Published in final edited form as:
Tetrahedron. 2007 April 30; 63(18): 3826–3839.

Sparsely substituted chlorins as core constructs in chlorophyll analogue chemistry. I. Synthesis

Marcin Ptaszek, **Brian E. McDowell**, **Masahiko Taniguchi**, **Han-Je Kim**, and **Jonathan S. Lindsey***
Department of Chemistry, North Carolina State University, Raleigh, NC 27695-8204, USA

Abstract

Five routes to stable chlorins bearing 0 or 1 meso substituents have been investigated, among which reaction of a 9-bromo-1-formyldipyrromethane and 2,3,4,5-tetrahydro-1,3,3-trimethyldipyrrin proved most effective. Application of this route afforded metallochlorins [Cu(II), Zn(II), Pd(II)] including the chlorin lacking any β-pyrrole and meso substituents.

Keywords

Chlorin; Hydroporphyrin; Hydrodipyrrin; Dipyrromethane

1. Introduction

The dihydroporphyrins known as chlorins constitute the chromophore of plant chlorophylls. In comparison with porphyrins, chlorins absorb more strongly in the red region of the spectrum.[1] The prototypical chlorins are chlorophyll *a* and chlorophyll *b*, whose structure and absorption spectra are shown in Figure 1. The spectra differ owing to the presence of the methyl group or the formyl group at the 7-position. Thus, chlorin spectra can be significantly altered upon modification of *even a single substituent*. To gain a deep understanding of the effects of substituents on the spectral properties of chlorins requires the ability to prepare chlorins bearing diverse patterns of substituents. To tailor chlorins for use in diverse applications also requires a fundamental understanding of how substituents alter reactivity. A comprehensive treatment of the effects of substituents requires access to chlorins bearing a systematic progression of substituents, beginning with no substituents and proceeding to one, two, or more groups at designated locations. An ultimate objective of this work is to be able to design and synthesize chlorins that exhibit desired spectral and photophysical properties for diverse applications ranging from artificial photosynthesis to photomedicine.

Surprisingly few systematic studies are available concerning the effects of substituents on chlorin properties. The dearth stems largely from synthetic limitations. Two simple routes to chlorins entail (1) derivatization of naturally occurring chlorins,[3] and (2) reduction/derivatization of synthetic porphyrins.[4] The former route is constrained by the numerous substituents present in the naturally occurring macrocycles. The lack of regioselectivity of the latter route typically limits the scope to the reduction of porphyrins having substitution patterns (giving 4-fold or 2-fold symmetry) wherein regioisomers cannot form. Benchmark chlorins of the latter type include *meso*-tetraphenylchlorin (**H_2TPC**)[5] and octaethylchlorin (**H_2OEC**),[6]

*Corresponding author. Tel.: +1 9195156406; fax +19195132830; e-mail: jlindsey@ncsu.edu

which are commercially available, and 5,15-diphenylchlorin.[7] Analogues such as *meso*-tetrakis(3-hydroxyphenyl)chlorin,[8] 2,3-dihydroxy-*meso*-tetraphenylchlorin,[9] and diverse 5,15-diarylchlorins[10] have been prepared for studies of photodynamic therapy.

The chlorin lacking any substituents, 2,3-dihydroporphine (known as "chlorin" itself, here termed **H_2Chlorin**; Chart 1), has been the subject of theoretical calculations[11] and numerous spectroscopic studies.[12-69] The latter include fundamental studies to probe chlorin features, as well as spectral hole-burning experiments to probe the utility of chlorins in optical information storage applications. However, such a potentially valuable benchmark has not been employed for studies of reactivity (other than dehydrogenation[70]), presumably owing to the limited quantities of available material. The only reported synthesis of **H_2Chlorin** entails Grignard-mediated cyclization of 2-(*N*,*N*-dimethylaminomethyl)pyrrole.[71,72] Photoreduction of zinc porphine affords the corresponding **ZnChlorin**[73] but no preparative procedure has been reported. Regardless, all of the hydroporphyrins shown in Chart 1 are susceptible in an aerobic environment to adventitious dehydrogenation to give the porphyrin, and thus have limited stability toward routine handling in the laboratory.

The naturally occurring chlorins bonellin (a non-photosynthetic pigment) and Faktor I (a biosynthetic intermediate) each contain a geminal dialkyl group in the pyrroline ring, which stabilizes the chlorin to dehydrogenation (Chart 2). Total syntheses of these "*C*-methylated chlorins" and other naturally occurring chlorins have been developed; however, such syntheses are necessarily elaborate owing to the challenges of installing the multiple β-pyrrolic and pyrrolinic substituents.[74]

The methodology developed for preparing bonellin and Faktor I has been extended to gain access to synthetic chlorins bearing more simple substituent patterns (while retaining the geminal dimethyl group).[75-78] Two routes that we developed in this regard include (I) reaction of a 9-bromodipyrromethane-1-carbinol (Eastern half) and a 1,3,3-trimethyltetrahydrodipyrrin (Western half),[76] and (II) reaction of a 9-bromodipyrromethane-1-carboxaldehyde (Eastern half) and the same 1,3,3-trimethyltetrahydrodipyrrin (Western half). The two routes are shown in Scheme 1. The Western half incorporates a geminal dimethyl group that ensures the presence of the reduced, pyrroline ring in the resulting chlorin, thereby precluding adventitious dehydrogenation leading to the porphyrin. In each case, the reaction proceeds in a two-step process of condensation of the Eastern and Western halves to give a 1-methyl-19-bromo-bilane derivative, and metal-mediated oxidative cyclization of the latter to give the corresponding chlorin.

The two routes are similar in a number of respects but also differ in the conditions for condensation, nature of the acyclic intermediate, and substituent patterns in the resulting chlorins. Route I has provided access to chlorins bearing two substituents (5,10-,[75,76] 5,12-,[79] 5,8-[79]) or three substituents (2,5,12-,[79] 5,10,15-,[80] 5,10,20-[80]) at sites other than the pyrroline ring, and each chlorin has contained a 5-substituent (see Figure 1 for chlorin numbering system). Reasonable yields of chlorin macrocycle formation (12-45%) have facilitated preparation of 5,10-disubstituted chlorins in >100-mg quantities, as required for a variety of applications. Route II, developed very recently and described herein, has been applied to access zinc chlorins bearing two substituents (3,13-), three substituents (3,10,13-), and no meso- or β-pyrrole substituents.[77] By contrast with route I where each chlorin contains a 5-substituent, the development of route II for the synthesis of sparsely substituted, 5-unsubstituted chlorins has presented a number of unexpected challenges.

In this paper, we describe the investigation of the synthesis of sterically uncongested, stable chlorins possessing no β-pyrrole substituents and no or only one meso substituent (at the 5- or 10-position). A 5-substituted chlorin was prepared via route I. Five routes were investigated

to prepare 5-unsubstituted chlorins. The investigation entailed use of two types of Western halves and five types of Eastern halves. The routes found suitable for preparing 5-unsubstituted chlorins include route II (described above), two modified versions of route II designed to facilitate implementation and increase the scope, and a new route that entails reaction of a 9-formyltetrahydrodipyrrin and a dipyrromethane. The synthetic routes described herein have enabled examination of the fundamental reactivity, structure, and spectral properties of stable chlorins bearing few or no substituents, as are described in the companion papers.[81,82]

2. Results and discussion

The shorthand nomenclature for the chlorins described herein employs the following abbreviations with superscripts to denote substituents and their positions: B (3,5-di-*tert*-butylphenyl), P (phenyl), M (mesityl), and T (*p*-tolyl).

2.1. Synthesis of chlorins bearing one substituent (5-position)

The synthesis of a chlorin bearing a lone substituent located at the 5-position was carried out following route I[76] (Scheme 1). Thus, acylation[83] of dipyrromethane (**1a**)[84] using benzothioate **2-B**[76] or **2-T**[85] gave the 1-acyldipyrromethane **3-B** or **3-T** in 71% or 39% yield, respectively (Scheme 2). Treatment of **3-B** with NBS afforded **4-B** in 53% yield. Reduction of **4-B** with $NaBH_4$ gave the corresponding carbinol **4-B-OH** (Eastern half), which upon condensation with 2,3,4,5-tetrahydro-1,3,3-trimethyldipyrrin (**5**, Western half)[76] using TFA gave the tetrahydrobilene-*a* (**6-B**) in 53% yield. Treatment of the latter to metal-mediated oxidative cyclization conditions [AgOTf, 2,2,6,6-tetramethylpiperidine (TMPi) and Zn $(OAc)_2$ in refluxing CH_3CN exposed to air] afforded chlorin **ZnC-B**[5] in 17% yield. The same approach was used with 1-acyldipyrromethane **3-T**, but the limited stability of the corresponding 9-bromo species **4-T** prompted *in situ* conversion to the chlorin. Thus, bromination of **3-T** and subsequent condensation with **5** yielded putative tetrahydrobilene-*a* **6-T**, which was converted to chlorin **ZnC-T**[5] in 7% overall yield (from **3-T**).

2.2. Synthesis of chlorins lacking a 5-substituent

(1) Retrosynthetic analysis—We investigated five routes (I–V) to the target chlorin bearing no substituents (R = H) or one substituent at the 10-position (R = aryl), as shown in Scheme 3. The routes are based on the ready availability of dipyrromethanes (**1**) and the tetrahydrodipyrrin **5**. The 2 + 2 synthesis of a chlorin entails condensation of an Eastern half (composed of two pyrrole units) and a Western half (composed of one pyrrole and one pyrroline unit). The two halves must have complementary sets of reactive nucleophilic and electrophilic positions. The routes differ from each other in the placement of reactive groups on the two halves: the α-pyrrolic position and the pyrrolinic methyl group react as nucleophiles, whereas the α-bromo-, formyl, and hydroxymethylpyrrolic groups serve as electrophiles.

The routes also differ in the nature of the intermediates expected upon condensation of the Eastern half and Western half. The intermediates are shown in the retrosynthetic scheme. Intermediate **A** is a 2,3,4,5-tetrahydrobilene-*a*, **B** is a 2,3,4,5-tetrahydrobiladiene-*ab*, and **C** is a 2,3,4,5-tetrahydrobilatriene-*abc*. While the intermediates obtained upon condensation are typically not characterized but instead are treated to the conditions for metal-mediated oxidative cyclization, the differing oxidation state of **A**, **B**, and **C** are expected to give rise to different properties and ease of oxidation.

A key issue in the condensation concerns the lability of the Eastern half and Western half under the reaction conditions employed, particularly the level of acid present in the condensation. A requirement for stronger acidic conditions is expected for the condensation in each of routes I–V (pyrrolic-carboxaldehyde or 1° pyrrole-carbinol) to give a 5-unsubstituted chlorin versus

that employed to give a 5-substituted chlorin (2° pyrrole-carbinol in route I). However, strong acid causes the Western half **5** to undergo irreversible rearrangement to a bicyclic product,[76] and Eastern halves can undergo cleavage. The liberation of free pyrrolic species upon acidolysis of an Eastern half opens the door to the formation of chlorin byproducts as well as porphyrin species. Dipyrromethanes bearing meso-aryl substituents are more prone to acidolysis than those lacking a meso substituent.[86] Even in the absence of acid, bromo-dipyrromethanes (e.g., many of the Eastern halves) are inherently reactive. Thus, conditions to force the reaction of Eastern and Western halves, such as strong acid or elevated temperature, are of limited utility.

(2) Route I—Access to a 5-unsubstituted chlorin via route I (Scheme 1) requires use of a 1° carbinol rather than a 2° carbinol. The synthesis of such chlorins required preparation of 1-formyldipyrromethanes. Thus, Grignard-mediated formylation (with phenyl formate) of dipyrromethane (**1a**), 5-phenyldipyrromethane (**1b**) and 5-mesityldipyrromethane (**1c**) gave the corresponding 1-formyldipyrromethanes **7a-c**.[87] Treatment of **7c** with NBS gave the 1-bromo-9-formyldipyrromethane **8c** in 67% yield. Reduction of **8c** with $NaBH_4$ afforded the 1-bromo-9-hydroxymethyldipyrromethane **8c-OH**. Reaction of **8c-OH** with **5** under the standard conditions[75] of TFA catalysis followed by metal-mediated oxidative cyclization afforded the corresponding chlorin **ZnC-M**^{10} in <1% yield (Scheme 4). We attributed the low yield to the poor reactivity of the 1° carbinol. Related studies of the reaction of similar dipyrromethane-carbinols in porphyrin-forming conditions have also given quite low yields.[88]

(3) Route II

(a) Standard procedure Route II utilizes a 1-bromo-9-formyldipyrromethane (Eastern half) and the tetrahydrodipyrrin (Western half). Treatment of a 1-formyldipyrromethane (**7a-c**) with NBS gave the corresponding 9-bromo-1-formyldipyrromethane **8a-c** in yields of 55-78%. The condensation of 9-bromo-1-formyldipyrromethane (**8a**) and Western half **5** was carried out with 1 equiv of $BF_3{\cdot}O(Et)_2$ in CH_3CN, which gave no reaction after 15 minutes, while excess $BF_3{\cdot}O(Et)_2$ resulted in decomposition of **5**. Battersby reported the condensation of a 1-formyldipyrromethane and a tetrahydrodipyrrin using *p*-toluenesulfonic acid (*p*-TsOH·H_2O) in MeOH, affording an intermediate 2,3,4,5-tetrahydrobiladiene-*ab* on the path to a copper chlorin.[89] Note that the Eastern half and Western half reactants employed by Battersby contained several β-substituents and no meso substituents. We performed the condensation of **8a** and **5** using 13.5 mM reactants and 5 molar equiv (68 mM) of *p*-TsOH·H_2O in methanol (Scheme 5). The putative protonated 2,3,4,5-tetrahydrobiladiene-*ab* was observed with a maximum absorption centered at 480 nm (to be compared with Battersby's tetrahydrobiladiene-*ab* at 496 nm[89]), an absorption characteristic of dipyrrin chromophores.

The crude mixture was then subjected to the standard conditions[76] for metal-mediated oxidative cyclization, affording the desired zinc chlorin **ZnC** in 9% yield. The similar reaction of 9-bromo-1-formyldipyrromethane **8b** or **8c** afforded **ZnC-P**^{10} or **ZnC-M**^{10} in 10% or 12% yield, respectively. A microscale study of the concentration dependence of the condensation of **8a** and **5** (and 5 mol equiv of *p*-TsOH·H_2O in CH_2Cl_2/MeOH) identified improved yields upon doubling the concentration of the condensation reactants. Thus, reaction using 26 mM Eastern and Western halves afforded workable quantities (66–104 mg) of **ZnC**, **ZnC-P**^{10} **ZnC-M**^{10} in 16%, 33% or 42% yield, respectively. The syntheses of **ZnC** and **ZnC-M**^{10} in this manner were reported in a separate publication.[77]

(3b) Streamlined route II The clean bromination of 1-formyldipyrromethane **7a** suggested a streamlined three-step procedure for chlorin synthesis. Thus, **7a** was brominated with NBS and the crude reaction mixture was carried through the two-step procedure for chlorin formation as described above. The yield of chlorin **ZnC** in the three-step procedure was 18% (145 mg)

versus ~12% (104 mg)[77] in the standard procedure (Scheme 5). The streamlined three-step procedure is advantageous in avoiding chromatography following step one, and employing a simple workup in step two.

(3c) AgOTf-free route II In several cases we attempted to isolate the tetrahydrobiladiene-*ab* intermediate. In the reaction of **8a** + **5**, the resulting unsubstituted tetrahydrobiladiene-*ab* (**9a-Br**) was not isolated due to decomposition upon flash chromatography. However, the phenyl-substituted tetrahydrobiladiene-*ab* (**9b-Br**, derived from **8b** + **5**) was more stable and was readily isolated by flash chromatography (silica, CH_2Cl_2). The ^{1}H NMR spectrum revealed a mixture of diastereomers, which made individual proton assignments difficult. However, two pyrrole NH protons were clearly observed at 7.83 and 8.18 ppm, consistent with a tetrahydrobiladiene structure.

We then turned to investigate alternative conditions for the metal-mediated, oxidative cyclization of the tetrahydrobiladiene-*ab*. The traditional method employs $Zn(OAc)_2$, AgOTf and 2,2,6,6-tetramethylpiperidine in refluxing acetonitrile exposed to air. Prior omission/reconstitution experiments concerning route I revealed that omission of $Zn(OAc)_2$ and 2,2,6,6-tetramethylpiperidine resulted in failure to form any detectable chlorin, whereas omission of AgOTf gave chlorin albeit in diminished yield.[76] Here we explored the cyclization in the presence of various metal salts and bases in refluxing solvents exposed to air, but without any AgOTf (i.e., a AgOTf-free step 3 in route II). In each case, the *p*-TsOH-catalyzed condensation of **5** and **8b** gave the crude reaction mixture containing **9b-Br**. The latter was neutralized with an appropriate base, dissolved in a given solvent, and treated with a base and metal salt (Scheme 6). The resulting reaction mixture was refluxed until the absorption spectrum remained relatively unchanged. The results are summarized in Table 1.

With a number of metal salts, the (AgOTf-free) metal-mediated oxidative cyclization of **9b-Br** gave the corresponding metallochlorin. Each metal reagent examined gave an absorption spectrum consistent with the metal complex of **9b-Br**, regardless of whether the chlorin ultimately was obtained. The metal reagents that successfully gave chlorin include Zn(II) (entries 1-3), Pd(II) (entries 4-6), Cu(II) (entries 7 and 8), In(III) (entries 9 and 10), and Sn(II) (entry 11) but not Mg(II), Co(II), Ni(II), Cd(II) or no metal (entries 12-17) under the conditions examined. The best yield typically was observed when 2,2,6,6-tetramethylpiperidine was used in acetonitrile. In the case of Cu(II), a better yield was observed for KOH/EtOH, conditions (entry 8) developed previously for the synthesis of palladium porphyrins.[90] The procedure of acid-catalyzed condensation followed by AgOTf-free metal-mediated oxidation was applied to give milligram quantities of **CuC**, **PdC**, **CuC-P^{10}**, **ZnC-P^{10}**, and **PdC-P^{10}**.

A few indium(III) reagents were examined in place of zinc acetate in the AgOTf-free chlorin-forming reaction [$InCl_3$, $InBr_3$, $In(OAc)_3$] to prepare **X-InC-P^{10}** where X is the counteranion. Each indium reagent afforded the corresponding indium(III)chlorin in ~30% yield (observed spectroscopically), with the cleanest reaction observed for $In(OAc)_3$. Contrary to other chlorin chelates examined herein, the indium(III)chlorin was highly polar and proved difficult to purify by chromatography. Moreover, we observed partial conversion of the indium(III)chlorin on silica (ethyl acetate) into another less polar chlorin. In the case of reaction with $InCl_3$, the two indium(III)chlorin species were separated (although not isolated in pure form), and exhibited spectroscopic properties (LD-MS, UV-vis, only slightly different ^{1}H NMR spectra) that were similar to each other. In the case of reaction with $In(OAc)_3$, chromatography [alumina, ethyl acetate → ethyl acetate/MeOH (10:1)] followed by preparative SEC (THF) afforded the expected indium(III)chlorin in nearly pure form as determined by TLC and ^{1}H NMR spectroscopy. However, attempts at further purification on alumina [ethyl acetate/MeOH (10:1)] caused formation of a second indium(III)chlorin in almost equal amount. The two chlorins were observed by TLC and ^{1}H NMR spectroscopy but could not be separated. In this

regard, it is noteworthy that Pandey's group observed the formation of two indium-chelated species upon metalation of a free base chlorin related to methyl pyropheophorbide.[91] Thus, an indium-chlorin of unambiguous identity was not obtained.

Attempts to form chlorin directly from **8b** and **5** by refluxing a mixture of both halves in EtOH in the presence of KOH and an appropriate metal salt (thereby avoiding *p*-TsOH-catalyzed condensation) resulted in a mixture of chlorin and porphyrin products (the latter formed by self-condensation of the Eastern half), or no macrocycle formation. We previously employed imine derivatives of 1,9-formyldipyrromethanes for condensation with zinc acetate (and no other acid) to give the *trans*-AB-porphyrin.[92] Condensation using the *N*-propyliminomethyl analogue of **8b** (**PrN-8b**) and Western half **5** (100 mM each) in ethanol afforded chlorin **ZnC-P[10]**, albeit in only 3.3% yield. Thus, the synthesis of chlorins requires the acid-catalyzed condensation of Eastern and Western halves.

In summary, following the acid-catalyzed condensation, various metallochlorins [Cu(II), Zn (II), Pd(II), and putative ClIn(III)] can be prepared via a AgOTf-free metal-mediated oxidative cyclization process. The indium chelate proved difficult to purify to homogeneity. Tetrapyrrolic complexes of Pd(II) and In(III) are potentially useful in the life sciences for photodynamic therapy, and ^{111}In chelates may be used for photosensitization, imaging, and/or radiotherapy applications. Although palladium and indium chelates of porphyrins are well known, there are only a few reports about Pd(II)[93] and In(III)[91,94] complexes of chlorins, hence this straightforward route to metallochlorins warrants further investigation.

(4) Route III—Route III employs the same Western half as in routes I and II, but uses a 1-bromo-9-formyldipyrrin as an Eastern half rather than a 1-bromo-9-formyldipyrromethane. This route was considered to be attractive owing to the greater stability of dipyrrins versus dipyrromethanes. The condensation should afford a 2,3,4,5-tetrahydrobilatriene intermediate, which is more oxidized than the 2,3,4,5-tetrahydrobiladiene formed in route II, and thereby require a lesser quantity of oxidant to yield the chlorin.

Dipyrromethane **8b** was treated with DDQ at room temperature in $CHCl_3$,[95] affording 1-bromo-9-formyldipyrrin **10b** in 50% yield (Scheme 7). Dipyrrin **10b** was subjected to *p*-TsOH-catalyzed condensation followed by metal-mediated oxidative cyclization. Absorption spectroscopy of the crude reaction mixture showed only a small amount of chlorin (<1%). The origin of the low yield appears to stem from the low reactivity of the formyl group in the dipyrrin moiety, because **10b** remained unreacted following attempted acid-catalyzed condensation.

(5) Route IV—Route IV employs the 9-formyltetrahydrodipyrrin (Western half) and a 1-bromodipyrromethane (Eastern half). 9-Formyltetrahydrodipyrrin **11** was obtained by standard Vilsmeier formylation of **5**.[96] The reaction of **1c** with NBS in THF at −78 °C afforded a mixture of the 1-bromodipyrromethane and 1,9-dibromodipyrromethane together with unreacted starting material. Column chromatography of the crude mixture afforded the known 1-bromodipyrromethane **12c**[75] in 35% yield. 1-Bromodipyrromethanes such as **12c** (as well as **12a** and **12b**, derived from **1a** and **1b**) are prone to decomposition during purification and routine handling.

The condensation of **11** and 1-bromodipyrromethane **12c** was carried out in CH_2Cl_2 in the presence of 5 equiv of *p*-TsOH·H_2O. Absorption spectroscopy of the crude reaction mixture showed a strong band at λ = 478 nm, attributed to the protonated tetrahydrobiladiene. After quenching with $NaHCO_3$, the crude biladiene was subjected to metal-mediated oxidative cyclization under standard conditions, affording the chlorin **ZnC-M[10]** in ~8% yield (Scheme 8). Attempts to use 1-cyano-5-phenyldipyrromethane[87] or 1-carboethoxy-5-phenyldipyrromethane[87] in place of **12c** did not give chlorin. The statistical bromination of

the dipyrromethane and the apparent instability of the resulting 1-bromodipyrromethane limited the utility of this route. Accordingly, no further studies of this route were performed.

(6) Route V—Route V avoids any functionalization of the starting dipyrromethane (Eastern half) by condensation of the dipyrromethane with a 9-formyltetrahydrodipyrrin (Western half). Subsequent 19-bromination of the resulting biladiene sets the stage for standard metal-mediated oxidative cyclization.

Treatment of a mixture of **11** and **1a** with 5 equiv of *p*-TsOH·H_2O in CH_2Cl_2/MeOH afforded the corresponding tetrahydrobiladiene **9b** (Scheme 9). (The tetrahydrobiladiene was formed in 21% yield if the peak molar absorption coefficient is 100,000 $M^{-1}cm^{-1}$.) Treatment of crude **9b** with NBS in THF at −78 °C afforded the putative 19-bromotetrahydrobiladiene **9b-Br**. The bromination proved difficult to verify: LD-MS did not show a peak corresponding to the expected **9b-Br**, and absorption spectroscopy did not show any changes compared with that of **9b**. Regardless, the crude reaction mixture after bromination was subjected to metal-mediated oxidative cyclization for 24 h, affording chlorin in ∼8% yield. The ^{1}H NMR and LD-MS analyses revealed the presence of various monobromochlorins in the purified sample. Separation of those species proved difficult, which makes this route completely unattractive.

(7) Comparison of routes—Of the routes investigated, route II and its variants appear most useful. Indeed, the streamlined route II was employed to prepare 145 mg of the benchmark chlorin **ZnC** lacking any meso- or β-pyrrole substituents. In addition, the AgOTf-free version of route II provides direct access to metallochlorins containing Cu(II), Zn(II), Pd(II), and ClIn (III).

3. Outlook

Three distinct methods of chlorin synthesis include modification of naturally occurring chlorins, reduction/derivatization of porphyrins, and de novo synthesis. Of these, de novo synthesis affords the most versatility. The reaction of 1-formyl-9-bromo-dipyrromethane and 2,3,4,5-tetrahydro-1,3,3-trimethyldipyrrin affords the corresponding chlorin bearing only a geminal dimethyl group at the 18-position. The reaction can be carried out with several variations: (i) in a three-step process (9-bromination of the 1-formyldipyrromethane, acid-catalyzed condensation to form the tetrahydrobiladiene-*ab*, and metal-mediated oxidative cyclization), (ii) in a streamlined manner where the 1-formyl-9-bromo-dipyrromethane is used in crude form, and/or (iii) with a AgOTf-free metal-mediated oxidative cyclization process. The AgOTf-free route provides direct access to a selection of metallochlorins. Similar reaction enables synthesis of a chlorin bearing one additional substituent at the 10-position. In conjunction with other synthetic methods, simple routes are now available for preparing stable chlorins that bear no substituents, a single substituent at the 5- or 10-position, or two or three distinct meso substituents. All of the synthetic chlorins prepared herein were stable upon routine handling in aerobic environments, including use of procedures such as chromatography, recrystallization, and standing in solution on the open benchtop. The ready synthesis and stability of the chlorins enabled the studies of derivatization chemistry and spectroscopic properties described in the companion papers.[81,82]

4. Experimental section

4.1. General methods

^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were collected at room temperature in $CDCl_3$ unless noted otherwise. NMR spectroscopy was not performed on Cu(II) chelates of the chlorins. Chlorins were analyzed by laser desorption mass spectrometry without a matrix (LD-MS).[76,97] Fast atom bombardment mass spectrometry (FAB-MS) data are reported for

the molecule ion or protonated molecule ion. Melting points are uncorrected. NBS was recrystallized (H_2O). Chromatography was performed with flash silica (80-200 mesh). Absorption and fluorescence spectra were obtained in toluene at room temperature.

4.2. Solvents

THF was distilled over sodium metal and benzophenone as required. Methanol, CH_3CN, and CH_2Cl_2 were used as anhydrous grade. Toluene used in absorption and fluorescence studies was spectroscopic grade. All other solvents were used as received.

4.3. Noncommercial compounds

Compounds **1a**,[84] **2-B**,[76] **2-T**,[85] **5**,[76,98] **7a–c**,[87] and **11**[96] were prepared as described in the literature. Compound **12c** was prepared as described in the Supporting Information of reference [75].

4.4. Synthesis of 5-substituted chlorins

4.4.1. 1-(3,5-Di-*tert*-butylbenzoyl)dipyrromethane (3-B)—Following a general procedure,[83] EtMgBr (16.4 mL, 16 mmol, 1.0 M in THF) was added to a solution of dipyrromethane **1a** (1.00 g, 6.48 mmol) in dry THF (10 mL) at room temperature under argon. The mixture was stirred at room temperature for 10 min and then cooled to −78 °C. A solution of *S*-2-pyridyl 3,5-di-*tert*-butylbenzothioate (**2-B**) (2.24 g, 6.84 mmol) in dry THF (10 mL) was added. The reaction mixture was maintained at −78 °C for 30 min, whereupon the cooling bath was removed. After 1 h, the reaction was quenched by addition of 100 mL of saturated aqueous NH_4Cl. The reaction mixture was extracted with CH_2Cl_2. The organic extract was washed with water, dried (Na_2SO_4), and concentrated under reduced pressure. Column chromatography [silica; packed and eluted with hexanes/CH_2Cl_2 (1:2), then eluted with hexanes/ethyl acetate (5:1)] afforded a white powder (1.76 g, 71%): mp 178–180 °C; ^{1}H NMR δ 1.34 (s, 18H), 4.09 (s, 2H), 6.04–6.08 (m, 1H), 6.09–6.13 (m, 1H), 6.14–6.17 (m, 1H), 6.55–6.59 (m, 1H), 6.78–6.82 (m, 1H), 7.61 (t, *J* = 1.8 Hz, 1H), 7.70 (d, *J* = 1.8 Hz, 2H), 8.76–8.96 (br s, 1H), 10.32–10.56 (br s, 1H); ^{13}C NMR δ 27.0, 31.6, 35.2, 106.6, 108.4, 110.3, 117.9, 122.5, 123.7, 126.3, 127.9, 131.0, 138.0, 140.5, 151.2, 186.4; FAB-MS obsd 363.2435, calcd 363.2436 [$(M + H)^+$, M = $C_{24}H_{30}N_2O$].

4.4.2. 1-(4-Methylbenzoyl)dipyrromethane (3-T)—Following the procedure described for **3-B**, EtMgBr (24.0 mL, 24 mmol, 1.0 M in THF) was added to a solution of dipyrromethane **1a** (1.46 g, 10.0 mmol) in dry THF (10 mL) at room temperature under argon. The mixture was stirred at room temperature for 10 min and then cooled to −78 °C. A solution of *S*-2-pyridyl 4-methylbenzothioate (**2-T**) (2.29 g, 10.0 mmol) in dry THF (10 mL) was added. The reaction mixture was maintained at −78 °C for 30 min, whereupon the cooling bath was removed. After 1 h, the standard workup afforded a white powder (1.03 g, 39%): mp 167–169 °C; ^{1}H NMR δ 2.43 (s, 3H), 4.08 (s, 2H), 6.03–6.06 (m, 1H), 6.08–6.12 (m, 1H), 6.14–6.17 (m, 1H), 6.53–6.56 (m, 1H), 6.80–6.83 (m, 1H), 9.04–9.20 (br, 1H), 10.72–10.88 (br, 1H); ^{13}C NMR δ 21.8, 27.0, 106.5, 108.4, 110.3, 117.8, 122.9, 128.2, 129.37, 129.39, 130.8, 136.0, 140.9, 142.8, 185.5; FAB-MS obsd 265.1338, calcd 265.1341 [$(M + H)^+$, M = $C_{17}H_{16}N_2O$].

4.4.3. 1-Bromo-9-(3,5-di-*tert*-butylbenzoyl)dipyrromethane (4-B)—Following a general procedure,[75] a solution of **3-B** (768 mg, 2.12 mmol) in dry THF (15 mL) was cooled to −78 °C under argon. NBS (377 mg, 2.12 mmol) was added, and the reaction mixture was stirred for 1 h at −78 °C. Hexanes (100 mL) and water (100 mL) were added. The mixture was allowed to warm to room temperature. The organic layer was separated. The aqueous phase was extracted with CH_2Cl_2. The hexanes and CH_2Cl_2 extracts were combined, dried ($NaHCO_3$) and concentrated *in vacuo* without heating. Column chromatography [silica packed

and eluted with hexanes/CH_2Cl_2 (1:1), then eluted with hexanes/ethyl acetate (7:1)] afforded a light brown powder (493 mg, 53%): mp 120 °C (dec.); ^{1}H NMR δ 1.31 (s, 18H), 4.08 (s, 2H), 5.92–5.94 (m, 1H), 5.95–5.97 (m, 1H), 6.18–6.20 (m, 1H), 6.86–6.88 (m, 1H), 7.61–7.64 (m, 1H), 7.70–7.73 (m, 2H), 9.66–9.76 (br s, 1H), 11.37–11.46 (br s, 1H); ^{13}C NMR (dec. in $CDCl_3$); FAB-MS obsd 441.1541, calcd 441.1541 [$(M + H)^+$, M = $C_{24}H_{29}BrN_2O$].

4.4.4. 19-Bromo-10-(3,5-di-*tert*-butylphenyl)-2,3,4,5-tetrahydro-1,3,3-trimethylbilene-*a* (6-B)—Following the procedure for preparing a tetrahydrobilene-*a*,[76] a sample of **4-B** (441 mg, 1.00 mmol) was reduced with $NaBH_4$ (378 mg, 10.0 mmol) in anhydrous THF/methanol (20 mL, 4:1). The resulting solid was dissolved in 10 mL of anhydrous CH_3CN, to which **5** (190 mg, 1.00 mmol) and TFA (77 μL, 1.0 mmol) were added. The reaction mixture was stirred at room temperature for 30 min. Then 10% aqueous $NaHCO_3$ (50 mL) was added, and the mixture was extracted with distilled CH_2Cl_2. The organic extract was washed with water, dried ($NaHCO_3$) and concentrated *in vacuo* without heating. The resulting brown solid was purified by chromatography [silica, hexanes/ethyl acetate (5:1) → ethyl acetate] to give a brown solid (325 mg, 53%; mixture of stereoisomers): mp 107–110 °C; ^{1}H NMR δ 0.91 (s, 3H), 1.06 (s, 3H), 1.26 (s, 18H), 1.86–1.90 (m, 3H), 2.18–2.34 (m, 2H), 2.56 (ABX, ^3J = 10.8 Hz, ^2J = 14.8 Hz, 1H), 2.71 (ABX, ^3J = 3.2 Hz, ^2J = 14.8 Hz, 1H), 3.60–3.64 (m, 1H), 3.85 (s, 2H), 5.27–5.31 (m, 1H), 5.70–5.99 (m, 6H), 7.05 (s, 2H), 7.26 (s, 1H), 7.81–7.90 (m, 1H), 8.21–8.39 (m, 1H), 8.97–9.10 (m, 1H); FAB-MS obsd 615.3062, calcd 615.3062 ($C_{36}H_{47}BrN_4$).

4.4.5. Zn(II)-5-(3,5-Di-*tert*-butylphenyl)-17,18-dihydro-18,18-dimethylporphyrin (ZnC-B^5)—Following the procedure for preparing chlorins,[76] a solution of **6-B** (283 mg, 0.460 mmol) in CH_3CN (46 mL) was treated with $Zn(OAc)_2$ (1.27 g, 6.90 mmol), AgOTf (355 mg, 1.38 mmol) and 2,2,6,6-tetramethylpiperidine (1.16 mL, 6.90 mmol). The reaction mixture was refluxed for 24 h. Standard workup and chromatography [silica, hexanes/CH_2Cl_2 (3:1)] gave a purple solid (45 mg, 17%): ^{1}H NMR δ 1.51 (s, 18H), 2.03 (s, 6H), 4.55 (s, 2H), 7.73–7.75 (m, 1H), 7.93–7.96 (m, 2H), 8.58–8.60 (m, 1H), 8.62 (s, 1H), 8.68–8.71 (m, 2H), 8.73–8.75 (m, 1H), 8.76–8.78 (m, 1H), 8.86–8.88 (m, 1H), 9.08–9.10 (m, 1H), 9.62 (s, 1H); LD-MS obsd 589.25; FAB-MS obsd 590.2380, calcd 590.2388 ($C_{36}H_{38}N_4Zn$); λ_{abs} 405 (log ε = 5.50), 605 (4.89) nm; λ_{em} 609 nm.

4.4.6. Zn(II)-17,18-Dihydro-18,18-dimethyl-5-(4-methylphenyl)porphyrin (ZnC-T^5)—Following the general procedure for preparing chlorins,[75] a solution of **3-T** (264 mg, 1.00 mmol) in 10 mL of dry THF was cooled to −78 °C under argon. NBS (178 mg, 1.00 mmol) was added, and the reaction mixture was stirred for 1 h at −78 °C. Hexanes (50 mL) and water (50 mL) were added, and the mixture was allowed to warm to room temperature. The organic layer was separated. The aqueous phase was extracted with CH_2Cl_2. The hexanes and CH_2Cl_2 extracts were combined, dried ($NaHCO_3$) and concentrated *in vacuo* without heating, affording crude **4-T** (367 mg, quantitative): ^{1}H NMR δ 2.43 (s, 3H), 4.08 (s, 2H), 6.03–6.06 (m, 1H), 6.08–6.12 (m, 1H), 6.14–6.17 (m, 1H), 6.53–6.56 (m, 1H), 6.80–6.83 (m, 1H), 9.04–9.20 (br, 1H), 10.72–10.88 (br, 1H). Following the procedure for preparing a tetrahydrobilene-*a*,[76] a sample of crude **4-T** (343 mg, 1.00 mmol) was reduced with $NaBH_4$ (378 mg, 10.0 mmol) in anhydrous THF/methanol (10 mL, 4:1). The resulting solid was dissolved in anhydrous CH_3CN (10 mL), to which **5** (190 mg, 1.00 mmol) and TFA (77 μL, 1.0 mmol) were added. The reaction mixture was stirred at room temperature for 30 min. Then 10% aqueous $NaHCO_3$ (50 mL) was added. The mixture was extracted with distilled CH_2Cl_2. The organic extract was washed with water, dried ($NaHCO_3$) and concentrated *in vacuo* without heating. The resulting brown solid was purified by chromatography [silica, hexanes/ethyl acetate (5:1) → ethyl acetate] to give **6-T** as a brown solid (110 mg, 21%). Following the procedure for preparing chlorins,[76] a solution of **6-T** (59.3 mg, 0.115 mmol) in CH_3CN (11

mL) was treated with $Zn(OAc)_2$ (317 mg, 1.73 mmol), AgOTf (88.6 mg, 0.345 mmol) and 2,2,6,6-tetramethylpiperidine (0.29 mL, 1.7 mmol). The reaction mixture was refluxed exposed to air for 24 h. Standard workup and chromatography [silica, hexanes/CH_2Cl_2 (3:1)] gave a purple solid (19.5 mg, 34%): ^{1}H NMR δ 2.02 (s, 6H), 2.68 (s, 3H), 4.50 (s, 2H), 7.49–7.52 (m, 2H), 7.95–8.00 (m, 2H), 8.61 (s, 1H), 8.62 (s, 1H), 8.64–8.66 (m, 1H), 8.67–8.70 (m, 1H), 8.72–8.75 (m, 1H), 8.82–8.85 (m, 1H), 8.99–9.02 (m, 1H), 9.54 (s, 1H); ^{13}C NMR δ 21.8, 31.2, 45.3, 50.5, 94.9, 96.3, 109.1, 124.4, 126.8, 127.1, 127.6, 128.1, 129.4, 132.8, 133.4, 133.9, 137.2, 139.7, 146.00, 146.01, 146.7, 147.4, 153.4, 153.7, 159.7, 170.6; LD-MS obsd 491.1; FAB-MS obsd 492.1295, calcd 492.1292 ($C_{29}H_{24}N_4Zn$); λ_{abs} 405, 605 nm; λ_{em} 608 nm.

4.5. Precursors for examination of routes I-V

4.5.1. 1-Bromo-9-formyl-5-phenyldipyrromethane (8b)—Following the procedure for the preparation of **8c**,[77] bromination of **7b** (150 mg, 0.600 mmol) with NBS gave a crude solid that upon recrystallization (EtOH/H_2O, 4:1) afforded a light brown solid (108 mg, 55%): mp 133 °C (dec.); ^{1}H NMR (THF-d_8) δ 5.42 (s, 1H), 5.59–5.61 (m, 1H), 5.86–5.88 (m, 1H), 5.92–5.94 (m, 1H), 6.79–6.81 (m, 1H), 7.16–7.30 (m, 5H), 9.40 (s, 1H), 10.51 (br s, 1H) 11.21 (br s, 1H); ^{13}C NMR δ 44.3, 97.2, 109.3, 109.5, 110.3, 120.4, 126.9, 128.3, 128.5, 133.5, 133.8, 141.7, 142.2, 177.9. Anal Calcd for $C_{16}H_{13}BrN_2O$: C, 58.38; H, 3.98; N, 8.51. Found: C, 58.31; H, 3.92; N, 8.45.

4.5.2. 1-Bromo-9-formyl-5-phenyldipyrrin (10b)—A solution of **8b** (0.033 g, 1.0 mmol) in $CHCl_3$ (2 mL) was treated with a suspension of DDQ (0.027 g, 1.0 mmol) in $CHCl_3$ (1 mL). The mixture was stirred at room temperature for 1 h. The mixture was concentrated. The residue was chromatographed (silica, CH_2Cl_2) to afford an orange solid (0.016 g, 50%): mp 121–123 °C; ^{1}H NMR δ 6.35 (d, J = 4.4 Hz, 1H), 6.20 (d, J = 4.4 Hz, 1H), 6.75 (d, J = 4.4 Hz, 1H), 6.88 (d, J = 4.4 Hz, 1H), 7.42–7.52 (m, 5H), 9.72 (s, 1H); ^{13}C NMR δ 119.7, 121.7, 128.3, 129.7, 129.8, 130.9, 137.6, 138.9, 150.6, 152.2, 180.3; FAB-MS obsd 327.0129, calcd 327.0133 [(M + H)$^+$, M = $C_{16}H_{11}N_2OBr$]; λ_{abs} 437 nm.

4.5.3. 2,3,4,5-Tetrahydro-9-(*N*-propyliminomethyl)-1,3,3-trimethyldipyrrin (PrN-8b)—Following a general procedure,[92] a sample of **11** (0.044 g, 0.20 mmol) was dissolved in 1-aminopropane (1 mL) at room temperature. After stirring for 1 h, the 1-aminopropane was removed by distillation under reduced pressure. The crude product was used in the next step without further purification: ^{1}H NMR δ 0.92 (s, 3H), 0.94 (t, J = 7.4 Hz, 3H), 1.09 (s, 3H), 2.04 (m, 3H), 1.61–1.70 (m, 2H), 2.27, 2.36 (AB, J = 16.6 Hz, 2H), 2.66 (ABX, ^2J = 14.8 Hz, ^3J = 10.6 Hz, 1H), 2.75 (ABX, ^2J = 14.8 Hz, ^3J = 4.0 Hz, 1H), 3.39–3.51 (m, 2H), 3.64–3.69 (m, 1H), 5.99 (d, J = 3.8 Hz, 1H), 6.35 (d, J = 3.8 Hz, 1H), 7.96 (s, 1H).

4.6. Route I

4.6.1. Attempted synthesis of ZnC-P^{10} using TFA—A solution of **7b** (32 mg, 0.10 mmol) in THF/MeOH (40 mL, 3:1) was treated with $NaBH_4$ (0.19 g, 5.0 mmol) and stirred at room temperature for 30 min. TLC [silica, CH_2Cl_2/ethyl acetate (5:1)] showed complete consumption of starting material. The reaction was quenched by addition of saturated aqueous NH_4Cl (~50 mL). The resulting mixture was extracted with ether. The organic extract was washed (water and brine) and dried ($MgSO_4$). Acetonitrile (1 mL) was added, and the volatile solvent (predominantly ether) was evaporated under low vacuum. (Note that complete evaporation of solvent caused complete decomposition of the carbinol.) A sample of **5** (19 mg, 0.10 mmol) was added, and the resulting solution was treated with TFA (8 μL, 0.1 mmol). The reaction mixture was stirred at room temperature for 30 min and then diluted with CH_3CN (9 mL). Samples of 2,2,6,6-tetramethylpiperidine (0.506 mL, 3.00 mmol), anhydrous $Zn(OAc)_2$ (0.276 g, 1.5 mmol) and AgOTf (0.077 g, 0.3 mmol) were added. The resulting mixture was refluxed exposed to air for 20 h. The yield observed spectroscopically was <1%. The

mixture was concentrated and filtered through silica (CH_2Cl_2) to afford a green solid. Characterization data (LD-MS, UV-vis) were identical as described for **ZnC-P[10]**.

4.6.2. Attempted synthesis of ZnC using $BF_3{\cdot}O(Et)_2$—A solution of **5** (38.0 mg, 0.198 mmol) and **8a** (50.0 mg, 0.198 mmol) in dry CH_3CN (1.98 mL) was treated with $BF_3{\cdot}O(Et)_2$ (25.0 μL, 0.198 mmol) and stirred for 15 min at room temperature. No reaction occurred upon examination by TLC, whereupon additional $BF_3{\cdot}O(Et)_2$ (50.0 μL) was added. The mixture was stirred for 20 min, quenched with water and extracted with CH_2Cl_2. The solvent was removed under reduced pressure to give a brown oil. TLC analysis and ^1H NMR spectroscopy of the crude mixture revealed only starting material **8a**.

4.7. Route II

4.7.1. Condensation study—A solution of **5** (10.0 mg, 39.5 μmol) and **8a** (7.50 mg, 39.5 μmol) in CH_2Cl_2 under argon was treated with *p*-TsOH·H_2O (37.6 mg, 0.198 mmol) in MeOH. The quantity of each of **5**, **8a**, and *p*-TsOH·H_2O was identical in each experiment, while the quantity of solvent was varied from 5.7 mL (6.92 mM) to 0.77 mL (51.3 mM). In each case, the ratio of CH_2Cl_2/methanol was held constant at 4:1. For example, samples of **5** and **8a** were dissolved in CH_2Cl_2 (2.34 mL) and subsequently treated with *p*-TsOH·H_2O in MeOH (0.59 mL) to give the desired concentration of 13.5 mM. The mixture was stirred for 30 min under argon and quenched by addition of 10% aqueous $NaHCO_3$ (10 mL). After extracting the mixture with CH_2Cl_2, the extract was dried (Na_2SO_4) and filtered. The filtrate was concentrated to give a brown solid. The crude solid was dissolved in CH_3CN (4 mL, 10 mM assuming quantitative formation) and treated with $Zn(OAc)_2$ (109 mg, 0.593 mmol), AgOTf (30.4 mg, 0.119 mmol), and 2,2,6,6-tetramethylpiperidine (0.101 mL, 0.593 mmol). The reaction mixture was heated at 70 °C for 19 h exposed to air. The mixture was concentrated. The resulting black residue was chromatographed [silica, CH_2Cl_2], affording a bluish-green solid. The isolated chlorin yield was then recorded after drying under vacuum, affording 1.8 mg (11%) of **ZnC**.

A study of the concentration dependence of the condensation conditions where 5 mol equiv of *p*-TsOH·H_2O was employed led to the following yields of **ZnC**: 10% (7 mM), 11% (14 mM), 22% (26 mM), and 22% (51 mM).

4.7.2. Route II: Zn(II)-17,18-Dihydro-18,18-dimethyl-10-phenylporphyrin (ZnC-P[10]) A mixture of **8b** (0.165 g, 0.500 mmol) and **5** (0.095 g, 0.50 mmol) in dry CH_2Cl_2 (10.8 mL) was treated with a solution of *p*-TsOH·H_2O (0.475 g, 2.50 mmol) in anhydrous MeOH (8.25 mL). The resulting red solution was stirred at room temperature for 30 min. A sample of 2,2,6,6-tetramethylpiperidine (0.630 mL, 3.71 mmol) was added. The mixture was concentrated. The resulting yellow solid was dissolved in CH_3CN (50 mL). Samples of 2,2,6,6-tetramethylpiperidine (2.10 mL, 12.4 mmol), anhydrous $Zn(OAc)_2$ (1.37 g, 7.50 mmol) and AgOTf (0.385 g, 1.50 mmol) were added. The mixture was refluxed in the presence of air for 20 h. The mixture was concentrated. The resulting black residue was chromatographed [silica, CH_2Cl_2/hexanes (1:1)] to afford a violet-green solid (79 mg, 33%): ^1H NMR δ 2.04 (s, 6H), 4.53 (s, 2H), 7.67–7.72 (m, 3H), 8.08–8.10 (m, 2H), 8.52 (d, J = 4.5 Hz, 1H), 8.62–8.64 (m, 2H), 8.69–8.70 (m, 2H), 8.78 (d, J = 4.1 Hz, 1H), 8.86 (d, J = 4.1 Hz, 1H), 9.09 (d, J = 4.1 Hz, 1H), 9.62 (s, 1H); ^{13}C NMR δ 31.0, 45.4, 50.4, 94.3, 97.0, 109.4, 123.8, 126.79, 126.84, 127.3, 127.6, 128.2, 129.2, 132.9, 133.3, 133.9, 142.6, 145.86, 145.97, 146.5, 147.4, 153.1, 154.0, 159.2, 171.0; LD-MS obsd 477.8; ESI-MS obsd 478.1154, calcd 478.1136 ($C_{28}H_{22}N_4Zn$); λ_{abs} 405 (log ε = 5.44), 605 (4.83) nm; λ_{em} 608 nm.

4.7.3. Streamlined route II (ZnC)—A solution of **7a** (344 mg, 2.00 mmol) in THF (40 mL) was treated with NBS (356 mg, 2.00 mmol) at −78 °C. After 1 h the mixture was allowed to warm to −20 °C. A mixture of water (30 mL) and hexanes (30 mL) was added. Excess

CH_2Cl_2 was added. The organic layer was separated, dried (Na_2SO_4) and concentrated. The resulting solid was dissolved in dry CH_2Cl_2 (43 mL), to which a sample of **5** (0.360 g, 2.00 mmol) and a solution of *p*-TsOH·H_2O (1.92 g, 10.0 mmol) in MeOH (33 mL) were added. The red mixture was stirred for 30 min. A sample of 2,2,6,6-tetramethylpiperidine (2.52 mL, 14.8 mmol) was added. The mixture was concentrated. The residue was dissolved in CH_3CN (200 mL). Anhydrous $Zn(OAc)_2$ (5.52 g, 30.0 mmol), AgOTf (1.55 g, 6.00 mmol) and 2,2,6,6-tetramethylpiperidine (8.40 mL, 49.5 mmol) were added. The mixture was refluxed exposed to air until the absorption spectrum showed no further change (typically 5-10 h). The mixture was concentrated. The resulting black mixture was chromatographed [silica, hexanes/CH_2Cl_2 (1:1)] to afford a blue-green solid (0.145 g, 18%). The characterization data ^{1}(H NMR, ^{13}C NMR, LD-MS, FAB-MS, UV-Vis) were consistent with those reported previously.[77]

4.7.4. AgOTf-free Route II: Pd(II)-17,18-Dihydro-18,18-dimethylporphyrin (PdC) Following the AgOTf-free route II, samples of **5** (95 mg, 0.50 mmol) and **8a** (126 mg, 0.500 mmol) were dissolved in CH_2Cl_2 (15 mL). A solution of *p*-TsOH·H_2O (475.0 mg, 2.50 mmol) in anhydrous MeOH (5 mL) was added. The resulting mixture was stirred for 30 min and then treated with 2,2,6,6-tetramethylpiperidine (2.50 mL). The mixture was concentrated. The resulting yellow solid was dissolved in CH_3CN (50 mL). Samples of 2,2,6,6-tetramethylpiperidine (2.54 mL, 15.0 mmol) and $Pd(OAc)_2$ (0.338 g, 1.50 mmol) were added. The resulting mixture was refluxed exposed to air for 1 h. The resulting dark-green mixture was concentrated and chromatographed [silica, hexanes/CH_2Cl_2 (1:1)] to afford a violet-green solid (7.5 mg, 3%): H NMR δ 2.02 (s, 6H), 4.62 (s, 2H), 8.98 (d, *J* = 4.4 Hz, 1H), 8.73 (s, 1H), 8.74 (d, *J* = 4.4 Hz, 1H), 8.81 (s, 1H), 8.95–8.96 (m, 2H), 8.98 (d, *J* = 4.4 Hz, 1H), 8.99 (d, *J* = 4.4 Hz, 1H), 9.72 (s, 1H), 9.74 (s, 1H); LD-MS obsd 443.7; FAB-MS obsd 444.0557, calcd 444.0566 ($C_{22}H_{18}N_4Pd$); λ_{abs} 388, 585 nm.

4.7.5. Cu(II)-17,18-Dihydro-18,18-dimethylporphyrin (CuC)—Following the AgOTf-free route II, samples of **5** (19.0 mg, 100 μmol) and **8a** (25.3 mg, 100 μmol) were dissolved in CH_2Cl_2 (3 mL). A solution of *p*-TsOH·H_2O (95.0 mg, 500 μmol) in anhydrous MeOH (1 mL) was added. The resulting mixture was stirred for 30 min and then neutralized with 2,2,6,6-tetramethylpiperidine (500 μL). The mixture was concentrated. The resulting yellow solid was dissolved in EtOH (4 mL). Samples of $Cu(OAc)_2$ (39.2 mg, 200 μmol) and KOH (42.0 mg, 750 μmol) were added. The resulting mixture was refluxed exposed to air for 21 h. The resulting mixture was concentrated and chromatographed (silica/CH_2Cl_2) to afford a green solid (2.2 mg, 5%): LD-MS obsd 400.6; FAB-MS obsd 401.0837, calcd 401.0827 ($C_{22}H_{18}N_4Cu$); λ_{abs} 396, 598 nm.

4.7.6. Pd(II)-17,18-Dihydro-18,18-dimethyl-10-phenylporphyrin (PdC-P^{10})— Samples of **5** (19.0 mg, 100 μmol) and **8b** (32.6 mg, 100 μmol) were dissolved in CH_2Cl_2 (3 mL). A solution of *p*-TsOH·H_2O (95.0 mg, 500 μmol) in anhydrous MeOH (1 mL) was added. The resulting mixture was stirred for 30 min and then neutralized with 2,2,6,6-tetramethylpiperidine (500 μL). The mixture was concentrated. The resulting yellow solid was dissolved in CH_3CN (10 mL). Samples of 2,2,6,6-tetramethylpiperidine (0.509 mL, 3.00 mmol) and $Pd(OAc)_2$ (0.338 g, 1.50 mmol) were added. The resulting mixture was refluxed exposed to air for 1 h. The resulting dark-green mixture was concentrated and chromatographed (silica, CH_2Cl_2) to afford a violet solid (6.0 mg, 12%): ^{1}H NMR δ 2.02 (s, 6H), 4.60 (s, 2H), 7.69–7.72 (m, 3H), 8.04–8.07 (m, 2H), 8.53 (d, *J* = 4.8 Hz, 1H), 8.57–8.58 (m, 2H), 8.69 (s, 1H), 8.72 d, *J* = 4.8 Hz, 1H), 8.79 (s, 1H), 8.84 d, *J* = 4.8 Hz, 1H), 8.96 d, *J* = 4.8 Hz, 1H), 9.69 (s, 1H); LD-MS obsd 519.9; FAB-MS obsd 520.0901, calcd 520.0879 ($C_{28}H_{22}N_4Pd$); λ_{abs} 394, 587 nm.

4.7.7. Cu(II)-17,18-Dihydro-18,18-dimethyl-10-phenylporphyrin (CuC-P^{10})—

Following the AgOTf-free route II, samples of **5** (19.0 mg, 100 μmol) and **8b** (32.9 mg, 100 μmol) were dissolved in CH_2Cl_2 (3 mL). A solution of *p*-TsOH·H_2O (95.0 mg, 500 μmol) in anhydrous MeOH (1 mL) was added. The resulting mixture was stirred for 30 min and then neutralized with 2,2,6,6-tetramethylpiperidine (500 μL). The mixture was concentrated. The resulting yellow solid was dissolved in EtOH (5 mL). Samples of KOH (42 mg, 0.75 mmol) and $Cu(OAc)_2$ (37.2 mg, 0.200 mmol) were added. The resulting mixture was refluxed exposed to air for 21 h. The resulting dark-green mixture was concentrated and chromatographed (silica, CH_2Cl_2) to afford a green solid (7.3 mg, 15%): LD-MS 476.9; FAB-MS obsd 477.1153, calcd 477.1140 ($C_{28}H_{22}N_4Cu$); λ_{abs} 394, 587 nm.

4.8. Routes III and IV

4.8.1. General procedure for attempted chlorin formation—

Samples of an Eastern half (0.10 mmol) and a Western half (0.10 mmol) were dissolved in anhydrous CH_2Cl_2 (4 mL) and treated with *p*-TsOH·H_2O (0.095 g, 0.50 mmol). The resulting mixture was stirred for 15 min at room temperature. The reaction was quenched by addition of 10% aqueous $NaHCO_3$. The resulting mixture was extracted with CH_2Cl_2. The organic phase was washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was dissolved in CH_3CN (10 mL) and treated with anhydrous $Zn(OAc)_2$ (0.276 g, 1.50 mmol), AgOTf (0.077 g, 0.30 mmol) and 2,2,6,6-tetramethylpiperidine (0.504 mL, 3.00 mmol). The reaction mixture was refluxed for 20 h exposed to air, during which time the spectroscopic yield of chlorin was checked. This procedure was applied for the reaction of **12c** + **11** to give **ZnC-M^{10}** (8% yield), and **10b** + **5** to give **ZnC-P^{10}** (<1% yield).

4.9. Route V

4.9.1. Zn(II)-17,18-Dihydro-18,18-dimethyl-10-phenylporphyrin (ZnC-P^{10})—

A solution of **1b** (0.111 g, 0.500 mmol) and **11** (0.109 g, 0.500 mmol) in CH_2Cl_2 (15 mL) was treated with a solution of *p*-TsOH·H_2O (0.478 g, 2.5 mmol) in MeOH (5 mL). The resulting mixture was stirred at room temperature for 30 min. The reaction mixture was neutralized with excess triethylamine, washed with water and brine, dried (Na_2SO_4), and concentrated to afford crude **9b** as an orange solid. Crude **9b** was dissolved in dry THF (5 mL) and treated with NBS (0.089 g, 0.50 mmol) at −78 °C. The reaction mixture was stirred at −78 °C for 1 h, allowed to warm to ∼ −20 °C, and then quenched by addition of a mixture of hexanes (5 mL) and water (5 mL). The resulting mixture was extracted with CH_2Cl_2. The organic extract was washed with water and brine, dried (Na_2SO_4) and concentrated to afford the crude 19-bromotetrahydrobiladiene (**9b-Br**) as a brown solid. The crude **9b-Br** was dissolved in CH_3CN (50 mL), to which anhydrous $Zn(OAc)_2$ (1.38 g, 7.50 mmol), AgOTf (0.385 g, 1.50 mmol) and 2,2,6,6-tetramethylpiperidine (2.52 mL, 15.0 mmol) were added. The reaction mixture was refluxed for 20 h. Standard workup and chromatography [silica, hexanes/CH_2Cl_2 (1:1)] gave a bluish-green solid (15 mg). The ^{1}H NMR and LD-MS data showed the presence of a significant amount of bromochlorins.

Acknowledgment

This work was supported by the NIH (GM36238). Mass spectra were obtained at the Mass Spectrometry Laboratory for Biotechnology at North Carolina State University. Partial funding for the facility was obtained from the North Carolina Biotechnology Center and the NSF.

References

1. Smith, JHC.; Benitez, A. Modern Methods of Plant Analysis. Paech, K.; Tracey, MV., editors. IV. Springer-Verlag; Berlin: 1955. p. 142-196.
2. Strain HH, Thomas MR, Katz JJ. Biochim. Biophys. Acta 1963;75:306–311. [PubMed: 14104939]

3. (a) Wang J-J. Chin. J. Org. Chem 2005;25:1353–1371. (b) Pavlov VY, Ponomarev GV. Chem. Heterocyclic Compounds 2004;40:393–425.Pandey, RK.; Zheng, G. The Porphyrin Handbook. Kadish, KM.; Smith, KM.; Guilard, R., editors. 6. Academic Press; San Diego, CA: 2000. p. 157-230.Hynninen, PH. Chlorophylls. Scheer, H., editor. CRC Press; Boca Raton, FL, USA: 1991. p. 145-209.
4. Vicente, MGH. The Porphyrin Handbook. Kadish, KM.; Smith, KM.; Guilard, R., editors. 1. Academic Press; San Diego, CA: 2000. p. 149-199.Jaquinod, L. The Porphyrin Handbook. Kadish, KM.; Smith, KM.; Guilard, R., editors. 1. Academic Press; San Diego, CA: 2000. p. 201-237.
5. Dorough GD, Huennekens FM. J. Am. Chem. Soc 1952;74:3974–3976.
6. Eisner U. J. Chem. Soc 1957:3461–3469.
7. (a) Wang TY, Chen JR, Ma JS. Dyes Pigments 2002;52:199–208. (b) Shan X, Wang T, Li S, Yang L, Fu L, Yang G, Wang Z, Ma JS. J. Photochem. Photobiol. B: Biol 2006;82:140–145.
8. Bonnett R, Djelal BD, Nguyen A. J. Porphyrins Phthalocyanines 2001;5:652–661.
9. Brückner C, Dolphin D. Tetrahedron Lett 1995;36:3295–3298.
10. (a) Sutton JM, Fernandez N, Boyle RW. J. Porphyrins Phthalocyanines 2000;4:655–658. (b) Wang TY, Liu HL, Chen JR, Liu FG, Gu Y, Ma JS. Bioorg. Med. Chem. Lett 2001;11:2049–2052. [PubMed: 11454478] (c) Sutton JM, Clarke OJ, Fernandez N, Boyle RW. Bioconjugate Chem 2002;13:249–263. (d) Ferrand Y, Bourré L, Simonneaux G, Thibaut S, Odobel F, Lajat Y, Patrice T. Bioorg. Med. Chem. Lett 2003;13:833–835. [PubMed: 12617902]
11. (a) Kuz'mitskii VA. J. Appl. Spectrosc 2005;72:360–370. (b) Linnanto J, Korppi-Tommola J. Phys. Chem. Chem. Phys 2000;2:4962–4970. (c) Almlöf J, Fischer TH, Gassman PG, Ghosh A, Häser M. J. Phys. Chem 1993;97:10964–10970.
12. Sevchenko AN, Solov'ev KN, Shkirman SF, Sarzhevskaya MV. Dokl. Akad. Nauk SSSR 1963:1391–1394.(Eng. Translation pp 1151–1155)
13. Sevchenko AN, Solov'ev KN, Mashenkov VA, Shkirman SF. Sov. Phys.–Dokl 1966;10:778–780.
14. Gradyushko AT, Sevchenko AN, Solovyov KN, Tsvirko MP. Photochem. Photobiol 1970;11:387–400. [PubMed: 5456267]
15. Solov'ev KN, Mashenkov VA, Gradyushko AT, Turkova AE, Lezina VP. Zh. Prikl. Specktr 1970;13:339–345.(Eng. Translation pp 1106–1111)
16. Gurinovich, GP.; Sevchenko, AN.; Solov'ev, KN., editors. Spectroscopy of Chlorophyll and Related Compounds. National Technical Information Service, U.S. Department of Commerce; Springfield, VA: 1971. p. 330-332.
17. Sinyakov GN, Poznyak AL, Gurinovich GP. Zh. Prikl. Specktr 1972;16:732–734.(Eng. Translation pp 543–545)
18. van der Bent SJ, de Jager A, Schaafsma TJ. Rev. Sci. Instrum 1976;47:117–121.
19. van der Bent SJ, Schaafsma TJ. J. Chem. Phys 1978;68:1857–1861.
20. Völker S, Macfarlane RM. J. Chem. Phys 1980;73:4476–4482.
21. Dicker AIM, Noort M, Thijssen HPH, Volker S, van der Waals JH. Chem. Phys. Lett 1981;78:212–218.
22. Dicker AIM, Dobkowski J, Noort M, Völker S, van der Waals JH. Chem. Phys. Lett 1982;88:135–137.
23. Keegan JD, Stolzenberg AM, Lu Y-C, Linder RE, Barth G, Moscowitz A, Bunnenberg E, Djerassi C. J. Am. Chem. Soc 1982;104:4317–4329.
24. Dicker AIM, Johnson LW, Noort M, van der Waals JH. Chem. Phys. Lett 1983;94:14–20.
25. Burkhalter FA, Suter GW, Wild UP, Samoilenko VD, Rasumova NV, Personov RI. Chem. Phys. Lett 1983;94:483–487.
26. Gladkov LL, Ksenofontova NM, Solov'ev KN, Starukhin AS, Shul'ga AM, Gradyushko AT. Zh. Prikl. Specktr 1983;38:598–605.(Eng. Translation pp 435–440)
27. Arabei SM, Egorova GD, Solov'ev KN, Shkirman SF. Zh. Prikl. Specktr 1986;44:117–123.(Eng. Translation pp 96–100)
28. Avarmaa RA, Rebane KK. Spectrochim. Acta 1985;41A:1365–1380.
29. Dzilinski K, Sinyakov GN, Shul'ga AM, Zotov NI. J. Structural Chem 1990;31:227–231.

30. Ellervee A, Jaaniso R, Kikas J, Laisaar A, Suisalu A, Shcherbakov V. Chem. Phys. Lett 1991;176:472–476.
31. De Caro C, Renn A, Wild UP. Appl. Optics 1991;30:2890–2898.
32. Ellervee A, Hizhnyakov VV, Kikas J, Laisaar A, Suisalu A. J. Luminescence 1992;53:223–226.
33. Kulikov S, Galaup JP. J. Luminescence 1992;53:239–243.
34. Al'shits EI, Kharlamov BM, Ulitsky NI. J. Opt. Soc. Am. B 1992;9:950–955.
35. Ellervee A, Kikas J, Laisaar A, Shcherbakov V, Suisalu A. J. Opt. Soc. Am. B 1992;9:972–977.
36. Al'shits EI, Kharlamov BM, Ulitsky NI, Nekhaev DV. Chem. Phys 1992;163:405–411.
37. Miles JR, Sarre PJ. J. Chem. Soc. Faraday Trans 1992;88:1075–1076.
38. Miles JR, Sarre PJ. J. Chem. Soc. Faraday Trans 1993;89:2269–2276.
39. Ellervee A, Kikas J, Laisaar A, Suisalu A. J. Luminescence 1993;56:151–156.
40. Kikas J, Schellenberg P, Friedrich J. Chem. Phys. Lett 1993;207:143–147.
41. Schellenberg P, Friedrich J, Kikas J. J. Chem. Phys 1994;100:5501–5507.
42. Shulga AM, Sinyakov GN, Filatov IV, Gurinovich GP, Dzilinski K. J. Mol. Struct 1995;348:65–68.
43. Dzilinski K, Synyakov GN, Shulga AM, Filatov IV, Gurinovich GP. Radiat. Phys. Chem 1995;45:923–928.
44. Shulga AM, Sinyakov GN, Filatov IV, Gurinovich GP, Dzilinski K. Biospectroscopy 1995;1:223–234.
45. Maniloff ES, Graf FR, Gygax H, Altner SB, Bernet S, Renn A, Wild UP. Chem. Phys 1995;193:173–180.
46. Müschenborn H-J, Wild UP. Optoelectronics–Dev. Technol 1995;10:311–332.
47. Huang W-Y, Riper EV, Johnson LW. Spectrochim. Acta Part A 1996;52:761–769.
48. Kikas J, Suisalu A, Zazubovich V. Mol. Cryst. Liq. Cryst 1996;291:215–222.
49. den Hartog FTH, Bakker MP, Koedijk JMA, Creemers TMH, Völker S. J. Luminescence 1996;66 & 67:1–7.
50. Altmann RB, Kador L, Haarer D. Chem. Phys 1996;202:167–174.
51. Kikas J, Suisalu A, Zazubovich V, Vois P. J. Chem. Phys 1996;104:4434–4440.
52. Huang W-Y, Rebane A, Wild UP, Johnson LW. J. Luminescence 1997;71:237–243.
53. Zazubovich V, Suisalu A, Kikas J. J. Luminescence 1998;76 & 77:615–618.
54. den Hartog FTH, Bakker MP, Silbey RJ, Völker S. Chem. Phys. Lett 1998;297:314–320.
55. Suisalu A, Zazubovich V, Kikas J, Friebel J, Friedrich J. Europhys. Lett 1998;44:613–619.
56. Kikas J, Laisaar A, Suisalu A, Kuznetsov A, Ellervee A. Phys. Rev. B 1998;57:14–17.
57. den Hartog FTH, van Papendrecht C, Silbey RJ, Völker S. J. Chem. Phys 1999;110:1010–1016.
58. Singh A, Huang W-Y, Johnson LW. J. Phys. Chem. A 2000;104:894–898.
59. Drobizhev M, Karotki A, Rebane A. Chem. Phys. Lett 2001;334:76–82.
60. Singh A, Huang W-Y, Egbujor R, Johnson LW. J. Phys. Chem. A 2001;105:5778–5784.
61. Zazubovich V, Suisalu A, Kikas J. Phys. Rev. B 2001;64(104203):1–7.
62. Singh A, Johnson LW. Spectrochim. Acta Part A 2002;58:1573–1576.
63. Singh A, Huang W-Y, Johnson LW. Spectrochim. Acta Part A 2002;58:2177–2183.
64. Renge I. J. Luminescence 2002;98:213–220.
65. Karotki A, Kruk M, Drobizhev M, Rebane A. J. Mod. Optics 2002;49:379–390.
66. Renn A, Wild UP, Rebane A. J. Phys. Chem. A 2002;106:3045–3060.
67. Berezin KV, Nechaev VV. Chem. Natural Compounds 2003;39:540–548.
68. Renge I. Chem. Phys 2003;295:255–268.
69. Berezin KV, Nechaev VV. Opt. Spectros 2004;97:707–713.
70. Eisner U, Linstead RP. J. Chem. Soc 1955:3749–3754.
71. Eisner U, Linstead RP. J. Chem. Soc 1955:3742–3749.
72. Egorova GD, Solov'ev KN, Shul'ga AM. J. Gen. Chem. USSR 1967;37:333–336.
73. Seely GR, Talmadge K. Photochem. Photobiol 1964;3:195–206.

74. Montforts F-P, Gerlach B, Höper F. Chem. Rev 1994;94:327–347.
75. Strachan J-P, O'Shea DF, Balasubramanian T, Lindsey JS. J. Org. Chem 2000;65:3160–3172. [PubMed: 10814212]
76. Taniguchi M, Ra D, Mo G, Balasubramanian T, Lindsey JS. J. Org. Chem 2001;66:7342–7354. [PubMed: 11681947]
77. Laha JK, Muthiah C, Taniguchi M, McDowell BE, Ptaszek M, Lindsey JS. J. Org. Chem 2006;71:4092–4102. [PubMed: 16709048]
78. O'Neal WG, Roberts WP, Ghosh I, Wang H, Jacobi PA. J. Org. Chem 2006;71:3472–3480. [PubMed: 16626128]
79. Balasubramanian T, Strachan JP, Boyle PD, Lindsey JS. J. Org. Chem 2000;65:7919–7929. [PubMed: 11073599]
80. Taniguchi M, Kim MN, Ra D, Lindsey JS. J. Org. Chem 2005;70:275–285. [PubMed: 15624933]
81. Taniguchi M, Ptaszek M, McDowell BE, Lindsey JS. Tetrahedron 2007;63companion paper (second paper in series of three)
82. Taniguchi M, Ptaszek M, McDowell BE, Boyle PD, Lindsey JS. Tetrahedron 2007;63companion paper (third paper in series of three)
83. Rao PD, Dhanalekshmi S, Littler BJ, Lindsey JS. J. Org. Chem 2000;65:7323–7344. [PubMed: 11076589]
84. Laha JK, Dhanalekshmi S, Taniguchi M, Ambroise A, Lindsey JS. Org. Process Res. Dev 2003;7:799–812.
85. Zaidi SHH, Muthukumaran K, Tamaru S-I, Lindsey JS. J. Org. Chem 2004;69:8356–8365. [PubMed: 15549807]
86. Geier GR III, Littler BJ, Lindsey JS. J. Chem. Soc., Perkin Trans. 2 2001:701–711.
87. Ptaszek M, McDowell BE, Lindsey JS. J. Org. Chem 2006;71:4328–4331. [PubMed: 16709082]
88. Brückner C, Posakony JJ, Johnson CK, Boyle RW, James BR, Dolphin D. J. Porphyrins Phthalocyanines 1998;2:455–465.
89. Battersby AR, Fookes CJR, Snow RJ. J. Chem. Soc. Perkin Trans. 1 1984:2725–2732.
90. Sharada DS, Muresan AZ, Muthukumaran K, Lindsey JS. J. Org. Chem 2005;70:3500–3510. [PubMed: 15844983]
91. Rosenfeld A, Morgan J, Goswami LN, Ohulchanskyy T, Zheng X, Prasad PN, Oseroff A, Pandey RK. Photochem. Photobiol 2006;82:626–634. [PubMed: 16277564]
92. Taniguchi M, Balakumar A, Fan D, McDowell BE, Lindsey JS. J. Porphyrins Phthalocyanines 2005;9:554–574.
93. (a) Sapunov VV, Egorova GD. J. Appl. Spectroscopy 1987;46:519–522. (b) Stolzenberg AM, Schussel LJ, Summers JS, Foxman BM, Petersen JL. Inorg. Chem 1992;31:1678–1686. (c) Singh A, Johnson LW. Spectrochim. Acta Part A 2003;59:905–908.
94. (a) Borisevich EA, Egorova GD, Knyukshto VN, Solovev KN. Opt. Spectrosc. (USSR) 1984;56:255–258. (b) Lomova TN, Mozhzhukhina EG, Shormanova LP, Berezin BD. J. Gen. Chem. USSR 1989;54:2077–2084. (c) Sengupta D, Robinson BC. Tetrahedron 2002;58:5497–5502. (d) Ciulla TA, Criswell MH, Danis RP, Snyder WJ, Small W IV. Retina 2004;24:521–529. [PubMed: 15300072] (e) Ciulla TA, Criswell MH, Snyder WJ, Small W IV. Br. J. Ophthalmol 2005;89:113–119. [PubMed: 15615758]
95. Yu L, Muthukumaran K, Sazanovich IV, Kirmaier C, Hindin E, Diers JR, Boyle PD, Bocian DF, Holten D, Lindsey JS. Inorg. Chem 2003;42:6629–6647. [PubMed: 14552615]
96. Kim H-J, Dogutan DK, Ptaszek M, Lindsey JS. Tetrahedron 2007;63:37–55. [PubMed: 17464365]
97. Srinivasan N, Haney CA, Lindsey JS, Zhang W, Chait BT. J. Porphyrins Phthalocyanines 1999;3:283–291.
98. Ptaszek M, Bhaumik J, Kim H-J, Taniguchi M, Lindsey JS. Org. Process Res. Dev 2005;9:651–659.

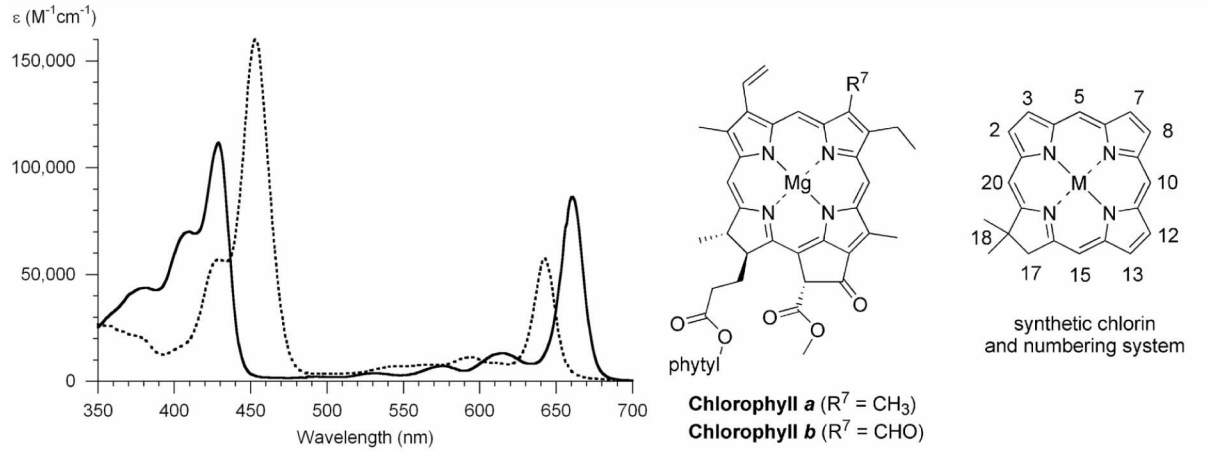


Figure 1.

Absorption spectra of chlorophyll *a* (solid line) and chlorophyll *b* (dashed line) in diethyl ether at room temperature.[2] The chlorin numbering system is shown at right.

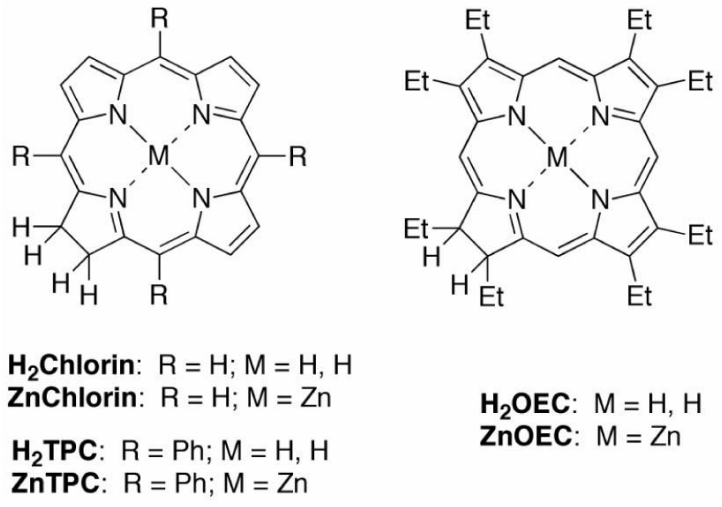


Chart 1.

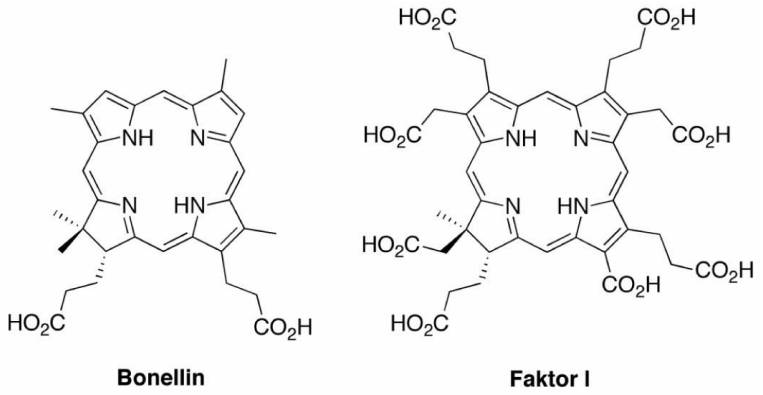
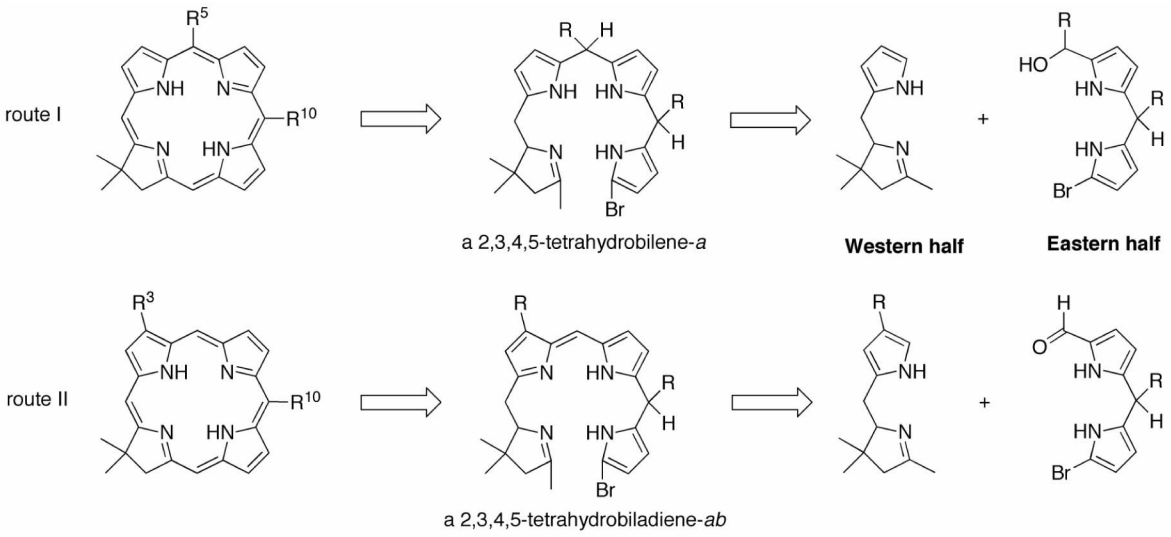
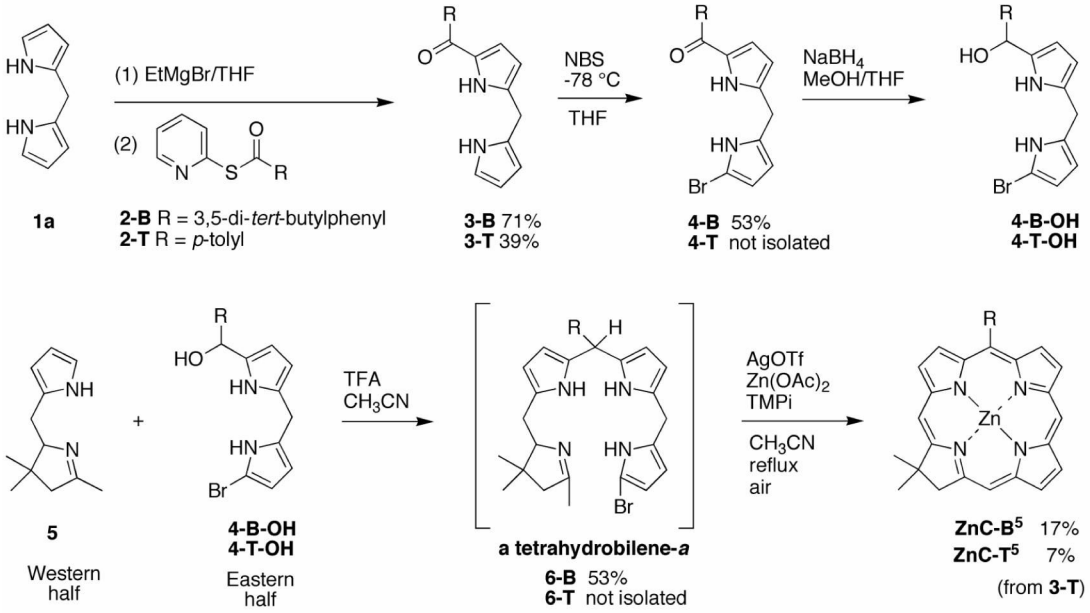


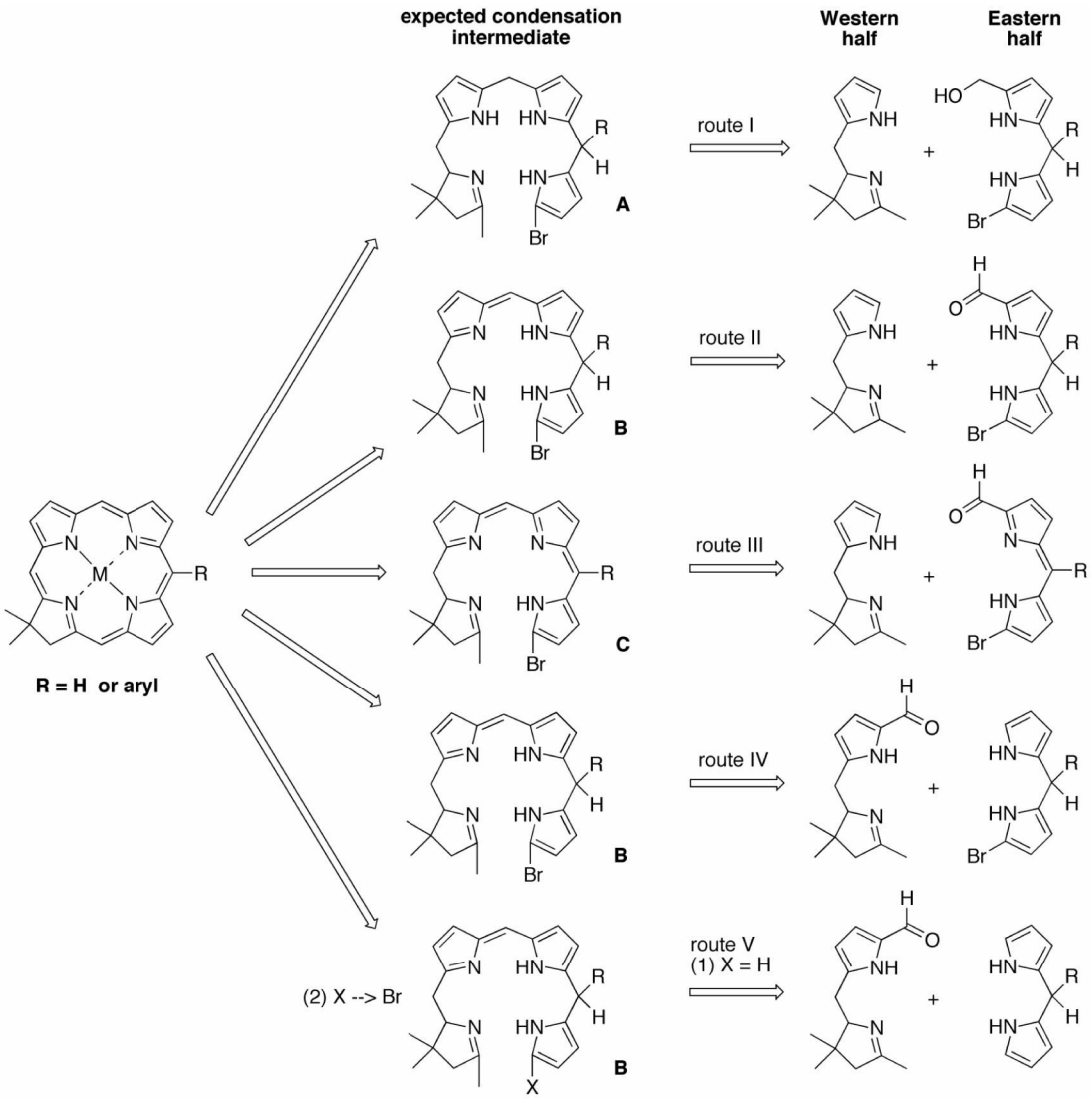
Chart 2.



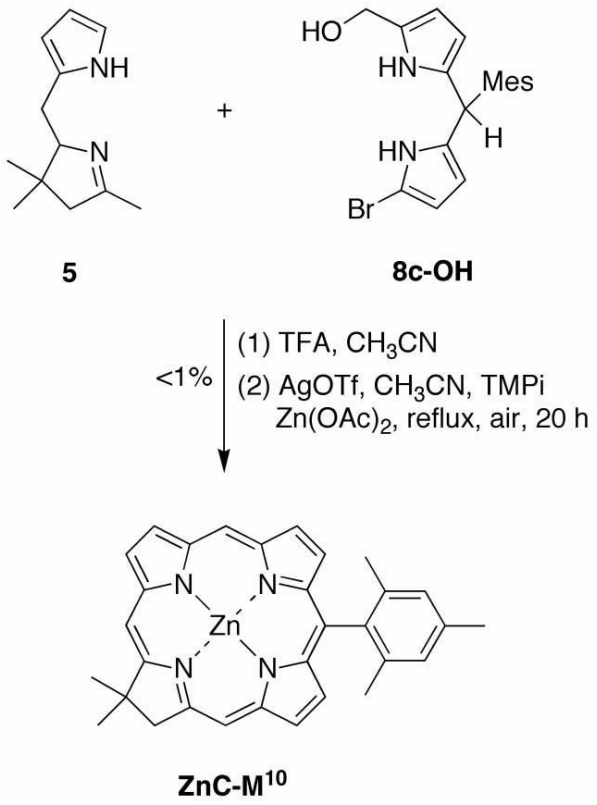
Scheme 1.



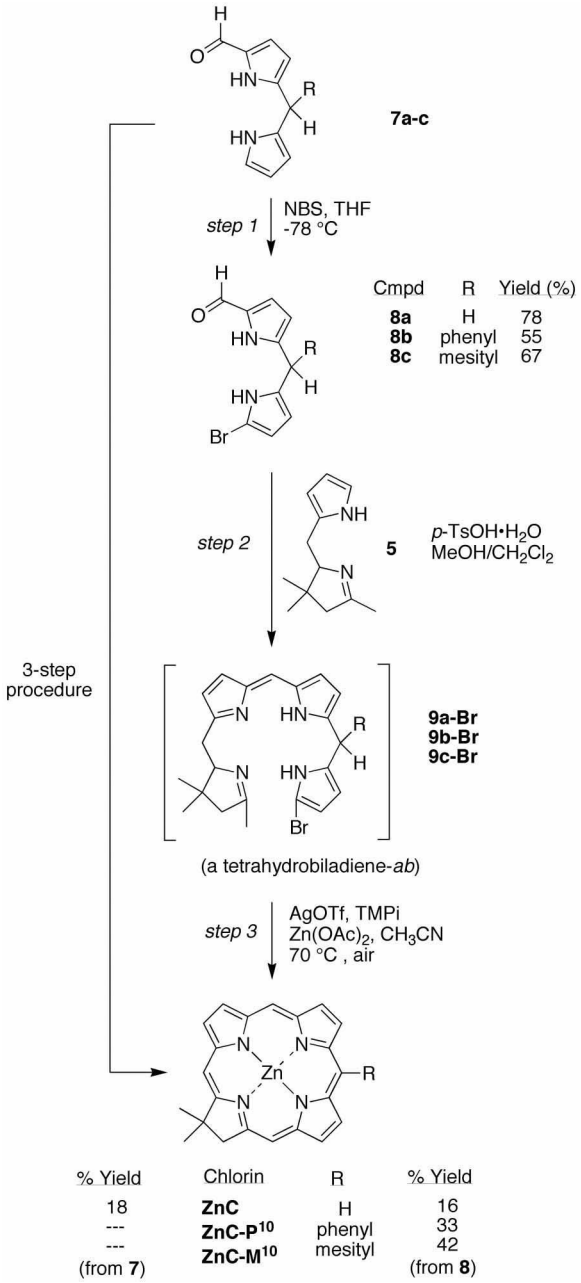
Scheme 2.



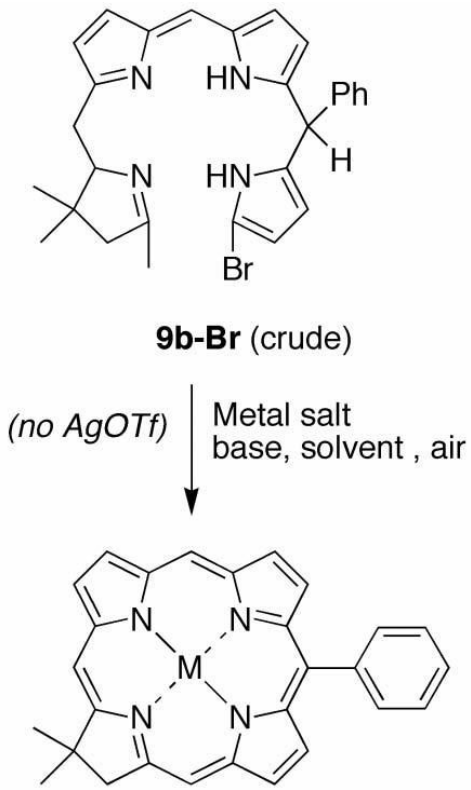
Scheme 3.
Routes to 5-unsubstituted chlorins



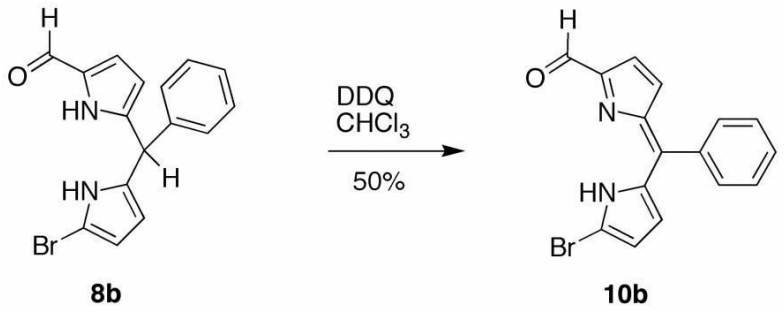
Scheme 4.
Route I



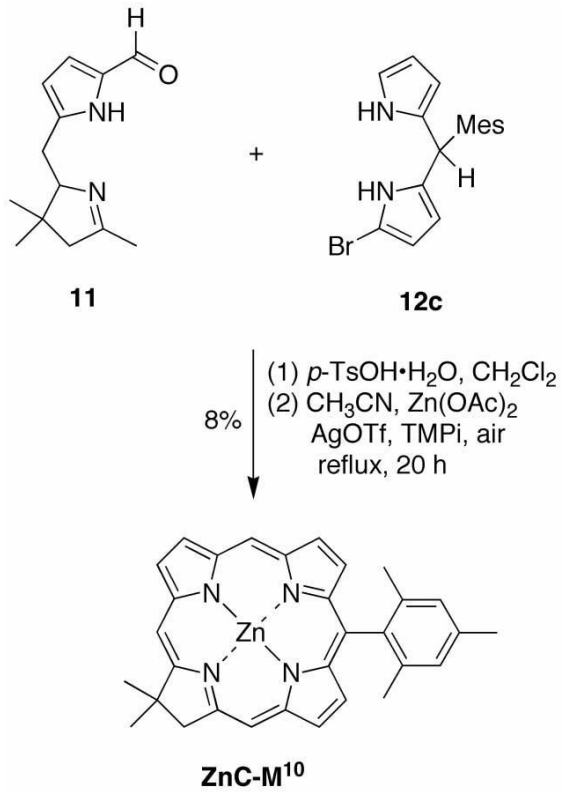
Scheme 5.
Route II



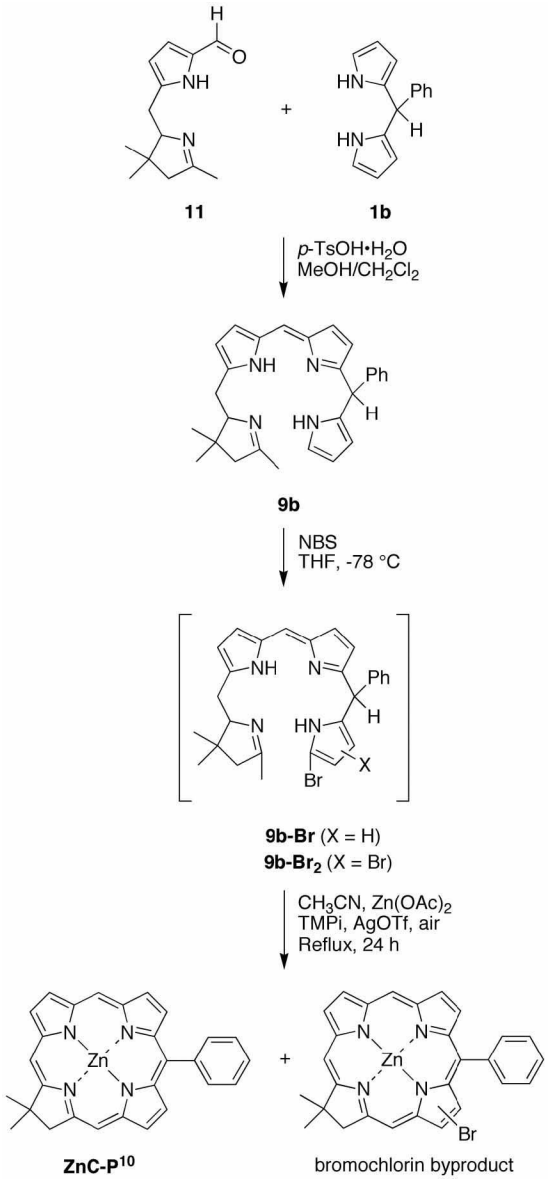
Scheme 6.
AgOTf-free step 3 of route II



Scheme 7.
Route III



Scheme 8.
Route IV



Scheme 9.
Route V

Table 1

Exploration of the metal-mediated oxidative cyclization of a tetrahydrobiladiene-*ab*[a]

Entry	Metal salt	Base[b]	Solvent	Product	Yield
1	$Zn(OAc)_2$	TMPi	MeCN	**ZnC-P[10]**	37%[c]
2	$Zn(OAc)_2$	DBU	MeCN	**ZnC-P[10]**	9%[c]
3	$Zn(OAc)_2$	DIEA	MeCN	**ZnC-P[10]**	10%[c]
4	$Pd(OAc)_2$	TMPi	MeCN	**PdC-P[10]**	12%[d]
5	$Pd(OAc)_2$	KOH[e]	EtOH	**PdC-P[10]**	5.6%[d]
6	$Pd(MeCN)_2Cl_2$	KOH[e]	EtOH	**PdC-P[10]**	6.2%[d]
7	$Cu(OAc)_2$	TMPi	MeCN	**CuC-P[10]**	4%[c]
8	$Cu(OAc)_2$	KOH[e]	EtOH	**CuC-P[10]**	14%[d]
9	$SnCl_2$	TMPi	MeCN	**SnC-P[10]**	5%
10	$MgBr_2$	TMPi	MeCN	--	0%
11	$Co(OAc)_2$	TMPi	MeCN	--	0%
12	$NiCl_2$	TMPi	MeCN	--	0%
13	$CdCl_2$	TMPi	MeCN	--	0%
14	No metal	TMPi	MeCN	--	0%
15	No metal	DBU	MeCN	--	0%
16	No metal	DIEA	MeCN	--	0%

[a] The crude biladiene **9b-Br** was prepared by *p*-TsOH-catalyzed condensation of **5** and **8b** under standard conditions. The reaction mixture was then neutralized by the base to be used in the metal-mediated oxidative cyclization (when KOH was used as a base in metal-mediated cyclization, crude **9b-Br** was neutralized by triethylamine). Unless noted otherwise each reaction was performed at 10 mM concentration with 15 equiv of metal salt and 30 equiv of base.

[b] Bases include 2,2,6,6-tetramethylpiperidine (TMPi), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and *N*,*N*-diisopropylethylamine (DIEA).

[c] Spectroscopic yield (from **8b**) unless noted otherwise, assuming a fixed molar absorption coefficient in all cases (see Experimental Section).

[d] Isolated yield.

[e] 5 Equiv was employed.