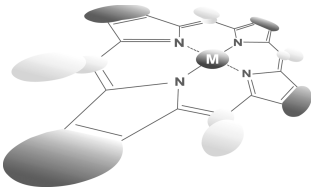
Journal of Porphyrins and Phthalocyanines
J. Porphyrins Phthalocyanines 2023; **27**: 1502–1551
DOI: 10.1142/S1088424623501171

Published at https://www.worldscinet.com/jpp/



Bacteriochlorin syntheses – Status, problems, and exploration

Vy-Phuong Tran, Pengzhi Wang, Nobuyuki Matsumoto, Sijia Liu, Haoyu Jing, Phattananawee Nalaoh, Khiem Chau Nguyen, Masahiko Taniguchi, and Jonathan S. Lindsey[◊,*]

Department of Chemistry, North Carolina State University, Raleigh, North Carolina 27695, USA

Received 25 May 2023
Accepted 3 July 2023

ABSTRACT: Bacteriochlorins – Nature's near-infrared (NIR) chromophores – are distinguished by an intense (ε ~10^5 $M^{-1}cm^{-1}$) long-wavelength absorption band in the ~700–1000 nm. The development of routes to prepare synthetic, tailorable bacteriochlorins holds promise for multiple disciplines where NIR-light-promoted photoactivity is of interest. A *de novo* route to bacteriochlorins equipped with a stabilizing gem-dimethyl group in each pyrroline ring was discovered in 2003. Continued development in this arena over 20 years has led to additional routes as well as methods to install substituents at selected positions about the perimeter of the macrocycle. The present paper reports studies that highlight substantial limitations of existing synthetic routes, including stymied access to multi-bacteriochlorin arrays and the inability to install (in a rational way) distinct groups at opposite sides of the macrocycle. The origins of the limitations are traced to particular stages of the chemistry ranging from derivatizing pyrroles, creating pyrrolines, constructing and elaborating dihydrodipyrrins, coupling dihydrodipyrrins, and forming macrocycles. Through exploration of a dozen aspects of bacteriochlorin syntheses, 60 new compounds (and nine known compounds via improved syntheses) have been prepared and characterized; the data include 20 single-crystal X-ray diffraction analyses. The research taken together points to areas of focus to fulfill the promise of this fascinating class of compounds.

KEYWORDS: bacteriochlorophyll, dihydrodipyrrin, dyad, pyrrole, pyrroline, near-infrared.

INTRODUCTION

Bacteriochlorophylls are Nature's chosen pigments for light-harvesting and energy transduction in anoxygenic photosynthetic bacteria [1]. Bacteriochlorophylls absorb strongly in the near-ultraviolet, strongly in the NIR, and moderately in the visible spectral region. A bacteriochlorin is the core chromophore of bacteriochlorophylls. The development of synthetic chemistry of bacteriochlorin macrocycles is potentially door-opening for photochemical studies in the relatively undeveloped NIR spectral region [2]. The archetype of bacteriochlorophylls is bacteriochlorophyll *a* (Chart 1).

The essential nomenclature of bacteriochlorins is outlined in Chart 2. A bacteriochlorin has alternating pyrrole (unsaturated) and pyrroline (saturated at the β-positions) rings. The rings are labeled A–D by convention, with the carbon skeleton numbered 1–20 beginning with ring A and proceeding clockwise [3]. The numbering system is fixed in this manner regardless of substituents and their IUPAC priorities [4]. The methine carbon that intervenes between pyrrole and pyrroline rings is termed the meso-carbon. The β-pyrrole positions are frequent sites of substitution. Native bacteriochlorophylls contain an isocyclic ring (ring E), where the two carbons of this annulated ring are labeled 13^1 and 13^2, and thereby constitute a special subset of bacteriochlorins. A bacteriophorbine represents the free base skeleton of bacteriochlorophylls. The alternating pyrrole and pyrroline rings engender two axes, the

[◊]SPP full member in good standing.

*Correspondence to: Jonathan S. Lindsey, e-mail: jlindsey@ncsu.edu

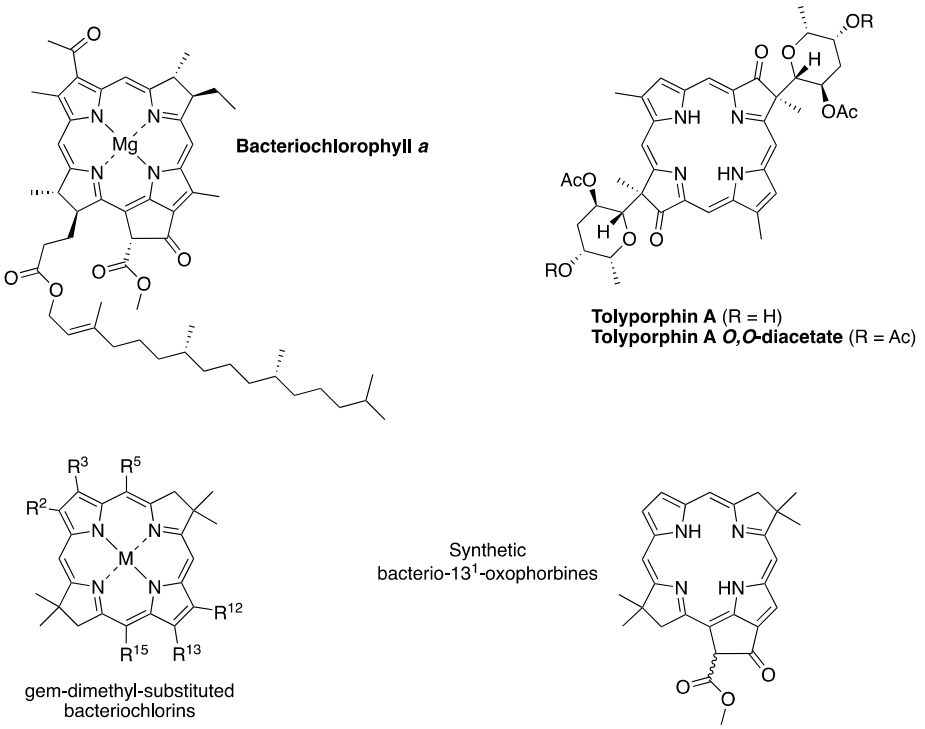


Chart 1. Structures of bacteriochlorophyll *a*, tolyporphin A, and related synthetic macrocycles.

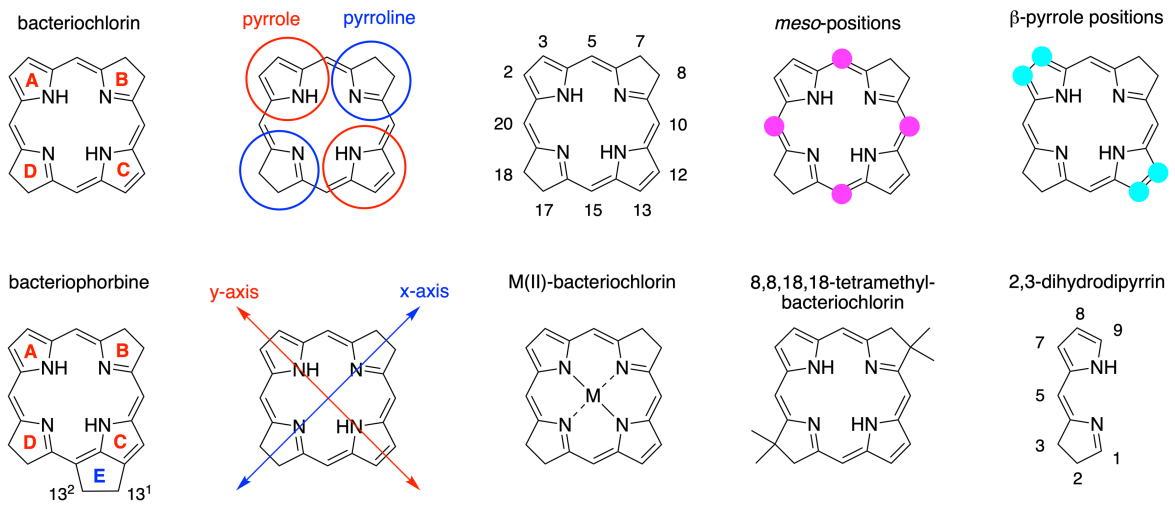


Chart 2. Nomenclature.

long axis (y-axis) and short axis (x-axis), which often are referred to in association with particular electronic transitions in the optical spectra. A divalent metal upon complexation with a bacteriochlorin dianion (formed by removal of the two N–H protons) forms a neutral metallobacteriochlorin. The gem-dimethyl-substituted bacteriochlorins described herein invariably have the four methyl groups located at the 8,8,18,18-positions. A 2,3-dihydrodipyrrin is a common precursor to bacteriochlorins and is comprised of a pyrrole and a pyrroline, with the latter having priority in numbering; hereafter, the "2,3" prefix generally is elided in the text.

There are multiple synthetic routes to bacteriochlorins:

- Semisynthesis from bacteriochlorophylls [5, 6] can afford desirable structural complexity but also can be limited by the inherent complexity and the typically tiny quantities available of the native macrocycles.
- Reduction of a porphyrin readily affords the tetrahydroporphyrin (i.e., bacteriochlorin) [7–9] but adventitious oxidation upon handling in air can give rise to the chlorin and can eventually regenerate the porphyrin.
- Cycloaddition with porphyrins [8, 10, 11], a more recent and quite efficacious strategy, can afford stable

bacteriochlorins but may afford limited control over the site of derivatization.

- *De novo* syntheses can afford, in principle, ultimate control over all features of the macrocycle. Total syntheses of native bacteriochlorophylls (or bacteriophorbines) have not been reported [12]. The *de novo* syntheses to date include (1) total synthesis of tolyporphin A diacetate (R = Ac, Chart 1), the *O,O*-diacetate of tolyporphin A, by Kishi and co-workers [13–17], but not tolyporphin A itself [12]; (2) the synthesis of gem-dimethyl-substituted bacteriochlorins (Chart 1), by two distinct routes [18, 19]; and (3) synthesis of substituted analogues of the skeleton of native bacteriochlorophylls (Chart 1) [20]. In general, the *de novo* syntheses install saturation characteristic of the pyrroline rings into the precursors of the macrocycle, as opposed to instituting the reduced features after the macrocycle has been constructed (e.g., the hydrogenation of or cycloaddition to a porphyrin). The gem-dimethyl-substituted bacteriochlorins are the focus here; the presence of a gem-dimethyl group in each pyrroline ring prevents adventitious dehydrogenation that could lead to the chlorin and the porphyrin. The impetus to embark on the use of the gem-dimethyl group came from the presence of a gem-dimethyl group in the native pigment bonellin, a non-photosynthetic chlorin for which a racemic synthesis was developed by Battersby and coworkers [21, 22] approximately 40 years ago [4]. Tolyporphin A also contains a gem-dialkyl group in each pyrroline ring. In practice, the *de novo* syntheses have generally been insufficiently developed to fulfill the promise of extensive positional malleability of substituents; moreover, the quantity of products often is small, thus suffering to date the same limitation as semisynthesis of native bacteriochlorophylls.

The limitations to the *de novo* syntheses of gem-dimethyl-substituted bacteriochlorins are highlighted here by two types of target compounds. The two types of target compounds are as follows: (1) bacteriochlorin dyads, and (2) water-soluble, wavelength-tunable bacteriochlorins bearing a single bioconjutable group.

In 2004, Dreuw and Head-Gordon studied *in silico* a dyad (**I**) composed of a free base bacteriochlorin and a zinc bacteriochlorin (Chart 3) [23]. The linker was a 1,4-phenylene-unit spanning meso-positions of the respective bacteriochlorins. The studies revealed the possible participation of charge-transfer states in excited-state energy-transfer and electron-transfer processes. In somewhat of a role reversal, the bacteriochlorin dyad was used as a proxy to probe limitations to computational methods of that era. Analogous systems (**II**, Chart 3) have been synthesized [24], characterized [25], and studied by calculations [26]. We sought to synthesize such 1,4-phenylene-linked dyads lacking any peripheral substituents (particularly the 5-methoxy group) but have been stymied by limitations of synthesis. The dyads devoid of any

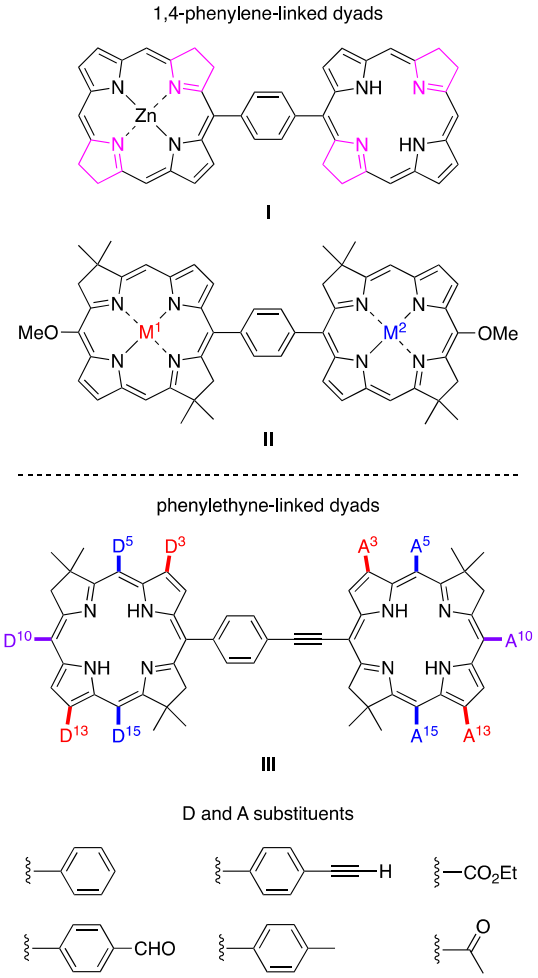


Chart 3. Bacteriochlorin dyads studied *in silico* (top) and synthesized (bottom).

substituents (i.e., "naked" other than the requisite gem-dimethyl groups) or substituted sparsely with strategically chosen substituents for wavelength tuning [27–29] were desired for fundamental studies of excited-state energy transfer [30, 31]. We ultimately settled on the synthesis of phenylethyne-linked bacteriochlorin dyads (**III**, Chart 3) for studies of possible vibrational coherences in excited-state energy transfer [30, 31], because the use of the phenylethyne linker presents fewer synthetic constraints on the availability of bacteriochlorin building blocks than does the phenylene linker. The challenges to the synthesis of *p*-phenylene-linked bacteriochlorin dyads reside in methods for the formation and derivatization of bacteriochlorins. As a point of contrast, a vast menagerie of *p*-phenylene-linked porphyrin dyads is known [32].

A second molecular design that presents unresolved challenges to synthesis encompasses wavelength-tunable, water-soluble bacteriochlorins each equipped with a single bioconjugatable group as illustrated by structure **IV** (Chart 4). For rational bioconjugation, the presence of a single bioconjugatable substituent (Z) is sought. Additional groups to be positioned strategically at the perimeter of the macrocycle can include a polar,

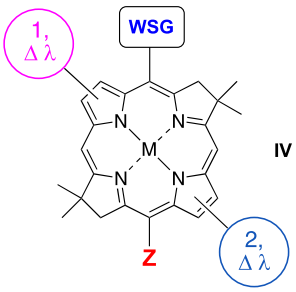


Chart 4. Wavelength-tunable, water-soluble, bioconjugatable bacteriochlorin.

water-solubilization group (WSG) and auxochromes for wavelength tuning (Δλ). The chief synthetic limitation arises because the present routes to gem-dimethyl-substituted bacteriochlorins entail a head-to-tail condensation of two dihydrodipyrrins. Consequently, the respective substituents on each half of the macrocycle are identical to each other. The positions of the auxochromes (Δλ), water-solubilization group (WSG), and bioconjugatable handle (Z) shown in Chart 4 are illustrative only. Ideally, one wants complete synthetic malleability to install such groups at will at any site about the perimeter of the macrocycle.

The exploration of a suite of auxochromes to tune the position of the long-wavelength (Q_y) absorption band has entailed the preparation of a substantial number of gem-dimethyl-substituted bacteriochlorins. The rationale for this interest is to open access to the NIR spectral region for use in photomedicine (therapy and diagnostics) and to capture NIR light for solar energy utilization. The two extreme examples to date are shown in Chart 5, with the shortest Q_y absorption band (680 nm) given by a 7,17-dioxobacteriochlorin (**BC-1**) [33], which contains a chromophore identical to that of tolyporphin A [34], and

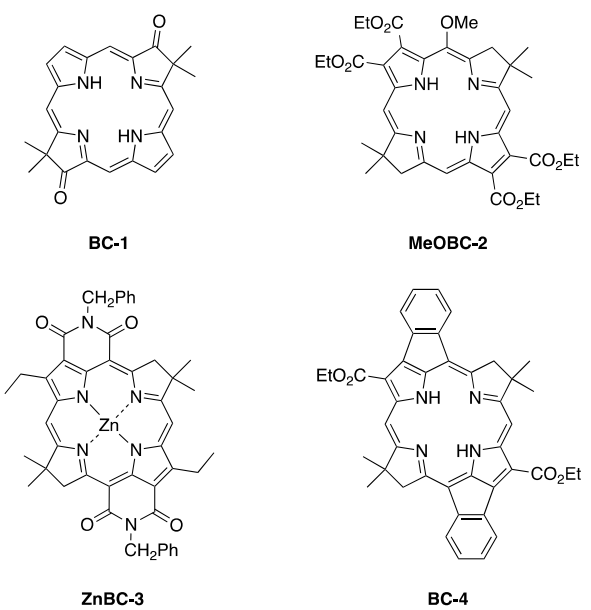


Chart 5. Wavelength-tuned bacteriochlorins.

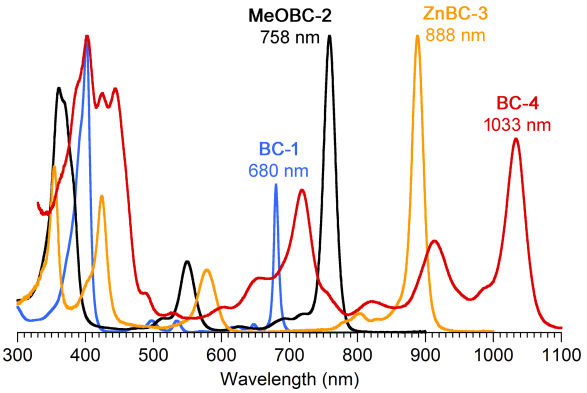


Fig. 1. Absorption spectra (normalized) in toluene at room temperature of selected synthetic bacteriochlorins.

the longest Q_y absorption band (1033 nm) given by an annulated bacteriochlorin (**BC-4**) [35], which has no biological counterpart. Spectra at intermediate wavelengths are illustrated by bacteriochlorins **MeOBC-2** (758 nm) [36] and **ZnBC-3** (888 nm) [37]. The absorption spectra are shown in Fig. 1. In each case, the bacteriochlorin is substituted symmetrically on opposite sides of the macrocycle. Many other wavelength-tunable bacteriochlorins [38] fill the gaps among the selected bacteriochlorins for which the spectra are displayed in Fig. 1. Significant unknowns, however, are how deep into the NIR region the Q_y band can be pushed with various structural alterations, and the nature of the photophysical features of the corresponding low-energy excited states.

The preparation of bacteriochlorin-bacteriochlorin arrays has been of longstanding interest but has proved quite difficult upon semisynthesis with native bacteriochlorophylls [39]. The gem-dimethyl-substituted bacteriochlorins enable the preparation of bacteriochlorin-bacteriochlorin arrays [31, 40] for studies of light-driven processes in the NIR including energy transfer [30], but not yet the phenylene-linked dyads proposed by Dreuw and Head-Gordon [23]. The gem-dimethyl-substituted bacteriochlorin monomers have been used for studies of photodynamic therapy [41, 42], redox-based catalysis [43, 44], and charge-separation studies [40]. Synthesis also has enabled isotopic labeling of the core atoms of bacteriochlorins [45] as well as peripheral sites [29], enabling a focused study of physical properties [46, 47]. The gem-dimethyl-substituted bacteriochlorins can subsequently be metalated [48] albeit with greater difficulty than chlorins and porphyrins. Synthetic studies with gem-dimethyl-substituted bacteriochlorins have also been carried out by the groups of Gros and Romieu [49, 50], Lin [51–53], de Oliveira [54], Ptaszek [24–26, 55–71], Ruppel [72], and Su [73]. Other groups have reported calculations of gem-dimethyl-substituted bacteriochlorins [74, 75].

The substantial promise of this class of compounds has driven extensive synthetic methodology development. In this paper, we report exploratory synthetic efforts directed toward surmounting the limitations described above. The

exploratory studies are presented in the broad context of the present status of the field. Many approaches fell into the well-known category of ostensibly reasonable *in charta* yet practically fruitless *in experimentum*. There appears no one single bottleneck that crimps synthetic access to bacteriochlorins; rather, limitations occur at a hierarchy of levels ranging from the small heterocycles pyrrole and pyrroline, to dihydrodipyrrins, to the macrocycles themselves. Altogether, established and prospective routes have been investigated, 60 new compounds have been prepared, and 20 single-crystal X-ray diffraction analyses are reported.

RESULTS AND DISCUSSION

The following material is organized beginning with results concerning the three routes to gem-dimethyl-substituted bacteriochlorins. The three routes are the Eastern-Western route, the Northern-Southern route, and the synthesis of bacteriochlorophyll analogues (Chart 6). The three routes share common features yet also possess distinct features. The Eastern-Western route and the Northern-Southern route both rely on the self-condensation of two equivalents of a 1-(1,1-dimethoxymethyl)dihydrodipyrrin (also referred to as a dihydrodipyrrin-dimethyl acetal) whereas bacteriochlorophyll analogues are created from a dihydrodipyrrin-1-carboxaldehyde (AD half) and a dihydrodipyrrin-dimethyl acetal bearing a β-ketoester attached to the pyrrole (BC half). The first three sections highlight attractive features as well as deficiencies of the present methodology. The stages wherein the deficiencies originate range widely including the nature of the reactive groups attached at the 1- and 9-positions of a dihydrodipyrrin, methods to prepare dihydrodipyrrins, and the scope of tolerable substituents at the 2-, 3-, 5-, 7-, and 8-positions in dihydrodipyrrins. The final section describes exploratory studies aimed at developing a directed synthesis of gem-dimethyl-substituted bacteriochlorins (where two distinct halves are joined), thereby complementing the self-condensation approaches in the Eastern-Western and Northern-Southern routes.

The Eastern-Western route to bacteriochlorins

Illustration of problems

The first route developed to prepare gem-dimethyl-substituted bacteriochlorins [18] is exemplified by a very recent synthesis (Scheme 1) [76]. The 2,5-unsubstituted pyrrole **1** underwent Vilsmeier formylation [77] with 10:1 selectivity in favor of the 4-carboethoxy-2-formylpyrrole **2a** versus the 3-carboethoxy-2-formylpyrrole **2b**, a positional isomer. Henry reaction [78] with nitromethane afforded the 2-(2-nitrovinyl) pyrrole. Reduction of the nitrovinyl group afforded the 2-(2-nitroethyl)pyrrole **3**; this seemingly simple reaction is now known to also afford a dimeric byproduct (derived by Michael addition of one molecule of product with one molecule of starting material [79]). Michael addition [80] with the α,β-unsaturated ketone **4** [81] gave the pyrrole-nitro-hexanone **5**. Subsequent McMurry-Melton reaction [76] gave the desired dihydrodipyrrin **6** accompanied in this case by an intermediate (or byproduct) dihydrooxazine **7**. Self-condensation [18, 36] of **6** in the presence of $BF_3{\cdot}OEt_2$ gave two bacteriochlorins, a 5-methoxybacteriochlorin (**MeOBC-5**) and a bacteriochlorin lacking any meso-substituents (**BC-5**). The 5-methoxybacteriochlorin stems from condensation wherein three molecules of methanol are released, with the lone methoxy group at the 5-position a vestige of one of the dimethyl acetal moieties [81]. The origin of the 5-unsubstituted bacteriochlorin must

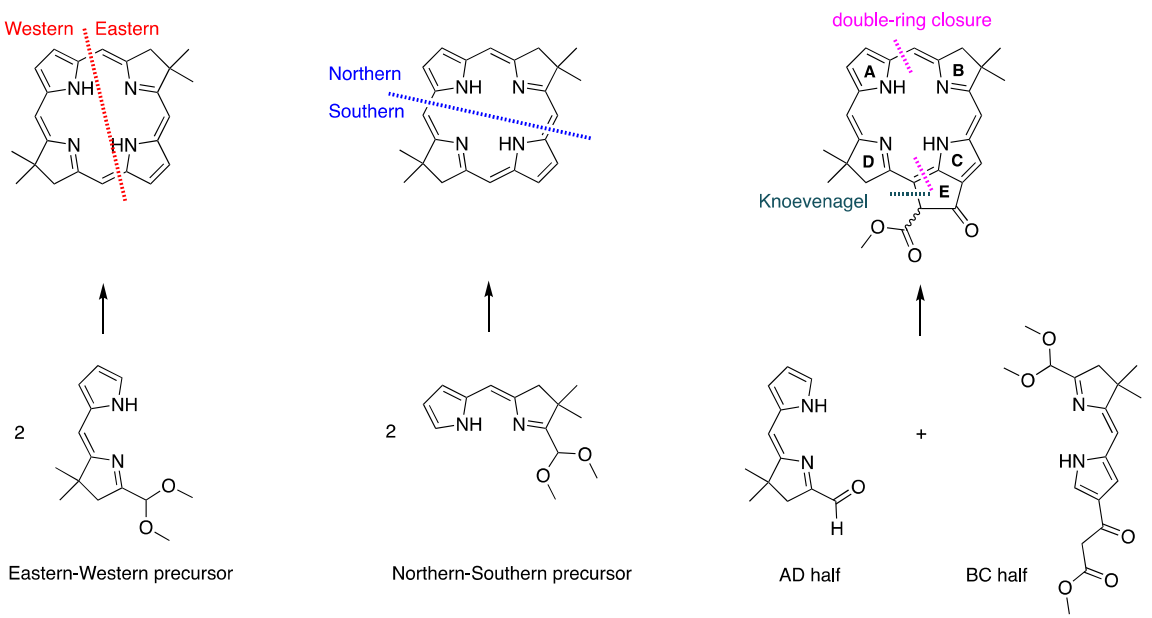
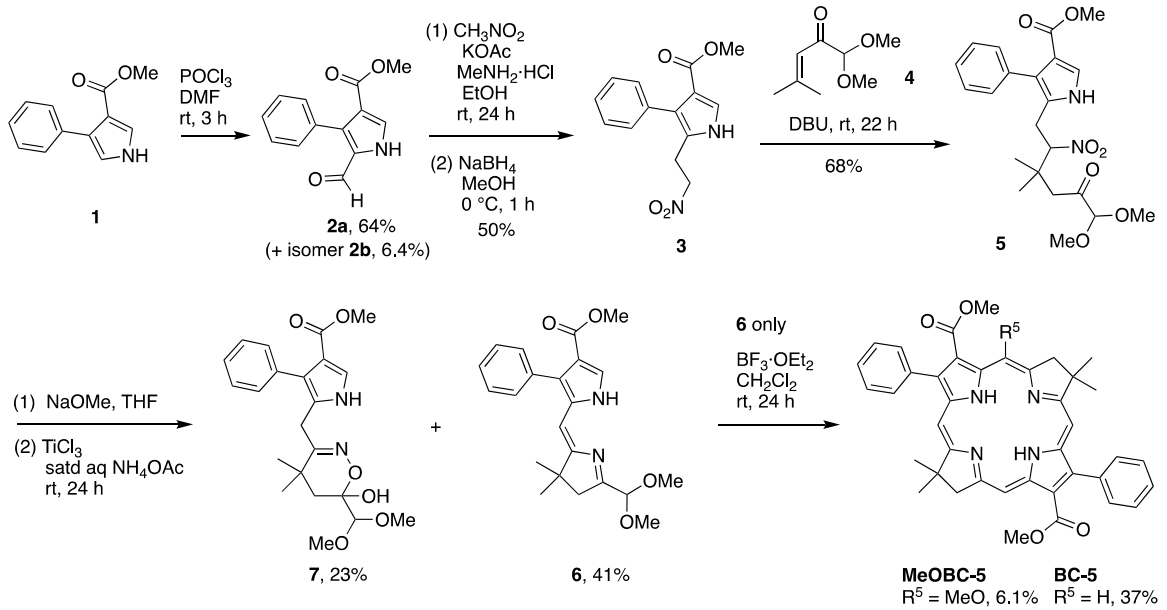


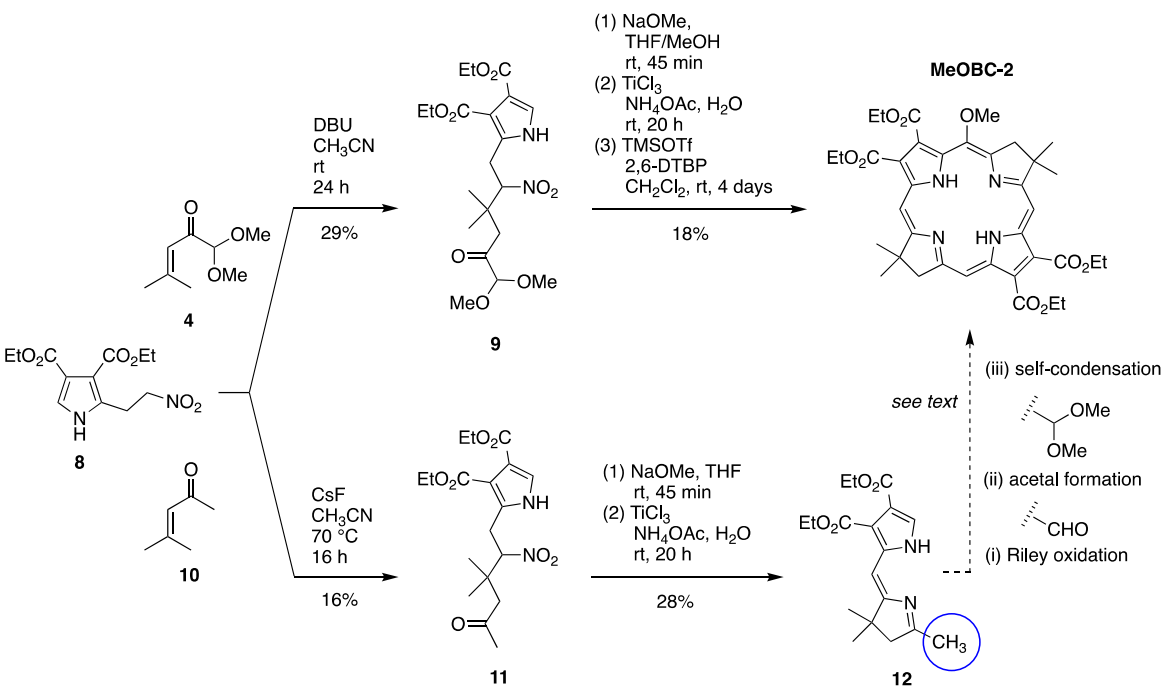
Chart 6. Distinct *de novo* routes to bacteriochlorins.



Scheme 1. Eastern-Western route to bacteriochlorins [76].

entail an additional reductive process of unknown origin at some point in the transformation [18, 82]. The X-ray diffraction (XRD) data for **6** and **7** have been published previously [76]. Here, the XRD data are reported for **2a**, **3**, **MeOBC-5**, and **BC-5**, which were synthesized previously (see Appendix 1) [76].

More explicit examples of challenges with dihydrodipyrrin syntheses are shown in Scheme 2. Bacteriochlorin **MeOBC-2** was prepared previously beginning with 2-(2-nitroethyl)pyrrole **8** [27] and Michael substrate **4** [27]. The yield of Michael addition to form the nitro-hexanone-pyrrole **9** was poor (29%), and the yield upon conversion of **9** via the dihydrodipyrrin (used directly) to the bacteriochlorin was 18% [27]. The condensation to form the bacteriochlorin **MeOBC-2** [27] proceeded under catalysis [36] by trimethylsilyl triflate (TMSOTf) and the hindered base 2,6-di-*tert*-butylpyridine (2,6-DTBP) [83] in CH_2Cl_2 at room temperature. Such catalysis conditions generally afford exclusively the 5-methoxybacteriochlorin without the 5-unsubstituted bacteriochlorin formed more predominantly upon the use of $BF_3{\cdot}OEt_2$ and other strong acids [36].



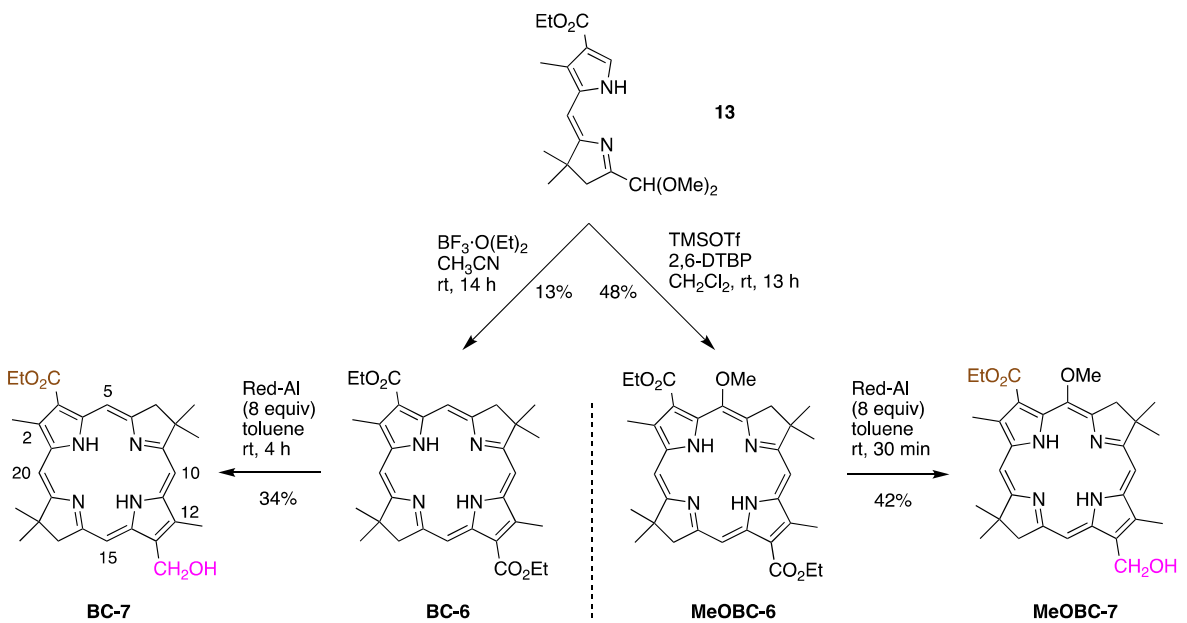
Scheme 2. Distinct routes to a bacteriochlorin-tetraester.

An alternative approach was explored subsequently and is reported here that relied on the use of mesityl oxide (**10**) rather than the dimethoxy-substituted Michael substrate **4**, anticipating that the dimethoxy groups would be introduced immediately before bacteriochlorin formation. The Michael addition with 2-(2-nitroethyl)pyrrole **8** [27] upon treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetonitrile, identical conditions to that for formation of **9**, gave **11** in only 7% yield (Table S1), whereas the use of tetra-*n*-butylammonium fluoride (TBAF) in THF or acetonitrile at room temperature or 65 °C did not afford the desired product. The use of CsF in acetonitrile gave the desired product **11** in 16% yield, but the yield was subtly affected by reactant ratios and reaction time. Subsequent cyclization of **11** gave dihydrodipyrrin **12** in 28% yield. The conversion of **12** to **MeOBC-2** would then require Riley oxidation (SeO_2 in 1,4-dioxane) of the 1-methyl group of **12** to give the dihydrodipyrrin-1-carboxaldehyde (not shown), which regardless of dihydrodipyrrin rarely proceeds in >50% yield [84], followed by dimethyl acetal formation (trimethyl orthoformate and $TsOH{\cdot}H_2O$ [19]) to give the 1-(1,1-dimethoxymethyl)dihydrodipyrrin (not shown). The low yield of the Riley oxidation [84] renders such late-stage transformations undesirable.

The syntheses shown in Scheme 1 and Scheme 2 embody the Eastern-Western route. The advantages are that (1) a wide variety of substituents can be incorporated in the pyrrole, as long as the pattern and composition of such substituents tolerate the presence or installation of the 2-formyl group; and (2) the dihydrodipyrrin is prepared without the use of any Pd-mediated coupling reactions, enabling halopyrroles to be carried through to the corresponding halobacteriochlorin. Disadvantages are numerous, however, as follows: (1) the yields of each reaction (Henry reaction, reduction, Michael addition, and McMurry-Melton reductive cyclization) are often in the range of only 20–50%; (2) the reliance on the Michael reaction precludes the use of almost [85] any geminal substituents other than dimethyl in the pyrroline ring; (3) a mixture of 5-unsubstituted and 5-methoxy-substituted bacteriochlorins is typically formed; (4) identical meso-substituents can be incorporated at the 10,20-positions (flanking the gem-dimethyl groups) [51,52] but much less so at the 5,15-positions (distal to the gem-dimethyl groups) [82]; and (5) perhaps most limiting, the use of a self-condensation of a dihydrodipyrrin starting material causes the substituents on the two sides of the bacteriochlorin to be identical with each other.

Statistical or selective transformations of intact bacteriochlorins

The preparation of a differentially substituted bacteriochlorin can be pursued by transformations of the isolated bacteriochlorin. Two examples are shown in Scheme 3. Here, condensation of dihydrodipyrrin **13** [36] in the presence of TMSOTf and 2,6-DTBP in dichloromethane gave the 5-methoxybacteriochlorin **MeOBC-6** [36], whereas condensation under $BF_3{\cdot}OEt_2$ in acetonitrile [18] gave the known [86] 5-unsubstituted bacteriochlorin **BC-6**. The treatment of bacteriochlorin **BC-6** with eight equivalents of Red-Al® (sodium bis(2-methoxyethoxy)aluminum hydride solution in toluene) gave the mono-hydroxy mono-ester bacteriochlorin **BC-7** in 34% yield. On the other hand, the analogous treatment of 5-methoxybacteriochlorin **MeOBC-6**, wherein the two esters are not equivalent, led to selective reduction of the ester group distal to the methoxy group. Bacteriochlorin **MeOBC-7** was obtained in a 42% yield.



Scheme 3. Synthesis and selective reduction of bacteriochlorin-diesters.

Table 1. ^{1}H NMR chemical shift assignments.

Substituent and position	Chemical shift δ (Δδ)[a] in ppm			
	BC-6	**BC-7**	**MeOBC-6**	**MeOBC-7**
CH_3 (2)	3.64	3.60 (–0.04)	3.40	3.36 (–0.04)
H^5	9.65	9.63 (–0.02)	–	–
H^{10}	8.63	8.42 (–0.21)	8.67	8.45 (–0.22)
CH_3 (12)	3.64	3.37 (–0.27)	3.66	3.38 (–0.28)
H^{15}	9.65	8.67 (–0.98)	9.62	8.65 (–0.97)
H^{20}	8.63	8.55 (–0.08)	8.52	8.46 (–0.06)

[a]Versus that of the parent bacteriochlorin-diester **BC-6** or **MeOBC-6**.

Evidence for the single reduction is straightforward by mass spectrometric analysis. Evidence for which of the two esters in **MeOBC-6** is reduced is obtained by ^{1}H NMR spectroscopy. Consider first **BC-6**, where the two esters are equivalent, as a benchmark. The ^{1}H NMR spectrum of bacteriochlorin **BC-6** shows a singlet from each of two pairs of meso-protons (H^5 and H^{15}, 9.65 ppm; H^{10} and H^{20}, 8.63 ppm), which are assigned owing to the relative location of the 2,12-diester groups, and a singlet from the two methyl groups (3.64 ppm); other resonances (gem-dimethyl, methylene, and NH) are not germane to the present discussion. Upon reduction, the product **BC-7** shows a profound shift of the resonance of H^{15} (Δδ = –0.98 ppm) and a modest shift of the resonance of H^{10} (Δδ = –0.21 ppm) – or H^5 and H^{20}, respectively, given the inherent symmetry – whereas only tiny shifts are observed of resonances from the other, now non-identical meso-protons (Table 1).

The ^{1}H NMR spectrum of bacteriochlorin **MeOBC-6**, which contains two non-equivalent esters, shows singlets from the three non-identical meso-protons and the two non-identical β-pyrrolic methyl groups (Table 1). Upon reduction, the product **MeOBC-7** shows a large shift of the resonance of H^{15} (Δδ = –0.97 ppm) and a modest shift of the resonance of H^{10} (Δδ = –0.22 ppm). The assignments were verified by NOESY spectroscopy, which showed the presence of a strong correlation between H^{15} and the peripheral (hydroxy) methylene protons (doublet resonance at 5.77 ppm). Meanwhile, the protons of the 5-methoxy group (singlet resonance at 4.20 ppm) exhibited a detectable correlation with that of the methyl terminus of the ethyl ester group (triplet resonance at 1.62 ppm). The NOESY spectrum is shown in the Supporting Information (Fig. S1).

In short, the two esters of **BC-6** are equivalent whereas those of **BC-7** are inequivalent. The effect – presumably chiefly steric but perhaps also in part electronic in origin – imparted by the 5-methoxy group to the neighboring 3-position was delineated by Ptaszek and coworkers, who carried out Sonogashira couplings with a 3,13-dibromo-5-methoxybacteriochlorin [55, 59]. This approach has proved valuable but to date has been demonstrated only for the 5-methoxybacteriochlorin [87].

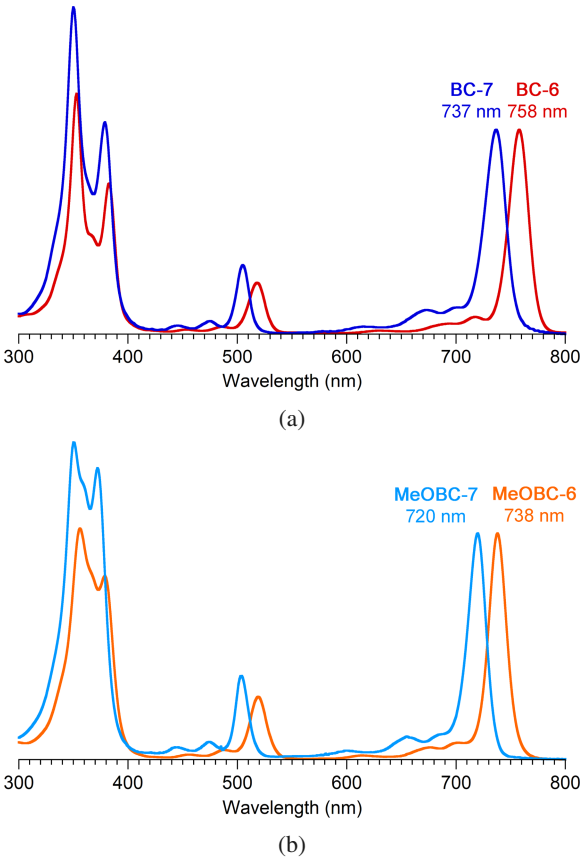
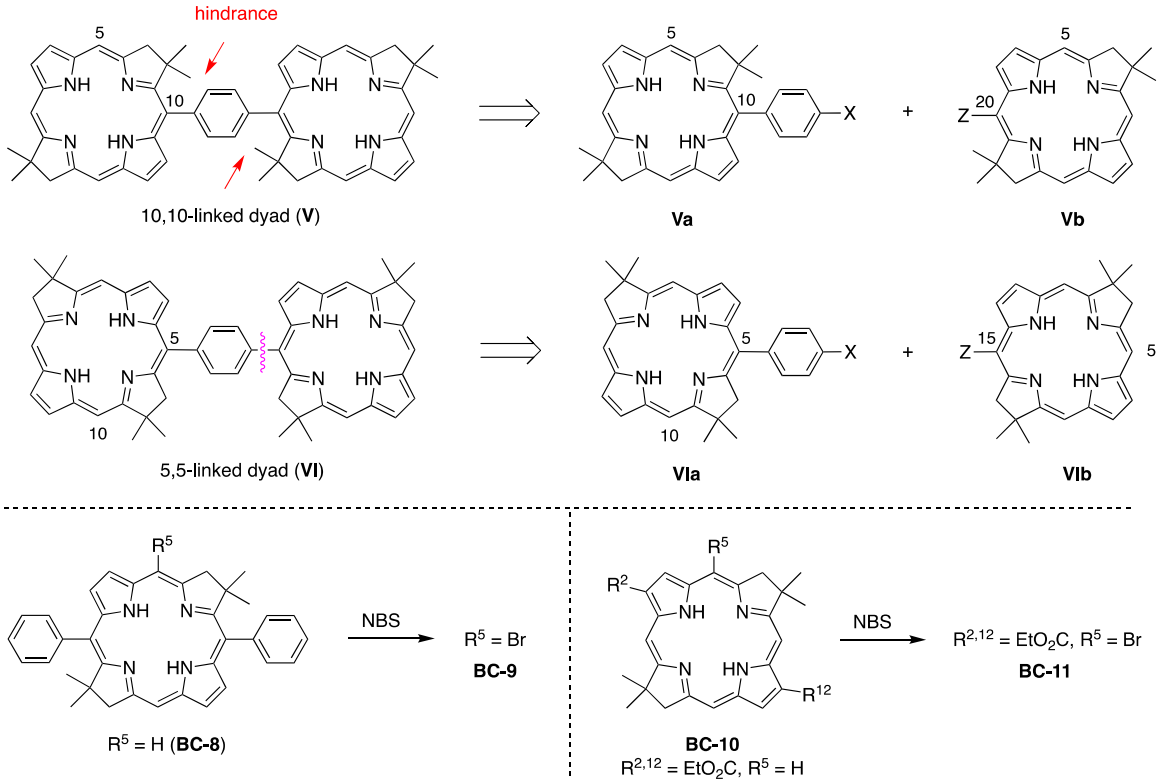


Fig. 2. Absorption spectra in toluene at room temperature of bacteriochlorins bearing two esters (**BC-6**, **MeOBC-6**) or one ester and one hydroxymethyl substituent (**BC-7**, **MeOBC-7**). The spectra are normalized at the Q_y band. The hypsochromic effect upon reducing one ester is shown for bacteriochlorin **BC-6** (forming **BC-7**) in panel (a), and for bacteriochlorin **MeOBC-6** (forming **MeOBC-7**) in panel (b).

The absorption spectra of a bacteriochlorin-diester (**BC-6** or **MeOBC-6**) and a bacteriochlorin-monoester-monoalcohol (**BC-7** or **MeOBC-7**) are shown in Fig. 2. The reduction of one ester to the hydroxymethyl unit imparts a hypsochromic shift of the Q_y absorption band of ~20 nm. The hypsochromic effect upon reducing one of two esters is shown in panel (a) for bacteriochlorin **BC-6**, and in panel (b) for bacteriochlorin **MeOBC-6**. The reduction demonstrated here illustrates tailoring one of two identical groups (derived by self-condensation in the Eastern-Western approach). With a symmetric bacteriochlorin (e.g., **BC-6**), the approach suffers from the inherently limited yield of statistical reactions. For the unsymmetric bacteriochlorin **MeOBC-6**, the process is selective for one ester versus the other due to the presence of the 5-methoxy group. Regardless, the yields in both cases were not high, and the statistical or selective reduction approach is a stopgap measure given the absence of a directed route to bacteriochlorins wherein distinct hydrodipyrrin halves are joined.



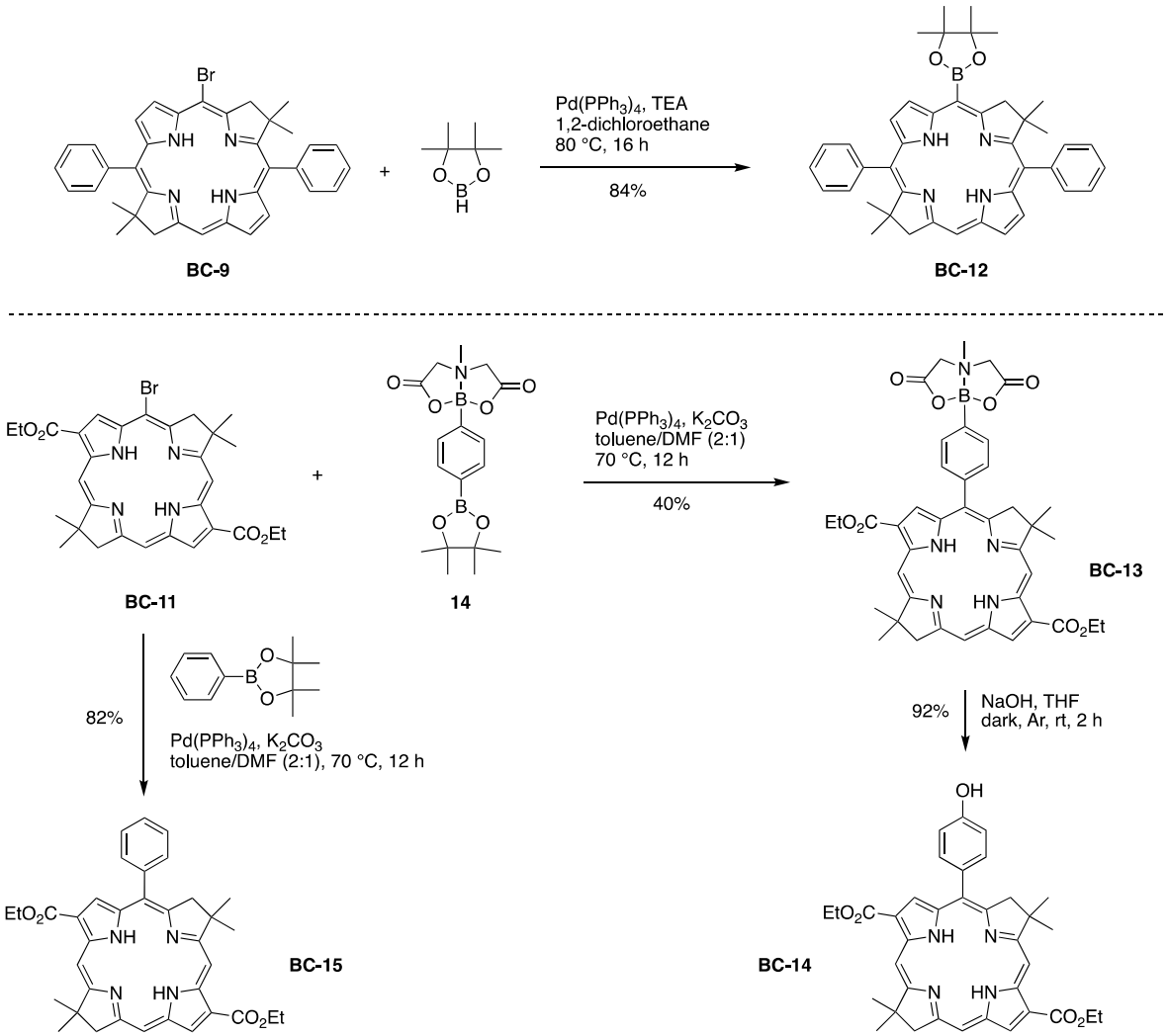
Scheme 4. Bacteriochlorin dyads (top) and 5-bromobacteriochlorins (bottom).

The bacteriochlorin dyads problems

Selective transformations as outlined above are viable in certain instances but are not supportive in general for rational syntheses of more complex architectures. Two architectures for *p*-phenylene-linked bacteriochlorin dyads – lacking (for clarity here) any peripheral substituents or chelated metals that would distinguish the two macrocycles – are shown in Scheme 4 top panel. The architectures differ in the position of attachment of the phenylene linker on the bacteriochlorins. Attachment of the phenylene linker to the 10-position (**V**) encounters hindrance with the flanking 8,8-dimethyl group, which is absent upon attachment at the 5-position (**VI**). The retrosynthetic analysis shows the necessity for a bacteriochlorin building block bearing a single substituent, suitable for Suzuki coupling, at the respective 10- or 20-position (**Va**, **Vb**) or 5- or 15-position (**VIa**, **VIb**). The bacteriochlorin building blocks with unfettered access to the site for Suzuki coupling are preferred over those with hindered access; in other words, **VIb** is considered a superior coupling partner to **Vb**. Moreover, dyad **VI** is considered more attractive than dyad **V** given the positions of the gem-dimethyl groups relative to the location of the *p*-phenylene linker.

Lin and coworkers [51, 52] found that a 10,20-diphenylbacteriochlorin (**BC-8**) could be prepared and would undergo selective bromination (in 85% yield) at the 5-position affording **BC-9** (Scheme 4, left bottom panel). We found that selected 2,12-disubstituted bacteriochlorins (e.g., **BC-10**) also would undergo selective bromination at the 5-position (**BC-11**) (Scheme 4, right bottom panel). The 2,12-substituents include carboethoxy (57% yield) as shown as well as acetyl (76% yield) [28]. Here, efforts are described to install a single aryl group suitably derivatized for subsequent Suzuki coupling en route to *p*-phenylene-linked bacteriochlorin dyads. Bacteriochlorins **BC-9** and **BC-11** each bear a bromine atom at an unhindered site and hence are attractive for use in Suzuki coupling reactions.

The first bacteriochlorin building blocks pursued the preparation of larger arrays containing a phenylboronic acid moiety. The coupling reaction of **BC-9** and pinacolborane as reported by Ptaszek and coworkers [24] afforded the 5-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl]bacteriochlorin **BC-12**, which can be used for the synthesis of bacteriochlorin dyads (Scheme 5, top). The coupling reaction [24] of **BC-11** and a reported MIDA-phenylborolane (**14**) [88] afforded the boron-masked bacteriochlorin **BC-13** (Scheme 5, bottom) along with triphenylphosphine oxide as a sizeable, co-chromatographing impurity. Treatment of **BC-13** with sodium hydroxide surprisingly afforded the 4-hydroxyphenyl-substituted bacteriochlorin **BC-14** rather than the bacteriochlorin phenylboronic acid (not shown). An attempt to trap the latter as the boronic ester upon treatment with pinacol was unsuccessful. The Suzuki coupling of **BC-11** with phenylboronic acid pinacol ester readily afforded the reference bacteriochlorin **BC-15**.

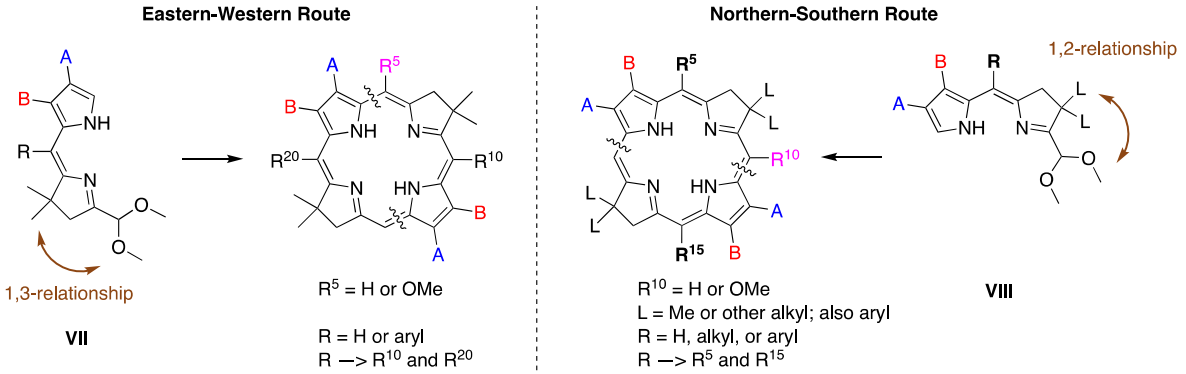


Scheme 5. Synthesis of bacteriochlorin building blocks with phenylene substituents.

In all of these derivatizations, the quantities were quite small due to the generally low yields of multiple steps on the path to the bacteriochlorin building blocks. An opening to prepare *p*-phenylene-linked bacteriochlorin dyads may be possible by the conversion of the bacteriochlorin-phenol **BC-14** to the corresponding triflate followed by Suzuki coupling with a 5-bromobacteriochlorin. Success in this direction will require larger quantities of building blocks and also remains constrained at present by the limited patterns of substituents that tolerate selective bromination at the 5-position. At present, access to single-tethered, gem-dimethyl-substituted bacteriochlorins relies on (1) 5-bromination of a 10,20-diphenylbacteriochlorin [51, 52] or a bacteriochlorin-bearing electron-withdrawing groups at the 2,12-positions [28]; (2) 15-bromination of a 5-methoxybacteriochlorin [89]; or (3) elaboration of a 5-alkoxy substituent [81, 90].

The Northern-Southern route to bacteriochlorins

The Northern-Southern route [19] to bacteriochlorins employs the same macrocyclization chemistry as the Eastern-Western route (Scheme 6). The two routes differ in the method of forming the dihydrodipyrrin-acetal and in the structure of the respective dihydrodipyrrin-acetals. In both routes, the dimethyl acetal moiety is located at the 1-position of the dihydrodipyrrin. The gem-dimethyl group is located at position 3 in the Eastern-Western route versus position 2 in the Northern-Southern route. While the two routes can be employed to prepare several bacteriochlorins that are identical, some key points of complementarity exist. In terms of bacteriochlorin products, the Eastern-Western route has the following advantages: (1) the 5-methoxybacteriochlorin can be obtained (to the exclusion of the 5-unsubstituted bacteriochlorin) through use of acid catalysis with TMSOTf and 2,6-DTBP [36]; (2) the route for preparing the dihydrodipyrrin does not employ any Pd-mediated coupling processes, thereby allowing the synthesis of halo-bacteriochlorins for late-stage derivatization [91]; and (3) the 5-methoxybacteriochlorin undergoes 15-bromination in high yield [89], enabling installation therein of a single substituent. The disadvantages of the Eastern-Western route include (1)

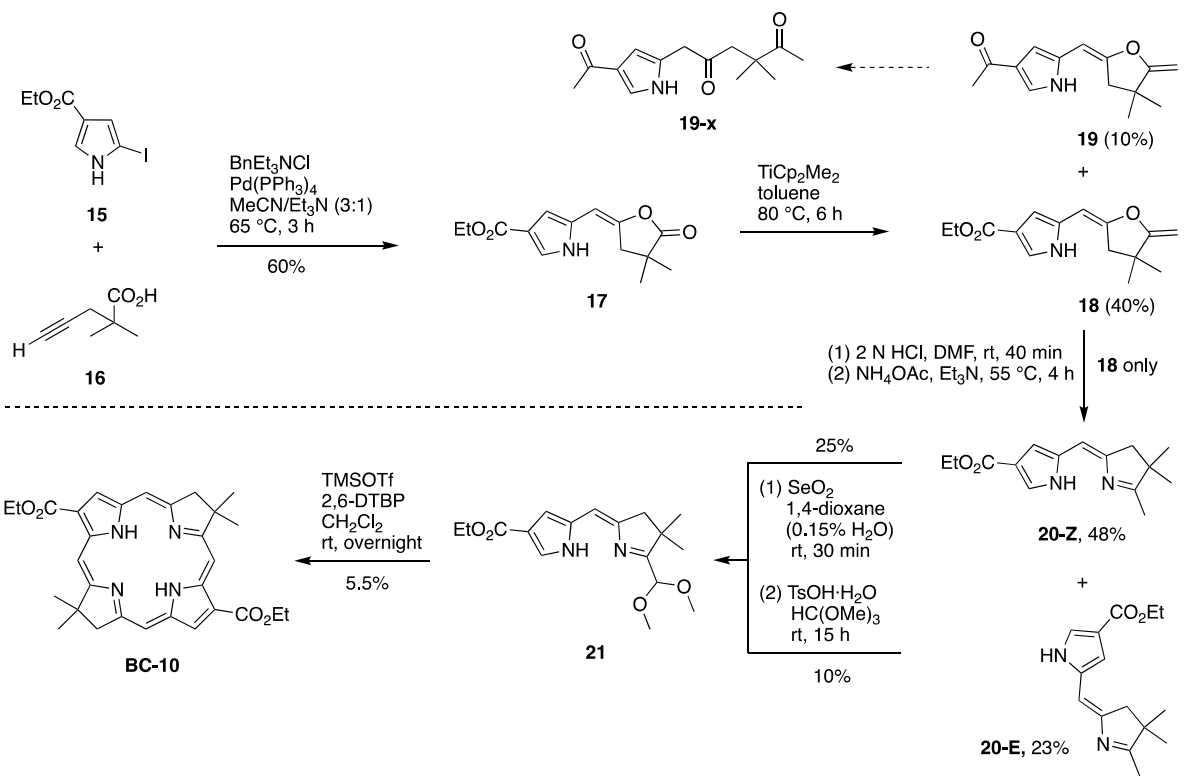


Scheme 6. Routes to gem-dimethyl-substituted bacteriochlorins.

almost total restriction to the gem-dimethyl group (as opposed to homologous alkyl groups [85]); and (2) a series of reactions of low-moderate yield leading to the dihydrodipyrrin (Scheme 1).

The Northern-Southern route [19] has come on stream only since 2016 and is less developed than the Eastern-Western route [18], but already has yielded bacteriochlorins that bear features unavailable via the latter including diverse meso-substituents (H, alkyl, aryl) [19], gem-dialkyl groups other than gem-dimethyl (e.g., phenyl or integral swallowtail substituents) [92], and annulated rings. The route also provides access to other patterns of β-substituents [27] and is central to studies concerning the total synthesis of bacteriochlorophyll *a* [20, 93–96]. Nonetheless, the Northern-Southern route also has distinct limitations as described in the following.

The synthesis of dihydrodipyrrins for the Eastern-Western route was extended from chemistry originally developed by Battersby and coworkers [4, 21, 22], whereas access to dihydrodipyrrins for the Northern-Southern route has been built on advances reported by Jacobi and coworkers [97–100]. A representative example of the Northern-Southern route is shown in Scheme 7 [27]. The route begins with the Pd-mediated coupling of 2-iodopyrrole **15** and 4-pentynoic acid **16**, which affords the pyrrole-lactone **17**. Petasis methenylation [101] affords the desired ene-lactone-pyrrole **18**, accompanied by the byproduct **19** derived by methenylation of the carboethoxy group attached to the pyrrole. The characterization of ene-lactone-pyrrole **19** (reported previously) entailed melting point determination, ^{1}H and ^{13}C{^{1}H} NMR spectroscopic examination, and ESI-MS analysis



Scheme 7. Northern-Southern route to bacteriochlorins [27].

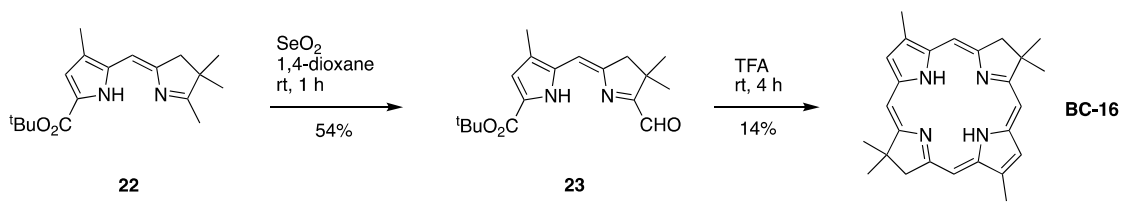
[27]. Examination of a single crystal drawn from the sample of **19**, several years following synthesis, revealed the diketone **19-x**, presumably derived by hydration of the ene-lactone moiety (see Appendix 1 for XRD data). Examination of the dated sample of **19** by ^{1}H NMR analysis showed a mixture of **19** and **19-x** in ratio of ~3:1. The structure of **19** was accurately determined based on the data in hand at the time [27]; one interpretation is that on standing or handling in the interim, **19** underwent hydration. While an isolated example, further study concerning the stability and lability of ene-lactone-pyrroles is warranted.

The Paal-Knorr reaction refers to the conversion of a 1,4-diketone and ammonia (or a primary amine) to the corresponding pyrrole [102]. While this classic 19th-century name reaction remains of great interest, the reaction of a gem-dimethyl-substituted 1,4-diketone engenders a "frustrated Paal-Knorr" reaction wherein the pyrroline results rather than the pyrrole. Thus, acid hydrolysis of **18** followed by the Paal-Knorr type reaction affords the 1-methyldihydrodipyrrin as *Z* and *E* isomers (**20-Z** and **20-E**). Subsequent Riley oxidation [84] followed by the formation of the acetal gives dihydrodipyrrin-acetal **21**. Macrocyclization gives the bacteriochlorin **BC-10** [27]. Bacteriochlorin-2,12-diester **BC-10** underwent selective bromination at the 5-position, a selectivity proposed to arise due to deactivation of the pyrrole 3,13-positions by the flanking esters and steric hindrance of the 10,20-positions by the neighboring gem-dimethyl groups, in which case the 5-position presented as the most reactive of sterically available sites [28] (Scheme 4). Bacteriochlorin **BC-10** was used to create dyads for studies of excited-state energy-transfer processes [30, 31].

While the yields in the Northern-Southern route shown in Scheme 7 are generally quite low, the partial intolerance for the ester substituent during the Petasis methenylation is only one particular limitation. More generally, the Northern-Southern route is limited by two steps during the formation of the dihydrodipyrrin-acetal: (1) use of Pd-mediated coupling in the first step, which precludes substituents carrying other halo atoms through the course of the synthesis to form the corresponding halobacteriochlorins, and (2) Riley oxidation toward the end of the synthesis.

A Hexamethylbacteriochlorin

Dihydrodipyrrin **22**, prepared via the general route shown in Scheme 7, contains a pyrrole that is equipped with a single β-methyl group as well as a stabilizing *tert*-butyl ester. The presence of a single alkyl group can profoundly increase the reactivity of a pyrrole [103] toward electrophiles and oxidants, a potentiation that is typically counterbalanced by the deliberate inclusion of an electron-withdrawing group such as an ester. Riley oxidation [84] of **22** [96] at a scale of 1.5 mmol with SeO_2 in 1,4-dioxane afforded dihydrodipyrrin-carboxaldehyde **23** in 54% yield (Scheme 8). The yield of Riley oxidation decreased to 21% upon reaction at a 5 mmol scale. A homologous dihydrodipyrrin-carboxaldehyde (bearing an alkyl group at each β-position of the pyrrole) underwent bacteriochlorin formation upon treatment with neat



Scheme 8. Synthesis of a 3,13-dimethylbacteriochlorin.

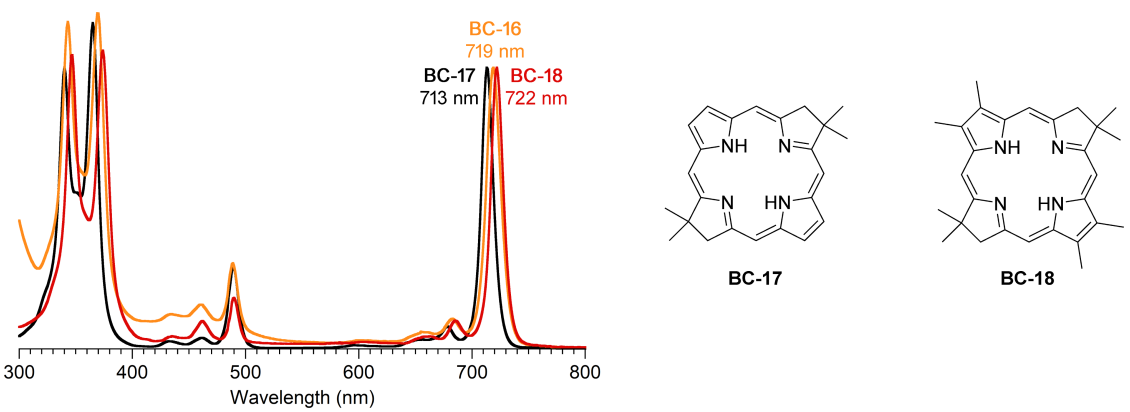


Fig. 3. Absorption spectra (normalized at the Q_y band) at room temperature of bacteriochlorins with zero (**BC-17**, in toluene), two (**BC-16**, in CH_2Cl_2), or four (**BC-18**, in toluene) methyl groups at the β-pyrrolic positions.

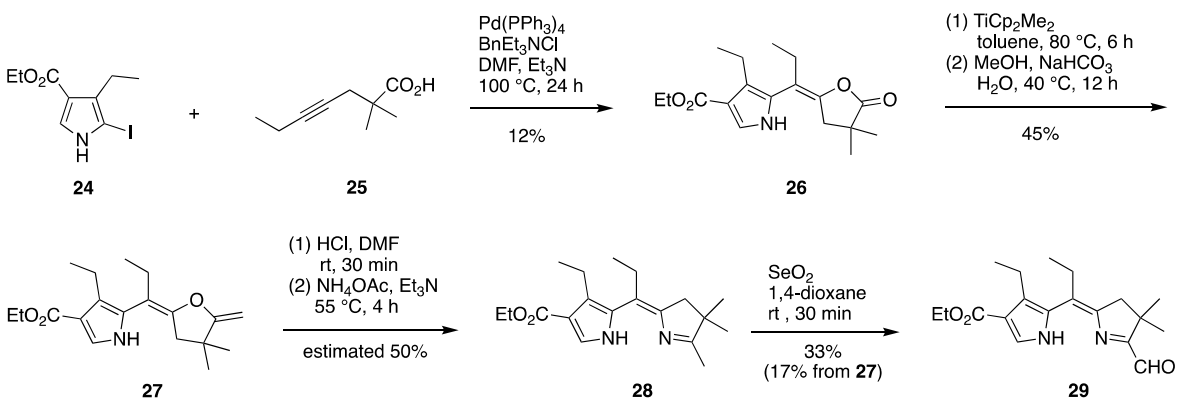
TFA [104]. Thus, treatment of **23** in neat TFA at room temperature for 4 h afforded 3,13-dimethylbacteriochlorin **BC-16** in 14% yield as determined by absorption spectroscopy (Q_y = 719 nm, assumed ε_{719} nm = 110,000 $M^{-1}cm^{-1}$ based on known values [18] for analogous bacteriochlorins). The reaction requires loss of the *tert*-butoxycarbonyl group, which is thought to occur by acid-mediated cleavage of the *tert*-butyl group followed by *ipso* protonation and decarboxylation, although the exact mechanism of decarboxylation remains under consideration [105] and may vary depending on nature of the acid catalyst and solvent including the presence of adventitious water. The absorption spectrum of **BC-16** in dichloromethane is shown in Fig. 3. ESI-MS analysis of the product showed the $[M + H]^+$ peak at *m/z* = 398.2467 (calcd *m/z* = 398.2465) for **BC-16**. However, **BC-16** was not stable following purification by chromatography or upon storage at –20 °C, where the green sample of **BC-16** gradually turned yellow. Due to the limited quantity and stability of **BC-16**, a ^1H NMR spectrum was not obtained. The challenges in handling **BC-16** may stem from the presence of two electron-releasing substituents and two unsubstituted positions at each pyrrole unit, which opens reactivity less encountered with either the fully unsubstituted or fully substituted counterparts. A deeper study of polyalkyl bacteriochlorins lacking electron-withdrawing groups is required to better understand the stability of this class of compounds.

Dihydrodipyrrin syntheses

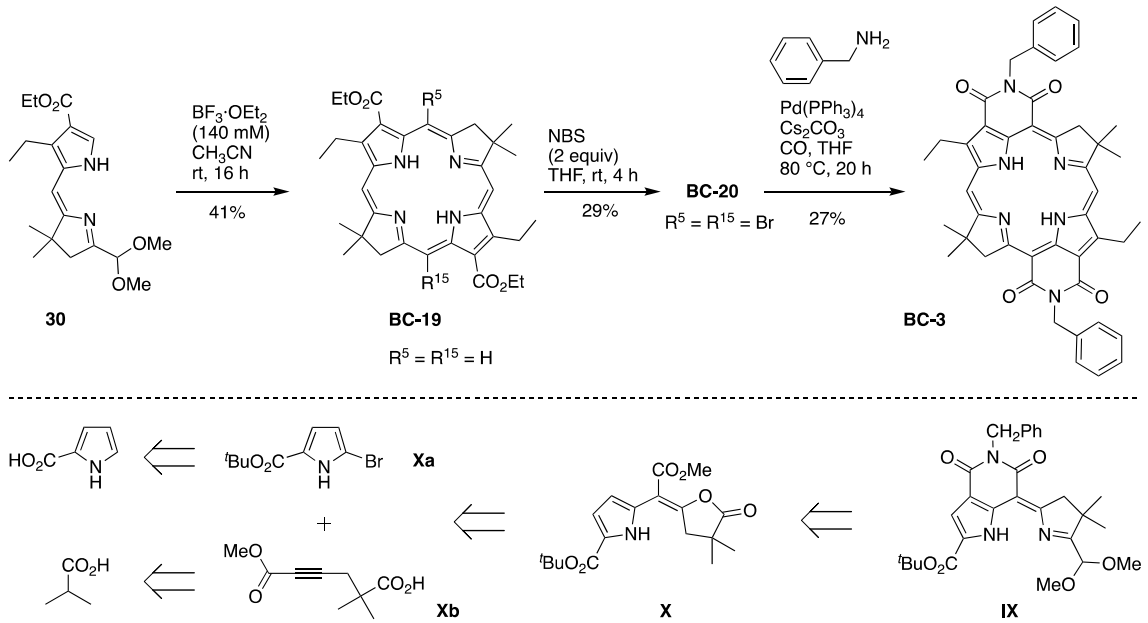
Additional dihydrodipyrrins were prepared for use in exploratory studies. The Pd-mediated coupling of 2-iodopyrrole **24** [19] and 2,2-dimethylhept-4-ynoic acid (**25**) [19] under established reaction conditions (1.0 equiv of **24** at 0.17 M and 2.0 equiv of **25** in the presence of 1.0 equiv of $BnEt_3NCl$ and 6.5% $Pd(PPh_3)_4$ in DMF and triethylamine at 100 °C for 24 h) [19] gave the lactone-pyrrole **26** albeit in only 12% yield (Scheme 9). The low yield is to be compared with those for similar compounds, namely 72% in the case of the compound containing a meso-ethyl group but no substituent at the flanking pyrrole site, or 41% for the case of a *p*-tolyl group at the meso-site along with the flanking pyrrole ethyl group [19]. Reaction at 120 °C (12% yield) or with larger equivalents (3.0 equiv of **25**, 1.7 equiv of $BnEt_3NCl$, 9% $Pd(PPh_3)_4$, 100 °C; 13% yield) had little effect. The low yield may stem from steric hindrance between the β-pyrrole and meso-substituents. Treatment of lactone-pyrrole **26** with the Petasis methenylation reagent afforded the corresponding ene-lactone-pyrrole **27** in 45% yield (Scheme 9). Acid-catalyzed ring opening of ene-lactone-pyrrole **27** followed by Paal-Knorr type ring closure in the presence of NH_4OAc and triethylamine afforded dihydrodipyrrin **28** in crude form as a mixture of isomers. The crude **28** was directly treated with SeO_2 in 1,4-dioxane to give dihydrodipyrrin-carboxaldehyde **29** in 17% yield over two steps. Single-crystal XRD structure analysis was carried out for pyrrole **24**, pyrrole-lactone **26**, and ene-lactone-pyrrole **27** (Appendix 1). While the resolution of the structure for **26** was low (1.00 Å), the XRD analysis of **26** and **27** revealed the *E* configuration rather than the *Z* as might be initially considered. The structures are displayed in Appendix 1. The configuration of dihydrodipyrrins **28** and **29** is not known with certainty.

Towards bacteriochlorin-bis(imide)s

Bacteriochlorin-bis(imide)s exhibit a Q_y absorption band in the NIR region, around 900 nm [37]. Although rich with promise in the photosciences given the position of the Q_y band, only a handful of such compounds have been prepared due to synthetic limitations. The present synthesis relies on the intermediacy of a 5-unsubstituted bacteriochlorin-2,12-diester (**BC-19**), which is obtained from the corresponding dihydrodipyrrin-acetal (**30**) via the Eastern-Western route (Scheme 10, top panel). Treatment with NBS affords the 5,15-dibromobacteriochlorin **BC-20**, which upon Pd-mediated carbamoylation with benzylamine gives the bacteriochlorin-bis(imide) **BC-3** [37]. The low yields of the dibromination and dicarbamoylation processes prompted the investigation of



Scheme 9. Synthesis of a Northern-Southern precursor.



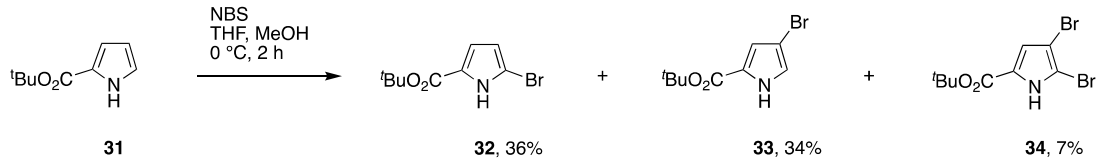
Scheme 10. Established route to bacteriochlorin-bis(imide) **BC-3** (top) [37] and a proposed retrosynthesis for the class of bacteriochlorin-bis(imide)s (bottom).

alternative synthetic routes. Moreover, the 5,15-dibromination of the bacteriochlorin-3,13-diester **BC-19** [37] appears in retrospect to be a special case: were the 2,12-diethyl groups not present, all four meso-positions would likely be susceptible to bromination (as seen in other studies [28]), thereby resulting in lack of control for creating the imide motifs. The situation for bromination of **BC-19** is different from that of the aforementioned bacteriochlorin-2,12-diester (**BC-10**, Scheme 4), where the 5,15-positions have no flanking substituents but each 10- or 20-position has two flanking substituents (gem-dimethyl and carboethoxy) thereby suppressing 10-/20-bromination and enabling 5-/15-bromination. Despite the clean meso-5-bromination of **BC-10**, subsequent imide formation is not possible because the requisite esters are located at the 2,12- rather than the 3,13-positions. There is a subtle interplay of position of substituents about the perimeter of the macrocycle and sites of bromination. The interested reader is referred to reference 28 for an in-depth discussion of this topic.

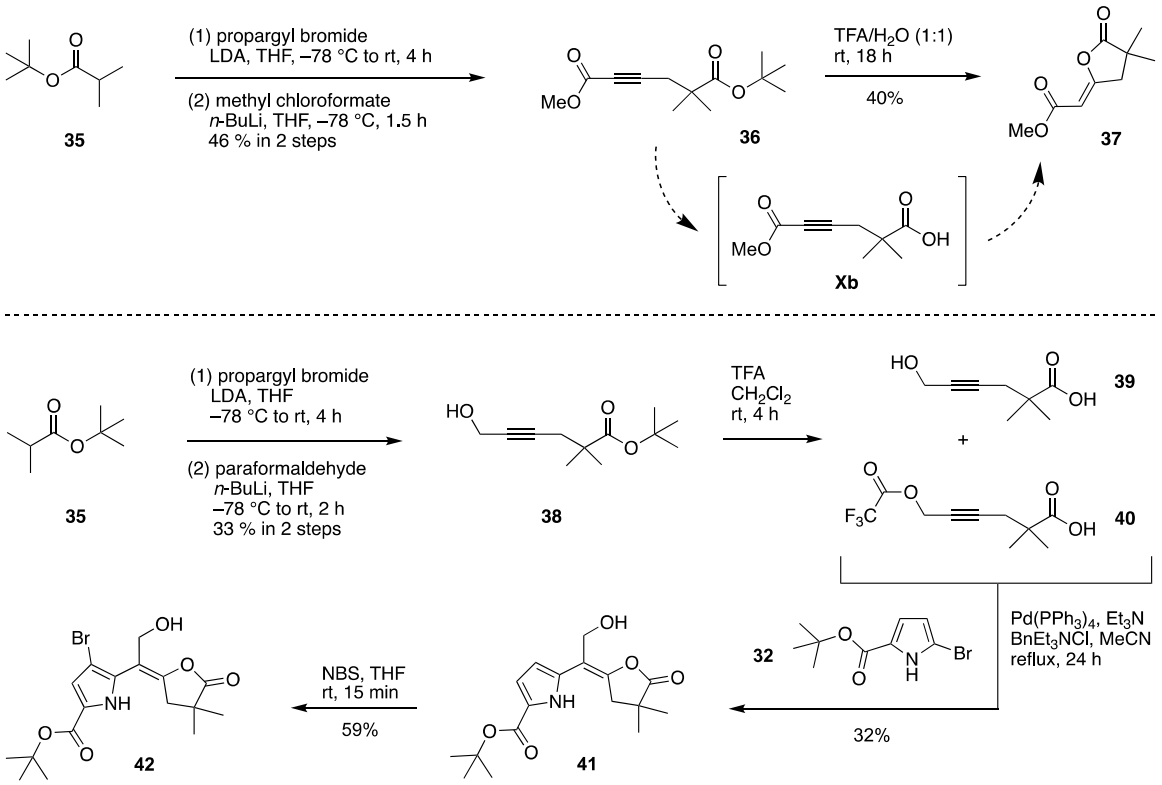
A plan for the synthesis and late-stage elaboration of bacteriochlorin-bis(imide)s is shown in Scheme 10 bottom panel. A key feature is the preformation of the annulated imide motif (**IX**) or at least the pre-installation of a carbomethoxy group at the meso-position of the dihydrodipyrrin precursor (**X**). In this manner, 5,15-dibromination of the bacteriochlorin would not be required. The following sections show efforts to develop such a route to bacteriochlorin-bis(imide)s.

Precursors for the palladium-catalyzed coupling reaction (**Xa** + **Xb**) were prepared as shown in the following diagrams. Treatment of *tert*-butyl pyrrole-2-carboxylate (**31**) [19,106] with NBS provided a mixture of products including the target 5-bromopyrrole **32** (= **Xa** in Scheme 10) (36%) as well as 4-bromopyrrole **33** (34%) and 4,5-dibromopyrrole **34** (7%) (Scheme 11); each **32–34** was isolated in the purity of 80% or greater, hence the yields while not exact provide a view of the trend in substitution upon bromination. The bromination of **31** has been reported previously to afford **32** in 40% yield but without isolation of any byproducts [19]. Pyrrole **33** was analyzed by single-crystal XRD (Appendix 1). While pyrrole **33** is commercially available, to our knowledge, a synthesis has not been reported.

The problem of selective 5-bromination of a pyrrole in the presence of an electron-withdrawing 2-substituent, such as a carboxylate, is well known [107–109]. More broadly, the distribution of products (**32–34**) from **31** comports with longstanding results concerning electrophilic substitution in pyrrole chemistry. Vilsmeier formylation of the ethyl ester analogue of **31** has also proceeded to give the 5-formylpyrrole-2-ester in low



Scheme 11. Synthesis of bromo-pyrroles as Pd-coupling precursors.



Scheme 12. Synthesis of alkynoic acids as Pd-coupling precursors (top) and conversion to the lactone-pyrrole (bottom).

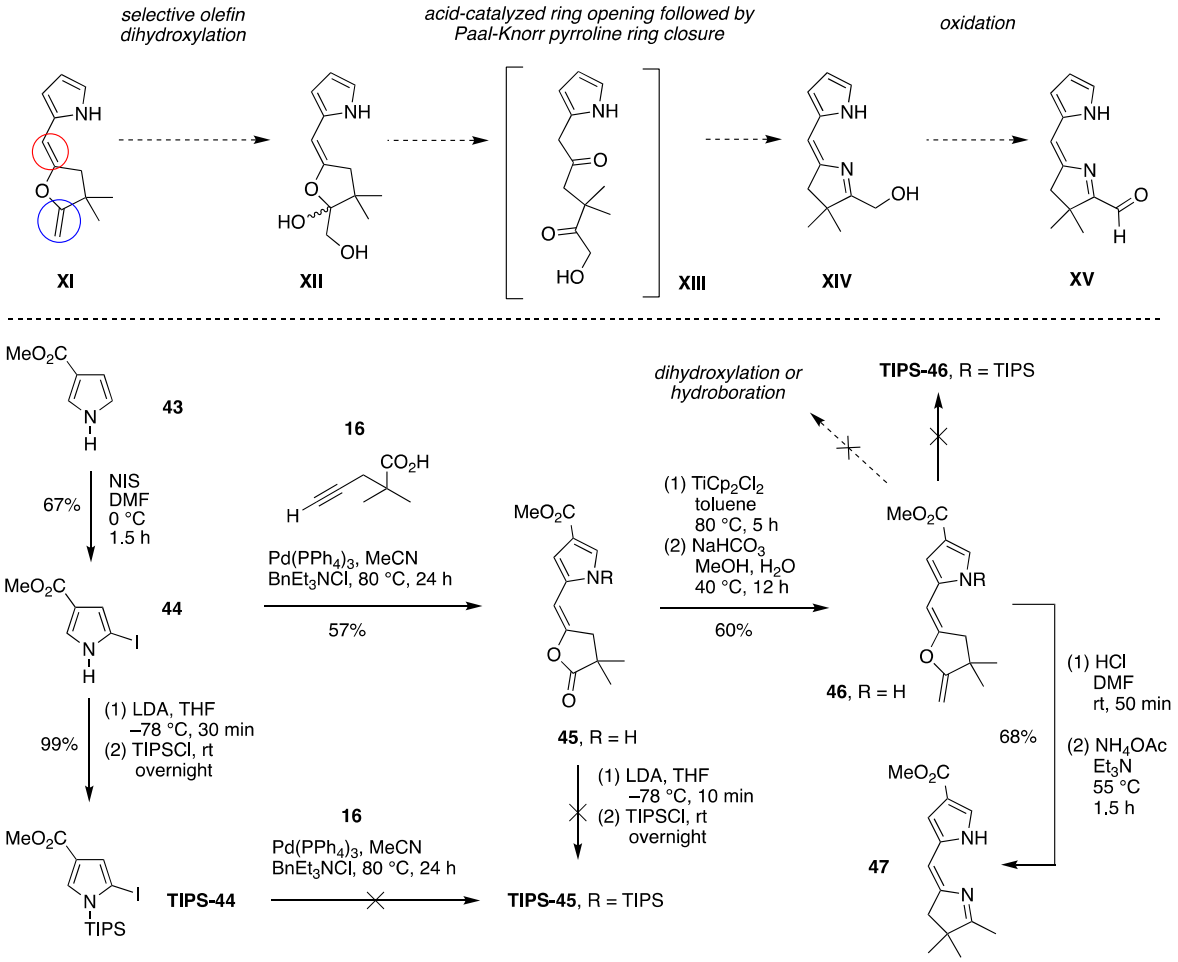
yield [110]. On the other hand, Warashina *et al.* recently described the high yield (99%) formylation of a pyrrole-2-ester through the use of a formylation reagent less reactive than the typical Vilsmeier reagent [111]. Whether merely an intriguing special case, or representative of a broad conceptual strategy that might be applied to increase the selectivity of bromination and other electrophilic substitutions, remains to be determined.

The addition of *tert*-butanol to isobutyryl chloride gave (97% yield) ester **35**, a known compound prepared identically but reported with characterization only by ^{1}H NMR spectroscopy [112]. Subsequent α-propargylation with propargyl bromide [113] followed by methoxycarbonylation with methyl chloroformate [114] gave the hexynoic ester **36** in 46% yield over two steps (Scheme 12, top panel). Treatment with aqueous TFA caused cleavage of the *tert*-butyl group to give **Xb** (evidenced by ^{1}H NMR spectroscopy of the crude product), but cyclization upon silica chromatography gave lactone **37**. Palladium-mediated reactions of pyrrole **32** and coupling partner **37** were attempted to obtain lactone-pyrrole **X** (Scheme 10); however, only recovered starting materials and dibromopyrrole **31** were observed. The α-position of the α,β-unsaturated ester was regarded as lacking sufficient reactivity for the Pd-mediated reaction to afford lactone-pyrrole **X**. Thus, an alternative coupling reactant was examined.

A new hexynoic acid was pursued in the same manner as **Xb** (Scheme 12, bottom panel). Treatment of ester **35** [112] to α-propargylation with propargyl bromide [113] followed by reaction of the resulting terminal alkyne (as the alkynyl anion) with paraformaldehyde [115,116] furnished alkynoic ester **38**. The latter upon treatment with TFA afforded alcohol-hexynoic acid **39** accompanied by trifluoroacetate **40**. The reaction time was found to affect the ratio of products **39** and **40**, with the trifluoroacetate **40** obtained predominantly at a long reaction time. One interpretation is that alkynoic acid **39** was transformed *in situ* to an intermediate allene-lactone (not shown), which upon attack of TFA at the terminal position gave trifluoroacetate **40**. The crude mixture of **39** and **40** was employed in the palladium-coupling reaction with pyrrole **32**, affording lactone-pyrrole **41** as a major product. Bromination of **41** afforded bromopyrrole **42**; however, the subsequent methenylation using the Petasis reagent gave a complex mixture, causing cessation of this line of inquiry. Regardless, the ability to install a hydroxymethyl group at the meso-position of a dihydrodipyrrin precursor may find a use for accessing targets of value in alternative syntheses en route to bacteriochlorins.

Manipulation of dihydrodipyrrins

An alternative proposal to prepare a dihydrodipyrrin-1-carboxaldehyde (**XV**) is shown in Scheme 13 top panel. The selective olefin dihydroxylation of ene-lactone-pyrrole **XI** would give the diol **XII** as a hydroxyhemiketal. Acid-catalyzed ring opening would afford intermediate **XIII**, which upon Paal-Knorr type ring



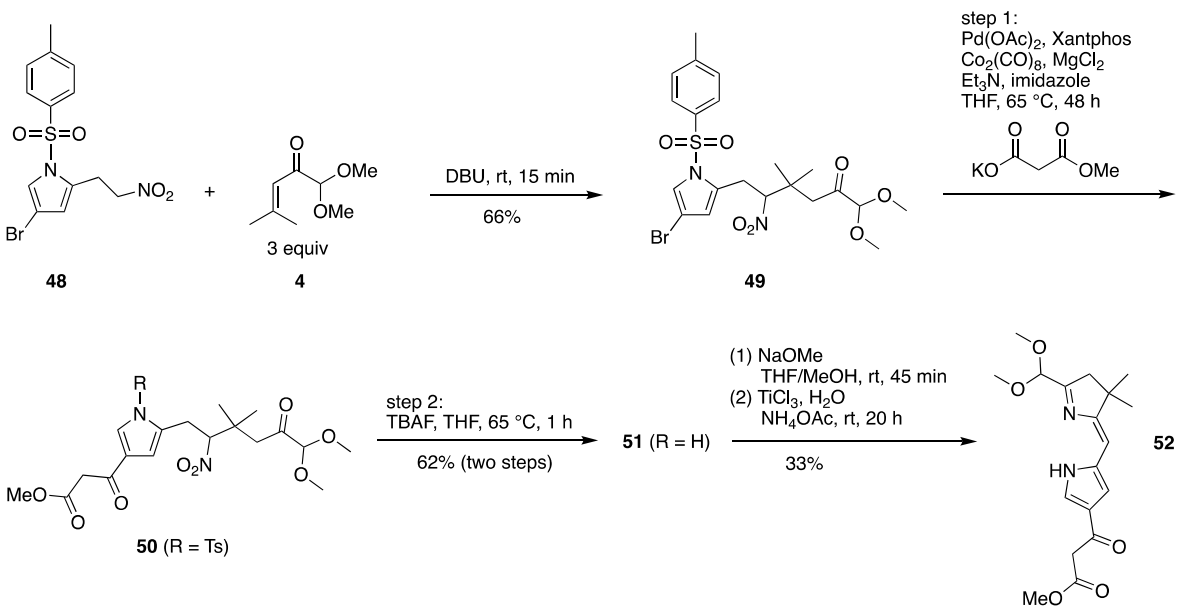
Scheme 13. Proposed route to a dihydrodipyrrin-carboxaldehyde (**XV**, top) and transformations investigated (bottom).

closure would afford 1-hydroxymethyldihydrodipyrrin **XIV**. Subsequent oxidation of the primary alcohol then generates bacteriochlorin precursor **XV**.

To assess whether the dihydroxylation can occur at the terminal versus internal alkene of ene-lactone-pyrroles, 3-carbomethoxypyrrole (**43**) [27,117] was treated with *N*-iodosuccinimide (NIS) [118] to give the 2-iodopyrrole **44** in 67% yield (Scheme 13, bottom panel). Installation of the bulky TIPS group [119] to sterically shield the double bond adjacent to the pyrrole was achieved by treatment of **44** with LDA and TIPS-Cl [120] to generate **TIPS-44** in 99% yield. Subsequent Pd-mediated reactions of **44** and **16** afforded the lactone-pyrrole **45** in 57% yield. Pyrrole **44** and lactone-pyrrole **45** were characterized by single-crystal XRD analysis (Appendix 1). Petasis methenylation produced the ene-lactone-pyrrole **46** in 60% yield. While the yield of Petasis methenylation was only 39% at a 1 mmol scale, running multiple batches enabled **46** to be prepared ultimately in a quantity of >3 g. Treatment to conditions with catalytic OsO_4 and additives (*N*-methylmorpholine *N*-oxide, methanesulfonamide, citric acid, *tert*-butyl hydroperoxide, K_2CO_3, and various combinations thereof), however, resulted in decomposition. On the other hand, the standard acid-catalyzed ene hydration and furan ring-opening to give the 1,4-diketone followed by Paal-Knorr type reaction gave the 1-methyldihydrodipyrrin **47** in 68% yield.

In a recent report aimed at the total synthesis of Tagetitoxin, the dihydroxylation of an enamine-cyclopentene to furnish the corresponding enamine-cyclopentanediol was successful only when the amine contained both an acetyl and a *tert*-butoxycarbonyl (Boc) group, not an acetyl group alone [121]. Therefore, masking the pyrrole nitrogen may be essential. The TIPS-protected lactone-pyrrole **TIPS-45** could not be accessed by the Pd-mediated reaction of **TIPS-44** and **16** or by silylation of **45** (~60% starting material recovery) (Scheme 13). The Boc group has been used for nearly 40 years in pyrrole chemistry [122]. Here however, treatment of **45** or **46** with di-*tert*-butyl dicarbonate [$(Boc)_2O$] in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP) failed to afford the corresponding *N*-Boc-pyrrole product (not shown here). The inaccessible ene-lactone-pyrroles containing a masked pyrrole prevented further dihydroxylation attempts.

Hydroboration of ene-lactone-pyrroles also was examined. Treatment of **46** with borane dimethylsulfide resulted in decomposition, whereas reaction with 9-borabicyclo[3.3.1]nonane (9-BBN) was carried out to



Scheme 14. Refined synthesis of a BC half precursor to a bacteriochlorophyll analogue.

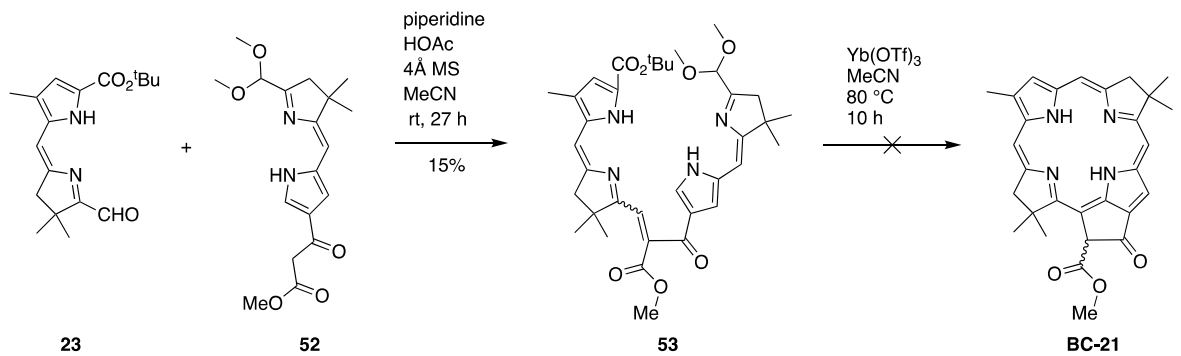
achieve anti-Markovnikov hydration selectively of the terminal alkene in the presence of the internal alkene, given expected higher reactivity [123,124] of the former versus the latter alkene. A product was isolated but the structural analysis was unclear (Supporting Information). In summary, the installation of the desired formyl or dimethoxymethyl groups at the 1-position of dihydrodipyrrins likely will require fundamentally new approaches for the construction of these essential precursors to bacteriochlorins.

Bacteriochlorophyll skeleton synthesis

The synthesis of the skeleton of native bacteriochlorophylls has been achieved by the reaction of an AD dihydrodipyrrin and a BC dihydrodipyrrin [20]. The compounds prepared are more highly substituted than the core bacteriochlorophyll macrocycle yet lack the structural complexity of native bacteriochlorophyll *a*. Each example is a free base macrocycle and contains the 13^2-substituted isocyclic ring as in the native macrocycles. Each pyrroline ring contains a gem-dimethyl or *trans*-dialkyl group. Each BC dihydrodipyrrin precursor is equipped with a 1-dimethoxymethyl group and a β-ketoester at the 8-position (β-site of the pyrrole).

A prior synthesis relied on Michael addition of 2-(2-nitroethyl)pyrrole **48** [125] with α,β-unsaturated ketone **4** (in excess) [81] in the presence of DBU to give the nitrohexylpyrrole **49** [126] (Scheme 14). The reaction of the latter with potassium monomethyl malonate proceeded to give the pyrrole containing the β-ketoester (**50**). Detosylation followed by McMurry-Melton reaction [20] gave **51** followed by **52**, respectively. A slightly refined conversion of **49** to BC-dihydrodipyrrin **52** is reported here. The new features are that (1) the conversion of **49** to **51** is carried out without explicit isolation of **50** (except for purification of a small sample for XRD analysis; see Appendix 1), and (2) the scale has been increased by 1.5-fold versus the previous [20] synthesis. The careful work of Senge and coworkers warrants mention as they have determined the XRD structure of **48** [79] and precursors thereto [127].

The next step is Knoevenagel condensation of an AD half (dihydrodipyrrin-carboxaldehyde) and a BC half (dimethyl acetal-substituted dihydrodipyrrin-β-ketoester) to form a propenone linker joining the two



Scheme 15. Attempted formation of a bacteriochlorophyll analogue.

dihydrodipyrrin halves, followed by a double-ring closure to form the bacteriochlorin macrocycle. The double-ring closure proceeds via Nazarov cyclization, electrophilic aromatic substitution, and elimination of methanol. A portal to the sizeable literature on such transformations (for other substrates) is provided by several papers concerning the formation of the bacteriochlorophyll skeleton and analogues [20, 93–95, 110]. Knoevenagel condensation [20, 94] of AD half **23** and BC half **52** initially was carried out in the presence of piperidine/HOAc in CH_2Cl_2 at room temperature for 20 h (Scheme 15), but multiple spots were detected by TLC analysis. The reaction in the presence of piperidine/HOAc in acetonitrile [94] for 27 h at room temperature afforded **53** as a *Z/E* mixture in 15% yield. The mixture of stereoisomers was treated to the standard conditions for one-flask double-ring closure (formation of both ring E and the bacteriochlorin macrocycle) [20, 94], which consisted of $Yb(OTf)_3$ in acetonitrile at 80 °C with reaction monitoring by absorption spectroscopy; however, the Knoevenagel propenone **53** gradually decomposed, and the expected bacteriochlorophyll model compound **BC-21** was not observed.

The poor results with AD dihydrodipyrrin **23** are surprising, as five other AD dihydrodipyrrins have been employed with **52** (**EH-1**) with good results. The set of

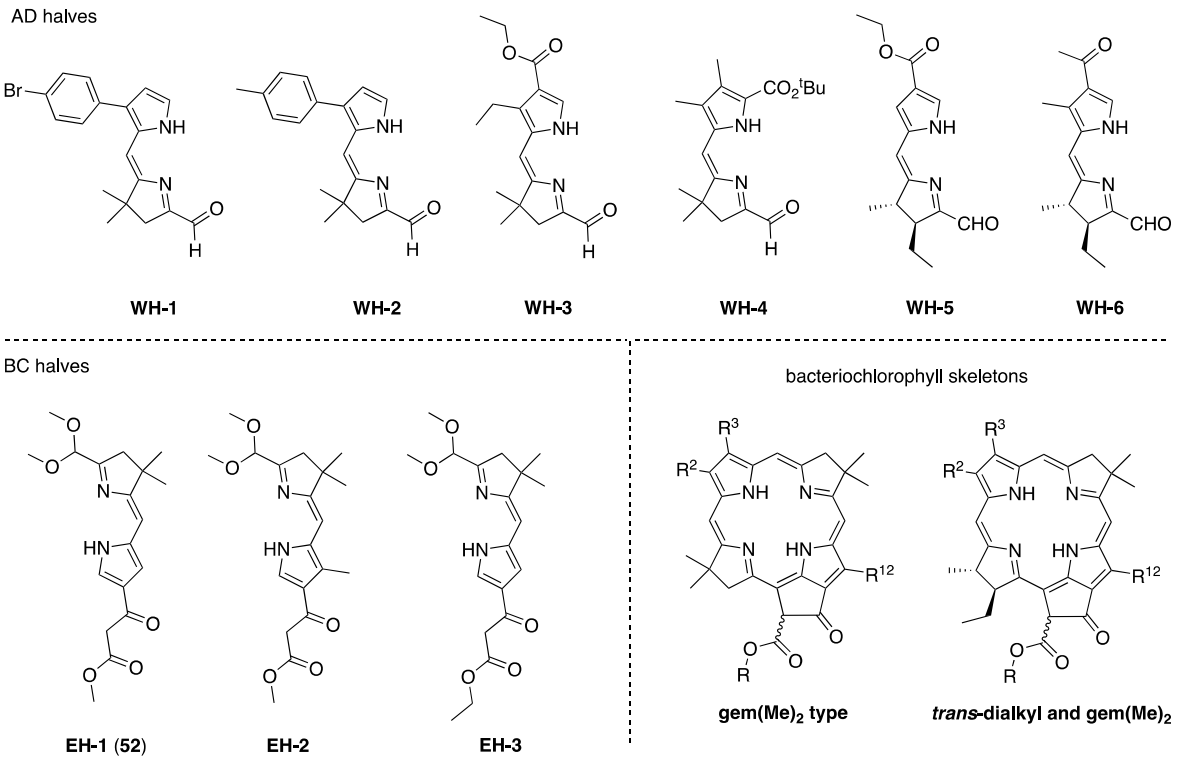


Chart 7. AD halves and BC halves for forming bacteriochlorophyll analogues.

Table 2. Prior syntheses of model bacteriochlorophyll macrocycles.

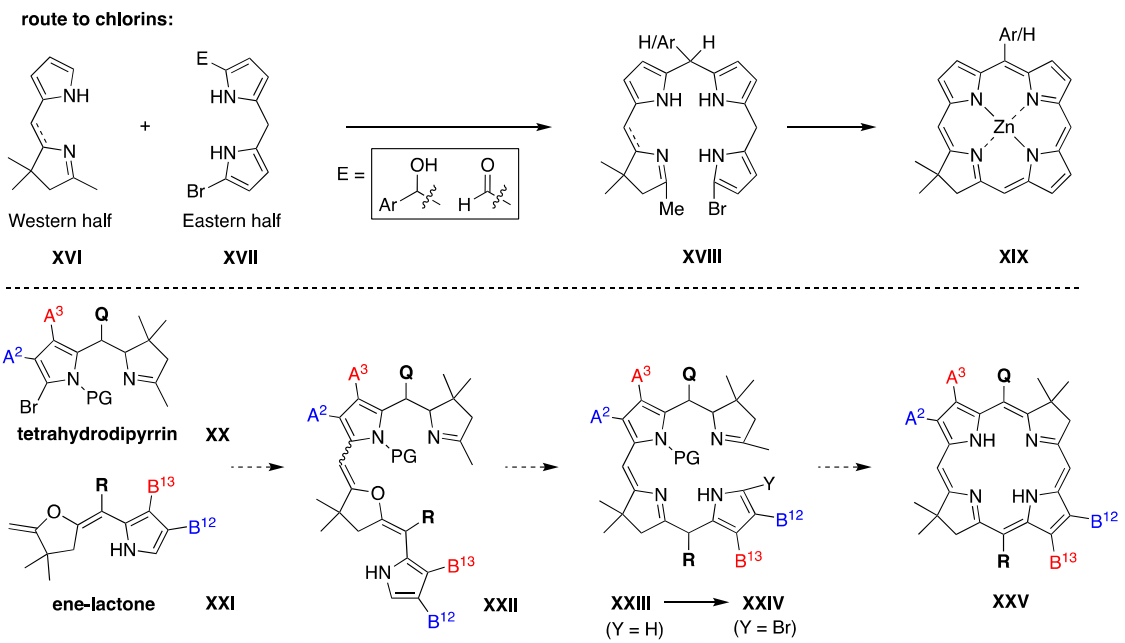
Entry	Reactants		Yield (%)		Reference
	AD half	BC half	Knoevenagel	BChl skeleton	
1	**WH-1**	**EH-1**	68	61	[20]
2	**WH-2**	**EH-1**	61	56	[20]
3	**WH-3**	**EH-1**	61	57	[20]
4	**WH-4**	**EH-1**	71	37	[20]
5	**WH-1**	**EH-3**	57	48	[20]
6	**WH-5**	**EH-1**	73	53	[93]
7	**WH-5**	**EH-2**	34	67	[95]
8	**WH-6**	**EH-2**	8.4, 10	42–53	[95]
9	**23**	**EH-1**	15	0	here

AD and BC halves examined previously in the formation of the bacteriochlorophyll skeleton are shown in Chart 7 [20, 93–95]. The chart includes six AD halves and three BC halves. Among the AD halves, four contain a gem-dimethyl group in the pyrroline ring (**WH-1** – **WH-4**) whereas two contain a *trans*-dialkyl group (**WH-5**, **WH-6**). The latter is aimed as a model for probing the total synthesis of native bacteriochlorophylls. Five contain an open 9-position for macrocyclization whereas one (**WH-4**), like **23**, contains a *tert*-butoxycarbonyl group at the 9-position. The *tert*-butoxycarbonyl group undergoes cleavage during the course of the acid-catalyzed macrocyclization process [20].

The results of the reaction of the various AD and BC halves are shown in Table 2. Concerning the Knoevenagel reaction, the yields range from 34–73% in entries 1–7; one low yield (entry 8) may stem from a competing reaction with the pyrrole acetyl substituent of **WH-6**. Concerning the macrocyclization, which occurs in a one-flask process, the yields range from 42–67% in all cases examined (entries 1–8) with the sole exception being the reaction of **23** and **52** (= **EH-1**). Given that **EH-1** has proved to be a viable reactant in half the trials examined (entries 1–4 and 6), the failure in the double-ring closure of Scheme 15 appears to originate with the gem-dimethyl group of the AD half. The gem-dimethyl group of **23** is located at the 2-position of the dihydrodipyrrin whereas **WH-1** – **WH-4** contain the gem-dimethyl group at the 3-position. The *trans*-dialkyl dihydrodipyrrins **WH-5** and **WH-6** contain only a single alkyl group at the 2-position. While the native bacteriochlorophylls contain *trans*-dialkyl rather than gem-dialkyl groups, the observations here bear on the synthesis of non-native compounds. The tentative conclusion, which requires additional studies for support, is that a gem-dimethyl group at the 2-position in a dihydrodipyrrin-carboxaldehyde as an AD half thwarts the double-ring closure, but one ethyl group does not. At a minimum, the results highlight that much remains to be done to understand the structural features that affect the Knoevenagel and macrocyclization processes.

Considerations of a directed route to bacteriochlorins

We sought to develop a directed route to bacteriochlorins – lacking ring E – wherein the substituents in the AC and BD rings could be distinct. Our prior efforts in this regard have yielded somewhat serendipitously a new route to tetradehydrocorrins, which reside at the same oxidation level as bacteriochlorins, but not to the desired bacteriochlorins [128]. A directed route is available for chlorins [4] but not yet for bacteriochlorins. The route to chlorins (Scheme 16, top panel) entails condensation of a Western half (**XVI**) and an Eastern half (**XVII**) to form a linear tetrapyrrolic ("bilane-like") intermediate (**XVIII**), followed by oxidative cyclization to afford the chlorin (**XIX**) [4]. The type of Western half (**XVI**) employed has chiefly been a 2,3,4,5-tetrahydrodipyrrin rather than a 2,3-dihydrodipyrrin [4]. If features of the Northern-Southern route to bacteriochlorins (Scheme 6 and Scheme 7) could be blended with those of chlorin synthesis, a directed path to bacteriochlorins might arise that accommodates non-identical dipyrrolic halves. Thus, a tetrahydrodipyrrin (**XX**), which resembles the Western half **XVI** of the chlorin route, is proposed to react with an ene-lactone-pyrrole (**XXI**) via a Heck-type coupling reaction. The latter is an intermediate of the established Northern-Southern route to bacteriochlorins.



Scheme 16. Directed route to chlorins (extant, top) and bacteriochlorins (proposed, bottom).

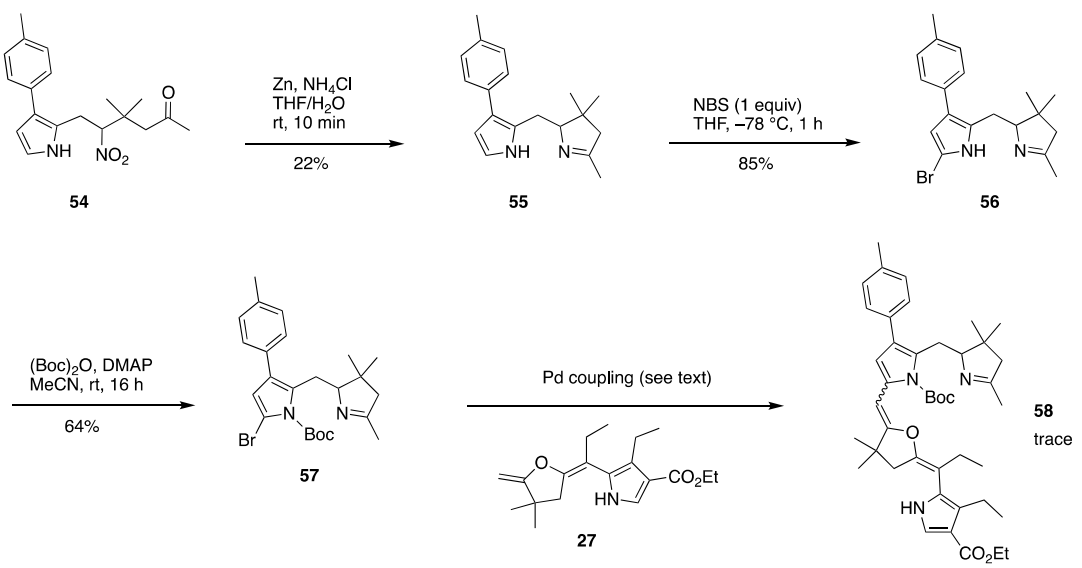
The resulting oxa-substituted linear tetrapyrrole **XXII** is treated to the Paal-Knorr conditions in the Northern-Southern route to form the corresponding linear tetrapyrrolic, bilane-like **XXIII** (tautomers and other isomers are possible; not shown). The follow-on reactions include pyrrole α-bromination to give **XXIV** and then oxidative cyclization (resembling chlorin ring-formation) to afford the bacteriochlorin **XXV** (Scheme 16, bottom panel). Bacteriochlorin **XXV** bears distinct groups at the two pyrrole rings and at the meso-positions, access to which would advance the design and synthesis for this class of macrocycles as described in the Introduction.

A perhaps subtle consequence of combining a tetrahydrodipyrrin and a dihydrodipyrrin has to do with the oxidation state of the immediately formed macrocycle. The self-condensation of a dihydrodipyrrin-acetal releases three molecules of methanol and affords the 5-methoxybacteriochlorin, where the lone 5-methoxy group is a vestige of the dimethyl acetal moiety of one of the two dihydrodipyrrin-acetals [18, 81]. The similar self-condensation of a tetrahydrodipyrrin-acetal, while not successful [82], in principle would release all four molecules of methanol and afford a dihydrobacteriochlorin; the latter upon $2e^-$, $2H^+$ oxidation (e.g., in air) would afford the bacteriochlorin. While the presence of the 5-methoxy group has turned out to be almost providential in enabling selective 15-bromination and subsequent 15-substitution of bacteriochlorins [89], an ideal route would afford a bacteriochlorin bearing only pre-ordained substituents and not uncontrolled remnants of the precursor reactive groups. The route shown in Scheme 16 (bottom panel) would require a $4e^-$, $4H^+$ oxidation process to afford the aromatic bacteriochlorin. The chlorin synthesis also requires a $4e^-$, $4H^+$ or $6e^-$, $6H^+$ oxidation process to go from **XVIII** to **XIX**; the latter ($6e^-$, $6H^+$ oxidation) process has been studied with the observation of reaction intermediates [129]. The directed route to bacteriochlorins is at best a sketch that we deemed worthy of exploration, thinking that while obviously imperfect even on paper and replete with uncertainties, and fully aware that many other retrosynthetic disconnections are plausible [128], perhaps information about multiple facets of the chemistry might be revealed for a later, more informed, approach to the problem. Here are reported preliminary results, which while not yet affording a viable path, have yielded fruitful insights.

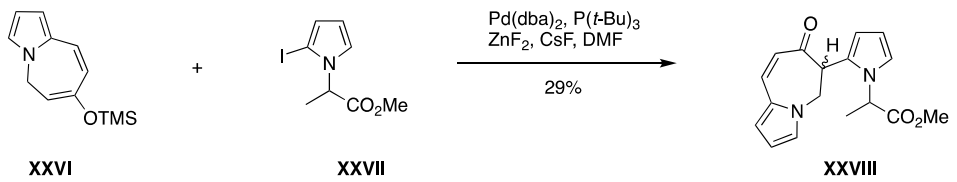
Exploratory studies of a directed synthesis

Considerable effort has been devoted to the synthesis of gem-dimethyl-substituted hydrodipyrrins of a given saturation level and bearing a variety of terminal (1- and 9-) groups [82, 126, 128, 130, 131], which could be used in support of directed syntheses of bacteriochlorins. A general reductive cyclization of γ-nitrohexanone-pyrroles has been used to create tetrahydrodipyrrins [128]. The conversion of nitrohexanone **54** [132] to tetrahydrodipyrrin **55** (Scheme 17) was achieved in 22% yield by exposure to 15 equiv of zinc and 4 equiv of NH_4Cl in THF/H_2O (1:1) at room temperature (see Table S2 for a short survey of conditions). Treatment of tetrahydrodipyrrin **55** with 1 equiv of NBS in THF at –78 °C afforded in 85% yield the α-bromo-tetrahydrodipyrrin **56**, which upon reaction with $(Boc)_2O$ and a catalytic amount of DMAP in acetonitrile afforded **57** in 64% yield. The Boc group was introduced to suppress complexation with Pd species [133] in the subsequent Heck reaction.

The reaction of tetrahydrodipyrrin **57** and ene-lactone-pyrrole **27** was examined under a variety of conditions (Scheme 17). Heck reactions usually require high temperatures (> 100 °C) [134]. However, the tetrahydrodipyrrin is somewhat unstable at elevated temperatures, which prompted the screening of some mild conditions



Scheme 17. Attempted directed synthesis of bacteriochlorins.



Scheme 18. Reported Heck coupling of a pyrrole and trimethylsilyl enol ether.

from the literature [135–137] (Table S3). No reaction was observed at 50 °C with $Pd_2(dba)_3$ or $Pd(OAc)_2$, whereas **57** decomposed at temperatures > 50 °C. The condition of $Pd(OAc)_2$, 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (Xphos), and tetrabutylammonium acetate in 1,4-dioxane gave a trace of the provisional oxa-bilane **58** product, as evidenced by observation of the molecular ion upon accurate mass measurement (*m/z* obsd 696.43691, calcd 696.43710 for the protonated oxabilane, $C_{43}H_{58}N_3O_5$).

The challenges of the Heck reaction of tetrahydrodipyrrin **57** and ene-lactone **27** may stem from (1) the stabilized, less reactive alkene in the ene-lactone; (2) steric hindrance around the alkene; and (3) limited temperature range available for use with the tetrahydrodipyrrin. More efficient catalyst systems are required for the Heck coupling to explore the utility of this proposed route. If the conditions of the Heck reaction can be modified to obtain oxabilane **58**, the subsequent elaboration will resemble features of the Northern-Southern route to bacteriochlorins and the formation of chlorins. The ineffective Heck coupling prompted an expansive study in this regard as described in the next section.

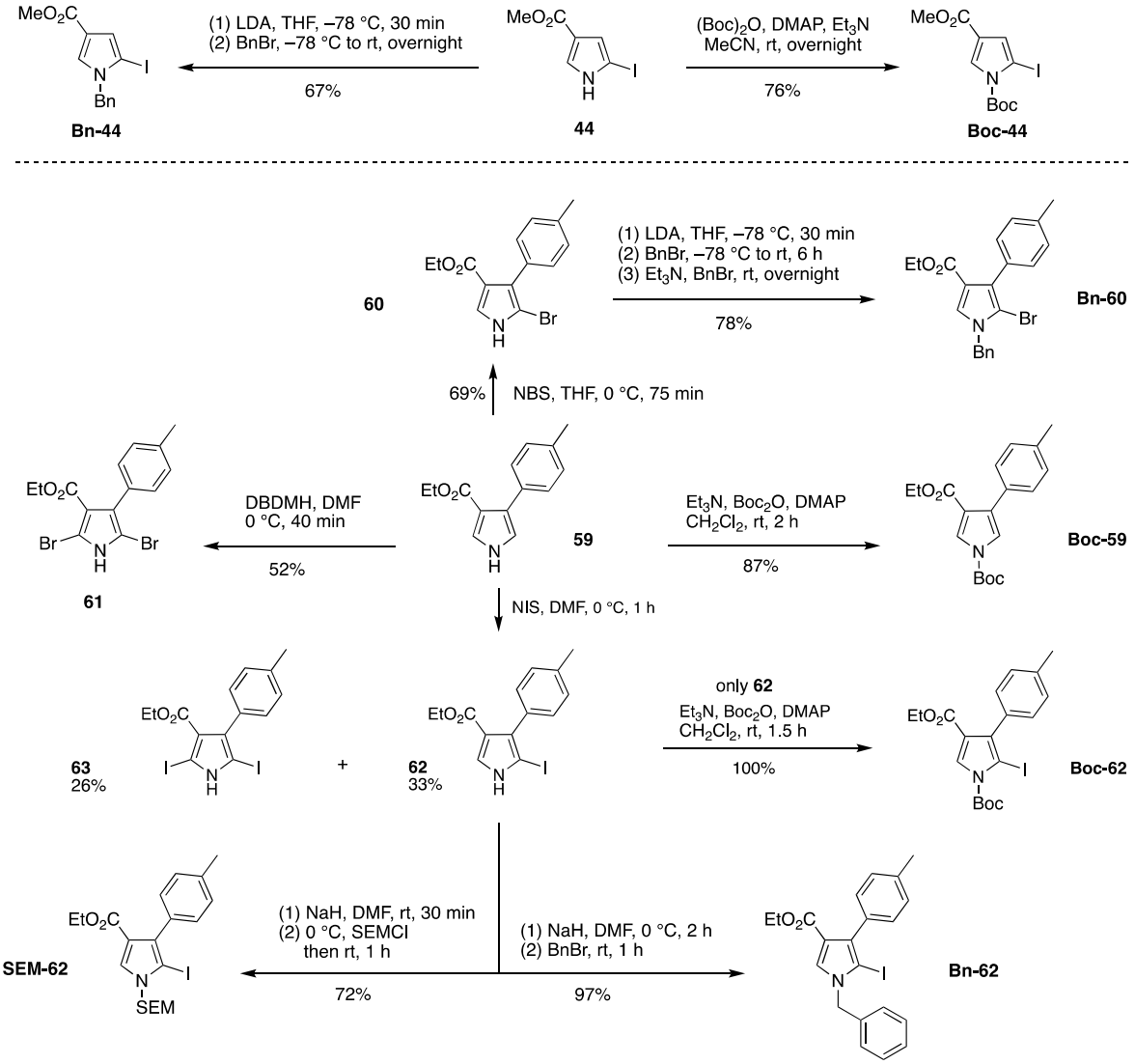
Pyrrole substitution via Heck-like reactions

A general method for Pd-mediated α-arylation of silyl enol ethers was reported by Su *et al.* [138]. Recently, Xuan *et al.* [139] reported a Heck-like reaction of a trimethylsilyl enol ether (**XXVI**) that unusually, is itself attached to a pyrrole, with a 2-iodopyrrole (**XXVII**) to form a product wherein the latter pyrrole bears a β-ketone at the 2-position (Scheme 18). We were propelled to explore analogous reactions with trimethylsilyl enol ethers that, following coupling to the pyrrole, could be elaborated to give a dihydrodipyrrin. Such reactions could support a new route to dihydrodipyrrins and also might be exploited in a directed synthesis of bacteriochlorins.

For the coupling studies, a small set of pyrroles was prepared (Scheme 19). 2-Iodo-4-carbomethoxypyrrole (**44**) was protected as the *N*-Boc (**Boc-44**) or *N*-benzyl (**Bn-44**) derivative. Pyrrole **59** [36] was treated with (1) NBS to give the desired 2-bromopyrrole **60**, which then was converted to the *N*-benzyl derivative **Bn-60**; (2) 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) to give the dibromopyrrole **61**; and (3) NIS to give the desired 2-iodopyrrole **62** [128] along with the 2,5-diiodopyrrole **63** in 33% and 26% yield, respectively. Pyrrole **62** was previously reported (2.90 g, 82%) [128] but without isolation of the diiodopyrrole product **63**. Masking of the pyrrole nitrogen with the Boc group was carried out with $(Boc)_2O$ in the presence of DMAP in dichloromethane [140], thereby converting **59** and **62** into **Boc-59** and **Boc-62**, respectively. The trimethylsilylethoxymethyl (SEM) or benzyl (Bn) group was routinely installed on pyrrole **62** upon treatment with sodium hydride and SEMCl [141] or benzyl bromide to give **SEM-62** or **Bn-62**, respectively. Pyrroles **Boc-44**, **Bn-44**, **60**, **62**, **63**, and **Boc-62** have been characterized by single-crystal XRD analysis (Appendix 1).

The desired trimethylsilyl enol ethers (Chart 8) were obtained commercially or prepared as shown in Appendix 2. The Heck coupling reaction of trimethylsilyl enol ether **TMS-63** and an iodopyrrole (**44**, **TIPS-44**, **Bn-44**, or **Boc-44**) was carried out under diverse conditions that varied the palladium reagent [$Pd(dba)_2$, $Pd(OAc)_2$); each with phosphine [$P(t\text{-}Bu)_3$], fluoride additive (CsF, ZnF_2, MnF_2), solvent (DMF, toluene), and temperature range (85–100 °C), but in no case was the 2-(pivaloylmethyl) pyrrole obtained (Scheme 20, left panel). In many cases, the starting pyrrole was largely recovered along with a trace of dehalogenated pyrrole. The failure with the pyrroles was in sharp contrast with the benchmark 3,5-di-*tert*-butyl-1-bromobenzene (**70**), which reacted reasonably well with trimethylsilyl enol ether **TMS-63** to give the corresponding product **71** (Scheme 20, right panel). Similar reactions of bromopyrrole **Bn-60** and **TMS-63** also failed to give the expected coupling product (not shown).

The next Heck coupling reactions that were carried out employed 2-iodopyrrole **62**, which bears two β-substituents, and derivatives thereof equipped with one of several *N*-protecting groups (**Boc-62**, **Bn-62**, **SEM-62**). The reactions were performed with a wide variety of trimethylsilyl enol ethers (Table 3). The coupling of pyrrole **62** and trimethylsilyl enol ether **TMS-64** was carried out under various conditions, but no Heck product was obtained although LC-MS analysis gave evidence of Boc cleavage and deiodination (entry 1). The nitrogen of the pyrrole ring likely interacts with the palladium catalyst, thwarting the Heck reaction. The reaction of **Boc-62** and trimethylsilyl enol ether **TMS-64** in the presence of $Pd(OAc)_2$ and $P(t\text{-}Bu)_3$ along with fluoride reagents (CsF, $n\text{-}Bu_3SnF$) in hot toluene gave the Heck product **Boc-72** in 15% yield; switching to $PdCl_2$ in the presence of $P(o\text{-tolyl})_3$ [142] and omitting CsF gave **Boc-72** in 59% yield (entry 2). The trialkyltin fluoride is believed to



Scheme 19. Preparation of 2-halopyrroles.

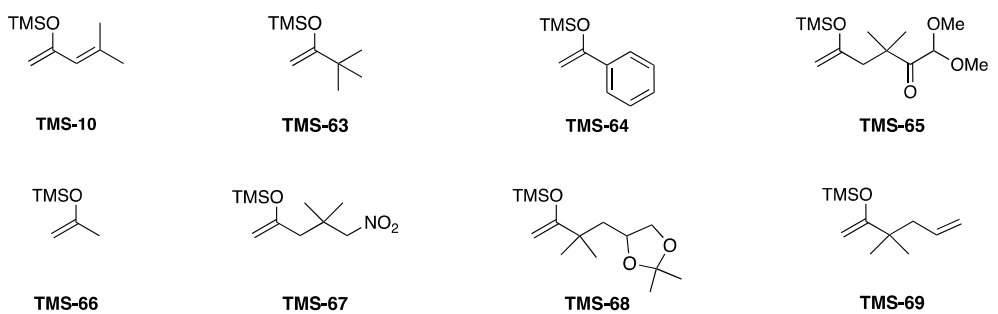
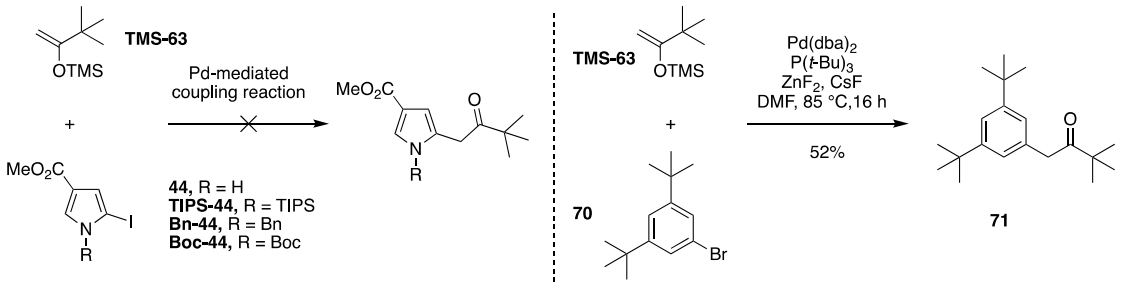


Chart 8. Trimethylsilyl enol ethers for Heck reactions.

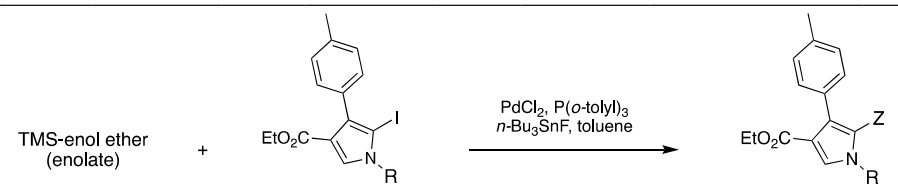
facilitate transition-metal-catalyzed cross-coupling reactions by two sequential processes [143]: (1) the exchange of stannyl versus silyl to form an α-stannyl ketone, and (2) a cross-coupling reaction involving the iodopyrrole. A sample of **Boc-72** was deprotected to give **72**, which was characterized by single-crystal XRD analysis (Appendix 1). With this validation experiment in hand, the reaction was examined of trimethylsilyl enol ether **TMS-65** (~70% purity), which would give the pyrrole bearing a 1,4-diketone and the terminal dimethyl acetal moiety for conversion to the pyrroline via a Paal-Knorr reaction (entry 3); however, the desired product was not obtained. Simpler trimethylsilyl enol ethers (**TMS-66**; **TMS-10**, 64% purity) did give reaction with pyrroles

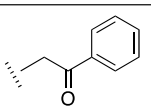
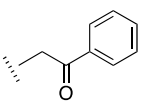
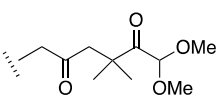
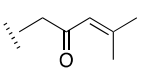
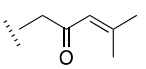
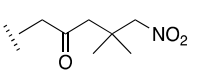
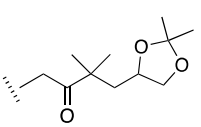
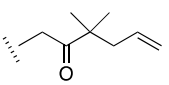


Scheme 20. Early Pd-coupling trials.

Bn-62, **SEM-62**, or **Boc-62** to form the respective product **Bn-74**, **SEM-74**, **SEM-75**, or **Boc-75** (entries 4–7). Pyrrole **Boc-75** was characterized by single-crystal XRD analysis (Appendix 1). Returning to a trimethylsilyl enol ether that afforded more full functionality for subsequent elaboration such as via a Nef reaction [144], the reaction of pyrrole **SEM-62** and nitro-substituted trimethylsilyl enol ether **TMS-67** did not afford the desired

Table 3. Heck coupling reactions

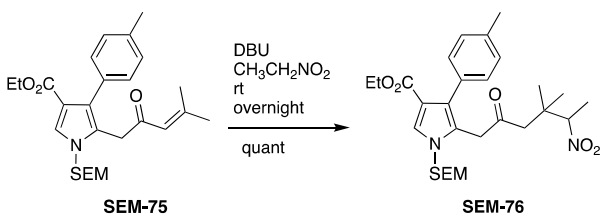


Entry	Pyrrole	Enolate	Product	Z in Product	Yield, %
1[a]	**62**	**TMS-64**	**72**[c]		0
2[b]	**Boc-62**	**TMS-64**	**Boc-72**		59
3	**Boc-62**	**TMS-65**	**Boc-73**[c]		0
4	**Bn-62**	**TMS-66**	**Bn-74**		29
5	**SEM-62**	**TMS-66**	**SEM-74**		43
6	**SEM-62**	**TMS-10**	**SEM-75**		72
7	**Boc-62**	**TMS-10**	**Boc-75**		62
8	**SEM-62**	**TMS-67**	-[c]		0
9	**Boc-62**	**TMS-68**	-[c]		0
10	**Boc-62**	**TMS-69**	-[c]		0

[a]The reaction conditions included the following: (i) 3 mol % $Pd(OAc)_2$, 5.4 mol % P(*t*-Bu)$_3$, CsF, toluene, 85 °C, overnight [143]; (ii) $Pd(dba)_2$, P(*t*-Bu)$_3$, ZnF_2, CsF, DMF, 70 °C, 5 h [139]; (iii) $PdCl_2$, P(*o*-tolyl)$_3$, *n*-Bu_3SnF, toluene, 110 °C, 5 h [142]. [b]The reaction under the following conditions gave a 15% yield of product: (i) 3 mol % $Pd(OAc)_2$, 5.4 mol % P(*t*-Bu)$_3$, CsF, *n*-Bu_3SnF, toluene, 85 °C, overnight. [c]Compound shown was not obtained.

product (entry 8). The use of trimethylsilyl enol ether **TMS-68** (crude form), a dioxolane-masked analogue of **TMS-65**, did not afford the desired product upon reaction with **Boc-62** (entry 9). Because **TMS-68** contains a gem-dimethyl group located adjacent to the trimethylsilyl enol ether carbon-oxygen bond, a simpler substrate, lacking the dioxolane mask (**TMS-69**), was examined, yet again the desired Heck product was not obtained (entry 10).

The failures shown in entries 3 and 9 of Table 3 were especially disheartening because the expected products would provide a convenient entry to target dihydrodipyrrins. On the other hand, the success in coupling smaller compounds containing a trimethylsilyl enol ether motif (e.g., entries 6 and 7) suggested that follow-on reactions might rescue an entrée to dihydrodipyrrins. Pyrrole **SEM-75** (from entry 6) underwent Michael addition with nitroethane to give **SEM-76** (Scheme 21). Attempts to remove the SEM protecting group of **SEM-76** upon treatment with TBAF even at elevated temperatures [145] were not successful. Attempts at bromination (with a mixture of Br_2, HBr and CH_3CO_2H) [146] of the methyl ketone of **Bn-74** were unsuccessful. The attempted Michael addition [81, 91, 147–149] of **SEM-75** and 2-nitroethanol or 2-nitroacetaldehyde dimethyl acetal also left **SEM-75** unchanged. Attempts to remove the Boc group of **Boc-75** (from entry 7) with TFA or with sodium methoxide were unsuccessful. A Stetter reaction [150] – where umpolung reactivity is exercised by the addition of an aldehyde equivalent to a Michael acceptor – of **Boc-75** and glyoxal dimethyl acetal also was unsuccessful. All considered, the Heck coupling, under present conditions and with the current halopyrrole substrates, does not appear to be a viable route to dihydrodipyrrins. In perspective, however, conditions for Heck coupling as well as other Pd-mediated reactions with pyrroles are under intense scrutiny at present [151], and perhaps new conditions will emerge that redress the present limitations.

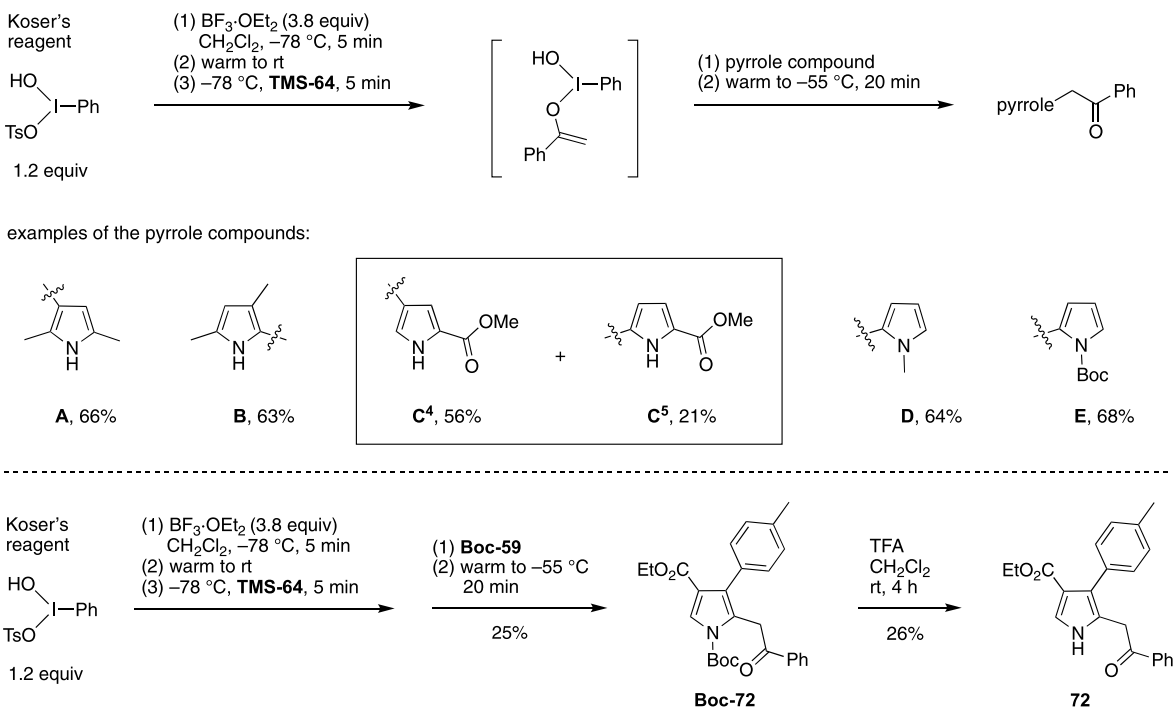


SEM-75 **SEM-76**

Scheme 21. Elaboration following Heck coupling.

Pyrrole substitution via enolium chemistry

Maksymenko *et al.* [152] reported the reaction of a trimethylsilyl enol ether with a variety of heterocycles, including five pyrroles, to form the corresponding heterocycle bearing a β-ketone (Scheme 22, top panel). The reaction is electrophilic in nature, thereby providing an attractive complement to Pd-mediated coupling processes. The reaction relies on the conversion of a trimethylsilyl enol ether with Koser's reagent and excess boron trifluoride-etherate to form an activated hypervalent iodine derivative [152]. This critical bond-forming



Scheme 22. Enolium substitution of pyrroles. The results in the top panel were reported by Maksymenko *et al.* [152]; those in the bottom panel are reported here.

reaction was examined with the des-iodo analogue of the pyrrole employed in the aforementioned Heck couplings. Thus, treatment of trimethylsilyl enol ether **TMS-64** with 1.2 equiv of Koser's reagent and excess boron trifluoride-etherate followed by pyrrole **Boc-59** delivered the desired product **Boc-72**, albeit in 25% yield (Scheme 22, bottom panel). An enticing feature of this reaction is the avoidance of any transition metal catalysts, which in principle would leave open the possibility of carrying halopyrroles through the synthesis. Nonetheless, the pursuit of this intriguing reaction was halted because it was not clear how to generate the requisite electrophile under conditions sufficiently mild for compatibility with other features in the desired substrates.

OUTLOOK

Bacteriochlorins comprise a compelling class of compounds that are photoactive in the NIR spectral region. The features of native bacteriochlorophylls provide a powerful paradigm and motivation to develop synthetic bacteriochlorin analogues. While a sizeable number of synthetic bacteriochlorins has been prepared, much remains to be done to create target bacteriochlorins at will. The two types of bacteriochlorin architectures presented in the Introduction – phenylene-linked bacteriochlorin dyads (barren of substituents) and singly substituted, bioconjugatable bacteriochlorins (also water-soluble and wavelength-tunable) – generally remain beyond the scope of present methods. The chemistry examined herein includes three known routes to bacteriochlorins (Eastern-Western, Northern-Southern, bacteriochlorophyll analogues); a prospective directed route to bacteriochlorins; derivatization of bacteriochlorins by reduction and bromination; several routes to dihydrodipyrrins (potential precursors to bacteriochlorin-bis(imide)s and the bacteriochlorophyll skeleton); and pyrrole derivatization (bromination, Pd-coupling, and enolium substitution).

The Eastern-Western and Northern-Southern routes differ in the position of the gem-dimethyl group relative to the 1-dimethyl acetal moiety: 3-position in the former versus 2-position in the latter. Otherwise, the double-ring closure processes are considered to be quite similar. The routes thus differ in the synthetic pathway for the construction of the dihydrodipyrrin-acetal. In the Eastern-Western route, the sequence entails Vilsmeier formylation of a pyrrole, Henry reaction with nitromethane, borohydride reduction of the nitrovinyl group, Michael addition with 1,1-dimethoxy-4-methyl-3-penten-2-one, and McMurry-Melton reaction (reductive cyclization). In the Northern-Southern route, the sequence entails a Sonogashira-like reaction of a 2-halopyrrole and a 4-pentynoic acid to form a lactone-pyrrole, Petasis methenylation to give the ene-lactone-pyrrole, acid hydrolysis, Paal-Knorr like reaction, and Riley oxidation. Both routes have limitations.

The synthetic difficulties encountered to date and surveyed in the discursive chemistry described herein include the following, which gave low yields, poor scope, or complex mixtures:

1. bromination of a pyrrole-2-ester;
2. Heck coupling of 2-halopyrroles with trimethylsilyl enol ethers;
3. conversion of a substantially deactivated dihydrodipyrrin-acetal to a bacteriochlorin, and many dihydrodipyrrin-acetals exclusively to the 5-unsubstituted bacteriochlorin;
4. pre-installation of features in a dihydrodipyrrin that engender formation of an imide spanning the 13–15-positions;
5. the Michael and McMurry-Melton reactions leading to dihydrodipyrrin-acetals in the Eastern-Western route, and the Riley oxidation in the Northern-Southern routes.

Taken together, new routes to dihydrodipyrrins (or equivalents) suitable for dimerization (self-condensation or addition) or directed joining – regardless of the location of a gem-alkyl group – are required to overcome many of the aforementioned limitations and thereby improve the quality (scope, yields, expediency) of bacteriochlorin syntheses. Strategies that combine a dihydrodipyrrin and a tetrahydrodipyrrin in a path resembling that in the directed synthesis of chlorins remain intriguing. The synthetic approaches to gem-dimethyl-substituted bacteriochlorins, after 20 years of development, offer much promise yet remain very much a work in progress. A new era of bacteriochlorin chemistry should enable the synthesis of diverse arrays (including *p*-phenylene-linked dyads); water-soluble, bioconjugatable, and wavelength-tunable bacteriochlorins; and annulated bacteriochlorins that are photoactive in the NIR spectral region.

Appendix 1. XRD analysis

The ORTEP diagrams for 20 compounds are shown in Fig. A1. The data quality was quite high in all cases except for **26**, where the resolution was 1.00 Å. The structures have been deposited at the Cambridge Crystallographic Data Centre. The CCDC deposition numbers are provided in the Experimental Section. Further information including crystallization solvents is listed in the Supporting Information (Table S4). Each structure displayed may be only one of the molecules in an asymmetric unit as follows: **2a** (1 out of 2 molecules is shown); **MeOBC-5** (1 out of 4 molecules is shown); **24** (1 out of 2 molecules is shown); **44** (1 out of 2 molecules is shown); and **63** (1 out of 3 molecules is shown).

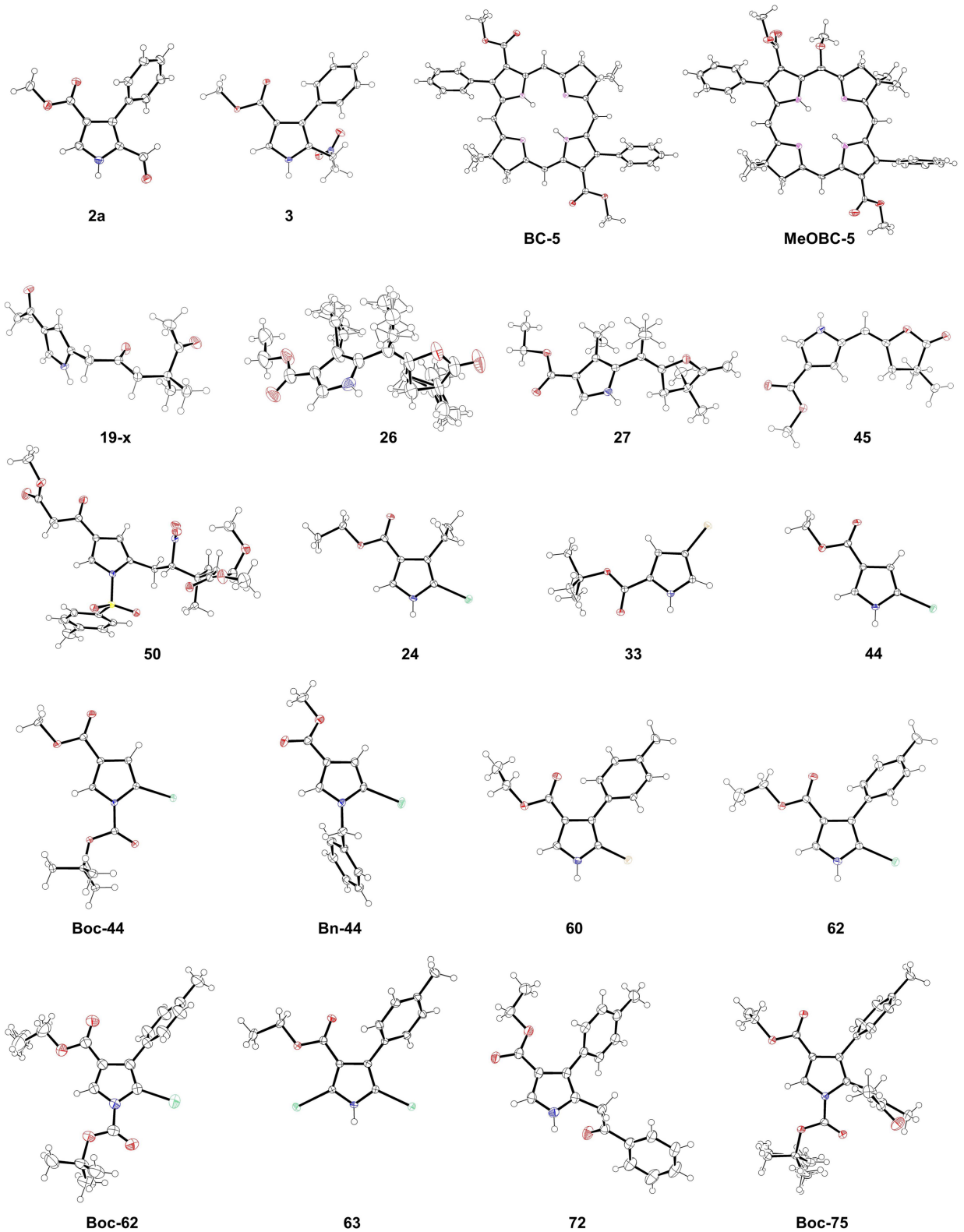


Fig. A1. ORTEP diagrams for 20 compounds.

Appendix 2. Synthesis of trimethylsilyl enol ethers

The syntheses of the target trimethylsilyl enol ethers are shown in Fig. A2. The commercially available ester methyl 2,2-dimethoxyacetate was hydrolyzed with lithium hydroxide to give the known carboxylic acid **77** [153] in quantitative yield, with no further purification necessary, and was prepared in a 5-fold larger scale than reported [153]. The reaction of **77** with triphosgene and

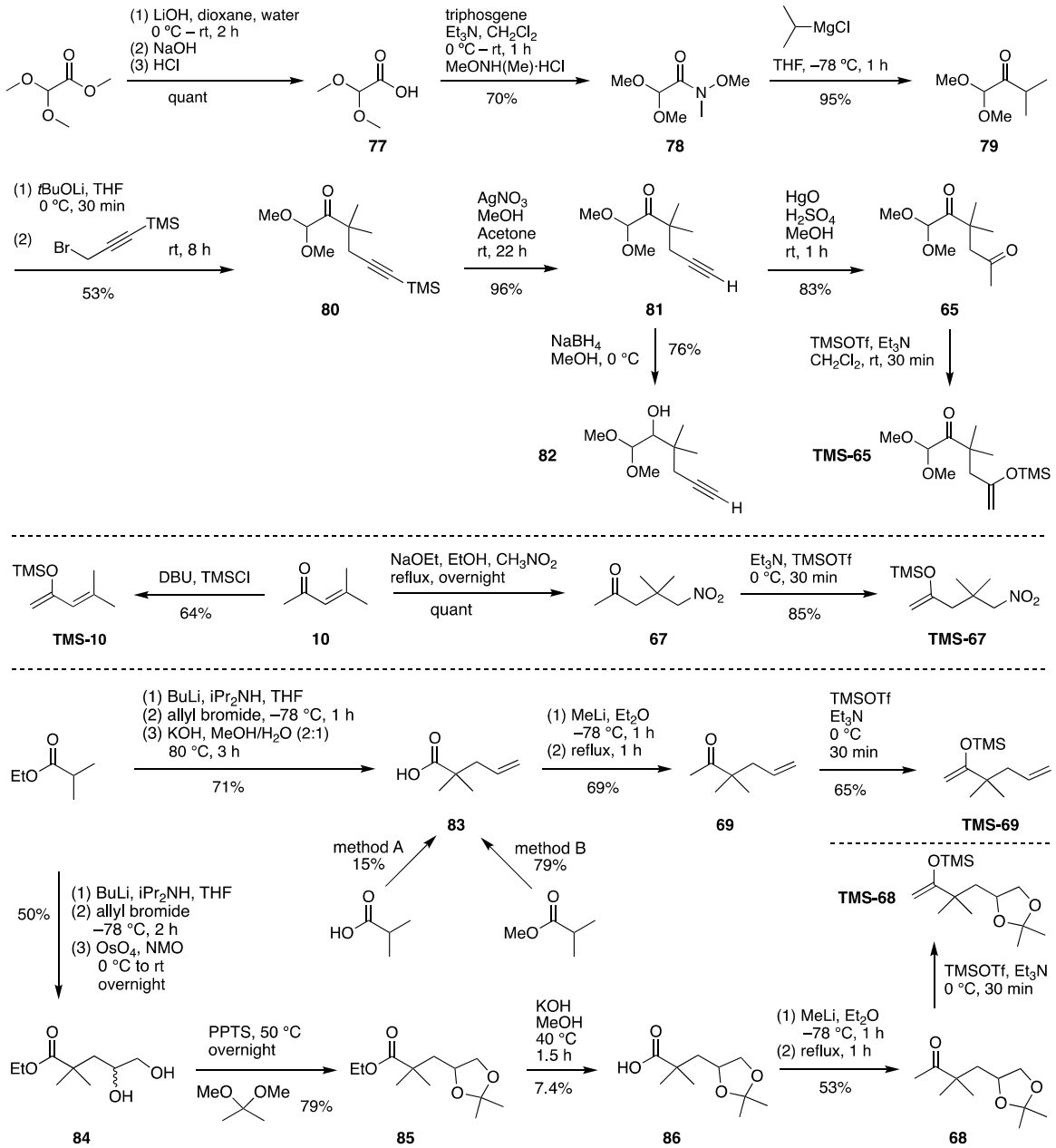


Fig. A2. Synthesis of target trimethylsilyl enol ethers.

N,O-dimethylhydroxylamine hydrochloride gave in 70% yield the known Weinreb amide **78**, which has been prepared here at a 120-fold larger scale than reported [154]. Treatment of **79** with isopropyl magnesium chloride followed by aqueous workup gave in 95% yield the corresponding α-ketoacetal **79** (prepared previously via a different route [81]), which could be used without further purification. The reaction of **79** with several bases (LiHMDS, LDA, *t*-BuOLi, or NaH) was examined to obtain the enolate; the use of *t*-BuOLi [155] was found to be suitable for reaction with propargyl bromide to afford **80** in 53% yield. Exposure to silver nitrate in methanol caused the elimination of the trimethylsilyl group to give **81** in 96% yield. The internal alkyne in **81** underwent Hg(II)-catalyzed hydration, perhaps facilitated by intramolecular coordination of the γ-ketone [156], affording 1,4-diketone **65** in 83% yield. The absence of hydrolysis of the dimethyl acetal must stem from the electron-withdrawing effect of the adjacent ketone. Subsequent reaction with TMSOTf in the presence of triethylamine [157] afforded the desired product **TMS-65** containing the terminal trimethylsilyl enol ether (Fig. A2, top panel).

To avoid intramolecular interaction of the γ-ketone with the reacting trimethylsilyl enol ether, **TMS-65** was treated with $NaBH_4$, but the corresponding hydroxy analogue was not obtained (not shown). On the other hand, **81** was reduced with $NaBH_4$ to give **82** in 76% yield; however, hydration of the alkyne was not successful,

hence efforts to obtain 1,1-dimethoxy-3,3-dimethyl-5-((trimethylsilyl)oxy)hex-5-en-2-ol were not pursued further (Fig. A2, top panel).

To examine the use of an alkyl nitro group as a latent keto moiety to possibly sidestep intramolecular interference with the Heck coupling, mesityl oxide (**10**) was treated [158] with nitromethane and DBU to give the Henry/reduced product **67** (a known compound prepared via a different route [159, 160]) in a quantitative fashion. Subsequent reactions with TMSOTf and triethylamine gave trimethylsilyl enol ether **TMS-67** in 85% yield. Mesityl oxide (**10**) was converted to **TMS-10** in the standard manner (Fig. A2, middle panel).

Ethyl isobutyrate was treated with *n*-BuLi followed by alkylation with allyl bromide. Saponification gave in 71% yield the carboxylic acid **83**, a known compound [161–165] prepared by different routes. Compound **83** also was prepared beginning with isobutyric acid (method A) at 80 mmol scale in 15% yield (versus 27% yield at 3 mmol scale [162]), or beginning with methyl isobutyrate (method B) at 100 mmol scale in 79% yield (versus 84% yield at 45 mmol scale [163], 64% yield at 20 mmol [164], or 81% yield at 43 mmol scale [165]). Reaction with excess methyl lithium following a known method [163] gave known ketone **69** [163]. Conversion to the trimethylsilyl enol ether in the standard way gave the target compound **TMS-69** (Fig. A2, bottom panel).

Ethyl isobutyrate was treated as before with *n*-BuLi followed by allyl bromide. Subsequent oxidation with OsO_4 in the presence of *N*-methylmorpholine *N*-oxide (NMO) gave diol **84**, a known compound [166] prepared by a slightly different route but without characterization data. Protection of the diol as the dioxolane in the presence of pyridinium *p*-toluenesulfonate (PPTS) [167] gave **85**, which was saponified [168] to give **86**. The latter was transformed to the ketone **68** upon reaction with excess methyl lithium, followed by the formation of the trimethylsilyl enol ether **TMS-68** (Fig. A2, bottom panel).

EXPERIMENTAL SECTION

General methods

^{1}H NMR and ^{13}C{^{1}H} NMR spectra were collected at room temperature in $CDCl_3$ unless noted otherwise. Silica (40 μm average particle size) was used for column chromatography. THF was freshly distilled from sodium/benzophenone. Reagent-grade solvents (CH_2Cl_2, hexanes, ethyl acetate, DMSO, ethylene glycol, CH_3CN, toluene, MeOH) and anhydrous solvents (DMF, diethyl ether, toluene, 1,4-dioxane) were used as received. All other solvents (anhydrous or reagent-grade) were employed as received from commercial suppliers. Electrospray ionization mass spectrometry (ESI-MS) data generally enable accurate mass measurements, were obtained in the positive-ion mode (unless noted otherwise) and are reported for the molecular ion or protonated molecular ion. Commercial compounds were used as received. Known compounds pyrrole **8** [27], dihydrodipyrrin-acetal **13** [36], MIDA-phenyl-borolane **14** [88], dihydrodipyrrin **22** [96], pyrrole **24** [19], 2,2-dimethylhept-4-ynoic acid (**25**) [19], *tert*-butyl isopropionate (**35**) [112], pyrrole **43** [27,117], γ-nitrohexanone-pyrrole **49** [126], γ-nitrohexanone-pyrrole **54** [132], pyrrole **59** [36], trimethylsilyl enol ether **68** [159, 160], bacteriochlorin **MeOBC-6** [36], bacteriochlorin **BC-9** [36], and bacteriochlorin **BC-11** [28] were prepared following literature procedures. The ^{1}H NMR spectra of all known compounds prepared herein were consistent with those in the literature. In general, the reported coupling constants have been rounded off to the nearest ".0" or ".5" Hz value.

Characterization

The new results reported as part of the perspective herein were obtained over the course of eight years including the Covid-19 era and lockdown. In general, each compound was characterized by high resolution mass spectrometry (HRMS), ^{1}H and ^{13}C{^{1}H} NMR spectroscopy, and where appropriate, by melting point analysis and by absorption spectroscopy. In a minority of cases, HRMS data were not obtained. In other cases, particularly with some of the silyl enol ethers, compounds were employed in partially purified form. Spectral data for several compounds were tabulated at the time of data collection but print or electronic copies were not available at the time of this writing, as described in the Supporting Information. Efforts have been made to delineate where characterization is incomplete and compound assignments are provisional.

6-(3,4-Dicarboethoxypyrrol-2-yl)-4,4-dimethyl-5-nitrohexan-2-one (11)

Following a reported procedure [18] with modification, a sample of CsF (1.00 g, 6.58 mmol, freshly dried by heating to 100 °C under high vacuum for 1 h) in a flask under argon was treated with a mixture of **8** (500 mg, 1.76 mmol) and mesityl oxide (**10**, 1.58 mL, 10.56 mmol) in anhydrous acetonitrile (30 mL). The mixture was heated in an oil bath at 70 °C and stirred for 16 h, whereupon TLC analysis showed the starting material was completely consumed. The reaction mixture was diluted with ethyl acetate and washed with water. The organic extract was dried (Na_2SO_4) and then concentrated under reduced pressure to a dark oil. Purification by chromatography [silica, hexanes/ethyl acetate (2:1)] afforded a pale-yellow oil (110 mg, 16%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (s, 3H), 1.27 (s, 3H), 1.28–1.32 (m, 3H), 1.33–1.37 (m, 3H), 2.14 (s, 3H), 2.45–2.60 (m, 2H), 3.32 (dd, J = 15.0 and 11.5 Hz, 1H), 3.53 (dd, J = 15.0 and 2.5 Hz, 1H), 4.22–4.28 (m, 2H), 4.29–4.35 (m, 2H), 5.17 (dd, J = 11.5 and 2.5 Hz, 1H), 7.13 (d, J = 3.0 Hz, 1H), 8.75 (br s, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 14.3,

14.4, 23.8, 24.2, 26.0, 31.9, 37.1, 51.2, 60.5, 60.6, 94.5, 113.5, 117.3, 123.4, 133.3, 164.2, 164.7, 206.6; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{27}N_2O_7$ 383.1813; found 393.1811.

7,8-Dicarboethoxy-2,3-dihydro-1,3,3-trimethyldipyrrin (12)

Following a general procedure [128] with modification, in a first flask, a solution of **11** (110 mg, 288 μmol) in freshly distilled THF (10 mL) was bubbled with a stream of argon for 15 min. Then, the solution was treated with NaOMe (117 mg, 2.16 mmol), and the resulting mixture was stirred for 45 min whereupon the color changed from pale yellow to orange. In a second flask, a solution of NH_4OAc (8.88 g, 115 mmol) in deionized water (12 mL) was bubbled with a stream of argon for 20 min. Then, the solution was treated with $TiCl_3$ (1.82 mL, 2.3 mmol, 20% w/v solution in 2 N HCl). The suspension was stirred for 15 min at room temperature under argon. The solution in the first flask containing the nitronate anion of **11** was transferred via a cannula to the buffered $TiCl_3$ solution in the second flask. The resulting brown mixture was stirred for 21 h under argon at room temperature. The reaction mixture was poured slowly into a stirred mixture of saturated aqueous $NaHCO_3$ (150 mL) and ethyl acetate (100 mL). The mixture was stirred vigorously at room temperature for 15 min. The mixture was extracted with ethyl acetate and washed with saturated aqueous $NaHCO_3$, whereupon the color of the aqueous phase changed from dark slate blue to white. The dark-orange organic layer was dried (Na_2SO_4) and then concentrated under reduced pressure to a yellow oil. The resulting oil was chromatographed on a short column [silica, hexanes/ethyl acetate (1:1)] to afford a colorless oil (27 mg, 28%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (s, 6H), 1.30–1.33 (m, 3H), 1.34–1.38 (m, 3H), 2.23 (s, 3H), 2.53 (s, 2H), 4.27 (q, *J* = 7.0 Hz, 2H), 4.32 (q, *J* = 7.0 Hz, 2H), 6.35 (s, 1H), 7.28 (d, *J* = 3.0 Hz, 1H), 11.62 (br s, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 14.4, 14.5, 20.9, 29.1, 41.6, 53.9, 60.1, 60.3, 102.0, 111.7, 116.3, 124.1, 136.2, 164.7, 165.3, 166.1, 180.3; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{25}N_2O_4$ 333.1809; found 333.1811.

9-(tert-Butoxycarbonyl)-1-formyl-2,3-dihydro-2,2,7-trimethyldipyrrin (23)

Following a general procedure [19], a solution of **22** (337 mg, 1.11 mmol) in 1,4-dioxane (24 mL, ACS grade) at room temperature was treated with SeO_2 (184 mg, 1.67 mmol). The reaction mixture was stirred for 30 min whereupon a sample of SeO_2 (184 mg, 1.67 mmol) was added. After 30 min, TLC analysis indicated the formation of the product [silica, R_f = 0.76 in hexanes/ethyl acetate (6:1)], and no starting material remained. Ethyl acetate and water were added. The organic layer was washed (brine and water), dried (Na_2SO_4), and concentrated under reduced pressure. Purification by chromatography [silica, hexanes/ethyl acetate (10:1)] afforded a bright red oil (189 mg, 54%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (s, 6H), 1.57 (s, 9H), 2.14 (s, 3H), 2.74 (d, *J* = 2.0 Hz, 2H), 6.25 (d, *J* = 2.0 Hz, 1H), 6.60–6.65 (m, 1H), 9.94 (s, 1H), 10.90 (br s, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 11.1, 25.8, 28.5, 46.4, 46.5, 80.9, 113.1, 116.0, 122.9, 125.8, 130.9, 150.7, 160.3, 177.9, 190.3; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{25}N_2O_3$ 317.1860; found 317.1860.

4-Carboethoxy-(E)-3-ethyl-2-{1-[4,4-dimethyl-5-oxodihydrofuran-2(3H)-ylidene] propyl}pyrrole (26)

Following a general procedure [19], anhydrous DMF and triethylamine were bubbled separately with argon for 30 min. A solution of pyrrole **24** (1.52 g, 5.18 mmol), alkynoic acid **25** (1.60 g, 10.4 mmol), and $BnEt_3NCl$ (1.18 g, 5.18 mmol) in argon-bubbled anhydrous DMF (24 mL) and argon-bubbled triethylamine (6 mL) in a Schlenk flask was deaerated by three freeze-pump-thaw cycles. Then, $Pd(PPh_3)_4$ (388 mg, 0.366 mmol) was added, and the reaction mixture was stirred in an oil bath at 100 °C for 24 h. The mixture was allowed to cool to room temperature, then diluted with ethyl acetate and washed with brine. The organic layer was dried (Na_2SO_4), concentrated under reduced pressure, and purified by chromatography [silica, hexanes/ethyl acetate (4:1)] to afford a white solid (201 mg, 12%): mp 123–125 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.94 (t, *J* = 7.5 Hz, 3H), 1.14 (t, *J* = 7.5 Hz, 3H), 1.26 (s, 6H), 1.35 (t, *J* = 7.0 Hz, 3H), 2.41 (q, *J* = 7.5 Hz, 2H), 2.49 (s, 2H), 2.59 (q, *J* = 7.5 Hz, 2H), 4.28 (q, *J* = 7.0 Hz, 2H), 7.39 (d, *J* = 3.0 Hz, 1H), 8.08 (br s, 1H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 13.1, 14.6, 15.9, 18.8, 24.1, 24.9, 40.2, 40.4, 59.6, 111.3, 114.9 124.3, 125.4, 125.8, 146.3, 165.3, 180.2; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{26}NO_4$ 320.1856; found 320.1850. A single-crystal was examined by XRD (CCDC 2263107).

4-Carboethoxy-(E)-3-ethyl-2-{1-[4,4-dimethyl-5-methylenedihydrofuran-2(3H)-ylidene]propyl} pyrrole (27)

Following a standard procedure [19], a solution of $TiCp_2Cl_2$ (3.05 g, 12.4 mmol) in anhydrous toluene (33 mL) in an ice bath at 0 °C under argon was treated dropwise with MeLi (1.6 M, 17 mL in Et_2O, 27 mmol). The reaction mixture was stirred at 0 °C for 1 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution to the reaction mixture. The organic layer was separated, washed with brine, dried (Na_2SO_4), and filtered. A sample of **26** (551 mg, 1.73 mmol) was treated with the filtrate (26 mL) above and additional $TiCp_2Cl_2$ (26 mg). The resulting mixture was stirred under argon in an oil bath at 80 °C in the dark for 6 h. Afterward, the mixture was allowed to cool to room temperature whereupon MeOH (2 mL), $NaHCO_3$ (86 mg), and water (21 μL) were added. The mixture was stirred at 40 °C

for 12 h. Then, the mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and then purified by chromatography [silica, hexanes/ethyl acetate (4:1), noted: the silica was pre-washed with 5% triethylamine in hexanes] to afford a yellow solid (247 mg, 45%): mp 107–110 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.93 (t, *J* = 7.5 Hz, 3H), 1.13 (t, *J* = 7.5 Hz, 3H), 1.17 (s, 6H), 1.34 (t, *J* = 7.0 Hz, 3H), 2.24 (s, 2H), 2.38 (q, *J* = 7.5 Hz, 2H), 2.59 (q, *J* = 7.5 Hz, 2H), 3.96 (d, *J* = 2.0 Hz, 1H), 4.27 (q, *J* = 7.0 Hz, 2H), 4.38 (d, *J* = 2.0 Hz, 1H), 7.35 (d, *J* = 3.0 Hz, 1H), 7.93 (br s, 1H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 13.4, 14.6, 15.9, 18.8, 23.6, 27.4, 39.8, 42.3, 59.4, 80.3, 105.3, 114.6, 123.5, 124.8, 128.1, 152.2, 165.5, 170.5; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{19}H_{28}NO_3$ 318.2064; found 318.2066. A single-crystal was examined by XRD (CCDC 2263087).

8-Carboethoxy-5,7-diethyl-2,3-dihydro-1-formyl-2,2-dimethyldipyrrin (29)

Following a standard procedure [19] with some modification, a solution of **27** (32 mg, 0.10 mmol) in DMF (1.0 mL) was treated with 1 M aqueous HCl (50 µL) at room temperature. After 30 min, TLC analysis indicated the formation of the presumed diketone intermediate. Then, samples of NH_4OAc (154 mg, 2.00 mmol) and triethylamine (274 µL, 2.00 mmol) were added, and the resulting reaction mixture was stirred at 55 °C in an oil bath for 4 h whereupon TLC analysis indicated the formation of the presumed product [silica, R_f = 0.48 in hexanes/ethyl acetate (3:1)]. The reaction mixture was allowed to cool to room temperature, and then saturated aqueous KH_2PO_4 solution was added. The mixture was extracted with ethyl acetate. The organic layer was dried (Na_2SO_4), concentrated under reduced pressure to a yellow oil, and purified by chromatography [silica, hexanes/ethyl acetate (3:1)] to afford a yellow oil (16 mg, 50%) as a mixture of isomers (intermediate **28**). The resulting oil (16 mg, 0.051 mmol) in 1,4-dioxane (1.0 mL, ACS grade) was treated with SeO_2 (8.3 mg, 0.075 mmol) at room temperature and exposed to the air. The reaction mixture turned brown during 30 min, at which point TLC analysis indicated the consumption of starting material and formation of the product [silica, R_f = 0.58 in hexanes/ethyl acetate (3:1)]. Then, a mixture of ethyl acetate and water was added, and the organic layer was dried (Na_2SO_4) and then concentrated under reduced pressure to a brown oil. The brown oil was purified by chromatography [silica, hexanes/ethyl acetate (3:1)] to afford a red oil (5.5 mg, 33%; 17% overall): ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.18 (t, *J* = 7.5 Hz, 3H), 1.23 (t, *J* = 7.5 Hz, 3H), 1.34 (t, *J* = 7.0 Hz, 3H), 1.37 (s, 6H), 2.57 (q, *J* = 7.5 Hz, 2H), 2.75 (s, 2H), 3.01 (q, *J* = 7.5 Hz, 2H), 4.28 (q, *J* = 7.0 Hz, 2H), 7.53 (d, *J* = 3.5 Hz, 1H), 9.87 (s, 1H), 11.50 (br s, 1H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 13.7, 14.6, 16.8, 18.9, 24.5, 26.1, 45.4, 45.6, 59.5, 115.3, 127.0, 127.9, 129.8, 133.6, 148.3, 165.1, 175.4, 189.9; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{19}H_{27}N_2O_3$ 331.2016; found 331.2021.

5-Bromo-2-tert-butoxycarbonylpyrrole (32) [19]

Following a general method [19,106] with modifications, a solution of 2-*tert*-butoxycarbonyl pyrrole (**31**, 101 mg, 603 µmol) in distilled THF (4.5 mL) and dry MeOH (1.5 mL) in an ice bath at 0 °C under argon was treated with NBS (105 mg, 591 µmol). The mixture was stirred for 2 h at 0 °C, and then concentrated under reduced pressure. Purification by chromatography [silica (50 g); hexanes/ethyl acetate (20:1)] gave the title compound 5-bromo-2-*tert*-butoxycarbonyl pyrrole (**32**, 65 mg, 36%) as a white solid, 4-bromo-2-*tert*-butoxycarbonyl pyrrole (**33**, 61 mg, 34%) as a white solid, and impure 4,5-dibromo-2-*tert*-butoxycarbonyl pyrrole (**34**, 17 mg, 7% given the presence of **34** and **32** in 4:1 ratio) as a white solid.

Data for the title compound: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.57 (s, 9H), 6.18 (dd, *J* = 4.0 and 3.0 Hz, 1H), 6.75 (dd, *J* = 4.0 and 3.0 Hz, 1H), 9.48 (br s, 1H) (contaminated with an unknown species; only the signals for **32** are listed here); HRMS (ESI-TOF) *m/z*: [M – H]$^-$ calcd for $C_9H_{11}O_2Br$ 243.9979; found 243.9975.

Data for 4-bromo-2-*tert*-butoxycarbonylpyrrole (**33**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.55 (s, 9H), 6.81 (dd, *J* = 3.0 and 2.0 Hz, 1H), 6.89 (dd, *J* = 3.0 and 2.0 Hz, 1H), 9.21 (br s, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 28.3, 81.6, 97.5, 116.2, 121.8, 124.7, 159.8. A single-crystal was examined by XRD (CCDC 2263088).

Data for 4,5-dibromo-2-*tert*-butoxycarbonyl pyrrole (**34**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.57 (s, 9H), 6.81 (d, *J* = 3.0 Hz, 1H), 9.91 (br s, 1H) (signals listed for **34**; signals for co-isolated **32** are omitted); HRMS (ESI-TOF) *m/z*: [M – H]$^-$ calcd for $C_9H_{10}Br_2O_3$ 321.9084, found 321.9089.

Methyl 6-tert-butoxy-6-oxo-5,5-dimethylhex-2-ynoate (36)

Following established methods [113, 114], a solution of *tert*-butyl isopropionate (**35**, 1.51 g, 10.5 mmol) in distilled THF (70 mL) at –78 °C was treated with LDA (8.0 mL, 16 mmol), and stirring was continued for 30 min under argon. The solution at –78 °C was treated dropwise with propargyl bromide (1.40 mL, 12.6 mmol), and stirring was continued for 30 min. The mixture was allowed to warm to room temperature over the course of 30 min. Stirring was continued for 3 h at room temperature. Then, the reaction was quenched by the addition of saturated aqueous NH_4Cl (100 mL) to the reaction mixture followed by stirring for 20 min. The mixture was treated with H_2O (200 mL) and extracted with Et_2O (50 mL × 3). The combined organic extract was washed with 2 N aqueous HCl (50 mL), H_2O (50 mL), and brine (50 mL). The organic extract was dried over Na_2SO_4 and then concentrated under reduced pressure. The resulting

residue was dissolved in distilled THF (100 mL) and cooled to –78 °C. A sample of *n*-BuLi (1.6 M in hexanes, 5.8 mL, 9.3 mmol) was added dropwise under argon, and stirring was continued for 30 min at –78 °C. The mixture was treated dropwise with methyl chloroformate (3.0 mL, 39 mmol) at –78 °C, and stirring was continued for 1.5 h under argon at –78 °C. Saturated aqueous NH_4Cl (100) and H_2O (200 mL) were added. The mixture was extracted with Et_2O (50 mL × 3). The combined organic extract was washed with H_2O (50 mL) and brine (50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by chromatography [silica (50 g), hexanes/ethyl acetate (20:1)] gave a pale yellow oil (1.05 g, 46% in 2 steps): ^{1}H NMR (700 MHz, $CDCl_3$) δ 1.26 (s, 6H), 1.45 (s, 9H), 2.54 (s, 2H), 3.75 (s, 3H); $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$) δ 24.7, 27.9, 29.6, 42.4, 52.5, 74.6, 80.9, 86.7, 154.0, 175.1; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{21}O_4$ 241.1434, found 241.1435.

Methyl (Z)-2-(4,4-dimethyl-5-oxodihydrofuran-2(3H)-ylidene)acetate (37)

A solution of alkynoic ester **36** (36.3 mg, 151 μmol) in 50% aqueous TFA (2 mL) was stirred for 18 h at room temperature. The mixture was concentrated under reduced pressure. Purification by chromatography [silica (5 g), hexanes/ethyl acetate (3:1)] gave a pale yellow oil (10.8 mg, 40%): ^{1}H NMR (700 MHz, $CDCl_3$) δ 1.35 (s, 6H), 2.81 (d, *J* = 2.0 Hz, 2H), 3.75 (s, 3H), 5.17 (t, *J* = 2.0 Hz, 1H); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_9H_{13}O_4$ 185.0808, found 185.0806. Rapid purification in one instance afforded the alkynoic acid **Xb**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (s, 6H), 2.63 (s, 2H), 3.77 (s, 3H); $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$) δ 24.5, 29.2, 41.8, 52.7, 74.9, 85.7, 154.0, 181.5.

tert-Butyl 6-hydroxy-2,2-dimethylhex-4-ynoate (38)

Following established methods [115,116], a solution of *tert*-butyl isopropionate (**35**, 3.00 g, 20.8 mmol) in distilled THF (140 mL) at –78 °C was treated with LDA (16 mL, 32 mmol). The mixture was stirred for 30 min under argon. The solution was treated dropwise with propargyl bromide (2.80 mL, 25.1 mmol) at –78 °C, and stirring was continued for 30 min. The mixture was allowed to warm to room temperature over the course of 30 min and then stirred at room temperature for 3 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl (200 mL) to the reaction mixture. The mixture was stirred for 20 min, treated with H_2O (300 mL), and extracted with Et_2O (100 mL × 3). The combined organic extract was washed with 2 N aqueous HCl (100 mL), H_2O (100 mL) and brine (100 mL). The organic extract was dried over Na_2SO_4 and then concentrated to dryness under reduced pressure. The residue was dissolved in distilled THF (140 mL) and cooled to –78 °C. A sample of *n*-BuLi (1.6 M in hexane, 5.8 mL, 9.3 mmol) was added dropwise under argon, and stirring was continued for 30 min at –78 °C. The mixture was treated with paraformaldehyde (1.87 g, 20.8 mmol) at –78 °C, and stirring was continued for 2 h under argon at –78 °C. Saturated aqueous NH_4Cl (200 mL) and H_2O (300 mL) were added. The mixture was filtered through a pad of Celite, and the precipitate was rinsed with Et_2O (50 mL × 3). The combined filtrate was extracted with Et_2O (100 mL × 3). The combined ethereal solution was washed with H_2O (100 mL) and brine (100 mL), dried over Na_2SO_4, and concentrated to dryness under reduced pressure. The residue was purified by column chromatography [silica (200 g), hexanes/ethyl acetate (4:1)] to give a pale yellow oil (1.44 g, 33% in 2 steps): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22 (s, 6H), 1.45 (s, 9H), 1.50 (br t, *J* = 6.0 Hz, 1H), 2.41 (t, *J* = 2.0 Hz, 2H), 4.24 (br s, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 24.5, 27.9, 30.0, 42.6, 51.3, 80.6, 83.3, 175.9; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{12}H_{21}O_3$ 213.1485, found 213.1477.

6-Hydroxy-2,2-dimethylhex-4-ynoic acid (39) and 6-Trifluoroacetoxy-2,2-dimethylhex-4-ynoic acid (40)

A solution of alkynoic ester **38** (118 mg, 554 μmol) in dry CH_2Cl_2 (6 mL) and TFA (0.6 mL) was stirred for 4 h at room temperature. The mixture was concentrated to dryness under reduced pressure. The crude product (130.9 mg) was used for the next reaction without purification. A part of the crude product was purified by silica column chromatography for analytical purposes.

Data for **39**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30 (s, 6H), 2.49 (t, *J* = 2.0 Hz, 2H), 4.26 (t, *J* = 2.0 Hz, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 24.5, 29.8, 42.2, 51.2, 80.7, 82.6, 182.5; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_8H_{12}O_3Na$ 179.0679; found 179.0678.

Data for **40**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.31 (s, 6H), 2.53 (t, *J* = 2.0 Hz, 2H), 4.92 (t, *J* = 2.0 Hz, 2H); $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$) δ 24.4, 29.5, 41.9, 56.0, 74.0, 86.5, 114.3 (q, $J_{C\text{-}F}$ = 284 Hz), 156.9 (q, $J_{C\text{-}F}$ = 41.0 Hz), 181.6.

tert-Butyl (Z)-5-(1-(4,4-dimethyl-5-oxodihydrofuran-2(3H)-ylidene)-2-hydroxyethyl)-1H-pyrrole-2-carboxylate (41)

A mixture of 5-bromo-2-*tert*-butoxycarbonyl pyrrole (**32**, 91 mg, 370 μmol), the above crude product of alkynoic acid (the mixture of **39** and **40**: 131 mg), benzyltriethylammonium chloride (84 mg, 370 μmol) and triethylamine (0.60 mL, 4.3 mmol) in dry acetonitrile (5 mL) was degassed by sonication accompanied by argon bubbling for 10 min. The mixture was treated with $Pd(PPh_3)_4$ (423 mg, 370 μmol), and stirring was continued for 29 h at reflux temperature in an oil bath under argon. After allowing to cool to room temperature, the mixture was treated with H_2O (30 mL) and extracted with CH_2Cl_2

(5 mL × 3). The combined organic extract was washed with H_2O (5 mL) and brine (5 mL), dried over Na_2SO_4, and concentrated to dryness under reduced pressure. The residue was purified by column chromatography [silica (25 g), hexanes/ethyl acetate (4:1)] to give a pale yellow film (38.9 mg, 32%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (s, 6H), 1.56 (s, 9H), 1.90 (br s, 1H), 2.95 (s, 2H), 4.65 (s, 2H), 6.04 (dd, *J* = 4.0 and 3.0 Hz, 1H), 6.82 (dd, *J* = 4.0 and 3.0 Hz, 1H), 9.91 (br s, 1H); ^{13}C{^{1}H} NMR (175 MHz, $CDCl_3$) δ 25.1, 28.3, 39.6, 41.2, 59.4, 80.9, 108.6, 108.9, 114.9, 123.8, 132.4, 146.9, 160.5, 179.1; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{24}NO_5$ 322.1649, found 322.1646.

tert-Butyl (Z)-4-bromo-5-(1-(4,4-dimethyl-5-oxodihydrofuran-2(3H)-ylidene)-2-hydroxyethyl)-1H-pyrrole-2-carboxylate (42)

A solution of lactone-pyrrole **41** (29.1 mg, 90.6 μmol) in distilled THF (5 mL) was treated with NBS (13.5 mg, 75.9 μmol), and stirring was continued for 15 min at room temperature under argon. Saturated aqueous $NaHCO_3$ (20 mL) and H_2O (10 mL) were added, then the mixture was extracted with ethyl acetate (5 mL × 3). The combined organic extract was washed with H_2O (5 mL) and brine (5 mL), dried over Na_2SO_4, and concentrated to dryness under reduced pressure. The residue was purified by column chromatography [silica (5 g); hexanes/ethyl acetate (3:1)] to give a pale yellow film (21.4 mg, 59%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.33 (s, 6H), 1.55 (s, 9H), 2.78 (s, 2H), 4.49 (s, 2H), 6.81 (d, *J* = 3.0 Hz, 1H), 9.52 (br s, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 24.9, 28.3, 39.9, 40.6, 59.7, 81.6, 97.5, 106.8, 116.7, 124.6, 129.8, 150.1, 159.6, 179.1; HRMS (ESI-TOF) *m/z*: $[M - H]^-$ calcd for $C_{17}H_{21}BrNO_5$ 398.6086, found 398.6031.

3-Carbomethoxy-5-iodopyrrole (44)

Following a reported procedure [118], a solution of **43** (3.75 g, 30.0 mmol) in anhydrous DMF (200 mL) in an ice bath at 0 °C under argon was slowly treated with NIS (6.75 g, 30.0 mmol). The reaction mixture was stirred for 1.5 h whereupon TLC analysis indicated the consumption of the starting material and formation of the product [silica, R_f = 0.35, hexanes/ethyl acetate (2:1)]. Then, a mixture of water and ethyl acetate (300 mL, 1:1, v/v) was added. The organic layer was separated and further washed with brine and water, dried (Na_2SO_4), and concentrated under reduced pressure. Purification by chromatography [silica, hexanes/ethyl acetate (10:1) to (2:1)] afforded a white solid (5.07 g, 67%): mp: 115–123 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.81 (s, 3H), 6.77 (t, *J* = 2.0 Hz, 1H), 7.41–7.42 (m, 1H), 8.51 (br s, 1H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 51.5, 63.6, 119.3, 127.4, 164.1; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_6H_7INO_2$ 251.9516; found 251.9511. A single-crystal was examined by XRD (CCDC 2263091).

1-Benzyl-3-carbomethoxy-5-iodopyrrole (Bn-44)

A solution of **44** (377 mg, 1.50 mmol) in anhydrous THF (5 mL) at –78 °C under argon was treated with LDA (0.75 mL, 2.2 mmol, 2.0 M in THF/heptane/ethylbenzene). The reaction mixture was stirred for 30 min at –78 °C followed by the addition of benzyl bromide (188 μL, 1.58 mmol). The resulting reaction mixture was allowed to warm to room temperature and stirred overnight, whereupon TLC analysis indicated the formation of the product [silica, R_f = 0.53, hexanes/ethyl acetate (6:1)]. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution to the reaction mixture, which was then extracted with ethyl acetate. The organic layer was separated, dried (Na_2SO_4), concentrated under reduced pressure, and purified by chromatography [silica, hexanes/ethyl acetate (6:1)] to afford a white solid (344 mg, 67%): mp: 60–64 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.78 (s, 3H), 5.09 (s, 2H), 6.85 (d, *J* = 2.0 Hz, 1H), 7.10 (dd, *J* = 8.0 and 1.5 Hz, 2H), 7.26–7.36 (m, 3H), 7.44 (d, *J* = 2.0 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 51.4, 54.8, 71.4, 118.8, 120.6, 127.3, 128.3, 129.1, 129.2, 136.3, 164.3; HRMS (ESI-TOF) *m/z*: $[M - H]^-$ calcd for $C_{13}H_{13}INO_2$ 339.9840; found 339.9842. A single-crystal was examined by XRD (CCDC 2263094).

1-(tert-Butyl)-3-carbomethoxy-5-iodopyrrole (Boc-44)

Following a reported procedure [118], a solution of **44** (377 mg, 1.50 mmol) in anhydrous acetonitrile (3 mL) at room temperature was treated with DMAP (37 mg, 0.30 mmol), triethylamine (0.25 mL, 1.8 mmol) and di-*tert*-butyl dicarbonate (393 mg, 1.80 mmol). The resulting reaction mixture was stirred overnight, whereupon TLC analysis indicated the formation of the product [silica, R_f = 0.55, hexanes/ethyl acetate (10:1)]. The mixture was concentrated under reduced pressure and then purified by chromatography [silica, hexanes and then hexanes/ethyl acetate (10:1)] to afford a white solid (398 mg, 76%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.62 (s, 9H), 3.81 (s, 3H), 6.90 (d, *J* = 2.0 Hz, 1H), 7.94 (d, *J* = 2.0 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 28.1, 51.7, 64.8, 86.4, 120.7, 125.2, 129.2, 147.6, 163.6; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{11}H_{15}INO_4$ 352.0040; found 352.0043. A single-crystal was examined by XRD (CCDC 2263092).

3-Carbomethoxy-5-iodo-1-triisopropylsilylpyrrole (TIPS-44)

Following a reported procedure [120], a solution of **44** (502 mg, 2.00 mmol) in anhydrous THF (10 mL) at –78 °C under argon was treated with LDA (1.1 mL, 2.2 mmol, 2.0 M in THF/heptane/ethylbenzene). The reaction mixture was stirred for 30 min at –78 °C followed by the addition of TIPSCl (642 μL, 3.00 mmol). The resulting reaction mixture was allowed to slowly warm to room temperature and then was stirred overnight, whereupon TLC analysis indicated the formation

of the product [silica, R_f = 0.60, hexanes/ethyl acetate (6:1)]. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ solution to the reaction mixture. The mixture was extracted with ethyl acetate. The organic layer was separated, dried (Na_2SO_4), and concentrated under reduced pressure to a yellow oil. Purification by chromatography [silica, hexanes/ethyl acetate (6:1)] afforded a clear pale-yellow oil (814 mg, 99%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15 (d, *J* = 8.0 Hz, 18H), 1.81 (hept, *J* = 7.5 Hz, 3H), 3.78 (s, 3H), 6.92 (d, *J* = 1.5 Hz, 1H), 7.48 (d, *J* = 1.5 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 13.3, 18.3, 51.3, 69.7, 120.3, 124.6, 135.0, 164.3; HRMS (ESI-TOF) *m/z*: [M – H]$^-$ calcd for $C_{15}H_{25}INO_2Si$ 406.0705; found 406.0703.

4-Carbomethoxy-(E)-2-{[4,4-dimethyl-5-oxodihydrofuran-2(3H)-ylidene]methyl}pyrrole (45)

Following a general procedure [19] with modification, a solution of **44** (3.76 g, 15.0 mmol), **16** (2.27 g, 18.0 mmol), and $BnEt_3NCl$ (3.42 g, 15.0 mmol) in anhydrous acetonitrile (150 mL, containing 4Å MS and pre-bubbled with argon for 15 min) and triethylamine (16.8 mL, containing 4Å MS and pre-bubbled with argon for 15 min) was deaerated by three freeze–pump–thaw cycles. A sample of $Pd(PPh_3)_4$ (867 mg, 0.750 mmol) was added, and the reaction mixture was stirred in an oil bath at 80 °C for 24 h whereupon TLC analysis indicated the formation of the product [silica, R_f = 0.35, hexanes/ethyl acetate (2:1)]. The reaction mixture was allowed to cool to room temperature, then a mixture of water and ethyl acetate was added. The organic layer was separated, dried (Na_2SO_4), and concentrated under reduced pressure. Purification by chromatography [silica, hexanes/ethyl acetate (10:1) to (2:1)] afforded a yellow solid (2.15 g, 57%): mp: 183–189 °C; ^{1}H NMR (500 MHz, acetonitrile-d_3) δ 1.30 (s, 6H), 2.98 (d, *J* = 2.0 Hz, 2H), 3.74 (s, 3H), 6.16 (s, 1H), 6.36 (s, 1H), 7.34 (d. *J* = 1.5 Hz, 1H), 9.58 (br s, 1H); ^{13}C{^{1}H} NMR (125 MHz, acetonitrile-d_3) δ 25.4, 40.7, 40.9, 51.5, 97.7, 107.5, 124.2, 124.4, 128.2, 149.8, 165.8, 180.8; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{13}H_{16}NO_4$ 250.1074; found 250.1072. A single-crystal was examined by XRD (CCDC 2263095).

4-Carbomethoxy-(E)-2-[(4,4-dimethyl-5-methylenedihydrofuran-2(3H)-ylidene)-methyl]pyrrole (46)

Following a general procedure [19], a solution of $TiCp_2Cl_2$ (9.44 g, 37.9 mmol) in anhydrous toluene (100 mL) in an ice bath at 0 °C under argon was treated with MeLi (1.6 M, 52.1 mL in Et_2O, 83 mmol). The reaction mixture was stirred at 0 °C in the dark for 1.5 h, and then saturated aqueous NH_4Cl solution was added. The resulting organic layer was washed with brine and water, dried (Na_2SO_4), and filtered. The filtrate (orange, ~74 mL) containing the Petasis reagent was added into a 100 mL flask containing **45** (993 mg, 4.00 mmol) under argon. The resulting reaction mixture was stirred in an oil bath at 80 °C under argon in the dark for 5 h, and was then allowed to cool to room temperature. MeOH (4.75 mL), $NaHCO_3$ (199 mg), and water (48 μL) were added, and the resulting reaction mixture was stirred at 40 °C in the dark for 12 h and then filtered through a pad of Celite. The filtrate was collected and then concentrated under reduced pressure to an orange oil. Purification by chromatography [silica, hexanes/ethyl acetate (5:1), noted: the silica column was pre-washed with 5% triethylamine in hexanes] afforded a yellow oil (592 mg, 60%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (s, 6H), 2.70 (d, *J* = 2.0 Hz, 2H), 3.81 (s, 3H), 4.01 (d, *J* = 2.5 Hz, 1H), 4.38 (d, *J* = 2.5 Hz, 1H), 5.83 (t, *J* = 2.0 Hz, 1H), 6.32 (t, *J* = 2.0 Hz, 1H), 7.33 (dd, *J* = 3.0 and 1.5 Hz, 1H), 8.52 (br s, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 28.0, 40.2, 42.7, 51.3, 80.9, 92.3, 105.6, 117.2, 122.6, 129.7, 155.0, 165.7, 169.6; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{14}H_{18}NO_3$ 248.1281; found 248.1280.

8-Carbomethoxy-2,3-dihydro-1,2,2-trimethyl-dipyrrin (47)

Following a general procedure [19], a solution of **46** (74 mg, 0.30 mmol) in anhydrous DMF (3.3 mL) was treated with 1.0 M aqueous HCl (75 μL, 0.075 mmol). The reaction mixture was stirred at room temperature for 50 min whereupon TLC analysis indicated the formation of the diketone intermediate [silica, R_f = 0.20, hexanes/ethyl acetate (2.5:1)]. Samples of NH_4OAc (462 mg, 6.00 mmol) and triethylamine (836 μL, 6.00 mmol) were added. The reaction mixture was maintained at 55 °C for 1.5 h whereupon TLC analysis indicated the formation of the product [silica, R_f = 0.53, hexanes/ethyl acetate (2.5:1)]. The reaction mixture was allowed to cool to room temperature, and then saturated aqueous KH_2PO_4 solution was added. Ethyl acetate was added. The organic layer was dried (Na_2SO_4), concentrated under reduced pressure, and purified by chromatography [silica, hexanes/ethyl acetate (3:1)] to afford a yellow oil (51 mg, 68%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.17 (s, 6H), 2.13 (s, 3H), 2.55 (d, *J* = 2.0 Hz, 2H), 3.79 (s, 3H), 5.80 (d, *J* = 2.0 Hz, 1H), 6.41 (t, *J* = 2.0 Hz, 1H), 7.41 (dd, *J* = 3.0 and 1.5 Hz, 1H), 11.19 (br s, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 15.6, 25.8, 44.1, 48.5, 51.1, 105.6, 108.1, 115.9, 124.2, 132.2, 150.4, 165.9, 187.5; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{14}H_{19}N_2O_2$ 247.1441; found 247.1436.

6-[4-(3-Methoxy-3-oxopropanoyl)pyrrol-2-yl]-1,1-dimethoxy-4,4-dimethyl-5-nitrohexan-2-one (51)

Following a reported procedure [20] in a streamlined manner, a mixture of **49** (1.99 g, 3.75 mmol), potassium monomethyl malonate (937 mg, 6.00 mmol), Xantphos (1.30 g, 2.25 mmol), $MgCl_2$ (571 mg, 6.00 mmol), and imidazole (536 mg, 7.88 mmol) in a 50 mL Schlenk flask was charged with argon. THF (38 mL) was added

followed by triethylamine (821 μL, 6.00 mmol). The mixture was degassed by three freeze-pump-thaw cycles. Then, $Pd(OAc)_2$ (672 mg, 3.00 mmol) and $Co_2(CO)_8$ (1.03 g, 3.00 mmol) were added under a stream of argon. The flask was sealed immediately and heated at 65 °C in an oil bath, with reaction progress monitored by TLC analysis. When the reaction was complete (48 h), the reaction mixture was allowed to cool to room temperature. The mixture was diluted with ethyl acetate and then filtered through a Celite pad. The filtrate was washed (brine and water), dried (Na_2SO_4), and concentrated to give a crude yellow solid. (A small sample for XRD analysis was further purified by chromatography [silica, hexanes/ethyl acetate (1:2)] to afford **50** as a pale yellow solid; XRD data are at CCDC 2263099.) The entire crude yellow solid was dissolved in TBAF solution (1.0 M in THF, 5.0 mL, 5.0 mmol) and heated at 65 °C for 1 h. The reaction mixture was allowed to cool to room temperature and then saturated aqueous $NaHCO_3$ solution was added. The resulting mixture was extracted with ethyl acetate. The organic phase was dried (Na_2SO_4), concentrated, and chromatographed [silica, hexanes/ethyl acetate (3:1)] to afford a yellow oil (919 mg, 62%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.12 (s, 3H), 1.20 (s, 3H), 2.57–2.73 (m, 2H), 2.99–3.03 (m, 1H), 3.32 (dd, J = 15.5 and 12.0 Hz, 1H), 3.42 (d, J = 3.0 Hz, 6H), 3.70 (s, 3H), 3.73 (s, 2H), 4.35 (s, 1H), 5.15 (dd, J = 12.0 and 2.5 Hz, 1H), 6.38–6.41 (m, 1H), 7.32 (dd, J = 3.0 and 1.5 Hz, 1H), 9.09 (br s, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 24.2, 24.4, 26.5, 36.6, 45.1, 46.6, 55.4, 94.3, 104.8, 107.8, 124.8, 125.4, 128.8, 168.6, 187.3, 203.9; HRMS (ESI-TOF) *m/z*: $[M - H]^-$ calcd for $C_{18}H_{25}N_2O_8$ 397.1616; found 397.1610.

2,3-Dihydro-1-(1,1-dimethoxymethyl)-8-(3-methoxy-3-oxo-propanoyl)-3,3-dimethyldipyrrin (52)

Following a reported procedure [20] with modification, in a first flask, a solution of **51** (878 mg, 2.20 mmol) in anhydrous THF/methanol (78 mL, 12:1, v/v) was bubbled with a stream of argon for 15 min. Then, the solution was treated with NaOMe (891 mg, 16.5 mmol) at room temperature, and the resulting mixture was stirred for 45 min. In a second flask, a solution of NH_4OAc (169.6 g, 2.20 mol) in deionized water (169 mL) was bubbled with a stream of argon for 20 min. Then, the solution was treated with $TiCl_3$ (15.8 mL, 20 mmol, 20% w/v solution in 2 N HCl). The suspension was stirred for 15 min at room temperature under argon. The solution in the first flask containing the nitronate anion of **51** was transferred via a cannula to the buffered $TiCl_3$ solution in the second flask. The resulting brown mixture was stirred for 20 h under argon at room temperature. The reaction mixture was poured slowly into a stirred mixture of saturated aqueous $NaHCO_3$ (450 mL) and ethyl acetate (300 mL). The mixture was stirred vigorously at room temperature for 15 min followed by the addition of another batch of saturated aqueous $NaHCO_3$ (300 mL), causing discharge of the color from dark slate blue to white. The organic layer (dark orange) was separated, dried (Na_2SO_4), and concentrated under reduced pressure. The resulting residue was purified by chromatography [silica, CH_2Cl_2/ethyl acetate (2:1)] to afford a yellow oil (253 mg, 33%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.20 (s, 6H), 2.63 (s, 2H), 3.44 (s, 6H), 3.72 (s, 3H), 3.77 (s, 2H), 5.02 (s, 1H), 5.82 (s, 1H), 6.52 (s, 1H), 7.49 (dd, J = 3.0 and 1.5 Hz, 1H), 11.18 (br s, 1H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 29.1, 40.3, 46.9, 48.5, 52.4, 54.7, 102.5, 106.5, 108.5, 125.2, 125.5, 132.7, 162.2, 168.6, 176.2, 187.1; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{25}N_2O_5$ 349.1758; found 349.1763.

2-Carbomethoxy-3-(9-tert-butoxycarbonyl-2,3-dihydro-2,2,7-trimethyldipyrrin-1-yl)-1-[2,3-dihydro-1-(1,1-dimethoxymethyl)-3,3-dimethyldipyrrin-8-yl]-prop-2-en-1-one (53)

Following a standard procedure [94], a mixture of **23** (30 mg, 94 μmol), **52** (28 mg, 94 μmol), and dried molecular sieves powder (4 Å, 30 mg) was treated with a solution of piperidine/acetic acid in acetonitrile (15mM/15mM, 2.6 mL, 39 μmol/39 μmol). The reaction mixture was stirred at room temperature for 27 h. The mixture was filtered through a Pasteur pipette containing a plug of Celite. The resulting filtrate was concentrated under reduced pressure, dried (Na_2SO_4), and purified by preparative TLC [silica, 1 mm thick, 20 cm × 20 cm, hexanes/ethyl acetate (10:1)]. A mixture of inseparable isomers was obtained as a bright-red gum (15%, 9 mg): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.06–1.26 (m, 12H for each isomer), 1.54 (s, 9H for minor isomer), 1.63 (s, 9H for major isomer), 2.04 (s, 3H for major isomer), 2.10 (s, 3H for minor isomer), 2.51–2.75 (m, 2H for each isomer; some undefined resonances are present in this cluster), 2.87 (dd, J = 15.5 and 2.5 Hz, 1H for major isomer), 3.03 (dd, J = 15.5 and 2.0 Hz, 1H for minor isomer), 3.18 (dd, J = 15.5 and 11.5 Hz, 1H), 3.35 (dd, J = 15.0 and 12.0 Hz, 1H), 3.41 (s, 6H for major isomer), 3.44 (s, 3H for minor isomer), 3.44 (s, 3H for minor isomer), 3.70 (s, 3H for each isomer), 3.79 (s, 3H for major isomer), 4.32 (s, 1H for major isomer), 4.35 (s, 1H for minor isomer), 4.91 (dd, J = 11.5 and 2.5 Hz, 1H for major isomer), 5.16 (dd, J = 12.0 and 2.5 Hz, 1H for minor isomer), 5.86 (s, 1H for major isomer), 6.01 (s, 1H for minor isomer), 6.33 (t, J = 2.0 Hz, 1H for major isomer), 6.46 (t, J = 2.0 Hz, 1H for minor isomer), 6.59 (d, J = 2.5 Hz, 1H for major isomer), 6.61 (d, J = 3.0 Hz, 1H for minor isomer), 7.02 (s, 1H for minor isomer), 7.31 (dd, J = 3.0 and 2.0 Hz, 1H for minor isomer), 7.40 (dd, J = 3.0 and 2.0 Hz, 1H for major isomer), 7.42 (s, 1H for major isomer), 8.70 (s, 1H for minor isomer), 8.78 (s, 1H for major isomer), 9.97 (s, 1H for major isomer), 10.43 (s, 1H for minor isomer).

Attempted synthesis of 13^2-carbomethoxy-2,8,8,17,-17-pentamethylbacterio-13^1-oxophorbine (**BC-21**). After

checking the ^{1}H NMR spectrum, the crude sample of **53** was diluted in anhydrous acetonitrile to 70 mL, then $Yb(OTf)_3$ (86.2 mg, 139 μmol) was added in one batch in a glove box filled with argon. The reaction mixture was then stirred at 80 °C for 10 h. The progress of the reaction was monitored by TLC and absorption spectroscopy, by which the desired bacteriochlorin was not evident; instead, the decomposition of **53** was observed.

2,3,4,5-Tetrahydro-1,3,3-trimethyl-7-p-tolyldipyrrin (55)

Following a general procedure [128] with some modification, a mixture of **54** (35 mg, 0.11 mmol) and NH_4Cl (25 mg, 0.46 mmol) in THF/H_2O (1:1, v/v, 2 mL) was treated with zinc dust (105 mg, 1.61 mmol). The reaction mixture was stirred at room temperature for 10 min. The mixture was diluted with ethyl acetate and filtered. The filtrate was washed with brine and water, dried (Na_2SO_4), concentrated under reduced pressure, and purified by chromatography [silica, hexanes/ethyl acetate (1:1)] to afford a yellow oil (7 mg, 22%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (s, 3H), 1.11 (s, 3H), 2.08 (s, 3H), 2.30–2.44 (m, 5H), 2.65 (dd, *J* = 15.0 and 12.0 Hz, 1H), 3.03 (dd, *J* = 15.0 and 2.5 Hz, 1H), 3.70 (d, *J* = 12.0 Hz, 1H), 6.29–6.33 (m, 1H), 6.75–6.79 (m, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 10.21 (br s, 1H); ^{13}C{^{1}H} NMR (175 MHz) δ 20.6, 21.2, 23.0, 26.5, 27.3, 29.8, 42.1, 54.4, 80.1, 108.2, 116.1, 120.9, 128.1, 129.2, 134.5, 134.8, 174.9.

9-Bromo-2,3,4,5-tetrahydro-1,3,3-trimethyl-7-p-tolyldipyrrin (56)

Following a general procedure [128], a solution of **55** (13 mg, 0.046 mmol) in anhydrous THF (0.9 mL) at –78 °C under argon was treated with NBS (8.3 mg, 0.046 mmol) in one portion. The mixture was stirred at –78 °C for 1 h. Then, water (0.6 mL) was added. The reaction mixture was allowed to warm to room temperature. The mixture was extracted with ethyl acetate. The organic layer was dried (Na_2SO_4), concentrated under reduced pressure, and purified by chromatography [silica, ethyl acetate] to afford a brown oil (14 mg, 85%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.92 (s, 3H), 1.09 (s, 3H), 2.07 (s, 3H), 2.31–2.41 (m, 5H), 2.56 (dd, *J* = 15.0 and 12.0 Hz, 1H), 2.93 (dd, *J* = 15.0 and 2.5 Hz, 1H), 3.64 (d, *J* = 12.0 Hz, 1H), 6.19 (d, *J* = 3.5 Hz 1H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 10.33 (br s, 1H); ^{13}C{^{1}H} NMR (150 MHz) δ 20.7, 21.2, 23.0, 26.4, 27.3, 42.0, 54.5, 80.0, 96.0, 109.9, 122.8, 128.0, 129.2, 129.3, 133.7, 135.1, 175.0; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{24}BrN_2$ 359.1117; found 359.1119.

9-Bromo-10,11-bis(N-tert-butoxycarbonyl)-2,3,4,5-tetrahydro-1,3,3-trimethyl-7-p-tolyldipyrrin (57)

Following a general procedure [133], a solution of **56** (53.0 mg, 0.148 mmol) and DMAP (3.5 mg, 0.030 mmol) in acetonitrile (600 μL) was treated with di-*tert*-butyl dicarbonate (12.9 mg, 0.0592 mmol). The reaction mixture was stirred at room temperature for 16 h. Then, the reaction mixture was concentrated under reduced pressure and purified by chromatography [silica, hexanes/ethyl acetate (2:1)] to afford a brown-yellow oil (43 mg, 64%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.77 (s, 3H), 0.95 (s, 3H), 1.64 (s, 9H), 1.95 (s, 3H), 2.20 (d, *J* = 17.5 Hz, 1H), 2.29 (d, *J* = 17.5 Hz, 1H), 2.35 (s, 3H), 3.05–3.14 (m, 2H), 3.62 (br s, 1H), 6.30 (s, 1H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H); ^{13}C{^{1}H} NMR (150 MHz) δ 20.5, 21.3, 22.8, 26.8, 27.1, 28.1, 42.1, 54.6, 85.0, 99.8, 116.6, 126.9, 128.9, 129.1 132.6, 136.3, 149.3 (three expected resonances were not observed); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{24}H_{32}BrN_2O_2$ 459.1642; found 459.1649.

Oxabilane 58 *(provisional assignment)*

Following a literature procedure [137], a solution of **57** (5.0 mg, 0.011 mmol), **27** (5.2 mg, 0.016 mmol), NH_4OAc (6.6 mg, 0.022 mmol), and XPhos (10.4 mg, 0.022 mmol) in argon-bubbled anhydrous 1,4-dioxane (40 μL) in an HPLC vial was deaerated by three freeze-pump-thaw cycles. $Pd(OAc)_2$ (2.4 mg, 0.011 mmol) was added. The reaction mixture was stirred at 50 °C for 48 h. HPLC-HRMS analysis afforded a peak, albeit of weak intensity, consistent with the title compound: HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{43}H_{58}N_3O_5$ 696.4371; found 696.4369.

1-(tert-Butoxycarbonyl)-3-carboethoxy-4-p-tolylpyrrole (Boc-59)

Following a general procedure [140] with modification, a solution of **59** (2.3 g, 10. mmol) in CH_2Cl_2 (5 mL) was treated with triethylamine (2.1 mL), di-*tert*-butyl dicarbonate (3.3 g, 15 mmol), and DMAP (122 mg, 1.00 mmol). After vigorous stirring for 2 h at room temperature, the reaction mixture was diluted with water. The mixture was extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4) and then concentrated under reduced pressure to afford a colorless liquid (2.86 g, 87%): mp 80–83 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26 (t, *J* = 7.0 Hz, 3H), 1.62 (s, 9H), 2.37 (s, 3H), 4.23 (q, *J* = 7.0 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 2.5 Hz, 1H), 7.35–7.36 (m, 2H), 7.88 (d, *J* = 2.5 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 14.4, 21.4, 28.1, 60.2, 85.2, 117.5, 119.2, 126.4, 128.6, 129.2, 130.7, 137.0, 148.2, 164.1 (one expected resonance was not observed).

2-Bromo-4-carbomethoxy-3-p-tolylpyrrole (60)

Following a reported procedure [120], a solution of **59** (917 mg, 4.00 mmol) in anhydrous THF (40 mL) in an ice bath at 0 °C under argon was treated with NBS (356 mg, 2.00 mmol). After 25 min, a further sample of NBS (356 mg, 2.00 mmol) was added to the reaction mixture. The reaction mixture was stirred for 50 min at 0 °C, whereupon TLC analysis indicated the formation of the product [silica, R_f = 0.74, hexanes/ethyl acetate (3:1)]. The reaction mixture was allowed to warm to room temperature, and then water was added. Ethyl acetate was added. The organic layer was separated, dried (Na_2SO_4), concentrated under reduced pressure, and purified by chromatography [silica, hexanes/ethyl acetate (4:1)] to afford an off-white solid (849 mg, 69%): mp over the range 144–165 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ 1.15 (t, *J* = 7.0 Hz, 3H), 2.35 (s, 3H), 4.09 (q, *J* = 7.0 Hz, 2H), 7.15–7.19 (m, 2H), 7.22–7.26 (m, 2H), 7.58 (d, *J* = 3.0 Hz, 1H), 11.17 (br s, 1H); ^{13}C{^{1}H} NMR (125 MHz, acetone-d_6) δ 14.5, 21.2, 59.8, 100.8, 116.1, 125.4, 126.3, 128.8, 131.3, 131.7, 136.9, 163.8; HRMS (ESI-TOF) *m/z*: $[M - H]^-$ calcd for $C_{14}H_{13}BrNO_2$ 306.0135; found 306.0138. A single-crystal was examined by XRD (CCDC 2263100).

1-Benzyl-2-bromo-4-carbomethoxy-3-p-tolylpyrrole (Bn-60)

A solution of **60** (637 mg, 2.07 mmol) in anhydrous THF (10 mL) at –78 °C under argon was treated with LDA (1.05 mL, 2.1 mmol, 2.0 M in THF/heptane/ethylbenzene). The reaction mixture was stirred for 30 min at –78 °C followed by the addition of benzyl bromide (369 μL, 3.11 mmol). The reaction mixture was stirred and allowed to warm to room temperature for 6 h. TLC analysis indicated the reaction was incomplete; thus, triethylamine (558 μL, 4.00 mmol) and benzyl bromide (237 μL, 2.00 mmol) were added to the reaction mixture. The reaction mixture was stirred overnight at room temperature, whereupon TLC analysis indicated formation of the product [silica, R_f = 0.69, hexanes/ethyl acetate (3:1)] and a trace amount of remaining starting material [silica, R_f = 0.40, hexanes/ethyl acetate (3:1)]. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution to the reaction mixture, which was then extracted with ethyl acetate. The organic layer was separated, dried (Na_2SO_4), concentrated under reduced pressure, and purified by chromatography [silica, hexanes/ethyl acetate (6:1)] to afford a colorless oil (642 mg, 78%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.21 (t, *J* = 7.0 Hz, 3H), 2.43 (s, 3H), 4.18 (q, *J* = 7.0 Hz, 1H), 5.21 (s, 2H), 7.24 (dd, *J* = 8.0 and 2.0 Hz, 4H), 7.32–7.44 (m, 5H), 7.53 (s, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 14.2, 21.4, 52.6, 59.7, 104.6, 115.1, 126.2, 127.3, 127.8, 128.2, 128.4, 129.0, 130.4, 130.8, 136.0, 136.7, 163.7; HRMS (ESI-TOF) *m/z*: $[M - H]^-$ calcd for $C_{21}H_{19}BrNO_2$ 396.0605; found 396.0612.

2,5-Dibromo-3-carbomethoxy-4-p-tolylpyrrole (61)

Following a reported procedure [96], a solution of **59** (2.29 g, 10.0 mmol) in anhydrous DMF (50 mL) in an ice bath at 0 °C under argon was treated with DBDMH (1.48 g, 5.20 mmol) in several batches. The resulting mixture was stirred at 0 °C for 40 min, whereupon TLC analysis indicated the formation of the product [silica, R_f = 0.61, hexanes/ethyl acetate (6:1)]. The reaction mixture was allowed to warm to room temperature and then washed with 20% aqueous $Na_2S_2O_3$ solution and water. The mixture was extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4), concentrated under reduced pressure, and purified by chromatography [silica, hexanes/ethyl acetate (10:1)] to afford a yellow solid (2.01 g, 52%): mp 100–108 °C (dec.); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.11 (t, *J* = 7.0 Hz, 3H), 2.37 (s, 3H), 4.15 (q, *J* = 7.0 Hz, 2H), 7.18 (d, *J* = 1.5 Hz, 4H), 8.92 (br s, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 14.0, 21.5, 60.5, 99.9, 105.2, 115.4, 127.1, 128.5, 130.1, 130.4, 137.1, 163.1; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{14}Br_2NO_2$ 385.9386; found 385.9391.

3-Carboethoxy-5-iodo-4-p-tolylpyrrole (62) [128]

Following a general procedure [95] with modification, a solution of **59** (2.00 g, 8.72 mmol) in DMF (40 mL) in an ice bath at 0 °C was treated with NIS (1.96 g, 8.72 mmol) in portions over 15 min. After vigorous stirring at 0 °C for 1 h, the reaction mixture was diluted with water and extracted with Et_2O. The organic extract was dried (Na_2SO_4), concentrated under reduced pressure, and purified by chromatography [silica, hexanes/ethyl acetate (5:1)] to afford the disubstituted **63** (0.75 g, 26%) followed by the title compound **62** (1.03 g, 33%).

Data for **62**: white solid; mp (dec) 140–147 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.18 (t, *J* = 7.0 Hz, 3H), 2.38 (s, 3H), 4.15 (q, *J* = 7.0 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.54 (d, *J* = 3.5 Hz, 2H), 8.57 (br s, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 14.3, 21.5, 59.9, 68.7, 116.1, 128.2, 128.5, 130.4, 131.7, 136.9, 163.5; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{15}O_2NI$ 356.0142; found 356.0132. A single-crystal was examined by XRD (CCDC 2263101).

Data for ***3-Carboethoxy-2,5-diiodo-4-p-tolylpyrrole (63)***: pale orange solid; mp 113–116 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.07 (t, *J* = 7.0 Hz, 3H), 2.37 (s, 3H), 4.12 (q, *J* = 7.0 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 9.21 (br s, 1H) (DMF peaks present in the sample are not listed here); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 14.0, 21.5, 60.3, 71.2, 73.8, 120.6, 128.5, 130.1, 132.2, 133.9, 137.0, 163.0 (one expected resonance was not observed; DMF peaks present in the sample are at ~3% of that of the isolated compound and are not listed here); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{14}O_2NI_2$ 481.9108; found 481.9097. A single-crystal was examined by XRD (CCDC 2263104).

1-(tert-Butoxycarbonyl)-3-carboethoxy-5-iodo-4-p-tolylpyrrole (Boc-62)

Following a general procedure [140] with modification, a solution of **62** (2.22 g, 6.25 mmol) in CH_2Cl_2 (5 mL) was treated with triethylamine (1.3 mL), di-*tert*-butyl dicarbonate (2.06 g, 9.38 mmol), and DMAP (76.0 mg, 0.625 mmol). After vigorous stirring at room temperature for 1.5 h, the reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4) and then concentrated under reduced pressure to afford a yellow oil (460 mg, 100%) that subsequently solidified: mp 73–78 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.14 (t, *J* = 7.0 Hz, 3H), 1.66 (s, 9H), 2.39 (s, 3H), 4.13 (q, *J* = 7.0 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.5 Hz, 2H), 8.16 (s, 1H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 14.2, 21.6, 28.1, 60.3, 70.4, 86.4, 119.1, 128.6, 130.3, 130.4, 132.0, 136.6, 137.4, 147.7, 163.0; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{23}O_4NI$ 456.0666; found 456.0655. A single-crystal was examined by XRD (CCDC 2263102).

1-(2-Trimethylsilyl)ethoxymethyl-3-carboethoxy-5-iodo-4-p-tolylpyrrole (SEM-62)

Following a general procedure [141] with modification, a solution of **62** (500 mg, 1.41 mmol) in DMF (3 mL) was added dropwise to a suspension of NaH (60% dispersion in mineral oil, 62 mg, 1.6 mmol) in DMF (3.43 mL). The mixture was stirred for 30 min at room temperature. The mixture was cooled in an ice bath to 0 °C, treated with (2-trimethylsilylethoxy)methyl chloride (255 μL, 1.41 mmol), and then stirred for 1 h at room temperature. The reaction mixture was treated with cold aqueous saturated $NaHCO_3$ and then extracted with Et_2O. The organic extract was dried (Na_2SO_4) and then concentrated under reduced pressure to afford a pale-yellow oil (485 mg, 72%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.02 (s, 9H), 0.95 (t, *J* = 8.5 Hz, 2H), 1.16 (t, *J* = 7.0 Hz, 3H), 2.39 (s, 3H), 3.59 (t, *J* = 8.5 Hz, 2H), 4.12 (q, *J* = 7.5 Hz, 2H), 5.30 (s, 2H), 7.20 (s, 4 H), 7.72 (s, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ –1.2, 0.2, 14.3, 17.9, 21.5, 59.8, 66.5, 75.8, 79.8, 116.9, 128.5, 130.5, 132.3, 133.2, 136.9, 163.6; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{29}INO_3Si$ 486.0956; found 486.0954.

1-Benzyl-3-carboethoxy-5-iodo-4-p-tolylpyrrole (Bn-62)

A solution of **62** (500 mg, 1.41 mmol) in DMF (2.82 mL) was added dropwise to a suspension of NaH (60% dispersion in mineral oil, 68 mg, 1.7 mmol) in DMF (5.7 mL) in an ice bath at 0 °C. The mixture was stirred for 2 h at 0 °C. The mixture was treated with benzyl bromide (313 mg, 1.83 mmol) and stirred for 1 h at room temperature. The reaction was quenched by the addition of saturated aqueous NH_4Cl to the reaction mixture, which then was extracted with ethyl acetate. The organic extract was dried (Na_2SO_4) and then concentrated under reduced pressure to afford a pale-yellow oil (610 mg, 97%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14 (t, *J* = 7.0 Hz, 3H), 2.39 (s, 3H), 4.11 (q, *J* = 7.0 Hz, 2H), 5.18 (s, 2H), 7.18–7.25 (m, 6H), 7.32–7.39 (m, 3H), 7.63 (s, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 14.3, 21.5, 55.2, 59.8, 116.5, 127.4, 128.2, 128.4, 129.1, 130.2, 130.5, 132.6, 132.9, 136.3, 136.8, 163.6; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{21}INO_2$ 446.0612; found 446.0606.

1,1-Dimethoxy-3,3-dimethylhexane-2,5-dione (65)

Following a general procedure [156] with modification, a 0.1 M solution of **81** (184 mg, 1.00 mmol) in methanol (10 mL) was added to a suspension of HgO (41.6 mg, 0.200 mmol) in 4% aqueous H_2SO_4 (3.84 mL). The resulting mixture was stirred at room temperature for 1 h. The reaction was quenched by the addition of H_2O to the reaction mixture, which then was extracted with ethyl acetate. The organic extract was dried (Na_2SO_4) and then concentrated under reduced pressure to afford a pale-yellow oil (168 mg, 83%), which was used in the next step without further purification: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23 (s, 6H), 2.07 (s, 3H), 2.86 (s, 2H), 3.40 (s, 6H), 5.02 (s, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 24.8, 30.0, 44.0, 54.4, 55.6, 101.0, 207.1; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{10}H_{18}O_4$ 203.1278; found 203.1272.

1,1-Dimethoxy-3,3-dimethyl-5-((trimethylsilyl)oxy) hex-5-en-2-one (TMS-65)

Following a general procedure [157] with modification, triethylamine (13 μL, 0.090 mmol) and TMSOTf (8 μL, 0.04 mmol) was added to a solution of **65** (6 mg, 0.03 mmol) in CH_2Cl_2 (120 μL) in an ice bath at 0 °C. After 30 min, the reaction was quenched by the addition of saturated aqueous NH_4Cl to the reaction mixture, which then was extracted with ethyl acetate. The organic extract was dried (Na_2SO_4) and then concentrated under reduced pressure to afford a crude pale-yellow oil (7.4 mg, 70% purity, 90%), which was used in the next step without further purification: ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.14 (s, 9H), 1.03 (s, 3H), 1.10 (s, 3H), 2.14 (d, *J* = 15.0 Hz, 1H), 2.49–2.52 (m, 1H), 3.40 (s, 3H), 3.52 (s, 3H), 3.83 (s, 1H), 4.20 (s, 1H), 4.24 (s, 1H).

4,4-Dimethyl-5-nitropentan-2-one (67) [159]

Following a general procedure [158] with modification, a solution of nitromethane (6.1 g, 10 mmol), mesityl oxide (**10**, 11.8 g, 120 mmol), and NaOEt (0.817 g, 12.0 mmol) in ethanol (50 mL) was refluxed overnight in an oil bath. Then, the mixture was neutralized by the addition of acetic acid. Dichloromethane was added. The organic phase was dried (Na_2SO_4) and then concentrated under reduced pressure to afford a pale-yellow oil (2.4 g, quant.): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.12 (s, 6H),

2.14 (s, 3H), 2.57 (s, 2H), 4.55 (s, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 25.8, 31.3, 34.1, 50.2, 83.2, 207.0; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_7H_{14}NO_3$ 160.0968; found 160.0968.

((4,4-Dimethyl-5-nitropent-1-en-2-yl)oxy) trimethylsilane (TMS-67)

Following a general procedure [157] with modification, triethylamine (137 μL, 0.942 mmol) and TMSOTf (86 μL, 0.47 mmol) were added to a solution of **67** (50.0 mg, 0.314 mmol) in CH_2Cl_2 (2 mL) in an ice bath at 0 °C. After 30 min, the reaction was quenched by the addition of saturated aqueous NH_4Cl to the reaction mixture, which then was extracted with ethyl acetate. The organic extract was dried (Na_2SO_4) and then concentrated under reduced pressure to afford a pale-yellow oil (61.8 mg, 85%), which was used in the next step without further purification: ^1H NMR (500 MHz, $CDCl_3$) δ 0.21 (s, 9H), 1.10 (t, 6H), 2.10 (s, 2H), 4.08 (s, 1H), 4.13 (s, 1H), 4.35 (s, 2H).

4-(2,2-Dimethyl-1,3-dioxolan-4-yl)-3,3-dimethylbutan-2-one (68)

Following a general method [163] with some modifications, MeLi (1.6 M, 1.07 mL in Et_2O, 1.7 mmol) was added to a solution of **86** (157 mg, 0.776 mmol) in Et_2O (3 mL) at –78 °C for 1 h. The mixture was then refluxed in an oil bath for 1 h. The mixture was cooled in an ice bath at 0 °C and then diluted with Et_2O. The organic extract was dried (Na_2SO_4) and then concentrated under reduced pressure to obtain a yellow oil (115 mg, 74%): ^1H NMR (600 MHz, $CDCl_3$) δ 1.16 (s, 3H), 1.17 (s, 3H), 1.29 (s, 3H), 1.35 (s, 3H), 1.69 (dd, *J* = 14.5 and 3.5 Hz, 1H), 1.92 (dd, *J* = 14.5 and 8.0 Hz, 1H), 2.15 (s, 3H), 3.43 (t, *J* = 7.0 Hz, 1H), 4.00–4.07 (m, 2H).

((4-(2,2-Dimethyl-1,3-dioxolan-4-yl)-3,3-dimethylbut-1-en-2-yl)oxy)trimethylsilane (TMS-68)

Following a general procedure [157] with modification, triethylamine (309 μL, 2.11 mmol) and TMSOTf (197 μL, 1.06 mmol) were added to a solution of **68** (141 mg, 0.704 mmol) in CH_2Cl_2 (282 μL) in an ice bath at 0 °C. After 30 min, the reaction was quenched by the addition of saturated aqueous NH_4Cl to the reaction mixture, which then was extracted with ethyl acetate. The organic extract was dried (Na_2SO_4) and then concentrated under reduced pressure to obtain a pale-yellow oil (161 mg), which was used in the next step without further purification: ^1H NMR (600 MHz, $CDCl_3$) δ 0.19 (s, 9H), 1.02 (s, 3H), 1.08 (s, 3H), 1.32 (s, 3H), 1.37 (s, 3H), 1.66–1.72 (m, 2H), 3.42 (t, *J* = 7.0 Hz, 1H), 3.98 (s, 1H), 4.00–4.05 (m, 2H), 4.08 (s, 1H). (^1H NMR analysis indicated that the sample contained the desired product and an unknown compound in a molar ratio of 2.5:1. The undefined product appears to be derived from the starting material **68** or is a derivative of the title compound. The ^1H NMR spectral tabulation here only lists the expected resonances of the title compound).

3,3-Dimethylhex-5-en-2-one (69) [163]

The known procedure [163] was implemented at a scale 2 times or 7 times the reported scale. Here, at 7 times the scale, a solution of **83** (9.70 g, 75.7 mmol) in anhydrous Et_2O (300 mL) was treated with MeLi (1.6 M, 100. mL in Et_2O, 160 mmol) at –78 °C under argon. The resulting reaction mixture was stirred at –78 °C for 1 h and then at reflux in an oil bath for 1 h. Then, the reaction mixture was cooled in an ice bath to 0 °C, treated with water, and extracted with Et_2O. The organic layer was separated, dried (Na_2SO_4), concentrated under reduced pressure, and purified by distillation (Vigreux column, 14/20, 200 mm height) at ambient pressure with heating in a sand bath to collect a colorless oil (6.56 g, 90% purity, 69%): bp 127–133 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 1.11 (s, 6H), 2.11 (s, 3H), 2.25 (dt, *J* = 7.5 and 1.5 Hz, 2H), 5.07–5.00 (m, 2H), 5.67 (ddt, *J* = 19.0, 9.5 Hz, and 7.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 24.1, 25.3, 44.0, 47.7, 117.9, 134.0, 213.5; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_8H_{15}O$ 127.1117; found 127.1116.

((3,3-Dimethylhexa-1,5-dien-2-yl)oxy)trimethylsilane (TMS-69)

Following a general procedure [157] with modification, triethylamine (695 μL, 4.74 mmol) and TMSOTf (442 μL, 2.37 mmol) was added to a solution of **69** (200 mg, 1.58 mmol) in CH_2Cl_2 (635 μL) in an ice bath at 0 °C. After 30 min, the reaction was quenched by the addition of saturated aqueous NH_4Cl to the reaction mixture, which then was extracted with ethyl acetate. The organic extract was dried (Na_2SO_4) and then concentrated under reduced pressure to afford a pale-yellow oil (205 mg, 65%), which was used in the next step without further purification: ^1H NMR (500 MHz, $CDCl_3$) δ 0.21 (s, 9H), 1.00 (s, 6H), 2.12 (d, *J* = 7.5 Hz, 2H), 3.97 (d, *J* = 1.5 Hz, 1H), 4.04 (d, *J* = 1.5 Hz, 1H), 4.96–4.98 (m, 1H), 5.00 (s, 1H), 5.70–5.78 (m, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 0.3, 25.9, 39.6, 44.6, 87.0, 116.4, 136.1, 165.4.

1-(3,5-Di-tert-butylphenyl)-3,3-dimethylbutan-2-one (71)

Following a reported procedure [138], a mixture of $Pd(dba)_2$ (8.6 mg, 15 μmol), P(*t*-Bu)$_3$ (5.6 mg, 28 μmol), ZnF_2 (72 mg, 0.70 mmol), CsF (31 mg, 0.20 mmol), and **70** (135 mg, 0.500 mmol) in anhydrous DMF (2.5 mL) was treated with **TMS-63** (151 μL, 0.70 μmol) in a 1-dram vial (fitted with a screw cap) in a glove box filled with argon. The resulting mixture was heated in an oil bath at 85 °C and stirred for 16 h. Then, the reaction vial was allowed to cool to room temperature and

moved out of the glove box. TLC analysis indicated the formation of the product [silica, R_f = 0.73, hexanes/ethyl acetate (10:1)]. The reaction mixture was poured into a beaker containing a mixture of water and ethyl acetate (20 mL, v/v, 1:1). The organic layer was separated, dried (Na_2SO_4), concentrated under reduced pressure, and purified by chromatography [silica, hexanes/ethyl acetate (20:1)] to afford a colorless oil (75 mg, 52%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.21 (s, 9H), 1.31 (s, 18H), 3.79 (s, 2H), 7.01 (d, *J* = 2.0 Hz, 2H), 7.29 (t, *J* = 2.0 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 26.7, 31.6, 34.9, 44.0, 44.8, 120.7, 124.0, 134.0, 150.7, 213.3; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{33}O$ 289.2526; found 289.2530.

3-Carboethoxy-5-(2-oxo-2-phenylethyl)-4-p-tolylpyrrole (72)

Following a general procedure [120] with modification, **Boc-72** (558 mg, 1.30 mmol) was treated with a solution of 25% TFA in CH_2Cl_2 (5.5 mL). The reaction mixture was stirred at room temperature for 4 h with monitoring by TLC analysis [silica, hexanes/ethyl acetate (3:1)]. The mixture was treated to a slow addition of saturated aqueous $NaHCO_3$ followed by extraction with CH_2Cl_2. The organic extract was dried (Na_2SO_4) and then concentrated under reduced pressure. The crude product was treated with hot toluene, which solubilized most of the sample. A small amount of ethanol was then added, which afforded a homogeneous solution. Hexanes and toluene (~1:1) were added. Upon cooling, a white solid formed and was isolated by filtration (90 mg, 20%). The filtrate was purified by chromatography [silica, hexanes/ethyl acetate (3:1)] to afford a pale orange solid (26.7 mg, 6%). The ^{1}H NMR spectra of the two solids were identical; hence the samples were combined to give a total yield of 26%: mp 185–188 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.78 (t, *J* = 7.0 Hz. 3H), 2.40 (s, 3H), 4.14 (q, *J* = 7.0 Hz, 2H), 4.22 (s, 2H), 7.20 (s, 4H), 7.39–7.42 (m, 2H), 7.47 (d, *J* = 3.0 Hz, 1H), 7.54–7.57 (m, 1H), 7.81–7.83 (m, 2H), 9.26 (br s, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 14.4, 21.4, 34.7, 59.5, 123.1, 124.0, 128.6, 128.7, 128.9, 130.5, 133.9, 136.1, 136.4, 164.7, 198.0 (two expected resonances were not observed); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{22}O_3N$ 348.1594; found 348.1583. A single-crystal was examined by XRD (CCDC 2263106).

1-(tert-Butoxycarbonyl)-3-carboethoxy-5-(2-oxo-2-phenylethyl)-4-p-tolylpyrrole (Boc-72) – via Heck coupling

Following a general procedure [142] with modification, a solution of **Boc-62** (910 mg, 2.00 mmol) and silyl enol **TMS-64** (1.0 mL, 5.0 mmol) in toluene (7 mL) was added to $PdCl_2$ (36 mg, 0.20 mmol), P(*o*-tolyl)$_3$ (122 mg, 0.400 mmol), and *n*-Bu_3SnF (865 mg, 2.80 mmol). The mixture was then refluxed for 5 h. After allowing to cool to room temperature, the mixture was filtered in a pipette containing a plug of Celite. The filtrate was concentrated under reduced pressure. Purification by column chromatography [silica, hexanes/ethyl acetate (8:1)] afforded a dark blue solid (512 mg, 59%): mp 112–115 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.18 (t, *J* = 7.0 Hz, 3H), 1.48 (s, 9H), 2.33 (s, 3H), 4.16 (q, *J* = 7.0 Hz, 2H), 4.42 (s, 2H), 7.11–7.15 (m, 4H), 7.42–7.44 (m, 2H), 7.53–7.57 (m, 1H), 7.93–7.94 (m, 2H), 7.97 (s, 1H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 14.3, 21.4, 28.0, 37.3, 59.9, 85.1, 116.8, 126.2, 126.9, 128.2, 128.6. 128.7, 128.7, 130.2, 130.6, 133.2, 136.9, 148.8, 164.0, 196.5; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{27}H_{30}O_5N$ 448.2118; found 448.2107.

1-(tert-Butoxycarbonyl)-3-carboethoxy-5-(2-oxo-2-phenylethyl)-4-p-tolylpyrrole (Boc-72) – via Koser's method

Following Koser's method [152], a suspension of Koser's reagent (150 mg, 1.53 mmol, 1.22 equiv) in 2 mL of dry CH_2Cl_2 under positive argon pressure was cooled to –78 °C. A sample of $BF_3{\cdot}OEt_2$ (1.22 mmol, 150 μL, 3.9 equiv) was added via a syringe. After stirring at –78 °C for 5 min, the mixture was allowed to warm to room temperature yielding a clear yellow solution. Then, the flask was cooled to –78 °C, and a solution of **TMS-64** (64 μL, 0.31 mmol, 1 equiv) was slowly introduced. The resulting mixture was stirred at –78 °C for 5 min, whereupon a solution of pyrrole **Boc-59** (164 mg, 0.500 mmol, 1.6 equiv) in 160 μL of CH_2Cl_2 was added slowly via a syringe. After the addition was complete, the mixture was allowed to warm to –55 °C and maintained at –55 °C for 20 min. Then, the reaction was quenched by the addition of water to the reaction mixture, and the flask was allowed to warm to ambient temperature. The reaction mixture was filtered through a pad of Celite and rinsed with CH_2Cl_2. The filtrate was purified by chromatography [silica, hexanes/ethyl acetate (8:1)] to afford a dark blue solid (35 mg, 25%). The ^{1}H NMR spectrum was identical to that prepared via Heck coupling.

1-Benzyl-3-carboethoxy-5-(2-oxopropyl)-4-p-tolylpyrrole (Bn-74)

Following a general procedure [142] with modification, a sample of **Bn-62** (22.8 mg, 50.0 μmol) was added to a mixture of $PdCl_2$ (1.8 mg, 10. μmol), P(*o*-tolyl)$_3$ (6.1 mg, 20. μmol), and *n*-Bu_3SnF (21.6 mg, 70.0 μmol). The mixture was then taken into a glovebox filled with argon. Silyl enol **TMS-66** (217 mg, 0.500 mmol) and toluene (0.18 mL) were added to the mixture in the glove box. The mixture was then heated on a heating block to reflux overnight. After allowing to cool to room temperature, the mixture was filtered through a pipette containing a plug of Celite. The filtrate was concentrated to dryness

under reduced pressure. Purification by chromatography [silica, hexanes/ethyl acetate (5:1)] afforded a blue paste (5.5 mg, 29%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.16 (t, *J* = 7.0 Hz, 3H), 1.95 (s, 3H), 2.37 (s, 3H), 3.47 (s 2H), 4.13 (q, *J* = 7.0 Hz, 2H), 5.02 (s, 2H), 7.09 (d, *J* = 3.0 Hz, 2H), 7.15 (d, *J* = 2.5 Hz, 4H), 7.31–7.38 (m, 3H), 7.39 (s, 1H) (unassigned resonances at 0.91–0.94, 1.27–1.40, and 1.60–1.68 ppm are likely from *n*-Bu_3SnF or its dimeric derivative); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 13.8, 14.4, 17.7, 21.4, 27.0, 28.0, 29.3, 40.1, 51.8, 59.5, 114.0, 125.0, 126.5, 127.1, 128.0, 128.2, 128.6, 129.2, 130.3, 132.0, 136.4, 136.5, 164.5, 205.8 (four additional resonances in the aliphatic region are likely from *n*-Bu_3SnF or its dimeric derivative).

3-Carboethoxy-5-(2-oxopropyl)-1-(2-trimethylsilyl) ethoxymethyl-4-p-tolylpyrrole (SEM-74)

Following a general procedure [142] with modification, a sample of **SEM-62** (24.3 mg, 50.0 μmol) was added to a mixture of $PdCl_2$ (1.8 mg, 10. μmol), P(*o*-tolyl)$_3$ (6.1 mg, 20. μmol), and *n*-Bu_3SnF (21.6 mg, 70.0 μmol). The mixture was then taken into a glovebox filled with argon. Silyl enol **TMS-66** (217 mg, 0.500 mmol) and toluene (0.18 mL) were added to the mixture in the glove box. The mixture was then heated on a heating block to reflux overnight. After allowing to cool to room temperature, the mixture was filtered through a pipette containing a plug of Celite. The filtrate was concentrated to dryness under reduced pressure. Purification by chromatography [silica, hexanes/ethyl acetate (5:1)] afforded a blue paste (9 mg, 43%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.00 (s, 9H), 0.87–0.90 (m, 2H), 1.16 (t, *J* = 7.0 Hz, 3H), 2.06 (s, 3H), 2.37 (s, 3H), 3.47 (t, *J* = 8.0 Hz, 2H), 3.66 (s, 2H), 4.13 (q, *J* = 7.5 Hz, 2H), 5.15 (s, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.40 (s, 1H) (unassigned resonances at 0.91–0.94, 1.24–1.42, and 1.58–1.64 ppm are likely from *n*-Bu_3SnF or a dimeric derivative); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ -1.3, 13.7, 14.4, 16.6, 17.7, 21.4, 26.8, 29.3, 29.5, 39.8, 59.5, 66.1, 114.1, 125.1, 126.9, 127.8, 128.6, 130.2, 131.7, 136.5, 164.5, 205.6 (four additional resonances in the aliphatic region are likely from *n*-Bu_3SnF or a dimeric derivative).

1-(tert-Butoxycarbonyl)-3-carboethoxy-5-(4-methyl-2-oxopent-3-en-1-yl)-4-p-tolylpyrrole (Boc-75)

Following a general procedure [142] with modification, a sample of **Boc-62** (275 mg, 60.4 μmol) was added to a mixture of $PdCl_2$ (13.6 mg, 76.7 μmol), P(*o*-tolyl)$_3$ (37.6 mg, 0.124 mmol), and *n*-Bu_3SnF (244 mg, 0.787 mmol). The mixture was then taken into a glovebox filled with argon. Silyl enol **TMS-10** (1.25 g, 64% purity) and toluene (2.1 mL) were added to the mixture in the glove box. The mixture was then heated on a heating block to reflux overnight. After allowing to cool to room temperature, the mixture was filtered through a pipette containing a plug of Celite. The filtrate was concentrated to dryness under reduced pressure. Purification by chromatography [silica, hexanes/ethyl acetate (5:1)] afforded a brown paste (167 mg, 62%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.19 (t, *J* = 7.0 Hz, 3H), 1.59 (s, 9H), 2.10 (s, 6H), 2.37 (s, 3H), 3.56 (s, 2H), 4.17 (q, *J* = 7.0 Hz, 2H), 5.68 (s, 1H), 7.11 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.95 (s, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 14.3, 20.1, 21.4, 28.0, 32.1, 36.7, 60.1, 85.2, 116.8, 122.8, 127.0, 128.4, 128.6, 128.6, 129.9, 130.5, 137.0, 148.4, 157.5, 163.9, 198.7. A single-crystal was examined by XRD (CCDC 2263105).

3-Carboethoxy-5-(4-methyl-2-oxopent-3-en-1-yl)-1-(2-trimethylsilyl)ethoxymethyl-4-p-tolylpyrrole (SEM-75)

Following a general procedure [142] with modification, a sample of **SEM-62** (108 mg, 0.300 mmol) was added to a mixture of $PdCl_2$ (11.9 mg, 0.0670 mmol), P(*o*-tolyl)$_3$ (40.4 mg, 0.133 mmol), and *n*-Bu_3SnF (128 mg, 0.410 mmol). The mixture was then taken into a glovebox filled with argon. Silyl enol **TMS-10** (297 mg, 64% purity, 1.10 mmol) and toluene (1 mL) were added to the mixture in the glove box. The mixture was then heated on a heating block to reflux overnight. After allowing to cool to room temperature, the mixture was filtered through a pipette containing a plug of Celite. The filtrate was concentrated to dryness under reduced pressure. Purification by chromatography [silica, hexanes/ethyl acetate (5:1)] afforded a brown paste (95.6 mg, 72%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.00 (s, 9H), 0.88 (m, 2H), 1.17 (t, *J* = 7.0 Hz, 3H), 1.83 (s, 3H), 2.12 (s, 2H), 2.36 (s, 3H), 3.48 (t, *J* = 8.0 Hz, 2H), 3.66 (s, 2H), 4.12 (q, *J* = 7.0 Hz, 2H), 5.17 (s, 2H), 5.93 (s, 1H), 7.15 (s, 4H), 7.41 (s, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ -1.3, 13.7, 14.4, 17.8, 21.0, 21.4, 27.9, 40.2, 59.5, 66.0, 77.5, 114.0, 122.7, 125.7, 126.6, 127.8, 128.5, 130.4, 131.9, 136.3, 157.2, 164.6, 196.9 (one additional resonance was unexpectedly observed). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{26}H_{37}O_4NSi$ 456.2565; found 456.2556.

3-Carboethoxy-5-(4,4-dimethyl-5-nitro-2-oxohexyl)-1-(2-trimethylsilyl)ethoxymethyl-4-p-tolylpyrrole (SEM-76)

Following a general procedure [81] with modification, a mixture of **SEM-75** (20 mg, 0.044 mmol) and nitroethane (25 mg, 0.33 mmol) was treated with DBU (22 μL, 0.11 mmol) and stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate, and water was added. The organic extract was dried (Na_2SO_4) and then concentrated under reduced pressure to afford a pale-yellow oil (23 mg, quant.): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.00 (s, 9H), 0.89 (t, *J* = 8.0 Hz, 2H), 0.95 (s, 3H), 1.05 (s, 3H), 1.16 (t, *J* = 7.0 Hz, 3H), 1.39 (d, *J* = 6.5 Hz, 3H), 2.25 (d, *J* = 18.0 Hz, 1H), 2.36 (s, 3H),

2.45 (d, *J* = 17.5 Hz, 1H), 3.49 (t, *J* = 8.0 Hz, 2H), 3.65 (d, *J* = 2.5 Hz, 2H), 4.13 (q, *J* = 6.5 Hz, 2H), 4.97 (dd, *J* = 13.5 and 7.0 Hz, 1H), 5.15 (d, *J* = 11.0 Hz, 1H), 5.21 (d, *J* = 11.0 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.41 (s, 1H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ -1.27, 13.7, 14.4, 17.8, 21.4, 23.3, 24.1, 36.6, 40.3, 49.5, 59.5, 66.1, 88.3, 114.0, 124.5, 126.9, 127.9, 128.6, 130.2, 131.6, 136.6, 164.5, 205.6.

2,2-Dimethoxyacetic acid (77) [153]

Following a reported procedure [153] at a 5-fold larger scale, a solution of methyl 2,2-dimethoxyacetate (20.0 g, 149 mmol) in 1,4-dioxane (90 mL) and water (90 mL) was treated with LiOH (4.28 g, 179 mmol). The mixture was stirred for 1 h in an ice bath at 0 °C and then for 1 h at room temperature. Sodium hydroxide (1 M aqueous solution) was added. The mixture was extracted with diethyl ether. The collected aqueous layer was acidified with HCl (6 M) until a pH of 1–2 was attained, then the solution was extracted with ethyl acetate. The combined organic extract was dried (Na_2SO_4) and then concentrated under reduced pressure to afford a colorless liquid (18.43 g, 91% purity, quant.): ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.46 (s, 6H), 4.86 (s, 1H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 54.2, 98.6, 170.4 (resonances of 1,4-dioxane were observed in both ^{1}H and ^{13}C NMR spectra since vacuum drying was avoided given the inherent volatility of the title compound); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_4H_9O_4$ 121.0495; found 121.0494.

N,2,2-Trimethoxy-N-methylacetamide (78) [154]

Following a known procedure [154] at a 120-fold larger scale, a solution of **77** (7.2 g, 60 mmol) in CH_2Cl_2 (500 mL) in an ice bath at 0 °C was treated with triphosgene (8.91 g, 30.0 mmol) and triethylamine (42 mL, 300 mmol). Then, the mixture was treated with *N,O*-dimethylhydroxylamine hydrochloride (6.47 g, 66.0 mmol). The ice bath was removed, and the mixture was stirred at room temperature for 1 h. The reaction was quenched by the addition of H_2O to the reaction mixture, which then was extracted with ethyl acetate. The organic extract was dried (Na_2SO_4) and then concentrated under reduced pressure. Purification via column chromatography [silica, hexanes/ethyl acetate (8:1)] afforded a pale-yellow oil (2.75 g, 70%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.21 (br s, 3H), 3.43 (s, 6H), 3.73 (s, 3H), 5.21 (br s, 1H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 32.2, 53.5, 61.7, 96.4, 167.6; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_6H_{14}O_4N$ 164.0917; found 164.0913.

1,1-Dimethoxy-3-methylbutan-2-one (79) [81]

Following a general procedure [154] with modification, a solution of **78** (12.65 g, 77.53 mmol) in THF (500 mL) at –78 °C was treated slowly with isopropylmagnesium chloride (77.5 mL, 155 mmol). The reaction mixture at –78 °C was stirred under argon for 1 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl to the reaction mixture, which then was extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4) and then concentrated under reduced pressure. Purification by column chromatography [silica, hexanes/ethyl acetate (10:1)] afforded a colorless oil (10.76 g, 95%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.10 (d, *J* = 7.0 Hz, 6H), 3.00 (sept, *J* = 7.0 Hz, 1H), 3.40 (s, 6H), 4.61 (s, 1H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 18.2, 35.8, 54.5, 103.0, 209.1; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_7H_{15}O_3$ 147.1016; found 147.1012.

1,1-Dimethoxy-3,3-dimethyl-6-(trimethylsilyl)hex-5-yn-2-one (80)

Following a general method [155] with some modifications, a solution of **79** (4.39 g, 30.0 mmol) in THF (72 mL) was cooled to 0 °C in an ice bath, and *tert*-BuOLi (3.6 g, 45 mmol) was added. The resulting solution was stirred in an ice bath at 0 °C for 30 min followed by the addition of 3-(trimethylsilyl)propargyl bromide (5.52 mL, 30.0 mmol). The reaction mixture was stirred at room temperature for 8 h. The reaction was quenched by the addition of H_2O to the reaction mixture, which then was extracted with ethyl acetate. The organic extract was dried (Na_2SO_4) and then concentrated under reduced pressure. Purification by column chromatography [silica, hexanes/ethyl acetate (100:1) to (5:1)] afforded a pale-yellow oil (4.08 g, 53%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.12 (s, 9H), 1.26 (s, 6H), 2.50 (s, 2H), 3.38 (s, 6H), 4.93 (s, 1H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 0.1, 23.9, 30.2, 46.4, 54.2, 87.5, 100.9, 103.9, 206.4; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{25}O_3Si$ 257.1568; found 257.1560.

1,1-Dimethoxy-3,3-dimethylhex-5-yn-2-one (81)

A solution of **80** (1.21 g, 4.72 mmol) in acetone (83 mL) was treated with water (0.83 mL) and $AgNO_3$ (170. mg, 1.00 mmol) and then stirred at room temperature for 22 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl to the reaction mixture, which then was extracted with ethyl acetate. The organic extract was dried (Na_2SO_4) and then concentrated under reduced pressure to afford a pale-yellow oil (842 mg, 96%), which was used in the next step without further purification: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28 (s, 6H), 2.00 (s, 1H), 2.47 (d, *J* = 3.0 Hz, 2H), 3.39 (s, 6H), 4.92 (s, 1H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 23.8, 28.8, 46.2, 54.2, 70.9, 81.2, 101.0, 206.3; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{10}H_{17}O_3$ 185.1172; found 185.1167.

6,6-Dimethoxy-5-hydroxy-4,4-dimethylhex-1-yne (82)

$NaBH_4$ (6.16 mg) was added to a solution of **82** (30 mg) in MeOH (0.8 mL) in an ice bath at 0 °C. The mixture was stirred at room temperature until no starting material remained as determined by TLC analysis. The reaction was quenched by the addition of water to the reaction mixture, which then was extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4) and then concentrated under reduced pressure to afford a pale-yellow oil (23 mg, 76%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00 (s, 3H), 1.04 (s, 3H), 1.98 (t, *J* = 3.0 Hz, 1H), 2.19 (dd, *J* = 16.5 and 2.5 Hz, 1H), 2.32 (dd, *J* = 15.5 and 3.0 Hz, 1H), 3.39 (s, 3H), 3.44 (s, 3H), 3.49 (t, *J* = 4.5 Hz, 1H), 4.34 (d, *J* = 5.0 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 22.6, 23.6, 29.4, 36.6, 54.0, 54.7, 70.2, 75.4, 82.5, 103.4.

2,2-Dimethylpent-4-enoic acid (83) [161–165]

Following a general method [164,165] with some modifications, *n*-BuLi (2.5 M in hexanes, 44 mL, 0.11 mol) was added dropwise over 15 min to a solution of diisopropylamine (15.4 mL, 0.110 mol) in THF (35 mL) at –78 °C. Ethyl isobutyrate (11.6 g, 0.100 mol) was added dropwise, and the solution was stirred for 1 h. Allyl bromide (13.3 g, 0.110 mol) was added dropwise, and the solution was stirred for 1 h at –78 °C. Saturated aqueous NH_4Cl was added to quench the reaction followed by the addition of CH_2Cl_2. The organic extract was dried (Na_2SO_4) and then concentrated under reduced pressure. Purification by column chromatography [silica, hexanes/ethyl acetate (5:1)] afforded the ethyl ester as a yellow oil (10.52 g). Because the target compound appeared to be volatile, the solvent was not removed completely. The yellow oil (10.52 g) was dissolved in 120 mL of EtOH/H_2O (2:1), which was then treated with KOH (24.6 g, 337 mmol) followed by heating in an oil bath at 80 °C for 3 h. After allowing to cool to room temperature, the mixture was acidified with 2 M HCl until pH = 1 was attained. The mixture was extracted with ethyl acetate. The organic extract was dried (Na_2SO_4) and then concentrated under reduced pressure to afford a red oil (6.08 g, 71%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20 (s, 6H), 2.30 (d, *J* = 7.5 Hz, 2H), 5.06–5.07 (m, 1H), 5.09 (s, 1H), 5.73–5.82 (m, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 24.7, 42.3, 44.6, 118.4, 134.0, 184.5; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_7H_{13}O_2$ 129.0910; found 129.0908.

2,2-Dimethylpent-4-enoic acid (83) [161–165]

Method A: Following a reported procedure [161], a stirred suspension of NaH (3.52 g, 60% dispersion in mineral oil, 88 mmol) and diisopropylamine (11.4 mL, 80.0 mmol) in anhydrous THF (100 mL) under argon was treated with isobutyric acid (7.45 mL, 80.0 mmol) via an addition funnel. The resulting suspension was heated at reflux for 30 min and then cooled in an ice bath to 0 °C for 15 min before the dropwise addition of *n*-BuLi (50.0 mL, 1.6 M in hexanes, 80. mmol). The resulting suspension was stirred at 0 °C for 15 min and then heated in an oil bath at 35 °C for 30 min. After cooling to 0 °C, the suspension was treated with allyl bromide (6.92 mL, 80.0 mmol) and then stirred for 2 h in an oil bath at 35 °C. The resulting off-white suspension was then cooled to 0 °C in an ice bath and quenched with the addition of water. The organic layer was washed with 5 M NaOH solution. The aqueous layers were combined and extracted with Et_2O. The combined aqueous layer was then acidified by the addition of 2 M HCl solution until pH 1–3 was attained and then extracted with Et_2O. The combined organic extract was dried (Na_2SO_4) and then concentrated under reduced pressure. The resulting residue was chromatographed [silica, hexanes/ethyl acetate/acetic acid (100:10:1)] to afford a colorless liquid (1.53 g, 15%).

Method B: A solution of methyl isobutyrate (11.4 mL 100. mmol) in anhydrous THF (100 mL) was treated with LDA (52.5 mL, 110 mmol, 2.0 M in THF/heptane/ethylbenzene) at –78 °C under argon. The resulting reaction mixture was stirred for 30 min at –78 °C followed by the addition of allyl bromide (8.66 mL, 100. mmol). The resulting mixture was allowed to warm to room temperature and then stirred for 1 h. TLC analysis indicated the formation of methyl 2,2-dimethylpent-4-enoate [silica, R_f = 0.53, hexanes/ethyl acetate (10:1) with 1% acetic acid, visualized by $KMnO_4$ stain]. The reaction was quenched by the addition of saturated aqueous NH_4Cl to the reaction mixture, which then was extracted with CH_2Cl_2. The organic layer was separated, dried (Na_2SO_4), and concentrated under reduced pressure. The resulting crude mixture was dissolved in a mixture of methanol/H_2O (510 mL, v/v, 2:1) followed by the addition of NaOH (20.0 g, 500 mmol). The resulting reaction mixture was stirred at reflux for 36 h and then allowed to cool to room temperature. The reaction mixture was acidified by the addition of 2 M HCl until pH = 1 was attained and then extracted with CH_2Cl_2. TLC analysis indicated the formation of the product [silica, R_f = 0.03–0.33, tailing in hexanes/ethyl acetate (10:1) with 1% acetic acid, visualized by $KMnO_4$ stain]. The organic layer was separated, dried (Na_2SO_4), and concentrated under reduced pressure. Purification by chromatography [silica, hexanes/ethyl acetate/acetic acid (100:10:1)] afforded a colorless liquid (10.1 g, 79%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20 (s, 6H), 2.30 (dt, *J* = 7.5 and 1.5 Hz, 2H), 5.08 (dq, *J* = 15.0 and 2.0 Hz, 2H), 5.71–5.84 (m, 1H), 11.42 (br s, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 24.6, 42.2, 44.4, 118.2, 133.9, 184.7; HRMS (ESI-TOF) *m/z*: calcd for $[M - H]^- C_7H_{11}O_2$ 127.0765; found 127.0765.

Ethyl 4,5-dihydroxy-2,2-dimethylpentanoate (84) [166]

Following two methods [164, 166] with streamlining, *n*-BuLi (2.5 M in hexanes, 18.9 mL, 0.047 mol) was

added dropwise over 15 min to a solution of diisopropylamine (6.6 mL, 0.047 mol) in THF (15 mL) at –78 °C. Ethyl isobutyrate (5.0 g, 0.043 mol) was added dropwise, and the solution was stirred for 1 h. Allyl bromide (5.7 g, 0.047 mol) was added dropwise, and the solution was stirred at –78 °C for 2 h. A saturated aqueous solution of NH_4Cl was added to quench the reaction followed by CH_2Cl_2. The organic extract was dried (Na_2SO_4) and then concentrated under reduced pressure to obtain a yellow oil (9 g, quant.). The entire oil was dissolved in CH_2Cl_2 (100 mL) followed by the addition of NMO (8.00 g, 7.63 mmol) and a crystal of OsO_4. The solution was stirred in an ice bath at 0 °C for 1 h and then stirred overnight at room temperature. Most of the solvent was removed under reduced pressure. The resulting residue was washed with water and extracted with ethyl acetate. The organic extract was dried (Na_2SO_4) and then concentrated under reduced pressure to obtain a yellow oil (4.1 g, 50% for 2 steps): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24–1.26 (m, 9H), 1.47 (dd, *J* = 15.0 and 3.0 Hz, 1H), 1.86–1.91 (dd, *J* = 14.5 and 9.0 Hz), 3.41 (dd, *J* = 11.0 and 7.5 Hz, 1H), 3.56 (dd, *J* = 11.0 and 3.5 Hz, 1H), 3.79–3.84 (m, 1H), 4.14 (q, *J* = 7.0 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 14.2, 24.7, 27.4, 41.2, 43.4, 61.0, 67.5, 69.4, 179.3; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_9H_{19}O_4$ 191.1278; found 191.1278.

Ethyl 3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethylpropanoate (85)

Following a general method [167] with some modifications, a solution of **84** (3.8 g, 20. mmol) in DMF (20 mL) was treated with 2,2-dimethoxypropane (4.88 mL, 40.0 mmol) and pyridinium *p*-toluenesulfonate (506 mg, 2.00 mmol). The mixture was stirred overnight in an oil bath at 50 °C. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ to the reaction mixture, which then was extracted with Et_2O. The organic extract was dried (Na_2SO_4) and then concentrated under reduced pressure to obtain a red oil (3.63 g, 79%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.21 (s, 3H), 1.23 (s, 3H), 1.25 (t, *J* = 7.0 Hz, 3H), 1.32 (s, 3H), 1.36 (s, 3H), 1.74 (dd, *J* = 14.0 and 5.0 Hz, 1H), 1.93 (dd, *J* = 14.0 and 7.0 Hz, 1H), 3.44 (t, *J* = 8.0 Hz, 1H), 4.02 (dd, *J* = 7.5 and 5.5 Hz, 1H), 4.07–4.16 (m, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 14.3, 25.7, 25.8, 26.0, 27.0, 41.2, 44.1, 60.6, 70.3, 73.5, 108.7, 177.7; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{12}H_{22}O_4Na$ 253.1410; found 253.1407.

3-(2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethylpropanoic acid (86)

Following a general method [168] with some modifications, a solution of **85** (3.20 g, 13.9 mmol) in MeOH (14 mL) was treated with KOH (1.56 g, 27.8 mmol). The solution was heated in an oil bath at 40 °C for 1.5 h. The mixture was treated with 2 M HCl solution (until pH = 4 was attained) and then extracted with Et_2O. The organic extract was dried (Na_2SO_4) and then concentrated under reduced pressure to obtain a red oil. Analysis by ^{1}H NMR spectroscopy showed the presence of trace impurities. Purification by column chromatography [silica, hexanes/ethyl acetate (5:1)] afforded a yellow oil (207 mg, 7.4%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.25 (s, 3H), 1.27 (s, 3H), 1.33 (s, 3H), 1.37 (s, 3H), 1.76 (dd, *J* = 14.5 and 4.0 Hz, 1H), 1.95 (dd, *J* = 14.5 and 8.0 Hz, 1H), 3.49 (t, *J* = 9.5 Hz. 1H), 4.06 (dd, *J* = 8.0 and 6.0 Hz, 1H), 4.13–4.18 (m, 1H).

3,13-Dicarboethoxy-2,8,8,12,18,18-hexamethylbacteriochlorin (BC-6)

Following a general procedure [18,36], a solution of **13** (200 mg, 0.598 mmol, 18 mM) in anhydrous CH_3CN (33 mL) was treated with $BF_3{\cdot}OEt_2$ (590 μL, 4.77 mmol, 140 mM) and then stirred at room temperature for 14 h. Excess triethylamine (1 mL) was added. The reaction mixture was concentrated under reduced pressure and then treated with CH_2Cl_2 (10 mL). The resulting mixture was filtered through filter paper several times. The filtrate was concentrated under reduced pressure. Purification by chromatography (silica, CH_2Cl_2) afforded a single green band, which was isolated and then concentrated under reduced pressure to afford a green-purple solid (21 mg, 13%): ^{1}H NMR (500 MHz, $CDCl_3$) δ −1.44 (s, 2H), 1.71 (t, *J* = 7.0 Hz, 6H), 1.94 (s, 12H), 3.64 (s, 6H), 4.41 (s, 4H), 4.78 (q, *J* = 7.0 Hz, 4H), 8.63 (s, 2H), 9.65 (s, 2H); ^{13}C{^{1}H} NMR (125 MHz) δ 13.4, 14.7, 31.0, 45.9, 51.9, 60.8, 94.6, 98.5, 119.9, 134.1, 134.7, 135.4, 160.4, 166.6, 171.0; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{32}H_{39}N_4O_4$ 543.2966; found 543.2964; λ_{abs} (CH_2Cl_2) 353, 383, 518, 758 nm. The characterization data match those obtained by an alternative route [86].

3-Carboethoxy-13-hydroxymethyl-2,8,8,12,18,18-hexamethylbacteriochlorin (BC-7)

A solution of **BC-6** (5.1 mg, 9.4 μmol) in anhydrous toluene was treated with Red-Al (6% wt. solution in toluene, diluted from commercially available 60% wt. solution in toluene, 300 μL, 77 μmol). The reaction mixture was stirred at room temperature under argon for 4 h. Water and CH_2Cl_2 were added. The organic phase was dried (Na_2SO_4), concentrated under reduced pressure, and purified by chromatography [silica, CH_2Cl_2 to CH_2Cl_2/ethyl acetate (4:1)] to afford an emerald solid (1.6 mg, 34%): ^{1}H NMR (500 MHz, $CDCl_3$) δ −1.28 (s, 1H), –1.18 (s, 1H), 1.70 (t, *J* = 7.0 Hz, 3H), 1.92 (s, 6H), 1.93 (s, 6H), 3.37 (s, 3H), 3.60 (s, 3H), 4.35 (s, 2H), 4.36 (s, 2H), 4.75 (q, *J* = 7.0 Hz, 2H), 5.77 (d, *J* = 5.5 Hz, 2H), 8.42 (s, 1H), 8.55 (s, 1H), 8.67 (s, 1H), 9.63 (s, 1H); ^{13}C{^{1}H} NMR (175 MHz, $CDCl_3$) δ 11.2, 13.5, 14.9, 30.8, 31.4, 45.3, 46.7, 51.0, 52.6, 56.4, 60.6, 92.8, 95.4, 95.5, 98.6, 117.4, 127.0, 127.8, 128.8, 131.2, 131.5, 132.40, 132.43, 133.6, 136.1, 138.3, 157.9, 161.3, 167.3, 167.6, 173.8 (one unexpected resonance was observed); HRMS (ESI-TOF)

m/z: $[M + H]^+$ calcd for $C_{30}H_{37}N_4O_3$ 500.2782; found 500.2784; λ_{abs} (CH_2Cl_2) 350, 379, 505, 737 nm.

3-Carboethoxy-5-methoxy-13-hydroxymethyl-2,8,8,12,18,18-hexamethylbacteriochlorin (MeOBC-7)

A solution of **MeOBC-6** (15.5 mg, 27.1 μmol) in anhydrous toluene was treated with Red-Al (6% wt. solution in toluene, diluted from commercially available 60% wt. solution in toluene, 850 μL, 220 μmol). The reaction mixture was stirred at room temperature under argon for 30 min. Water and CH_2Cl_2 were added to the mixture. The organic phase was dried (Na_2SO_4), concentrated under reduced pressure, and purified by chromatography [silica, CH_2Cl_2 to CH_2Cl_2/ethyl acetate (4:1)] to afford an emerald solid (6.1 mg, 42%): ^{1}H NMR (500 MHz, $CDCl_3$) δ −1.70 (s, 1H), −1.56 (s, 1H), 1.62 (t, *J* = 7.0 Hz, 3H), 1.91 (s, 6H), 1.92 (s, 6H), 3.36 (s, 3H), 3.38 (s, 3H), 4.20 (s, 3H), 4.32 (s, 2H), 4.35 (s, 2H), 4.75 (q, *J* = 7.0 Hz, 2H), 5.77 (d, *J* = 4.0 Hz, 2H), 8.45 (d, *J* = 3.5 Hz, 2H), 8.65 (s, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 11.2, 11.6, 14.8, 30.9, 31.4, 45.3, 46.5, 47.1, 52.5, 56.5, 61.7, 64.0, 93.5, 94.5, 94.7, 122.6, 126.2, 131.7, 131.9, 132.3, 135.2, 136.2, 136.8, 152.0, 161.3, 168.1, 169.4, 170.5; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{31}H_{39}N_4O_4$ 500.2888; found 530.2883; λ_{abs} (CH_2Cl_2) 351, 372, 504, 655, 720 nm.

5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-8,8,18,18-tetramethyl-10,20-diphenylbacteriochlorin (BC-12)

Following a general procedure [24] with modification, a solution of **BC-9** (3.3 mg, 5.5 μmol), 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (120 μL, 830 μmol), and anhydrous triethylamine (100 μL, 717 μmol) in anhydrous 1,2-dichloroethane (1.8 mL) was degassed by four freeze-pump-thaw cycles. A sample of $Pd(PPh_3)_4$ (2.0 mg, 1.7 μmol) was then added. The resulting mixture was stirred in an oil bath at 80 °C for 16 h and then allowed to cool to room temperature. Then, CH_2Cl_2 and water were added. The organic layer was dried (Na_2SO_4), concentrated under reduced pressure, and purified by chromatography [silica, hexanes/CH_2Cl_2 (2:1) to CH_2Cl_2] to afford a green solid (3.0 mg, 84%): ^{1}H NMR (500 MHz, $CDCl_3$) δ −1.65 (s, 1H), −1.56 (s, 1H), 1.50 (s, 6H), 1.51 (s, 6H), 1.66 (s, 12H), 4.33 (s, 2H), 4.47 (s, 2H), 7.52-7.68 (m, 6H), 7.80–7.92 (m, 5H), 7.94 (dd, *J* = 5.0 and 2.0 Hz, 1H), 8.49 (dd, *J* = 4.5 and 2.0 Hz, 1H), 8.76 (s, 1H), 8.92 (dd, *J* = 4.5 and 2.0 Hz, 1H); ^{13}C{^{1}H} NMR (175 MHz, $CDCl_3$) δ 25.2, 29.7, 29.9, 30.3, 47.0, 47.4, 54.8, 56.4, 84.4, 100.1, 114.5, 115.2, 121.6, 122.2, 122.9, 123.7, 126.2, 126.3, 127.4, 127.5, 133.8, 133.8, 134.4, 138.2, 138.4, 138.5, 141.1, 141.2, 155.8, 160.7, 166.3, 166.8; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{42}H_{46}BN_4O_2$ 649.3708; found 649.3697; λ_{abs} (CH_2Cl_2) 351, 375, 509, 729 nm. Decomposition of the product was observed after storing it at room temperature in the dark for months.

2,12-Dicarboethoxy-5-(4-(4-methyl-2,6-dioxotetrahydro-2H-4λ^4,8λ^4-[1,3,2]oxazaborolo[2,3-b][1,3,2]oxazaborol-8-yl)phenyl-8,8-18,18-tetramethylbacteriochlorin (BC-13)

Following a general procedure [24] with modification, samples of **BC-11** (3.0 mg, 5.1 μmol), MIDA boronate **14** (3.5 mg, 9.7 μmol), and K_2CO_3 (8.7 mg, 63 μmol) were mixed with anhydrous DMF/toluene (2.4 mL, 2:1) under argon in a Schlenk flask. The flask was deaerated by four freeze-pump-thaw cycles. A sample of $Pd(PPh_3)_4$ (2.3 mg, 2.0 μmol) was then added at room temperature under argon, and the resulting mixture was stirred in an oil bath at 75 °C for 12 h and then allowed to cool to room temperature. Then, CH_2Cl_2 and water were added. The organic layer was dried (Na_2SO_4), concentrated under reduced pressure, and purified by chromatography [silica, CH_2Cl_2 to ethyl acetate/CH_2Cl_2 (1:1); ethyl acetate was anhydrous] to afford a purple solid (2.9 mg). The isolated product contained 50% triphenylphosphine oxide as the main impurity based on ^{1}H NMR spectroscopy, in which case the yield of the title compound was 40%. The mixture was used directly in the next step without further purification. Data for the title compound: ^{1}H NMR (600 MHz, $CDCl_3$) δ −1.27 (s, 1H), −1.18 (s, 1H), 1.64 (t, *J* = 7.0 Hz, 3H), 1.70 (t, *J* = 7.0 Hz, 3H), 1.87 (s, 6H), 1.97 (s, 6H), 2.91 (s, 3H), 3.89 (s, 2H), 3.99 (d, *J* = 17.0 Hz, 2H), 4.07 (d, *J* = 17.0 Hz, 2H), 4.37 (s, 2H), 4.68 (q, *J* = 7.0 Hz, 2H), 4.76 (q, *J* = 7.0 Hz, 2H), 7.86 (s, 4H), 8.51 (d, *J* = 2.0 Hz, 1H), 8.70 (s, 1H), 9.18 (d, *J* = 2.0 Hz, 1H), 9.71 (s, 1H), 9.74 (s, 1H) (triphenylphosphine oxide peaks present in the sample are not listed here); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{41}H_{45}BN_5O_8$ 746.3356; found 745.3355; λ_{abs} (CH_2Cl_2) 355, 380, 531, 713, 756 nm.

2,12-Dicarboethoxy-5-(4-hydroxyphenyl)-8,8,18,18-tetramethylbacteriochlorin (BC-14)

A solution of **BC-13** (1.2 mg, 1.6 μmol) in freshly distilled THF (2.0 mL) was bubbled with argon for 30 min. A sample of 1 M aqueous NaOH solution (50 μL, bubbled with argon for 30 min) was added to the mixture. The resulting solution was stirred at room temperature for 2 h with shielding from light. Then, water and ethyl acetate were added. The organic layer was dried (Na_2SO_4), concentrated under reduced pressure, and purified by chromatography in a dimly lit environment [silica, CH_2Cl_2 to CH_2Cl_2/ethyl acetate (5:1)] to afford a purple solid (0.9 mg, estimated 92%): ^{1}H NMR (500 MHz, $CDCl_3$) δ −1.29 (s, 1H), −1.22 (s, 1H), 1.63 (t, *J* = 7.0 Hz, 3H), 1.70 (t, *J* = 7.0 Hz, 3H), 1.88 (s, 6H), 1.97 (s, 6H), 3.95 (s, 2H), 4.37 (s, 2H), 4.68 (q, *J* = 7.0 Hz, 2H), 4.76 (q, *J* = 7.0 Hz, 2H), 7.17 (d, *J* = 8.5 Hz, 2H), 7.68 (d, *J* = 8.5 Hz, 2H), 8.62 (d, *J* = 2.5 Hz, 1H), 8.69 (s, 1H), 9.17 (d, *J* = 2.0 Hz, 1H), 9.71 (s, 1H), 9.76 (s, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 14.7, 29.7, 31.01, 31.04, 45.8, 46.2, 51.1, 51.3, 60.8, 60.9, 97.6, 97.7, 100.3, 114.9, 115.5, 121.4, 122.8,

125.6, 125.9, 133.2, 133.9, 134.3, 134.7, 135.7, 125.8, 155.2, 159.9, 160.8, 165.6, 165.8, 173.0; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{36}H_{39}N_4O_5$ 607.2915; found 607.2892; λ_{abs} (CH_2Cl_2) 356, 380, 531, 756 nm.

2,12-Dicarboethoxy-8,8,18,18-tetramethyl-5-phenylbacteriochlorin (BC-15)

Following a general procedure [24] with modification, samples of **BC-11** (1.1 mg, 1.9 μmol), phenylboronic acid pinacol ester (1.4 mg, 6.9 μmol), and K_2CO_3 (3.5 mg, 25 μmol) were added to toluene/DMF (2.4 mL, 2:1) under argon in a Schlenk flask. Three freeze-pump-thaw cycles were performed. A sample of $Pd(PPh_3)_4$ (1.5 mg, 1.3 μmol) was then added, and the resulting mixture was stirred in an oil bath at 70 °C for 12 h and then allowed to cool to room temperature. Then CH_2Cl_2 and water were added. The organic layer was dried (Na_2SO_4), concentrated under reduced pressure, and purified by chromatography [silica, hexanes/CH_2Cl_2 (1:1)] to afford a purple solid (0.9 mg, estimated 82%): ^{1}H NMR (600 MHz, $CDCl_3$) δ −1.28 (s, 1H), −1.21 (s, 1H), 1.61 (t, *J* = 7.0 Hz, 3H), 1.70 (t, *J* = 7.0 Hz, 3H), 1.87 (s, 6H), 1.97 (s, 6H), 3.93 (s, 2H), 4.38 (s, 2H), 4.67 (q, *J* = 7.0 Hz, 2H), 4.76 (q, *J* = 7.0 Hz, 2H), 7.68–7.72 (m, 3H), 7.80–7.82 (m, 2H), 8.58 (d, *J* = 2.0 Hz, 1H), 8.71 (s, 1H), 9.17 (d, *J* = 2.0 Hz, 1H), 9.71 (s, 1H), 9.77 (s, 1H); ^{13}C{^{1}H} NMR (175 MHz, $CDCl_3$) δ 11.0, 14.7, 23.0, 23.7, 28.9, 29.7, 30.4, 38.7, 45.9, 46.2, 51.1, 51.2, 60.8, 60.9, 68.2, 97.6, 97.8, 100.3, 115.9, 121.5, 122.9, 125.5, 126.0, 127.6, 128.0, 128.8, 130.9, 132.0, 132.5, 133.97, 133.99, 135.6, 135.9, 142.3, 159.4, 160.9, 165.5, 165.8, 167.8, 172.4, 173.1; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{36}H_{39}N_4O_4$ 591.2966; found 591.2961; λ_{abs} (CH_2Cl_2) 355, 380, 497, 530, 690, 715, 755 nm.

3,8,8,13,18,18-Hexamethylbacteriochlorin (BC-16)

Following a general procedure [104], a sample of **23** (3.4 mg, 11 μmol) was dissolved in TFA (514 μL) under argon and stirred for 4 h at room temperature. The absorption spectrum of a sample from the reaction mixture in CH_2Cl_2 (neutralized with triethylamine) was consistent with the formation of the title bacteriochlorin. A 14% yield was determined based on the absorption spectrum (ε for $\lambda(Q_y)$ assumed to be 110,000 $M^{-1}cm^{-1}$). Then, the reaction mixture was poured into a saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Purification by chromatography [silica, hexanes/CH_2Cl_2 (2:1)] gave a green film that decomposed quickly at room temperature before a quality ^{1}H NMR spectrum could be obtained. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{26}H_{31}N_4$ 398.2465; found 398.2467; λ_{abs} (CH_2Cl_2) 343, 369, 489, 719 nm. Given the limited data, the assignment for this compound must remain provisional.

General procedure for early Heck couplings (see text)

Following a reported procedure [138], samples of 0.5 mmol of pyrrole **Bn-60** (1.0 equiv), 0.7 mmol of trimethylsilyl enol ether **TMS-63** (1.4 equiv), 0.03 equiv of $Pd(dba)_2$, 0.055 equiv of P(*t*-Bu)$_3$, 1.4 equiv of ZnF_2, and 0.4 equiv of CsF (dried overnight under high vacuum at 100 °C before use) were mixed in 2.5 mL of DMF and heated on a heating block at 85 °C for 16 h. Each reaction was monitored by TLC analysis and ^{1}H NMR spectroscopy. The reaction mixture was chromatographed in search of new products.

General procedure for Heck coupling (see Table 3)

Following a general procedure [142] with modification, a sample of **Boc-62** (36.4 mg, 0.0800 mmol) was added to $PdCl_2$ (1.4 mg, 0.0080 mmol), P(*o*-tolyl)$_3$ (4.9 mg, 0.016 mmol), and *n*-Bu_3SnF (34.6 mg, 0.112 mmol). The resulting mixture was taken into a glovebox filled with argon. Trimethylsilyl enol ether **TMS-65** (54.9 mg, 0.200 mmol) and toluene (0.28 mL) were added to the reaction mixture in the glove box. The reaction flask was heated on a heating block to cause reflux for 5 h. After allowing to cool to room temperature, the mixture was filtered through a Pasteur pipette containing a plug of Celite. The filtrate was then concentrated to dryness under reduced pressure and examined by TLC, LC-MS, and ^{1}H NMR spectroscopy. In cases where a new product was observed, the reaction mixture was worked up via chromatography for the isolation and characterization of a pure sample. The trimethylsilyl enol ethers were used as obtained from commercial sources or as prepared herein; **TMS-10**, **TMS-65**, and **TMS-68** were used in crude form.

Single-crystal X-ray diffraction analyses.

Samples for XRD analysis were collected of single crystals in the standard way. The CCDC registries for new compounds are listed in the Experimental section whereas those for previously synthesized compounds are listed here: **2a**, CCDC 2263053; **3**, 2263058; **BC-5**, 2120132; **MeOBC-5**, 2263078; **19-x**, 2263079; **24**, 2263081. A full description of the solvents of crystallization, X-ray instrument, and locale for data determination are provided in the Supporting Information (Table S4).

Acknowledgment

This work was supported by a grant from the Chemical Sciences, Geosciences and Biosciences Division, Office of Basic Energy Sciences, of the U.S. Department of Energy (DE-FG02-05ER15661), except for research concerning the synthesis of bacteriochlorophyll skeletons, which was supported by the NSF (CHE-1760839, CHE-2054497). MS and NMR data were obtained in the

Molecular Education, Technology, and Research Innovation Center (METRIC) at NC State University. XRD data were obtained at METRIC; at Vidyasirimedhi Institute of Science and Technology (VISTEC) in Rayong, Thailand; or at the University of Tennessee at Knoxville. XRD data from the latter two institutions were obtained by coauthor Dr. Phattananawee Nalaoh, who is now located at University of Tennessee at Knoxville.

Conflicts of interest

The authors declare no competing interests.

ORCID

M. Taniguchi https://orcid.org/0000-0003-3735-0584
H. Jing https://orcid.org/0000-0001-7839-9582
K. C. Nguyen https://orcid.org/0000-0002-6968-6405
N. Matsumoto https://orcid.org/0000-0002-1178-8345
P. Wang https://orcid.org/0000-0003-4813-6639
P. Nalaoh https://orcid.org/0000-0002-8470-3322
S. Liu https://orcid.org/0000-0003-3898-7966
V.-P. Tran https://orcid.org/0000-0001-9196-8364
J.S. Lindsey https://orcid.org/0000-0002-4872-2040

Supporting information

Survey data for selected reactions. Single-crystal XRD information. ^{1}H NMR and ^{13}C{^{1}H} NMR spectra of new compounds. This material is available free of charge *via* the Internet at https://www.worldscientific.com/doi/suppl/10.1142/S1088424623501171

Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre (CCDC) under the numbers CCDC-2263053, 2263058, 2120132, 2263078, 2263079, 2263081, 2263107, 2263087, 2263088, 2263091, 2263092, 2263094, 2263095, 2263099, 2263100, 2263101, 2263102, 2263104, 2263105, 2263106. Copies can be obtained on request, free of charge, *via* https://www.ccdc.cam.ac.uk/structures/ or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223-336-033 or email: deposit@ccdc.cam.ac.uk)

REFERENCES

1. Kobayashi M, Akiyama M, Kano H and Kise H. In *Chlorophylls and Bacteriochlorophylls: Biochemistry, Biophysics, Functions, and Applications;* Grimm B, Porra RJ, Rüdiger W and Scheer H. (Eds.), Springer: Dordrecht, The Netherlands, 2006, pp 79–94.
2. Pucelik B, Sułek A and Dabrowski JM. *Coord. Chem. Rev.* 2020; **416**: 213340.
3. Moss GP. *Pure Appl. Chem.* 1987; **59**: 779–832.
4. Lindsey JS. *Chem. Rev.* 2015; **115**: 6534–6620.
5. Grin MA and Mironov AF. *Russ. Chem. Bull., Int. Ed*. 2016; **65**: 333–349.
6. Dudkin SV, Makarova EA and Lukyanets EA. *Russ. Chem. Rev.* 2016; **85**: 700–730.
7. Whitlock HW Jr, Hanauer R, Oester MY and Bower BK. *J. Am. Chem. Soc*., 1969; **91**: 7485–7489.
8. Brückner C, Samankumara L and Ogikubo J. In *The Handbook of Porphyrin Science*, Kadish KM, Smith KM and Guilard R. (Eds.), World Scientific: Singapore, 2012, Vol. 17, pp. 1–112.
9. Pinto SMA, Almeida SFF, Tomé VA, Prata AD, Calvete MJF, Serpa C and Pereira MM. *Dyes Pigm*. 2021; **195**: 109677.
10. Taniguchi M and Lindsey JS. *Chem. Rev*. 2017; **117**: 344–535.
11. Moura NMM, Monteiro CJP, Tomé AC, Neves MGPMS and Cavaleiro JAS. *Arkivoc* 2022; part ii, 54–98.
12. Liu Y, Zhang S and Lindsey JS. *Nat. Prod. Rep.* 2018; **35**: 879–901.
13. Minehan TG and Kishi Y. *Tetrahedron Lett*. 1997; **38**: 6811–6814.
14. Minehan TG and Kishi Y. *Tetrahedron Lett*. 1997; **38**: 6815–6818.
15. Minehan TG and Kishi Y. *Angew. Chem. Int. Ed*. 1999; **38**: 923–925.
16. Minehan TG, Cook-Blumberg L, Kishi Y, Prinsep MR and Moore RE. *Angew. Chem. Int. Ed*. 1999; **38**: 926–928.
17. Wang W and Kishi Y. *Org. Lett*. 1999; **1**: 1129–1132.
18. Kim H-J and Lindsey JS. *J. Org. Chem*. 2005; **70**: 5475–5486.
19. Liu Y and Lindsey JS. *J. Org. Chem.* 2016; **81**: 11882–11897.
20. Zhang S and Lindsey JS. *J. Org. Chem*. 2017; **82**: 2489–2504.
21. Dutton CJ, Fookes CJR and Battersby AR. *J. Chem. Soc., Chem. Commun.* 1983; 1237–1238.
22. Battersby AR, Fookes CJR and Snow RJ. *J. Chem. Soc. Perkin Trans. 1* 1984; 2725–2732.
23. Dreuw A and Head-Gordon M. *J. Am. Chem. Soc.* 2004; **126**: 4007–4016.
24. Esemoto NN, Yu Z, Wiratan L, Satraitis A and Ptaszek M. *Org. Lett*. 2016; **18**: 4590–4593.
25. McCleese C, Yu Z, Esemoto NN, Kolodziej C, Maiti B, Bhandari S, Dunietz BD, Burda C and Ptaszek M. *J. Phys. Chem. B* 2018; **122**: 4131–4140.
26. Aksu H, Maiti B, Ptaszek M and Dunietz BD. *J. Chem. Phys.* 2020; **153**: 134111.
27. Jing H, Wang P, Chen B, Jiang J, Vairaprakash P, Liu S, Rong J, Chen C-Y, Nalaoh P and Lindsey JS. *New J. Chem*. 2022; **46**: 5534–5555.
28. Jing H, Liu S, Jiang J, Tran V-P, Rong J, Wang P and Lindsey JS. *New J. Chem*. 2022; **46**: 5556–5572.
29. Jing H, Tang Q, Bocian DF and Lindsey JS. *Organics* 2022; **3**: 22–37.

30. Magdaong NCM, Jing H, Diers JR, Kirmaier C, Lindsey JS, Bocian DF and Holten D. *J. Phys. Chem. Lett.* 2022; **13**: 7906–7910.
31. Jing, H, Magdaong NCM, Diers JR, Kirmaier C, Bocian DF, Holten D and Lindsey JS. *Phys. Chem. Chem. Phys.* 2023; **25**: 1827–1847.
32. Jing H, Rong J, Taniguchi M and Lindsey JS. *Coord. Chem. Rev.* 2022; **456**: 214278.
33. Liu M, Chen C-Y, Hood D, Taniguchi M, Diers JR, Bocian DF, Holten D and Lindsey JS. *New J. Chem.* 2017; **41**: 3732–3744.
34. Hood D, Niedzwiedzki DM, Zhang R, Zhang Y, Dai J, Miller ES, Bocian DF, Williams PG, Lindsey JS and Holten D. *Photochem. Photobiol.* 2017; **93**: 1204–1215.
35. Fujita H, Jing H, Krayer M, Allu S, Veeraraghavaiah G, Wu Z, Jiang J, Diers JR, Magdaong NCM, Mandal AK, Roy A, Niedzwiedzki DM, Kirmaier C, Bocian DF, Holten D and Lindsey JS. *New J. Chem*. 2019; **43**: 7209–7232.
36. Krayer M, Ptaszek M, Kim H-J, Meneely KR, Fan D, Secor K and Lindsey JS. *J. Org. Chem*. 2010; **75**: 1016–1039.
37. Vairaprakash P, Yang E, Sahin T, Taniguchi M, Krayer M, Diers JR, Wang A, Niedzwiedzki DM, Kirmaier C, Lindsey JS, Bocian DF and Holten D. *J. Phys. Chem. B* 2015; **119**: 4382–4395.
38. Yang E, Kirmaier C, Krayer M, Taniguchi M, Kim H-J, Diers JR, Bocian DF, Lindsey JS and Holten D. *J. Phys. Chem. B* 2011; **115**: 10801–10816.
39. Lindsey JS, Mass O and Chen C-Y. *New J. Chem*. 2011; **35**; 511–516.
40. Jing H, Magdaong NCM, Diers JR, Kirmaier C, Bocian DF, Holten D and Lindsey JS. *Phys. Chem. Chem. Phys.* 2023, **25**: 1781–1798.
41. Yang E, Diers JR, Huang Y-Y, Hamblin MR, Lindsey JS, Bocian DF and Holten D. *Photochem. Photobiol.* 2013; **89**: 605–618.
42. De Pinillos Bayona AM, Mroz P, Thunshelle C and Hamblin MR. *Chem. Biol. Drug Des*. 2017; **89**: 192–206.
43. Jiang J, Matula AJ, Swierk JR, Romano N, Wu Y, Batista V, Crabtree RH, Lindsey JS, Wang H and Brudvig GW. *ACS Catal.* 2018; **8**: 10131–10136.
44. Diers JR, Kirmaier C, Taniguchi M, Lindsey JS, Bocian DF and Holten D. *Phys. Chem. Chem. Phys.* 2021; **23**: 19130–19140.
45. Chen C-Y, Bocian DF and Lindsey JS. *J. Org. Chem.* 2014; **79**: 1001–1016.
46. Chen C-Y, Taniguchi M and Lindsey JS. *J. Porphyrins Phthalocyanines* 2014; **18**: 433–456.
47. Diers JR, Tang Q, Hondros CJ, Chen C-Y, Holten D, Lindsey JS and Bocian DF. *J. Phys. Chem. B* 2014; **118**: 7520–7532.
48. Chen C-Y, Sun E, Fan D, Taniguchi M, McDowell BE, Yang E, Diers JR, Bocian DF, Holten D and Lindsey JS. *Inorg. Chem.* 2012; **51**: 9443–9464.
49. Ponsot F, Desbois N, Bucher L, Berthelot M, Mondal P, Gros CP and Romieu A. *Dyes Pigm.* 2019; **160**:747–756.
50. Ponsot F, Bucher L, Desbois N, Rousselin Y, Mondal P, Devillers CH, Romieu A, Gros CP, Singhal R and Sharma GD. *J. Mater. Chem. C* 2019; **7**: 9655–9664.
51. Chakraborty S, You H-C, Huang C-K, Lin B-Z, Wang C-L, Tsai M-C, Liu C-L and Lin C-Y. *J. Phys. Chem. C* 2017; **121**: 7081–7087.
52. Chakraborty S, You H-C, Huang C-K, Lin B-Z, Wang C-L, Tsai M-C, Liu C-L and Lin C-Y. *J. Phys. Chem. C* 2020; **124**: 2728–2728.
53. Chakraborty S, Tsai M-C, Su X-D, Chen X-C, Su T-T, Tsao C-K and Lin C-Y. *RSC Adv.* 2020; **10**: 6172–6178.
54. De Assis FF, Ferreira MAB, Brocksom TJ and de Oliveira KT. *Org. Biomol. Chem.* 2016; **14**: 1402–1412.
55. Yu Z and Ptaszek M. *Org. Lett.* 2012; **14**: 3708–3711.
56. Alexander VM, Sano K, Yu Z, Nakajima T, Choyke PL, Ptaszek M and Kobayashi H. *Bioconjugate Chem.* 2012; **23**: 1671–1679.
57. Yu Z and Ptaszek M. *J. Org. Chem.* 2013; **78**: 10678–10691.
58. Harada T, Sano K, Sato K, Watanabe R, Yu Z, Hanaoka H, Nakajima T, Choyke PL, Ptaszek M and Kabayashi H. *Bioconjugate Chem.* 2014; **25**: 362–369.
59. Yu Z, Pancholi C, Bhagavathy GV, Kang HS, Nguyen JK and Ptaszek M. *J. Org. Chem.* 2014; **79**: 7910–7925.
60. Kang HS, Esemoto NN, Diers JR, Niedzwiedzki DM, Greco JA, Akhigbe J, Yu Z, Pancholi C, Bhagavathy GV, Nguyen JK, Kirmaier C, Birge RR, Ptaszek M, Holten D and Bocian DF. *J. Phys. Chem. A* 2016; **120**: 379–385.
61. Meares A, Satraitis A, Akhigbe J, Santhanam N, Swaminathan S, Ehudin M and Ptaszek M. *J. Org. Chem.* 2017; **82**: 6054–6070.
62. Meares A, Satraitis A and Ptaszek M. *J. Org. Chem.* 2017; **82**: 13068–13075.
63. Esemoto NN, Satraitis A, Wiratan L and Ptaszek M. *Inorg. Chem.* 2018; **57**: 2977–2988.
64. Tiwari V, Matutes YA, Konar A, Yu Z, Ptaszek M, Bocian DF, Holten D, Kirmaier C and Ogilvie JP. *Opt. Express* 2018; **26**: 22327.
65. Ogata F, Nagaya T, Maruoka Y, Akhigbe J, Meares A, Lucero MY, Satraitis A, Fujimura D, Okada R, Inagaki F, Choyke PL, Ptaszek M and Kobayashi H. *Bioconjugate Chem.* 2019; **30**: 169–183.
66. Meares A, Yu Z, Bhagavathy GV, Satraitis A and Ptaszek M. *J. Org. Chem.* 2019; **84**: 7851–7862.
67. Uthe B, Meares A, Ptaszek M and Pelton M. *J. Chem. Phys.* 2020; **153**: 074302.
68. Yu Z, Uthe B, Gelfand R, Pelton M and Ptaszek M. *J. Porphyrins Phthalocyanines* 2021; **25**: 724–733.

69. Riahin C, Meares A, Esemoto NN, Ptaszek M, LaScola M, Pandala N, Lavik E, Yang M, Stacey G, Hu D, Traeger JC, Orr G and Rosenzweig Z. *ACS Appl. Mater. Interfaces* 2022; **14**: 20790–20801.
70. Roy A, Diers JR, Niedzwiedzki DM, Meares A, Yu Z, Bhagavathy GV, Satraitis A, Kirmaier C, Ptaszek M, Bocian DF and Holten D. *J. Phys. Chem. A* 2022; **126**: 5107–5125.
71. Kato T, Riahin C, Furusawa A, Fukushima H, Wakiyama H, Okuyama S, Takao S, Choyke PL, Ptaszek M, Rosenzweig Z and Kobayashi H. *Nanomed. (Lond.)* 2023; **18**: 659–666.
72. Dolewski RD, Kerbs S and Ruppel JV. *Tenth Annual South Carolina Upstate Research Symposium* 2014; pp. 43–45.
73. Su Y-L, You H-C, Cheng S-H and Lin C-Y. *Anal. Chim. Acta* 2020; **1123**: 44–55.
74. Balanay MP and Kim DH. *J. Phys. Chem. A* 2017; **121**: 6660–6669.
75. Peymani S, Izadyar M and Arkan F. *Res. Chem. Intermed.* 2021; **47**: 1071–1085.
76. Tran V-P, Matsumoto N, Nalaoh P, Jing H, Chen C-Y and Lindsey JS. *Organics* 2022; **3**: 262–274.
77. Jones G and Stanforth SP. *Org. React.* 1997; **49**: 1–330.
78. Luzzio FA. *Tetrahedron* 2001; **57**: 915–945.
79. Sample HC, Twamley B and Senge MO. *Acta Cryst.* 2023; **E79**: 592–595.
80. Tokoroyama T. *Eur. J. Org. Chem.* 2010; 2009–2016.
81. Mass O and Lindsey JS. *J. Org. Chem.* 2011; **76**: 9478–9487.
82. Reddy MN, Zhang S, Kim H-J, Mass O, Taniguchi M and Lindsey JS. *Molecules* 2017; **22**: 634.
83. Brown HC and Kanner B. *J. Am. Chem. Soc*. 1966; **88**: 986–992.
84. Wang P and Lindsey JS. *Molecules* 2020; **25**: 1858.
85. Reddy KR, Lubian E, Pavan MP, Kim H-J, Yang E, Holten D and Lindsey JS. *New J. Chem.* 2013; **37**: 1157–1173.
86. Krayer M, Yang E, Kim H-J, Kee HL, Deans RM, Sluder CE, Diers JR, Kirmaier C, Bocian DF, Holten D and Lindsey JS. *Inorg. Chem.* 2011; **50**: 4607–4618.
87. Jiang J, Reddy KR, Pavan MP, Lubian E, Harris MA, Jiao J, Niedzwiedzki DM, Kirmaier C, Parkes-Loach PS, Loach PA, Bocian DF, Holten D and Lindsey JS. *Photosynth. Res.* 2014; **122**: 187–202.
88. Churches QI, Hooper JF and Hutton CA. *J. Org. Chem.* 2015; **80**: 5428–5435.
89. Fan D, Taniguchi M and Lindsey JS. *J. Org. Chem.* 2007; **72**: 5350–5357.
90. Zhang N, Reddy KR, Jiang J, Taniguchi M, Sommer RD and Lindsey JS. *J. Porphyrins Phthalocyanines* 2015; **19**: 887–902.
91. Taniguchi M, Cramer DL, Bhise AD, Kee HL, Bocian DF, Holten D and Lindsey JS. *New J. Chem.* 2008; **32**: 947–958.
92. Liu Y, Allu S, Reddy MN, Hood D, Diers JR, Bocian DF, Holten D and Lindsey JS. *New J. Chem.* 2017; **41**: 4360–4376.
93. Chau Nguyen K, Wang P, Sommer RD and Lindsey JS. *J. Org. Chem.* 2020; **85**: 6605–6619.
94. Chau Nguyen K, Wang P and Lindsey JS. *New J. Chem.* 2021; **45**: 569–581.
95. Chung DTM, Tran PV, Chau Nguyen K, Wang P and Lindsey JS. *New J. Chem.* 2021; **45**: 13302–13316.
96. Wang P and Lindsey JS. *J. Org. Chem.* 2021; **86**: 11794–11811.
97. Jacobi PA, Lanz S, Ghosh I, Leung SH, Löwer F and Pippin D. *Org. Lett.* 2001; **3**: 831–834.
98. O'Neal WG, Roberts WP, Ghosh I and Jacobi PA. *J. Org. Chem.* 2005; **70**: 7243–7251.
99. O'Neal WG, Roberts WP, Ghosh I, Wang H and Jacobi PA. *J. Org. Chem.* 2006; **71**: 3472–3480.
100. Jacobi PA, Brielmann HL, Chiu M, Ghosh I, Hauck SI, Lanz S, Leung S, Li Y, Liu H, Löwer F, O'Neal WG, Pippin D, Pollina E, Pratt BA, Robert F, Roberts WP, Tassa C and Wang H. *Heterocycles* 2010; **82**: 1029–1081.
101. Petasis NA and Bzowej EI. *J. Am. Chem. Soc.* 1990; **112**: 6392–6394.
102. Khaghaninejad S and Heravi MM. *Adv. Heterocycl. Chem.* 2014; **111**: 95–146.
103. Nigst TA, Westermaier M, Ofial AR and Mayr H. *Eur. J. Org. Chem.* 2008; 2369–2374.
104. Zhang S, Kim H-J, Tang Q, Yang E, Bocian DF, Holten D and Lindsey JS. *New J. Chem.* 2016; **40**: 5942–5956.
105. Cheng X, Wang J, Tang K, Liu Y and Liu C. *Chem. Phys. Lett.* 2010; **496**: 36–41.
106. Routier S, Saugé L, Ayerbe N, Coudert G and Mérour J-Y. *Tetrahedron Lett.* 2002; **43**: 589–591.
107. Anderson HJ and Lee S-F. *Can. J. Chem.* 1965; **43**: 409–414.
108. Hodge P and Rickards RW. *J. Chem. Soc.* 1965; 459–470.
109. Trost BM and Dong G. *J. Am. Chem. Soc*. 2006; **128**: 6054–6055.
110. Nguyen Tran AT, Wu Z, Chung DTM, Nalaoh P and Lindsey JS. *New J. Chem.* 2023; **47**: 13626–13637.
111. Warashina T, Matsuura D, Sengoku T, Takahashi M, Yoda H and Kimura Y. *Org. Process Res. Dev*. 2019; **23**: 614–618.
112. Barbay JK, Chai W, Hirst GC, Kreutter KD, Kummer DA, McClure KJ, Nishimura RT, Shih AY, Venable JD, Venkatesan H and Wei J. US 2020/0055874.
113. Crimmins, MT, Mascarella WS and Deloach JA. *J. Org. Chem*. 1984; **49**, 3033–3035.

114. Fritzemeier R, Gates A, Guo X, Lin Z and Santos WL. *J. Org. Chem*. 2018; **83**, 10436–10444.
115. Millar JG and Oehlschlager AC. *J. Org. Chem*. 1984; **49**, 2332–2338.
116. Köpfer A and Breit B. *Angew. Chem. Int. Ed*. 2015; **54**, 6913–6917.
117. Laha JK, Sharma S, Kirar S and Banerjee UC. *J. Org. Chem.* 2017; **82**: 9350–9359.
118. Chau Nguyen K, Nguyen Tran AT, Wang P, Zhang S, Wu Z, Taniguchi M and Lindsey JS. *Molecules* 2023; **28**: 1323.
119. Bray BL, Mathies PH, Naef R, Solas DR, Tidwell TT, Artis DR and Muchowski JM. *J. Org. Chem*. 1990; **55**: 6317–6328.
120. Wang P, Chau Nguyen K and Lindsey JS. *J. Org. Chem.* 2019; **84**: 11286–11293.
121. He C, Chu H, Stratton TP, Kossler D, Eberle KJ, Flood DT and Baran PS. *J. Am. Chem. Soc.* 2020; **142**: 13683–13688.
122. Grehn L and Ragnarsson U. *Angew. Chem. Int. Ed*. 1984; **23**: 296, 301.
123. Brown HC, Vara Prasad JVN and Zee S-H. *J. Org. Chem.* 1985; **50**: 1582–1589.
124. Dhillon RS. *Hydroboration and Organic Synthesis: 9-Borabicyclo[3.3.1] nonane (9-BBN)*, Springer: New York, 2007.
125. Laha JK, Muthiah C, Taniguchi M, McDowell BE, Ptaszek M and Lindsey JS. *J. Org. Chem*. 2006; **71**: 4092–4102. *Additions and Corrections:* Laha JK, Muthiah C, Taniguchi M, McDowell BE, Ptaszek M and Lindsey JS. *J. Org. Chem.* 2009; **74**: 5122.
126. Krayer M, Balasubramanian T, Ruzié C, Ptaszek M, Cramer DL, Taniguchi M and Lindsey JS. *J. Porphyrins Phthalocyanines* 2009; **13**: 1098–1110.
127. Kingsbury CJ, Sample HC and Senge MO. *Acta Cryst.* 2021: **E77**; 341–345.
128. Zhang S, Reddy MN, Mass O, Kim H-J, Hu G and Lindsey JS. *New J. Chem.* 2017; **41**: 11170–11189.
129. Taniguchi M, Ra D, Mo G, Balasubramanian T and Lindsey JS. *J. Org. Chem.* 2001; **66**: 7342–7354.
130. Kim H-J, Dogutan DK, Ptaszek M and Lindsey JS. *Tetrahedron* 2007; **63**: 37–55.
131. Liu M, Ptaszek M, Mass O, Minkler DF, Sommer RD, Bhaumik J and Lindsey JS. *New J. Chem.* 2014; **38**: 1717–1730.
132. Sun R, Liu M, Wang P, Qin Y, Schnedermann C, Maher AG, Zheng S-L, Liu S, Chen B, Zhang S, Dogutan DK, Lindsey JS and Nocera DG. *Inorg. Chem.* 2022; **61**: 12308–12317.
133. Wang P, Lu F and Lindsey JS. *J. Org. Chem*. 2020; **85**: 702–715.
134. Beletskaya IP and Cheprakov AV. *Chem. Rev*. 2000; **100**: 3009–3066.
135. Littke AF and Fu GC. *J. Am. Chem. Soc*. 2001; **123**: 6989–7000.
136. Chandrasekhar S, Narsihmulu C, Sultana SS and Reddy NR. *Org. Lett*. 2002; **4**: 4399–4401.
137. Xu H-J, Zhao Y-Q and Zhou X-F. *J. Org. Chem*. 2011; **76**: 8036–8041.
138. Su W, Raders S, Verkade JG, Liao X and Hartwig JF. *Angew. Chem. Int. Ed*. 2006; **45**: 5852–5855.
139. Xuan J, Haelsig KT, Sheremet M, Machicao PA and Maimone TJ. *J. Am. Chem. Soc*. 2021; **143**: 2970–2983.
140. Stawski W, Hurej K, Skonieczny J and Pawlicki M. *Angew. Chem*. 2019; **131**: 11062–11066.
141. Cantos-Llopart C. Ph.D. thesis. The University of Manchester, 2003.
142. Schaus JM and Xu Y-C. U.S. Patent 6,608,079.
143. Kuwajima I and Urabe H. *J. Am. Chem. Soc*. 1982; **104**: 6831–6833.
144. Noland WE. *Chem. Rev*. 1955; **55**: 137–155.
145. Figliola C, Greening SM, Lamont C, Groves BR and Thompson A. *Can. J. Chem*. 2018; **96**: 534–542.
146. Bist S, Dangel B and Sherer B. WO 2009/106885 A1.
147. Smith AC, Cabral S, Kung DW, Rose CR, Southers JA, García-Irizarry CN, Damon DB, Bagley SW and Griffith DA. *J. Org. Chem*. 2016; **81**: 3509–3519.
148. Zheng J, Zeng Q, Zhang R, Xing D and Zhang Y. *J. Am. Chem. Soc*. 2019; **141**: 19226–19230.
149. Cao H, Ma S, Feng Y, Guo Y and Jiao P. *Chem. Commun*. 2022; **58**: 1780–1783.
150. Stetter H. *Angew. Chem. Int. Ed*. 1976; **15**: 639.
151. Hunjan MK, Panday S, Gupta A, Bhaumik J, Das P and Laha JK. *Chem. Rec.* 2021; **21**: 715–780.
152. Maksymenko S, Parida KN, Pathe GK, More AA, Lipisa YB and Szpilman AM. *Org. Lett.* 2017; **19**: 6312–6315.
153. Munyemana F, George L, Devos A, Colens A, Badarau E, Frisque-Hesbain A-M, Loudet A, Differding E, Damien J-M, Rémion J, Van Uytbergen J and Ghosez L. *Tetrahedron* 2016; **72**: 420–430.
154. Ayala-Mata F, Barrera-Mendoza C, Jiménez-Vázquez HA, Vargas-Díaz E, Zepeda L. *Molecules* 2012; **17**: 13864–13878.
155. Ishikawa T, Kadoya R, Arai M, Takahashi H, Kaisi Y, Mizuta T, Yoshikai K and Saito S. *J. Org. Chem*. 2001; **66**: 8000–8009.
156. Valerio V, Mostinski Y, Kotikalapudi R and Tsvelikhovsky D. *Chem. Eur. J.* 2016; **22**: 2640–2647.
157. Brimble MA, Finch OC, Heapy AM, Fraser JD, Furkert DP and O'Connor PD. *Tetrahedron* 2011; **67**: 995–1001.
158. Lui K-H and Sammes MP. *J. Chem. Soc. Perkin Trans 1* 1990; 457–468.
159. Kisanga PB, Ilankumaran P, Fetterly BM and Verkade JG. *J. Org. Chem*. 2002; **67**: 3555–3560.
160. Uchida N, Kuwabara J, Taketoshi A and Kanbara T. *J. Org. Chem*. 2012; **77**: 23, 10631–10637.

161. Nicolai S, Erard S, González DF and Waser J. *Org. Lett*. 2010; **12**: 384–387.
162. Nicolai S, Piemontesi C and Waser J. *Angew. Chem*. 2011; **123**: 4776–4779.
163. Schnabel C, Sterz K, Müller H, Rehbein J, Wiese M and Hiersemann M. *J. Org. Chem*. 2011; **76**: 512–522.
164. Baader S, Ohlmann DM and Goossen LJ. *Chem.–Eur. J*. 2013; **19**: 9807–9810.
165. Deng B, McNelles SA, Da-Ré G, Marando VM, Ros S, Stöver HD and Adronov A. *Macromolecules* 2021; **55**: 270–275.
166. Shen HC, Ding F-X, Raghavan S, Deng Q, Luell S, Forrest MJ, Carballo-Jane E, Wilsie LC, Krsmanovic ML, Taggart AK, Wu KK, Wu T-J, Cheng K, Ren N, Cai T-Q, Chen Q, Wang J, Wolff MS, Tong X, Holt TG, Waters MG, Hammond ML, Tata JR and Colletti SL. *J. Med. Chem*. 2010; **53**: 2666–2670.
167. Kobayashi T, Tanaka K, Ishida M, Yamakita N, Abe H and Ito H. *Chem. Commun*. 2018; **54**: 10316–10319.
168. Angehrn P, Buchmann S, Funk C, Goetschi E, Gmuender H, Hebeisen P, Kostrewa D, Link H, Luebbers T, Masciadri R, Nielsen J, Reindl P, Ricklin FH, Schmitt-Hoffmann A and Theil FP. *J. Med. Chem*. 2004; **47**: 1487–1513.