22.6, 23.0, 26.7, 38.1, 41.9, 55.3, 55.8, 79.9, 97.9, 114.6, 124.1, 125.9, 127.1, 128.9, 129.6, 130.3,
2,3,4,5-Tetrahydro-1-(dimethoxymethyl)-3,3-dimethyl-7-(4-methylphenyl)-N\(^{11}\)-p-tosyldipyrinn (22). Following a general procedure [42], TiCl\(_4\) (5.35 mL, 5.35 mmol, 1.0 M in CH\(_2\)Cl\(_2\)) was slowly added with stirring to THF (15.3 mL) under argon at 0 °C. The resulting yellow solution was slowly treated with LiAlH\(_4\) (3.82 mL, 3.82 mmol, 1.0 M in THF). The resulting black mixture was stirred at room temperature for 15 min. TEA (4.78 mL, 34.4 mmol) was added. The resulting black mixture was stirred for 2 min at room temperature. The black mixture was slowly poured into a solution of 21 (378 mg, 0.740 mmol) in THF (12.7 mL) at 0 °C. The mixture was stirred for 1 h at room temperature. Water and ethyl acetate were added. The organic extract was washed (brine), dried (\(\text{Na}_2\text{SO}_4\)), concentrated and chromatographed (silica, CH\(_2\)Cl\(_2\)/ethyl acetate (5:1)) to afford a white solid (300 mg, 82%): m.p. 105–107 °C; \(^1\)H-NMR (400 MHz) \(\delta\) 0.79 (s, 3H), 1.05 (s, 3H), 2.32 (s, 3H), 2.35 (s, 2H), 2.40 (s, 3H), 2.94–4.12 (m, 1H), 4.65 (s, 1H), 6.36 (d, \(J = 3.3\) Hz, 1H), 7.09 (d, \(J = 8.1\) Hz, 2H), 7.27 (d, \(J = 8.1\) Hz, 2H), 7.32–7.36 (m, 3H), 7.64 (d, \(J = 8.1\) Hz, 2H); \(^{13}\)C-NMR (100 MHz) \(\delta\) 21.6, 22.1, 23.3, 27.1, 27.4, 42.0, 49.1, 54.9, 55.2, 79.7, 94.8, 103.7, 115.0, 123.6, 127.0, 129.3, 129.4, 130.5, 133.1, 136.7, 137.2, 145.2, 173.6; ESI-MS obsd 495.2307, calcd. 495.2313 [(M + H)\(^+\)].

2,3,8,12,13,18,18-Octamethyl-5,15-bis(4-methylphenyl)bacteriochlorin (B1-T\(_2\)). A solution of 6a-Ac (32.0 mg, 0.0689 mmol) in CH\(_3\)CN (3.83 mL) was treated with BF\(_3\)·O(Et)\(_2\) (67.9 µL, 0.536 mmol). The reaction mixture was heated to 80 °C for 2 h in a round-bottomed flask (air atmosphere) fitted with a rubber stopper, which itself was pierced with a syringe needle. The reaction mixture was allowed to cool to room temperature and then treated with TEA (89.6 µL, 0.643 mmol). The resulting mixture was diluted with ethyl acetate (~15 mL), washed with water, dried (\(\text{Na}_2\text{SO}_4\)), and concentrated. Column chromatography (silica, hexanes/CH\(_2\)Cl\(_2\) (1:1)) afforded a greenish solid (3.8 mg). Trituration with CH\(_2\)Cl\(_2\)/hexanes gave a green solid (3.3 mg, 16%): m.p. 105–107 °C; \(^1\)H-NMR (300 MHz) \(\delta\) 0.79 (s, 3H), 1.05 (s, 3H), 2.32 (s, 3H), 2.35 (s, 2H), 2.40 (s, 3H), 2.94–2.98 (m, 2H), 3.30 (s, 3H), 3.35 (s, 3H); 3.87 (q, \(J = 7.2\) Hz, 4H), 3.95 (s, 4H), 7.44 (d, \(J = 7.5\) Hz, 4H), 7.65 (d, \(J = 8.0\) Hz, 4H), 8.59 (s, 2H); MALDI-MS obsd 607.7; ESI-MS obsd 606.3714, calcd. 606.3717 [(M)\(^+\)], M = C\(_{42}\)H\(_{46}\)N\(_4\)O\(_4\); \(\lambda_{abs}\) (toluene) 356, 382, 504, 726 nm.

5,15-Bis(4-methylphenyl)-2,3,4,5,8,12,13,18-octamethylbacteriochlorin (B1-A\(_2\)). A solution of 6b-Ac (2.2 mg, 4.6 µmol) in CH\(_3\)CN (0.25 mL) was treated with BF\(_3\)·O(Et)\(_2\) (4.4 µL, 36 µmol) in a glass vial (air atmosphere) fitted with a rubber stopper, which itself was pierced with a syringe needle. The reaction mixture was stirred at room temperature for 24 h. The yield of bacteriochlorin was 41% upon absorption spectroscopic examination. (The weight of the vial was checked to confirm the absence of any significant solvent loss, the occurrence of which would inflate the spectroscopic yield determination; no correction was required.) The reaction mixture was treated with TEA (11 µL, 72 µmol). The resulting mixture was diluted with ethyl acetate (5 mL) and washed with water, dried (\(\text{Na}_2\text{SO}_4\)), and concentrated. Silica chromatography afforded a greenish brown solid, which exhibited limited solubility in diverse organic solvents (hexanes, ethyl acetate, dichloromethane, methanol); MALDI-MS obsd 639.4, calcd. 638.36 (C\(_{42}\)H\(_{46}\)N\(_4\)O\(_2\)); \(\lambda_{abs}\) (CH\(_2\)Cl\(_2\)) 355, 382, 503, 726 nm.

3,13-Dicarbethoxy-2,12-diethyl-8,8,18,18-tetramethyl-5,15-bis(4-methylphenyl)bacteriochlorin (B2-T\(_2\)). A solution of 8a-Ac (31 mg, 71 µmol) in CH\(_3\)CN (3.9 mL) was treated with BF\(_3\)·O(Et)\(_2\) (68 µL, 0.55 mmol) for 4 h following the procedure for A\(_2\)-BC1. The reaction mixture was treated with TEA (77 µL, 0.55 mmol) and diluted with ethyl acetate (20 mL), and then washed with water, dried (\(\text{Na}_2\text{SO}_4\)), and concentrated. Column chromatography (silica, hexanes/ethyl acetate (4:1)) afforded a green solid (3.1 mg, 12%): \(^1\)H-NMR \(\delta\) −1.28 (br, 2H), 1.29 (t, \(J = 7.2\) Hz, 6H), 1.67 (t, \(J = 7.2\) Hz, 6H), 1.83 (s, 12H), 2.59 (s, 6H), 3.78 (q, \(J = 7.2\) Hz, 4H), 3.87 (q, \(J = 7.2\) Hz, 4H), 3.95 (s, 4H), 7.44 (d, \(J = 7.5\) Hz, 4H), 7.71 (d, \(J = 7.5\) Hz, 4H), 8.62 (s, 2H); \(^{13}\)C-NMR \(\delta\) 14.2, 17.7, 20.1, 21.6, 31.2, 45.5, 51.6, 61.2, 94.5, 113.5, 125.6, 128.3, 131.9, 132.0, 133.0, 137.1, 137.5, 138.7, 159.9, 168.1, 169.0; MALDI-MS obsd 751.3; ESI-MS obsd 751.41805, calcd. 751.42178 [(M + H)\(^+\)], M = C\(_{48}\)H\(_{34}\)N\(_4\)O\(_4\); \(\lambda_{abs}\) (toluene) 358, 382, 516, 739 nm.
3,13-Dicarboxethoxy-2,12-diethyl-5,15-bis(4-methoxyphenyl)-8,8,18,18-tetramethylbacteriochlorin (B2-A2). A solution of 8b-Ac (14 mg, 31 µmol) in CH2CN (1.7 mL) was treated with BF3·OEt2 (30 µL, 0.24 mmol) for 2 h following the procedure for A2-BC1. The reaction mixture was treated with TEA (33 µL, 0.24 mmol). The resulting mixture was diluted with ethyl acetate (20 mL) and then washed with water, dried (Na2SO4), and concentrated. Column chromatography (silica, CH2Cl2) afforded a green solid (1.9 mg, 16%): 1H-NMR δ = −1.31 (br, 2H), 1.30 (t, J = 7.5 Hz, 6H), 1.67 (t, J = 7.5 Hz, 6H), 1.84 (s, 12H), 3.77 (br, 4H), 3.95 (q, J = 7.5 Hz, 8H), 4.01 (s, 6H), 7.16 (d, J = 8.7 Hz, 4H), 7.73 (d, J = 8.7 Hz, 4H), 8.62 (s, 2H); MALDI-MS obsd 783.8; ESI-MS obsd 783.41449, calcd. 783.41161 [(M + H)+, M = C46H54N4O4]; λabs(toluene) 358, 382, 517, 739 nm. In this reaction one additional bacteriochlorin was observed in trace quantities upon chromatography (following the title compound), although not isolated in pure form (LD-MS m/z = 739.1; λabs = 382, 549, 759 nm).

3,13-Dicarboxethoxy-8,8,18,18-tetramethyl-5,15-bis(4-methylyphenyl)-10,20-diphenylbacteriochlorin (B3-P2 T2). A solution of 15 (10 mg, 23 µmol) in CH2Cl2 (1.3 mL) was treated with trifluoroacetic anhydride (16 µL, 0.12 mmol) in a glass vial. The reaction flask was sealed with a rubber stopper and heated at 40 °C for 24 h. Upon cooling to room temperature, the reaction mixture was treated with TEA (33 µL, 0.24 mmol). The resulting mixture was concentrated and chromatographed (silica, CH2Cl2) to afford a pink solid (1.3 mg, 13%): 1H-NMR δ = −0.46 (br, 2H), 1.18 (t, J = 7.2 Hz, 6H), 1.30 (s, 12H), 2.54 (s, 6H), 3.67 (s, 4H), 3.77 (q, J = 7.2 Hz, 4H), 7.30 (d, J = 8.4 Hz, 4H), 7.59–7.61 (m, 7H), 7.71–7.73 (m, 7H), 8.03 (d, J = 2.1 Hz, 2H); MALDI-MS obsd 847.6; ESI-MS obsd 847.41996, calcd. 847.42178 [(M + H)+, M = C36H34N4O4]; λabs(toluene) 382, 533, 743 nm.

4.4. Plotting Absorption Spectra

A major challenge in the evaluation of the absorption spectra of the bacteriochlorins is how to normalize the spectra for comparison. In general, the absorption spectra of porphyrinic macrocycles (porphyrins, chlorins, bacteriochlorins) are normalized on the basis of their intensities (at either the B or Q band), which can be misleading for many bacteriochlorins due to the splitting/merging of the Bx and By bands (in some cases more than two). To overcome such shortcomings, the integrated area of the Qy bands relative to the total integrated full spectrum (ΣT) based on wavenumbers (cm⁻¹) provides a better gauge of any relative hyperchromic/hypochromic change of the Q bands [36,53]. In displays such as Figure 5, the integrated area is assessed on an energy basis (i.e., wavenumber (cm⁻¹)) while the x-axis display is in the more conventional wavelength (nm); accordingly, the shorter wavelength bands (the B bands) have stronger impact compared to the longer wavelength bands (the Q bands).

5. Conclusions

A new synthetic route to meso-aryl bacteriochlorin has been developed that relies on the acid-catalyzed self-condensation of a dihydrodipyrrin–carbinol or dihydrodipyrrin–acetate followed by air oxidation. The E-W route affords meso-diarylbacteriochlorins whereas the N-S route provides access to meso-tetraarylbacteriochlorins. Comparison of the yield of a meso-unsubstituted bacteriochlorin from a tetrahydrodipyrrin–acetal (0%) versus a dihydrodipyrrin–acetal (41%) implies the importance of resonance stabilization, by the distant pyrrole, of the oxocarbenium ion in the dihydrodipyrrin structure. A hypsochromic shift of the Qy band (~20 nm) occurs when meso-aryl and pyrrole-β-carbethoxy groups are juxtaposed. Further development of these approaches would benefit from more concise routes to the dihydrodipyrrin–carboxaldehyde, or alternative routes to install the aryl group(s) leading to the dihydrodipyrrin–acetate.

Supplementary Materials: Supplementary materials are available online. 1H-NMR and 13C-NMR spectra of new compounds are available online.

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-FG02-05ER15651). Partial support
to H.-J.K. was provided by Gongju National University of Education (grant 2016). Mass spectra were obtained at the Mass Spectrometry Laboratory for Biotechnology at NC State University. Partial funding for the facility was obtained from the NC Biotechnology Center and the National Science Foundation.

Author Contributions: Muthyala Nagarjuna Reddy, Shaofei Zhang, and Han-Je Kim carried out the methodology development and syntheses leading to bacteriochlorins. Olga Mass synthesized and tested the reactivity of the tetrahydrodipyrrin–acetal. Masahiko Taniguchi assembled the section concerning the absorption and fluorescence properties of various bacteriochlorins. Jonathan S. Lindsey made occasional suggestions and wrote most of the paper.

Conflicts of Interest: Methods of synthesis of bacteriochlorins and their use have been licensed to NIRvana Sciences, Inc., of which JSL and MT are cofounders. All authors read and approved the final manuscript.

Appendix A

Appendix A.1 Acid Survey for the Self-Condensation of 6a and 6a-Ac

The self-condensation was carried out under a variety of acid-catalysis conditions, typically open to air, with monitoring of the reaction by absorption spectroscopy and LD-MS. The conditions employed were those used previously for dihydrodipyrrin–acetals, including (1) 140 mM BF$_3$·O(Et)$_2$ in CH$_3$CN [18]; or (2) 72 mM TMSOTf/144 mM DTBP in CH$_2$Cl$_2$ [31]; or the conditions employed for dihydrodipyrrin–carboxaldehydes: neat TFA [36]. Thus, reaction of 6a in CH$_3$CN containing BF$_3$·O(Et)$_2$ at room temperature gave <1% yield (Table A1, entry 1), but ~4% yield upon reflux for several hours (entry 2).

The self-condensation of 6a-Ac in the presence of TFA or TMSOTf/DTBP gave di-p-tolylbacteriochlorin B1-T$_2$ in at most ~1% yield (entries 3–5) and absorption spectra reminiscent of tetradehydrocorrin-type compounds, which were not further analyzed. The reaction in CH$_3$CN containing BF$_3$·O(Et)$_2$ gave yields that varied depending on the concentration of BF$_3$·O(Et)$_2$ (entries 6–9), with the highest yield (17%) obtained with 140 mM BF$_3$·O(Et)$_2$ (entry 7). Reaction at lower concentration of 6a-Ac (5 mM) and BF$_3$·O(Et)$_2$ (50 mM) gave only 4.7% yield (entry 10). Segueing from entry 7, the same conditions but at reflux gave a higher yield (22%, entry 11) in shorter reaction time (2 vs. 21 h). Nitroarenes are known to provide oxidative conversion of a porphyrinogen to a porphyrin [56], yet PhNO$_2$ did not give any significant improvement in yield (entries 12–14). Attempts to use an atmosphere of O$_2$ (instead of air) did not afford increased yields (entry 15) nor did the reaction in TFA with use of DDQ as oxidant (entry 16); indeed, the latter gave evidence by LD-MS for the presence of an oxobacteriochlorin product as well as uncharacterized species. Otherwise, a single bacteriochlorin (B1-T$_2$) macrocycle was reliably observed by TLC and LD-MS analyses across the reaction survey.

Appendix A.2 Acid Survey for the Self-Condensation of 15-Ac

The self-condensation of 15-Ac was examined under a variety of conditions (Table A2). The use of BF$_3$·O(Et)$_2$ gave no bacteriochlorin (entries 1–4), and moreover, the crude samples gave data suggestive of tetradehydrocorrin-like macrocycles (upon examination by LD-MS and absorption spectroscopy). Bacteriochlorin formation was not observed under neat TFA, TMSOTf/DTBP or InCl$_3$ (entries 5–8), even using 1,2-dichloroethane (DCE) or toluene as solvent at 80 °C. The self-condensation of dihydrodipyrrin–acetate 15-Ac in the presence of Bi(OTf)$_3$ gave bacteriochlorin in 0.8% yield (entry 9) and 1.2% yield with FeCl$_3$/AgOTf (entry 10). Bacteriochlorin formation was observed in up to 2% yield with p-TsOH·H$_2$O as the acid catalyst (entries 11 and 12).
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Table A1. Survey of Conditions for the Self-condensation of Carbinol 6a or Acetate 6a-Ac a.

| Entry | Reactant (mM) | Acid (mM) | Solvent | Oxidant | Conditions | Yield (%) b |
|-------|----------------|-----------|---------|----------|------------|-------------|
| 1     | 6a [18]        | BF₃·O(Et)₂ [140] | CH₃CN | air      | r.t., 16 h | <1          |
| 2     | 6a [18]        | BF₃·O(Et)₂ [140] | CH₃CN | air      | reflux, 2 h | 4.3         |
| 3     | 6a-Ac [18]     | Neat TFA e | CH₂Cl₂ | air      | r.t., 21 h | 0.6         |
| 4     | 6a-Ac [18]     | TMSOTf [72], DTBP [144] | CH₂Cl₂ | air      | r.t., 4 h d | 0.9         |
| 5     | 6a-Ac [18]     | BF₃·O(Et)₂ [70] | CH₃CN | air      | r.t., 21 h | 13          |
| 6     | 6a-Ac [18]     | BF₃·O(Et)₂ [140] | CH₃CN | air      | r.t., 21 h | 17          |
| 7     | 6a-Ac [18]     | BF₃·O(Et)₂ [280] | CH₃CN | air      | r.t., 21 h | 12          |
| 8     | 6a-Ac [18]     | BF₃·O(Et)₂ [560] | CH₃CN | air      | r.t., 21 h | 4.4         |
| 9     | 6a-Ac [5]      | BF₃·O(Et)₂ [50] | CH₃CN | air      | reflux, 2 h | 22          |
| 10    | 6a-Ac [18]     | BF₃·O(Et)₂ [140] | CH₂CN | air e | reflux, 2 h | 4.3         |
| 11    | 6a-Ac [5]      | BF₃·O(Et)₂ [70] | CH₂CN | air e | reflux, 2 h | 22          |
| 12    | 6a-Ac [18]     | BF₃·O(Et)₂ [140] | PhNO₂ | air | reflux, 2 h | 7.1         |
| 13    | 6a-Ac [18]     | BF₃·O(Et)₂ [140] | CH₂CN | O₂ | reflux, 2 h | 8.6         |
| 14    | 6a-Ac [18]     | BF₃·O(Et)₂ [140] | CH₂CN | – | – | 7.0 f |

a Each reaction was carried out in a 4 mL vial containing a magnetic stir bar. In each reaction, 1.0 mg of reactant (6a-Ac) and 120 µL of solvent was used (entry 10 used 427 µL of solvent). b Yields were determined spectrophotometrically by the intensity of the Qy band (~726 nm, assumed Qy = 120,000 M⁻¹ cm⁻¹ [18,19]) of crude samples. The crude sample was prepared by removal of a specific amount (5–10 µL) of sample from the reaction mixture and dilution with 3 mL of CH₂Cl₂. c The color of the reaction mixture changed quickly (in 1 h) to a strong greenish blue. The overall shape of the absorption spectrum was closer to that of tetradehydrocorrin-like compounds; d The reaction was monitored for 21 h. The intensity of the Qy band was weak, broad and of uncertain magnitude; e Also contains PhNO₂ (810 mM); f The quantity of DDQ employed was 3 equiv. The product was likely an oxobacteriochrome.

Table A2. Survey of Conditions for the Self-condensation of Dihydrodipyrrin–acetate 15-Ac a.

| Entry | Acid (mM) | Solvent | Oxidant | Conditions | Yield (%) b |
|-------|-----------|---------|----------|------------|-------------|
| 1     | BF₃·O(Et)₂ [140] | CH₃CN | air      | r.t., 24 h | – c |
| 2     | BF₃·O(Et)₂ [140] | CH₃CN | air      | 80 °C, 2 h | TDC d |
| 3     | BF₃·O(Et)₂ [560] | CH₃CN | air      | 80 °C, 10 min | TDC d |
| 4     | Neat TFA | – | air      | r.t., 19 h | TDC d |
| 5     | Neat TFA | – | air      | r.t., 19 h | – e |
| 6     | TMSOTf [72], DTBP [144] | CH₂Cl₂ | air      | r.t., 19 h | – e |
| 7     | TMSOTf [72], DTBP [144] | CH₂Cl₂ | air      | 80 °C, 19 h | – e |
| 8     | InCl₃ [140] | Toluene | air      | 80 °C, 2 h | – c |
| 9     | Bi(OtBu)₃ [36] | CH₂Cl₂ | air      | r.t., 16 h | 0.8 |
| 10    | FeCl₃ [9], AgOTf [18] | CH₂Cl₂ | air      | r.t., 16 h | 1.2 |
| 11    | p-TsOH·H₂O [90] | AcOH | air      | 80 °C, 2 h | 1.9 |
| 12    | p-TsOH·H₂O [360] | DCE | air      | 50 °C, 1 h | 1.2 |

a Each reaction was carried out in a 4 mL vial containing a magnetic stir bar. In each reaction, 2.0 mg of reactant (15-Ac, 18 mM) and 0.23 mL of solvent was used; b Yields were determined spectrophotometrically by the intensity of the Qy band (~741 nm, εQy = 120,000 M⁻¹ cm⁻¹ [18,19]) of crude samples. The crude sample was prepared by removal of a specific amount (5 µL) of sample from the reaction mixture and dilution with 3 mL of CH₂Cl₂; c No bacteriochlorin was formed; d The absorption spectrum was suggestive of tetradecahydrocorrin (TDC)-like compounds; e TLC analysis shows the starting material 15-Ac and no bacteriochlorin.
Appendix A.3 Acid Survey for the Self-Condensation of 15

The self-condensation of dihydrodipyrrin–carbinol 15 was examined under a variety of conditions (Table A3). The formation of bacteriochlorin was not observed under TFA (neat) at room temperature or 50 °C for 24 h (entry 1).

Table A3. Survey of Conditions for the Self-condensation of Dihydrodipyrrin–carbinol 15.

| Entry | Reactant (mM) | Acid (mM) | Solvent | Oxidant | Conditions | Yield (%) |
|-------|---------------|-----------|---------|---------|------------|-----------|
| 1     | 15 [18]       | Neat TFA  | –       | air     | 50 °C, 24 h | ~c        |
| 2     | 15 [18]       | TFAA [45] | CH₂Cl₂  | air     | 40 °C, 24 h | 4.5       |
| 3     | 15 [18]       | TFAA [90] | CH₂Cl₂  | air     | 40 °C, 24 h | 10        |
| 4     | 15 [18]       | TFAA [180]| CH₂Cl₂  | air     | 40 °C, 24 h | 5.8       |
| 5     | 15 [18]       | TFAA [45] | CH₂Cl₂  | air     | 40 °C, 24 h | 4.2       |
| 6     | 15 [18]       | TFAA [90] | CH₂Cl₂  | air     | 40 °C, 24 h | 5.8       |
| 7     | 15 [18]       | TFAA [180]| CH₂Cl₂  | air     | 40 °C, 24 h | 4.0       |
| 8     | 15 [50]       | TFAA [90] | CH₂Cl₂  | air     | 40 °C, 20 h | 2.4       |
| 9     | 15 [18]       | TFAA [90] | CHCl₃   | 5.8     | 4.8       |
| 10    | 15 [2]        | TFAA [180]| CH₂Cl₂  | air     | 40 °C, 24 h | 17        |
| 11    | 15 [2]        | TFAA [180]| CH₂Cl₂  | air     | 40 °C, 24 h | 10        |
| 12    | 15 [18]       | TfO [90]  | CH₂Cl₂  | air     | 40 °C, 24 h | 10        |
| 13    | 15 [18]       | TfO [90]  | CH₂Cl₂  | air     | 40 °C, 24 h | 10        |
| 14    | 15 [18]       | TfO [90], PPh₃O [180]| CH₂Cl₂ | air     | 40 °C, 16 h | 5.2       |

* Each reaction was carried out in a 4 mL vial containing a magnetic stir bar. In each reaction, 2.0 mg of reactant (15, 4.5 µmol) was used; b Yields were determined spectroscopically by the intensity of the Qₐ band (~741 nm, εQₐ = 120,000 M⁻¹cm⁻¹ [18,19]) of crude samples. The crude sample was prepared by removal of a specific amount (5 µL from 18 mM, 2.5 µL from 50 mM and 10 µL from 2 mM reactions) of sample from the reaction mixture and dilution with 3 mL of CH₂Cl₂; c No bacteriochlorin formation; d Reaction at 23 µmol gave 13% yield; e Reaction at 23 µmol gave 11% yield.

Treatment of the dihydrodipyrrin–carbinol 15 (18 mM) with trifluoroacetic anhydride (TFAA) (45 mM) at room temperature for 24 h gave the meso-tetrayral/bacteriochlorin in 1.8% yield (entry 2), and with 90 or 180 mM TFAA, the yield was ~4% (entries 3 and 4). The reaction at 40 °C gave better yields compared to room temperature, with TFAA at 45 mM (4.5%), 90 mM (10%), or 180 mM (5.8%) (entries 5–7). Maintaining the TFAA concentration fixed (90 mM) but varying the concentration of 15 (entries 8–10) gave 10% yield at 2 mM (entry 10); a further increase in TFAA concentration to 180 mM gave 17% yield (entry 11). Although a 17% yield was observed by using 180 mM of TFAA and 2 mM of 15 (4.5 µmol), increasing the scale of the reaction to 23 µmol gave only 11% yield (entry 11 footnote). The reaction of 15 with triflic anhydride (entries 12 and 13) or in combination with triphenylphosphine oxide (entry 14) failed to improve the yield.

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**Sample Availability:** The small-scale syntheses, repetitive studies of reaction conditions, and photophysical studies preclude availability of most of the compounds from the authors.

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